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Blood Groups in Infection and Host Susceptibility

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(continued)

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This work is dedicated to the late John Moulds and George Garratty, two highly esteemed serologists who made significant contributions to the field of immunohematology.

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SUMMARY

Blood group antigens represent polymorphic traits inherited among individuals and populations. At present, there are 34 recognized human blood groups and hundreds of individual blood group antigens and alleles. Differences in blood group antigen expression can increase or decrease host susceptibility to many infections. Blood groups can play a direct role in infection by serving as receptors and/or coreceptors for microorganisms, parasites, and viruses. In addition, many blood group antigens facilitate intracellular uptake, signal transduction, or adhesion through the organization of membrane microdomains. Several blood groups can modify the innate immune response to infection. Several distinct phenotypes associated with increased host resistance to malaria are overrepresented in populations living in areas where malaria is endemic, as a result of evolutionary pressures. Microorganisms can also stimulate antibodies against blood group antigens, including ABO, T, and Kell. Finally, there is a symbiotic relationship between blood group expression and maturation of the gastrointestinal microbiome.

INTRODUCTION

Since the discovery of the ABO blood group, there has been an ongoing interest in the potential role of blood groups in infectious disease. Blood groups are frequent targets in epidemiological investigations since they are genetically determined traits with known polymorphic expression among individuals and populations. Many blood groups are receptors for toxins, parasites, and bacteria, where they can facilitate colonization or invasion or evade host clearance mechanisms. Blood groups can also serve as false receptors, preventing binding to target tissue. Finally, bacteria can stimulate antibodies against blood group antigens, including ABO. ABO antibodies can be considered part of the innate immune system against some bacterial pathogens and enveloped viruses that carry ABO-active antigens.

At present, there are 34 blood group systems recognized by the International Society for Blood Transfusion (ISBT) (1, 2). As noted in Table 1, blood group antigens may reflect polymorphisms on red cell glycoproteins or are carbohydrate epitopes (ABO and Lewis) on glycoproteins and glycolipids (1, 2). Many blood groups reside on proteins critical for red cell maturation and function. Several blood group proteins are clustered at the red cell band 3-ankyrin metabolon (Diego, MNSs, Duffy, Colton, and LW) and junctional complexes (Diego, Gerbich, and MNSs), which anchor the membrane to the underlying cytoskeleton (3, 4). Interestingly, many of these same proteins are receptors for intraerythrocytic pathogens (malaria, *Bartonella* species, and *Babesia* species), with a loss of red cell deformability upon infection (5). Other blood groups are associated with membrane microdomains (for example, P^k, P, Cromer, GIL, Colton, and Raph) and play a role in endocytosis, cell signaling, and the immune response. Some systems, such as ABO, have multiple associations with infectious disease. Likewise, many pathogens can utilize or interact with several different blood group antigens. This is particularly true of malaria, which has potential interactions with 8 to 9 different blood group systems.

This review is organized by blood group system, based on commonalities in blood group structure and disease associations. The first half of the review focuses on the carbohydrate-based blood groups ABO, Lewis and Secretor, and globo-related antigens (P_1, P^k, and LKE). The succeeding sections describe blood groups most often associated with malaria and other parasites, followed by antigens normally involved with complement regulation (Cromer and Knops), cell adhesion (CD44 and Raph), and other functions. This review does not cover the utilization of blood groups as bacterial nutrients.

ABO, LEWIS, AND SECRETOR BLOOD GROUPS

ABO Serology

The ABO histo-blood group consists of two antigens (A and B antigens) and four blood types (types A, B, AB, and O). The A and B antigens are the product of the ABO gene and are autosomal codominant. The group O phenotype is an autosomal-recessive phenotype due to the homozygous inheritance of two null ABO alleles. Group O individuals express the H antigen, the biosynthetic precursor to A and B antigens (Fig. 1). ABO, therefore, is the blood type, whereas A, B, and H refer to the antigens. The relative distribution of ABO types can vary among different ethnic populations, although group O tends to be the most common (Table 2) (2, 6–27). In addition to red cells, ABH antigens are widely expressed in many tissues and secretions, including intestinal mucosa, endothelium, kidney, heart, and other organs.

ABO is unique among all human blood groups in that it requires the typing of both red cells and plasma or serum (Table 3) (1, 28). In forward or red cell typing, red cells are typed for the expression of A and B antigens on red cells by hemagglutination using monoclonal or polyclonal antibodies. Reverse typing or serum grouping is performed by incubating plasma or serum with commercial group A and B red cells to detect the presence of naturally occurring anti-A and anti-B antibodies (referred to as isohemagglutinins in the older literature). In general, the individual should possess antibodies against any missing A/B antigens. For example, a group O person possesses both anti-A and anti-B, whereas group AB, which expresses both antigens, is negative for ABO antibodies. Clinically, the forward and reverse grouping results must match for a blood type to be determined (1, 28).

Several genetic, developmental, and clinical conditions can affect ABO typing, with implications for epidemiology studies. In many epithelial tissues, ABO expression is heavily dependent on the inheritance of the *Secretor/FUT2* gene (see below), which cannot always be ascertained by red cell typing alone. There are several known variant ABO alleles that are associated with weak A/B

TABLE 1 Human blood group systems[c]

Blood group system					Gene			
CD[a]	Group no.	Name	Symbol	No. of Ags[b]	Chromosome	Designation(s)	Protein function(s)	No. of molecules per RBC[d]
—[e]	001	ABO	ABO	4	9q34.2	*ABO*	Glycosyltransferase	0–1 million
CD235	002	MNS	MNS	46	4q31.21	*GYPA* *GYPB*	Red cell zeta potential Band 3-ankyrin complex Junctional complex	GYPA, 1 million; GYPB, 250,000
CD77	003	P1PK	P1PK	4	22q13.2	*A4GALT1*	α1,4-Galactosyltransferase	
CD240	004	Rh	Rh	52	1p36.11	*RHD* *RHCE*	Ammonium transport Band 3 metabolon	100,00–200,000 trimers
CD239	005	Lutheran	Lutheran	20	19q13.32	*LU*	Laminin receptor, erythroid maturation	1,500–4,000
CD238	006	Kell	KEL	34	7q34	*KEL*	Endothelin-3-converting enzyme	3,500–18,000
—	007	Lewis	LE	6	19p13.3	*FUT3*	α3/4-Fucosyltransferase	Adsorbed from plasma
CD234	008	Duffy	FY	5	1q23.2	*DARC*	Chemokine receptor	6,000–13,000
—	009	Kidd	JK	3	18q12.3	*SLC14A1*	Urea transport	14,000
CD233	010	Diego	DI	22	17q21.31	*SLC4A1*	Band 3/AE1/anion exchange, membrane-cytoskeleton stability, band 3 metabolon-gas exchange, RBC senescence	1 million dimers, tetramers
—	011	Cartwright	YT	2	7q22.1	*ACHE*	Acetylcholinesterase	7,000–10,000
CD99	012	Xg	XG	2	Xp22.33	*XG*, *MIC2*	Adhesion molecule	200–2,000
—	013	Scianna	SC	7	1p34.2	*ERMAP*	Unknown, adhesion?	Unknown
CD297	014	Dombrock	DO	8	12p12.3	*ART4*	ADP-ribosyltransferase	Unknown, likely raft associated
—	015	Colton	CO	4	7p14.3	*AQP1*	Water transport, band 3 metabolon	120,000–160,000 tetramers
CD242	016	Landsteiner-Wiener	LW	3	19p13.2	*ICAM4*	Adhesion molecule	2,800–4,400
—	017	Chido/Rodgers	CH/RG	9	6p21.3	*C4A*, *C4B*	Complement C4	Adsorbed from plasma
CD173	018	H (SE[f])	H H	1 1	19q13.33 19q13.33	*FUT1* *FUT2*	α1,2-Fucosyltransferase, type 2 H antigen α1,2-Fucosyltransferase, type 1, 3, and 4 H antigens, secretor (ABH, Le^b)	
—	019	Kx	KX	1	Xp21.1	*XK*	Unknown	1,000
CD236	020	Gerbich	GE	11	2q14.3	*GYPC*	Glycophorins C and D, junctional complex protein, lateral membrane stability	GYPC, 135,000; GYPD, 50,000
CD55	021	Cromer	CROM	16	1q32.2	*CD55*	DAF, complement regulation	20,000, raft associated
CD35	022	Knops	KN	9	1q32.2	*CR1*	Complement receptor 1, complement regulation	20–1,500
CD44	023	Indian	IN	4	11p13	*CD44*	Cell adhesion	2,000–5,000
CD147	024	Ok	OK	3	19p13.3	*BSG*	Basigin, RBC trafficking and senescence, cytophilin receptor, cell adhesion and signaling	3,000

CD151	025	Raph	RAPH	1	11p15.5	*CD151*	Tetraspanin, cell adhesion	Unknown, likely raft associated
CD108	026	John Milton Hagen	JMH	6	15q24.1	*SEMA7A*	T-cell-mediated inflammation, integrin receptor (α1β1)	Unknown, likely raft associated
—	027	I	I	1	6p24.2	*GCNT2*	β1,6-*N*-Acetylglucosaminyltransferase	
—	028	Globoside	GLOB	2	3q26.1	*B3GALNT1*	β1,3-*N*-Acetylgalactosaminyltransferase	>10% RBC lipids, 70% RBC GSLs
—	029	Gill	GIL	1	9p13.3	*AQP3*	Aquaglyceroporin; water, glycerol, peroxide transport	25,000
CD241	030	Rh-associated glycoprotein	RHAG	4	6p21-qter	*RHAG*	Ammonium transport, associated RhD and RhCE	100,000–200,000 trimers
—	031	Forssman	FORS	1	9q34.13	*GBGT1*	α1,3-*N*-Acetylgalactosaminyltransferase	Rare expression
CD338	032	Jr	JR	1	4q22	*ABCG2*	ATP-dependent transport, multidrug resistance, folate homeostasis	Unknown
—	033	Lan	LAN	1	2q36	*ABCG6*	Porphyrin/heme transport	Unknown
—	034	Vel	VEL	1	1p36.32	*SMIM1*	Regulation of red cell formation	Unknown

[a] CD, cluster designation.
[b] Number of RBC antigens recognized by the ISBT.
[c] See references 1 and 2.
[d] No. of blood group-active proteins or glycans per red cell.
[e] —, no CD designation.
[f] SE, Secretor. Secretor is related to H but has no official ISBT designation.

FIG 1 Synthesis of H, A, and B antigens. The H antigen is formed by the addition of an α1-2 fucose (blue diamonds) by FUT1 or H-glycosyltransferase. H antigen can then serve as a substrate for ABO glycosyltransferase. Group A individuals express an α1-3 *N*-acetylgalactosamine (GalNAc) (red trapezoid), and group B individuals express an α1-3 galactose (Gal) (orange circles). Group O individuals have inactive ABO genes and express only the H-antigen precursor. The Bombay phenotype (O_h) lacks H, A, and B antigens due to null *FUT1* alleles.

antigen expression, accompanied by elevated H antigen expression. For example, 20% of group A individuals belong to the A_2 subgroup (Table 3), which has only 25% of normal A expression on red cells and virtually no A antigen in platelets, the endothelium, and secretions (29–32). ABO is also an oncofetal antigen with altered expression in certain populations. For example, ABO is markedly depressed on newborn red cells due to developmental delays in I blood group gene expression, which is responsible for branching and multivalent ABO expression (33). In addition, newborns lack ABO antibodies for the first 4 to 6 months of life and achieve adult titers only at 5 to 10 years of age (28, 29). ABO grouping problems can also occur in patients with cancer, congenital or acquired immunodeficiencies, protein-losing enteropathies, recent transfusion, and other conditions (1, 28).

ABO Biosynthesis

ABH antigens are carbohydrate antigens expressed on glycosphingolipids (GSLs) and glycoproteins (28, 29). In normal adult red cells, there are ~800,000 to 1 million ABH antigens per cell (29). Like all carbohydrate antigens, ABH antigens are synthesized by the sequential addition of carbohydrates to an oligosaccharide backbone. On red cells, the H antigen is synthesized by the *FUT1/H* gene, an α1,2-fucosyltransferase that adds a terminal fucose to lactosamine to form Fucα1-2Galβ1-4GlcNAc-R (Fig. 1). H antigen can then serve as a substrate for ABO, which adds either an *N*-acetylgalactosamine (GalNAc) (A antigen) or galactose (Gal) (B antigen), in an α1-3 linkage, to the same subterminal galactose. In the absence of ABO activity, only H or "O" antigen is expressed. A, B, and H are also absent in the rare Bombay (O_h) and para-Bombay phenotypes, which cannot synthesize H antigen due to mutations in *FUT1* (Table 3).

TABLE 2 Distribution of blood types in different populations

Blood group system	Blood group phenotype	Population distribution (%) by country[c]						References
		United States						
		Whites	Blacks	Africa[a]	Brazil	China	India	
ABO	A	40	27	19	41	22–29	22	2, 6–8, 29, 713
	B	11	20	14	9	26	33	
	AB	4	4	<1	3	6–13	7	
	O	45	49	67	47	28	37	
Lewis	Le(a+b−)	27	23	14	8	0	21	2, 9–12, 29
	Le(a−b+)	72	55	54	67	71	61	
	Le(a+b+)	0	0	0	0	20[b]	0	
	Le(a−b−)	6	22	14	25	9	18	
P	P_1	79	94	NA	NA	25–29	72	2, 7, 9, 12, 13, 29
	P_2	21	6	NA	NA	69–75	28	
MNSs	$M^+ N^-$	28	25	37	25	31	34.6	2, 7, 8, 12, 14–20, 29
	$M^+ N^+$	50	49	36	51	50	54.1	
	$M^- N^+$	22	26	27	24	19	11.3	
	$S^+ s^-$	11	7	27	6	<1	11.3	
	$S^+ s^+$	44	24	40	39	6	43.9	
	$S^- s^+$	45	69	55	55	94	44.7	
	Henshaw	0	3	6–27	0	0	0	
	Mi.III	<0.1	<0.1	NA	NA	6	NA	
Diego	Di(a+)	0.01	0.01	0.01	2–54	4–10	NA	2, 9, 21–23, 29
Duffy	Fy(a+b−)	17	9	3	33	93	42.1	2, 8, 12, 14, 15, 17, 24, 29
	Fy(a+b+)	49	1	<1	27	7	4.5	
	Fy(a−b+)	34	22	8	35	<1	12.3	
	Fy(a−b−)	0	68	89–100	5	0	0.3	
Knops	Kn^a	98	99	100	98	100	98	25–27
	Kn^b	4	<1	NA	2	0	2	
	McC^a	98	90	89–92	93	100	78	
	McC^b	1	44	49–54	42	0	22	
	Sl1	99	51–61	30–38	70	100	48	
	Sl2	<1	80	95	86	0	52	
	KCAM	98	NA	20	53	57–82	NA	

[a] Values are for West or Central Africa.
[b] High incidence of Le(a+b+) in other Asian Pacific populations (for example, Japan).
[c] NA, not available.

ABH can be expressed on several different oligosaccharide backbones, which are tissue and species specific (Table 4) (1). The oligosaccharide backbone contributes to ABH recognition by antibodies as well as many microorganisms. On human red cells, platelets, and endothelium, ABO is expressed primarily on type 2 chain or lactosamine-type structures (Galβ1-4GlcNAc-R). In contrast, genitourinary and gastrointestinal epithelial cells are rich in type 1 chain structures, which differ from type 2 structures based on the galactose linkage (Galβ1-3GlcNAc-R). Type 1 chain ABH antigens are also found in fluids and secretions, including saliva, mucus, and plasma. Whereas the synthesis of type 2 chain ABH requires the *FUT1* gene, synthesis of type 1 chain ABH requires Secretor or *FUT2*, an α1,2-fucosyltransferase that preferentially recognizes Galβ1-3GlcNAc acceptors. Unlike type 2 chain precursors, type 1 chain synthesis is highly regulated and can be downregulated in response to inflammation and neoplastic transformation (34, 35).

Like the type 1 chain, type 3 and type 4 chain ABH antigens are tissue restricted (Table 4). Both types share a terminal Galβ1-3GalNAc-R structure that can serve as a substrate for FUT2. As a result, these structures are also found primarily on genitourinary and/or gastrointestinal tissue. Type 3 chain A, also known as mucinous A, is a polymer of repeating A motifs and is unique to group A_1 individuals (36). Type 4 chain ABH, or globo-ABH, is a glycosphingolipid-specific antigen related to the P blood group system. Animals can also express ABH on ganglio-family GSLs (Table 4), including ABH-GM1 active species capable of weakly binding cholera toxin (CTx) (37). Both FUT1 and FUT2 are capable of synthesizing type 3 H, type 4 H, and H-GM1 glycolipids, which share a Galβ1-3GalNAc acceptor (38–40).

Lewis and Related Blood Groups

Lewis is a type 1 blood group related to the ABO blood group. Like the ABO blood group, the Lewis blood group reflects the actions of two distinct glycosyltransferases, FUT2/Secretor and Lewis/FUT3, an α1,3/4-fucosyltransferase (28, 29). Lewis synthesis is tissue re-

TABLE 3 ABO typing of red cells and plasma/serum

ABO type	Gene[a]		RBC grouping[b] (forward or antigen type)			Serum grouping[c] (back type)		
	FUT1	*ABO*	Anti-A	Anti-B	UEA-1[b]	A_1 RBC	B RBC	O RBC
A_1	+	+	++	0	0	0	+	0
A_2[d]	+	+	+	0	+	+/0	+	0
B	+	+	0	++	0	+	0	0
O[e]	+	0	0	0	++	+	+	0
O_h[f] (Bombay)	0 (*hh*)	+	0	0	0	+	+	+

[a] Inheritance of at least one functional H gene (*FUT1*) and *ABO* gene.
[b] Testing for ABO antigens on red cells with monoclonal anti-A and anti-B. H antigen is detected with the *Ulex europaeus* lectin (UEA-1).
[c] Testing of plasma/serum against red cells of a known ABO type to detect anti-A, anti-B, or anti-H.
[d] A_2 is the most common weak A phenotype, is characterized by increased H antigen levels, and may possess anti-A_1. A_2 and other weak A red cells do not agglutinate with the anti-A lectin of *Dolichos biflorus*.
[e] Group O is due to the homozygous inheritance of *ABO* amorph alleles.
[f] Bombay O_h is a rare autosomal-recessive phenotype due to amorph *FUT1* (*hh*) and *FUT2/Secretor* (*se/se*). Bombay individuals lack H, A, and B antigens and possess hemolytic anti-A, anti-B, and anti-H.

stricted, with strong expression in fluids and respiratory, gastrointestinal, and genitourinary tissues (35). Lewis-active GSLs can be found in other tissues, such as red cells, lymphocytes, and endothelium, that do not synthesize type 1 antigens. In these tissues, Lewis antigens are passively adsorbed onto cell membranes from circulating GSL in plasma (1, 28).

There are two Lewis antigens (Le^a and Le^b) and four potential Lewis red cell phenotypes, although only three types are considered common (Table 5). Le(a+b−), Le(a−b+), and Le(a−b−) constitute the majority of Lewis types and display ethnic and geographic variation (Table 2). Le(a+b+) is observed only in very young children and some Asian populations (2, 28). Because it terminates in a Fucα1-2Galβ1-3GlcNAc epitope, Le^b is also considered an H(O)-active antigen. In group A and B individuals, Le^b can be further modified to form ALe^b and BLe^b (Table 4). In A_1 individuals, ALe^b is the predominant antigen found in plasma (41). This interaction of ABO and Lewis can have important implications for microbial recognition, especially in gastrointestinal tissue.

The synthesis of Lewis antigens, and their relationship to type 1 and type 2 chain ABH antigens, is shown in Fig. 2. Le^a is synthesized by FUT3/Lewis, which adds an α1-4 fucose to the subterminal GlcNAc of the type 1 chain precursor (Le^C). In contrast, Le^b requires the initial synthesis of type 1 H (Le^D) by FUT2, which can then serve as a substrate for FUT3/Lewis. Le^b cannot be synthesized directly from Le^a due to steric blocking by α1-4 fucose. Once formed, Le^b can then serve as a substrate for ABO to produce ALe^b and BLe^b. Because Le^b requires FUT2/Secretor for synthesis, it is always accompanied by the synthesis of type 1 chain ABH as well. In the absence of the type 1 chain substrate, FUT3 can utilize type 2 chain substrates to form Le^X and Le^Y antigens (Fig. 2). This is observed in gastrointestinal tissue, where deep glandular epithelial stem cells synthesize predominantly type 2 chain structures with Le^X and Le^Y expression but switch to type 1 chain synthesis with Le^a and Le^b expression upon further differentiation (42, 43).

The presence and relative activity of FUT2 and FUT3 determine the Lewis phenotype (Table 5). The Le(a+b−) phenotype reflects the inheritance of a functional *FUT3/Lewis* gene and two null *FUT2/Secretor* (*se/se*) genes. As a result, Le(a+b−) individuals are ABH "nonsecretors" and express only Le^a (or Le^X) on tissues and in secretions. Conversely, Le(a−b+) individuals are always "secretors" of ABH and Lewis antigens. The apparent absence of Le^a in these individuals is relative, since both Le^a and Le^b are synthesized. It appears that FUT2 outcompetes FUT3 for Le^C, resulting in more Le^b synthesis (44). This can be observed in newborns, who are transiently typed as Le(a+b+) due developmental delays in FUT2 activity (28). Le(a+b+^{W}) is observed in up to 20% of individuals in many Japanese, Chinese, and Polynesian populations due to a weak *FUT2* allele (2) (Table 2).

The Le(a−b−) phenotype is a *FUT3/Lewis*-null phenotype. Le(a−b−) individuals can be typed as nonsecretors or secretors (Se^+), depending on whether they have inherited a functional *FUT2* allele. This can be determined by molecular typing of the *FUT2* gene and screening for soluble ABH antigens in blood and secretions by Western blotting or by hemagglutination inhibition assays (HAI) using saliva. The latter involves preincubation of saliva with anti-A/B antibodies, followed by the addition of red cells (groups A, B, and O). In the presence of soluble ABH antigens, anti-A/B is neutralized, and no red cell agglutination occurs. If soluble ABH antigens are absent (nonsecretor), hemagglutination is observed (1).

Effect of Lewis on Soluble ABH Antigens

The interaction between Lewis, Secretor, and ABO directly impacts the amount of soluble ABH antigen in blood and secretions. A_1 nonsecretors have twice the amount of soluble A as A_1 Le(b+) secretors (138 versus 72 U; $P < 0.001$) (32). This difference is due to the synthesis of type 1 A in nonsecretors, whereas secretors preferentially synthesize ALe^b (Fig. 2) (41, 44, 45). In one study, ALe^b was 3 times more plentiful than type 1 A, making up almost 3% of the total plasma neutral GSLs and ~66% of the Le^b-active GSLs (41). Because fucosylation of terminal galactose inhibits chain elongation, nonsecretors synthesize more elongated and branched variants of ABH, Le^a, and/or Le^X antigens (45, 46).

Differences in soluble A antigen can impact HAI and other assays. Using A-antigen analogues conjugated to bovine serum albumin (BSA), LePendu was able to demonstrate distinct differences between ALe^b, type 1 A, and type 2 A antigens (47). Polyclonal anti-A readily reacted with either type 1 or type 2 A antigens, with 50% activity at 0.08 to 0.13 μg/ml. In contrast, ALe^b was poorly recognized, with only 40% activity at 100-μg/ml concentrations.

TABLE 4 Examples of A-active antigens, expression, and synthesis

Antigen	Structure[a]	RBC type or other cell type[b]		Fucosyltransferase		
		A_1	A_2/A^{wk}	FUT1	FUT2	FUT3
Type 1 A (A-1)	GalNAcα1→3Galβ1→3GlcNAc→R[c] ↑2 Fucα1	+	↓	−	+	−
Type 1, ALe^b	GalNAcα1→3Galβ1→3GlcNAc→R ↑2 ↑4 Fucα1 Fucα1	+	↓/0	−	+	+
Type 2 A (A-2)	GalNAcα1→3Galβ1→4GlcNAc→R ↑2 Fucα1	+	↓	+	−	−
Type 2, ALe^Y	GalNAcα1→3Galβ1→4GlcNAc→R ↑2 ↑3 Fucα1 Fucα1	+	↓	+	−	+
Type 3 A (A-3)[d] (mucinous A)	GalNAcα1→3Galβ1→3GalNAcβ1→3Galβ1→R ↑2 ↑2 Fucα1 Fucα1	+	0	+	+	−
Type 4 A (A-4)[e] (globo-A)	GalNAcα1→3Galβ1→3GalNAcβ1→3Galα1→4Galβ1→4Glc→Cer ↑2 Fucα1	+	0	+	+	−
Ganglio-A[e]	GalNAcα1→3Galβ1→3GalNAcβ1→4Galβ1→4Galβ1→4Glc→Cer ↑2 Fucα1	Pig red cells, intestine		+/−	+	−
O-glycan[f] A, H active	Fucα1→2Galβ1→3GalNAc-O-Ser/Thr ↑6 GalNAc1→3Gal1→3GlcNAcβ1 ↑2 Fucα1	Gastric mucosa (ALe^b)		−	+	−

[a] Abbreviations: Cer, ceramide; Fuc, fucose; Gal, galactose; GalNAc, *N*-acetylgalactosamine; Glc, glucose; GlcNAc, *N*-acetylglucosamine.
[b] Relative expression on A_1 versus A_2 and other A_{weak} subtypes.
[c] R, upstream sequence of various sizes, which may be expressed on the glycoprotein or glycosphingolipid.
[d] Found on A_1 cells only and composed of repeating terminal A motifs, also known as repetitive A motifs.
[e] Found as glycosphingolipids only.
[f] Core 2 O-glycan with A and H activity found on gastric mucosa (15% of total ALe^b individuals).

TABLE 5 Relationship between Lewis and Secretor genotypes and phenotypes

Lewis phenotype	Gene[a]		Secretor type[b]	Secreted antigen[c]		
	FUT2	*FUT3*		Le^a	Le^b	ABO
Lewis positive						
Le(a+b−)	0	+	N	+	0	0
Le(a−b+)	+	+	Y	+	+	+
Le(a+b+^{w})[d]	+ (*Se^w*)	+	Y	+	↓	↓
Lewis null						
Le(a−b−)	+	0	Y	0	0	+
Le(a−b−)	0	0	N	0	0	0

[a] Inheritance of at least one functional glycosyltransferase gene.
[b] Ability to secrete ABH antigens in saliva and other secretions. N, nonsecretor; Y, secretor.
[c] Presence of Lewis and type 1 ABH antigens in saliva and other secretions.
[d] Very weak Le^b expression due to inheritance of an *Se^W* FUT2 allele. Le(a+b+) may reflect either the *Se^W*/*Se^W* or *Se^W*/*se* genotype. *Se^W*/*se* can also be typed as Lewis null.

ABO and Other Cell Surface Glycoconjugates

ABO is a terminal modification that impacts cell surface glycosylation in many ways. The presence of fucose stops further chain elongation as well as branching (33, 45, 46). Because both fucosyltransferases and sialyltransferases compete for terminal galactose residues, ABH expression decreases sialylation and negative charge. As a result, there is an inverse relationship between sialylation and fucosylation (33). ABH antigens can be displayed on a variety of glycoconjugates, including N-linked and O-linked glycoproteins (33). On red cells, ABH antigens are expressed predominantly on N-linked glycoproteins, including highly branched type 2 chain structures. Gastrointestinal tissues, on the other hand, are rich in type 1, type 2, and type 3 ABH structures present on glycolipids and O-linked and N-linked glycans (48, 49).

ABO and Lewis Genetics

FUT1 (H). The *FUT1* and *FUT2* genes are highly homologous (70%) and are located together on chromosome 19q13 as a result

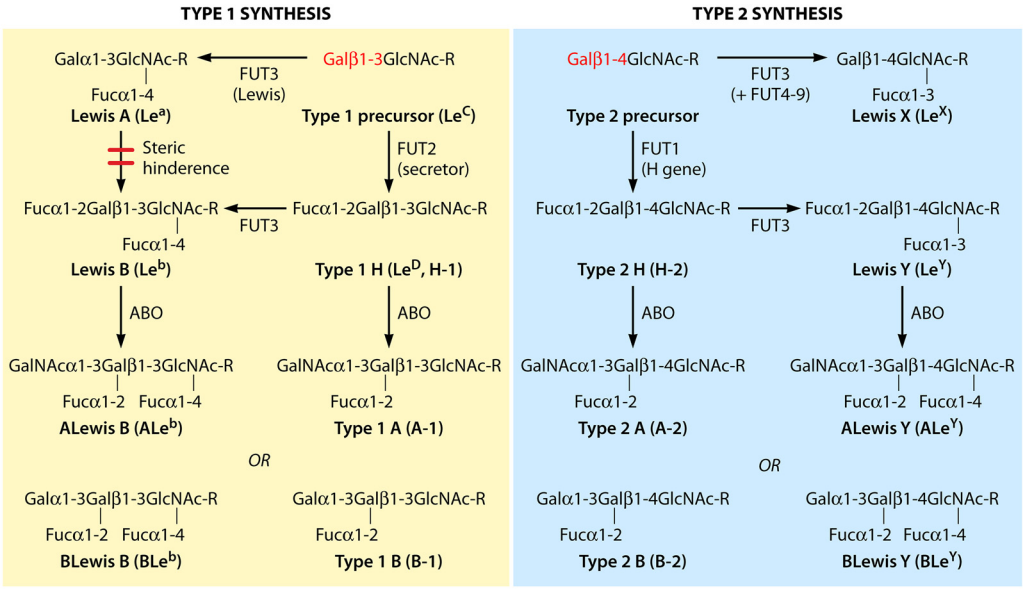

FIG 2 Relationship and synthesis of type 1 (Le^a and Le^b) and type 2 (Le^X and Le^Y) antigens by Lewis (FUT3) and Secretor (FUT2) enzymes and their modification by ABO.

of gene duplication. *FUT1* is relatively specific for type 2 chain polylactosamine substrates and is responsible for ABH expression on erythrocytes (RBC). *FUT1* mRNA is widely expressed in most tissues, with the exception of salivary and parotid glands, which express only *FUT2* (35).

The ISBT currently lists 19 null alleles and 23 weak *FUT1* alleles associated with a loss of or weak H (and AB) expression (http://www.isbtweb.org/). Bombay and para-Bombay are rare autosomal-recessive phenotypes due homozygosity for two *FUT1*-null alleles (*h/h*) (Table 3). Both phenotypes lack type 2 chain ABH antigens on red cells, although individuals with the para-Bombay phenotype still express type 1 chain ABH in secretions, intestinal mucosa, and other tissues due to an active *FUT2* gene (1, 28, 29). Bombay individuals are also nonsecretors (*se/se*) and therefore have no ABH synthesis on cells or in secretions.

FUT2 (SE). *FUT2* is responsible for the synthesis of type 1 chain ABH and Le^b antigens. As discussed above, *FUT2* is also able to synthesize type 3 and type 4 ABH antigens. *FUT2* is highly expressed in trachea, parotid and salivary glands, gastric and intestinal mucosa, uroepithelium (bladder and kidney), and female reproductive tract (vagina, cervix, and ovary); little or no *FUT2* mRNA is observed in placenta, bone marrow, or spleen, which uses FUT1 almost exclusively (35). Individuals inheriting at least one functional *FUT2* allele are considered secretors (Se^+) of ABH substances in saliva, blood, and other body fluids. A polymorphism in the *FUT2* promoter shows evidence of natural selection (50).

The ISBT currently lists 29 null and weak *FUT2* alleles (http://www.isbtweb.org/). Individuals homozygous for two *FUT2*-null alleles are considered nonsecretors and express only Le^a and type 1 precursor substance (Le^C) in their secretions and tissues (Table 5). In Caucasians, se^{428} (Trp143stop) is the most common nonsecretor allele and is often used in genomic studies (G428A; rs601338). The se^{428} allele is also common among Africans, Iranians, and Turks (2, 51). *FUT2* variants with weak activity (Se^W) are common in Asia. In China and neighboring Asian countries, Se^{385} (Ile129Phe) is the predominate Se^W allele (52–54). Se^W/Se^W and Se^W/se individuals can be typed as Le(a+b^W), Le(a+b−), or Le(a−b−). Individuals with a Se^W/se genotype are particularly at risk for having a nonsecretor phenotype (53).

***ABO* gene.** The *ABO* gene is located on chromosome 9q33-34 and encodes a 354-amino-acid (aa) glycoprotein (55) (Fig. 3). This gene is organized over 7 exons, although the bulk of the enzyme (225 amino acids) resides in exon 7. Exon 6 encodes the stem region and is a hot spot for recombination (29). The two major active alleles, A^1 (*ABO*A1*) and *B* (*ABO*B*), differ in their

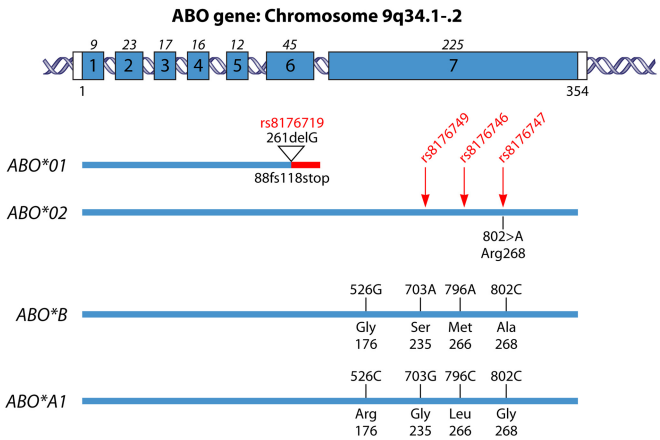

FIG 3 ABO gene and major A, B, and O alleles. The ABO gene resides on chromosome 9q34.1 and contains 7 exons, which encode a 354-aa glycoprotein. The glycoproteins encoded by the A (*ABO*A1*) and B (*ABO*B*) consensus alleles differ by 4 aa, 3 of which are functionally important (aa 235, 266, and 268). Group O alleles belonging to the O^1 family contain a deletion in exon 6, leading to a frameshift and a premature stop codon. Alleles belonging to the O^2 family share a mutation at aa 268. Shown in red are the SNP designations commonly used in genomic studies for ABO typing.

recognition and utilization of nucleotide-sugar donors. The enzyme encoded by the *ABO*A* allele recognizes UDP-GalNAc with synthesis of the A antigen, whereas the B-type enzymes prefer UDP-Gal donors. The *ABO*A* allele is generally considered the ancestral gene, with groups B and O arising through convergent evolution (56). A more recent study, however, suggests that ABO is an ancient balanced polymorphism that originated early in hominid history (20 million years ago) and has been maintained in multiple primate lineages (57).

A comparison of A^1 and *B* consensus alleles shows that they are essentially identical, differing by only 4 amino acids, 3 of which are enzymatically important for nucleotide-sugar donor recognition: Gly235Ser, Leu266Met, and Gly268Ala (Fig. 3) (55). Amino acids 235 and 266 are also required for H-antigen acceptor recognition (58). At present, there are >100 alleles associated with weak group A and B expression and another 13 with hybrid activity (synthesis of both A and B [*cis*-AB]) (1, 2). A common weak A allele in Caucasians is *ABO*A201* (1061ΔC; fs384), which is 20 amino acids longer than normal due to a frameshift mutation near the stop codon. The A_2 phenotype is found in 20% of white group A donors but is virtually absent among Asians, who tend to express weak B alleles (2, 7).

The *ABO*O* alleles are amorphs, usually as a result of mutations leading to a truncated enzyme (2, 29, 55). There are many group O alleles documented, but most can be classified as either O^1 or O^2 (Fig. 3) (1, 2). Alleles belonging to the O^1 family share a nucleotide deletion (G261Δ; fs88stop118) and account for 95% of all group O alleles (2). O^2 alleles carry a G802→A mutation, leading to Gly268→Arg. Crossover events between *O* and *A*, or *O* and *B*, alleles are not uncommon and can lead to errors in molecular typing and even rare cases of apparent nonpaternity (2, 29). Heterozygous inheritance (for example, A^1/O^1) does not affect ABO expression on red cells but can be associated with weaker ABO expression on other tissues (59).

Recent genomic studies typically include 3 to 4 different single nucleotide polymorphisms (SNPs) as a surrogate for ABO typing (Fig. 3). The most common SNPs cover the 3 polymorphisms between A and B (positions 235 [rs8176743], 266 [rs1876746], and 268 [rs8176747]) plus the O^1 allele (G261Δ [rs8176719]). Any O^2 alleles (Gly268) should also be identified by using this scheme. Genomic typing does not take into account other known mutations that impact enzyme activity (1, 2, 29, 55), upstream *cis*-regulatory elements (60, 61), differences in gene methylation (62), or loss of heterozygosity (63). For many reasons, blood centers and transfusion services do not rely on the results of genetic assays for ABO typing.

FUT3 (LE; Lewis). The Lewis gene (*Le* or *FUT3*) is an α1,3/4-fucosyltransferase capable of utilizing both type 1 and type 2 chain substrates to generate Le^a, Le^b, sialyl-Le^a, Le^X, and Le^Y (Fig. 2) (64). This gene is located on chromosome 19p13.3 as a cluster of three related glycosyltransferases, FUT5-FUT3-FUT6 (65). *FUT3* is tissue restricted and correlates fairly well with *FUT2* expression (35). The strongest *FUT3* mRNA expression is observed in the trachea, intestine, bladder, and lower female reproductive tract (35).

The Blood Group Antigen Gene Mutation Database (http://www.ncbi.nlm.nih.gov/projects/gv/mhc/xslcgi.cgi?cmd=bgmut) lists 37 *FUT3*-null alleles (*le*) associated with Lewis-negative [Le(a−b−)] expression on red cells. A majority of *le* alleles (33/37; 89%) have at least two SNPs, and many alleles contain four or more. Many mutations show a distinct geographic or ethnic distribution. In Caucasians, alleles containing T202C (Trp68Arg) and C314T (Thr105Met) mutations are common ($le^{202,314}$), whereas le^{59}, $le^{59,508}$, and $le^{59,1067}$ are predominant in Japan, China, South Korea, northern India, Asia, and the Brazilian Amazon (2, 29, 66–71). In African and U.S. black populations, several additional SNPs have been identified, especially G13A (Gly5Ser), G484A (Asn162Asp), G667A (Gly223Arg), and A808G (Val270Met) (69, 72, 73). The most common alleles in these populations are $le^{13,484,667}$, $le^{484,667}$, and $le^{59,308}$ (69, 72). The diversity of *FUT3*-null alleles is a challenge for genetic studies. One study of cystic fibrosis patients relied on 4 SNPs common in Caucasians and many other populations: T59G (rs2836549), T202C (rs812936), C314T (rs778986), and T1067A (rs3894326) (74).

Apparent discrepancies between red cell, saliva, and tissue expression have been well described. Some *le* alleles have an apparently greater effect on Lewis GSL synthesis. Nishihara et al. showed that le^{59} (Leu20Arg) leads to a loss of Lewis GSL in plasma (and, therefore, red cells) but retains weak Lewis expression on intestinal glycoproteins (75). *FUT3* also displays a gene dosage with reduced enzyme activity in heterozygous individuals (*Le/le*). *Le/le* individuals show 50% decreased FUT3 activity in saliva and tissues. Lewis antigen can still be detected in intestinal tissues; however, red cells may be typed as Le(a−b−) (54, 76).

Role of Bacteria in ABH and Lewis Expression

At birth, the intestinal tract expresses sialylated glycans but switches to fucosylated antigens, including ABH and Lewis antigens, with changes in diet and bacterial colonization (77). In adults, there is a spatial relationship between bacterial density and fucosylation, with the highest density of organisms and fucosylation being found in the colon and rectum. Commensal bacterial species that utilize fucose as a nutrient can specifically induce *FUT2* in intestinal tissue, a demonstration of a mutually beneficial symbiotic relationship (77–79). In animal studies, adult mice raised in a germfree environment retained an immature intestinal phenotype but quickly transitioned to an adult, H-active phenotype after colonization with *Bacteroides fragilis* and *Bacteroides thetaiotaomicron* (77, 78). It is tempting to speculate that the low Le^b expression levels in cord and neonatal red cells reflect the immaturity and simplicity of the gut flora at birth. Most children acquire a normal "adult-type" microbiome by 1 year of age (80).

Bacteria and Development of Anti-A/B and Other Naturally Occurring Antibodies

Anti-A and anti-B are naturally occurring antibodies, arising in the absence of blood transfusion or pregnancy. Bacteria, particularly Gram-negative intestinal flora, appear to be the primary immune stimuli underlying their development (81–84). In a survey of 282 Gram-negative organisms, A-, B-, and/or H-like activity was detected in 137 organisms (49%) (81). In many instances, ABO activity on lipopolysaccharide (LPS) is a serotype-specific feature (for example, *Escherichia coli* O86 and group B antigen).

Using Leghorn chickens as an animal model, George F. Springer and colleagues provided the first direct evidence that bacteria can stimulate ABO antibodies (82). Chickens express Forssman antigen, a group A-like GSL that reacts with polyclonal anti-A via a terminal α1-3GalNAc (see Table 7). Like human newborns, newly hatched chicks lack isohemagglutinins but gradually acquire a naturally occurring anti-B antibody as they mature. To test the impact of bacteria on anti-B development, chicks were raised in a

germfree environment and fed either a sterile diet or a diet spiked with *E. coli* O86, a B-active strain. Chicks raised on a germfree diet failed to produce anti-B after 8 weeks. In contrast, chicks fed a diet spiked with *E. coli* O86, even once, produced anti-B at the same rate and often with higher titers than those in the normal controls. Similar results were observed for the development of anti-T and anti-Tn, two naturally occurring antibodies against carbohydrate structures on red cell glycophorins (see sections on the MNSs and Gerbich blood groups, below) (83).

This phenomenon can be observed in humans. Feeding of *E. coli* O86 to group O and A volunteers led to a specific stimulation of anti-B titers (81). Likewise, an 8- to 32-fold rise in the anti-A/B titer was reported for patients undergoing bowel surgery, presumably in response to bacterial exposure at the time of surgery (85). More recently, very high titers of anti-B in individuals taking probiotic supplements, which contain a mix of bacterial strains with B-like activity, have been documented (86). Conversely, low levels of or absent ABO antibodies, particularly anti-B, can be observed in young children receiving long-term parenteral nutrition (87). Like the chicken experiment described by Springer et al., parenteral and enteral nutrition are essentially "sterile" and lead to decreased levels of and alterations in fecal flora (88). In fact, the current Western diet of processed, "pasteurized" food has led to a dramatic decrease in mean ABO titers compared to those in historical controls (89).

Finally, infections can stimulate naturally occurring antibodies, sometimes leading to hemolysis and blood grouping problems. Cold agglutinins, which tend to react to A/B precursors (anti-i, anti-I, anti-H, and anti-HI), are not uncommon following infection with *Mycoplasma*, mononucleosis, and other viral illnesses (33). In some instances, increased levels of cold agglutinins are due to cross-reactive epitopes on bacterial LPS. Organisms known to express lactosamine-type structures include *Mycoplasma pneumoniae*, *Neisseria* species, and *Pneumococcus* species (33). Infection can also nonspecifically stimulate cold agglutinin activity due to generalized increases in the levels of IgM antibodies bearing the VH4-34 variable heavy chain. VH4-34 recognizes lactosamine epitopes, regardless of antibody specificity, due to conserved sequences in the amino-terminal FR1 domain (33).

ABO Antibodies in Host Defense against Bacteria

The association between fecal flora and ABO antibodies led to speculation that ABO and other naturally occurring antibodies are part of the innate host defense against bacterial infection. In animal studies, naturally occurring IgM is critical in preventing sepsis and death following surgical ligation of the cecum (90). It was hypothesized that IgM antibodies bind and fix complement on bacteria to facilitate phagocytosis. Supporting evidence comes from *in vitro* studies with *E. coli* O86, a group B-active strain (91). Human polyclonal anti-B, but not anti-A, led to a 10-fold increase in the level of bacterial phagocytosis by neutrophils (10.9 versus 1.19 bacteria per cell) (91).

One of the largest and earliest prospective studies compared ABO type and culture results for 944 pediatric patients (92). These investigators reported that B and AB patients were more likely to be infected with enteric organisms, including a 55% increased risk of *E. coli* infection ($P = 0.009$) and a 131% increased risk of *Salmonella* infection ($P = 0.007$). A later retrospective study of 23,135 hospitalized patients focused on the incidence of *E. coli* sepsis relative to ABO and Rh types (93). Again, group B and AB patients had a 60% greater risk of *E. coli* sepsis (relative risk [RR] = 1.6; $P = 0.01$). Finally, there is a small report showing an increased risk of reactive arthritis following urinary tract infections (UTIs), which tend to be caused by *E. coli* strains (94).

The relative protection afforded by ABO antibodies may be modest due to redundancy in the innate immune system. Two intestinal galectins, Gal-4 and Gal-8, specifically recognize and kill bacteria expressing B-like epitopes (95). Other host defense mechanisms include Toll-like receptors and NOD receptors, which recognize a broad range of microbial constituents (96). Finally, the ABO type may influence the makeup of the normal intestinal flora. A study of Finnish adults reported differences in the intestinal microbiome among group B and AB individuals (97).

Vibrio cholerae

One of the first studies to suggest an association between ABO type and cholera was reported in 1977 by Barua and Paguio, who studied a group of patients undergoing treatment at the Cholera Pavilion, San Lazaro Hospital, Manila (98). Among patients presenting with diarrheal illness, there was a higher percentage of group O (77% versus 45%) and a lower percentage of group A (14% versus 26%) individuals than expected. There was no significant difference, however, in ABO phenotypes when these same patients were compared by culture results: the incidences of groups O and A were equivalent in *Vibrio*-positive and *Vibrio*-negative patients. A subsequent study found a 2-fold increase in the proportion of group O individuals (61.5% versus 33%), accompanied by a decreased proportion of group B individuals (14.5% versus 35%), among hospitalized Bengalese patients (99). To test whether these results could be recapitulated in a controlled setting, Levine and colleagues infected 66 human volunteers with *Vibrio cholerae* (100). Although the majority of patients (55/66; 83%) experienced diarrhea, group O subjects were twice as likely to develop severe cholera (64% versus 36% of non-group O individuals). A group O phenotype was also reported to significantly decrease cholera vaccine efficacy (101).

Two studies reported a possible role for *FUT2* in cholera infection. In a study of 51 patients, one-third were nonsecretors, which was 2-fold higher than population controls (33% versus 17%; $P < 0.02$) (102). These findings were confirmed in a much larger study ($n = 522$) that included pediatric and adult patients ($n = 77$), household contacts ($n = 144$), and healthy controls (103). The prevalence of a nonsecretor, Le(a+b−) phenotype was significantly increased in patients (39% versus 28%; $P = 0.014$ to 0.39), especially among group A individuals, where 55% of group A patients were nonsecretors, compared to asymptomatic household contacts, who were overwhelmingly secretors (72%).

The association between cholera and blood types has been an area of investigation for over 3 decades. There is no association between *Vibrio* adherence, fucose recognition, and virulence (104). Quite the contrary, *V. cholerae* was recently shown to recognize a trisaccharide epitope common to type 1 and 2 chain glycolipids (-GlcNAcβ1-3Galβ1-3/4GlcNAc-) unless modified by a terminally placed fucose (105). Neither *V. cholerae* El Tor nor classical *V. cholerae* strains recognized any GSLs bearing a terminal A, B, H, or Le^b epitope. Interestingly, *V. cholerae* tolerated internal fucose residues (105). In human intestine, *V. cholerae* recognized high-molecular-weight (HMW) type 1 GSLs (7 to 8 sugars) with an internal Le^a-type epitope [Galβ1-3GlcNAcβ1-3(Fucα1-4)GlcNAcβ1-3Galβ1-4Glcβ1-1ceramide]. As discussed

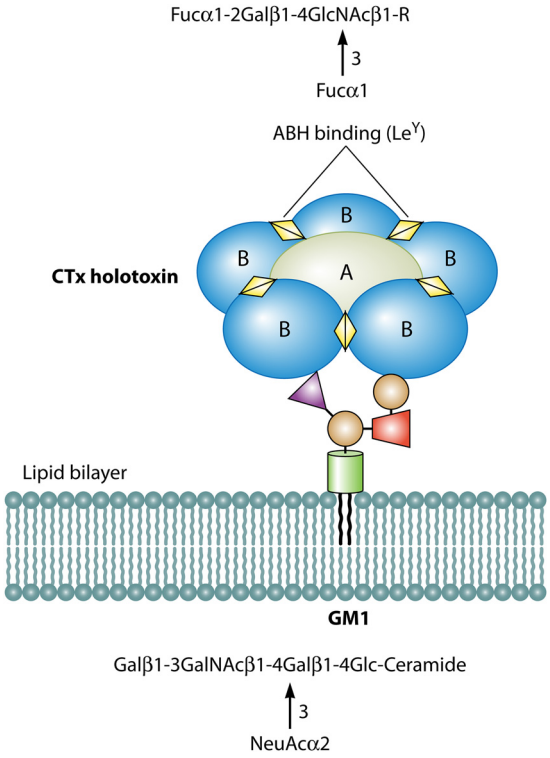

FIG 4 Cholera lectin binding sites. Ganglioside GM1 is the primary CTx receptor. The binding site involves residues on adjacent B subunits. A second, weaker binding site for Le^Y-type epitopes is located along the other face of the B subunit (yellow diamonds).

above, the synthesis of HMW type 1 chain antigens is favored in nonsecretors (45, 46).

With the isolation of cholera toxin (CTx), most studies have focused on the potential role of ABO in toxin binding. CTx holotoxin, or choleragen, is a hexameric protein complex composed of five B subunits and a single A subunit (AB_5) (Fig. 4) (106). Cholergenoid (B_5) is composed of the five B subunits (CTx-B) and is not biologically active. During infection, the B subunits recognize GSL receptors on the intestinal epithelium, followed by cellular uptake and activation of the A subunit (A_1). The A_1 subunit activates adenylate cyclase, with the production of cyclic AMP (cAMP) and induction of secretory diarrhea (106). CTx also binds neurons (107), with some investigators believing that diarrhea also has a neurogenic origin (108, 109).

The physiologic receptor for CTx is GM1, a sialylated GSL or ganglioside (106). The GM1 binding site is located along a shallow groove between two adjacent CTx-B subunits on the membrane face of the toxin (106). Each CTx holotoxin, therefore, is capable of cooperatively binding five GM1 molecules, permitting high-affinity lectin adhesion to target membranes (106). In addition, multivalent binding is believed to recruit GM1 into lipid rafts, enhancing CTx uptake and toxicity (110). The latter may be critical, since GM1 constitutes only 1% of the total ganglioside and <0.01% of all the GSLs in the human small intestine (111). Although GM1 is the biological receptor for CTx, the toxin can bind structurally related gangliosides *in vitro* albeit with a significantly lower affinity than that for GM1. Ganglio-series gangliosides shown to bind CTx include GD1a and unusual ABO-active GM1 derivatives found in some animal species (37, 106).

How ABO might affect cholera infection became clear only in studies with enterotoxigenic *E. coli* (ETEC) heat-labile toxin (hLT). hLT is a classic AB_5 multimeric toxin with 80% sequence homology to CTx (106). Like CTx, hLT recognizes GM1 as its physiologic cell receptor. Interestingly, hLT can bind complex GSLs and glycoproteins with blood group A and AB activity (112–116). This binding was attributed to a second lectin binding site on the hLT-B subunit that recognizes type 2 chain A and B antigens (117). This site is located on the face of the hLT-B subunit opposite the GM1 site and does not interfere with toxin binding to GM1 (Fig. 4). This site interacts extensively with type 2 chain oligosaccharides with a distinct preference for difucosylated ABH antigens, i.e., those with an ALe^Y or BLe^Y terminal epitope (Table 4) (116). CTx-B also bears a shallow pocket along its upper face despite the apparent absence of ABO binding *in vitro*. A/B binding can be induced, however, through the introduction of hLT sequences into the CTx-B subunit (118, 119).

The identification of a second binding site on hLT, and potentially CTx, led to the hypothesis that group A, B, and AB individuals may be protected from severe cholera through adsorption of CTx by A/B-active glycoconjugates. Group O individuals are at risk for more severe disease due to higher concentrations of free toxin available to bind GM1 on intestinal epithelial cells. One long-held objection to this theory is the apparent lack of ABO group dependence observed in many human ETEC hLT infections (120, 121). Likewise, little or no ABO group association is observed with the *V. cholerae* O1 classical strain (119).

A more recent theory has emerged from studies of the *V. cholerae* El Tor biotype. Unlike the classical O1 strains, *V. cholerae* El Tor shows a strong association between disease severity and ABO type. Mandal and colleagues were able to demonstrate that both El Tor CTx and hLT can bind Le^Y; however, only hLT binds BLe^Y (119). The inability of El Tor CTx to bind BLe^Y was attributed to a Thr47→Ile polymorphism in the Le^Y binding site (Table 6). This was confirmed by nuclear magnetic resonance (NMR) analysis using a CTx Ile47 mutant. It is believed that classical *V. cholerae* O139 (Bengal) also displays group O specificity due to the same Thr47→Ile polymorphism (119).

Based on these findings, Mandal et al. proposed a novel role for ABO in which ABH-type epitopes capture and concentrate free toxin, bringing the toxin in close proximity to GM1 on the intestinal epithelium (119). The loss of A/B binding observed with the El Tor CTx variant therefore acts to protect group A and B individuals, who are no longer able to capture the toxin. Group O individuals, however, are still able to capture toxin via Le^Y epitopes on intestinal glycoconjugates. As a result, group O individuals are more susceptible to infection and severe disease with El Tor and O139 strains. This theory also accounts for the apparent lack of association between ABO group, ETEC, and *V. cholerae* classical O1 strains, since hLT and CTx of the classical biotype can bind Le^Y, ALe^Y, and BLe^Y. Interestingly, CTx binding to GM1 may actually upregulate ABH-active coreceptors: CTx was shown to upregulate *FUT1* and *FUT2* expression in murine epithelial cells (122).

Enterotoxigenic *Escherichia coli*

ETEC is a major cause of diarrhea, with an incidence of 840 million cases annually in the developed world (123). Possible host factors include a very young age and Lewis and ABO phenotypes. Children <5 years of age have a 4- to 5-fold increased incidence of

TABLE 6 Comparison of blood group binding by CTx and hLT variants

Toxin	↑ disease severity group O	B-subunit amino acid participating in blood group antigen recognition[a,b] at position:											Toxin binding[a]	
		3	7	16	18	45	46	47	48	89	92	94	Le^Y	BLe^Y
Classical serotype O1 Ogawa	N	Q	D	Q	H	G	A	**T**	F	N	T	R	+	+
Classical serotype O1 Inaba	N	Q	D	Q	H	G	A	**T**	F	N	T	H	+	+
Classical serotype O139 (Bengal)	Y	Q	D	Q	Y	G	A	I	F	N	T	H	+	−
El Tor serotype O1 Inaba	Y	Q	D	Q	Y	G	A	I	F	N	T	H	+	−
El Tor serotype O1 Inaba (I47→T)	NA[c]	Q	D	Q	Y	G	A	**T**	F	N	T	H	+	+
ETEC hLT	N	Q	E	Q	Y	G	A	**T**	F	N	T	N	+	+

[a] Data were extrapolated from references 117 and 119.
[b] Thr47 associated with BLe^Y binding is highlighted in boldface type.
[c] NA, not available. The mutant was not tested clinically but is hypothesized to lack ABO specificity relative to disease severity (119).

infection relative to older children (123). One hypothesis for the fall in infection rates with age is acquired immunity from prior infections. Alternatively, it is possible that age-related developmental changes in ABO and Lewis expression might also influence host susceptibility.

ETEC can express several pathogenic factors, including colonization factor antigen I (CFA/I) fimbriae, hLT, and heat-stable (ST) toxin. The ETEC fimbrial adhesin CFA/I has been reported to recognize several GSLs in pig intestine, including lactosylceramide (LacCer) (124). LacCer is a common receptor for bacteria and is highly expressed in human intestinal epithelial cells (111, 125). CFA/I also binds several type 1 and type 2 chain GSLs, reminiscent of *V. cholerae* although with some subtle differences (105, 124). Like *V. cholerae*, CFA/I fimbriae did not bind GSLs with A, B, and Le^b activity but tolerated type 2 H-active structures (H-2) (Le^Y) (124).

As discussed above, hLT can bind Le^Y, with no apparent ABO preference (119). Despite the latter, ABO preferences have been reported in animal models. Galvan et al. were able to demonstrate hLT binding to ABO epitopes, with the production of secretory diarrhea, in a rabbit model (116). The level of hLT binding to group AB rabbit intestine was 4-fold higher than that in group H rabbits (48.7 versus 11.4 fmol/μg protein) and could be blocked by anti-A lectins and anti-AB. Moreover, hLT binding to AB glycoconjugates was able activate adenylate cyclase with fluid secretion, independent of GM1 receptors. Toxin binding was enhanced by papain digestion, suggesting possible GSL receptors (116). This was confirmed by the isolation of rabbit intestinal GSLs, which showed hLT binding to A- and AB-active GSLs but not group H GSLs (115). A preference for group A glycoproteins was also observed by Western blotting, with strong hLT binding to AB-active glycoproteins (120 to 140 kDa). hLT binding to HMW, A-active glycolipids from human red cells and group A pigs was also observed (113).

Data from the literature regarding ETEC and ABO types in human infections are conflicting. Black et al. infected human volunteers with several different ETEC strains, including many that coexpressed both hLT and ST (120). Fifty-seven percent of subjects developed diarrhea, with only a slight preference for group O (58% versus 54%; $P = 0.04$). There was no correlation between infection and ABO type among individuals exposed to strains expressing only hLT (RR = 1.0). Likewise, a large epidemiological study in Bangladesh ($n = 510$ cases) found no relationship between ABO type and ETEC, even after correction for toxin type (121). Conversely, Qadri et al. found a higher incidence of diarrhea in group A, B, and AB children ($P = 0.02$ to 0.03) (126), analogous to the results with rabbits. Groups A and AB were particularly at risk for clinical diarrhea, especially group AB children (80% versus 56 to 62%; odds ratio [OR] = 2.5).

This same group also examined the role of the Lewis phenotype and ETEC infection (127). In general, nonsecretor children were more likely to have symptomatic infection (71% versus 29%; $P < 0.0001$), particularly by strains expressing CFA/I adhesins ($P = 0.03$). When data on ABO type were included, there was a higher incidence of diarrhea among group A nonsecretors (82% versus 43%; $P = 0.06$). These authors also examined the role of maternal secretor status in pediatric disease, since breast milk contains Lewis-active substances (127). ETEC infection was more likely when the mother was Le(a−b+) (63% versus 37%; $P < 0.001$).

Helicobacter pylori

Helicobacter pylori is a flagellated, Gram-negative bacillus with infection rates reaching 80 to 90% in some populations (128). Infection is transmitted through the oral-oral and oral-fecal routes, with most individuals being infected early in childhood. Although infection rates are falling due to diagnosis and treatment, it is estimated that 50% of the world population is infected (128). *H. pylori* infects the gastric epithelium and is a cause of chronic gastritis and gastroduodenal ulcers. Chronic infection and inflammation can lead to intestinal metaplasia, gastric adenocarcinoma, and gastric lymphoma. In 1994, the World Heath Organization designated *H. pylori* a class I carcinogen (129).

The identification of *H. pylori* as the principal etiologic agent in peptic ulcer disease led to a search for bacterial colonization factors able to overcome the hostile environment of the stomach. In microscopic studies, *H. pylori* is located within the mucin layer in close proximity (25 μm) to the foveolar gastric epithelium, with little or no binding to the deeper glandular epithelium (130, 131). The foveolar epithelium is rich in type 1 chain structures and secretes the mucin 5AC (MUC5AC), the major constituent of the surface mucous layer (132). Analysis of surface O-glycans shows predominantly fucosylated, branched-core 2 O-glycans bearing ABO-active epitopes (Table 4); few structures are modified by sialic acid or sulfation, which would be susceptible to acid hydrolysis (48). Of 70 O-glycans characterized, 30 to 50% express H and/or Le^b epitopes, with the highest density being found for group O individuals (48). In contrast, the deep glandular epithelium expresses type 2 antigens (Le^X and Le^Y) on MUC6, including growth-inhibitory mucins capped with a terminal α1,4-GlcNAc (132).

A role for fucose in *H. pylori* binding was inferred from early inhibition studies with secretory IgA from human colostrum (131). Boren et al. later showed that colostrum rich in Le^b, but not Le^a, inhibited *H. pylori* binding to the gastric epithelium by 78% (133). This was confirmed by inhibition studies with anti-Le^b and commercial Le^b antigen. Moreover, *H. pylori* was shown to directly recognize Le^b and H-active GSLs by thin-layer chromatography analysis (133). It took another 5 years to isolate the *H. pylori* fucose binding lectin BabA (134), a 78-kDa glycosylated protein. It is estimated that *H. pylori* carries ~500 copies of BabA per bacterium. Surveys of BabA-positive *H. pylori* strains from around the world show that most of these strains (95%) are "generalists," capable of binding to (O)Le^b, ALe^b, and BLe^b (135). Le^b, however, is the preferred receptor in binding assays (Le^b > type 1 H, ALe^b, and BLe^b). BabA can also recognize novel Le^b-ganglio structures in a recombinant Le^b mouse strain (136). BabA does not bind Le^a, Le^X, or Le^Y, a difucosylated type 2 antigen with H activity (Fig. 2) (133).

In addition to BabA, *H. pylori* expresses other adhesins and virulence factors (for example, CagA) that promote chronic infection and inflammation (130, 132, 137). Many *H. pylori* strains can express adhesins that recognize sialic acid (SabA) (30% of strains), lipoproteins (AlpA and AlpB), and sulfated glycans (132). Because infection and chronic inflammation can alter the epithelial "glycotype," it is speculated that adaptive changes in adhesin expression are required for long-term infection. Chronic gastritis is typically associated with decreases in ABH and Le^b expression accompanied by increased Le^a, Le^X, and sLe^X expression (137–139). *H. pylori* may actually promote this shift in glycan expression through upregulation of β3GlcNAcT5, a key enzyme in type 2 chain synthesis on GSLs (132, 140).

Given the importance of Le^b/H antigens in initial *H. pylori* adhesion, several studies have examined the role of host ABO type in *H. pylori* infection. Early studies noted that patients with gastric and duodenal ulcers were more likely to belong to group O (141–143). In a study of 147 peptic ulcer disease patients, Mentis et al. found no correlation between group O and *H. pylori* culture and concluded that they were independent risk factors (143). A lack of correlation between ABO and *H. pylori* immune status has also been reported in several small studies of patients undergoing endoscopy (138, 144–146). In contrast, De Mattos et al. observed a strong association between ABO type and *H. pylori* infection among Brazilian patients (147). Group O individuals were 2-fold more prevalent in the group of patients with PCR-confirmed *H. pylori* infection than in the uninfected-control group (57% versus 24%; $P = 0.003$). A second Brazilian study also reported an increased number of group O and A_2 individuals among *H. pylori*-infected individuals (138). For healthy asymptomatic individuals, however, there is no apparent correlation between *H. pylori* IgG immune status and ABO type (148–152).

It is estimated that *H. pylori* infections, especially with CagA-positive, BabA-positive strains, may be responsible for 70% of all gastric carcinomas, with gastric cancer developing in 3% of infected individuals (153–155). In a large-scale genetic study, both CagA status and group A were identified as risk factors for the development of gastric dysplasia (156). The authors of this study speculated that group A individuals may mount a more robust inflammatory response to *H. pylori*.

The impact of Lewis and Secretor types on *H. pylori* risk is modest, despite early studies showing an increased incidence of ulcers among nonsecretors (142, 157). Dickey et al. examined 101 patients undergoing endoscopy relative to histology, Lewis phenotype, and *H. pylori* infection (diagnosed by histology and urease test) (158). Nonsecretors [Le(a+b−)] were significantly more likely to have histologic gastric disease (53% versus 28%; $P = 0.02$); however, there was no difference in *H. pylori* rates by secretor status ($P = 0.73$). A later study compared histology and secretor status in 84 endoscopy patients with confirmed *H. pylori* infection (159). Among patients with ulcer disease, a nonsecretor phenotype was associated with more inflammation and higher grades of lymphocyte ($P = 0.01$) and neutrophil ($P = 0.012$) infiltration. Rothenbacher et al. also found an association between nonsecretor status and *H. pylori* in newly delivered mothers (160). It should be noted that these investigators determined Lewis status by immunoblotting serum samples, thereby avoiding false-negative Lewis typing results that can occur in late pregnancy (28). Although the rate of *H. pylori* infection was relatively low among ethnic Germans (15.5%), nearly half of infected women were nonsecretors, a rate which was significantly higher than that in the general population (45% versus 29.4%; $P = 0.009$). In contrast, two Brazilian studies found no correlation between *H. pylori* and a Secretor or Lewis phenotype (138, 147).

The apparent increase in the incidence of disease among nonsecretors in some studies is perplexing given the importance of Le^b in initial *H. pylori* colonization by BabA strains. One hypothesis is that *H. pylori* may bind H/Le^b substances in saliva and prevent gastric colonization in Se^+ individuals. Likewise, *H. pylori* binding to gastric surface mucin could promote bacterial clearance during peristalsis and gastric emptying. Finally, the results of past studies may be hampered by the method and sample used for Lewis and Secretor typing, which may not accurately predict gastric Lewis expression. In a recent South Korean study, discrepancies between gastric Lewis expression and genotype were well documented, with most discrepancies being observed for Le(a+b−) individuals (54).

Campylobacter jejuni

Campylobacter jejuni is a flagellated, Gram-negative, thermophilic, microaerophilic bacterium and a common cause of foodborne illness in industrialized countries. In the United States alone, there are an estimated 2.5 million cases of *Campylobacter* infection per year (161). Most outbreaks of *C. jejuni* are linked to consumption of contaminated poultry, although outbreaks due to raw milk and contaminated water have been documented (161). Infection with *C. jejuni* typically lasts 7 to 10 days and is characterized by 1 to 3 days of fever, vomiting, and headaches, followed by 3 to 7 days of diarrhea and abdominal pain. It has been hypothesized that *C. jejuni* may contribute to the development of inflammatory bowel disease in some patients (161). More importantly, *C. jejuni* is a common precipitator of Guillain-Barre syndrome, a rapidly progressive ascending autoimmune peripheral neuropathy that can lead to quadriplegia, ventilator dependence, and death for some patients. It is estimated that one-third of Guillain-Barre cases are attributable to recent *C. jejuni* infection (162).

The pathophysiology of *C. jejuni* is still an area of active investigation and may involve host factors. Most individuals exposed to *C. jejuni* remain asymptomatic, with only 1% developing clinical enteritis (163). *C. jejuni* bacteria preferentially adhere to and colonize the mucus layer of the jejunum, helped by bipolar flagella. A minor population may attach directly to intestinal epithelial cells,

with histologic evidence of bacterial invasion, translocation, and bacteremia (161, 163). Invasive *C. jejuni* strains can induce mucosal damage by stimulating the synthesis of proinflammatory mediators (for example, interleukin-8 [IL-8]). *C. jejuni* virulence factors include cytolethal distending toxin, which is capable of inducing apoptosis (161).

Like many gastrointestinal pathogens, *C. jejuni* can bind intestinal mucosa and epithelium via fucose. One of the earliest studies showed that high concentrations of free fucose were capable of inhibiting *C. jejuni* in INT407 intestinal epithelial cells *in vitro* (164, 165). Moreover, breast milk, which is rich in fucosylated oligosaccharides, is protective against *C. jejuni* infection in breastfed infants (166, 167). Ruiz-Palacios et al. provided the first definitive evidence for a role of H(O) antigen in *C. jejuni* infection, using a panel of clinical *C. jejuni* strains isolated from pediatric patients (166). Initial studies showed a correlation between pathogenic strains and adhesion to fucosylated glycans. Furthermore, neutral fucosylated oligosaccharides purified from human milk were capable of inhibiting bacterial adhesion to human intestinal mucus. Subsequent experiments by these investigators identified type 2 chain H(O) antigen as the preferred receptor for pathogenic *C. jejuni* strains. Lectins and monoclonal antibodies (MAbs) against type 2 chain epitopes (H-2; Le^Y) were able to inhibit *C. jejuni* adhesion in both cell cultures and Western blots. In CHO-transfected cell lines, *C. jejuni* adhered to CHO-*FUT1* cells, which express type 2 chain H, but not cells transfected with *FUT3* (Le^a/Le^X) or *FUT4* (Le^X) (166). How *C. jejuni* recognizes H antigen is not clear; no pilus-related genes were identified in the *C. jejuni* genome (163).

The preference of pathogenic *C. jejuni* strains for type 2 H antigen may explain the colonization of the lower gastrointestinal tract. In general, type 1 chain ABH expression levels are highest in the stomach but progressively decrease along the small and large intestine (168). Low levels of type 2 ABH antigens can be detected on jejunal GSLs and glycoproteins (168, 169), with stronger expression in group O, Lewis-null individuals (168, 714). Type 2 ABH GSLs are also expressed by swine intestinal epithelial cells (170), which are often used to study *C. jejuni* invasion (171). Tropism for type 2 chain H antigen may also underlie the protective effect of butyrate against *C. jejuni* invasion in Caco-2 cells. Caco-2 cells strongly express type 2 chain H antigen but switch to a predominantly type 1 H phenotype upon butyrate exposure (43).

There are essentially no epidemiological studies on the impact of host ABO, Lewis, or Secretor status on *C. jejuni* infection. One study of breastfed infants found a strong correlation between the H-antigen content of milk and *Campylobacter*-associated infant diarrhea ($P = 0.004$) (167). The protective effect of H-active oligosaccharides in milk is also supported by data from murine models (166). BALB/c mice fed fucosylated human milk oligosaccharides or 2′-fucosyllactose were relatively protected from *C. jejuni* colonization. Relatively few organisms were shed in stool of treated animals 5 days after *C. jejuni* challenge. Similar results were observed in a *FUT1*-BG/SJL transgenic mouse strain, which selectively secretes H antigen in breast milk. *C. jejuni* was absent from the lower gut of pups within 1 week, regardless of the size of the *C. jejuni* inoculum (166).

Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) is primarily a disease of premature infants (weighing <1,500 g), with an incidence of 7 to 10% and a morality rate of 20 to 30% (172). It usually occurs within the first 2 weeks of life and is characterized by bowel inflammation and necrosis, with evidence of a disturbed intestinal microbiota, especially by clostridial species. Besides prematurity, other NEC risk factors include prolonged use of antibiotics, enteral nutrition, and lack of breastfeeding.

Secretor was recently identified as a biomarker for NEC in premature infants (173). Infants <32 weeks of gestational age were screened for H antigen in saliva and *FUT2* genotype (G428A; rs601338). Among 410 eligible infants, 30 developed NEC and 96 developed sepsis. Infants with low salivary H levels were either nonsecretors or *FUT2* heterozygotes (*Se/se*; 17% with low H levels). Low H levels were associated with an increased risk of death (14.8% versus 1.6%; $P < 0.001$), especially from NEC (OR, 9.6) and sepsis (OR, 17.9). When examined by genotype, the rate of survival was highest among *Se/Se* individuals (98%), followed by *Se/se* individuals (95%) and nonsecretors (*se/se*) (87%). The prevalence of the nonsecretor phenotype was increased among patients with Gram-negative sepsis (44%, versus 23% of uninfected individuals; $P = 0.05$). In animal models, the absence of fucosylation is associated with chronic colitis and diarrhea, whereas *FUT2* protects against mucosal injury, with rapid recovery (78, 174). Interestingly, a nonsecretor status is also linked to Crohn's disease, a chronic inflammatory bowel disorder with altered microflora (175).

Pseudomonas aeruginosa

Pseudomonas aeruginosa is an aerobic, Gram-negative bacterium widely found in the environment. *P. aeruginosa* is an unusual organism in normal fecal flora (5%) but is common among long-term-hospitalized patients (176). This organism possesses multiple virulence factors, including lectin-type adhesins, a mucoid polysaccharide, proteases (elastin, phospholipase C, and collagenase), and exotoxin A, an inhibitor of protein synthesis. Patients at risk for *P. aeruginosa* infection include patients with wounds, with urinary catheters, and on mechanical ventilation; immunocompromised patients; and patients with cystic fibrosis. It is estimated that 80% of cystic fibrosis patients are colonized with *P. aeruginosa* by the age of 18 years (74).

P. aeruginosa possesses two related, calcium-dependent lectin adhesins: PA-IL (LecA) and PA-IIL (LecB). PA-IL and PA-IIL are homotetrameric proteins composed of single subunits of 12.7 kDa and 11.7 kDa, respectively. Both adhesins are capable of agglutinating human red cells, with some evidence of blood group specificity (177). PA-IL is a galactose-specific lectin, which can agglutinate all red cells regardless of ABO type, including Bombay cells (O_h). PA-IL, however, shows slightly stronger agglutination against group B red cells and P^k and P_1 red cells (see LKE and P1PK, GLOB, and FORS Blood Group Systems section), suggesting a preference for αGal epitopes (177, 178). Mapping studies indicate that PA-IL possesses a disaccharide binding site with strong binding to P_1- and B-active glycans, where Galα1-6 > Galα1-4 (P^k and P_1) > Galα1-3 (group B) (179). PA-IL is also capable of recognizing the terminal β-galactosidase (βGal) on type 1 and type 2 chain precursors (Galβ1-3GlcNAc > Galβ1-4GlcNAc) unless modified by a terminal fucose (H, Le^b, and Le^Y), αGalNAc, or sialic acid (179).

PA-IIL is considered a fucose/mannose lectin, although fucosylated ligands display the highest level of binding: significant mannose binding is observed only for polymannosylated glycans like

yeast mannan (180). In glycan arrays, PA-IIL is able to bind AB- and Lewis-active glycoproteins but not their nonfucosylated precursors (181). Consistent with these results, PA-IIL only weakly agglutinates Bombay (O_h) red cells, which lack ABH and Le^b antigens (177). In inhibition assays, Le^a (K_d [dissociation constant] of ~0.21 μM) was 10- to 38-fold more active than its type 2 chain equivalents (Le^X and sLe^X) and 120-fold more active than mannose. Antigens with terminal fucose epitopes, including Le^b and Le^Y, are relatively inactive (181). Mapping studies indicate that PA-IIL binds fucose along a shallow groove and is highly dependent on van der Waals interactions between PA-IIA and the C-5 methyl group of fucose (182). The hydroxyl groups on C-2, C-3, and C-4 of fucose also contribute to binding through electrostatic interactions with calcium ions, water, and PA-IIL.

Although there is a correlation between PA-1 and blood types in tests of red cells, clinical evidence is weak, at best, and may involve additional adhesins. A small retrospective Taiwanese study of 23 children reported that group B was associated with *Pseudomonas* sepsis (62% versus 24%; $P < 0.0001$; OR, 6.5) (183). There is also some evidence suggesting a role for ABO in otitis externa or "swimmer's ear." Steuer et al. found that ~60% of patients with diffuse otitis externa were infected with *P. aeruginosa* (184–186). Of those patients, most were of blood groups A and AB (87% versus 13% group O; $P = <0.001$; $n = 154$), with no cases of *P. aeruginosa* infection in group B patients. Epithelial cells of the outer ear canal express ABH antigens and are able to bind *P. aeruginosa* via GalNAc-type ligands. *P. aeruginosa* binding was inhibited by soluble GalNAc and A antigen but not by other glycans (184, 185). The recognition of A epitopes is inconsistent with either PA-IL and PA-IIL. *Pseudomonas* strains associated with otitis media may express additional lectins capable of recognizing A-type epitopes.

There has been considerable interest in the potential role of ABO and Lewis types in cystic fibrosis patients, who have high rates of *P. aeruginosa* colonization and pneumonia due to an inability to clear mucous. In mice, both intrabronchial fucose and mannose decreased pulmonary toxicity and improved survival following *P. aeruginosa* pneumonia (187). Data from similar studies in cystic fibrosis patients using inhaled galactose and/or fucose have been encouraging. Sputum samples from treated patients showed a significant decrease in *P. aeruginosa* CFU and leukocyte and tumor necrosis factor alpha (TNF-α) levels (188). Given the importance of PA-IL and PA-IIL in *P. aeruginosa* pathogenicity, it was hypothesized that blood types that favor *P. aeruginosa* adhesion could be host susceptibility factors (74). In an early study of 17 patients, no correlation with ABO type or a nonsecretor phenotype was identified (189), although this study was underpowered for the detection of any significant difference (74). More recently, a registry study of 808 cystic fibrosis patients examined *ABO*, *Se/FUT2*, and *Le/FUT3* genotypes and disease outcomes. There was no correlation between blood type and the severity of cystic fibrosis, pulmonary function, history of meconium ileus, or age of patients during *P. aeruginosa* colonization (74).

Streptococcus

Group A *Streptococcus*. In the years following World War II, there was considerable interest in a possible correlation between ABO and Secretor types and rheumatic fever. Between 1932 and 1968, 20 studies on ABO types in patients with pharyngitis (190, 191), scarlatina (192–194), and rheumatic heart disease (191) were reported, with most studies showing a trend between streptococcal disease and a non-group O status. For rheumatic fever/heart disease patients, non-O individuals had a slightly increased risk, which varied between 1.02 and 1.55 (191). When data from all studies are combined (16 studies; $n = 203{,}454$), there is virtually no difference in the incidences of non-group O between patients and controls (58% versus 55%). Eight studies also typed patients for secretor status by using HAI assays, which showed an increased risk of rheumatic disease among nonsecretors (1.12 to 1.51) (191). When data from these studies are combined, there is a slight increase in the prevalence of the nonsecretor status among patients (28% versus 23% of controls).

The relative protection found with group O and the Se^+ phenotype led to the hypothesis that H substance was inhibitory, possibly by decreasing the incidence of colonization. Haverkorn and Goslings attempted to address the latter through repeated surveillance cultures in three populations: children <5 years of age, schoolchildren, and military recruits (191). The rate of carriage in individuals with at least two surveillance cultures was 13 to 15%. In general, rates of carriage tended to be higher among nonsecretors, especially children <5 years of age (30% versus 20%) and military recruits (27% versus 22%). There was no significant correlation between secretor status and anti-streptolysin O (ASO) titers or the development of pharyngitis, rheumatic fever, and poststreptococcal nephritis. There was, however, a higher rate of tonsillectomy among nonsecretors (35% versus 18%; $P < 0.05$). There was no correlation between ABO group and carrier status.

Group B *Streptococcus*. Group B *Streptococcus* is a major pathogen in newborns and is generally acquired during labor. Maternal colonization is the single greatest risk factor associated with neonatal infection. In a retrospective observational study, Regan and colleagues found an increased prevalence of group B *Streptococcus* in blood group B mothers and infants (195). Among 1,062 mothers, 11% were culture positive for group B *Streptococcus*. When examined by ABO type, the rates of group B *Streptococcus* colonization were nearly 2-fold higher in colonized mothers (28% versus 16%), colonized infants (30%), and infected infants (30%). In contrast, no correlation was found in an Ohio study that included 50% African Americans or in a prospective case-control study (196, 197).

***Streptococcus* lectinolysin.** Cytolysins are expressed by some pathogenic streptococcal strains, including *Streptococcus pneumoniae* (pneumolysin), *S. intermedius* (interilysin), and *S. mitis* (mitilysin). Recently, a fourth cytolysin with lectin-like properties was isolated (198). Lectinolysin (LLY) is related to other *Streptococcus* cytolysins with the exception of a 162-peptide lectin domain at the amino-terminal end. The lectin domain shares 33% sequence identity with the fucose binding lectin *Anguilla anguilla* agglutinin (AAA). Glycan arrays have confirmed that LLY binds terminal H-active glycans, with a preference for Le^Y and Le^b. LLY is not specific to *S. mitis* strains and was identified in strains of *S. pneumoniae*, *S. pseudopneumoniae*, and *S. mitis/S. oralis*. At this time, there are no epidemiological studies of LLY-positive (LLY^+) infections relative to blood groups and outcomes. Interestingly, LLY is able to bind platelets with pore formation, which led to its original description as a platelet-activating factor. The toxicity of LLY is variable between platelet donors, suggesting host-specific differences (198, 199). The fucosylated ligand for LLY on platelets has not been identified.

Staphylococcus aureus

Staphylococcus aureus possesses an array of adhesins, with the majority recognizing adhesive proteins of the extracellular matrix and blood (200). Some adhesins, however, recognize carbohydrates. Many *S. aureus* strains causing bovine mastitis (23 to 73%) are able to hemagglutinate sheep red cells via a 145-kDa protein (201, 202). Parallel testing against human red cells showed weaker agglutination, although some donor red cells agglutinated as strongly as sheep red cells (202). Likewise, 7 to 13% of *S. aureus* strains causing human bacteremia were able to agglutinate sheep red cells, with titers ranging from 1 to 128 (201). Hemagglutination was significantly enhanced when tested against neuraminidase- and trypsin-treated red cells, suggesting that the host ligand might be a GSL (202). More recently, the *S. aureus* SraP adhesin (227 kDa) was shown to recognize sialylated type 2 chain antigens (NeuAcα2-3Galβ1-4GlcNAc-R) via an L-lectin-type domain in the molecule (203). SraP is related to two streptococcal adhesins (GsPB and Hsa) that also recognize terminal sialic acid and are able to bind platelets (204). It has been hypothesized that sialic acid adhesion to platelets plays a role in endocarditis caused by *S. aureus* and viridans group streptococci (203, 204).

One group implicated the Le^a antigen as a receptor for some *S. aureus* strains. Telford et al. showed a high rate of *S. aureus* infection among infants who died of sudden infant death syndrome (SIDS) (41% versus 28%), leading to speculation that toxigenic *S. aureus* colonization could be a risk factor for SIDS (205). Saadi et al. screened several toxigenic *S. aureus* strains for adhesion to buccal epithelial cells and found that 3/8 strains had higher levels of binding to epithelial cells from nonsecretors (206). Moreover, binding was decreased by prior treatment with anti-Le^a (206). A 67-kDa bacterial membrane protein was subsequently isolated by using a Le^a adsorption column (207). The isolated protein eluate represented nearly 9% of the total *S. aureus* cell wall proteins and was able to decrease bacterial adhesion 2- to 4-fold when tested against buccal cells from Le(a+) donors (207). The authors of this study hypothesized that young infants may be particularly susceptible to colonization by some toxigenic *S. aureus* strains due to developmental delays in *Se/FUT2* expression. As supporting evidence, the same investigators screened respiratory secretions from deceased SIDS patients for Le^a antigen. Le^a was detected in 63/71 (71%) specimens tested (206), which is a higher rate than that observed for adults (54).

One older Russian study reported that group A was associated with a higher *S. aureus* carriage rate (208). A later prospective German study examined both pharyngeal and nasal *S. aureus* carriage in 227 healthy volunteers by ABO, Lewis, and Secretor status (209). Study subjects included 156 individuals with persistent nasal carriage and 77 pharyngeal carriers. A comparison of carriers and noncarriers found no correlation between ABO group and Secretor status upon univariate analysis; however, distinct trends were observed when results were analyzed based on Secretor status in a multivariate analysis. Among nonsecretors, there was an increased rate of pharyngeal colonization for group O individuals (60%, versus 40% of non-O individuals; OR, 6.5 [95% confidence interval {CI}, 1.23 to 33.03]; $P = 0.02$), with the lowest rate being observed in group A individuals (3/16; 20%). Conversely, pharyngeal carriage was uncommon among secretors (Se^+), regardless of ABO type (65 to 73%; OR, 0.24 [95% CI, 0.07 to 0.77]; $P = 0.02$). There was no correlation between blood groups and nasal carriage. As discussed by the authors of that study, nasal keratinocytes are of ectodermal origin and not likely to express either *FUT3* or *FUT2*.

Yersinia pestis

In the 1950s to 1960s, there was widespread speculation that the variation in ABO frequencies between human populations was a consequence of epidemic plague (210). Specifically, there was a hypothesis that group O was a host susceptibility factor, increasing the odds for *Yersinia pestis* infection. Indirect evidence cited was the relatively low incidence of group O in areas that were spared from severe plague outbreaks in medieval times (211). This was supported by some anthropology studies, which showed a shift in ABO frequencies over several centuries. Doughty ABO typed the remains of 213 individuals who had resided in rural Northamptonshire, England (211). In 1349, this region was decimated by a severe outbreak of plague, which killed 37% of the population. A comparison of individuals interred in the 1300s and those interred in the 1600s showed a significant decrease in the prevalence of group O (59% to 39%; $P = 0.01$). It should be noted that this investigator inferred the ABO type by using a modified HAI assay. Instead of saliva to inhibit hemagglutination, this investigator used a slurry of ground bone prepared from exhumed skulls, using surrounding dirt samples as a negative control. Finally, there was a report that *Y. pestis* reacted with group O typing reagents (81).

A possible link between *Y. pestis* and ABO was refuted by Springer and others based on several lines of evidence (81, 212). First, most strains of *Y. pestis* tested (8/9) had little or no evidence of ABH-active epitopes. Second, the strains circulating in modern times may not be immunologically equivalent to ancient plague strains. Third, the H antigen is present, to some degree, in all ABO types except the rare Bombay and para-Bombay phenotypes. Anti-H antibodies, if present, are low-titer, cold autoantibodies with little or no reactivity at 37°C (28, 29). Finally, there is no potential linkage between ABO and the CCR5Δ32 polymorphism, which reside on chromosomes 9 and 3p21.31, respectively.

One study compared ABO and Lewis types in patients with reactive arthritis following *Yersinia* infection (94). Although there was a slight increase in the prevalence of nonsecretors among reactive arthritis patients, it did not reach clinical significance.

Candida

***Candida* adhesion.** The potential role of blood groups in *Candida* infection has been the subject of several epidemiological studies, with mixed and contradictory results. Some of the strongest evidence comes from studies searching for *Candida* colonization factors. *Candida* can recognize stratherin, hydroxyapatite, and RGD-containing proteins such as fibronectin and fibrinogen (213). *Candida* species also possess lectin-like adhesins, with binding to LacCer, asialo-GM1, Le^a, and H-active glycans (213–219). The type of adhesin expressed varies by strain and is influenced by growth conditions (218–220).

One of the best-studied *Candida* adhesins is the fucose binding lectin. Brassart and colleagues were able to inhibit *C. albicans* adhesion with a panel of milk and meconium oligosaccharides (217). Oligosaccharides bearing a terminal Fucα1-2Gal-R (O/H antigen), but not internal fucose residues (Le^a, Le^b, and Le^X), were able to decrease yeast adhesion by 30 to 40%. Subsequent investigators have confirmed these findings by using 2′-fucosyllactose (Fucα1-2Galβ1-4-Glc), H-active O-glycans, and the anti-H lectin *Ulex*

europaeus agglutinin (UEA) (213, 218, 219). The fucose adhesin was partially purified by affinity chromatography using an H-antigen adsorption column. The adhesin was characterized as a 15.7-kDa protein of ~152 amino acids (219).

***Candida* vaginitis.** *Candida* vaginitis is a common disorder among women. It is estimated that 75% of all women experience at least once episode of vulvovaginitis, with 5 to 10% of women suffering recurrent infections (221). Several factors increase the risk of *Candida* vaginitis, including diabetes and the use of systemic steroids, antibiotics, and oral contraceptives. Symptoms include intense burning and itching accompanied by a thick white vaginal discharge. Interestingly, symptoms are typically worse immediately prior to menses and during pregnancy, presumably due to changes in reproductive hormones.

Three small epidemiology studies have reported an association between *Candida* vaginitis and *Secretor/FUT2* (222–224). Hilton et al. reported an increased prevalence of Le(b−) in women with recurrent vaginitis (>5 episodes/year); however, there was no attempt to determine secretor type by genotyping or testing of saliva (222). When the same data are analyzed by comparing only Le(a+b−) with Le(a−b+) individuals, there is no significant difference ($P = 0.39$). In contrast, Chaim and colleagues reported a 2.5-fold-higher incidence (42% versus 17%) of Le(a+b−) among 38 patients with recurrent vaginitis (223). Finally, Kulkarni and Venkatesh studied ABO secretor status and vaginal candidiasis in 120 Indian patients with a history of leucorrhea (224). Unlike the studies by Hilton et al. and Chaim et al., secretor status was determined by HAI assays using patient saliva. Among patients with *Candida* vaginitis, 76% were nonsecretors, versus 23% of patients without evidence of *Candida*. When data from the three studies are combined, the relative risk of *Candida* vaginitis among nonsecretors is 2.52 (95% CI, 1.84 to 34.5; $P = <0.0001$). There was no significant correlation between *Candida* and ABO type (223, 224).

Animal studies also support *Secretor* as a protective host factor against *Candida* vaginitis. *FUT2* is expressed by endocervical glands and ectocervical squamous cells, which synthesize mucins bearing Le^b and H-active epitopes (225, 226). In *FUT2*-null mice, there is a selective loss of H-active mucins, although mucins with Le^a and Le^X activity are still synthesized and secreted (226). When challenged with *C. albicans*, *FUT2*-null mice showed a 3-fold increase in total fungal burden over the wild-type (wt) controls (226, 227). This increase could be eliminated by intravaginal administration of H-active mucins or by surgical removal of the cervix through hysterectomy (227). It is important to note that *FUT2* is upregulated by estrogen (225–228): Estrogen is required for *Candida* proliferation and adhesion *in vivo*, possibly through modulation of host-microbe interactions (226, 229).

Oral *Candida*. *Candida* is a common oral commensal, with an average rate of carriage of 40 to 45% in healthy subjects. Carriage of oral candida is reportedly increased in diabetics, patients with dentures, smokers, immunosuppressed individuals, and individuals with xerostomia (230). Clinical conditions associated with oral and gastrointestinal candida include thrush, chronic hyperplastic candidosis, oral dysplasia, esophagitis, and even gastritis. *C. albicans* is the most common species (80 to 90%) isolated from oral secretions.

There are conflicting data regarding the role, if any, of ABO or secretor type in oral candidiasis. Early small studies reported an increased rate of carriage among group O individuals (231, 232), although this was not substantiated in subsequent studies (233–235). The association between oral candida and secretor status is more conflicted. Several studies found an increased rate of carriage in nonsecretors among healthy Israelis (233) and diabetics (232, 234), whereas others found no association (235, 236). In one negative study of healthy Chinese men, a subanalysis of smokers uncovered an association between candida and nonsecretor status (235). Nonsecretor status was also identified as a risk factor for chronic hyperplastic candidosis (68% versus 38%) (237).

A few studies examined blood types and candida colonization of the upper gastrointestinal tract. A small Indian study compared ABO type and candida in patients with duodenal ulcers (238). Yeast was isolated in 24/45 patients with *C. albicans*, accounting for 21/24 isolates. Colonized patients were more likely to be group O individuals (68.5% versus 42% of yeast-negative individuals). Likewise, Burford-Mason et al. reported a higher incidence of group O in colonized patients with peptic ulcer disease (40% versus 19% of yeast-negative individuals) (239). The same investigators also reported a higher incidence of nonsecretor status among colonized ulcer patients (58% versus 26%; $P < 0.0001$) (239).

Norovirus

Norovirus is a small, nonenveloped, highly infectious, single-stranded RNA calicivirus. Infection is typically characterized by severe gastroenteritis with fever, malaise, abdominal pain, diarrhea, and explosive projectile vomiting (240). Large outbreaks are not uncommon due to potential widespread surface contamination, the long virus shedding period (10 days), environmental stability, low infectious dose, and common association with foodborne outbreaks. In epidemiologic studies, norovirus was found to be responsible for 96% of nonbacterial gastrointestinal illnesses, 50 to 67% of all foodborne illnesses, and 40% of all epidemic outbreaks of gastrointestinal illnesses (240).

The presence of host factors has long been suspected. Epidemiologic studies of outbreaks often identified familial clusters of resistant individuals, suggesting the presence of inherent genetic factors. Controlled studies with volunteers also supported the presence of nonimmune host defense factors (241): between 12 and 40% of individuals infected with norovirus fail to develop infection or are clinically asymptomatic (241, 243). Susceptible individuals, on the other hand, can be reinfected with severe symptoms, despite evidence of humoral immunity (241).

A correlation between ABO type and norovirus was postulated by Hutson et al., who demonstrated that norovirus empty capsids were capable of agglutinating human RBC in an ABO-specific manner (242). Recombinant norovirus empty capsids strongly agglutinated RBC from group O, A, and AB donors but not group B or rare Bombay cells (O_h) (242). These authors subsequently reexamined stored serum samples from 51 volunteers previously exposed to norovirus to compare donor ABO types with symptomatic infection and immune responsiveness (243). It is important to note that the ABO types were inferred based on the presence or absence of anti-A and anti-B in serum (back type or plasma grouping) (Table 3); no RBC were available for a full valid determination of ABO type. Group O subjects had a greater risk of infection (OR = 11.8), with 96% of individuals showing laboratory evidence of infection. In contrast, 22 to 40% of group A and group B donors were resistant to infection. Among individuals with symptomatic infection (29/51), all were group A or group O, whereas group B individuals were asymptomatic or resistant ($P =$

0.025). Similar findings were reported following an outbreak among British troops serving in Afghanistan (244).

In addition to ABO, virus binding and host susceptibility are also heavily dependent on the presence of *Secretor*. In solid-phase studies, viral capsids prefer type 1 H and Le^b over type 2 chain H-active substrates (Le^Y; type 2 H), with no binding to related Le^a and Le^X antigens (242). Virus binding to type 3 and type 4 chain H structures, which also require FUT2 for their synthesis, has also been demonstrated (245). In cell cultures, transfection of the *FUT2* gene into normally nonpermissive cells lines (CHO and TS/A) results in *de novo* virus binding (245, 246).

In human samples, the virus binds saliva from group O and A secretors but not saliva from nonsecretors or group B individuals (241, 245–247). The virus was also shown to bind gastrointestinal biopsy specimens from Le(b+) patients (245). Finally, at least five studies demonstrated a role for *Secretor* in host susceptibility in human subjects. In a nursing home outbreak, 97% of all affected patients were genotyped as Se^+, whereas only 1/16 nonsecretors developed illness (247). In a second smaller outbreak among oncology and transplant patients, 11/11 patients were genotyped as Se^+ (248). In Nicaragua, group O secretors were more likely to develop symptomatic infection, especially with G1 strains (249). Likewise, African children infected with G1 strains were overwhelmingly group O secretors (86%; $P = 0.02$) (11). Among 77 volunteer subjects, 62% of Se^+ individuals had laboratory evidence of infection, regardless of the virus dose, whereas no infection was identified in 22 nonsecretors (241). Among Se^+ individuals, group O individuals had a much higher rate of infection (75% versus 50%), with 71% developing vomiting or diarrhea. *Secretor* may play a protective role in infant diarrhea due to norovirus. Breast milk rich in Le^b oligosaccharides from Secretor-positive mothers confers substantial protection from calicivirus-associated diarrhea ($P = 0.012$) (167).

The preference for type 1 ABH structures is consistent with the pathobiology of norovirus infection. Animal studies with human norovirus strains show viral tropism for enterocytes along the tips of intestinal villi of the duodenum and proximal small intestine (250). This correlates well with developmental changes in ABH expression during enterocyte maturation. Intestinal stem cells deep within villus crypts express type 1 and type 2 chain ABH antigens but switch to type 1 and type 3 upon differentiation (251, 252). This can also be modeled *in vivo* with Caco-2 cells, an undifferentiated intestinal epithelial cell line (43). Undifferentiated Caco-2 cells strongly express type 2 chain H antigen and are resistant to norovirus infection. With differentiation, Caco-2 cells synthesize type 1 H antigen with virus binding and uptake (43, 245). Once infected, the epithelium shows a loss of tight junctions, anion secretion, apoptosis, and villus blunting (253).

The norovirus ABH binding site has been mapped. The norovirus capsid is an icosahedron composed of 90 dimers of the VP1 capsid protein (254). VP1 has two domains, a shell domain and a P or "protruding" globular domain, which mediates virus adhesion. Polymorphisms in the VP1 protein are responsible for both strain and receptor diversity. Two major genogroups are recognized among human norovirus strains: group I (GI), which recognizes primarily A, H, and Le^b epitopes, and group II (GII), which is highly diverse relative to receptor recognition (255). It appears that the GI and GII strains possess slightly different lectin sites along the VP1 protein (256). Crystallography studies with GI strains show extensive interactions between VP1, fucose, and either Gal (type 1 H) or the terminal GalNAc (type 1 A) (256). The absence of detectable binding to group B antigen is attributed to the absence of an *N*-acetyl group, which forms critical hydrophobic and hydrogen interactions with VP1 (Trp375 and Asp327). Similar studies with a GII strain identified a second binding site that interacts primarily with fucose, allowing a diverse number of receptors for virus binding (257). This includes GII strains that can bind all saliva regardless of ABO or secretor status (255).

Because GI and GII strains differ in their host receptors, the impact of ABO type varies among outbreaks and populations, especially over time. Group O Le(b+) secretors are clearly more susceptible to GI strains than are individuals with other blood types (43, 243, 244). In contrast, GII strains infect secretors, regardless of ABO type (247, 249, 258). In Nicaragua, GII strains were present in 74% of infected children and were unrelated to ABO type (258). Similar results were observed in China and in West Africa, where GII strains infected children regardless of ABO type, with a preference of some GII.4 strains for blood group B (78%; $P = 0.019$) (43, 259). GII strains, especially GII.4, tend to induce more severe and prolonged symptoms than do GI strains (43). An analysis of 843 norovirus outbreaks over 18 years found that GII.4 was associated with higher rates of hospitalization (RR = 14) and death, especially for patients in long-term-care facilities (260).

Norovirus binding to ABH groups could play a role in the global dissemination of virus strains. Oysters and other shellfish are a known source of foodborne outbreaks, with 10% of oysters testing positive for norovirus (261, 262). Oysters, mussels, and clams are able to bind norovirus via blood group A antigens on gastrointestinal epithelial cells (263, 264). It has been speculated that this specific binding is responsible for virus concentration as well as the unusual resistance of norovirus to standard depuration procedures (264). Pigs also express A and H antigens (37, 113, 250, 265) and serve as animal models for norovirus infection (250). Surveys have found evidence of past human norovirus exposure in 50 to 63% of pigs, with 2 to 25% being positive for viral RNA by PCR (266, 267).

Rotavirus

Rotavirus is a nonenveloped, double-stranded RNA virus and a major cause of acute infectious diarrhea. Very young children are at the highest risk for infection, with 75% of children showing evidence of humoral immunity by 5 to 6 years of age (268). Infection is spread by the fecal-oral route, with a 48-h incubation period followed by sudden vomiting and diarrhea. Diarrhea may last for up to a week, with a high risk of dehydration and electrolyte abnormalities. Extraintestinal disease and complications include intussusception, mild hepatitis, meningitis, encephalopathy, and encephalitis.

Like norovirus, rotavirus appears to infect the upper small intestine. Histologic studies show patchy epithelial lesions, villus shortening, and inflammatory infiltrates within the lamina propria (268). Diarrhea may be secretory due to nonsecretory protein 4 (NSP4), an enterotoxin that affects the myenteric plexus. There is also evidence of impaired disaccharidase activity and increased mucosal permeability, which suggests a contribution by osmotic and exudative processes as well (268).

Rotavirus is highly polymorphic, with 35 known P or capsid genotypes that display species-specific infectivity (269). In addition to humans, rotavirus can infect a wide range of mammals,

including monkeys, birds, cows, pigs, goats, canines, and antelopes. Three P genotypes (P4, P8, and P6) are responsible for the vast majority of human infections (71%) (270). P4 and P8 are the two most common genotypes and bind Le^b and type 1 H. P6 is less frequent and is specific for type 1 H (270). Human infections can also occur with P9, P14, and P25 strains, which recognize blood group A (269). P9, P14, and P25 belong to the PIII supergroup, which includes strains capable of infecting animals (269). Animal rotavirus strains tend to recognize sialic acid, including strains specific for *N*-glycolylneuraminic acid (NeuGc), a sialic acid variant found in many animal species but absent in humans. Clustal analysis of P9, P14, and P25 indicates that they arose from classic sialic acid-specific animal strains. The loss of sialic acid binding, and *de novo* recognition of A antigen, is attributed to an amino acid insertion immediately adjacent to a short peptide sequence within the binding pocket. The insertion subtly alters the conformation of the binding site (271).

The rotavirus capsid is composed of two major proteins, VP4 and VP7 (272). VP4 forms the major spike protein responsible for host recognition and binding. VP4 is proteolytically cleaved into two proteins: VP8*, the globular lectin domain, and VP5*, which forms the stalk domain. Studies with a recombinant VP8* capsid protein show blood group specificity against saliva, mucins, and commercial glycoconjugates (269). In crystallography studies with a group A-specific strain (P14), VP8* recognized A antigen along the GalNAcα1-3Gal backbone, with no fucose interaction; the latter was orientated perpendicularly and away from the capsid (271). Recognition of the GalNAcα1-3Gal disaccharide may be particularly helpful in the upper intestine, which is rich in type 3 or mucinous A antigen (Table 4), a repeating polymer of A antigen epitopes (252).

There are few reported studies on the impact of host blood types on rotavirus infection. In immortalized cell lines, there is a clear correlation between ABO expression, VP genotype, and infectivity (271). Likewise, rotavirus replication is inhibited by human milk and jejunum mucins, which are rich in ABH epitopes (273, 274). A prospective longitudinal study of 254 newborns, however, found no correlation between rotavirus infection and Lewis phenotypes (127). There is evidence that differences in population blood types have exerted evolutionary pressure on the distribution of viral genotypes. This may explain the frequency of P6 strains (type 1 H specific) in Africa, which has a high incidence of group O Le(a−b−) individuals (275, 276). In West Africa, P6 can account for 20 to 36% of all pediatric infections, with evidence of recombination between cattle and human strains (275). In Europe, where there is a higher incidence of group A (Table 2), there have been case reports of human P14 infections in group A individuals (271, 277).

HIV

HIV is an enveloped retrovirus that can adopt a host glycan profile. The Env glycoprotein gp120, which mediates cell adhesion, possesses 25 N-glycan sites, with carbohydrates constituting 50% of the total molecular weight (278). The types of N-glycans expressed can range from high-mannose, intermediate hybrids to mature, complex N-glycans with bi- and triantennary structures (279). Because HIV glycosylation is dependent on the host cell, the HIV glycome can differ between cell types (279). Alterations in N-glycan often accompany the transition from a CCR5- to a CXCR4-tropic virus and can affect both host immune responsiveness and HIV infectivity (278).

Not surprisingly, some HIV and gp120 isolates can react with blood group-active monoclonal antibodies and lectins (278). ABH-active gp120 can be produced *in vitro* by propagating HIV in cell lines expressing the appropriate glycosyltransferases (280). ABH-active HIV can also be produced by propagating HIV in lymphocytes of a known ABO type (280, 281), despite the reported absence of ABH on lymphocyte glycoproteins (282). However, lymphocytes adsorb ABH-active GSLs from plasma (283). Host cell GSLs have been isolated from HIV, and it has been hypothesized that HIV could acquire ABH-active GSLs during viral budding (280). HIV infection could also potentially induce ABH synthesis in lymphocytes (280, 281): HIV infection of T lymphocyte cell lines can induce Le^Y neoantigen expression (284).

N-glycans with ABH and related blood group activity (for example, Le^Y) can serve as targets for neutralizing antibodies. Hansen et al. were the first to report the ability of blood group-active antibodies to neutralize HIV (285). These investigators preincubated HIV with a panel of 20 different antibodies against carbohydrate epitopes prior to infection of MT4 cells. Antibodies against blood group A and Le^Y inhibited HIV infection in a dose-dependent fashion, with 80% virus inhibition at micromolar concentrations (0.32 to 1.16 μg/50% infectious dose [ID_{50}]). Likewise, HIV passaged in human lymphocytes of a known ABO type can be neutralized by the appropriate ABO-specific monoclonal antibodies (281). HIV grown in blood group A-positive cell lines was partially neutralized by ABO-incompatible serum (groups O and B) but not by group A serum or heat-inactivated serum (280). These results suggest that ABO incompatibility at the time of primary virus exposure may offer some protection. Finally, a retrospective 16-year study of 271,000 Brazilian blood donors reported a slightly higher incidence of HIV among group B donors (286). Among the 389 HIV^+ donors (0.01%) found upon screening, 14% were group B individuals, a rate which was slightly higher than that in the general population (9%; OR, 1.5 [95% CI, 1.13 to 2]).

There has been some interest in the role of Secretor in HIV progression and infection, especially heterosexual HIV transmission. An early study by Blackwell et al. compared Secretor statuses of heterosexual partners of HIV-positive individuals ($n = 54$) (287). Although this study was small, these authors found significantly higher numbers of Se^+ individuals among partners who contracted HIV (88% versus 54% who were HIV negative; $P < 0.025$). In contrast, there was no difference in secretor status among individuals who contracted HIV by intravenous drug use or homosexual transmission ($n = 191$). A later, larger study focused on HIV transmission in female commercial sex workers working in Senegal ($n = 377$) (288). Again, HIV-1-positive women were more likely to be Se^+ (86% versus 72%), even after adjusting for coinfection by other sexually transmitted diseases. When data from the two studies are combined, a nonsecretor phenotype appears to provide mild protection against heterosexual HIV transmission, with an OR of 0.39 (95% CI, 0.21 to 0.72; $P = 0.0022$). One caveat with the Senegalese study was the reliance on allele-specific PCR for a single FUT2 polymorphism (se^{428}). Finally, one small European study compared the rates of HIV progression by Secretor status in 31 HIV-infected men (289). The nonsecretor phenotype was overrepresented only among men

with long-term asymptomatic disease (66.7% versus 21%; $P < 0.001$).

One investigator proposed that the Le(b+) phenotype might actually be protective against HIV infection. Puissant et al. reported a moderate increase in the prevalence of the Le(a−b−) red cell type (16% versus 12%; $P = 0.007$) among 968 HIV-infected patients (290). When corrected for ABO type, however, an increase in the prevalence of the Le(b−) phenotype was found only for group A and AB individuals. These authors hypothesized that Le^b-active glycans might function as a competitive inhibitor of DC-SIGN on mucosal dendritic cells. If this is true, then an Le(b+) maternal phenotype might protect against perinatal HIV transmission in breastfed infants. This question was addressed in an elegant retrospective study by Bode et al., who had access to stored milk samples and data on clinical outcomes for 167 HIV-infected women (291). These authors found no correlation between Lewis-active milk oligosaccharides and HIV transmission. In contrast, perinatal HIV transmission was linked increased levels of sialylated milk oligosaccharides.

SARS and ABO

Severe acute respiratory syndrome (SARS) is caused by the SARS coronavirus (SARS-CoV), an RNA virus. The original SARS outbreak in the winter of 2002 to 2003 infected >8,000 individuals worldwide, with a fatality rate of 10% (292). Like other human coronaviruses, SARS-CoV infects the mucosal epithelium, causing an acute respiratory illness often accompanied by gastroenteritis. In a Hong Kong outbreak, there was an apparent association between disease transmission and ABO type (293). An epidemiology study of 34/45 hospital workers who contracted SARS after exposure to a single index patient showed that most of the infected individuals (23/34) were non-group O individuals (groups A, B, and AB). Group O individuals were relatively resistant to infection, with an OR of 0.18 (95% CI, 0.04 to 0.81; $P = 0.03$).

Like HIV, coronavirus is an enveloped virus that targets host cells via a viral adhesion glycoprotein. The SARS-CoV spike (S) protein is a 210- to 230-kDa glycoprotein with 23 potential N-glycosylation sites (292). Glycan analysis shows a wide range of structures, including complex N-glycans with 2 to 4 antennae capable of supporting ABH epitopes (292, 294). Because the virus targets respiratory and gastrointestinal mucosa, it is highly likely that most human isolates express ABH antigens on the S protein and host envelope GSLs. Like the Env protein, S protein expressing A antigen can be blocked by monoclonal anti-A and human anti-A (292).

Based on both epidemiologic and *in vitro* studies, Guillon et al. hypothesized that group O individuals are more resistant to SARS-CoV due to ABO antibodies and could decrease the rate of infection throughout the population (292). The degree of protection, however, may be influenced by the ABO antibody titer, secretor status, and incidence of group O in the population. Studies with human anti-A showed effective blocking with higher-titer anti-A (≥1:256) only; low-titer anti-A was ineffective (292). The latter finding has implications for individuals in industrialized countries, who tend to have low ABO titers (89). A nonsecretor phenotype would also nullify viral neutralization, since virus transmitted from a nonsecretor lacks ABH expression.

Influenza and Parainfluenza Viruses

Influenza virus is an enveloped, single-stranded RNA orthomyxovirus (295). Influenza is a highly contagious, upper respiratory tract infection causing fever, sore throat, cough, myalgia, headache, and fatigue. Severe infections can be complicated by primary viral or secondary bacterial pneumonia, myocarditis, encephalitis, Reye syndrome, and Guillain-Barré syndrome. Influenza A virus strains are responsible for most pandemic outbreaks, including the 1918 Spanish flu and the 2009 H5N1 outbreak. Epidemiology studies of large outbreaks have shown severe infections often clustering within families (296). Although this may be attributed to common social and environmental conditions, the occurrence of cases in family members separated by time and space hints at heritable genetic factors (296, 297).

Following the 2009 pandemic, the World Heath Organization sponsored a systematic literature review to identify potential host factors for influenza, including ABO (296). There were 13 studies on the impact of host ABO and influenza infection published between 1962 and 1977. Many of these studies were focused on the possible protective role of ABO antibodies. Nearly all studies were observational, involving different influenza virus strains and diagnostic criteria for infection (clinical or serologic). In addition, ABO typing was often inferred based on the back type using stored serum samples (298). As noted by Horby et al., "the data are inconsistent," with different studies reporting an increased risk of influenza infection with blood groups O, A, and B (296). Significant confounders included successive exposures to the same or similar influenza virus strains with development of humoral immunity, which could obscure the impact of genetic host factors (298). A single older study found an increased risk of respiratory viral illness, in general, among Se^+ individuals (299). The incidence of Le(b+) in patients with influenza A or B virus infection was 86%, versus an incidence of 72% among controls.

Influenza virus initially colonizes nonciliated epithelial cells in the tracheobronchial tree via a sialic acid-specific viral hemagglutinin. Studies of animal and human strains show that virus binding is dependent on the neuraminic acid type (NeuAc or NeuGc) and the glycosidic linkage (α2-3 or α2-6) and is influenced by fucosylation and the length of the polylactosamine scaffold (300–303). Human strains typically prefer terminal NeuAcα2-6Gal epitopes, which are richly expressed along the upper respiratory tract (304, 305). In contrast, avian strains prefer terminal NeuAcα2-3Gal epitopes, which are enriched in the lower respiratory tract of humans (304–306). Epizoonotic transmission of avian strains, such as H5N1, can lead to severe infection and viral pneumonia due to an expansion of viral receptors (304). Parainfluenza virus, a frequent cause of croup, also recognizes NeuAcα2-3Galβ1 receptors (304).

With the advances in molecular and glycan analyses, there may be a need to reexamine the potential impact of *ABO*, *Lewis*, and *Secretor* on influenza susceptibility in future outbreaks. FUT2 directly competes with sialyltransferases for acceptor substrates, potentially altering the density and array of sialylated glycans available to influenza virus. It is well known that influenza virus pathogenicity is moderated by changes in cell surface sialylation. This can be observed *in vitro* by the desialylation of cell membranes or through overexpression of ST6GAL1, the sialyltransferase responsible for NeuAcα2-6Gal synthesis (307). Respiratory mucins from group O Le(a+b−) nonsecretors show an increased number of sialylated O-glycans, especially structures with sLe^X

activity, relative to group O secretors (308, 309). Influenza virus strains that preferentially recognize sLe^X epitopes have been described (300, 303).

Plasmodium falciparum

Plasmodium falciparum is a parasitic protozoan transmitted by *Anopheles* mosquitoes (310). Like all malarial species, this organism initially infects the liver, followed by the release of merozoites and infection of red cells. *P. falciparum* can be associated with particularly heavy parasitemia, with up to 30% of erythrocytes being infected. Cases of heavy infections can present with severe anemia (hemoglobin, <5 g/dl), cerebral malaria with coma or convulsions, acidosis, respiratory distress, prostration, and multiorgan failure. Young children are particularly susceptible to cerebral malaria and increased mortality. In areas where the disease is highly endemic, malaria is responsible for 17% of child deaths, with >1 million deaths worldwide (311, 312).

It is estimated that 25% of the biologic variation in malaria severity is genetic (312). The preponderance of group O in African and many Asian populations has long led to speculation that ABO type may be a host factor. Cserti and Dzik carefully examined the incidences of ABO types relative to malaria and documented an increasing prevalence of group O in tropical areas along the equator (313). In the Amazon basin and Nigeria, the incidence of group O reaches 87 to 90%, with <10% of the population being typed as group A. In contrast, group A predominates among northern European populations who are not exposed to malaria. These authors hypothesized that group O arose in response to selective pressure by malaria, especially *P. falciparum*.

Several studies over the last 50 to 60 years have compared ABO type and malaria infection. Most of the early studies concluded that ABO type played no role in malaria since there was no observed difference in the distribution of ABO types between infected patients and the general population (314). Later investigators also found no correlation between ABO type, malaria incidence, parasite density, and immune response (315). ABO received renewed interest only after it was demonstrated that some *P. falciparum* strains rosette red cells in an ABO-specific manner (316, 317). Specifically, the size and strength of red cell rosettes were dependent on ABO type, where AB and A > B > O. Rosetting is a known virulence factor and is thought to contribute to microvascular ischemia and thrombosis (313, 317).

More recent studies have focused on ABO type and the risk of severe malaria, particularly in young pediatric patients (312, 317–323). Fischer and Boone found that group O individuals were protected against cerebral malaria and coma in a study of 489 patients in Zimbabwe (3% versus 9% for group A; $P = 0.008$) (318). Likewise, Rowe et al. studied 587 Malian children with malaria and case-matched controls by ABO type and disease severity (317). As before, the prevalence of group O was much lower in children with severe malaria (21% versus 44 to 45%; $P < 0.0005$) and was accompanied by a lower frequency of red cell rosettes on peripheral smears ($P = 0.003$). Conversely, there was a strong association between rosette frequency and severe malaria in group A, B, and AB children (OR, 15.2; $P < 0.0001$). Similar findings have been reported in studies from Sri Lanka, India, and Ethiopia (320–323), even after correction for malnourishment and coexisting helminth infections (323). Three large genomic studies involving nearly 6,000 patients confirmed that group O is an independent genetic factor that decreases the risk of severe malaria (312, 319, 320).

A few studies have examined the impact of ABO type on pregnancy, with most studies showing a selective advantage with group O (324–328). A small study of 198 Gambian mothers reported an inverse relationship between ABO type, malaria, and parity (324). Among women having their first child, 63% had evidence of active placental infection, especially group O women (OR, ~3.0). For multiparous women, group O was found to be protective against active malaria. Group O women with malaria also had higher mean hemoglobin levels, fetoplacental weight ratios, and fetal birth weights. The same investigators performed a larger cross-sectional study of 647 women in Malawi, an area with perennial malaria (325). As before, group O primiparae were at an increased risk of active placental malaria (OR, 2.18; $P = 0.02$). Two other studies from Sudan ($n = 293$) and Gabon ($n = 378$) found no increased risk of malaria in group O primiparae but confirmed some protection against placental malaria in multiparous group O women (OR, 0.6) (326, 327). No correlation between active malaria, placental malaria, parasitemia, parity, and ABO type was identified for 447 Myanmar refugees in western Thailand (328).

Rosetting is mediated by *Plasmodium falciparum* erythrocyte membrane protein 1 (PfEMP1) proteins expressed on malaria-infected red cells. The PfEMP1 extracellular domain comprises several distinct adhesion domains, including the Duffy binding-like domain (DBL) and the cysteine-rich interdomain region (CIDR). PfEMP1 is highly polymorphic between strains (329); however, all strains that recognize A/B antigens share the same DB1α1-CDR1γ amino-terminal head region (330). The ABO lectin site is located within the amino-terminal DBLα1 domain, although CIDR1γ significantly enhances binding (330). Recombinant DBL1α binds human RBC in an ABO-specific fashion, where binding is inversely related to H expression ($A_1 > A_2$, and B > A_x > O; $R = -0.67$; $P = 0.001$) (330). Crystallography and molecular modeling analyses confirmed an A-antigen binding site near the N-terminal segment (NTS)–DBLα1 hinge region, on the opposite face from the heparin binding site (330). Heparin can disrupt rosetting, possibly by inducing conformational changes in PfEMP.

Group O may moderate *P. falciparum* infection through several different mechanisms. As discussed above, group O is protective against rosetting by certain *P. falciparum* strains. In addition, infected group O red cells appear differentially sensitive to oxidative damage. Mendez et al. showed that although all red cells showed evidence of oxidative damage following *P. falciparum* infection, the pattern of carbonylation was distinct in group O red cells, with involvement of band 4.2 and band 4.1 (331). Other evidence for enhanced "senescence" upon infection includes hemichrome formation and band 3/anion exchanger 1 (AE1) clustering (331–333). This may account for the increased phagocytosis of group O RBC by macrophages *in vivo* and *in vitro* (334). Senescent changes and phagocytosis may facilitate clearance of infected red cells and parasite load in group O individuals.

Schistosomiasis

Schistosomes are trematodes or flukes that require freshwater snails as an intermediate host (335). Human infection typically occurs after swimming in or prolonged exposure to contaminated water. After invading softened skin, cercariae migrate to the portal

venous system, where they mature and undergo sexual reproduction with egg formation. Complications result from chronic granulomatous inflammation and can include hepatosplenomegaly, periportal fibrosis, glomerulonephritis, and calcification of the bladder. Three species are associated with most human infections: *Schistosoma mansoni*, *S. haematobium*, and *S. japonicum*. It is estimated that 200 million people worldwide are afflicted with schistosomiasis (336).

There are reports suggesting a link between blood group A and increased susceptibility to schistosoma infections, particularly *S. mansoni* (337–340). Ndamba et al. found that group A patients were three times more likely to have *S. mansoni* infection (30.7%, versus 10.1% of group O individuals) and had a 2-fold-higher rate of periportal fibrosis (Symmers fibrosis) (50.2%, versus 20.45% of group O individuals; $P < 0.005$) (337). Similar results were reported in two older Brazilian studies, which also found an association between hepatosplenic infection and group A (59%, versus 28% of group O individuals; $P < 0.001$) (338, 339). Group A individuals may be at higher risk for *S. japonicum* and *S. haematobium* infections as well (337, 340). It has been hypothesized that group A individuals are at an increased risk for *S. mansoni* infection due to the absence of anti-A antibodies. Haseeb et al. reported evidence that chemoattraction between adult flukes likely involves GalNAc epitopes on females (336). Anti-A may provide protection against *S. mansoni* by blocking GalNAc structures necessary for fluke mating.

LKE AND P1PK, GLOB, AND FORS BLOOD GROUP SYSTEMS

History and Evolution of the P Blood Group System

The system historically known as the "P blood group" was initially discovered in 1927 by Landesteiner and Levine after immunization of rabbits with human red cells (341). The resulting antibody recognized the P_1 blood group antigen, which was expressed on most, but not all, human red cells. The P^k and P antigens were added to the system after the discovery of rare null phenotypes. Over the last 15 years, the glycosyltransferases necessary for the synthesis of P^k, P, and P_1 antigens have been cloned. The P blood group has now expanded into three blood group systems and six serologic antigens, which are assigned based on the last glycosyltransferase necessary for their synthesis (1). P1PK encompasses P^k, P_1, and NOR antigens, which all share a terminal α1,4-Gal epitope. GLOB contains the classic P and PX2 antigens, which share a terminal β1,3-GalNAc epitope. FORS contains a single antigen, Forssman, present on rare A_{pae} cells (342). The LKE or Luke antigen is still classified under GLOB collection 209 (2). Globo-H and galactosylgloboside (Gb5; stage-specific embryonic antigen 3 [SSEA-3]) are immunologically active and can be recognized by human polyclonal antibodies on stem cells and other cell lines (38, 343).

Biochemistry and Synthesis

Unlike ABO and Lewis antigens, which can be found on both GSLs and glycoproteins, the antigens of the "P system" are present only as GSLs. Chemically, GSLs consist of a carbohydrate head group covalently linked to a ceramide lipid tail (Fig. 5), which anchors the molecule within the outer cell membrane. GSLs are generally classified into four families based on the sequence and anomeric linkages in the first 3 to 4 carbohydrates (globo, ganglio, lacto [type 1 chain], and neolacto [type 2 chain]). Most members of the "P family" are globo-family GSLs and share a Galα1-4Galβ1-4Glcβ-ceramide core (Table 7). This family includes P^k (globotriaosylceramide [Gb3]), P (globoside [Gb4]), Gb5, LKE (monosialylgalactosylgloboside [MSGG] [SSEA-4]), NOR, and Forssman antigens. In contrast, the P_1 and PX2 antigens are neolacto- or type 2 chain antigens derived from paragloboside (nLc4) (Table 7). The older literature sometimes refers to sialylparagloboside (SPG) as p antigen because its level is increased on rare p red cells (341).

GSL synthesis proceeds from the stepwise addition of sugars to LacCer (CDH), a precursor of nearly all neutral GSLs (Fig. 5). In the globo-family, α1,4-galactosyltransferase (α4GalT1) modifies LacCer to form Gb3/P^k antigen, the first globo-antigen. Gb3 can then serve as a substrate for β3GalNacT1, which adds a terminal β1→3GalNAc epitope to form Gb4/P antigen. The synthesis of long-chain globo-GSLs requires the synthesis of Gb5 by β3GalT5, a rate-limiting enzyme in the synthesis of both Gb5 and lacto-family GSLs (343, 344). Gb5 may be sialylated to form LKE/MSGG or fucosylated to form globo-H (type 4 ABH). Both FUT1 and FUT2 appear to be capable of fucosylating Gb5 (38–40), although FUT2 likely predominates in genitourinary tissue, a fact highly relevant to urinary tract infections. Gb5, globo-H, and LKE/MSGG are oncofetal antigens and can serve as stem cell markers in some tissues (345–347).

The P_1 antigen, like Gb3/P^k, is synthesized by α4GalT1 through the addition of an α1→4Gal epitope to paragloboside. Paragloboside can also serve as a substrate for β3GalNAcT1, which adds a β1→3GalNAc epitope to form PX2. Unlike P_1 antigen, PX2 is found in appreciable quantities only on rare p red cells (Table 7) (348). Both P_1 and PX2 are recognized by polyclonal anti-P^k and anti-P antibodies, respectively (348, 349).

In a few rare individuals, there can be synthesis of unusual globo-GSLs due to mutations in glycosyltransferase genes. NOR is a very rare phenotype due to a missense mutation in *A4GALT1* that permits Gb4 to serve as an acceptor. NOR red cells express P^k-Gb4 derivatives that possess a Gb4 core and a terminal α1-4Gal epitope (342) (Table 7). A related globo-GSL can be observed in 10% of platelet donors (band 0.03; Galα1-4–Gb5) and is associated with increased Gb3 synthesis (350, 351). The Forssman antigen is a common globo-GSL in animals (for example, chickens and sheep) but is absent from humans (352). Forssman is distinctive for a GalNAcα1-3GalNAcβ terminus that can react with polyclonal anti-A and anti-A lectins (81, 82). Trace amounts of Forssman are present on A_{pae} red cells due to a mutation in the *GBGT1* gene (G887→A or Q296→R) that restores enzyme activity (342, 352).

Many factors can inhibit or alter globo-GSL synthesis. Several compounds that inhibit GSL synthesis are available, leading to a global decrease in the rate of GSL synthesis (353). Targeted downregulation of globo-GSLs with 2-deoxy-D-glucose has been reported (354). Globo-GSLs are also sensitive to mutations and agents affecting Golgi function. Mutations in FAPP2 or treatment of cells with brefeldin leads to a loss of globo-GSL, with increased GM3 and LacCer levels (355, 356). Glycosyltransferases necessary for the synthesis of early precursors (GlcCer, LacCer, and GM3) reside in the endoplasmic reticulum and *cis*-Golgi network, whereas glycosyltransferases necessary for globo-GSL synthesis reside in the *trans*-Golgi network (357). There is evidence that α4GalT1 and LacCer synthase form an intra-Golgi complex to efficiently synthesize globo-GSLs (356).

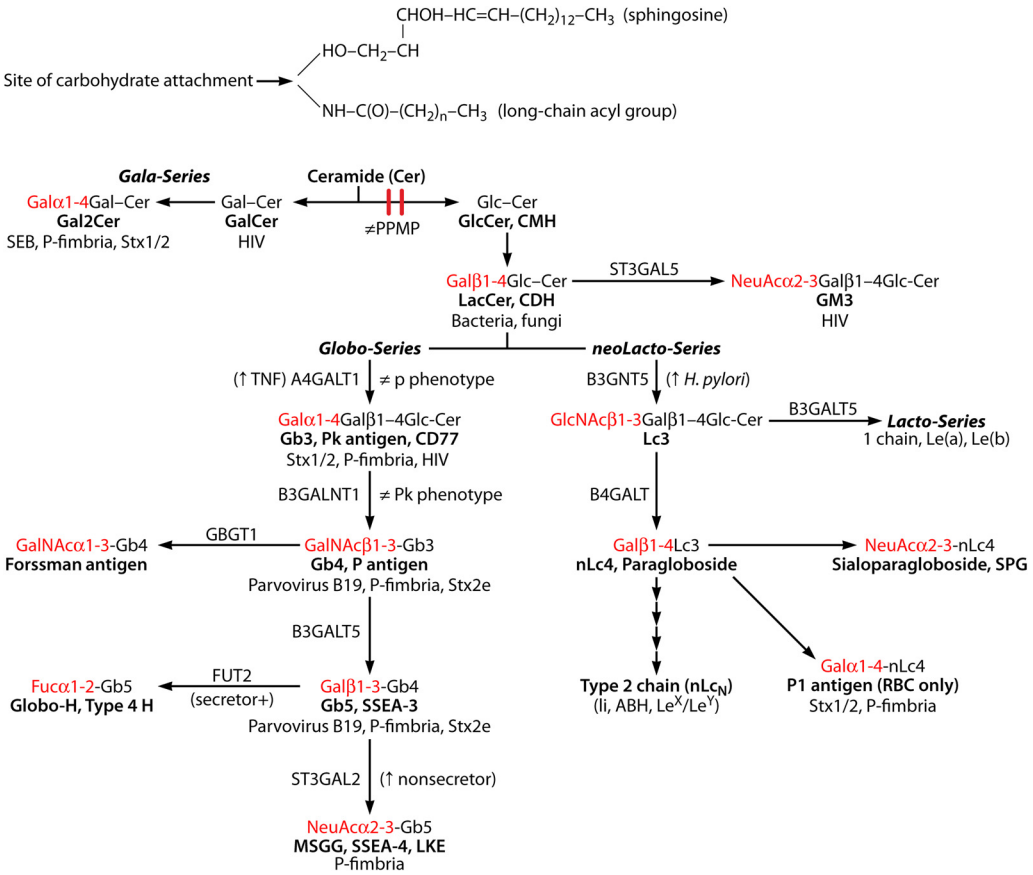

FIG 5 Synthesis of globo- and related neolacto- and gala-series GSLs. Also shown are agents capable of inhibiting GSL synthesis (PPMP), inducing enzyme expression (TNF and *H. pylori*), and inactivating mutations (P^k and p phenotypes). Microbial lectins recognizing GSL antigens are included.

Serology

With rare exceptions, all human red cells express both Gb3/P^k and Gb4/P antigens (Table 8). Gb4 is the predominant GSL, representing nearly 10% of the total red cell lipids (358). P_1 expression is the most common red cell polymorphism encountered. Serologically, individuals are typed as P_1 (P_1^+) or P_2 (P_1^- P^+) based on the presence or absence of P_1 antigen (Table 8). P_1 is the most common phenotype, with the highest incidence in blacks, whereas P_2 predominates in areas of China (Table 2). P_2 red cells are reported to have higher Gb3 levels than do P_1 cells (359).

LKE expression also varies between individuals, with 80 to 90% of individuals being typed as LKE strong, 10 to 20% being typed as LKE weak, and 1 to 2% being typed as LKE negative (Table 8) (360). LKE-negative individuals still express trace quantities of LKE/MSGG, often accompanied by a 2- to 3-fold increase in Gb3 levels (360). Variation in Gb3 and LKE is also observed in platelets (351). In other tissues, LKE/MSGG can be suppressed by *FUT2*, which favors the synthesis of globo-ABH (Fig. 5). Nonsecretors have the highest LKE/MSGG levels on the genitourinary epithelium (361).

Rare Phenotypes

P^k phenotype. The P^k phenotype is an autosomal-recessive phenotype due to homozygous *B3GALNT1*-null alleles (Table 8). Individuals with this phenotype lack Gb4 and more-complex globo-GSLs (for example, Gb5, LKE, and globo-H) and make potent anti-P that can cause hemolytic transfusion reactions and spontaneous abortion (29, 340). P^k red cells show increased Gb3, LacCer, and neolacto-GSL expression (361, 362). P^k can occur on either a P_1 (P_1^k) or P_2 (P_2^k) background. There are no known physiologic abnormalities associated with the P^k phenotype, although the marked increase in Gb3/P^k expression may represent a host risk factor for *Streptococcus suis* and Shiga toxin (Stx)-related infections (Table 7). In mice, deletion of *B3GALNT1* is embryonic lethal (715).

The *B3GALNT1* gene was cloned in 1998 and was originally identified as a β1,3-galactosyltransferase (β3GalT3) (342). It was renamed *B3GALNACT1* after mutations in the enzyme were linked to the P^k phenotype. This gene is ubiquitously expressed in most tissues (35). Seven null alleles associated with the P^k phenotype have been reported to date (2).

p and NOR phenotypes. The p phenotype is a true globo-null phenotype due to amorph *A4GALT1* alleles (Table 8). The GSLs from p red cells resemble granulocytes, with high concentrations of LacCer, paragloboside, and sialylparagloboside (364). Individuals with this phenotype also synthesize appreciable quantities of PX2 (348). Red cells from heterozygous individuals (*A4GALT1*$^{+/-}$) appear to have normal GSL expression (364). It is not known whether a dosage effect is present in nonerythroid tissues. Serum from p individuals contains potent naturally occurring antibodies against P, P_1, and P^k (Table 8) (29, 341).

The p phenotype occurs sporadically in many populations and

TABLE 7 Globo-, gala-, and related neolacto-GSLs[a]

GSL	Alias(es)	GSL structure	GSL binding[b]						
			Stx1/2	SEB	*S. suis*	PA-IL	PapG	Parvovirus B19	HIV
Gala-GSL									
GalCer	Cerebroside	Gal-Cer							+
SO_4-GalCer	Sulfatide	SO_4-Gal-Cer							+
Gal_2Cer	Galabiosyl-Cer	Galα1-4Gal-Cer	+	++	+		+		
LacCer	CDH	Galβ1-4Glc-Cer							+
GM3		NeuAcα2-3Galβ1-4Glc-Cer							+
Globo-GSL									
Gb3	P^k, CD77	Galα1-4Galβ1-4Glc-Cer	++		++	+	+		+
Gb4	P, globoside	GalNAcβ1-3Galα1-4Galβ1-4Glc-Cer	w+		+		+	++	
Gal-Gb4	NOR1	Galα1-4GalNAcβ1-3Galα1-4Galβ1-4Glc-Cer	?				+		
Forssman	Forssman	GalNAcα1-3GalNAcβ1-3Galα1-4Galβ1-4Glc-Cer					+	+	
Gb5	SSEA-3	Galβ1-3GalNAcβ1-3Galα1-4Galβ1-4Glc-Cer					+	+	
Fuc-Gb5	Globo-H	Fucα1-2Galβ1-3GalNAcβ1-3Galα1-4Galβ1-4Glc-Cer					+		
MSGG	LKE, SSEA-4	NeuAcα2-3Galβ1-3GalNAcβ1-3Galα1-4Galβ1-4Glc-Cer					++	+	
Gal-Gb5	Band 0.03	Galα1-4Galβ1-3GalNAcβ1-3Galα1-4Galβ1-4Glc-Cer	+				+		
Neolacto-GSL									
Lc3		GlcNAcβ1-3Galβ1-4Glc-Cer							
nLc4	Paragloboside	Galβ1-4GlcNAcβ1-3Galβ1-4Glc-Cer							
αGal-nLc4	P1	Galα1-4Galβ1-4GlcNAcβ1-3Galβ1-4Glc-Cer	+		+	+	+		
GalNc-nLc4	PX2	GalNAcβ1-3Galβ1-4GlcNAcβ1-3Galβ1-4Glc-Cer							
NeuAc-nLc4	SPG	NeuAcα2-3Galβ1-4GlcNAcβ1-3Galβ1-4Glc-Cer							

[a] Abbreviations: Cer, ceramide; Fuc, fucose; Gal, galactose; GalNAc, *N*-acetylgalactosamine; Glc, glucose; GlcNAc, *N*-acetylglucosamine; NeuAc, *N*-acetylneuraminic acid; SSEA, stage-specific embryonic antigen; SPG, sialylparagloboside. The underlining represents the critical Galα1-4Gal linkage that is shared by all globo-GSLs.
[b] + indicates recognition and binding to specific GSLs. Strong binding is indicated by ++. w+ indicates weak binding, and ? indicates unknown/not tested.

is more frequently encountered than P^k. Northern Europe has the highest incidence of p individuals where populations were relatively isolated by geography (29, 341). In the United States, p is most often encountered among Amish communities. The p phenotype is not associated with any known physiologic or congenital abnormalities, and individuals with this phenotype may display increased resistance to several infections, including parvovirus, *Shigella*, and enterotoxigenic and uropathogenic *E. coli*. In mice, the absence of globo-GSLs is associated with increased susceptibility to sepsis (see the section on innate immunity and Toll receptors, below).

A4GALT1 resides on chromosome 22q13 and is widely expressed in most tissues (2, 35). This gene contains 3 exons, although exon 3 encodes the active enzyme (342). A mutation (C631→G), leading to Q211→E, is responsible for the NOR phenotype (342). The basis for the P_1/P_2 polymorphism is still not entirely resolved. An early study from Japan reported an association between P_2 and a polymorphism in the promoter region

TABLE 8 P blood group phenotypes

Type	Incidence (%)	Glycosyltransferase gene[a]			GSL expressed on RBC[c]							
		A4GALT1	*B3GALNT1*	*GBGT1*	CDH	Gb3	Gb4	Gb5	MSGG	P_1	Other	Antibody
P_1	80[b]	+	+	0	+	+	+++	tr	+	+		
P_2	20[b]	+	+	0	+	+	+++	tr	+	0		Anti-P_1
LKE-S	80–90[b,d]	+	+	0	+	+	+++	tr	+	+/0		
LKE-W	10–20[b,d]	+	+	0	+	+	+++	tr	↓	+/0		
LKE-N	1–2[b,d]	+	+	0	+	++	++	tr	tr	+/0		Anti-LKE (rare[e])
P_1^k	Rare	+	0	0	++	+++	0	0	0	+		Anti-P
P_2^k	Rare	+	0	0	++	+++	0	0	0	0		Anti-P
p	Rare	0	+	0	+++	0	0	0	0	0	PX2	Anti-PP_1P^k (Tj^a)
NOR	Rare	+	+	0	+	+	+++	NA	NA	+/0	NOR	
A_{pae}	Rare	+	+	+	+	+	+++	NA	NA	+/0	Fors	

[a] Inheritance of at least one functional glycosyltransferase gene (+).
[b] Incidence in the U.S. white population. See Table 1 for distributions in other populations.
[c] Relative GSL expression on red cells. See Table 7 and Fig. 5 for structures and biosynthetic relationships. ↓, decreased; tr, trace.
[d] LKE frequencies as summarized by Cooling and Kelly (360). Note that LKE is independent of P_1 expression. The LKE type can occur on either the P_1 or P_2 background.
[e] See reference 363.

(−551insC, −160A), although this was not universally true for Europeans (365, 366). A subsequent study identified a minor *A4GALT1* transcript arising from an alternate exon and transcription start site (367). The transcript included an additional 28-amino-acid peptide and contained a single SNP linked to the P_2 phenotype and lower *A4GALT1* mRNA levels. Furthermore, there was evidence of gene dosage, with the lowest level of activity in P^2/P^2 individuals. The p phenotype has been associated with a variety of mutations, with ~30 known null alleles (2).

Tissue Distribution

The P_1 antigen is red cell specific and is labile during storage at 4°C (341, 350). In contrast, Gb3/P^k and Gb4/P antigens are widely expressed on tissues, particularly those arising from the embryonic mesoderm (368, 369). These antigens are major neutral GSLs on red cells, platelets, lymphocytes, endothelium, kidney, heart, lung, and smooth muscle (368). They are absent on mature granulocytes, although they are present on early myeloid precursors and circulating monocytes (370). Gb3 and Gb4 are minor GSLs in intestinal mucosa, with some investigators attributing their presence to contaminating smooth muscle in mucosal scrapings (111, 368). Strong globo expression, including globo-H and LKE, is a feature of genitourinary tract tissue (38, 39, 361, 368, 371).

In many tissues, globo-GSLs are relatively cryptic and undetectable by routine flow cytometric or immunofluorescence methods using IgM monoclonal antibodies (372, 373). Neutral GSLs, in particular, are susceptible to masking by membrane gangliosides and sialylated glycoproteins (373). To enhance detection, cells can be enzymatically treated with proteases or neuraminidase (360, 373). Expression levels may vary between cells due to differential GSL synthesis during the cell cycle, cell activation, and differentiation (374–378). Fresh (or frozen) tissue should be used for immunological analysis and isolation (369). Paraffin-embedded tissues should never be used, since this process involves organic solvents and may elute lipid-based antigens.

Lipid Rafts

A natural property of GSLs is their tendency to repel glycerophospholipids, resulting in the formation of highly ordered, hydrophobic microdomains or "rafts" enriched in sphingomyelin, GSLs, and cholesterol (379, 380). It is estimated that the localized sphingomyelin/GSL content in lipid rafts is 50% higher than that in the rest of the membrane (379). Rafts are resistant to disruption by detergents, leading to the terms "detergent-resistant membrane," "detergent-insoluble glycolipid complexes," or glycolipid-enriched microdomains (GEMs). This feature of rafts is due to a dense, rigid lateral concentration of tightly packed, saturated lipids with extensive intermolecular hydrogen bonds. Raft properties are profoundly influenced by the type and concentration of individual GSL species synthesized by individual cell types (379, 380). Finally, cholesterol is critical to raft integrity, which acts as a "filler" or molecular spacer between sphingolipid molecules. The disruption or loss of cholesterol by agents such as β-methyl cyclodextrin disrupts raft integrity.

Rafts are highly dynamic and coordinate several physiological processes, including signal transduction, endocytosis, receptor trafficking, and innate immunity (379–382). They are known to serve as an organizing platform for transmembrane receptors, Src family kinases, and cytoskeletal elements (379, 380, 383). In some cells, rafts serve as glycosynapses capable of carbohydrate-carbohydrate recognition and signaling (384, 385). Because of their unique hydrophobic properties, many integral membrane proteins are preferentially located on or recruited to rafts (380–383). These proteins include multipass proteins, integrins, and glycosylphosphatidylinositol (GPI)-linked glycoproteins. Blood group antigens located on or recruited to rafts include the CD55/Cromer, CD44/Indian, band 3/Diego, aquaporin 1/Colton, and, possibly, DARC (Duffy antigen receptor for chemokines)/Duffy blood groups.

GEMs enriched in globo-GSLs have been identified in several cell types. Human red cells contain large GEMs rich in Gb4 (386). Gb4- and Gb3-rich GEMs contribute to the binding and uptake of Shiga toxins, parvovirus B19, and HIV and inflammatory signaling (387, 388). Neutrophils and monocytes are rich in LacCer, which contributes to chemotaxis, phagocytosis, and superoxide generation (369, 381, 382). GEMs containing Gb5 and globo-gangliosides are found on embryonic stem cells and cancer cells, where they may contribute to oncogenic potential and metastasis (389–391).

Globoside and the Innate Immune System

LPS is a bacterial glycolipid composed of a glycosylated O-antigen head group linked to lipid A (392). The lipid A molecule is highly hydrophobic, consisting of a β-1′,6-linked glucosamine disaccharide bearing up to six long fatty acid acyl chains. Because lipid A is a feature shared by all Gram-negative bacteria, it is recognized as a conserved microorganism-associated molecular pattern (MAMP) by the innate host defense system (96, 392).

A pattern recognition receptor that interacts with lipid A is the Toll-like receptor 4 (TLR4)-MD2 complex on leukocytes and other phagocytic cells (392). MD2 binds the lipid A moiety within a deep hydrophobic cavity. Upon binding, LPS can trigger endocytosis of the LPS-TLR4-MD2 complex or can activate an MD88-dependent signaling pathway, leading to intense inflammation accompanied by many of the clinical findings associated with Gram-negative sepsis. Differences in the number and composition of lipid A acyl chains can modify and temper the inflammatory response to LPS (392).

Recently, Gb4 was identified as an endogenous ligand for TLR4-MD2 (393). Preliminary evidence came from studies in *A4GALT1* knockout mice, which lack all globo-GSLs (p phenotype) but have normal TLR4-MD2 expression. When challenged with LPS, $A4GALT1^{-/-}$ mice developed severe inflammation and had significantly higher mortality rates than did wild-type mice (70% versus 10%; $P = 0.068$). In wild-type mice, LPS upregulated *A4GALT1* transcription, leading to increased Gb4 synthesis and expression on cells (393). Furthermore, there was recruitment of TLR4-MD2 into Gb4-enriched GEMs. Treatment of $A4GAT1^{-/-}$ mice with exogenous Gb4 reduced LPS-induced inflammation and end-organ tissue damage. MD2 appears to bind Gb4 primarily via the ceramide lipid tail, with additional hydrogen bonds between MD2 and the oligosaccharide head group. Kinetic assays indicate that Gb4 and LPS are noncompetitive inhibitors, binding MD2 at slightly different sites. Compared to LPS, Gb4 is a relatively weak ligand (K_d of 238 μM, versus a K_d of 1 μM for LPS).

The mechanism by which Gb4 moderates the TLR4-MD2 inflammatory response may be analogous to that of other lipid A antagonists. LPS with fewer acyl chains can evade or block TLR4 signaling due to altered MD2 binding. This is observed in many pathogens (i.e., *Y. pestis*) and is the primary mechanism by which

lipid A is detoxified *in vivo* (393). Ceramide, with only two acyl chains, is sufficiently hydrophobic to block LPS-MD2 binding but is unable to induce inflammation via the MD88 pathway (393). TLR4 is most strongly expressed by monocytes, spleen, and placenta, which also express Gb4 (368, 369). Gb4 is also present in plasma (368). There is evidence linking TLR4 signaling with P fimbria binding to uroepithelium (394). P fimbriae bind Gb4 and other globo-GSLs (see below).

Uropathogenic *E. coli*

E. coli is the most common cause of urinary tract infections (UTIs), accounting for 80 to 90% of all cases in otherwise healthy individuals (395). Uropathogenic *E. coli* strains express a variety of virulence factors, including several adhesins (P, type 1, S, and Dr) necessary for bacterial colonization. P fimbria is a particularly important adhesin and is expressed by nearly 100% of strains associated with pyelonephritis (395). P-fimbriated *E. coli* is able to bind the uroepithelium as well as proximal renal tubules, glomerular epithelium, and vascular endothelium (396, 397). P fimbriae not only facilitate multivalent bacterial adhesion to uroepithelium but also stimulate the release of inflammatory mediators through ceramide and Toll-like receptor (TLR4) pathways (394, 398, 399). In human volunteers, recombinant P-fimbriated *E. coli* specifically provoked increases in IL-8 and IL-6 levels and pyuria (400).

Structurally, P pili are composed of a long heteropolymeric protein fibrillum bearing the PapG adhesin at the fimbrial tip (401). The PapG lectin binding domain is relatively large and lies along one side of a folded, "jelly roll" structure (402). The minimum P-fimbria epitope is a Galα1-4Gal disaccharide present on all globo-series GSLs (Table 7) as well as digalactosylceramide and P_1 antigen (403). The physiological epitope, however, is larger, encompassing between 3 and 4 oligosaccharides (402). Several PapG variants are known, which are classified into three subgroups based on hemagglutination and relative binding to globo-GSLs (404, 405). PapGI generally favors Gb3/P^k, PapGII prefers Gb4/P antigen, and PapGIII recognizes extended globo-GSLs. Despite this classification, there is considerable overlap in receptor binding between the three PapG types (404, 405). PapGII and PapGIII variants are found in human *E. coli* isolates. Uropathogenic *E. coli* strains frequently harbor more than one *pap* gene (406).

Early studies searching for host genetic factors compared the incidence of UTI with P_1/P_2 status, despite the fact that P_1 is a trace, red cell-specific GSL and is not expressed on uroepithelium. Older studies tend to support some increased risk among P_1 children, whereas P_1/P_2 has little impact in adults. An initial study of 28 female children with recurrent UTI showed a slight increase in the incidence of the P_1 phenotype (27/28; 96%, versus 75% of controls; $P < 0.02$) (407). A follow-up study with 68 female children with recurrent pyelonephritis again showed an increase in the incidence of P_1 in patients with mild reflux (97%; $P < 0.01$) and bacteriuria (68% versus 25%; $P < 0.001$) but not in children with severe reflux (408). Ziegler et al., on the other hand, found no increase in the prevalence of P_1 among 53 adult women with *E. coli* UTI, although P_1 individuals tended to have a longer history of disease, more frequent episodes, and more renal damage (409). Likewise, no correlation between P_1 and recurrent UTI in adult females was reported by Sheinfeld et al. (410). A P_1 phenotype is also not associated with increased *E. coli* binding to uroepithelial cells by flow cytometry (397). It is important to note that all these older studies relied on serologic P_1 typing, which varies in strength between P_1 individuals. Given new evidence that *A4GALT1* mRNA, P^k, and P_1 are influenced by gene dosage, it may be useful to reexamine the risk of *E. coli* UTI by P^1/P^2 genotype.

Like *Candida* vaginitis, *E. coli* infection is influenced by host secretor type. Sheinfeld et al. serologically phenotyped 49 Caucasian women and found a 3.4-fold increased risk of recurrent UTI in Le(b−) individuals or presumed nonsecretors (410). Similar findings were reported by Biondi et al., who reported a 26-fold increased risk of UTI in pregnant women who were typed as nonsecretors (76%, versus 12% of controls) (411). The impact of the nonsecretor phenotype, however, is tempered by reproductive and hormonal status. In a study of Japanese women, pyelonephritis was associated with a nonsecretor phenotype in premenopausal women only (57% versus 30%; $P < 0.001$) (412). This is consistent with the known epidemiology of *E. coli* UTI and vaginal colonization in women, which is much more likely to occur during the first half of the menstrual cycle as estrogen levels are rising (413–415). Estrogen can increase *E. coli* adherence to epithelial cells *in vitro* and *in vivo* and is known to upregulate *FUT2* expression in genitourinary tissues (225, 415, 416).

UTIs are also extremely common in young pediatric patients, with an average incidence of 7 to 8% in the first year of life (417). Some of this risk could reflect developmental delays in FUT2 activity, with the majority of neonates being typed as Le(a−b−) or Le(a+b+) (1, 28). Jantausch et al. studied 62 children with UTI, including 34 children <1 year of age and 41 children <2 years old (418). Children who were typed as Le(a−b−) had a 3.2-fold relative risk of UTI. This study was particularly interesting since 60% of children studied were black, a population with a lower incidence of UTI than whites ($P = 0.007$) (417, 419). In older children, the nonsecretor phenotype is associated with a heightened inflammatory response and an increased risk of renal scarring (420, 421). Nonsecretors with *E. coli* UTI had both elevated levels of C-reactive protein ($P = 0.02$ to 0.01) and an elevated erythrocyte sedimentation rate ($P = 0.02$) (420).

FUT2 is able to decrease the risk of UTI from P-fimbriated *E. coli* strains due to direct interference with globo-ganglioside synthesis (Fig. 5). Although P-fimbriated *E. coli* strains can bind a range of globo-GSLs, quantitative studies with isolated kidney GSLs show a clear preference for the globo-ganglioside MSGG, also known as LKE antigen and SSEA-4 (422). *E. coli* strains, regardless of the PapG type, exhibit significantly greater binding to MSGG than to Gb3, Gb4, and disialogalactosylgloboside (DSGG). *E. coli* binding to MSGG can also be demonstrated by immunohistochemistry (423). A preference for MSGG/LKE, a developmentally and tissue-restricted antigen, might explain the tropism of P-fimbriated *E. coli* for genitourinary tissues. MSGG synthesis is highly dependent on β3GalT5, a tissue-restricted β1,3-galactosyltransferase responsible for both type 1 chain precursor (Le^C) (Fig. 5) and galactosylgloboside (Gb5) synthesis (344, 424). The genitourinary epithelium expresses both globo- and β3GalT5 glycosyltransferases necessary for synthesizing MSGG and type 1 chain antigens (35, 368, 371).

Stapleton et al. were the first to show that Secretor is able to decrease MSGG levels on the vaginal epithelium (361). In nonsecretors, MSGG was identified on 100% of cells by immunofluorescence microscopy, whereas no detectable MSGG was observed in Se^+ individuals. MSGG was also identified in vaginal GSLs isolated from nonsecretors, but not secretors, by thin-layer chromatography using both an anti-MSGG antibody and radiolabeled

P-fimbriated *E. coli*. Stapleton et al. hypothesized that FUT2 competes for Gb5, leading to preferential synthesis of type 4 ABH antigens. In the absence of FUT2, Gb5 is sialylated to form MSGG.

The ability of *FUT2* to divert Gb5 toward the synthesis of ABH-active globo-GSLs raises the question of whether the host ABO type also affects *E. coli* adhesion. Some PapGIII strains were reported to have ABO specificity, hemagglutinating group A and sheep red cells (Forssman antigen) but not group O cells (425). By thin-layer chromatography, these strains strongly bound MSGG, Forssman antigen, and globo-A (type 4 A) but did not recognize A antigen on type 1 or type 2 chain backbones (A-1-6, A-2-6, and ALe^b-7) (422, 425). There were also early reports that the LKE-weak phenotype was increased in group A and AB individuals, although these findings were not confirmed by later studies (360, 426).

In general, there is no strong evidence that ABO type contributes to clinical UTI. No study has linked a group A Se^+ phenotype with increased UTI risk. Kinane et al. reported that group B and AB nonsecretors had a 3-fold increased risk of UTI (427). A much later German study also reported a higher rate of recurrent UTI among group B women (23% versus 14.5%) (409). These studies speculated that group B nonsecretors could have a cumulative increased risk due to (i) an absence of anti-B that might react with B-like epitopes on *E. coli* LPS (81, 427) and/or (ii) an absence of αGal epitopes on secreted mucins, which could theoretically serve as a weak, false receptor (409). Other studies, however, found no association between UTI and patient ABO type (410, 411, 418). Likewise, human anti-A and anti-B failed to agglutinate several *E. coli* serotypes commonly isolated from *E. coli* UTIs (428).

Shigella, Enterohemorrhagic *E. coli*, and Shiga Toxins

Shigella is an enteroinvasive, pathogenic, Gram-negative bacillus and a cause of bacillary dysentery. Infections with *Shigella dysenteriae* type 1 are particularly serious due to copious production of Shiga toxin (Stx) (429). Clinically, *S. dysenteriae* is a serious, potentially life-threatening illness characterized by fever, leukocytosis, abdominal cramps, painful defecation, and a bloody, mucoid diarrhea. Infected patients can develop dysentery and rapid dehydration, sepsis, seizures, and acute renal failure. During epidemics, the mortality rate can reach 5 to 15%, especially among the very young (430). Hemolytic-uremic syndrome (HUS) occurs in 13% of patients and is strongly associated with antibiotic treatment, which can increase Stx production (431). *S. dysentariae* HUS has a 36% mortality rate and is a leading cause of death in outbreaks (431).

HUS is also a common complication following infection with enterohemorrhagic *E. coli* (EHEC). Unlike *Shigella*, EHEC strains are not invasive, but they do carry Stx-type toxins on antibiotic-inducible lambdoid prophages (432). HUS occurs in 5 to 15% of patients, with the highest rate of occurrence being found in young children and the elderly (433). Like *S. dysenteriae*, exposure to antibiotics can raise the risk of HUS through increased Stx production and bacterial lysis (433). Although EHEC-associated HUS has a low mortality rate (3 to 5%), it carries a significant risk of long-term renal insufficiency (25%) and renal failure (12%) (433).

Like CTx and hLT, Stxs are AB_5 toxins composed of a biologically active A subunit and five B subunits responsible for lectin-mediated binding to target tissue (429). Actively proliferating cells are more sensitive to toxin due to differential synthesis and expression of GSL receptors during the cell cycle (375, 376). Once bound, B subunits trigger cell signaling and receptor-mediated endocytosis with retrograde transport to the endoplasmic reticulum (434). Within the endoplasmic reticulum, the A subunit undergoes enzymatic processing to produce the catalytically active form of the toxin (A_1 [27 kDa]), an rRNA *N*-glycosidase (429). Like ricin, the A_1 subunit cleaves a critical adenine on 28S rRNA, with inhibition of protein synthesis. Ribosomal toxicity is accompanied by the induction of stress-activated protein kinases and inflammatory mediators (IL-1, IL-6, and TNF-α) that can further hamper normal protein synthesis (435). Finally, there is activation of apoptosis with cleavage and degradation of DNA (435).

Stx can be classified into two major categories: Stx1 and Stx2. Stx2 shares ~56 to 60% sequence homology with Stx1 in both the A and B subunits (429). *S. dysenteriae* always expresses Stx1, whereas EHEC can express either Stx1 or Stx2 (429). In general, Stx recognizes GSLs bearing a terminal galabiose or Galα1-4Gal disaccharide (350, 436). These GSLs include P_1, Gb3, galabiosylceramide (Gal_2Cer), and an extended globo-GSL, "band 0.03." The latter is a trace GSL, related to MSGG/LKE, found on some platelet donors (350). Stx1 and Stx2 also display weak binding to Gb4 by thin-layer chromatography, enzyme-linked immunosorbent assays (ELISAs), and surface plasmon resonance (350, 437, 438). Gb3 is considered the primary physiological receptor for Stx1 and human Stx2 strains (Stx2, Stx2c, and Stx2d). Stx holotoxin may bind between 5 and 15 molecules of Gb3 (439).

Clinically, there is a good correlation between Gb3 expression and disease. The gut epithelium expresses Gb3, although it is a minor GSL (111, 350, 368). Stx is toxic to colonic epithelial cell lines and can induce colonic secretion in animal models (378, 387, 433). Epithelial necrosis and hemorrhage permit Stx to enter the circulation, where it can target the renal endothelium and epithelium, with development of HUS (435). The renal epithelium is especially rich in globo-GSLs and galabiosylceramide (350, 368, 440). Stx-mediated renal damage leads to localized inflammation, with recruitment of neutrophils and platelets, complement and platelet activation, thrombosis, microvascular hemolysis, vasoconstriction, and pigment nephropathy (435). Stx can also bind monocytes, with the release of inflammatory mediators, which upregulates Gb3 on adjacent tissue, thereby amplifying Stx toxicity (433, 435). Finally, Stx binds to a subset of platelets, with platelet activation and the formation of platelet-leukocyte aggregates (350, 441, 442).

Although $Gb3/P^k$ is necessary for Stx binding, Gb3 expression is not sufficient to explain the targeted sensitivity of kidney and other tissues. Toxicity is also influenced by the Stx subtype, Gb3 characteristics, other membrane GSLs, and lipid raft composition. A comparison of Stx1 and Stx2 shows very different binding affinities and dissociation constants for Gb3. Stx1 has a 10-fold-higher binding affinity than does Stx2; however, Stx2 has a very low dissociation rate, which favors toxin uptake (438). As a result, Stx2 is 1,000-fold more toxic against endothelial cells and more frequently associated with EHEC HUS (435). Subtle differences in ceramide composition, including the size of the fatty acid acyl group, also impact Gb3-Stx binding and intracellular trafficking (434, 437, 443). Other membrane GSLs can also alter the sensitivity of tissues to Stx. Both cholesterol and GlcCer enhance Gb3-Stx binding (437, 438) and promote raft formation (379, 380), endocytosis (443), and cytotoxicity (444). In contrast, asialo-GM2 and asialo-GM1 depress Stx-Gb3 binding (437), and neolacto-GSLs

can interfere with GEM formation (445). Gb3-enriched GEMs are critical to Stx membrane signaling, uptake, and internalization via caveola- and clathrin-dependent endocytosis (383, 387, 443).

Patient-specific differences in Gb3/P^k expression or availability may also play a role. In epidemic outbreaks, only 20 to 30% of infected individuals go on to develop HUS (433, 435). Young children (<5 years of age) are more likely to develop HUS than are adults and show more diffuse Stx binding to renal glomeruli (435). Limited studies on human endothelial cells have shown some donor-specific differences in Stx cytotoxicity (446). Likewise, we have documented distinct inherent platelet glycotypes among normal blood donors, where the level of Gb3/P^k can range from <5% to 40% of the total platelet neutral GSL (350, 351). In platelets, 30% of donors possess a globo-rich platelet glycotype reminiscent of kidney epithelium (Gb3 ~ Gb4 ≫ LacCer), including 13% who expressed Stx receptor band 0.03 (350, 351). Conversely, nearly half (52%) of normal donors have very little Gb3 or Gb4 on platelet membranes.

Globo-null mice are resistant to Stx (447); however, the risk and outcomes in humans with variant globo types is unknown. Like *A4GALT1* knockout mice, p individuals should be inherently resistant to Stx-mediated disease, whereas P^k individuals should be more susceptible due to elevated Gb3 levels on endothelium, kidney, and other tissues. LKE-negative individuals may also be at increased risk, assuming that elevated Gb3 expression is also present on nonerythroid tissues such as the endothelium (350, 360). It should be noted that many Stx-sensitive immortalized cell lines (for example, ACHN, Caco-2, and Daudi) possess a "P^k-like" phenotype where Gb3 ≫ Gb4 (363, 387, 448).

Several small studies compared the incidences of P_1/P_2 phenotypes in patients with *E. coli*-associated HUS, with very mixed results. Two studies suggested that the P_1 phenotype may be protective (449, 450). Taylor et al. examined 32 patients following recovery from *E. coli* HUS and reported an association between poor renal function and P_2 and P_1^{weak} phenotypes (6/7 patients; $P < 0.05$) (449). In a second study of 32 children, Robson et al. found that P_2 children tended to be younger (24 versus 42.3 months of age; $P = 0.07$) and had a shorter duration of colitis (2.3 versus 5.6 days; $P = 0.02$) (450). Three studies from Japan, Manitoba, Canada, and Scotland involving 108 patients found no correlation between P_1/P_2 type, *E. coli* HUS risk, and clinical outcome (451–453). Finally, a study from the *E. coli* O157:H7 network in the northwestern United States suggested that P_1, especially strong P_1 expression, may represent an HUS risk factor (454). In multivariate analysis, P_1^{strong} individuals had a 6.3-fold risk of developing HUS over P_2 individuals. In logistic regression analysis, a P_1 type was associated with a 4-fold risk of developing HUS (OR, 4.44; 95% CI, 1.2 to 16.4; $P = 0.012$).

Two studies have compared ABO types and *E. coli* HUS. The largest study was performed by Shimazu et al., following an epidemic outbreak that infected 9,523 patients, with 121 cases of *E. coli* HUS (455). Of the latter cases, the authors were able to obtain records for 49 patients. Among HUS patients, regardless of age, there was an increase in the prevalence of group A (59% versus 38%; $P < 0.01$) and a decrease in the prevalence of group B (16% versus 22%; $P < 0.05$) relative to the normal population. There was no correlation between ABO type and severity of illness or long-term sequelae. The authors of this study speculated that the B antigen might act as a false receptor for Stx. This question was specifically examined by the *E. coli* O157:H7 surveillance network (454). They found no significant difference in distribution or disease severity by patient ABO type.

Streptococcus suis

Streptococcus suis is a Gram-positive coccus and a highly infectious veterinary pathogen (456, 457). In pigs, *S. suis* infection can cause pneumonia, meningitis, septicemia, and endocarditis. Zoonotic illness has been reported in humans, particularly in areas with dense livestock operations and heavy pork consumption. Like pigs, *S. suis* can cause serious infections, with sepsis, purulent meningitis, endocarditis, and arthritis. In a large outbreak in China affecting 215 individuals, meningitis occurred in nearly half of patients (48%), followed by sepsis (28%), streptococcal toxic shock syndrome (28%), hepatic insufficiency (74%), disseminated intravascular coagulopathy, and death (456). Zoonotic transmission in humans may occur by direct contact with infected blood and tissues or potentially by droplet exposure during slaughter and processing. Not surprisingly, individuals at the highest risk are farmers and butchers, who have the greatest exposure to infected animals. To date, >400 human infections have been reported (456).

S. suis possesses several virulence factors, including a polysaccharide capsule, proteases, and adhesive proteins (457, 458). In pigs, the organism initially adheres to and colonizes the upper respiratory tract, followed by penetration and invasion into the bloodstream. Meningitis occurs as the organisms breach the blood-brain barrier, possibly by invading choroid plexus papilloma cells. *S. suis* may further compromise the blood-brain barrier by activating plasminogen and macrophages (458). Human and porcine meningitis are commonly caused by *S. suis* type 2 (457).

S. suis strains express a galactose-specific lectin, streptococcal adhesion P (SAdP) (459). The latter is a 76-kDa streptococcal wall protein with a classic LPXTG anchor motif and seven C-terminal tandem repeats (460). The galactose lectin domain lies near the amino terminus and has no homology with PapG or Stx (460). The lectin preferentially binds glycans with a terminal Galα1-4Gal disaccharide, although it is able to bind Galα1-3Gal epitopes as well. The latter would account for the strong hemagglutination of rabbit red cells (461), which express long, branched GSLs bearing Galα1-3Gal epitopes (462). Likewise, pigs express Gb3, isoGb3, and other Galα1-3Gal-active structures on the endothelium, providing several receptors for this organism (463).

Hemagglutination studies with human red cells show that this organism agglutinates P_1, P_2, and P^k red cells but does not agglutinate p (globo-null) cells (461). In addition, hemagglutination is enhanced after digestion of red cells with neuraminidase, which is consistent with a glycolipid receptor (464). By thin-layer chromatography analysis, the organism strongly bound Gb3, with some binding to galabiosylceramide, P_1, and Gb4 (464). Based on hemagglutination data alone, p individuals may have enhanced resistance to *S. suis*, although this has never been shown due to the rarity of the p phenotype in most populations. One potential study population is the Amish, a rural farming community with frequent exposure to animal livestock and local butchering. Any future *S. suis* outbreaks among European or North American Amish should be investigated relative to rare globo-null blood types.

Staphylococcal Enterotoxin B

Staphylococcal enterotoxin B (SEB) is a 28-kDa protein produced by *S. aureus* and is responsible for staphylococcal food poisoning.

In animals, SEB produces extensive inflammatory changes along small intestinal mucosa, with blunting of villi and inflammatory infiltrates (465). The toxin appears to interact with lamina propria T cells, resulting in T-cell activation and extensive cytokine release. Most of the toxin (75%) eventually enters the circulation, with rapid localization to the kidney and proximal renal tubules. In rhesus monkeys, SEB leads to increased renal vascular resistance and decreased renal function (466).

The GSL receptor for SEB is galabiosylceramide, a gala-series GSL (467, 468). Although not technically a blood group antigen, galabiosylceramide shares a Galα1-4Gal disaccharide and is capable of binding P-fimbriated *E. coli*, Stx, and *S. suis* (350, 403, 464). Galabiosylceramide is also tissue restricted, with detectable expression only on intestinal mucosa and kidney, both target organs for SEB (350). Even in these two tissues, galabiosylceramide is a minor neutral GSL (350, 468). SEB demonstrates high-affinity binding to renal tubular cells (467), whereas the intestinal mucosa shows scarce weak patchy binding to isolated lipid rafts (469). SEB binding to purified Gal_2Cer is biphasic, with high-affinity binding at low GSL concentrations in solid-phase assays (467).

Unlike CTx and Stx, SEB is a monomeric toxin, which may account for its apparent weak binding to lipid rafts (469). As a superantigen, SEB has a characteristic structure with two domains at each end of the molecule. Domain I (aa 127 to 120) has a classic "oligosaccharide β-barrel fold" found in CTx and pertussis toxin (470). Domain II (aa 127 to 239) contains the T-cell receptor binding site and a "β-grasp" motif composed of six antiparallel β-sheets. Surprisingly, the galabiosylceramide lectin domain is localized in domain II (aa 191 to 220), immediately adjacent to the T-cell binding site (aa 210 to 214) (470, 471). The β-grasp motif is present among many bacterial proteins involved in Gram-positive cell wall synthesis and is believed to be a conserved, ancestral polysaccharide/sugar binding domain (472). Sequences in domain II (aa 130 to 160) have also been linked to apoptosis, possibly through the sphingomyelinase/ceramide signaling pathway (471, 473).

Parvovirus B19

Parvovirus B19 is a nonenveloped, single-stranded DNA virus and a common pathogen in early childhood. Erythema infectiosum or "fifth disease" is typically characterized by fever, malaise, upper respiratory tract symptoms, rash, and transient arthralgias and is often accompanied by transient decreases in levels of red cells, platelets, and leukocytes (474). Parvovirus B19 can be a cause of pure red cell aplasia and is found in 27 to 40% of patients with aplastic anemia (475). During pregnancy, B19 can precipitate life-threatening anemia, fetal hydrops, and fetal death (476). B19 infection in patients with chronic hemolysis, such as sickle cell disease, can evolve into aplastic crises and bone marrow necrosis. Likewise, rates of B19 infection are 10-fold higher in malaria patients (14.2% versus 1.2%; $P < 0.0001$), and B19 contributes to anemia severity (477). In organ transplant patients, acute and chronic B19 infections have been reported in 18 to 31% of patients and can compromise long-term organ function (478–480).

Parvovirus has a particular affinity for early erythroid precursors, earning it the genus classification of *Erythrovirus*. It is not uncommon to observe characteristic ground-glass viral inclusions in marrow erythroblasts during acute infection. The virus's tropism for erythroblasts makes it particularly difficult to propagate *in vitro*, with most investigators using $CD36^+$ erythroid progenitors or erythroblastic cell lines (UT7/Epo-S1 and KU812Ep6). Successful infection requires capsid binding to noncaveolar glycolipid-enriched lipid rafts, followed by clathrin-mediated endocytosis and endosomal acidification (377). B19 infection is enhanced in the presence of chloroquine, an antimalarial which destabilizes endosomal membranes (377). Once released, B19 inhibits erythropoiesis by inducing cell cycle arrest necessary for viral replication, followed by apoptosis and viral release (481). As a consequence, patients experience anemia, reticulocytopenia, and marrow erythroid hypoplasia. Patients with erythroblast hyperplasia due to chronic hemolytic anemia (for example, sickle cell disease) are particularly susceptible to severe B19 infection.

The primary receptor for parvovirus B19 is globoside (Gb4; P). Brown et al. were the first investigators to demonstrate that B19 was capable of agglutinating red cells (482, 483). Moreover, hemagglutination was enhanced by trypsin treatment, a common method to expose glycolipid antigens (482). When tested against red cells of different P phenotypes, B19 agglutinated P_1 and P_2 cells but not P^k or p red cells (483). B19 was shown to bind Gb4 and Forssman antigen by thin-layer chromatography and HAI assays, although recognition of Forssman was 10-fold weaker than that of Gb4 (483). In addition to Forssman, B19 also weakly recognizes Gb5 and MSGG/LKE, two related extended globo-GSLs (368). In HAI experiments, Gb5 was as effective as Gb4 in inhibiting B19-induced hemagglutination (484). Gb4/P is expressed by most tissues capable of harboring B19 DNA, including platelets, endothelium, heart, liver, lung, and synovium (Fig. 6) (368, 370). In addition to Gb4, Ku80 and α5β1 integrin have been identified as possible coreceptors that may contribute to infection in some tissues and cell lines (485, 486).

B19-Gb4 binding appears considerably weaker than that of many other microbial adhesins. Hemagglutination, cell adhesion, and HPTLC immunostaining require, or are significantly enhanced by, incubation at 4°C (368, 482, 487, 488). At 37°C, nearly two-thirds of bound viral particles rapidly dissociate from cell membranes (Fig. 6) (487). The B19 capsid is composed of two related proteins, VP2 (95% capsid; 58 kDa) and VP1 (5%; 83 kDa), which is identical to VP2 except for a unique immunodominant 227-amino-acid N-terminal region (VP1u) (484). Data from studies with recombinant empty capsids suggest that VP2 is primarily responsible for hemagglutination, although hemagglutination is enhanced by the presence of VP1 (482). Inhibition studies with monoclonal anti-VP2 and cryo-electron microscopy mapped a possible Gb4 binding site that may accommodate up to three Gb4 molecules (489). More recent studies have failed to find evidence of specific VP2-Gb4 binding using microcalorimetry and surface plasmon resonance, stating that Gb4 must synergize with other coreceptors to mediate virus binding (484).

Attempts to elucidate the nature of the B19-Gb4 interaction have focused on VP1 and specifically the unique VP1 N-terminal domain. Capsids containing VP1 are more effective in hemagglutinating red cells than are VP2-only capsids (482). Moreover, VP1u peptides and anti-VP1u antibodies are capable of inhibiting B19 infection (490). VP1/VP2 capsids and VP1u peptides are able to bind UT-7 cells, with internalization and endosomal trafficking (488). Interestingly, the VP1u peptide is normally cryptic and inaccessible to anti-VP1u antibodies. It is hypothesized that B19 undergoes a conformational change upon binding to Gb4, with externalization of VP1u (Fig. 6) (487). The modified B19 virus may either detach or bind a secondary coreceptor, with stabiliza-

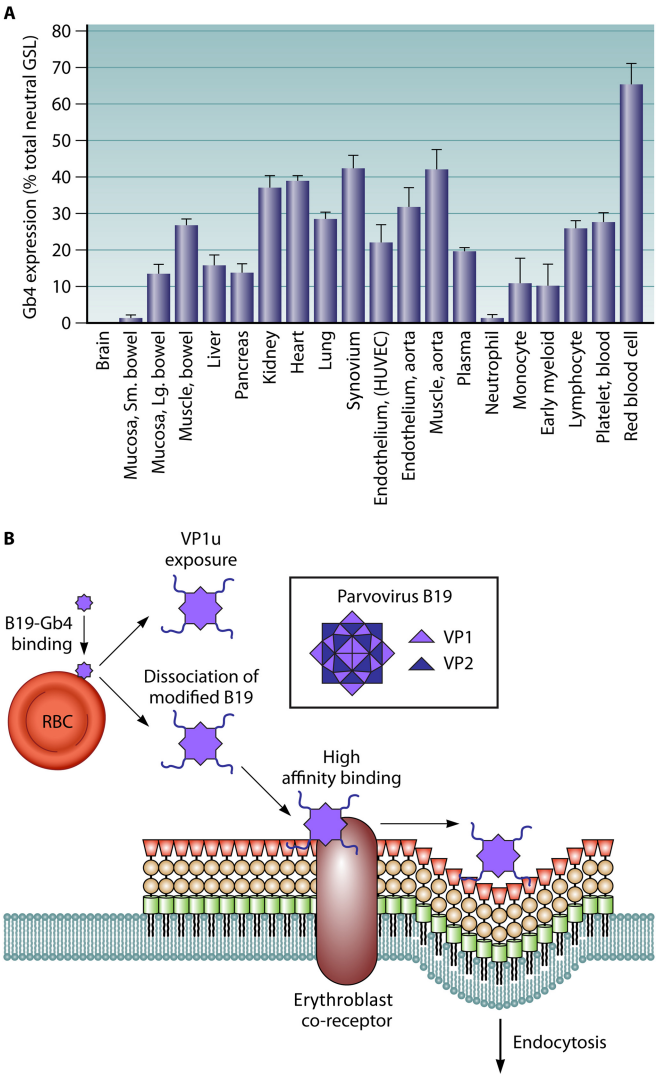

FIG 6 Globoside and parvovirus B19. (A) Distribution of Gb4 in human tissues (mean percent total neutral GSLs ± standard deviation). HUVEC, human umbilical vein endothelial cell. (B) The parvovirus B19 capsid is composed of VP2 (light blue) and VP1 (dark blue) protomers. B19 binds to Gb4 on cell membranes (for example, red cells), inducing a conformational change in VP1 with surface expression of the VP1u peptide. The majority of the modified B19 dissociates, where it may adhere to a high-affinity coreceptor on erythroblast membranes. It is likely that the receptor lies within a Gb4-enriched microdomain that facilitates B19 uptake.

tion of the capsid-receptor complex and endocytosis. Any detached virus possesses enhanced membrane binding capacity and avidity, increasing the odds of successful infection upon subsequent cell attachment (487).

Many investigators have focused on B19's tropism for early erythroid precursors. Brown et al. demonstrated that Gb4 is necessary for infection by showing that erythroblasts from p individuals were resistant to B19 *in vitro* (483). Likewise, B19 binding and infection can be blocked by disruption of lipid rafts (377). One factor that may favor erythroid cells is their high Gb4 content relative to that in other tissues (368). On normal red cells, Gb4 accounts for 60 to 70% of the total red cell GSL content and 10% of the total red cell lipid (358, 368). As a result, Gb4 forms large, receptor-rich membrane domains available for B19 binding (386). VP1u also determines B19 tropism, recognizing a coreceptor present on UT-7 and $CD36^+$ erythroblasts (KU812Ep6 cells) but not other cells, including mature circulating red cells (488). Finally, erythropoietin, cell cycle arrest, and erythroid transcription factors may also favor B19 replication in erythroid precursors (481, 491).

The interaction between Gb4, Ku80, and/or β1 integrins in supporting B19 infection in nonpermissive cell lines is unclear. Ku80 was proposed to be an alternate receptor in reportedly Gb4-negative cell lines (ACHN and HT9) (486). One major issue with the latter study was its dependence on flow cytometry to identify Gb4. ACHN cells, for example, express Gb4, Gb5, and MSGG/LKE (363, 389). As noted above, B19 can bind Gb5 and MSGG, and Gb5 inhibits B19-associated hemagglutination *in vitro* (368, 484). There is no direct evidence showing B19 binding to β1 integrins; however, β1 integrins might facilitate viral internalization through integrin cross talk and signaling in some cell lines (492).

HIV

HIV gp120 can bind several GSLs *in vitro*, including galactosylceramide (Gal-Cer), sulfatide, LacCer, GM3, and Gb3 (388). Gb3 is implicated as a coreceptor for HIV in lymphocytic and monocytic cells. Some of the early evidence implicating GSLs, and Gb3 in particular, was the acquired resistance of GSL-depleted cell lines to HIV (493, 494). Puri et al. showed a loss of gp120-mediated cell fusion in cells grown in phenyl-2-hexadecanoylamino-3-morpholino-propanol (PPMP), an inhibitor of glucosylceramide synthesis. More importantly, HIV fusion and infectivity were restored after the addition of Gb3. Gb3 was not sufficient to support gp120-cell fusion alone but acted to facilitate the interaction between HIV, CD4, and CXCR4.

In contrast to the data reported by Puri et al., other investigators found an inverse relationship between Gb3 and HIV, with increasing Gb3 levels being associated with HIV resistance. Studies with THP-1 cells, an X4-tropic cell line ($CD4^+$ $CXCR4^+$ $Gb3^+$), showed increased HIV resistance after treatment of cells with 1-deoxygalactonojirimycin, an inhibitor of α-galactosidase that increased cellular Gb3 levels (495). Conversely, globo-GSL depletion by PPMP (353) or by targeted inhibition with a small interfering RNA against *A4GALT1* (siRNA-A4GALT1) potentiated HIV infection (495, 496). Similar results can be observed by using peripheral blood cells from patients with p and P^k phenotypes (496–498) and Fabry's disease, an X-linked inborn error of metabolism due to a defect in α-galactosidase (497, 498). Globo-null (p) lymphocytes are hypersusceptible to HIV infection, whereas P^k and Fabry monocytes are relatively resistant to X4- and R5-tropic HIV strains (496, 497).

HIV reportedly binds GSLs via the V3 loop of the gp120 envelope between amino acids 206 and 275 (499, 500). Molecular models suggest that GSL binds a hairpin structure and involves several aromatic amino acids (His, Tyr, and Phe) (501). Early investigators proposed that a terminal galactose (or, in the case of ganglioside GM3, a penultimate galactose) with a free C-4 hydroxyl group is necessary for binding (499). It is now clear that HIV-GSL interactions occur at GEMs. Rafts are believed to play a role in HIV fusion, endocytosis, as well as HIV assembly and budding (388).

Helminth Infections and Anti-P_1

Approximately 25% of P_2 individuals have naturally occurring anti-P_1 (341). Normally, anti-P_1 is of low titer (titer, 1 to 2) and clinically insignificant. High-titer anti-P_1 can be observed in P_2 patients with certain helminth infections (502–504). One study reported the presence of high-titer anti-P_1 in all P_2 patients diagnosed with fascioliasis, with titers 20- to 200-fold higher than those in uninfected P_2 controls (502). Anti-P_1 is also common in patients with echinococcus or hydatid cyst disease, with 10% of patients having titers 5 to 20 times higher than those of controls (502, 503). The higher titer and incidence of anti-P_1 in fascioliasis may reflect earlier diagnosis and extensive host-parasite interactions (502). Fascioliasis is associated with larval migration and is usually diagnosed within a few months of infection. In contrast, echinococcus is an encysted parasitic infection that may not be diagnosed for several years.

P_1-active substances have been identified in *Echinococcus*, *Fasciola*, *Paragonimus*, and *Ascaris* (505). P_1 substances can be detected in hydatid cyst fluid but only in the presence of scolices (503). In *Echinococcus granulosa* infections, P^k- and P_1-active substances can be identified at the site of host invasion and the protoscolex (506). It is unknown whether the P_2 phenotype and development of anti-P_1 are advantageous in helminth infections. It is interesting, however, that China has the highest incidences of echinococcus infection and the P_2 phenotype in the world (Table 2) (13, 507).

DUFFY BLOOD GROUP

Biochemistry and Genetics

The Duffy blood group (FY) resides on the Duffy antigen receptor for chemokines (DARC), a 236-amino-acid integral membrane glycoprotein (Fig. 7). DARC consists of seven transmembrane domains, a 62-amino-acid extracellular N-terminal domain, and two disulfide bonds, which link the extracellular loops and N-terminal domain to form a hepatohelical structure (29). Although DARC is able to bind 11 different chemokines of the CC and CXC families, it is unable to mount an intracellular signal due to the lack of a G-protein motif (508). Considered a "silent chemokine receptor," DARC is now believed to facilitate transcytosis of chemokines across the endothelium, with leukocyte recruitment and activation (508). DARC is widely expressed on human tissues, including the vascular endothelium, alveoli, renal tubular epithelium, and red blood cells (2). There are an estimated 12,000 to 14,000 DARC molecules per red cell, possibly associated with the band 3/AE1 metabolon complex (2, 3). On circulating red cells, the DARC level is highest on young reticulocytes (509).

The Duffy blood system consists of five antigens: two autosomal-codominant antigens (Fy^a and Fy^b) and three high-incidence antigens (Fy3, Fy5, and Fy6). Fy^a/Fy^b and Fy6 reside within the putative *Plasmodium vivax* binding site on the extracellular N-terminal domain (29, 510). The Fy6 epitope is a 6-amino-acid stretch (17–24) between two N-glycan sites (aa 16 and 27), whereas Fy^a/Fy^b antigens are located at amino acid 42, just upstream of the cytokine binding pocket (Fig. 7). Like many blood group antigens, Fy^a/Fy^b antigens are the result of a SNP, leading to either a Gly42 (Fy^a) or Asp (Fy^b) substitution (2). The distribution of Fy phenotypes is highly dependent on ethnic background (Table 2), with a majority of Central Africans and African Americans being typed as Fy(a−b−) (24).

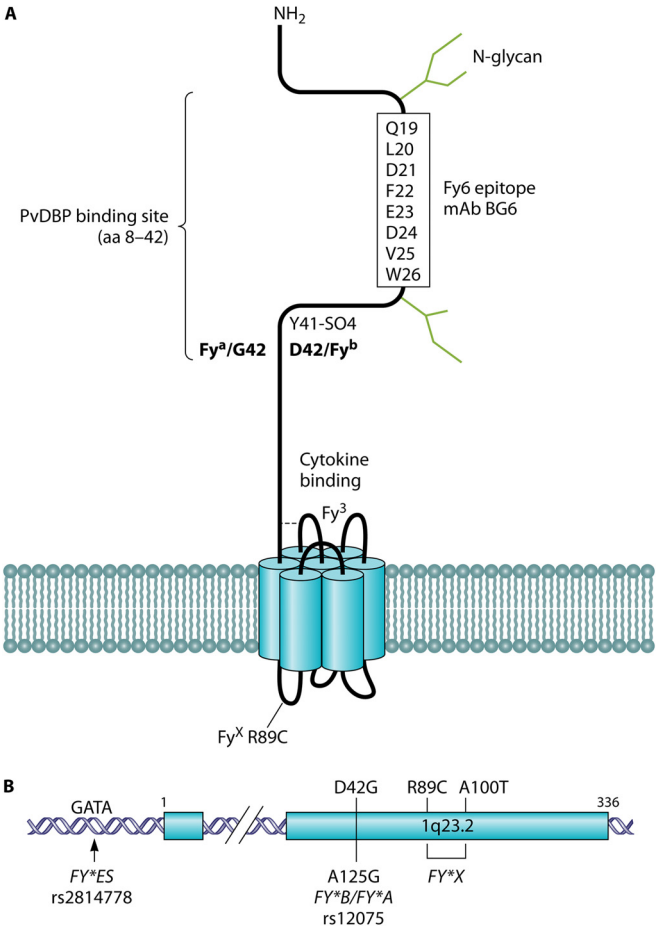

FIG 7 Duffy or DARC antigen and gene. (A) The DARC glycoprotein contains a large extracellular domain and 7 transmembrane domains. The amino-terminal extracellular domain contains the *P. vivax* PvDBP binding site (aa 8 to 42), of which the negatively charged Fy6 epitope (aa 19 to 26) is critical. The $Fy^{a/b}$ polymorphism resides at amino acid 42. A missense mutation in the first cytoplasmic loop of the transmembrane domain (Arg89Cys) is responsible for the Fy^X phenotype, which is associated with weak DARC expression. (B) The DARC gene resides on chromosome 1q23.2. DARC expression on red cells is silenced in the $FY*B^{ES}$ allele, which contains a mutation in a GATA promoter site. The SNP designations and the location of $FY*B^{ES}$, *FY*B/FY*A*, and *FY*X* are shown.

There have been several *FY* alleles described to date (2, 509). *FY*A* and *FY*B* encode Fy^a and Fy^b (Table 9). *FY*X* encodes a weak Fy^b antigen, with only 10% of normal Fy^b expression. $FY*B^{ES}$ encodes a silent Fy^b allele due a single point mutation in the DARC promoter (−33) (Fig. 7). The latter abolishes a critical GATA motif leading to a selective loss of DARC expression on red blood cells only (2, 29, 509). $FY*A^{ES}$ is similar, characterized by the same GATA mutation on an *FY*A* background. Phylogenetic studies indicate that *FY*B* is the ancestral allele. $FY*B^{ES}$ and *FY*A* arose fairly recently in human evolution due to selective pressure from *P. vivax* (509).

P. vivax and the Fy-Null Phenotype

The earliest studies suggesting inherent resistance to malaria arose from research on syphilis (509). It was noted as early as the 1920s that neurosyphilis was uncommon in patients with malaria and in areas where malaria is endemic. Furthermore, syphilis patients

TABLE 9 Relationship between DARC genotype, phenotype, and *P. vivax* infection[f]

DARC genotype[a]	Red cell phenotype	Dosage of DARC[b]	PvDBP binding[c]	Clinical infection[d]	
				Relative risk	95% CI
*FY*A/FY*B*^{ES}	Fy(a+b−)	+	~2.0×10^4	0.204	0.09–0.87
*FY*A/FY*A*	Fy(a+b−)	++	~4.5×10^4	0.715	0.31–1.21
*FY*A/FY*X*	Fy(a+b^w)[e] Fy(a+b−)[e]	+	ND	ND	
*FY*A/FY*B*	Fy(a+b+)	++	~5.8×10^4	1.00	
*FY*B/FY*B*	Fy(a−b+)	++	~7.2×10^4	2.70	1.36–5.79
*FY*B/FY*X*	Fy(a−b+)	+	ND	ND	
*FY*B/FY*B*^{ES}	Fy(a−b+)	+	ND	2.17	0.91–4.77
*FY*X/FY*B*^{ES}	Fy(a−b^w)[e] Fy(a−b−)[e]	w	ND	ND	Resistant to blood-stage infection (?)
*FY*B*^{ES}*/FY*B*^{ES}	Fy null	0	0		Resistant to blood-stage infection

[a] *FY*A*, DARC allele carrying the Fy^a antigen; *FY*B*, allele carrying the Fy^b antigen; *FY*X*, allele encoding weak Fy^b expression on all tissues; *FY*B*^{ES}, Fy-null allele carrying a GATA promoter mutation leading to a loss of DARC expression on red cells only (ES, erythroid silent).
[b] Relative dose of DARC glycoprotein (+, 1 copy; ++, 2 copies; w, very weak [5% of normal]) on red cells based on genotype.
[c] Binding of recombinant PvDBPII to human red cells (mean fluorescence intensity × percent positive red cells) by DARC genotype. Data are estimates based on graphed data reported by King et al. (515).
[d] Relative risk of clinical *P. vivax* infection in the Brazilian Amazon by DARC genotype (515).
[e] *FY*X* red cells can be serologically typed as Fy(b−) or Fy(b^w) due to very weak Fy^b expression (5% of normal).
[f] ND, not done.

deliberately infected with *P. vivax* malaria often showed significant clinical improvement. As "malariotherapy" practice spread to the United States, African American patients were noted to be resistant to *P. vivax* infection, even after repeated inoculation with infected blood. Experiments in humans confirmed that many blacks not only were resistant to *P. vivax* but also displayed resistance to *Plasmodium knowlesi* and *P. cynomolgi* as well. Serologic studies subsequently showed that blacks, especially those residing in areas where *P. vivax* is endemic, had a high incidence of the Fy(a−b−) phenotype. The most recent global maps show the highest incidence of the Duffy-null phenotype in sub-Saharan Africa, where frequencies of the Fy(a−b−) phenotype reach 98 to 100% in western, central, and southeastern Africa (24). The high incidence of the Fy-null phenotype coincides with a low incidence of *P. vivax* (0.6%) (24).

A direct link between the Duffy-null [Fy(a−b−)] phenotype and *P. vivax* resistance was not demonstrated until the 1970s. Zimmerman et al. and Miller et al. showed that Fy(a−b−) red cells were resistant to *P. vivax* infection *in vitro* and *in vivo* (509, 511). DARC was eventually identified as the cell receptor for PvDBP (*P. vivax* Duffy binding protein), a 140-kDa invasion protein expressed on *P. vivax* merozoites that is necessary for blood-stage infection. PvDBP recognizes a 35-amino-acid epitope (aa 8 to 42) along the DARC amino-terminal domain and requires tyrosine sulfation (Y41) (Fig. 6) (29, 509, 510). Fine mapping using DARC mutants identified the Fy6 epitope (aa 19 to 26 [QLDFED VW]) as being critical for PvDBP binding (510). Although both Fy-positive and Fy-negative individuals are susceptible to hepatic-stage infection, only Fy-positive individuals develop blood-stage infection: Fy(a−b−) individuals are resistant due to the absence of DARC on red cells (512). *P. vivax* prefers to infect reticulocytes, which have higher DARC/Fy expression levels than do older red cells (513).

P. vivax and Fy^a and Fy^b Phenotypes

Individuals heterozygous for a silent *FY*B*^{ES} allele have a 50% lower DARC expression level and a decreased risk of malaria (17, 509, 514). The first large-scale study suggesting a selective advantage for the *FY*A* allele was reported by Cavasini et al. in the Brazilian Amazon (17). These investigators serologically phenotyped 826 adults, including 417 blood donors and 407 patients with clinical malaria. Patients with *P. vivax* tended to be Fy(b+), and the risk of infection was related to the Fy^b dosage, i.e., homozygous > heterozygous. A later study by the same investigators compared *FY* genotype and *P. vivax* (514). In patients with *P. vivax* infection, the *FY*B* allele was overrepresented ($P = 0.03$), whereas the prevalence of the *FY*A/FY*B*^{ES} genotype was significantly lower than predicted (10.9% versus 18.8%; $P = 0.005$). There was no difference in the frequencies of the *FY*B/FY*B*^{ES} genotype between patients and controls ($P = 0.32$).

King et al. subsequently provided direct evidence that Fy^a lessens *P. vivax* infection, showing that Fy^a is a less efficient receptor than Fy^b (515). Using labeled PvDBP protein, King et al. demonstrated a dose-response relationship between PvDBP binding and *FY*B* genotype, where *FY*B/FY*B* > *FY*B/FY*A* > *FY*A/FY*A* > *FY*A/FY*B*^{ES}. On average, the level of PvDBP binding to *FY*A* homozygous red cells was 40 to 50% lower than that for *FY*B* homozygotes ($P < 0.0001$). Additional evidence comes from a longitudinal study of 400 individuals living along the Iquiri River in the Brazilian Amazon region (Table 9) (515). The risk of *P.*

vivax infection in Fy(a+b−) individuals was 220 to 270% lower than that in Fy(a−b+) individuals, even after correction for the *FY* genotype (515).

It is now believed that Fy^a also arose in response to *P. vivax* and may explain the prevalence of the *FY*A* allele in many Asian and South American countries (24, 515). Why Fy^a is a less efficient receptor than Fy^b is still under investigation. One hypothesis is a difference in DARC negative charge, which might affect binding by the positively charged PvDBP protein (515). Fy^b (Asp42) contributes to DARC's negative electrostatic charge, whereas Fy^a (Gly42) is charge neutral. In addition, Fy^a increases the susceptibility of Tyr41 to arylsulfatase, potentially leading to an enhanced loss of sulfate groups necessary for PvDBP binding (515). Finally, PvDBP binding to Fy^a is significantly more susceptible to antibody inhibition. In inhibition assays, anti-PvDBP antibodies were 200 to 300% more effective in blocking PvDBP binding to *FY*A/FY*A* red cells (515).

There is controversial evidence that the *FY* genotype may influence the immune response to *P. vivax* as well. Maestre and colleagues compared antibody responses to *P. vivax* in Colombia, an area where *P. vivax* and *P. falciparum* are endemic (512). DARC heterozygous individuals (*FY*A/FY*B*^{ES} and *FY*B/FY*B*^{ES}) were more likely to make antibodies against *P. vivax* blood-stage antigens (PvDBP and PvMSP1) than were DARC "double-positive" individuals, who have 2-fold-higher DARC levels on red cells. Those authors hypothesized that the poor humoral immune response observed in "high-DARC" individuals is a consequence of the higher parasite burden and parasite-mediated immune suppression. Inheritance of a silent *FY* allele (*FY*B*^{ES}) not only limits parasite invasion but also may increase the ability of the host to mount an immune response, further limiting parasitemia during subsequent infections. These results have been challenged by King et al., who found no difference in anti-PvDBP antibody responses in 400 *FY*-genotyped individuals (515).

Fy-Null Phenotype and *P. falciparum*

The Fy(a−b−) phenotype is not considered protective against *P. falciparum* and in fact may be detrimental based on data from recent studies of platelets (516). Blood platelets participate in the host response by recognizing and binding infected red cells. Once bound, activated platelets release platelet factor 4 (PF4), which is subsequently internalized by red cells. Intracellular PF4 appears to exert a lethal effect on malarial growth and survival, with 90% parasite death within 24 h (516). PF4 is a CXC chemokine that binds red cells via DARC. Not surprisingly, Fy(a−b−) red cells, which are unable to bind PF4, are resistant to platelet-mediated killing (516). Clinical data regarding disease severity and FY genotypes in *P. falciparum* infection are not available.

Fy-Null Phenotype, Neutropenia, and Severe Malaria

The Fy(a−b−) phenotype is linked to benign ethnic neutropenia, characterized by a mild decrease in the number of neutrophils (517). This decrease may reflect a decline in early bone marrow progenitors and/or impaired marrow demargination (518). Because DARC can regulate endothelial inflammation and leukocyte recruitment (508), there is some speculation whether Fy(a−b−) and neutropenia could be advantageous against the development of severe malaria. Neutrophils are implicated in the pathogenesis of severe malaria (519). Furthermore, neutrophil depletion is protective against cerebral malaria in mice (520).

Fy-Null Phenotype and HIV

The high HIV burden in Africa has led to searches for heritable traits that could influence HIV susceptibility in this population. As a chemokine receptor, DARC can bind HIV *in vitro* (521). In addition, HIV bound to FY^+ red cells can facilitate HIV infection in susceptible cells (522). Finally, there is significant geographic overlap between HIV prevalence and the Fy-null phenotype on the African continent (522).

Early clinical studies reported that the Fy(a−b−) phenotype may increase susceptibility to HIV infection while delaying disease progression (522). These results were disputed by other investigators, who found no correlation between the *FY* genotype, CD4 counts, HIV load, and disease progression (523, 524). Subsequent studies specifically stratified HIV infection by *FY* genotype and white cell count. Among leukopenic patients, an Fy-null phenotype actually provided a survival advantage (518). This finding was attributed to the frequency of benign neutropenia among Fy-null African Americans, whereas leukopenia among European Americans was more likely disease related and evidence of advanced infection.

Recently, a longitudinal study of South African sex trade workers was reported, which again suggested a link between Fy(a−b−) and benign neutropenia in HIV susceptibility (525). A baseline absolute neutrophil count of <2,500 was associated with an Fy-null genotype and a 3-fold increased risk of HIV seroconversion. Because of the codependent relationship between low neutrophil counts and the Fy-null phenotype, the authors of that study could not ascribe an independent effect of either on HIV susceptibility. Those authors theorized that the Fy-null phenotype may have higher circulating levels of inflammatory cytokines, which could promote HIV transmission (508, 525).

DIEGO BLOOD GROUP

Biochemistry

Band 3, or red blood cell anion exchanger (AE1/SCL4A1), is a major integral membrane glycoprotein on all red cells, regardless of species. AE1 is a large, 991-amino-acid protein with two distinct functional domains: a multipass, transmembrane domain responsible for anion exchange and a cytoplasmic domain that interacts extensively with several red cell cytoskeleton proteins (spectrin, ankyrin, and proteins 4.1 and 4.2) (Fig. 8). AE1 exists as dimers and tetramers along the spectrin cytoskeletal lattice, providing vertical and lateral stability to the membrane due to deformation and shear stress (3, 4). The AE1 cytoplasmic domain also reversibly binds several key glycolytic enzymes as well as deoxyhemoglobin, methemoglobin, and denatured hemoglobin (526). Alterations in AE1-cytoskeletal interactions can lead to decreased deformability, altered red cell shape, membrane loss, and clearance of red cells (4).

The membrane domain of AE1 is the anion exchanger, responsible for exchanging Cl^- and HCO_3^- necessary for gas transport and acid-base equilibrium (526). It is physically associated with several other membrane proteins important to red cell function (Rh, glycophorin, carbonic anhydrase, glucose transporter 1, CD47, and aquaporin) and is often referred to as the band 3 metabolon or macrocomplex (3). Several amino acid polymorphisms along the six extracellular loops account for antigens of the Diego blood group system (Fig. 8) (2). Most Diego antigens are low-incidence antigens, except for the Di^a/Di^b polymorphism. Di^a

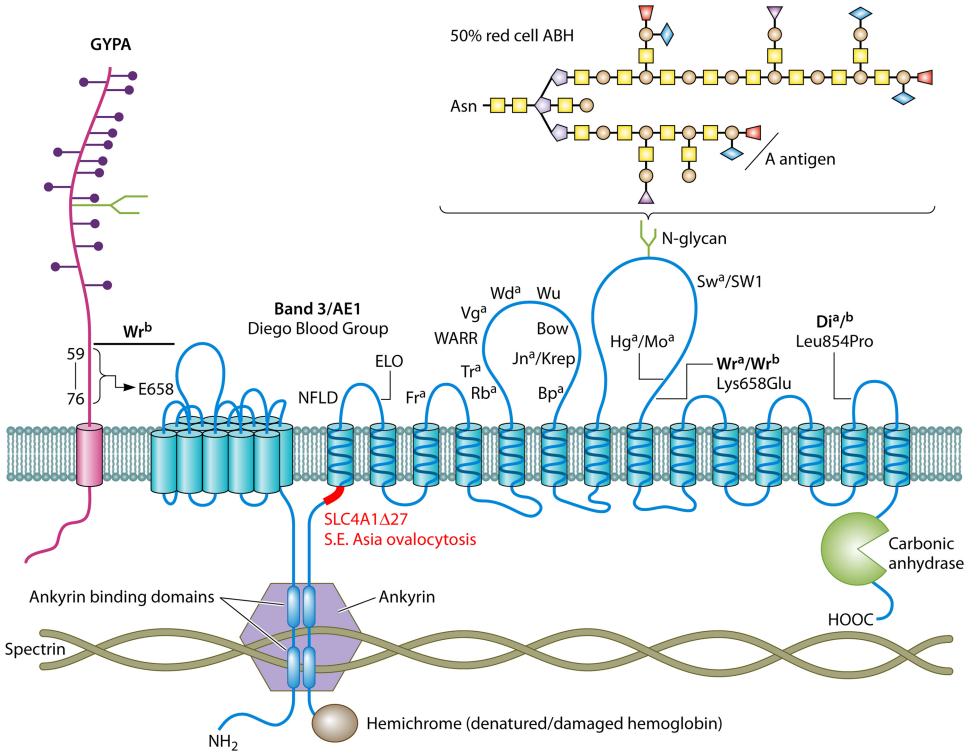

FIG 8 Diego blood group (AE1; band 3; SLC4A1). AE1 exists as dimers and tetramers and is preferentially located at junctional complexes and the "band 3-ankyrin" metabolon (shown). The amino-terminal cytoplasmic domain is involved in oligomerization and interacts with the underlying cytoskeleton. Several glycolytic enzymes and hemoglobin derivatives or hemichromes (methemoglobin and denatured hemoglobin) associate with the amino-terminal domain. Carbonic anhydrase is associated with the cytoplasmic carboxy tail. The large transmembrane domain is an anion transporter, exchanging Cl^-/HCO_3^- anions. Several high/low-incidence antigens are located along the extracellular loops. The high-incidence Wr^b antigen requires interaction with glycophorin A for expression. A 27-bp deletion at the junction of the amino-terminal and transmembrane domain is responsible for Southeast Asian ovalocytosis (SLC4A1Δ27) (in red). AE1 contains a single massive N-glycan that expresses ABO and is responsible for 50% of all the ABO antigens on red blood cells.

is exceedingly rare in most populations, except China and South American Indians, where the incidence can reach 50% in some regions (Table 2). AE1 numbers ~1 million copies per RBC and is responsible for 50% of all the ABO epitopes on red cells (Fig. 8) (526). Unlike many other blood group antigens, there are no known AE1-null phenotypes in humans.

In addition to red cells, a truncated form of AE1 is expressed along the basolateral membrane of the α-intercalated cells of the distal nephron and participates in urine acidification (527). Several point mutations in AE1 are associated with distal renal tubular acidosis. Interestingly, mutations responsible for hereditary ovalocytosis and spherocytosis are not associated with renal tubular acidosis.

Malaria and AE1

Southeast Asian ovalocytosis (SAO), also known as Melanesian ovalocytosis, is an autosomal-dominant mutation of AE1. The mutation is a 27-bp in-frame deletion (aa 400 to 408) at the junction between the AE1 membrane transport and N-terminal cytoplasmic domains (Fig. 8) (4, 526, 527). The mutation compromises red cell deformability by increasing membrane rigidity (528), leading to ovalocytosis. In addition, the truncated protein is unable to transport anions and actually reduces the transport capability of normal AE1 (527). All SAO individuals identified to date are heterozygous for the mutation (wt/SLC4A1Δ27); homozygous inheritance is considered embryonic lethal (529).

In areas of the western Pacific where malaria is endemic, the incidence of SAO can reach 35% of the population. It was initially believed that increased red cell rigidity may interfere with parasite invasion, based on early reports of decreased parasitemia in SAO individuals (530–532). Later studies, however, found no difference between SAO and the incidence of asymptomatic malaria (529, 533), type of malarial species (533, 534), or level of parasitemia (533, 535). SAO was shown to reduce severe *P. vivax* malaria (OR, 0) and may protect against *P. vivax* reinfection, possibly through an enhanced immune response (509, 536). Among young children, SAO was associated with a 43% reduction in *P. vivax* infection ($P = 0.006$) and high-titer inhibitory antibodies (22%; $P = 0.008$) (536). One study looked at coinheritance of SAO and Gerbich-negative phenotypes (GYPCΔex3) and malaria susceptibility in the Madang Province of Papua New Guinea (535). There was no selective advantage of SAO and GYPCΔex3 coinheritance relative to malaria.

SAO is advantageous against cerebral malaria, which has a fatality rate of 8 to 40% (534). Genton et al. showed an inverse correlation between SAO (wt/SLC4A1Δ27) and the risk of cerebral malaria. Of 35 individuals with *P. falciparum* cerebral malaria, all carried normal AE1 (wt/wt), whereas 15% of controls carried

the SAO-SLC4A1Δ27 allele ($P < 0.001$) (529). Allen and colleagues examined malaria severity relative to the SAO phenotype in hospitalized children (534). Those authors also found that a normal AE1 phenotype (wt/wt) was associated with a high risk of cerebral malaria ($P = 0.013$) and impaired consciousness ($P = 0.0025$) compared to patients with SAO. When data from both studies are combined, SAO-SLC4A1Δ27 offered significant protection against cerebral malaria ($P = 0.0018$; OR, 0 [95% CI, 0 to 0.35]) (534). SAO may be more effective against *P. vivax* or *P. malariae* than against *P. falciparum*. In a recent study of children with severe *P. falciparum* malaria, 3.4% (3/236) possessed the SAO genotype, including 3/8 (37%) children with cerebral malaria and deep coma (536).

How SAO protects against cerebral malaria is still a matter of conjecture. Older studies were able to demonstrate inhibition of *P. falciparum* invasion with liposomes bearing AE1, suggesting a role for AE1 in malaria invasion (537). AE1 is closely associated with known malarial receptors, especially glycophorins A and C. Malarial infection is accompanied by altered AE1 on membranes, with aggregation and neoantigen expression (332, 333). In areas where malaria is endemic, antibodies against AE1 neoantigens are common and are believed to constitute part of the immune response (333). Relative to normal red cells, SAO cells show a high proportion of AE1 tetramers and higher-order oligomers that could alter red cell rigidity and antigenicity (528). Using single-particle tracking, Mirchev et al. documented significant decreases in membrane diffusion and mobility for AE1 and other red cell proteins (528). As a consequence, infected SAO red cells may be more susceptible to extravascular hemolysis, opsonization, and splenic clearance. This may account for the lower hemoglobin levels observed for children with malaria and SAO (median, 4.8 versus 6 g/dl; $P = 0.035$) (534). In addition, the altered deformability of SAO red cells may interfere with adhesive properties following parasitic invasion. Both lower hemoglobin levels and decreased adhesion directly impact blood viscosity and improve blood flow within inflamed cerebral vasculature (534). SAO does not impact red cell rosetting.

Interestingly, a recent phylogenetic study of AE1 in primates found evidence for adaptive mutations in the AE1 cytosolic domain, but not in the transmembrane and extracellular loops, in humans and great apes (538). Because humans and great apes (gorillas, chimpanzees, and bonobos) are uniquely susceptible to malaria, the results suggest "that African apes and humans may share some common mechanisms of adaptation to *P. falciparum*-related parasites" (538). One fascinating difference in great apes is a 27-bp insertion in exon 3 that could enhance AE1-ankyrin binding (538, 539). Theoretically, an increase in ankyrin-AE1 binding could also increase membrane rigidity, analogous to the SAO polymorphism.

Finally, one study reported a link between severe *P. falciparum* infection in children and a polymorphism in the AE1 promoter (540). The polymorphism is T→C at nucleotide −5699 ($SLC4A1^{-T5699C}$), ~500 bp upstream of the transcription start site. Although allelic variants were equally represented (50% frequency) in the population, the prevalence of the $SLC4A1^{-5699C}$ allele was increased among fatal cases, with the highest relative risk of death being observed for homozygous patients. In luciferase assays, the $SLC4A1^{-5669C}$ variant displayed 18 to 27% higher promoter activity in K562 erythroleukemia cells (540). It is unknown whether increased promoter activity is associated with higher AE1 expression levels or altered red cell deformability.

AE1 and *Bartonella*

Bartonella bacteria are small, curved, facultative, intracellular Gram-negative organisms that display host and tissue specificity (541). Human *Bartonella* infections include Oroya fever (*B. bacilliformis*), trench fever (*B. quintana*), and "cat scratch" disease (*B. henselae*). In immunocompromised patients, *Bartonella* can cause severe infections with the development of bacillary angiomatosis, a vasoproliferative disorder involving skin, visceral organs, and brain. Infection is usually acquired through an insect vector (ticks and fleas) or direct contact (for example, cat bite).

Early in infection, *Bartonella* invades and proliferates in the vascular endothelium, followed by bacteremia and invasion of erythrocytes (541). Unlike malaria, *Bartonella* proliferates within red cells harmlessly, with prolonged red cell survival and chronic bacteremia. In *B. henselae* and *B. quintana*, red cell invasion is mediated by the type IV secretion system (T4SS) Trw proteins (541). In a murine model, bacteriophages bearing TrwJ2 proteins specifically bound AE1 (542). Furthermore, polyclonal antibodies against AE1 were able to inhibit *Bartonella* binding and invasion by 60%. T4SS Trw proteins are absent from *B. bacilliformis*, which may recognize and adhere to red cells by its flagella (542). Investigators have described *B. bacilliformis* binding to several proteins belonging to the AE1 macrocomplex, including AE1, spectrin, and glycophorin (543).

In areas of Peru, there are differences in clinical *B. bacilliformis* infection, with some populations being more likely to develop Carrion's disease (Oroya fever), whereas in others, the verrucous or eruptive phase (Peruvian wart) is predominant (544). A recent epidemiologic study compared the incidence and presentation of *B. bacilliformis* relative to the Duffy, MN, Ss, and Diego ($Di^{a/b}$) blood types (544). There was no difference in Di^a expression between individuals with Oroya fever and those in the verrucous phase (15% versus 19%). There was also no difference in MN, Ss, or Duffy phenotypes between infected and uninfected individuals.

MNSs BLOOD GROUP

Biochemistry

The MNSs blood group system was identified in 1927 and is the second oldest blood group system after the ABO system (545). The MN antigens reside on glycophorin A, one of the most abundant red cell proteins, at 1 million copies per red cell. It is a 131-amino-acid type 1 glycoprotein that includes a 72-amino-acid amino-terminal extracellular domain, a single transmembrane domain, and a 36-amino-acid cytoplasmic domain (Fig. 9) (2, 29, 545). It is heavily glycosylated, with one N-glycan and 21 potential O-glycan sites, although only ~15 sites actually bear O-linked glycans in the mature molecule (29, 545). Glycophorin A is localized and physically associated with AE1 at the AE1-ankyrin macrocomplex and junctional complexes (3). Despite its prevalence on red cells, glycophorin A is not essential for red cell development or survival. Glycophorin A-null phenotypes are not associated with anemia or altered red cell function (29).

Glycophorin B is a 72-amino-acid glycoprotein related to glycophorin A and bears the S/s antigen. Its extracellular domain is

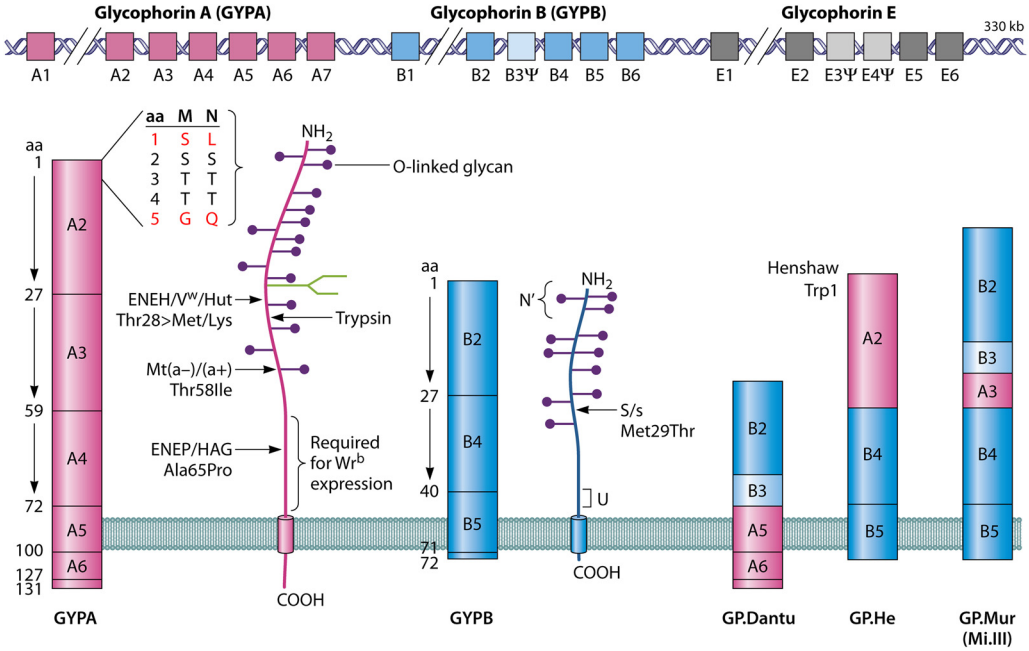

FIG 9 MNSs blood group (GYPA and GYPB). Glycophorins A, B, and E are located together on chromosome 4q28-q31 and can undergo recombination, leading to hybrid glycophorins (for example, Henshaw, GP.Mur, and GP.Dantu) and null phenotypes [En(a−), U^-, and M^k]. The MN antigens are defined by the first 5 amino acids and O-linked glycans on glycophorin A. Glycophorin A contains 15 O-glycan sites and >20 high/low antigens. Glycophorin A is physically associated with AE1/band 3 and participates in Wr^b antigen expression located on AE1. The location of 3 high/low polymorphisms showing evidence of selection (16) and the trypsin cleavage site are shown. The S/s antigens are a single polymorphism on glycophorin B. The U antigen is located along a short peptide segment near the membrane.

only 44 amino acids, with 11 O-glycan sites, and essentially lacks a cytoplasmic domain (Fig. 9). It is also less abundant than glycophorin A, numbering only 170,000 to 250,000 molecules per red cell (2, 29). Glycophorin B also clusters at the AE1/band 3-ankyrin macrocomplex, possibly as a heterodimer with glycophorin A. Glycophorin B is not essential for red cell development or function.

Because of the large number of O-glycan residues, glycophorins A and B are considered "sialomucins." As such, they account for 60% of the sialic acid on red cells and contribute significantly to the red cell overall negative charge or "zeta potential" (29, 341). Most of the O-glycan (70%) consists of a classic type 1 core O-linked tetrasaccharide bearing two sialic acids and is located at Ser/Thr residues along the first 30 amino acids of the amino-terminal domain (Table 10) (341). Variations in O-glycan structure are known, including enzymatic desialylation (T antigen), congenital glycosylation deficiencies (Tn syndrome), and substitution by GlcNAc (Tm, Can, and M_1) or GalNAc (Cad) (341). Differ-

TABLE 10 Effect of O-linked glycans on *P. falciparum* RBC invasion

Antigen(s)	O-linked glycan structure	Susceptibility to *P. falciparum*[a]	Description
M/N	EBA-175 receptor NeuAcα2→3Galβ1→3GalNAc-*O*-Ser/Thr ↑6 NeuAcα2	Sensitive	>70% O-glycan on GYPA, GYPB Epitope anti-P^r
Can, Tm, M_1, Sj	NeuAcα1→3Galβ1-3GalNAc-*O*-Ser/Thr ↑6 (±Fuc-)Galβ1-3/4GlcNAcβ1	Unknown	Blacks > whites
Cad	GalNAcβ1-4 〉Galβ1→3GalNAc-*O*-Ser/Thr NeuAcα2-3 ↑6 NeuAcα2	Resistant	Rare, GM2 active
T	Galβ1→3GalNAc-*O*-Ser/Thr	Resistant	Neuraminidase
Tn	GalNAc-*O*-Ser/Thr	Resistant	Rare

[a] Sensitivity of red cells to *P. falciparum* infection *in vitro*.

ences in glycosylation can affect malaria invasion *in vitro* (see below).

Genetics and Serology

The genes for glycophorin A (GYPA) and glycophorin B (GYPB) are on chromosome 4, as part of a 330-kb gene cluster (A-B-E) (Fig. 9) (2, 29). The mature glycophorin A is encoded by exons A2 to A7. Glycophorin B is encoded by exons B2 and B4 to B6; exon B3 is a pseudogene. The genes are highly homologous and subject to both recombination and gene conversion, leading to hybrid glycophorin molecules with the generation of new low-incidence antigens. Recombination is also responsible for three null phenotypes. En(a−) cells lack glycophorin A due to recombination between exons A2 and B2 and deletion of exons A3 to A7. Glycophorin B-negative (S^- s^- U^-) cells, a phenotype observed in 1% of blacks, is due to recombination and deletion of exons B2 and B4/B5. Finally, the M^k phenotype (M^- N^- S^- s^- U^-) is due to recombination between GYPA and GYPE, with the loss of expression of both GYPA and GYPB. Individuals with glycophorin-null phenotypes have decreased sialic acid content and increased resistance to malarial infection (546–548).

The MNSs system is diverse, with 46 antigens to date (2, 28, 545). The M and N antigens are two autosomal-codominant antigens encoded by the first 5 amino acids on glycophorin A and include 3 O-linked glycans as part of the epitope (29, 341). The M and N antigens differ at two amino acids (aa 1 and 5), where M is a ^{1}Ser-Ser-Thr-Thr-Gly^5 and N is ^{1}Leu-Ser-Thr-Thr-Glu^5 (Fig. 9). M is considered the ancestral *GYPA* allele and is common in all human populations (74 to 78%) and Old World apes (16, 29). Several allelic antigens due to amino acid polymorphisms have been identified in exons A3 and A4 (2, 545).

The amino terminus of glycophorin B is essentially identical to that of glycophorin A except that glycophorin B always expresses the N antigen, denoted N′ (29, 341, 545). Clinically, the most important antigens are S/s antigens, the result of an amino acid polymorphism (Met29Thr). S/s is encoded by exon B4 and can be lost in variant glycophorins due to recombination and gene conversion (for example, GP.Henshaw). The U antigen refers to a short amino acid sequence near the membrane. Unlike glycophorin A, glycophorin B is resistant to trypsin (2).

Malaria and Glycophorin O-Glycans

It is well established that sialic acid is a receptor for *P. falciparum*. Treatment of red cells with neuraminidase or trypsin markedly decreases *P. falciparum* adhesion and invasion. Glycophorins A and B, the two major sialylated glycoproteins on red cells, were identified early as probable receptors for *P. falciparum*. Pasvol et al. showed that individuals with glycophorin A- and B-null phenotypes were relatively resistant to malaria invasion *in vitro* (546–548). The importance of O-linked glycans was also inferred by the profound resistance of Tn and Cad red cells, which have altered O-glycan expression (Table 10) (546, 549).

Glycophorin A and Malaria

Glycophorin A is a receptor for the *P. falciparum* erythrocyte binding antigen EBA-175 (550). EBA-175 recognizes sialylated O-glycan epitopes (NeuAcα2-3Gal-R) along the amino-terminal domain. Antibodies against glycophorin A can block *P. falciparum* invasion and coprecipitate EBA-175 (547, 550). In a glycophorin A knockdown model, glycophorin A expression was decreased by 79% ± 9%, accompanied by a 58% decrease in *P. falciparum* invasion (551). Unfortunately, glycophorin A knockout mice have proven to be a poor model for human malaria infection; murine malarial species do not require glycophorin A for infection (552). Murine red cells are relatively resistant to human *P. falciparum* strains, even using humanized and immunodeficient mouse strains (553).

A few studies have examined the impact of glycophorin A polymorphisms on malaria. The M and N antigens, in particular, reside in a densely sialylated portion of the glycophorin A molecule and include three O-linked glycans as part of their epitopes. Rare En(a−) red cells, which are M^- N^- due to the deletion of exon A2, are 50% more resistant to *P. falciparum* infection than normal (546, 547). In addition, blacks are much more likely to possess M/N variants (Can, Tm, and M_1) with altered O-glycans and decreased sialic acid, which could potentially impact *P. falciparum* binding (Table 10) (554).

Epidemiologic and *in vitro* experiments show no evidence for a role of M/N antigens in malaria susceptibility. *P. falciparum* invasion is equivalent in MM, MN, and NN red cells *in vitro* (547). Similar results were observed with rare M^g (Thr4Asn) and M^c (Leu1Ser) red cells, which also type as M^- N^- and have altered glycosylation (331, 549). In large population studies in Africa and the Brazilian Amazon, there were no significant differences in M and N allele frequencies in areas where the disease is hyperendemic (16, 17). Finally, Naka et al. studied 312 adult patients admitted for *P. falciparum* infection in northern Thailand (555). These authors found no differences in M or N genotypes between patients with mild malaria and those with cerebral malaria.

Genomic studies show that glycophorin A is subject to ongoing positive selection along the extracellular domain (16). At this time, there are very little data regarding the influence of other glycophorin A polymorphisms and mutations on susceptibility to malaria. The En(a−) null phenotype, which shows resistance to malaria *in vitro*, is extremely rare, with most cases arising in Northern Europeans (331). Decreased sialic acid and malarial resistance can also be demonstrated in rare recombinant A-B glycophorins (e.g., Mi.V) (29, 546). A recent study of 15 native African populations identified several fixed polymorphisms, possibly as a result of selective pressures (Thr28Lys, Ala35Pro, Thr58Asn, Ala65Val, and His67Arg) (16). Lys28 is a previously identified low-frequency antigen (HUT; MNS19) and leads to a loss of the N-glycan at Asn26 (Fig. 9) (2, 29) as well as a potential O-glycan at Thr28. Thr58Asn could also result in the loss of an O-glycan and is the site of the Mt^a antigen (Thr58Ile), which is present in 1% of Thailand natives (2). The Ala65→Val change leads to a loss of the high-incidence antigen ENEP (Fig. 9) (2, 545).

For me, the most intriguing fixed polymorphisms identified by Ko et al. are His67Arg and Ala65Val (16), which could potentially impact Wr^b. Wr^b is a high-incidence, composite antigen involving AE1 (Glu658) and glycophorin A (Fig. 8 and 9) (2, 556). As discussed above, glycophorin A promotes AE1 translocation to the cell surface and is physically associated with AE1 at the AE1-ankyrin macrocomplex. It is believed that the proper orientation and presentation of the Wr^b antigen require a short peptide sequence (aa 61 to 70) on glycophorin A (29). Not surprisingly, recombination and amino acid polymorphisms within this short peptide region can alter or suppress Wr^b expression, regardless of the AE1 genotype. Wr^b is absent on En(a−) and A-B glycophorin mutants (for example, GP.Hil), which lack the short peptide re-

gion encoded by exon A4. Wr^b is also altered/depressed on MAR^+ (MNS43; Glu63Lys) and HAG^+ (MNS41; Ala65Pro) red cells (557).

In early studies with rare red cell phenotypes, Wr(b−) red cells were quite resistant to *P. falciparum in vitro*, with invasion rates being only 10% of those of controls (546). This was equivalent to the resistance observed with Tn and Cad red cells or after treatment of red cells with trypsin and neuraminidase (546–549). In fact, the resistance of Wr(b−) cells was equal to or greater than that observed with En(a−), U^-, and M^kM^k glycophorin-null red cells (546–548), although these results were later challenged (558). In addition, polyclonal and monoclonal anti-Wr^b antibodies can inhibit *P. falciparum* invasion (546). On the other hand, there is no evidence of impaired *P. falciparum* invasion in HAG^+ red cells, which have altered Wr^b expression (557). Interestingly, Wr^b is overexpressed on Mi.III red cells, an unusual hybrid glycophorin commonly encountered in Asia (559, 560). The $Wr^{a/b}$ site in AE1 shows evidence of positive evolution in primates and other mammals (538).

Glycophorin B and Malaria

Glycophorin B is a receptor for the *P. falciparum* erythrocyte binding ligand EBL-1 (561). Glycophorin B has been a subject of intensive investigation due to the occurrence of variant glycophorin B alleles in blacks and in East Asia (Table 2) (2, 29). Glycophorin B-deficient red cells (S^- s^- U^-) show moderate resistance to malarial invasion (72%) but show nearly complete resistance (5%) after trypsin treatment to remove glycophorin A. The S^- s^- U^- phenotype is found exclusively in those of African ancestry, occurring in <1% of African Americans (2).

The S/s polymorphism defined by Met29Thr shows distinct racial variation (Table 2). The *GYPB*s* (s^+) allele is the predominant allele in most populations, including Caucasians (85%), African Americans (93%), and populations in Thailand (90%) and Brazil (92%). The prevalence of *GYPB*S* (S^+) is variable between populations, being significantly higher in Caucasians than in African Americans (55% versus 30%) (29, 331). In native Africans, the prevalence of the *GYPB*S* allele in the population can range from 6 to 50% (562). Two South American studies have found an association between an S^+ phenotype and increased susceptibility to malaria (17, 562). Tarazona-Santos et al. examined *P. falciparum* infection relative to S/s genotype and ancestry (562). The incidence of the *GYPB*S* and S^+ s^+ genotype in malaria patients was significantly higher than that in case controls (66% versus 42%; $P < 0.01$). One possible hypothesis forwarded was the potential loss of an O-glycan site with *GYB*S* (Thr→Met) that could alter protein conformation and binding by EBL-1 (562). Alternatively, differences in susceptibility to malaria could simply reflect differences in glycophorin B levels: both S^+ s^- and S^+ s^+ red cells possess more glycophorin B than do S^- s^+ cells (29). On average, S^+ s^- red cells express 1.5-fold more glycophorin B than do S^- s^+ cells (29, 341).

Hybrid glycophorin alleles are typically uncommon, although a few variants show increased prevalence in Africans and Asians. The Henshaw phenotype is a variant B-A-B glycophorin (GP.He) as a result of gene conversion between the B2 and A2 gene loci (Fig. 9) (29). This leads to a loss of the N′ antigen and can lead to a loss of the s/S antigen but no significant change in glycosylation. Henshaw is absent in Caucasians but occurs in 3% of African Americans and 3 to 14% of Africans (2, 16, 29, 545). Henshaw is particularly frequent in the Congo (14%), a region where *P. falciparum* is hyperendemic. Field et al. examined *P. falciparum* invasion and growth in Henshaw cells (s^+ He^+) by flow cytometry and [^{3}H]hypoxanthine incorporation assays (563). Relative to controls, Henshaw cells displayed only a mild decrease in parasitemia after 48 h (81%).

The Dantu phenotype is the consequence of a crossover between the GYPA and GYPB genes, to form a B-A hybrid bearing a glycophorin B amino terminus and a glycophorin A transmembrane and cytoplasmic domain (GP.Dantu, s^+; B3-B4/A5-A6-A7), with a loss of the Wr^b antigen (29). In addition, GP.Dantu can be associated with "copy number variation," with duplication of the GP.Dantu mutant gene. As a result, Dantu red cells often show increased synthesis of GP.Dantu, coupled with a 40 to 50% decrease in the level of glycophorin A and increased resistance to *P. falciparum* (29, 563). Despite its potential selective advantage, Dantu is still quite rare, with incidences of 0.5% in African Americans and 1.1% in South African Khoi (2, 29).

Finally, the Miltenberger III (Mi.III) glycophorin family (GP-.Mur, GP.Bun, and GP.Hop) are found in many Pacific Asian populations. Mi.III glycophorins are B-A-B hybrids due to gene conversion with the incorporation of exon A3 into glycophorin B (Fig. 9). The incidence of GP.Mur is 3 to 4% among Han Taiwanese and reaches 90% in Taiwanese aboriginal populations that reside along the low costal regions (Table 2). GP.Mur cells have 25 to 67% more AE1 than normal, with increased CO_2 respiration, buffering capacity, and osmotic resistance. There is speculation that this could be advantageous against malaria-associated acidosis (559). As noted above, these cells also have elevated Wr^b expression (559).

Glycophorin A and *Babesia*

Babesiosis or piroplasmosis is a tick-borne, zoonotic illness endemic in the Northeastern and Midwestern United States (564). Infections in immunocompetent individuals may range from asymptomatic infections to those causing mild constitutional symptoms with fever, chills, malaise, and anemia. Severe, life-threatening infections can be observed in splenectomized and immunocompromised patients. The most common species implicated in human infections are *Babesia microti* and *B. divergens*.

Babesia is an intraerythrocytic parasite, replicating in host red cells as a critical part of its life cycle (564). Like malaria, Babesia invasion is dependent on neuraminic acid on red cell glycophorins. Investigators at the New York Blood Center were able to demonstrate a decrease in *B. divergens* invasion after treating human red cells with either neuraminidase or trypsin to remove glycophorin A (565). Studies with various null phenotypes showed a 45% decrease in *Babesia* invasion with En(a−) cells but not Kell-null or Duffy-null cells (565). En(a−) cells were also significantly more resistant than U-negative red cells. In a mouse model, glycophorin A knockout mice were resistant to *B. rodhaini* (566). Whereas wild-type mice succumbed to lethal parasitemia within 6 days, glycophorin A-deficient mice survived up to 6 weeks.

Using a panel of 10 monoclonal antibodies, Cursino-Santos et al. identified glycophorin A bearing the M antigen ($GYPA^M$) and glycophorin B bearing the S epitope (GYPB-S) as possible ligands; antibodies recognizing s, U, or En(a) had no impact on *Babesia* invasion (567). Monoclonal antibodies against $GYPA^M$ were more potent inhibitors of *B. divergens* invasion than was anti-S (35%

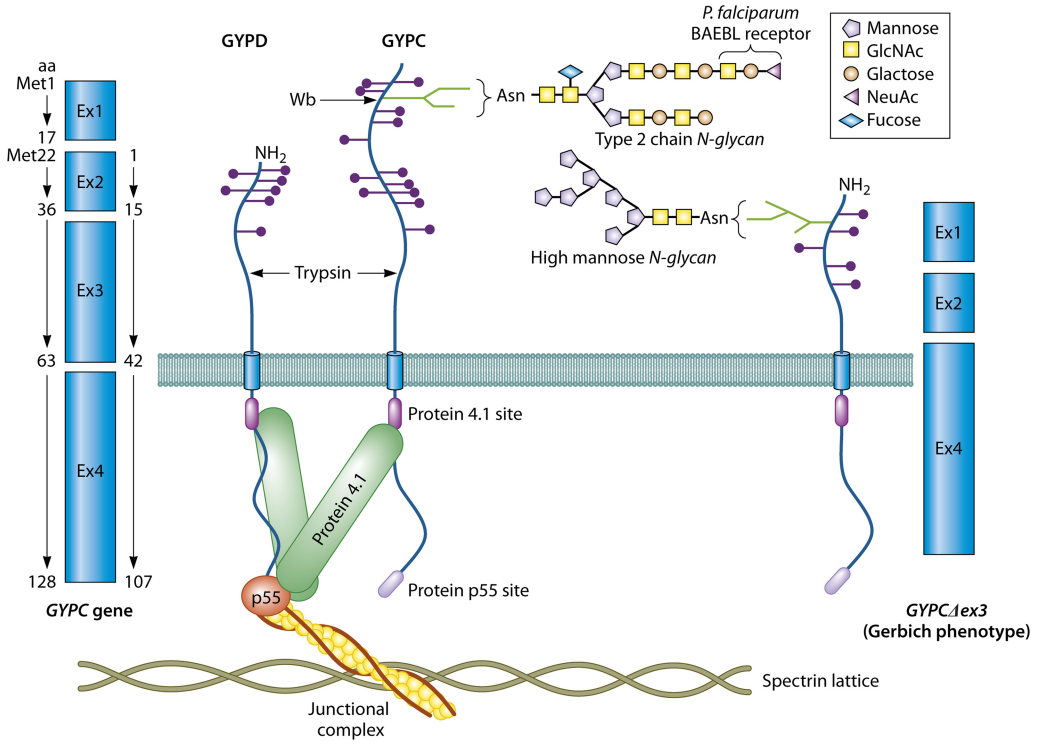

FIG 10 Gerbich blood group (GYPC and GYPD). Glycophorins C and D are products of the GYPC gene and differ by 21 amino acids at the amino-terminal end. Both proteins interact with the cytoskeleton elements at junctional complexes. GYPC contains a single N-glycan that binds the *P. falciparum* protein EBA140/BAEBL. The Gerbich phenotype is a deletion mutant lacking exon 3. The altered protein is underglycosylated and expresses an immature, high-mannose N-glycan. In addition, there is an altered interaction with the junctional complexes, leading to ovalocytosis.

versus 17%; $P < 0.05$), consistent with previous results with En(a−) and U$^-$ red cells (266, 267). These authors speculated that some of this difference reflected the higher prevalence of glycophorin A on red cells. Unfortunately, these authors were unable to test anti-N (GYPA^N) antibodies due to the propensity of anti-N to independently cause changes in the red cell membrane.

MNSs and Bacterial Infection

Severe bacterial and viral infections that lead to the secretion of neuraminidase (for example, influenza) can lead to the modification of glycophorins A and B, leading to "T activation." Neuraminidase converts the normal O-linked tetrasaccharide to the asialo-T antigen (Table 10). T activation becomes clinically detectable only after a 25 to 55% loss of sialic acid (568). T-activated red cells can be agglutinated by lectins (*Arachis hypogaea*) as well as normal sera which contain naturally occurring anti-T antibodies. Although T activation is most often observed with *Clostridium* and *S. pneumoniae* infections, many Gram-negative organisms can produce neuraminidase (569, 570). Clinically, T activation most frequently occurs in the setting of NEC, ruptured bowel, sepsis, invasive *Streptococcus* pneumococcal infections, and *Streptococcus*-associated HUS (570).

Bacterial infections can also stimulate antibodies against glycophorins A and B. Cold agglutinins with anti-Pr specificity are thought to recognize the O-tetrasaccharide on glycophorin (Table 10) (29). More interesting is the occurrence of "naturally occurring" anti-M. The latter occurs almost exclusively in young children with acute bacterial infections. Naturally occurring anti-M antibodies are benign and transient, resolving within a few months (571). Naturally occurring anti-M has been reported for *Haemophilus influenzae* type b, *Proteus mirabilis*, *S. aureus*, and *Neisseria meningitides* infections (571). The presence of an anti-N antibody in a patient with *E. coli* and *S. aureus* sepsis was recently reported (572).

Finally, M antigen has been reported to be a receptor for some strains of *E. coli*. Jokinen et al. reported that a uropathogenic *E. coli* strain (IH11165) specifically recognized M antigen; no binding was observed with NN red cells (573). Surprisingly, binding was sensitive to periodate but not neuraminidase, suggesting that the terminal serine was necessary for recognition. This was confirmed by HAI with free serine. M is also recognized by some enteropathogenic *E. coli* animal strains expressing the F41 adhesin (574).

GERBICH BLOOD GROUP

Biochemistry and Genetics

The Gerbich blood group antigens are high-incidence antigens that reside on glycophorins C and D (2, 29). Both proteins are the products of the GYPC gene on chromosome 2, a 13.5-kb gene organized over four exons (Fig. 10). Glycophorin C is a 128-amino-acid protein bearing potentially 12 O-linked glycans, and 1 critical N-linked glycan, near the amino terminus of the molecule. Glycophorin D is a product of leaky translation due to an alternate methionine in exon 2. As a result, glycophorin D is small (107 amino acids) and lacks several glycosylation sites, including the amino-terminal N-glycan. Rare truncated mutant forms due to deletion of exon 2 (Yus phenotype) or exon 3 (Gerbich phenotype) (GYPCΔex3) are known. The Leach phenotype is a true null

phenotype due to the deletion of exon 3 and exon 4, which encode the transmembrane and cytoplasmic domains, respectively.

There are estimated to be 250,000 molecules of glycophorins C and D per red cell (2). In the membrane, glycophorins C and D are associated with AE1 dimers and compose part of the red cell junctional complex (Fig. 10), which is responsible for maintaining the lateral stability of the red cell membrane (3). The cytoplasmic tails of both glycophorins interact with several cytoskeletal elements, including spectrin, actin, protein 4.1, and p55. The Gerbich and Leach deletion phenotypes are associated with ovalocytosis. A decrease in glycophorin C and D levels can also be seen in cases of ovalocytosis due to mutations in actin and other junctional complex proteins (4).

Gerbich and Malaria

Gerbich-negative red cells show increased resistance to *P. falciparum* invasion *in vitro* (575). It is now recognized that glycophorin C, but not glycophorin D, is a receptor for BAEBL (EBA-140) (576). Amino acid polymorphisms in the Duffy binding-like domains (F1 and F2) can alter receptor recognition. Among BAEBL/EBA140 variants, only BAEBL-VSTK specifically recognizes glycophorin C (576).

EBA140/BAEBL binding is dependent on sialic acid and the single N-glycan near the glycophorin C amino terminus, with contributions by sialylated O-linked glycans and the glycophorin C protein backbone (577). Recombinant EBA140 does not bind red cells treated with neuraminidase (578). Mutational and crystallography studies suggest that the F1 domain is absolutely essential for binding of the N-glycan (576, 579). It has been postulated that the F2 domain may engage with sialylated O-glycans (579).

It has been unclear why individuals with the Gerbich phenotype (GYPCΔex3) should display resistance to *P. falciparum*, since a deletion of exon 3 is not associated with a loss of any glycosylation sites. Despite the latter, GYPCΔex3 is abnormally glycosylated, with a 3-fold decrease in the level of sialylated O-linked glycans and a switch to immature, high-mannose structures on the terminal N-glycan (Fig. 10) (577). GYPCΔex3 is not recognized by recombinant EBA140 *in vitro* (578). High-mannose glycans are normally synthesized early in the endoplasmic reticulum but are then processed to mature forms in the Golgi complex. It has been hypothesized that the truncated GYPCΔex3 protein interferes with normal Golgi processing or trafficking, leading to aberrant glycosylation (577).

It had long been recognized that there was an unusually high prevalence of ovalocytosis and the "Gerbich-negative" phenotype among Melanesians of Papua New Guinea, a region where all four species of malaria are holoendemic. An early study by Serjeantson examined the incidence of malaria and Gerbich positivity in 266 Melanesians from Northern New Guinea (580). The overall rate of parasitemia among Gerbich-negative individuals was one-third that of Gerbich-positive individuals (5.7% versus 18.6%; $P = 0.06$). When examined by malarial species, the Gerbich-negative phenotype was reportedly protective against *P. falciparum* and *P. vivax* but not against *P. malariae*.

A larger study of 705 genotyped individuals from the Wosera region identified the Gerbich GYPCΔex3 allele in 71% of the population, including homozygosity in 22% (581). As expected, there was a correlation between the GYPCΔex3 genotype and the relative number of circulating ovalocytes. Unlike Serjeantson, however, these investigators found no correlation between GYPCΔex3 genotype and *P. vivax* and *P. falciparum* parasitemia over a 7-month observation period. Likewise, Fowkes et al. found no correlation between SAO and either parasitemia or seroconversion rates in 566 children from the Madang Province of New Guinea (582). It is important to note that both studies looked only at parasitemia and not disease severity. In addition, these investigators did not examine the BAEBL variant type, which determines the requirement for glycophorin C. It is unknown whether GYPCΔex3, like Southeast Asian ovalocytosis (see Diego Blood Group, above), is protective against cerebral malaria (581).

One other GYPC variant should theoretically display *P. falciparum* resistance. The Webb$^+$ (Wb) (GE5) phenotype is a rare phenotype due to an Asn8→Ser polymorphism near the GYPC amino terminus. This change eliminates the N-glycan, with substitution of an O-glycan (583). The Wb$^+$ phenotype is rare in all populations (0.01%), with the highest incidences being found in Australia and Wales (0.1 to 0.2%) (2, 584).

KNOPS BLOOD GROUP

Biochemistry

The Knops blood group resides on complement receptor 1 (CR1; CD35), a complement regulatory protein of both the classical and alternative pathways (25, 585). CR1 binds complements C3b and C4b, leading to clearance of immune complexes by the reticuloendothelial system. In the presence of factor 1, CR1 can facilitate the degradation of C3b and C4b to iC3b and iC4b, respectively. CR1 also accelerates the decay of C3 and C5 convertases and may interact with C1q and mannose binding lectin (25). CR1 is expressed on many blood cells, including red cells, T and B lymphocytes, monocytes, granulocytes, dendritic cells, and glomerular podocytes (2). Red cells, however, account for 85% of the total CR1 in humans (25).

CR1 is a large glycoprotein (30 kDa) with four isoforms and variable membrane expression (25, 585). Structurally, CR1 is composed of a string of short consensus or complement control protein (CCP) repeats (Fig. 11). Each CCP contains ~60 amino acids and 4 cysteine residues, forming two disulfide bonds per CCP. The CCPs are grouped into larger domains, called long homologous repeats (LHRs) (LHR-A to -E), composed of 7 CCP units. Each LHR typically contains a complement binding domain composed of three consecutive CCP repeats; however, most of the complement factor I cofactor activity is located in LHR-B "site 2" (CCP8 to -10) (29). Based on plasmon resonance studies, C3b is a better substrate (K_D = 0.8 to 1.1 μM) than C4b (K_D = 5.0 to 5.3 μM) and C1q (K_D = 5.5 to 5.7 μM) (586). LHR-A and LHR-B also serve as cofactors in the decay of C3a and C5a convertases (29, 586). LHR-D may serve as a binding site for mannose binding lectin. Differences in the numbers of CCPs, LHRs, and complement binding domains are responsible for the CR1 isoforms CR1*1 (220 kDa), CR1*2 (250 kDa), CR1*3 (190 kDa), and CR1*4 (280 kDa). CR1*1 and CR1*2 are the two most common allelic forms in humans (25, 585). CR1*1 is the most common form in most populations and is composed of 30 CCPs, 4 LHRs, and 3 complement binding domains (2, 25).

Serology

In normal individuals, the CR1 density on red cells can vary 10-fold between individuals, ranging from 200 to 1,200 molecules per cell (2, 25, 587). The Helgesson phenotype refers to an extremely-low-CR1

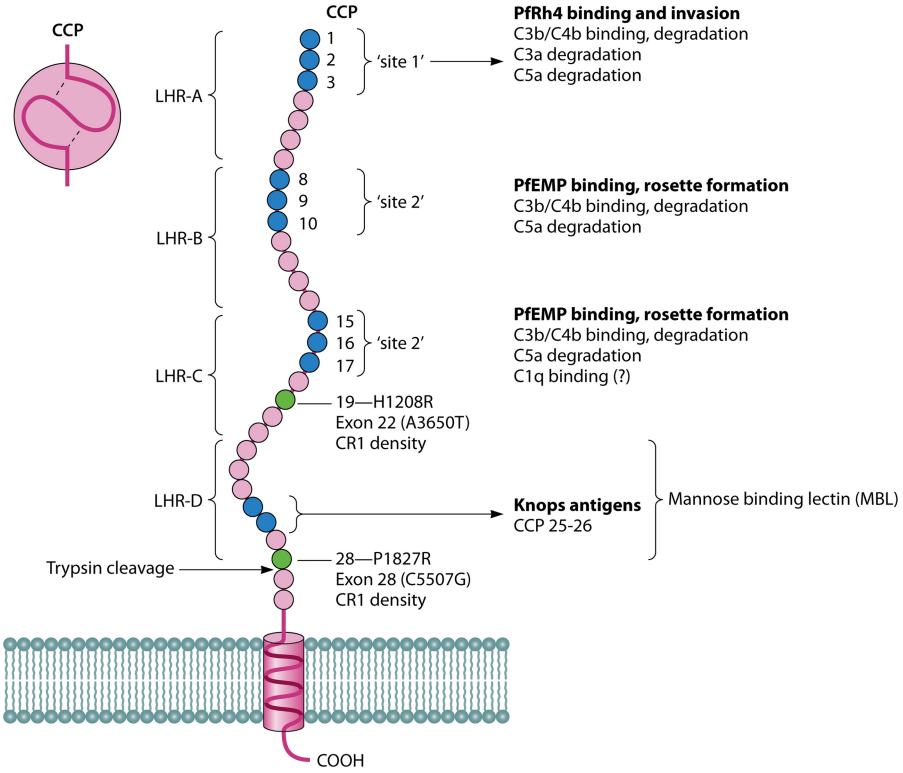

FIG 11 Knops blood group (CR1; CD35). The CR1 variant on red cells is composed of 30 complement consensus repeats arranged as 4 long homologous repeats (LHR-A to -D). CCPs involved in complement binding are highlighted (purple) and referred to as sites 1, 2, and 2′. These sites also serve as binding sites for malarial proteins (PfRh4 and PfEMP). LHR-D may interact with mannose binding lectin. The Knops antigens are located in CCP25 and CCP26 (blue). The sites of two mutations associated with weak CR1/Knops expression are highlighted in green. Also shown is the trypsin cleavage site on CR1.

phenotype, with only 50 to <150 CR1 molecules per cell (587). These individuals are serologically typed as Knops negative by routine testing since there are insufficient CR1 molecules to support hemagglutination. Multiple genetic polymorphisms have been linked with high and low CR1 densities (587). Among the most commonly studied low-CR1 polymorphism is rs11118133, an A→T transition in intron 27 of LHR-D. The intron 27 polymorphism is in linkage disequilibrium with three other polymorphisms, including Q1022H (CCP16), H1208R (exon 22) (CCP19), and P1827R (CCP28) (588). As a consequence, genomic studies often screen for multiple CR1 polymorphisms when testing for CR1 density. The CR1 density can also be decreased in patients with infection and autoimmune disorders due to high levels of circulating immune complexes (25).

CR1 is home to the Knops (KN) blood group system, which is located within LHR-D (Fig. 11) (25, 28). Knops currently contains 9 allelic antigens (KN1 to -9 [Kn^a/Kn^b, $McC^a/McC^b/McC^c$, Sl1/Sl2/Sl3, Yk^a, and $KCAM^{+/-}$]) resulting from amino acid polymorphisms in CCP25 and CCP26. Many Knops antigens show very pronounced differences between blacks and whites, leading to speculation that Knops/CR1 has been subject to selective pressure by malaria or some other infectious disease (Table 2). Antigens prevalent in blacks, but not whites, include McC^b, Sl2, and KCAM (25). Studies with CR1 variants that differ only in McC and Sl antigens show no effect on CR1 function or structure (586). Specifically, there was no difference in C3b, C4b, or C1q binding or in C3b and C4b degradation (586).

CR1 and *P. falciparum* Invasion

P. falciparum can invade red cells via sialic acid-dependent (glycophorins) and sialic acid-independent mechanisms. Sialic acid-independent invasion pathways are a necessary adaptation as patients develop immunity to glycophorin-dependent invasion proteins (589). Sialic acid-independent invasion also nullifies the impact of unusual glycophorin phenotypes present in some populations (589). CR1 was suspected to be a candidate red cell receptor because of its exquisite sensitivity to trypsin (25), which inhibits sialic acid-independent invasion (589). Initial studies demonstrated merozoites binding to CR1-coated microspheres. On red cells, merozoite binding induces CR1 capping and is inhibitable by soluble CR1 and anti-CR1 (589, 590). CR1 was subsequently identified as the receptor for the reticulocyte binding-like protein PfRh4 (589, 591). PfRh4 binding has been mapped to the C3b/C4b binding domain in LHR-A, located at CCP-1 to -3 ("site 1"), with a K_D of 2.9 μM (Fig. 11) (586, 591).

The roles of both CR1 density and CR1 allotypes in *P. falciparum* infection have been examined *in vitro* and in epidemiologic studies. As expected, there is a correlation between red cell CR1 expression, PfRh4, and merozoite binding, with significantly higher rates of invasion in CR1-high expressors (586, 591). In Papua New Guinea, an area where malaria is endemic, there is a high incidence of the CR1-L (low) allele, with 60% of individuals being typed as LL and only 5% being typed as HH (CR1 high; wild type) (582, 592). Average CR1 levels in this population are among the lowest in the world, averaging only 124 CR1 molecules per red

cell (592). Not surprisingly, LL individuals tended to have less-frequent episodes of parasitemia than did HL heterozygotes ($P = 0.07$) (582). In a case-control study involving 358 individuals, the CR1-L allele was protective against severe malaria even in heterozygotes (OR, 30; $P = 0.04$) (592).

Panda et al. also examined CR1 density relative to malaria in 494 Indian patients, including 353 patients with severe malaria (593). CR1 density was determined by typing for both the intron 27 and exon 22 polymorphisms. As predicted, patients with severe malaria tended to have CR1-H alleles ($P < 0.0001$) and overall poor survival (61% versus 36.6%; $P = 0.0007$). Homozygosity for CR1-L alleles was protective against severe malaria ($P < 0.0001$; OR, 0.28 to 0.32), especially cerebral malaria (OR, 0.18 to 0.21) and multiorgan dysfunction (OR, 0.18 to 0.21). Haplotypes possessing both intron 27 and exon 22 CR1-L polymorphisms showed 2- to 3-fold protection against severe malaria (OR, 2.35), cerebral malaria (OR, 3.03), and multiorgan dysfunction (OR, 3.01).

These same investigators also performed a meta-analysis of CR1 density polymorphisms in 6 studies conducted in Thailand, India, and Papua New Guinea (593). Cumulatively, the studies covered 1,858 patients, including 1,040 patients with severe malaria. For the exon 22 polymorphism, homozygosity (OR, 0.56; $P = 0.01$) and heterozygosity (OR, 0.41; $P = 0.02$) for a CR1-L allele were associated with protection against severe malaria. In contrast, there was no significant difference in intron 27 alleles between patients with severe malaria and those with uncomplicated malaria.

A few studies have examined the possible impact of CR1/Knops polymorphisms, especially McCoy (McC^a/McC^b) and Swan-Langley (Sl1/Sl2) antigens, on the risk of malaria. Early studies suggested that the Sl^- (Sl2/2) genotype is associated with a decreased risk of severe malaria (594). A Brazilian study suggested that Kn^b, and especially a Kn^a/Kn^b genotype, increased susceptibility to *P. falciparum* (28% versus 3.7%; $P = 0.04$) (595). When examined by CR1 haplotype, risk was specifically associated with the H8 allele with coinheritance of Kn^b and KCAM antigens (14% versus 2% of controls; $P = 0.027$). Other studies found no correlation between Knops phenotypes and severe malaria (596–598). In India, the incidence of McC and Sl antigens was virtually identical to that observed for Caucasians (26). Likewise, CR1 constructs bearing different combinations of McC and Sl antigens had no effect on PfRh4 binding or invasion (586).

CR1 and *P. falciparum* Rosetting

P. falciparum can also induce rosetting through recognition of CR1. Rowe et al. demonstrated that some *var* genes showed a preference for CR1, forming very few rosettes with "Knops-null" cells (Helgesson phenotype) (599). In normal red cells, rosette formation could be blocked with soluble CR1 (sCR1) and antibodies against CR1 (599, 600). It was hypothesized that CR1-L alleles should be protective against cerebral malaria, although this would be highly dependent on *var* gene expression (592, 599). These same investigators reported that red cells with an Sl(a−) or Sl2/2 phenotype also demonstrated weak rosetting, although many of the samples tested also had very low CR1 expression levels (599). One case-control study of Kenyan children reported a decreased incidence of cerebral malaria in Sl2/2 individuals (OR, 0.17 [95% CI, 0.04 to 0.72]; $P = 0.02$) but did not correlate these findings with evidence of rosette formation (594).

The site of PfEMP1 binding is mapped to the C3b binding sites located in LHR-B and LHR-C (CCP8 to -10 and CCP15 to -17) (Fig. 11) (600). More recent studies with CR1 constructs suggest that CCP15 to -17, especially CCP17, are receptors (586). PfEMP1 binding does not require the presence of bound complement for rosette formation (600). CR1 variants bearing different McC and Sl antigens were able to equally disrupt rosetting and played no direct role in PfEMP1 binding (586).

Leishmania

Leishmania is an obligate intracellular parasite transmitted by sand flies that can manifest as cutaneous sores, mucocutaneous infections, and visceral leishmaniasis, a disseminated infection of reticuloendothelial tissues (spleen, lymph nodes, and liver) (601). Active infection involves recognition of and binding by naturally occurring antibodies, followed by complement activation and opsonization of *Leishmania* promastigotes by monocytes (602). The complement-coated organisms are able to bind cells by either CR1 (C3b) or CR3 (iC3b), although CR1-mediated phagocytosis appears to predominate in monocytic cells (600, 601). Both CR1 downregulation and CR1 blockade inhibit *Leishmania* adhesion and infection of monocytes *in vitro* (602–604).

Leishmania species belonging to the *L. braziliensis* complex can produce a latent or chronic infection in a small proportion of people, suggesting host susceptibility factors. Robledo et al. compared monocytes from individuals with a history of leishmania infection of >12 months in duration to those from individuals with a positive skin test but no history of active infection (604). Rates of leishmania attachment and infection were nearly 2-fold higher in monocytes from chronically infected individuals. These authors attempted to look at CR1/CR3 activity on monocytes indirectly, by measuring the ability of monocytes to bind and rosette complement-coated sheep red cells. Although these authors were able to show a direct correlation between rosetting and leishmania infection in noninfected controls, there was no relationship in patients with a history of chronic infection. To date, there do not appear to be any studies examining the CR1 genotype with leishmania infection and outcomes.

Mycobacteria

Active tuberculosis has been linked with lower CR1 levels on red cells due, in part, to elevated levels of circulating immune complexes in these patients (25, 605). A genetic study in Africa suggested an association between low CR1 expression levels and an increased susceptibility to *Mycobacterium tuberculosis*; however, the incidence of the CR1 (LL) genotype was very low in both patients and control individuals (4% versus 2%) (606). This finding was reexamined by Senbagavalli et al., who carefully compared the impacts of CR1 genotype, CR1 red cell expression, and immune complex levels in 125 Indian patients with active tuberculosis (605). Patients with tuberculosis were more likely to be genotyped as CR1-H homozygotes (70% versus 56%; $P = 0.012$). CR1 levels in patient red cells, regardless of the CR1 genotype, tended to be significantly lower than normal and were directly related to disease severity and high levels of circulating immune complexes.

Two studies have examined the role of Knops antigens in mycobacterial infections (607, 608). One small study in Mali, Africa, reported that individuals heterozygous for both McCoy ($McC^a/$

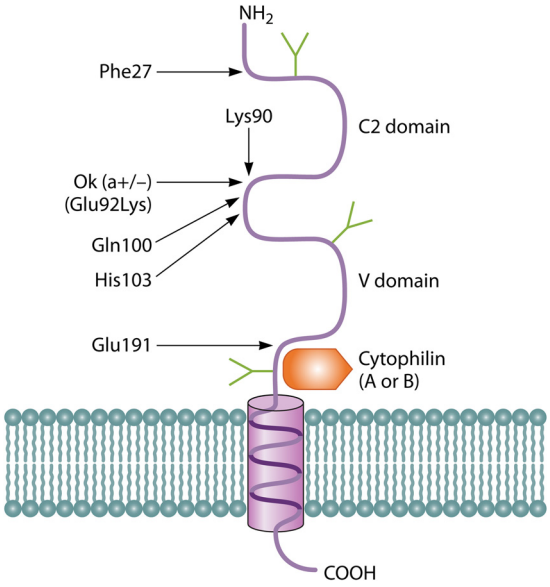

FIG 12 OK blood group (Basigin; CD147). CD147 is a member of the immunoglobulin superfamily. The most common isoform contains single C-type and V-type domains. The Ok(a+/a−) polymorphism is located at amino acid 92. Several amino acids that are believed to participate in PfRh5 binding are highlighted (612, 615). CD147 is also able to bind cyclophilins (A and B) and plays a role in many viral infections (HIV, measles virus, and SARS-CoV).

McC^b) and Swain-Langly (Sl1/Sl2) antigens were less likely to have tuberculosis (OR, 0.25; $P = 0.008$) (606). A genetic study in Northern Malawi reported that a McC$^{b/b}$ homozygous genotype was protective against leprosy (OR, 0.3 [95% CI, 0.1 to 0.8]; $P = 0.02$), although the number of individuals with this genotype was very small ($n = 33$) (608). It was speculated that differences in Knops antigens, which reside in LHR-D, might alter binding by mannose binding lectin (607). Mannose binding lectin can promote phagocytosis of virulent mycobacterial strains through recognition of lipoarabinomannan (609).

OK BLOOD GROUP

Biochemistry and Serology

Basigin or CD147 is a member of the immunoglobulin superfamily, with four known isoforms due to alternate splicing (610, 611). Basigin-2 (35 to 69 kDa) is the common isoform found on most tissues, including red cells. The basigin-2 extracellular domain is composed of two immunoglobulin-type domains: D1, a C2-set-like domain, and D2, an I-set category domain (Fig. 12). In the membrane, CD147 is present as a homodimer, often in complex with other proteins such as β1 integrins, monocarboxylic acid transporters, CD44 (Indian blood group), γ-secretase, caveolin, and syndecan. The extracellular domain is a receptor for the leukocyte chemotactic factors cyclophilins A and B. CD147 also interacts with platelets (GPVI) and leukocytes (CD43) and can promote tumor metastasis through the induction of metalloproteases and vascular endothelial growth factor (610, 611). CD147 is widely expressed on epithelial tissues, blood cells, retina, and neural cells (2). There are ~3,000 molecules of CD147 per human red cell (2).

The OK blood group resides on CD147 and contains three high-incidence antigens, Ok^a, OKGV, and OKVM (2). The Ok(a−) phenotype has been identified in only 8 individuals of Japanese heritage due to a polymorphism in D1 (Glu92Lys) (2). Four additional amino acid polymorphisms are known (K36N, V60L, L90P, and G153V), but these polymorphisms have not resulted in alloantibody formation (612). CD147 is thought to play a role in red cell trafficking, recirculation, and senescence (613, 614). During red cell aging, CD147 is lost on membranes, leading to splenic trapping and removal (613). Antibodies against CD147 can induce splenomegaly and anemia in mouse models (614).

P. falciparum

Basigin/CD147 is the receptor for the *P. falciparum* erythrocyte binding protein PfRh5. PfRh5 is unique among all the identified malarial adhesion proteins in that it is absolutely essential for invasion and parasite growth in blood-stage cultures (612). All laboratory and wild-type *P. falciparum* isolates express PfRh5, and mutants lacking PfRh5 are incapable of red cell invasion. *In vitro*, PfRh5 binding and parasite invasion can be inhibited by anti-CD147, soluble CD147, and short hairpin RNA (shRNA) against CD147 (612). In shRNA knockdown experiments, a modest 50 to 60% decrease in CD147 levels reduced *P. falciparum* binding and invasion by 80 to 90% (612). A preference for CD147 favors infection of reticulocytes and young red cells, which still have high CD147 levels (613, 614). CD147 is believed to dictate the tropism of *P. falciparum* for humans (615). The level of PfRH5 binding to human CD147 ($K_d = 0.8$ μM) is 10-fold higher than that for chimpanzee ($K_d = 10.4$ μM) (615).

The PfRH5 binding site is not yet elucidated but appears to involve both the D1 and D2 domains: PfRh5 does not bind CD147 constructs expressing only D1 or D2 alone (612). Evidence for specific D2 interactions comes from studies with human CD147 variants (612). There was a 30 to 50% decrease in *P. falciparum* parasitemia in Ok(a−) cells, which express Lys92. Kinetic studies with purified PfRh5 showed lower association and higher dissociation rates with Ok(a−) (612). The adjacent Lys90Pro polymorphism leads to a complete loss of PfRh5 binding, possibly as a result of protein misfolding. Studies of primate CD147 show a high degree of conservation between humans, chimpanzees, and gorillas (615). Several residues (F27, Q100, H103, and K191) along one face of the CD147 molecule favor PfRH5 binding to human, but not ape, red cells (615).

HIV and Other Viruses

CD147 is a receptor for cyclophilin A, an intracellular peptidyl-prolyl isomerase important in protein folding (610). The incorporation of cyclophilin A into HIV-1 particles increases their infectivity by nearly 6-fold (616). Conversely, the absence of cyclophilin A as a result of viral mutations, or by growing HIV in the presence of cyclosporine, severely attenuates virus infectivity (616).

It has been theorized that cyclophilin A may play a role in HIV-1 adhesion during virus-cell fusion. This was demonstrated by Pushkarsky et al., using CHO cells transfected with CD147 (616). CHO-CD147 cells were significantly more sensitive to HIV than were controls, and infection could be blocked by either cyclosporine or anti-CD147. Immunoprecipitation experiments showed that HIV binding was mediated by virus-associated cyclophilin A, which presumably interacts with the cyclophilin binding domain near the CD147 transmembrane domain (610, 616). Unlike solu-

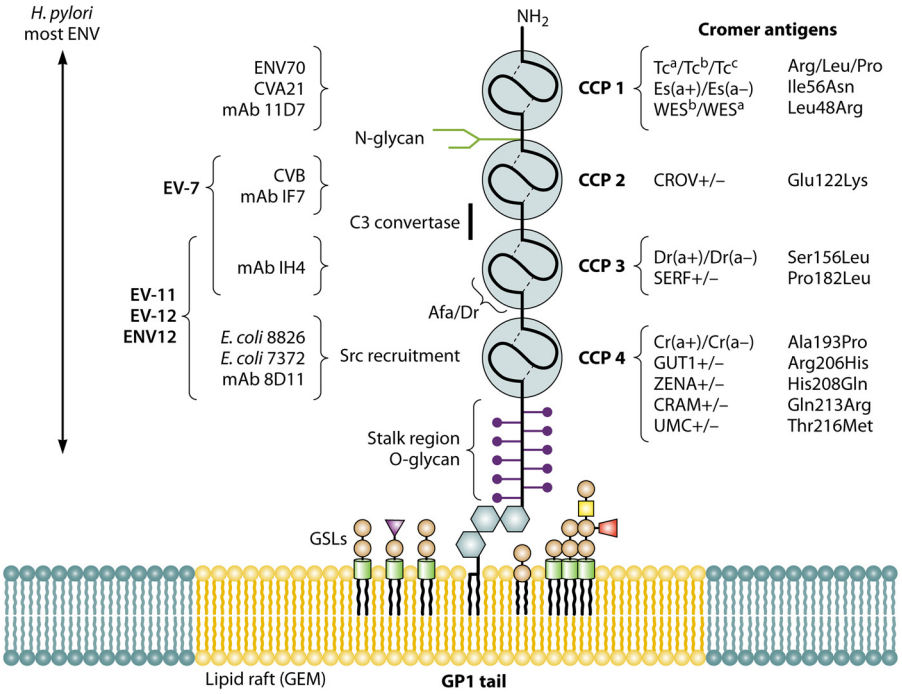

FIG 13 Cromer blood group. Decay-accelerating factor (DAF) (CD55) is a GPI-linked glycoprotein composed of 4 complement consensus domains (CCPs), a heavily glycosylated stalk region, and a GPI tail. The location of Cromer antigens is shown on the right. C3 convertase binding is located along CCP2-CCP3. CCP domains involved in binding specific echoviruses (EV), enteroviruses (ENV), bacteria, and MAbs are shown. *H. pylori* and many enteroviruses appear to require the entire molecule for binding. Like most GPI-linked glycoproteins, DAF is a raft protein and is localized at or recruited into glycolipid-enriched microdomains (GEMs).

ble cyclophilin A, HIV does not induce cell signaling upon binding CD147 (617).

CD147 is also implicated in other viral infections. Like HIV, cytophilin A is incorporated into the SARS coronavirus envelope and can interact with CD147 (618). Measles virus, on the other hand, binds CD147 via virus-associated cyclophilin B. The ability of measles virus to bind CD147, which is widely distributed on epithelial and neuronal cells, may explain the occurrence of diarrhea and encephalitis observed in severe measles virus infections (619).

CROMER BLOOD GROUP

Biochemistry

CD55 or decay-accelerating factor (DAF) (Fig. 13) is a 70-kDa, highly glycosylated, 319-amino-acid glycoprotein (2). The large extracellular domain contains four CCP repeats at the amino-terminal end, anchored by a 67-amino-acid Ser/Thr-rich domain containing, on average, 11 O-linked glycans (620). The latter acts as a rigid stalk or spacer, extending the functional CCP domain 17.7 Å above the cell membrane (620). The entire molecule is anchored by a glycosylphosphatidylinositol (GPI) tail and tends to segregate and localize within GEMs (716). As a consequence, CD55 is sensitive to glycophosphoinositol-specific phospholipase C, a GPI-specific phospholipase, as well as reagents that disrupt lipid rafts. CD55/DAF is absent in individuals with paroxysmal nocturnal hemoglobinuria (PNH) due to defects in GPI synthesis (2, 29). Soluble CD55 (sCD55) arises from alternate splicing and is found in secretions and body fluids (620).

CD55/DAF is a complement regulatory protein, and its absence is associated with inappropriate complement activity, tissue damage, and hemolysis (620). CD55 binds and dissociates C3 convertase (C3bBb; C4b2a), with the release of Bb or C2a. It is believed that C3 convertase lies in a fold between adjacent CCP units, since deletion of CCP2, CCP, or CCP4 abolishes complement regulatory activity (621). CD55 may also interfere with leukocyte adhesion (620). As a lipid raft resident, CD55 is a member of the LPS receptor complex, and as a resident molecule in raft domains, it can modulate intracellular signaling and cytoskeletal alterations through interactions with ERM (ezrin, radixin, and moesin) proteins, NF-κB, mitogen-activated protein (MAP), and Src family kinases (622, 623). CD55 is widely expressed in tissues and secretions, including blood cells, the endothelium, and gastrointestinal and genitourinary epithelia (2). There are ~20,000 CD55 molecules per red cell (2).

Genetics and Serology

The gene for CD55 is located on chromosome 1q32 and is organized over 11 exons. Genetic studies indicate antagonistic selection for promoter polymorphisms that may regulate tissue-specific expression (50). The Cromer system contains 23 antithetical antigens along the four CCP domains (Fig. 13). Most polymorphisms are low-incidence antigens present in rare individuals (2, 624). Exceptions are Tc^b, which is present in 6% of blacks, and GUT1(−), which is highly prevalent among Mapuche Indians (2). CROV is adjacent to at least one amino acid residue (Phe123) critical for complement-inhibitory activity (625).

Weak CD55/Cromer expression is observed for the Dr(a−) phenotype, which arises from a point mutation that leads to both

an amino acid polymorphism (Ser165Leu) and a new alternate splice site (624). Use of the alternate splice site abolishes normal protein expression due to a deletion and a frameshift. As a consequence, the Dr(a−) mutation is associated with very weak CD55 expression, with only a small fraction of full-length CD55 being synthesized, all carrying the Dr(a−) polymorphism in CCP3. In monocytes, differences in CD55 expression have been linked to a promoter polymorphism (626). CD55 is absent or its expression is reduced in individuals with PNH and the Inab phenotype (Cr_{null}). The latter may arise due to genetic mutation or may be an acquired phenotype (624).

E. coli Dr Adhesin

The Afa/Dr family of adhesins was named after their inability to agglutinate rare Dr(a−) and PNH red cells. Dr^+ *E. coli* strains are considered diffusely adhering *E. coli* (DAEC) strains and belong to the type 4 pathotype of uropathogenic *E. coli* (623). *E. coli* strains expressing Dr fimbriae are found in 30 to 50% of cystitis isolates and show strong binding to renal tubules and Bowman's capsule (627). They are involved in recurrent UTIs and are nearly always multiantibiotic resistant (628). Dr^+ strains are a common cause of intestinal infections, especially in children, and can account for 25% of extraintestinal infections (629). In cell cultures, Dr^+ *E. coli* recruits CD55, with CD55 clustering at the site of bacterial binding (629). This phenomenon is the basis for the "DAF clustering assay" used to screen for Afa/Dr DAEC strains (623).

The Afa/Dr family contains at least 13 adhesins and fimbriae that differ in their ability to recognize CD55, type IV collagen, and CEACAMs (carcinoembryonic antigen-related cellular adhesion molecules) (623). Afa/Dr family members known to bind CD55 include Dr; F1845 fimbriae; and the afimbrial adhesins Dr-II, AfaE-I, and AfaE-III. Epitope mapping with CCP-specific antibodies indicated that CCP3, which contains the Dr^a antigen, is critical to Afa/Dr binding (620, 630). Similar results were obtained by using CD55 deletion mutants lacking specific CCP domains (630). Hasan et al. subsequently prepared CD55 variants containing single point mutations within the CCP3 domain to map the Dr binding site (625). Three amino acids were identified as being critical to Afa/Dr binding: Ser155, Cys156, and Ser165 (Dr^a). Three additional amino acids (Gly159, Tyr160, and Leu162) were found to participate in Dr binding. Molecular modeling showed that the identified amino acids form a pocket toward the bottom of the CCP3 domain. Interestingly, several of the amino acids identified (aa 155, 156, 160, and 162) also play a role in the binding of enteroviruses (coxsackie B virus [CVB], echovirus 7 [EV-7], and EV-12) (631). The site of Afa/Dr binding is distinct from complement regulatory functions (625).

Dr binding to CD55 results in rapid Src activation, leading to the recruitment and clustering of CD55 and Src around adherent bacteria (632). Surprisingly, Src activation requires the presence of the CCP4 domain: CD55-ΔCCP4 deletion mutants failed to demonstrate either Src activation or CD55 mobilization (632). CD55 subsequently mediates bacterial invasion in a raft-dependent process with endocytosis of bacterium-CD55 complexes. Bacterial endocytosis can be inhibited by a loss of the GPI anchor or through disruption of lipid rafts with β-methyl-β-cyclodextrin (628, 630, 632). Once internalized, there is no evidence of significant bacterial growth or multiplication (630). Bacterial binding to CD55 and bacterial internalization may promote chronic infection by avoiding complement-mediated destruction (630).

Helicobacter pylori

H. pylori can recognize and utilize a number of host ligands as an adaptive response to inflammation and altered glycosylation. Interest in CD55 arose after observations that *H. pylori* infection was associated with elevated CD55 expression on inflamed gastric mucosa (633). O'Brien et al. were the first to show *H. pylori* binding to CD55 using CHO-CD55 transfectants (634). Furthermore, *H. pylori* was shown to transcriptionally upregulate CD55 mRNA expression (635). CD55 upregulation requires live bacteria expressing a functional *cag* type IV secretion system.

In animal models, CD55 knockout mice infected with a rodent-adapted *H. pylori* strain (SS1) had very little inflammation and gastritis relative to wild-type mice ($P = 0.013$) (634). Similar experiments in a $CD55^+$, hypergastrinemic (INS-GAS) mouse strain showed that *H. pylori* accelerated gastric inflammation, with a marked upregulation of CD55 on gastric epithelial cells (635). These results suggest that CD55 contributes to chronic inflammation and the persistence of virulent *H. pylori* strains (635).

H. pylori appears to bind CD55 along the entire extracellular domain, including the stem region (634). Adhesion experiments with CD55 deletion constructs found a 70% to 100% reduction in binding following the loss of even one CCP domain. Likewise, attempts to block binding with individual CCP-specific monoclonal antibodies failed to appreciably decrease *H. pylori* adhesion (634). Inhibition was observed only when an antibody cocktail containing antibodies against all four CCP domains was used.

Plasmodium falciparum

There are observational studies linking severe malaria to low CD55 expression by elevated circulating immune complexes. A study of 342 Kenyans showed that CD55 levels was strongly correlated with the percentage of $C3b^+$ red cells (636). Gwamaka et al. studied red cell CD55 and CD59 expression in malaria patients (637). CD55 expression was found to progressively decrease with red cell age; however, the degree of the decrease was significantly greater in children with malaria. In contrast, CD59 expression on red cells was unchanged. Since CD59 regulates immune complex formation, this argues against significant complement-mediated lysis with malaria infection (637). Low CD55 levels could promote increased erythrophagocytosis and accelerated splenic clearance.

Influenza Virus

CD55 is highly expressed on human lung and is believed to protect the lung from complement-mediated tissue damage (626). Infection of respiratory epithelial cells transcriptionally upregulates CD55, presumably as a host defense strategy against complement damage (626). During the 1957 and 2009 flu outbreaks, patients with severe infection had evidence of complement activation, with circulating immune complexes, low C3 levels, and extensive complement deposition along bronchioles (638). A small genomic study of 425 Chinese patients during the 2009 H1N1 pandemic identified two functionally distinct promoter genotypes associated with disease severity (626). Individuals homozygous for the rs2564978-T allele had a higher incidence of severe disease (OR, 1.85; $P = 0.019$) than did C/C individuals. There was a clear association between T/T genotype and low CD55 expression levels on monocytes (3-fold). The T/T genotype was associated with low mRNA levels and decreased transcriptional activity *in vivo* and *in*

vitro (626). In mice, monocytes are critical to clearing virus and moderating inflammation (639).

Hantavirus

Hantavirus is zoonotic illness spread by mice and other rodents (640). Viral strains are typically classified as either New World or Old World based on the location and clinical presentation. In general, New World hantaviruses cause an acute pulmonary syndrome, whereas Old World hantaviruses (Hantaan and Puumala viruses) are a cause of hemorrhagic fever with renal syndrome, including acute and chronic renal failure. Hantavirus readily infects endothelial cells, a significant factor in pulmonary and renal pathology.

β3 integrins, C1q, and CD55 have been shown to bind hantaviruses *in vitro* (640). Hantavirus can be inhibited by incubation of target cells with anti-CD55 or soluble CD55 or by treating cells with phosphoinositol-specific phospholipase C to destroy GPI-linked glycoproteins (641, 642). Treatment of cells with methyl-β-cyclodextrin, which disrupts lipid rafts, also increases cell resistance (641). Kinetic studies indicate high-affinity binding of hantaviruses to CD55, with a K_d of 25 to 30 nM (643). This affinity is significantly higher than that for many enteroviruses, which have K_d values in the micromolar range.

Enteroviruses

Enteroviruses are highly infectious single-stranded RNA viruses belonging to the *Picornaviridae* family (644). These viruses are characterized by a small, nonenveloped, icosahedral capsid containing positive-strand RNA. Human enteroviruses include poliovirus, enterovirus (ENV), coxsackie virus (CV), and echovirus (EV) (enteric cytopathic human orphan). Enteroviruses are spread by fecal-oral transmission, binding to epithelial receptors in the small intestine, followed by symptomatic viremia 4 to 6 days later. These viruses are a common cause of febrile illness in young children, aseptic meningitis, and myocarditis.

Receptors for enterovirus include coxsackievirus-adenovirus receptor (CAR), intercellular adhesion molecule 1 (ICAM), α2β1 integrin, and CD55 (645). In many cases, CD55 is a low-affinity receptor for these viruses, with many investigators hypothesizing that CD55 is a high-density scaffold that serves to capture virus for delivery to other receptors (646).

Coxsackie B virus. Although the primary receptor for CVB is CAR, a tight-junction protein, CD55 is recognized as a coreceptor by some coxsackie B virus serotypes (CVB1, CVB3, and CVB5) (646). In polarized intestinal and trophoblastic epithelial cells, CVB binds CD55 on apical membranes and is then transported toward the tight junctions to bind CAR, followed by caveolin-dependent endocytosis (647, 648). Both membrane trafficking and invasion are dependent on lipid rafts and can be disrupted by methyl-β-cyclodextrin and simvastatin. Like Dr adhesins, virus uptake involves signaling through raft-associated Src kinases (648). In cell cultures, CVB infection can be blocked by soluble CD55 and CD55 antibodies (645, 646). CD55 knockout mice infected with CVB3 have low viral titers but still develop myocarditis and pancreatitis (649).

Several investigators have studied how CVB binds CD55. As in all enteroviruses, the CVB capsid is constructed of 60 protomers, each containing four viral proteins (VP1 to -4) (631, 644). Crystallography studies have shown extensive binding between VP2 and CCP2 of the CD55 molecule (631). There are a few interactions between VP2 and CCP3 (D141, P143, and Y160), but these interactions account for only 25% of the total contacts. This is consistent with data from studies using DAF deletion constructs, which showed an absolute requirement for CCP2 (650). There are no direct interactions with Cromer alloantigens, although VP2 interacts with V121, adjacent to CROV (E122). CVB3 binding to CD55 is quite weak compared to that of hantavirus, with a K_D of 0.38 μM and high on/off rates (651).

Coxsackie A virus. Coxsackievirus A21 (CVA21), like the related rhinoviruses, is associated with cold-like illnesses. CVA21 recognizes CD55 as a coreceptor, although it requires ICAM-1 for cell invasion (645). CVA21 binding is reduced after treatment of cells with phosphoinositol-specific phospholipase C. Using MAbs against specific CCP domains, the CVA21 binding epitope was localized to CCP1 (645, 652).

Enterovirus. Enterovirus 70 (ENV70) is the etiologic agent of acute hemorrhagic conjunctivitis, a highly contagious form of conjunctivitis that has caused widespread outbreaks. ENV70 was shown to bind HeLa cells via CD55. Epitope mapping with anti-CD55 MAbs suggested binding to CCP1, -2, and -3 (653, 654). Experiments with DAF deletion constructs localized binding primarily to CCP1. CCP2 was theorized to play a scaffolding role, presenting CCP1 in the correct conformation for ENV70 recognition (654).

Several additional enteroviruses have been shown to bind CD55, including ENV3, ENV6, ENV7, ENV11, ENV12, ENV13, ENV19, ENV24, ENV29, and ENV33 (652). Epitope mapping studies with CCP-specific antibodies and CD55 deletion constructs indicate that most enteroviruses require nearly full-length CD55 for binding (CCP1-4 and CCP2-4). The exception is ENV12, which appears to recognize epitopes on CCP3 and/or CCP4 (652).

Echovirus. Studies in HeLa cells provided the first evidence of EV binding to CD55 (655). A screen of six echovirus strains showed that 4/6 isolates (EV-6, -7, -12, and -20) could be blocked by anti-CD55. Epitope mapping with CCP-specific MAbs implicated EV-7 binding to CCP2-CCP3 (655). CD55 facilitates EV-7 uptake via clathrin-mediated endocytosis and is independent of lipid rafts (656). Studies with other echovirus strains show various roles for CD55 in virus uptake. EV-11-207, like CVB, binds CD55 with transfer to tight junctions in a raft-dependent manner, followed by internalization (657). Unlike CVB, echovirus can be internalized as a CD55-virus complex.

The interaction of CD55 and echoviruses has been studied for EV-7, EV-11, and EV-12 by transmission electron microscopy and surface plasmon resonance (658, 659). In general, CD55 is a weak receptor, with K_D values ranging from 0.7 to 4 μM (659). As predicted from antibody studies, EV-7 binds primarily across the CCP2 and CCP3 domains, with some binding to CCP4. In contrast, EV-11 and EV-12 preferentially interact with CCP3 and CCP4. A comparison of EV-7 and CVB3 showed a few shared contacts on the CD55 molecule (aa 104, 112, 121, 141, and 160); however, the binding sites of the two viruses are quite distinct (631). Likewise, EV-7 and EV-12 share only two contacts on CD55 (aa 155 and 214). It is important to note that Ser155 was identified as a critical amino acid for Afa/Dr adhesins (625).

A comparison of echovirus binding with Cromer antigens showed several possible interactions (631). EV-7 recognizes a short peptide sequence on CCP4 (aa 213 to 216) that includes the

CRAM (Gln213Arg) and UMC (Thr216Met) antigens. EV-7 also interacts with a short CCP2 peptide (aa 120 to 124) that includes the CROV antigen (Glu122Lys) as well as several amino acids (160, 162, 166) adjacent to the Dr^a antigen (Ser165; CCP3). EV-12 does not directly bind Cr antigens but interacts with several residues near CRAM (aa 211, 212, and 214).

INDIAN BLOOD GROUP

Biochemistry

The Indian blood group resides on CD44, a ubiquitously expressed type 1 glycoprotein involved in cell adhesion, signaling, cell differentiation, motility, and innate and adaptive immunity. The CD44 gene consists of 20 exons, resulting in several tissue-specific CD44 isoforms (80 to 200 kDa) due to alternative splicing and differences in posttranslational glycosylation (29, 660). The molecule consists primarily of a large amino-terminal extracellular domain composed of a 90-amino-acid, globular hyaluronan binding domain and a variable stem region rich in O-linked glycans (Fig. 14). Several arginine (R41 and R78) and tyrosine (Y42 andY79) residues important for hyaluronic acid binding are located near disulfide bonds (C77 and C79) (661, 662). The carboxy-terminal cytoplasmic domain interacts with ankyrin and band 4.1 proteins (ERM proteins) of the cytoskeleton as well as several intracellular signaling proteins (Src, LCK, FYN, protein kinase C [PKC], Rho kinase, and Rho GTPase). The interaction of CD44 with band 4.1 ERM proteins is required for the formation and extension of microvilli and cell motility. CD44 tends to localize along the basolateral edge of polarized epithelia and lamellipodia of migrating cells (660).

As a cell adhesion molecule, CD44 is implicated in a variety of biological functions. It recognizes hyaluronan and glycosaminoglycans on the extracellular matrix, mediating both cell adhesion and migration. CD44 also catabolizes hyaluronan, which may be critical in tempering local inflammation. CD44 is associated with several innate and adaptive immune processes, including downregulation of Toll receptor signaling, lymphocyte and monocyte activation, phagocytosis, and cell-mediated cytotoxicity by natural killer cells (660).

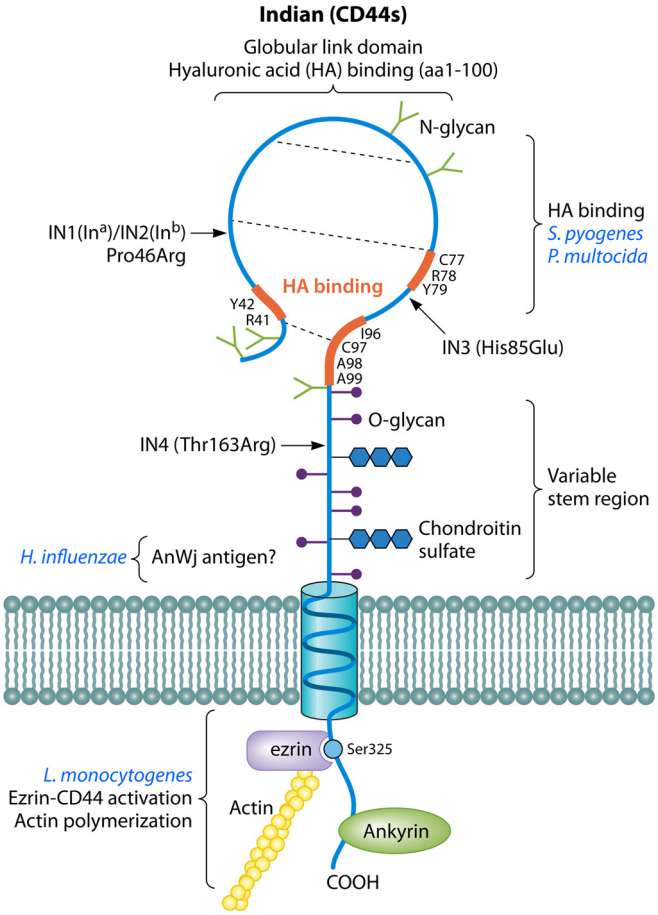

FIG 14 CD44/Indian blood group. CD44s is a 341-aa glycoprotein that possesses a globular link domain with three disulfide bonds (hatched lines) and 5 to 6 N-glycans. The globular domain is capable of binding hyaluronic acid (HA), including hyaluronic acid on *S. pyogenes*. Peptide regions critical for HA binding are highlighted in red. The glycosylated stem region expresses both O-linked glycans (purple) and chondroitin sulfate (blue hexagons) and can vary between tissues due to alternate splicing and glycosylation. The AnWj epitope is hypothesized to lie in the stalk region and is a receptor for *H. influenzae*. The molecule contains a long cytoplasmic domain that interacts with ankyrin and ERM proteins to modulate the cytoskeleton. Binding by *L. monocytogenes* invokes ezrin binding and phosphorylation with actin polymerization.

Serology

Red cells express 6,000 to 10,000 molecules of the common CD44 isoform (CD44s), an 80- to 85-kDa glycoprotein bearing a globular hyaluronan binding domain (amino acids 32 to 123), a short stem region, and potentially six N-glycans, one chondroitin sulfate, and five to six O-glycans (29, 660). The Indian system contains four alloantigens (IN1 to IN4), including two antithetical antigens (IN1 [In^a] and IN2 [In^b]). In^b, IN3, and IN4 are high-incidence antigens (2, 664). In^a is a low-incidence antigen (<1%) in most populations except Indian (4%) and Arab (11 to 12%) populations (2). IN1/2 and IN3 are located proximal to several amino acids critical for hyaluronic acid recognition but are not believed to affect binding (663). The high-incidence blood group antigen Anton (AnWj) is also believed to reside in the Indian blood group system, although its exact location is unknown. There are no known CD44-null individuals, although Indian antigens are depressed on *In*(*Lu*) red cells, a rare autosomal-dominant phenotype due a KLF1 transcription factor mutation that is characterized by decreased expression of Lutheran, Indian, and P_1 antigens (666). To my knowledge, neither the In(a+) nor the *In*(*Lu*) phenotype has been linked with any infectious disease.

Streptococcus pyogenes

Streptococcus pyogenes, or group A streptococcus, is an invasive, capsulated, Gram-positive coccus and a common cause of skin infections and pharyngitis. Severe sequelae include necrotizing fasciitis, sepsis, toxic shock syndrome, and rheumatic fever. Virulent strains of *S. pyogenes* express a capsular polysaccharide composed of hyaluronic acid, which plays an essential role in *S. pyogenes* adhesion (667–669). On human keratinocytes and mucosal epithelium, CD44 recognizes *S. pyogenes* via the hyaluronic lectin binding domain, leading to cytoskeletal rearrangements, disruption of intercellular junctions, and tissue penetration (667). *S. pyogenes* adhesion can be inhibited by anti-CD44 and hyaluronic acid *in vitro* and *in vivo* (667, 669). In CD44-deficient mice, *S. pyogenes* adhesion is reduced 75% with rapid clearance of bacteria

from the upper airway (667). CD44 recognition of hyaluronic acid has also been reported for *Pasteurella multocida* serogroup A (670).

Haemophilus influenzae and AnWj Antigen

H. influenzae type b is a Gram-negative, capsulated coccobacillus and a major cause of illness in young children. Infections include otitis media, acute epiglottitis, pneumonia, and meningitis. Unlike *S. pyogenes*, the *H. influenzae* polysaccharide capsule is primarily composed of ribose (671). *H. influenzae* type b possesses adhesive fimbriae capable of hemagglutinating red cells (672). Studies by Van Alphen et al. in the late 1980s tentatively identified the AnWj antigen as a possible receptor (673). At that time, AnWj was assigned to the Lutheran blood group system based on observations that Lu(a−b−) red cells were also AnWj negative. This association was subsequently disproven in a family study of rare AnWj-negative individuals (674). Although not verified, there is reason to believe that AnWj is a member of the CD44/Indian blood group: Jurkat cells transfected with CD44 acquire AnWj positivity (675). The AnWj epitope still has not been characterized, but indirect evidence suggests that it may be located in the glycosylated stem region just proximal to the membrane (675).

CD44 would fit the original data for *H. influenzae* hemagglutination. *H. influenzae* strains agglutinated true Lu(a−b−) red cells, which have normal Indian/CD44 expression, but not *In*(*Lu*) and cord red cells, which have suppressed CD44 expression (672). CD44 is present in saliva, which was reported to possess variable quantities of AnWj (676). Moreover, salivary AnWj levels were noted to vary relative to AnWj expression on the oral epithelium (676, 677). CD44 levels are usually quite low in saliva but can be increased with smoking, periodontal disease, oral dysplasia, and cancer due to higher CD44 expression levels on buccal epithelium (678, 679).

Shigella

Shigellosis or bacillary dysentery is typically characterized by bacterial invasion and multiplication within intestinal epithelial cells (680). Shigella invades cells through a type III secretion apparatus, in which contact with the host cell initiates bacterial secretion of Ipa and other proteins (681). These proteins interact with the host cell to induce membrane and cytoskeletal rearrangements to form an entry focus for bacterial uptake (681). IpaB, IpaC, and IpaD proteins are essential for bacterial entry, forming an IpaB-IpaC complex that inserts into host membranes (680).

There is strong evidence implicating CD44 in both *Shigella* adhesion and invasion (681). There is a positive correlation between CD44 expression, bacterial adherence, and bacterial invasion. Confocal studies show CD44 recruitment at entry focus sites, particularly along the tips of membrane extensions during bacterial entry. In CD44-positive cell lines, anti-CD44 monoclonal antibodies can inhibit the formation of entry foci ($P < 0.0001$) and bacterial invasion (70% decrease). CD44 was subsequently shown to bind IpaB by Western blotting, affinity chromatography, and immunoprecipitation.

Listeria

Listeria monocytogenes is a Gram-positive, facultative intracellular organism capable of direct cell-cell transmission (682). The organism is widely distributed in soil, water, and livestock, with several large outbreaks being linked to contaminated dairy products and vegetables. Pregnant and immunocompromised patients are at particular risk for infection. In pregnant patients, listeriosis can initially present as a flu-like illness but can progress to amnionitis with premature labor or septic abortion in days (682). Severe infections, including meningitis, are observed for nearly half of immunocompromised patients.

Cell-to-cell infection involves CD44 and ezrin, an ERM band 4.1 protein. A key step in this process is the formation of actin protrusions that penetrate adjacent cells, each carrying a bacterium at its forward tip (683). Both CD44 and ezrin localize at the site of listeria protrusions, with ezrin serving to link the membrane to the growing actin tail. This process requires ezrin phosphorylation and activation, which opens an F-actin binding site on the molecule. CD44 can also block actin polymerization through interactions with merlin, another band 4.1 protein that competes with and displaces ezrin (683, 684). Unlike ezrin, merlin lacks an F-actin binding motif and cannot support protrusion formation. Hyaluronic acid binding to CD44 leads to the activation of merlin (683).

A role for CD44 in listeria infection has been demonstrated in mice (684). In CD44 knockout mice, listeria proliferation is decreased, with an increased rate of intracellular bacterial killing. The latter is not due to inflammatory mediators or an inability to escape from the phagolysosome. CD44-null cells still showed evidence of listeria actin tail formation, although the authors of this study did not look at protrusions under a scanning electron microscope, nor did they examine cells for ERM protein expression.

Bacterial Pneumonia and Other Infections

Several investigators have examined the role of CD44/Indian in the response to and outcome of bacterial pneumonia by using a CD44-deficient mouse model. Wang and colleagues studied the acute response to *S. pneumoniae* and *E. coli* pneumonia (685). In CD44-deficient mice, there was an enhanced inflammatory response and neutrophil influx after exposure to *E. coli*. With the same mouse model, Van der Windt et al. showed elevated hyaluronic acid levels, pulmonary inflammation, and edema for up to 10 days after infection with *Klebsiella pneumoniae* and *S. pneumoniae* (664, 686). These investigators concluded that CD44 promotes the resolution of pneumonia, possibly through clearance of hyaluronic acid; hyaluronic acid can induce NF-κB inflammatory pathways and inhibit the downregulation of Toll-like receptors (664, 686).

The same mouse model has been used to study *E. coli* peritonitis and tuberculosis. In *E. coli* peritonitis, the absence of CD44 resulted in significant activation of peritoneal macrophages, elevated CXC chemokine expression levels, and altered Toll receptor regulation (687). CD44 also mediates macrophage recruitment, phagocytosis, and immunity to *Mycobacterium tuberculosis* (688, 689).

GIL BLOOD GROUP

Biochemistry and Serology

Aquaglyceroporin 3 (AQP3) is host to the GIL blood group system and a member of the major intrinsic protein (MIP) family of membrane channels regulating intracellular water, glycerol, and hydrogen peroxide (690, 691). It is a 292-amino-acid multipass protein containing six transmembrane domains and a single N-glycosylation site. In the membrane, it is believed to reside in

detergent-resistant microdomains as homodimers, although trimers and tetramers can occur (692). AQP3 is highly expressed in RBCs, kidney, small intestine, stomach, colon, and lung (693). AQP3 has also been identified in peripheral blood leukocytes and dendritic cells (693, 694).

The AQP3 gene spans 6 kb on chromosome 9p13 and is highly conserved: no missense mutations in the translated protein were identified in a recent study of European and African individuals (665). Two SNPs were identified in the promoter region (A-14G and C-46A); however, neither polymorphism had an impact on AQP3 mRNA levels (665). The one example of a GIL-negative phenotype is the result of splice site and frameshift mutations, resulting in a truncated 218-amino-acid protein (690).

P. falciparum

There is increasing interest in the role of water channels in malaria. AQP4 is the predominant water channel in brain and plays multiple roles in regulating water homeostasis, edema, and inflammation (695). In mouse models, AQP4 knockout mice exhibited worse and earlier-onset cerebral malaria and edema (695). In contrast, mice lacking AQP9, a glycerol channel found on murine red cells, had increased survival rates during early *P. berghei* infection (696). Glycerol is necessary for lipid synthesis and parasite plasma membrane synthesis during the intraerythrocytic malarial stage (696). Malaria requires the action of transporter proteins from both the host red cell and parasite to successfully move glycerol across the host, parasitophorous vacuole, and parasite plasma membranes (696).

GIL/AQP3 is not expressed on brain, but studies in human red cells suggest a possible role in blood-stage infection. In infected red cells, AQP3 was shown to preferentially relocate from the red cell membrane to the cytoplasmic parasitophorous vacuole (692). Because AQP3 protects against hydroxyl radicals and osmotic stress, internalization and loss of AQP3 from the red cell membrane could accelerate red cell damage (665). AQP3 mRNA levels were shown to be decreased in children with severe malaria and anemia. It was hypothesized that decreased AQP3 expression could be multifactorial due to quinine, hypoglycemia, and inhibition of erythropoiesis (665).

Role of AQP3 in Innate and Adaptive Immunity

AQP3 is present on immature dendritic cells and is implicated in the uptake and concentration of soluble antigens by macropinocytosis (694). On peritoneal macrophages, AQP3 is localized along the leading edge of pseudopodia and the phagocytic cup and is implicated in both macrophage migration and phagocytosis (697). In a bacterial peritonitis animal model, the absence of AQP3 led to a 50% decrease in bacterial uptake, impaired bacterial killing, and a 3-fold decrease in the survival rate (697).

AQP3 was recently identified on cutaneous T cells ($CD4^+$ and $CD8^+$) and may play a role in adaptive immunity. The ability of AQP3 to transport hydrogen peroxide, with increases in intracellular peroxide concentrations, appears to signal chemokine-dependent T-cell migration (698). Like monocytic cells, AQP3 is localized along the leading edge of the plasma membrane of migrating, activated T cells.

KELL BLOOD GROUP

The Kell antigen is a 732-amino-acid, erythrocyte-specific glycoprotein with a complex tertiary structure due to multiple disulfide bonds (2, 29). It is a member of the neprilysin family of zinc-neutral endopeptidases and has endothelin-3 convertase activity. It is not required for normal red cell development, and its exact role in red cell biology is still unclear. It is highly polymorphic, with 34 antigens, including several with distinct racial differences (K, Kp^a, and Js^a) (2, 28).

There are no reports of Kell acting as a receptor for microbial pathogens; however, there are several case reports of severe bacterial infections stimulating cross-reactive antibodies with anti-Kell activity. Organisms associated with anti-Kell antibodies include *E. coli* O125 (699, 700), *Morganella morganii* (701), *Enterococcus faecalis* (702), *Streptococcus faecium* (703), and *M. tuberculosis* (704). Neprilysin homologues have been identified in several bacterial species (705).

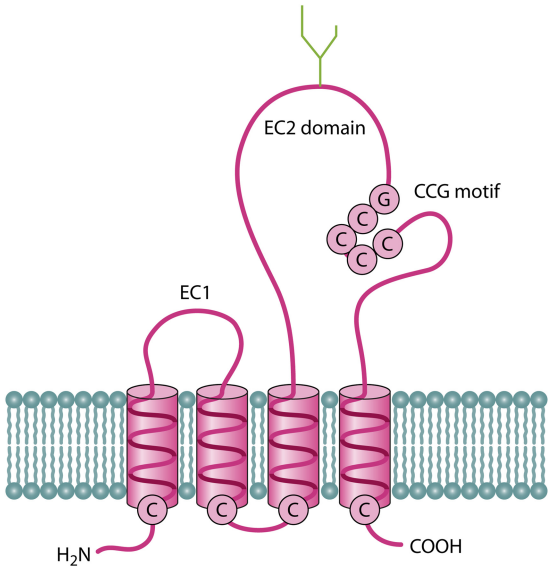

FIG 15 Raph blood group (CD151; MER2). Raph is located on the tetraspanin CD151. Like all tetraspanins, CD151 is a multipass protein with two extracellular loops. The EC2 domain is functionally critical for protein function. Tetraspanins can act as receptors for viruses or may help organize receptors within tetraspanin-enriched membrane domains.

RAPH BLOOD GROUP

Biochemistry and Serology

Raph resides on CD151, a member of the tetraspanin family (2). In the cell membrane, tetraspanins are often concentrated in membrane microdomains (TEMs [tetraspanin-enriched microdomains]) composed of integrins, adhesion molecules belonging to the Ig superfamily (CD44, ICAM, and vascular cell adhesion molecule [VCAM]), signaling molecules, and gangliosides (706). Tetraspanins play a role in cell adhesion, tumor metastasis, cell signaling, and several viral infections, including hepatitis C virus (HCV) (CD81) and HIV (CD81 and CD63) (706).

CD151 is a 253-amino-acid, 28- to 32-kDa multipass protein with four transmembrane domains, four cysteine residues, two extracellular loops, and a single N-glycosylation site (Fig. 15) (2, 29). The second, large extracellular loop (EC2) contains a QRD motif for integrin binding (aa 194) and is the site of polymorphisms associated with alloantibody formation (707). CD151 is widely expressed on epithelia, fibroblasts, endothelia, muscle, re-

nal glomeruli and tubules, CD34 cells, early erythroid precursors, megakaryocytes, and platelets (2, 708). CD151 is strongly expressed in early erythroblasts but is progressively lost with increasing maturation (2).

The Raph blood group system contains a single antigen, RAPH or MER2. MER2 red cell expression is variable, with 8% of adults typing as MER2 negative. MER2-negative donors, however, still express CD151 on other cells such as platelets and lymphocytes. Two SNPs (R171C and R178H) have been identified in three individuals with MER2 alloantibodies (707). A MER2-negative, autosomal-recessive, CD151-null phenotype was identified in three individuals of Indian ancestry due to a nucleotide insertion (exon 5; G383) and a frameshift (707). All three individuals had nephrotic syndrome with end-stage renal disease and neurosensory deafness.

Human Papillomavirus

Human papillomaviruses (HPVs) are nonenveloped DNA viruses capable of infecting epithelial cells. Specific HPV subtypes are associated with genital herpes, cervical cancer, and anogenital cancer. HPV16 is the most prevalent high-risk HPV type, followed by HPV18 (709). In the cervix, HPV infects basal cells of the stratified epithelium in a multistep process that involves interactions with glycosaminylglycans, integrins, and CD151 (710). HPV16 was shown to specifically colocalize with CD151 along basal cells, with lateral movement, recruitment into TEMs, and internalization. CD151 was not required for initial HPV16 binding but was required for HPV16 internalization. HPV infection could be inhibited with anti-CD151, short hairpin CD151 (shCD151) knockdown, and transfection with CD151 mutants (710). Subsequent experiments by the same investigators were able to show that other pathogenic HPV strains (HPV18 and HPV31) also utilize CD151 for viral entry (711). The mechanism underlying CD151-mediated endocytosis is still unresolved but does not require clathrin, caveolin, dynamin, or lipid rafts.

Neisseria

Neisseria meningitidis is a Gram-negative diplococcus and a cause of meningitis, a feared and highly contagious pathogen. *Neisseria* can express several adhesins, including type 4 pili, which recognize CD46 (709). CD46 has been shown to associate with two tetraspanins, CD151 and CD9, leading to speculation that TEMs could play a role in *Neisseria* infection (712). In tissue culture experiments, the impact of CD151 on *N. meningitidis* adherence was cell line dependent: CD151 had little impact in the pharyngeal epithelium; however, an anti-CD151 antibody was able to decrease adherence 50% in HEC-1-B cells, an endometrial cell line (712).

Competitive inhibition was also observed by using only the CD151-EC2 domain (712). The inhibition observed was not specific for CD151, since the EC2 domains of other tetraspanins (CD9 and CD63) were equally effective, nor were the results specific for *Neisseria*: similar results were observed when testing *E. coli*, *S. pneumoniae*, and *S. aureus*. How tetraspanins affect bacterial binding is not clear, since *N. meningitidis* did not recognize any tetraspanin in solid-phase assays (712). The authors of that study hypothesized that tetraspanins may help optimize the organization of receptors into adhesion platforms for *Neisseria* and other bacteria.

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