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## Blood Type Biochemistry and Human Disease

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### Abstract

Associations between blood type and disease have been studied since the early 1900s when researchers determined that antibodies and antigens are inherited. In the 1950s, the chemical identification of the carbohydrate structure of surface antigens led to the understanding of biosynthetic pathways. The blood type is defined by oligosaccharide structures, which are specific to the antigens, thus, blood group antigens are secondary gene products, while the primary gene products are various glycosyltransferase enzymes that attach the sugar molecules to the oligosaccharide chain. Blood group antigens are found on red blood cells, platelets, leukocytes, plasma proteins, certain tissues, and various cell surface enzymes, and also exist in soluble form in body secretions such as breast milk, seminal fluid, saliva, sweat, gastric secretions, urine, and amniotic fluid. Recent advances in technology, biochemistry, and genetics have clarified the functional classifications of human blood group antigens, the structure of the A, B, H, and Lewis determinants and the enzymes that produce them, and the association of blood group antigens with disease risks. Further research to identify differences in the biochemical composition of blood group antigens, and the relationship to risks for disease, can be important for the identification of targets for the development of nutritional intervention strategies, or the identification of druggable targets.

### INTRODUCTION

Serological research has focused on identifying and understanding the structure, function, and interactions of serum antibodies and blood groups. Landsteiner's discovery of blood groups in the early 1900s was based on the observation that some individuals' red cells agglutinated when mixed with plasma from other individuals.<sup>1</sup> His classification of the ABO blood groups and subsequent research by others confirmed that antibodies and antigens were inherited characteristics.<sup>2</sup> In the mid-1940s, the antiglobulin test was developed, which allowed the detection of non-agglutinating antibodies,<sup>1</sup> and biochemical genetic investigations were undertaken, which established that the specificity of antigens was determined by their oligosaccharide structures.<sup>2</sup> Thus by definition, blood group antigens are secondary gene products; the primary gene products are the various glycosyltransferase enzymes that attach the sugar molecules to the oligosaccharide chain. These carbohydrate

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CONFLICT OF INTEREST

None.

moieties are recognized as foreign by the immune systems of other individuals, which produce antibodies to them.<sup>3</sup>

Despite the relatively primitive research technology available in the mid-1900s, intense, painstaking, and rigorous scientific research efforts enabled precise chemical identification of the carbohydrate structure of a human red blood cell (RBC) surface antigen by 1957, and in 1959 the biosynthetic pathways of the antigens known at that time were proposed.<sup>2</sup> Since then, exponential advances in technology and the sequencing of the genome have resulted in the identification of hundreds of blood group antigens, classified into more than 30 blood group systems, and the genes which they express have been cloned and sequenced.<sup>1</sup> Although the molecular genetic sequences are known for these genes and their enzymes have been identified, there is still much research to be done in order to fully understand the structure, function, and interactions of the antigens they synthesize.

Similarly, human leukocyte antigens (HLAs), which are found on every nucleated cell in the human body, have been grouped into major histocompatibility complex (MHC) classes; the MHC Class I and Class II HLAs function as antigen-presenting molecules to activate the immune system, while MHC Class III molecules include complement components, heat shock proteins, and several lymphotoxins and other factors important in inflammation.<sup>4</sup> Nucleated cells generate MHC molecules as needed for their immunogenic functions,<sup>4</sup> and the HLA antigens and other surface markers found on nucleated cells play a vital role in fighting disease.

One of the notable differences between HLA antigens and human blood group antigens is that only one phenotype is associated with HLA antigens, while three phenotypes are associated with blood group antigens. But the most important difference may be that mature RBCs are non-nucleated; all of the blood group antigens are generated prior to maturation, when RBCs lose the ability to generate new antigens.<sup>1</sup> For this reason, RBCs do not function as antigen-presenting cells. Thus, the association of blood group antigens with disease risk is far more nuanced than the association of HLA antigens with diseases. Disease risk is clearly multifactorial and causation is not implied by association, but blood group antigens may be one of the predisposing factors that contribute to or prevent disease processes.

Table 1 presents these antigens grouped by function, but it should be noted that some antigens have more than one function and can therefore be grouped differently with equal justification. As researchers continue to identify new blood group antigens and functions, the blood group systems and classifications will continue to evolve. Indeed, in the process of compiling Table 1 from similar presentations by various authors, the dynamic nature of these classifications was readily apparent; not only were new blood groups added over time, but some were renamed, and other were reclassified. It is beyond the scope of this review to discuss every human blood group antigen, but for those readers who are interested, such discussions can be found in the publications referenced in Table 1.

## BLOOD GROUP ANTIGENS

Most antigens are the end product of a single gene, so changes at the genetic level such as insertions, deletions, inversions, alternative splicing, or single nucleotide polymorphisms (SNPs) lead to antigenic differences, but can also give rise to new antigens or even complete loss of expression.<sup>3</sup> Human blood group antigens can also be used as receptors by pathogens or mimicked by bacteria;<sup>6</sup> even small variations in structure are recognized by the immune system, which produces antibodies in self-defense.<sup>3</sup> Blood group antigens are found on RBCs, platelets, leukocytes, plasma proteins, certain tissues, and various cell surface enzymes,<sup>10</sup> and also exist in soluble form in body secretions such as breast milk, seminal fluid, saliva, sweat, gastric secretions, urine, and amniotic fluid.<sup>1</sup> The ABO blood group antigens are perhaps the most important and widely-studied, and were the first to be identified.<sup>11</sup>

The initial interactions of the *ABO*, *Hh*, *Sese*, and *Lele* genes were derived in 1959 from the double-helix structure of DNA and the inheritance patterns of the A, B, H, Le<sup>a</sup> and Le<sup>b</sup> antigens, and although these pathways have been revised as new information was obtained, the basic premise was correct.<sup>2</sup> The primary structure of these antigens is either a glycolipid or a glycoprotein, with an oligosaccharide “precursor” sequence and one or more specific sugar molecules attached to it in specific locations.<sup>10</sup> The five blood group antigens, A, B, H, Le<sup>a</sup> and Le<sup>b</sup>, are produced from the enzymes expressed by these four genes and are the basis of the ABO “blood type” phenotypes.<sup>2</sup> It is important to understand the relationship between the *ABO*, *Hh*, *Sese* (secretor), and *Lele* (Lewis) genes, because they each play different roles in the final ABO antigen structure of an individual’s body tissues and secretions.

There are two precursor oligosaccharide sequences for ABO(H) antigens, which only differ in their terminal residues; Type 1 chains end with a Gal  $\beta$ 1-3 GlcNAc  $\beta$ 1-R sequence (Figure 1), and Type 2 chains end with a Gal  $\beta$ 1-4 GlcNAc  $\beta$ 1-R sequence (Figure 2).<sup>1, 10</sup> Only the precursor Type 1 chain is required for Le<sup>a</sup> antigen formation. Le<sup>b</sup> is a hybrid of the H antigen and Le<sup>a</sup>. Similarly, only the precursor Type 2 chain is required for Le<sup>x</sup> antigen formation but Le<sup>y</sup> is a hybrid of the H antigen and Le<sup>x</sup>. There are two  $\alpha$ 1,2-fucosyltransferases with different acceptor specificity and tissue-specific expression: one is a product of the *H* gene located in hematopoietic tissues, and the other is a product of the *Se* gene located in secretory tissues.

Only Type 2 chains are found on RBCs and other body tissues (primarily epithelial and endothelial cells<sup>11</sup>) and are not affected by secretor status; while both Type 1 and Type 2, but primarily Type 1, chains are found in secretions of those who are secretors (*Se/Se* or *Se/se*), neither are found in those who are non-secretors (*se/se*).<sup>10</sup> The fucosyltransferase expressed by the *Sese* gene (subsequently identified as the *FUT2* gene) is found in secretory glands and attaches fucose in  $\alpha$ 1-2 linkage to the terminal galactose residue of both Type 1 and Type 2 chains.<sup>10</sup> The *Sese* gene does not affect the production of the ABO antigens found in the plasma or the secretion status of other antigens.<sup>1</sup>

The fucosyltransferase expressed by the *H* gene (subsequently identified as the *FUT1* gene) is found in hematopoietic tissues and attaches fucose in  $\alpha$ 1-2 linkage to the terminal galactose residue of Type 2 chains.<sup>10</sup> This H antigen completes the acceptor substrate and is required for attachment of the final monosaccharide that distinguishes the A and B antigens.<sup>1</sup> In non-O blood group individuals, the *N*-acetylgalactosaminyltransferase expressed by individuals with an *A* allele attaches *N*-acetylgalactosamine in  $\alpha$ 1-3 linkage to the terminal galactose residue of Type 1 and Type 2 chains, while the galactosyltransferase expressed by those with a *B* allele adds galactose in  $\alpha$ 1-3 linkage to those residues.<sup>1, 10</sup>

Even though the H antigen is expressed in individuals who are homozygous for the *O* allele, they do not form A or B antigens because they lack both of the glycosyltransferase enzymes that attach the final monosaccharide to the oligosaccharide chain.<sup>1, 10</sup> In contrast, individuals who are homozygous *h/h*, known as the Bombay phenotype, do not generate the necessary substrate to form the A and B antigens, even when they have the *A* or *B* allele and the necessary glycosyltransferase enzymes.<sup>1, 10</sup>

The antigens of the Lewis blood group system are unique in several ways. The *Le* gene (subsequently identified as the *FUT3* gene) expresses a fucosyltransferase that adds fucose in  $\alpha$ 1-4 linkage to the sub-terminal GlcNAc of the Type 1 chain only; galactose is already in  $\alpha$ 1-4 linkage to the sub-terminal GlcNAc of the Type 2 chain.<sup>10</sup> The *Ie* allele is silent, while the *Le* allele produces a single antigen that is found as  $Le^a$  in non-secretors (a glycosphingolipid with the oligosaccharide chain attached via D-glucose) and as  $Le^b$  in secretors (a glycoprotein with the oligosaccharide chain attached via *N*-acetyl-D-galactosamine).<sup>10</sup> Thus, the  $Le(a+b-)$  or  $Le^a$  individual is a non-secretor (*Le* and *se/se*), the  $Le(a-b+)$  or  $Le^b$  individual is a secretor (*Le* and either *Se/Se* or *Se/se*), while the  $Le(a-b-)$  individual (*Ie/Ie*) can be either a secretor or non-secretor.<sup>1</sup> In a similar manner, the addition of fucose in  $\alpha$ 1-3 linkage to the subterminal GlcNAc of the Type 2 chain generates the  $Le^x$  and  $Le^y$  antigens. In the plasma, the Lewis blood group antigens are attached to circulating RBCs, platelets, and lymphocytes by direct insertion of their lipid anchor into the plasma membrane of these cells; in the body secretions, the Lewis antigens are similarly attached by the amino acid component of the glycoprotein.<sup>10</sup>

The Rh blood group system is the most complex, and perhaps the second most studied blood group system. There are 49 known antigens in the Rh system,<sup>12</sup> with the D, C/c, and E/e antigens as the major types<sup>13</sup> expressed by the *RHD* and *RHCE* genes in the *RH* locus. The D antigen is a polypeptide produced by the *RHD* gene, while the *RHCE* gene produces a polypeptide with the C/c and E/e antigens; the remaining antigens are produced by partial deletion, recombination, mutation, or polymorphisms of one or both genes.<sup>13</sup> RhD-positive people have the *RHD* gene, while RhD-negative people are missing the *RHD* gene; there are significant differences in the racial frequency of the RhD-negative genotype, which can be traced back to Paleolithic and Neolithic ancestry.<sup>12</sup>

The ABO, Lewis, and Rh blood group systems demonstrate how antigens can be grouped based on structural homology, secondary structure, and biological function of certain molecules; once structure is defined, antigens can be classified into functional categories of structural proteins; enzymes; transporters and channels; adhesion molecules; and receptors

for exogenous ligands, viruses, bacteria, and parasites.<sup>8, 9</sup> Because structure often dictates function, when function is not known, antigens can be classified based on similarity of structure.<sup>9</sup> As our knowledge of molecular genetics increases, we are better able to understand the role of antigens and study the relation between structure and function.<sup>11</sup>

## BLOOD GROUPS AND DISEASE

Because much of the research on blood antigens has focused on understanding blood transfusions, the antigens are commonly referred to as blood group antigens.<sup>14</sup> Blood group antigens are primarily tissue antigens, and are widely distributed throughout the body. The antigens evolved earlier in ectodermal and endodermal tissue than in RBCs and hematopoietic cells, and for this reason are also referred to as histo-blood group antigens.<sup>14</sup> Antibodies to these tissue antigens cause rejection of transplanted tissues and organs<sup>11</sup> and can cause spontaneous abortions.<sup>14</sup>

Both the ABO and Rh blood groups systems have been associated with a number of diseases, but this is more likely related to the presence or absence of these tissue antigens throughout the body and not directly or primarily related to their presence on RBCs.<sup>14</sup> Although early research relied on using statistical methods to associate the blood groups with diseases such as infection, malignancy, and coagulation, these associations have more recently been given scientific validation through extensive research in infectious disease, tumor immunology, and membrane chemistry.<sup>14</sup>

Some of the known associations between blood group antigens and disease are presented here and summarized in Table 2. Research is complicated for several reasons: the ABO blood group system is highly polymorphic, with more than 20 distinct sub-groups; study findings are usually related to ABO phenotype, but rarely to the ABO genotype, secretor status, and Lewis phenotype; and animal models are unsatisfactory because their antigen glycosylation structure is different from humans.<sup>15</sup> Molecular biology techniques, transgenic animals, and computer modeling are being explored as possible investigative tools for studying the complex mechanisms and processes involved in glycosylation, and how glycosylation affects proteins and individual cells, as well as entire organisms; the lack of adequately robust analytical tools is perhaps the biggest impediment faced by researchers.<sup>15</sup>

### The role of cell adhesion molecules in disease

Although the exact mechanisms are not yet known that will explain all of the reported associations between blood group antigens and disease, what is known about their structure and functions provides some intriguing clues. An unexpected number of the antigenic structures found on RBCs act as cell adhesion molecules (CAMs); some contribute to normal RBC development and some play a role in human disease.<sup>16, 60</sup> These antigens can serve as receptors and ligands for microbes, and may play a role in movement of normal and malignant cells throughout the body.<sup>14</sup> CAM moieties include carbohydrates, glycosylphosphatidylinositol-anchored proteins, and transmembrane proteins,<sup>16</sup> and are grouped into 5 families: cadherins, selectins, integrins, the immunoglobulin superfamily (IgSF), and cell surface proteoglycans; blood group antigens are associated with all but cadherins.<sup>14</sup> Selectins are expressed by leukocytes, platelets, and endothelial cells, and

RBCs are capable of binding to them.<sup>16</sup> Selectins participate in attaching leukocytes to endothelial cells, and integrins participate in cell-to-cell and cell-to matrix communication.<sup>14</sup> Selectins, integrins, the IgSF, the cartilage link protein family, and sialomucins play a role in hematopoiesis.<sup>16, 60</sup>

RBCs, especially sickled red cells, contain sialylated glycolipids and glycoproteins, which facilitate cell-cell interactions.<sup>16</sup> Sickle RBCs are strongly adherent to thrombospondin, fibronectin, and especially to laminin; adhesion to endothelial cells induces pathological changes in them, especially cell retraction and upregulation of procoagulants and adhesion molecules.<sup>16</sup> RBCs are also responsive to epinephrine, with sickle RBCs showing significantly more responsiveness and greater adherence post-exposure.<sup>16</sup> The adhesion receptor CD44, a cartilage link protein, is primarily a receptor for hyaluronan, but also binds to fibronectin, osteopontin, and endothelial cells; it mediates aggregation of leukocytes and T-cell activation, cooperates with integrin to bind erythroid progenitor cells to bone marrow matrix fibronectin, and anchors tumor cells during metastasis.<sup>16</sup>

### Hemolytic diseases

In the early 1940s, maternal antibodies to the RhD antigen of the fetus were identified as the cause of hemolytic disease of the newborn (HDN),<sup>12</sup> which can now be prevented by administration of Ig anti-D to the RhD-negative mother upon delivery; this prevents the formation of antibodies to RhD.<sup>17</sup> In addition to the RhD-negative genotype, there is an extremely rare Rh-null genotype, in which the RBCs lack all Rh antigens, resulting in membrane polypeptides that are missing or severely deficient, and abnormalities in RBC shape, membrane phospholipid organization, and cation transport.<sup>13</sup> There are two Rh-null types: the *amorph* type is associated with a silent allele due to a mutation of the *RHCE* gene in a RhD-negative person, while the *regulator* type is due to homozygosity of an autosomal suppressor gene unrelated to the *RH* locus.<sup>17</sup>

All Rh antigens can potentially play a role in autoimmune hemolytic anemias as well as hemolytic reactions due to immune activation following pregnancy or transfusion, but Rh-null individuals experience chronic hemolytic anemias of non-immune origin. Further investigations into the Rh-null phenotype revealed that Rh antigens are part of a non-covalently-bound complex of proteins, with a core tetramer of two Rh and two Rh-associated glycoprotein (RhAG) subunits, and CD47, LW, and GPB accessory proteins; this complex is anchored in the lipid bilayer by the N-terminal and C-terminal domains of the Rh and RhAG proteins.<sup>17</sup> This complex is linked to the actin-spectrin based cytoskeleton of the RBC through direct interaction with protein 4.2 and ankyrin, and with protein Band 3, the erythroid anion exchanger, through their common interaction with ankyrin; when Rh or RhAG proteins are missing, this complex is not assembled or transported to the cell membrane, resulting in the characteristic osmotic fragility and RBC abnormalities found in chronic hemolytic anemia.<sup>17</sup>

### Circulatory diseases

Historically, non-O blood groups have been associated with greater incidence of vascular disorders such as cerebral arterial ischemia, venous thromboembolism, peripheral vascular

disease, angina, and myocardial infarction, and these associations were confirmed in 2008 with a systematic review and meta-analysis, and further validated by subsequent GWAS studies.<sup>1</sup> Recent reviews of the published literature quantified the risk in non-O blood group individuals for venous thrombosis (OR=1.79), peripheral vascular disease (OR=1.45), coronary heart disease (OR=1.25), myocardial infarction (OR=1.25), and ischemic stroke (OR=1.14), as compared with blood group O individuals.<sup>19, 21</sup> Von Willebrand factor (vWF) and Factor VIII (FVIII) are plasma coagulation glycoproteins, which act by forming a non-covalently bound complex; vWF stabilizes FVIII and transports it to the site of vascular injury, and then interacts with platelets as part of the clotting process.<sup>1</sup> vWF is partially regulated by the cleavage action of a metalloprotease, which clears it from the plasma; it is thought that the A and B antigens interfere with access to the cleavage site, thereby reducing clearance of vWF.<sup>1</sup>

FVIII and vWF are approximately 25%–30% lower in the plasma of blood group O people (specifically, Bombay < O < B < A < AB, with A/O and B/O having less than A/A and B/B individuals), and group O individuals are therefore at lower risk for venous and arterial thromboembolism, but at greater risk of excessive bleeding than group A individuals.<sup>1, 11, 14</sup> Higher average levels of FVIII in blood group A individuals increase the risk of ischemic heart disease and venous thromboembolism,<sup>11</sup> and group A people are more likely to thrombose or have myocardial infarctions than group O individuals.<sup>14</sup> The risk for myocardial infarction in the presence of coronary atherosclerosis is 44% lower for group O individuals than for other blood groups.<sup>11</sup> Non-O blood group individuals have an 11% greater relative risk of developing coronary heart disease than blood group O individuals,<sup>20</sup> and group AB individuals have a high risk of stroke compared to group O individuals.<sup>18</sup> A recent report found that 60% of stroke risk in blood group AB individuals was associated with FVIII levels.<sup>22</sup>

### Cognitive Disorders

In addition to their association with circulatory diseases, higher levels of vWF and FVIII in non-O blood group individuals have been associated with increased risk of dementia and cognitive impairment, indicating that coagulation factors may play a role in these disorders.<sup>23</sup> A large prospective case-control study found an increased risk of cognitive impairment (OR = 1.82) in blood group AB individuals, which was independent of age, race, gender, or geographic region, and that FVIII levels differed significantly by blood group, with O < A < B < AB.<sup>22</sup> This study also found that hypertension, dyslipidemia, obesity, diabetes, and cardiovascular disease (CVD) were more prevalent in those with cognitive impairment, which indicates that a common etiology is likely; blood group influences CVD risk and CVD risk factors are known to be associated with dementia and cognitive impairment. Interestingly, blood groups B and AB were more frequent in blacks (in both cases and controls),<sup>22</sup> which may be an overlooked factor in increased rates of stroke and CVD in this population.

### Bacteria, viruses, and parasites

Epithelial cells express ABH and Lewis antigens, which are effectively cell-surface glycoconjugates used by parasites, bacteria, and viruses as receptors for attachment,

resulting in different susceptibilities depending on the antigen profile of an individual.<sup>11</sup> By using the same blood group antigens as their host, certain microbial parasites utilize molecular mimicry as a defense against the host's immune system.<sup>11</sup> The chemical signatures on the membranes of many gram-negative organisms such as *Escherichia coli* resemble A and B blood group antigens; *in vitro* experiments have shown that anti-B antibodies kill *E. coli*, and anti-A and anti-B antibodies may therefore play a similar role in destroying gram-negative bacteria *in vivo*.<sup>14</sup>

Type O blood group is associated with increased incidence of plague, cholera, mumps, and tuberculosis infections; type A blood group is associated with increased incidence of smallpox and *Pseudomonas aeruginosa* infection; type B blood group is associated with increased incidence of gonorrhea, tuberculosis, *Streptococcus pneumoniae*, *E. coli*, and *salmonella* infections; and type AB blood group is associated with increased incidence of smallpox, *E. coli*, and *salmonella* infections.<sup>14</sup> Non-secretors have an increased incidence of *Neisseria meningitides*, *Haemophilus influenza*, *Candida albicans*,<sup>14</sup> *S. pneumoniae*, *E. coli* urinary tract infections,<sup>1</sup> *Streptococcus pyogenes*, and *Vibrio cholerae*.<sup>24</sup>

**H. pylori**—In 1954, it was reported that the incidence of peptic ulcers (gastric and duodenal) was 20% higher for group O individuals than group A individuals, with the incidence of duodenal ulcers 35% higher in group O individuals than in group A, B, and AB individuals, and 50% higher in non-secretors (who make up 20% of the population).<sup>14</sup> For group A and B non-secretors, the relative risk was 1:6; for group O secretors, the relative risk was 1:35; and for group O non-secretors, the relative risk was 2:5.<sup>14</sup> Secretor status and *H. pylori* infection are independent and significant risk factors for gastroduodenal disease, with a relative risk of 1.9 for non-secretors vs secretors.<sup>25</sup> Although gastritis and gastric ulcers are associated with *H. pylori* infection, more recent studies have reported that different strains of *H. pylori* showed varying preferences for each blood group antigen, and in fact, 95% of the strains did not show a preference for blood group O antigens.<sup>11</sup> Interestingly, although only 5% of the strains prefer the H antigen in the general population, in those of American Indian heritage (a group O-dominant population), 60% of the strains show this preference.<sup>11</sup>

**Noroviruses**—The Norovirus appears to be another strain-dependent pathogen, but blood group B individuals have less risk of infection (OR, 0.096) and symptomatic disease (OR, 0), and group O individuals have a much greater risk of infection (OR, 11.8).<sup>11</sup> The Norovirus binds to difucosylated Lewis antigens (secretors) and to A and H antigens, and but not to B antigens,<sup>27</sup> while non-secretors appear to be resistant to symptomatic infection with most strains.<sup>1</sup> In 3 outbreaks in Sweden, 29% of non-secretors were asymptomatic, while among those with symptoms, none were non-secretors (*se/se*); 51% were heterozygous (*Se/se*) and 49% were homozygous (*Se/Se*).<sup>1</sup> However, recent research has shown that non-secretors are not immune to infection; the genogroup and genotype of the Norovirus strains have different binding capacities due to extensive structural differences in certain domains of the capsid protein, which are critical for attachment to host cells and determine whether binding can occur in non-secretors.<sup>28</sup> Although non-secretor status provides resistance to Norovirus infection, it is thought to increase susceptibility to Crohn's



disease and to autoimmune gastritis, which increases the risk of malabsorption and deficiency of vitamin B<sub>12</sub>, and the risk of pernicious anemia.<sup>29</sup>

**Malaria**—There are 4 species of *Plasmodium*, but the most virulent is *P. falciparum*, which accounts for 50% of the cases and 80% of the deaths, while *P. vivax* accounts for another 40% of cases.<sup>30</sup> The Duffy blood group system, which has 6 discrete antigens, is involved in *P. vivax* infections; mutations of the *FY* gene that result in RBCs without the Duffy antigen protect against infection by this strain of malaria.<sup>30</sup> The Knops blood group system, which has 9 discrete antigens, appears to play a role in the severity of *P. falciparum* infection; mutations of several of these antigens appear to provide a protective effect in African blacks.<sup>30</sup>

The severity of *P. falciparum* malaria is directly correlated with the presence or absence of blood group A and B antigens; O blood group individuals tend to be less severely affected by malaria, while A and B blood group individuals are at greater risk of malarial anemia (OR, 1.18).<sup>11</sup> Infected RBCs express membrane proteins that bind the A antigen, and possibly to a lesser extent the B antigen, of uninfected RBCs, forming large clusters or rosettes; RBCs with just the H antigen form smaller and less robust rosettes,<sup>1</sup> while RBCs with the A antigen form larger and stronger rosettes.<sup>30</sup> A and B antigens also act as adhesion molecules during sequestration, allowing infected RBCs to adhere to the microvascular endothelial cells, which remove them from circulation and protect the parasite from destruction, but also block circulation and reduce oxygen supply.<sup>1, 11</sup> Rosetting and sequestration correlate with the increased severity of malaria and contribute to the high mortality rate among children with cerebral malaria; this is a major selection pressure behind the population distribution of those with blood group O relative to non-O in the areas of the world where malaria is still prevalent.<sup>1, 11</sup>

### Mosquito-Borne Diseases

Mosquito-borne diseases add layers of complexity to the efforts to correlate blood groups with disease risk, and highlight the need for interdisciplinary, collaborative research. The *Aedes* mosquito is the common vector for transmission of yellow fever, dengue fever, chikungunya, and zika viruses; a common vector increases the risk of host co-infections, and the risk of genetic recombination and reassortment in these viruses.<sup>61</sup> Both dengue and chikungunya infections can be asymptomatic, mild, severe, or fatal, and similarity of symptoms results in misclassification without laboratory diagnosis.<sup>62</sup> Studies must also consider normal blood group distribution frequencies for affected populations, as well as the number of serotypes, topotypes, sub-types, clades, and strains for a given virus, especially if some are more virulent than others (as seen with malarial parasites). Even landing preferences and feeding patterns of mosquitoes may affect blood group infection rates; *Aedes* mosquitoes were reported to be more attracted to some host blood types than others.<sup>63, 64</sup> There are no published studies correlating blood groups with zika virus, and only a few for dengue or chikungunya fever;<sup>65–69</sup> the findings of one<sup>68</sup> are consistent with gene association studies,<sup>70</sup> which found that the AB blood group (which lacks antibodies to both A and B antigens) was independently associated with increased susceptibility to severe dengue hemorrhagic fever in secondary infections. Understanding

how blood group antigens affect disease risk, prevalence, and severity will contribute to more effective prevention, improved treatments, and faster vaccine development. Time is of the essence, and right now, the mosquitoes are winning.

**Cholera**—The predominant cause of endemic and epidemic cholera is the bacteria *Vibrio cholera* O1, which has been associated with a lower risk of colonization in exposed blood group O individuals, but a higher risk of more severe disease if colonized in those individuals.<sup>27</sup> A study in Bangladesh reported the distribution of O:A:B:AB blood groups in healthy controls as 28%, 23%, 38%, and 11%, respectively; in patients as 43%, 19%, 34%, and 4%, respectively; and in asymptomatic contacts as 47%, 18%, 27%, and 8%, respectively.<sup>27</sup> This study found that the Lewis antigen was significantly different in symptomatic cholera infections, when compared to controls and healthy contacts.

The overall distribution in the study participants was 28% Le(a+b-) or non-secretors with the Lewis antigen, 55% Le(a-b+) or secretors with the Lewis antigen, and 17% Le(a-b-), who do not express the Lewis antigen and can be either secretors or non-secretors.<sup>27</sup> Comparing cholera patients vs contacts/healthy controls, the distribution was 39% vs 25%/25% Le(a+b-), 40% vs 60%/58% Le(a-b+), and 21% vs 15%/17% Le(a-b-), indicating that non-secretors were more likely to get symptomatic cholera than contacts (OR, 1.91) and healthy controls (OR, 1.90), and that secretors were less likely than contacts (OR, 0.45) and healthy controls (OR, 0.48), while no difference was found in the Lewis-null group.<sup>27</sup>

When comparing patients to contacts by blood group, within the A and B blood groups the secretor phenotype was significantly less common, while non-secretors and Lewis-null phenotypes were more common; this difference was not seen in the O blood group individuals, but since this blood group is itself a risk factor for cholera, the Lewis blood group effect may have been masked.<sup>27</sup> Additionally, secretors required less intravenous fluid than non-secretors, which is consistent with the severity findings, and Lewis-null individuals had the longest duration of diarrhea and required the most intravenous fluids, suggesting an increased severity of infection if it occurs; this may be related to the finding that the Lewis-null group also had the lowest IgA response to lipopolysaccharide antigens at day 7.<sup>27</sup>

**Bacterial Meningitis**—Three species of bacteria, *N. meningitides*, *H. influenza*, and *S. pneumoniae*, cause about 75% of all bacterial meningitis; the capsules of these bacteria contain polysaccharide antigens, which the immune defense of the host must recognize and respond to with the appropriate antibodies.<sup>31</sup> These bacteria can generate either A or B antigens, depending on the blood group environment in which they find themselves, and also contain an enzyme that can alter B antigen to A antigen; perhaps not surprisingly, blood group B individuals have the lowest prevalence of infection by these bacteria because their anti-A antibodies respond as natural antibodies to the bacterial antigens.<sup>31</sup> In contrast, blood group A, AB, and O individuals must rely on specific anti-pneumococcal antibodies, which their immune system must generate in response to the invading organisms.<sup>31</sup> Non-secretors are significantly more susceptible to these bacteria than secretors; non-secretors make up

20% to 25% of the general population of western Europe, but in several studies, the proportion of non-secretors in patients with these infections ranged from 47.0% to 73.3%.<sup>31</sup>

## Cancer

Blood group antigens participate in cell signaling, cell recognition, and cell adhesion, and are therefore likely to play a role in tumorigenesis, metastasis, and prognosis.<sup>46</sup> During cellular differentiation, development, and aging, expression of ABH and related antigens varies; this is particularly true during pathological phenomena and carcinogenesis.<sup>11</sup> The epithelial tissues of the mouth, gastrointestinal tract, lung, bladder, breast, uterine cervix, and prostate have ABH antigens, but these antigens are often missing from the glycoproteins and glycolipids of malignant tissues in these areas.<sup>1</sup> For example, it is thought that DNA methylation in the promoter region for the blood group *A* gene may inhibit transcription of the associated enzyme and therefore loss of the *A* antigen, but different mechanisms for reduction of mRNA have been found in *A* tumors, which appear to be specific to each tumor cell line.<sup>35</sup>

Loss of *A* and *B* antigens precedes metastasis, results from down-regulated transcription of ABO with associated loss of *A*- or *B*-transferase activity, and increases accumulation of other antigens which act as ligands for selectins and facilitate the metastatic process.<sup>1</sup> As malignancy progresses, normal antigens are lost and so-called tumor antigens are acquired; the decrease in *A*, *B*, and *H* antigens is inversely proportional to the metastatic potential of the tumor.<sup>14</sup> Blood group antigens are known to have procoagulant and angiogenic properties, act as ligands for selectins, increase cellular motility, and increase resistance to apoptosis; these biological roles may facilitate tumor progression, and a model has been proposed that may account for the described associations between the presence or loss of these markers and the outcome of disease.<sup>71</sup>

Some people who are not blood group *A* have tumors with true *A* antigens or with “*A*-like” antigens that have very similar properties to *A* antigens; in these people, the tumor antigens would be recognized as foreign and would interact with anti-*A* antibodies, resulting in attack of the tumor.<sup>14</sup> This may explain why blood group *A* people have a higher incidence of cancer than group *O* people; the *A* or “*A*-like” properties of these tumor antigens are not seen as foreign in blood group *A* people.<sup>14</sup> When compared to group *O* people, group *A* people have a higher incidence of cancer in the salivary glands (64%); stomach (22%); ovaries (28%); uterus (15%); cervix (13%); and colon/rectum (11%).<sup>14</sup> It should be noted that although ABO genotypes are significantly correlated with the risk of certain cancers, they do not *cause* cancer; they only indicate susceptibility.<sup>11</sup> Conversely, lack of correlation does not confer protection: multiple studies have failed to find an association between blood type and breast cancer.<sup>32–34, 37</sup>

**Leukemia and Lymphoma**—In patients with acute leukemia, and sometimes in aplastic anemia, *A* and *B* antigens commonly decrease until they are undetectable; as the patient’s condition improves, the antigens increase again to their former levels.<sup>14</sup> This loss of antigens may not be due to deficiency in transferase synthesis or activity, but instead may be due to an inhibitory factor related to antigen-antibody binding, or an abnormal distribution or

density of antigen sites in the RBC membrane.<sup>38</sup> In patients with leukemia, between 17% and 37% had significantly lower expression of A, B, or H antigens when compared to healthy controls; of A, B, or AB patients with myeloid malignancies, 55% had reduced expression of A or B antigens, and 21% of O patients had reduced H antigens, when compared with healthy controls of the same ABO genotype.<sup>1</sup>

Non-Hodgkin's primary central nervous system lymphoma (PCNSL) begins in and typically remains confined to the central nervous system (CNS),<sup>40</sup> while secondary central nervous system lymphoma (SCNSL) typically does not begin in the CNS but may later involve the CNS in 10% to 30% of cases.<sup>39</sup> A multi-center study of 36 patients with PCNSL reported that the incidence was 55.6% in blood group O, 8.3% in blood group A, 27.8% in blood group B, and 8.3% in blood group AB,<sup>40</sup> while a second study evaluated 202 patients with secondary central nervous system lymphoma (SCNSL), and reported that the incidence was 29.7% in blood group O, 5.0% in blood group A, 61.9% in blood group B, and 3.5% in blood group AB.<sup>39</sup> In both studies, the same population of healthy controls was used, in which the blood group proportions were 35.6% in blood group O, 37.1% in blood group A, 22.2% in blood group B, and 6.1% in blood group AB; the dramatically lower incidence in blood group A in both studies is highly significant in light of the fact that blood group A is the most common blood group in Iran.<sup>39, 40</sup>

There are very few studies of the association between ABO blood groups and children with leukemia and lymphoma. A ten-year retrospective study of pediatric patients with acute myeloid leukemia (AML; n=116), acute lymphoblastic leukemia (ALL; n=522), Hodgkin's lymphoma (n=63), and non-Hodgkin's lymphoma (n=78) reported significant differences in the overall distribution of blood groups when compared to the source population for all but the AML patients.<sup>41</sup> This study reported that the incidence of Hodgkin's lymphoma was 45.6% higher in blood group B patients and 56.5% lower in blood group A patients; the incidence of non-Hodgkin's lymphoma was 52.9% lower in blood group A patients; the incidence of ALL was 14.3% higher in blood group O patients; but there was no difference in the distribution of blood groups in patients with AML.<sup>41</sup> A separate multi-center pediatric study of 682 patients with ALL and 224 patients with AML reported the incidence of ALL was 56.5% higher in blood group O patients, 35.8% lower in blood group A patients, and 26.9% lower in blood group B patients, while the incidence of AML was 28.8% higher in blood group A patients.<sup>42</sup>

**Stomach cancer**—Worldwide, gastric cancer is the fourth most common type of cancer and the second leading cause of cancer deaths; studies since the 1950s have consistently shown that blood group A individuals have about a 20% greater risk of stomach cancer than blood group O individuals.<sup>20</sup> A meta-analysis in 2012 gave group A individuals an odds ratio of 1.11 and group O individuals an odds ratio of 0.91 for gastric cancer, and also found that blood group A individuals had significantly higher rates of *H. pylori* infection than non-A blood group patients (OR=1.42).<sup>43</sup> This is significant because a recent investigation of ABO blood groups and *H. pylori* found that the risk of advanced precancerous gastric lesions was significantly affected by the presence or absence in the bacterial DNA of two SNPs in the cytotoxin-associated gene *A* (*CagA*), distinguished as *CagA* positive and *CagA* negative strains.<sup>26</sup>

In individuals infected with *CagA* positive *H. pylori*, the risk was significantly higher in blood group A than in blood group O for intestinal metaplasia (OR=1.36) and dysplasia (OR=1.78), with a combined OR of 1.42, while in those with *CagA* negative strains or who were not infected with *H. pylori*, blood group A individuals had a significantly lower risk than blood group O individuals for intestinal metaplasia and dysplasia (OR=0.60).<sup>26</sup> Thus, ABO blood group is a risk factor in the development of precancerous lesions in individuals with *CagA* positive *H. pylori* infection; ABO antigens on the gastric epithelium are binding sites for the *H. pylori* bacterium, which then injects CagA virulence protein into the cellular cytoplasm.<sup>26</sup> Both factors play a role in the severity of gastric precancerous lesions and progression to gastric cancer.

**Pancreatic cancer**—Pancreatic cancer is the seventh most frequent cause of cancer death worldwide, and is one of the most aggressive cancers, with mortality rates nearly equal to incidence rates.<sup>20</sup> Non-O individuals have a 25% greater risk of stomach and pancreatic cancer, with a 17% overall greater risk of pancreatic cancer alone; when compared to blood group O, the risk of exocrine pancreatic cancer is highest in blood group B (OR, 1.72), and lower for blood groups AB (OR, 1.51) and A (OR, 1.32);<sup>11</sup> secretor status had no significant effect on this risk, but the behavior of *H. pylori*, which is also influenced by blood group, may have an influence on risk.<sup>1</sup> Non-O blood group individuals infected with *CagA* negative *H. pylori* have an even higher risk for pancreatic cancer (OR=2.78).<sup>20</sup> The higher rate of pancreatic cancer in non-O blood group individuals may have been explained by a genome-wide association study, which found that the SNP rs505922 mapped to the first intron of the ABO blood group gene in the 9q34 locus and was in complete linkage disequilibrium with the O/non-O allele.<sup>44</sup> Other studies have found that blood group O is strongly associated with pancreatic disease in patients with Von Hippel-Lindau (VHL) syndrome and is significantly correlated with solid pancreatic lesions in patients with pancreatic neuroendocrine tumors (PNETs); VHL patients have a high risk of developing multiple tumors throughout the body and their risk of developing both benign and malignant PNETs is 8% to 17%.<sup>45</sup>

**Multiple Endocrine Neoplasia Type I**—In 105 patients diagnosed with multiple endocrine neoplasia type I (MENS-1), 46 (43.8%) were diagnosed with a neuroendocrine tumor; of these 46 patients, 14 had more than one tumor for a total of 60 tumors, located in the duodenum (n=13), stomach (n=3), lung (n=5), pancreas (n=34), gallbladder (n=1), or thymus (n=4).<sup>46</sup> In patients with metastatic tumors, 16 of 17 (93.8%) had blood group O, while 32 of 43 (74.4%) with benign tumors were blood group O; in patients with neuroendocrine tumors, 35 of 46 (76.1%) had blood group O, while only 31 of 59 (52.5%) with non-neuroendocrine tumors were blood group O.<sup>46</sup> Of the 59 patients with non-neuroendocrine tumors, 31 (52.5%) were blood group O, 15 (25.4%) were blood group A, 7 (11.9%) were group blood B, and 6 (10.2%) were blood group AB, while of the 46 patients with neuroendocrine tumors, 35 (76.1%) were blood group O, 9 (19.6%) were blood group A, 2 (4.3%) were blood group B, and none were blood group AB.<sup>46</sup> Blood group AB is found in 4% of the general population, and was found in 3.8% of the study cohort, so the absence of group AB in patients with neuroendocrine tumors was notable.<sup>46</sup>

**Cancer of the colon/rectum**—Increased activity of the  $\alpha$ 1,2-fucosyltransferase of the *FUT2* gene (Secretor) and the  $\alpha$ 1,4-fucosyltransferase of the *FUT3* gene (Lewis) appear to be involved in the development and control of cancers of the distal colon; Type 1 and Type 2 chains and Lewis antigens are normally present in the fetal colon and disappear in healthy adults, but they reappear in adults who have distal colon cancers.<sup>1, 48</sup> In the normal colon, only Type 1 chains are expressed by secretors, while no Type 1 or Type 2 chains are expressed by non-secretors in normal or cancerous colon tissue.<sup>47</sup> In normal colon and colon cancer tissue, secretor status also determines whether the H antigen (blood group O) expresses.<sup>47</sup> The secretory part of the goblet cells in the normal colon is responsible for expression of blood group antigens.<sup>48</sup> Blood group A antigen is sometimes expressed on malignant tumors of group O or group B individuals; about 10% of colon tumors of homozygous type O people express A antigen and have *N*-acetylgalactosaminyltransferase activity.<sup>1</sup>

### Metabolic diseases

The role of blood groups in metabolic diseases is more complex; this is most likely because they are multifactorial diseases that are not controlled by just one gene or antigen. However, some intriguing associations have been found which are presented here.

**Hypertension**—Hypertension can have many different causes, so it is not surprising that different studies have found different associations between blood group antigens and hypertension. One study found that the rate of hypertension was highest in blood group B, followed by blood group A, and that blood group AB had the lowest rate of hypertension,<sup>49</sup> while another study reported a link between blood group A and systolic blood pressure in Caucasians but not in Blacks.<sup>15</sup> In essential hypertension due to abnormal erythrocyte sodium and potassium transport, no association was found with the ABO, Rh, Duffy, Kidd, P, or MNS blood groups, or with the major histocompatibility HLA antigens.<sup>50</sup> In essential hypertension due to abnormal erythrocyte sodium-lithium countertransport, no association was found with the MNS blood group polymorphism.<sup>52</sup>

Essential hypertension is diagnosed when secondary forms of hypertension can be ruled out, but it can also be diagnosed due to renal stenosis (renovascular hypertension), atherosclerotic or fibromuscular etiology, or primary aldosteronism associated with low plasma renin levels; individuals with these conditions were compared to normotensive controls and to individuals with secondary hypertension, and no significant differences were found in ABO, Rh, Kidd, Kell, Duffy, P, haptoglobin, PGM-1, or acid phosphatase systems.<sup>51</sup> However, there were significant differences in the frequencies of the MNS blood group antigens when comparing normotensive controls with individuals who had essential or renovascular hypertension; when compared to normotensives, essential hypertensives were significantly different among Whites, while a similar difference was not seen among Blacks.<sup>51</sup> Three distinctly different phenotypic frequencies were seen when individuals with atherosclerotic renovascular hypertension were compared to essential hypertensives and normotensives.<sup>51</sup>

**Hyperlipidemia**—Studies since the early 1980s have investigated the genetic basis for differences in LDL cholesterol, HDL cholesterol, and triglycerides, and several have found an association between the MN blood group and LDL cholesterol levels.<sup>53</sup> Participants in a dietary intervention program with homozygous MM and NN genotypes (47%) had similar responses to a low-fat diet, which resulted in almost all of the reported reduction in LDL cholesterol; in contrast, those with the heterozygous MN genotype (53%) had little or no response to the low-fat diet.<sup>53</sup> This finding is relevant when prescribing a low-fat diet for LDL cholesterol management because it indicates that about half of the general population at large would have a similar response to a low-fat diet.<sup>53</sup>

Researchers have also investigated the association between ABO blood group antigens and hyperlipidemia. One study reported that total cholesterol, LDL cholesterol, and triglycerides were higher, and HDL cholesterol was lower, in blood groups A and B, and that blood group AB was protective for hyperlipidemia,<sup>49</sup> while another study reported that blood group A was associated with higher total cholesterol and LDL cholesterol, but reported no association with HDL cholesterol.<sup>15</sup>

Perhaps the most interesting finding was the association of ABO and secretor blood groups with serum levels of intestinal alkaline phosphatase (I-ALP) and apolipoprotein B-48 (apo B-48); I-ALP is required for transport of chylomicrons from the intestines into the circulation and is therefore a marker for chylomicron absorption, and apo B-48 is a protein that stabilizes the chylomicron membrane, and is therefore a marker for chylomicron production.<sup>55</sup> There are significant differences in serum I-ALP and apo B-48 between blood group O and B secretors and all other blood groups; the O and B secretors have very elevated serum levels of these markers compared with blood group A/AB secretors and non-secretors of all blood groups.<sup>55</sup>

ABO non-secretors only have about 20% of the serum I-ALP of secretors, and among secretors, blood group A has very low activity ( $2.8 \pm 1.1$  IU/L; mean  $\pm$  SEM) compared to blood group B and O ( $14.1 \pm 1.1$  IU/L and  $19.0 \pm 2.5$  IU/L, respectively).<sup>54</sup> It is thought that I-ALP binds with ABO antigens on RBCs of non-secretors and is also adsorbed by the A antigens of secretors, therefore being rapidly eliminated from circulation in these individuals, but the soluble circulating antigens of O and B secretors preferentially bind with I-ALP and prevent its elimination in these individuals.<sup>55</sup> Blood group A individuals also have lower serum apo B-48 levels, which may be due to a genetic down-regulation of I-ALP activity in their intestines, resulting in reduced chylomicron secretion<sup>55</sup> and possibly lower serum cholesterol levels.

**Diabetes mellitus**—A large prospective study in France found no association between risk of type 2 diabetes mellitus (T2DM) and Rh blood group, but those in blood group O had the lowest risk of T2DM while blood group B individuals were at the highest risk, followed by group AB and then group A people, but the risk for group AB individuals did not reach statistical significance.<sup>18</sup> When ABO and Rh groups were evaluated together, blood group B<sup>+</sup> individuals had the highest risk, followed by group AB<sup>+</sup>, then A<sup>-</sup> and then A<sup>+</sup> individuals, but no difference in risk was seen for the other groups.<sup>18</sup> When adjusted for metabolic covariates (fasting blood glucose and lipids), blood group AB individuals had the

highest risk of T2DM (OR, 1.95), followed by group B (OR, 1.26) and group A (OR, 1.21) as compared with blood group O individuals, who had the lowest risk.<sup>18</sup>

Other studies have reported contradictory results: a study in Yemen reported that the highest random blood sugar and insulin levels were found in blood group A, while blood group AB showed a protective effect;<sup>49</sup> a study in Iraqi individuals reported higher total cholesterol, higher blood glucose, and higher blood pressure in blood group O individuals, followed by lower risk in group A, group B, and then group AB individuals, who had the lowest risk;<sup>18</sup> a large study in Bangladesh reported no association between ABO blood groups and T2DM; and a study in Malaysia found lower risk of T2DM in blood groups A and O.<sup>56</sup> It has also been reported that non-secretors are more likely to have T2DM.<sup>15</sup>

Convincing evidence has been reported of a genetic association in those of European ancestry between non-secretor status (*se/se*; homozygous for the *A/A* alleles of the *FUT2* gene) and insulin-dependent type 1 diabetes mellitus (T1DM). In the case-control population, the odds ratio for non-secretor status was 1.29 ( $p=7.3 \times 10^{-14}$ ); in the diabetic family population, the relative risk for non-secretor status was 1.22 ( $p=6.8 \times 10^{-6}$ ); and the combined results clearly indicated a locus for T1DM in the *FUT2* gene ( $p=4.3 \times 10^{-18}$ ).<sup>29</sup>

The I-ALP findings by blood group for diabetes were similar to the findings for hyperlipidemia, with significantly higher serum I-ALP and total ALP levels in blood group B and O secretors (including controls) when compared to A secretors or ABO non-secretors, but no significant difference in serum I-ALP or total ALP between A secretors and ABO non-secretors (including controls).<sup>59</sup> However, when comparing blood group B and O secretor diabetics to controls, I-ALP activity was similar between type 1 and type 2 diabetics but significantly higher in both types than in the controls; similarly, there was no significant difference in I-ALP activity between type 1 and type 2 diabetics in the A secretor and ABO non-secretor groups, but both types of diabetics had significantly higher I-ALP activity than the controls in these groups.<sup>59</sup>

Additional comparisons were made between the diabetics and controls in the group B and O secretors: in most cases, fasting I-ALP activity was higher in the diabetics than in the controls; both types of diabetics had significantly higher liver ALP activity than the controls; type 2 diabetics had higher liver ALP than type 1 diabetics; and type 2 diabetics also had more abnormal ALT and GGT values than type 1 diabetics.<sup>59</sup> Disturbed liver function could impair clearance of I-ALP by the liver and would explain the higher ALP levels found in the diabetics; high I-ALP has been reported in patients with cirrhosis of the liver.<sup>59</sup>

**The Role of the Microbiome**—Considerable research has focused on the role of intestinal bacteria in the development of diabetes. There are significant differences between the composition of the gut microbiome in healthy children and children with T1DM, and it is believed that T1DM occurs as a result of a pathogenic inflammatory response resulting in damage to the  $\beta$ -cells of the pancreas.<sup>58</sup> In addition, intestinal bacterial strains have been identified that can regulate the immune system and induce antigen-specific pathogenic T cells, which may be involved in the development of T1DM.<sup>58</sup> Differences were also found in both phylum and class levels for those with newly-diagnosed T2DM, those who were pre-



diabetic, and those with normal glucose tolerance, indicating that the progression of glucose intolerance is associated with specific changes in the gut microbiome.<sup>58</sup>

Obesity is strongly correlated with T2DM, but there are metabolically normal obese people who are insulin sensitive and euglycemic, and metabolically obese normal weight people who have metabolic syndrome despite maintaining a healthy weight.<sup>57</sup> In addition, discordance in obesity between monozygotic and dizygotic twins clearly indicates that other factors than genetics are involved in obesity; fecal transplants between fat and thin mice have resulted in changes in metabolism, morphology, and composition of the gut microbiome to match the donor mouse.<sup>58</sup> There is a strong association between obesity and alterations of the gut microbiome, but it is not known whether these changes are a consequence or a cause of obesity.<sup>58</sup>

## CONCLUSION

There is compelling evidence that risks for disease are related to the chemistry of blood, including the blood group classification, the structures of A, B, H, and Lewis determinants, and the enzymes which induce these structures. How the blood group and surface antigens play a role in disease is only beginning to be investigated with sophisticated modern technologies, including recent studies of microbiome and metabolome associations with blood groups. ABO antigens provide glycoproteins that are degraded by microbes in the mucosal layer of the intestines. A small Finnish study recently demonstrated that the blood group of the host has a statistically significant association with the composition of the microbiome. Here, the overall profile of the mucosal microbes as well as the relative proportions of the major bacterial groups were reported to be different when the B antigen was present, as it would be in blood group B or AB individuals.<sup>72</sup> This study did not distinguish between secretors and non-secretors status, but it is known that secretor status strongly influences the composition of the human intestinal microbiome.<sup>73</sup>

Because we know that the blood type is defined by oligosaccharide structures, it is reasonable to believe that differences in biochemical profiles of individuals may also be related to differences in blood type, antigens, and secretor status. Metabolomics studies have revealed differences in the biochemical profiles based on ethnicity,<sup>74, 75</sup> and blood type is also known to be distributed differently among different ethnicities.<sup>76</sup> Recent work by Sumner and colleagues at the NIH Common Fund Eastern Regional Metabolomics Resource Core have demonstrated differences in the metabolotypes of individuals based on blood groups.<sup>77</sup> While research on the metabolotypes of blood types and the influence on disease and health has just started, this area of research can greatly contribute to the identification of targets for the development of nutritional intervention strategies, as well as the identification of druggable targets for drug discovery.

### Metabolomics in Antigen Research

Metabolomics is a robust analytical tool that identifies and quantifies the small metabolites produced in living, biological systems, speeds up identification of metabolic biomarkers that reflect the physiological status of cells, and reveals metabolic mechanisms of cellular activity.<sup>78</sup> In humans, it has been used to distinguish the different

metabolic profiles of normal and sickle cell erythrocytes,<sup>79</sup> and to study the mechanisms and pathogenesis of osteoarthritis;<sup>80</sup> xenobiotic toxicity; liver, breast, colon, and prostate cancer; inflammatory bowel disease; liver disease; and Alzheimer's disease.<sup>81</sup> Metabolomics has also proven invaluable for understanding the pathogenesis of Barth Syndrome,<sup>82</sup> metabolic consequences of chronic inflammation,<sup>83</sup> and metabolic dysregulation, molecular complexities, and nutrient imbalances behind T2DM.<sup>84</sup> There is now compelling evidence that human commensal microbiota play a significant role in health and disease; the microbiome has the ability to generate biochemical compounds in sufficient quantities to be detected in blood metabolites,<sup>85</sup> and in turn, the composition of the microbiome can be quite affected by dietary changes.<sup>72, 84</sup> Of more significance is the finding that blood group antigens and secretor status are genetically determined host factors that influence the composition of the human intestinal microbiome.<sup>72, 73</sup> The associations between blood groups and diseases are well documented; the use of metabolomics in blood group antigen research would finally reveal the complex mechanisms and processes involved. Metabolomics has great potential to streamline diagnosis, treatment, monitoring, and prevention of disease, and will greatly simplify collaboration between the fields of clinical research, drug development, personalized medicine, and personalized nutrition.<sup>78, 86</sup>

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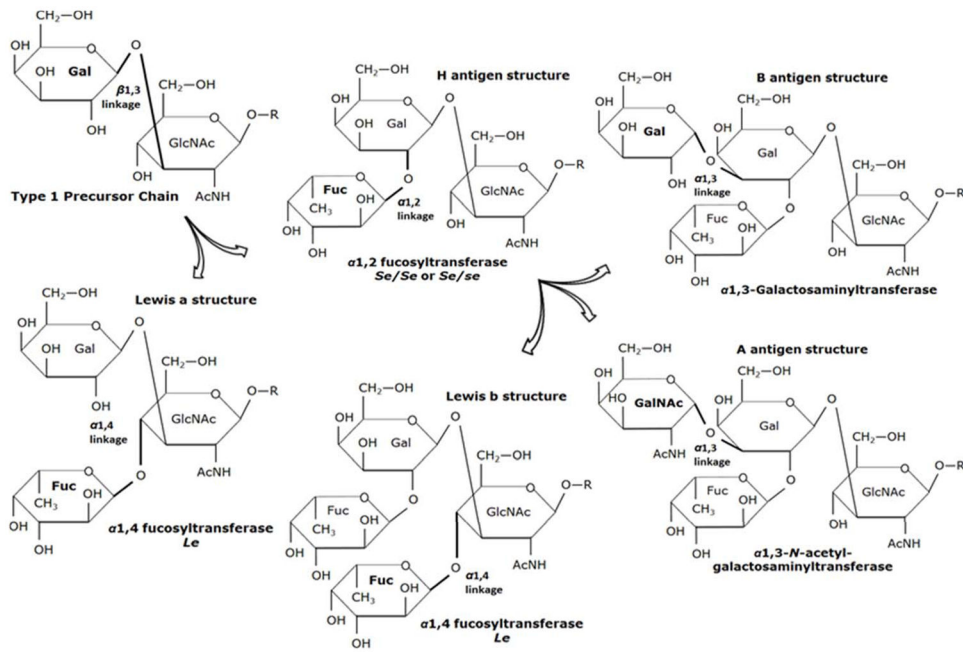
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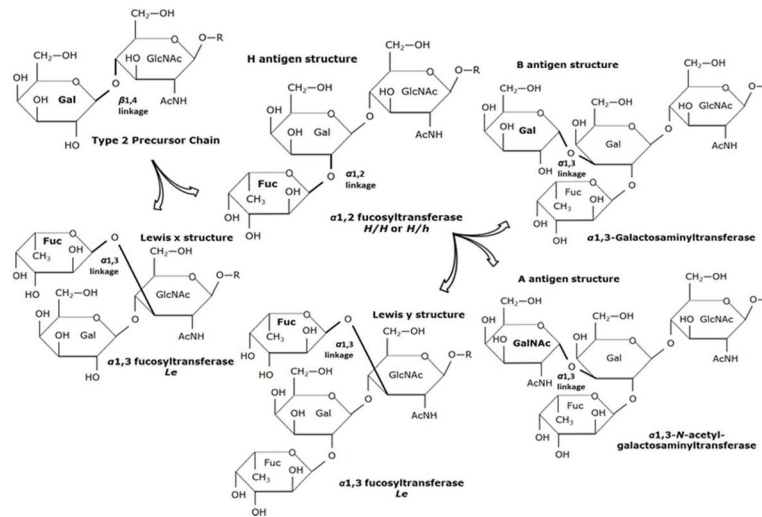
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**Figure 1.** Antigen structures generated from Type 1 precursor chains, which are primarily found in body secretions.





**Figure 2.** Antigen structures generated from Type 2 precursor chains, which are primarily found on body tissues and RBCs.

Table 1

Functional classifications of human blood group antigens<sup>1, 5-9</sup>

Type of Molecule	System		Gene Symbol	HGNC Symbol <sup>1</sup>	CD No.	Known or Proposed Function
	No.	Name				
Transferase	001	ABO	ABO	<i>ABO</i>		Prevent infection, cell recognition
	018	H	H	<i>FUT1</i>	CD173	Prevent infection, cell recognition
	007	Lewis	LE	<i>FUT3</i>		Prevent infection, cell recognition
	027	I	I	<i>GCNT2</i>		Prevent infection, cell recognition
	003	P1PK	P	<i>A4GALT</i>		Prevent infection, cell recognition
	028	Globoside	GLOB	<i>B3GALT3</i>		Prevent infection, cell recognition, Parvovirus B19 receptor
	031	Forssman	FORS	<i>GBGT1</i>		Prevent infection, cell recognition
Enzyme	006	Kell	KEL	<i>KEL</i>	CD238	Cell signaling, cleaves Big endothelin, Zh-metalloproteinase
	011	Yt	YT	<i>ACHE</i>		Esterase
	014	Dombrock	DO	<i>ART4</i>	CD297	Erythropoiesis, regulate protein function, ADP-ribosyltransferase
Complement Regulation	017	Chido/Rodgers	CH/RG	<i>C4A, C4B</i>		Complement component
	021	Cromer	CROM	<i>CD55</i>	CD55	Complement regulation; <i>E. coli</i> receptor
	022	Knops	KN	<i>CR1</i>	CD35	Complement regulation; <i>P. falciparum</i> receptor
Structural	002	MNS	MNS	<i>GYPA, GYPB, GYPE</i>	CD235 A & B	Chaperonin
	020	Gerbich	GE	<i>GYPC</i>	CD236	Cytoskeleton attachment to membrane; <i>P. falciparum</i> receptor
Transport/ Channel	004	Rh	RH	<i>RHD, RHCE</i>	CD240 D & CE	Ammonium transport
	030	RHAG	RHAG	<i>RHAG</i>	CD241	RBC membrane integrity, ammonium transport
	010	Diego	DI	<i>SLC4A1</i>	CD233	Band 3, Anion exchange
	015	Colton	CO	<i>AQP1</i>		Water channel
	029	Gill	GIL	<i>AQP3</i>		Water channel, urea transport
	009	Kidd	JK	<i>SLC14A1</i>		Urea transport
	019	Kx	XX	<i>XX</i>		Transport ?
	032	Junior	JR	<i>ABCG2</i>		ATP-binding cassette transport
	033	Lan	LAN	<i>ABCB6</i>		ATP-binding cassette transport

Type of Molecule	System		Gene Symbol	HGNC Symbol <sup>1</sup>	CD No.	Known or Proposed Function
	No.	Name				
<b>Adhesion</b>	023	Indian	IN	<i>CD44</i>	CD44	Erythropoiesis, binds hyaluronate, collagen, fibronectin
	005	Lutheran	LU	<i>BCAM</i>	CD239	Erythropoiesis, binds laminin
	016	Landsteiner-Weiner	LW	<i>ICAM4</i>	CD242	Cell-cell interaction, RBC turnover, binds $\beta 1$ -, $\beta 2$ -, $\beta 3$ -, $\beta 5$ -laminins
	026	John Milton Hagen	JMH	<i>SEMA7A</i>	CD108	Erythropoiesis, binds RGD peptides; <i>P. falciparum</i> receptor
	012	Xg	XG	<i>XG, CD99</i>	CD99*	Apoptosis
	024	Ok	OK	<i>BSG</i>	CD147	Erythropoiesis, binds LFA integrins
<b>Receptor</b>	008	Duffy	FY	<i>DARC</i>	CD234	Chemokine clearance; <i>P. vivax</i> receptor
	012	Scianna	SC	<i>ERMAP</i>		Signal transduction; IgSF
	025	Raph	RAPH	<i>CD151</i>	CD151	Signal transduction, binds integrins

HGNC, Human Genome Organization Gene Nomenclature Committee; IgSF, immunoglobulin superfamily.

\* Xg glycoprotein excluded.

**Table 2**

## The Relationship of Blood Group with Disease Risks

Disease	Risk Factor	Blood Group/Antigens
Sickle cell anemia <sup>16</sup>	Increased adhesion	Adhesion Molecules
Hemolytic disease of the newborn <sup>12, 17</sup>	Antibodies to RhD	RhD
Chronic and autoimmune hemolytic anemias <sup>13, 17</sup>	Rh null	Rh, RhAG
Vascular disorders, venous and arterial thromboembolism, coronary heart disease, ischemic stroke, myocardial infarction <sup>1, 11, 14, 18–22</sup>	Reduced clearance of von Willebrand factor and FVIII	Groups A > AB > B
Dementia, cognitive impairment <sup>22, 23</sup>	Coagulation factors	Groups AB > B > A
Plague, cholera, tuberculosis, mumps <sup>14</sup>	Antigen profile	Group O
Smallpox, <i>Pseudomonas aeruginosa</i> <sup>14</sup>	Antigen profile	Group A
Gonorrhea, tuberculosis, <i>S. pneumoniae</i> , <i>E. coli</i> , salmonella <sup>14</sup>	Antigen profile	Group B
Smallpox, <i>E. coli</i> , salmonella <sup>14</sup>	Antigen profile	Group AB
<i>N. meningitidis</i> , <i>H. influenza</i> , <i>C. albicans</i> , <i>S. pneumoniae</i> , <i>E. coli</i> urinary tract infections, <i>S. pyogenes</i> , <i>V. cholera</i> <sup>1, 14, 24</sup>	Antigen profile	Non-secretors
<i>H. pylori</i> <sup>1, 11, 14, 25, 26</sup>	Strain-dependent	Group A; 95% non-O
Peptic ulcers, gastroduodenal disease <sup>11, 14, 25</sup>	Secretor status, <i>H. pylori</i> strain	All non-secretors; Group O
Norovirus <sup>1, 11, 27–29</sup>	Strain-dependent	Secretors; groups O, A
<i>P. falciparum</i> malaria <sup>1, 11, 30</sup>	Receptor/antigen profile	Knops antigens; groups A, B
<i>P. vivax</i> malaria <sup>30</sup>	Antigen profile	Duffy FY antigens
Cholera <sup>27</sup>	Severity differs by antigen profile	Lewis antigen; non- secretors; non-O groups
Bacterial Meningitis ( <i>N. meningitidis</i> , <i>H. influenza</i> , <i>S. pneumoniae</i> ) <sup>31</sup>	Antigen profile	Non-secretors; A, AB, O blood groups
Cancer (tissue specific) <sup>1, 11, 14, 32–37</sup>	Increased tumor antigens and ligands	A, B, H antigens lost; “A- like” antigens gained
Leukemia and Lymphoma <sup>14, 38</sup>	RBC membrane changes	A, B, H antigens lost
Non-Hodgkin’s central nervous system lymphoma (primary and secondary) <sup>39–41</sup>		Group O, B
Hodgkin’s lymphoma <sup>41</sup>		Group B
Acute lymphoblastic leukemia <sup>41, 42</sup>		Group O
Acute myeloid leukemia <sup>1, 41, 42</sup>		Group A
Stomach Cancer <sup>20, 26, 43</sup>	<i>H. pylori</i> strain	Group A
Pancreatic Cancer <sup>1, 11, 20, 44</sup>	<i>H. pylori</i> strain	Group B > AB > A
Von Hippel-Lindau and Neuroendocrine <sup>45</sup>	Multiple tumors	Group O
Multiple Endocrine Neoplasia Type 1 <sup>46</sup>	Strongly associated	Group O
Colon/Rectum Cancer <sup>1, 47, 48</sup>	Type 1 and 2 chains; Lewis antigens	Secretors; “A-like” antigens expressed
Hypertension <sup>15, 49–52</sup>	3 phenotypes differ	Group B>A>AB
Hyperlipidemia <sup>15, 49, 53–55</sup>	Low fat diet Ineffective;	LDL: Heterozygous MN; Group A, B; ALP/apoB-48: Group O and B secretors

Disease	Risk Factor	Blood Group/Antigens
	Intestinal ALP and apoB-48 vary by secretor status	
Type 2 Diabetes <sup>15, 18, 49, 56-59</sup>	Rh group modifies	Group AB > B > A
Type 1 Diabetes <sup>29, 58, 59</sup>	<i>FUT2</i> gene locus	Non-secretors

The risk factors and blood groups or antigens associated with various diseases, based on the research presented in this review.

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