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Secretory Immunoglobulin A Carries Oligosaccharide Receptors for *Escherichia coli* Type 1 Fimbrial Lectin

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Type 1 fimbriae with mannose-specific lectins are widely distributed among members of the family *Enterobacteriaceae* and confer the ability to attach to a range of host cells, including colonic epithelial cells. The mucosal surfaces are protected by secretory immunoglobulin A (IgA), which agglutinates microorganisms and prevents their attachment to host epithelial cells. This action has been attributed to a specificity of the antigen-combining site of mucosal immunoglobulins for bacterial and viral surface components. Here, we report a novel mechanism for the antibacterial effect of secretory IgA. Secretory IgA and IgA myeloma proteins, especially those of the IgA2 subclass, were shown to possess carbohydrate receptors for the mannose-specific lectin of type 1-fimbriated *Escherichia coli*. The presence of the high-mannose oligosaccharide chain Manα1-6(Manα1-3)Manα1-6(Manα1-3)Manβ1-4GlcNAcβ1-4GlcNAc correlated with binding activity. The interaction between bacterial mannose-specific lectins and IgA receptor oligosaccharide resulted in agglutination of the bacteria and in inhibition of bacterial attachment to colonic epithelial cells. Thus, this interaction could form the basis for a broad antibacterial function of secretory IgA against enterobacteria regardless of the specificity of antibody molecules.

Bacteria adhere to mucosal surfaces by means of lectins, which are proteins with specificity for oligosaccharide sequences on host cell membrane lipid or protein (19). Type 1 fimbriae, which are expressed by a wide range of gram-negative bacteria of the family *Enterobacteriaceae*, confer on the bacteria the ability to bind to target cells in a mannose-sensitive manner (9). The mannose-specific lectin of type 1 fimbriae mediates binding to human phagocytes (4), buccal epithelial cells (27), and colonic epithelial cells (8, 34).

The mucosal surfaces are protected by secretory immunoglobulin A (S-IgA), the predominant immunoglobulin isotype synthesized in humans (5). In contrast to other major immunoglobulin isotypes, S-IgA does not activate complement or promote phagocytosis (18) but protects the host by agglutination of bacteria and inhibition of their attachment (12, 30, 33). The antimicrobial properties of S-IgA have been attributed to the specificity of the antigen-binding site for bacterial and viral surface components.

It has been proposed that the receptors for type 1 fimbriae belong to asparagine-linked oligosaccharides of glycoproteins, especially of the high-mannose type (10, 11, 26). Since immunoglobulins are glycoproteins with asparagine-linked oligosaccharide moieties (2, 32), we tested the hypothesis that mannose-specific lectins of *Escherichia coli* could interact with human immunoglobulin molecules, especially IgA.

MATERIALS AND METHODS

Immunoglobulin preparations. S-IgA and free secretory component were isolated from human colostrum (21). Cells and milk lipids were removed by centrifugation. Casein was removed by acidification and centrifugation, and immunoglobulins were precipitated with ammonium sulfate. IgA was purified by molecular sieve chromatography on columns of Sephadex G-200 and Sepharose 6B (or Ultrogel AcA 22) and by ion-exchange chromatography on DEAE-cellulose (21, 22). To remove trace amounts of IgM and lactoferrin-IgA complexes, S-IgA was passed through affinity columns with covalently linked anti-IgM or heparin (21). Polyacrylamide gel electrophoresis in sodium dodecyl sulfate or alkaline urea under nonreducing or reducing conditions (0.2 M 2-mercaptoethanol) revealed the presence of α, J, and light chains (22). No other proteins were detected. S-IgA1 and S-IgA2 were separated by affinity chromatography on Jacalin (Vector Laboratories, Burlingame, Calif.) (17).

Polymeric myeloma proteins of the IgA1 and IgA2 isotypes were purified from serum as described above, with the addition of starch block electrophoresis and affinity chromatography on Jacalin (to purify IgA1 or to remove IgA1 from IgA2 preparations) (21). Purity was tested by immunoprecipitation and polyacrylamide electrophoresis (20). Three IgA2 (Map, Bil, and Kur) and three IgA1 (Wms, Lay, and Xoc) purified myeloma proteins were given to us by A. Solomon (University of Tennessee, Knoxville). IgA2 myeloma proteins Bel and Kaw were obtained from P. Aucouturier and J. L. Preud'homme (Centre Hospitalier Régional et Universitaire de Poitiers, France) and K. Kobayashi (Hokkaido University, Sapporo, Japan), respectively.

The gamma globulin fraction of normal human plasma was purchased from a commercial source (16.5% gamma globulin; Kabi, Stockholm, Sweden). IgG myeloma proteins were kindly provided by F. Skvaril, Bern, Switzerland. Their IgG subclasses, light-chain isotypes, and designations were as follows: IgG1(κ) (Sch), IgG1(λ) (no. 10), IgG2(κ) (G236),

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IgG2(λ) (Fi), IgG3(κ) (Rey), IgG3(λ) (Ruf), and IgG4(κ) (Bru and Ste).

Five purified IgM myeloma proteins, IgM(κ) (Lew, Pom, Cor, and Dau) and IgM(λ) (Gra), were kindly provided by R. E. Schrohenloher (University of Alabama at Birmingham). IgM(κ) (Lim) was prepared in this laboratory.

Bacteria. *E. coli* 506MS was derived from a nonadhering fecal strain by transformation with the chromosomal-DNA fragment *pil*, which encodes type 1 fimbriae with mannose specificity (13, 14). The homologous strain 506MR was derived by transformation of the same parental strain with the *pap* fragment (14), which encodes P fimbriae with specificity for the sequence Galα1→4Galβ found in the globoseries of glycolipids (19). 506MS and 506MR share the serotype O:19,22K:1H−.

Bacterial agglutination by immunoglobulins. The immunoglobulin preparations at 1 mg/ml were titrated by twofold dilutions in phosphate (0.01 M)-buffered saline (pH 7.2; PBS) in microtiter plates (96-well, U-shaped microtest plates; Labora, Upplands Väsby, Sweden). An equal volume of PBS or of 2.5% methyl-α-D-mannoside in PBS was added, and twice this volume of bacteria was suspended at 2×10^9/ml in PBS. The plates were shaken and incubated at 37°C for 30 min and then at 4°C overnight. Agglutination was read by eye and by bright-field microscopy at ×250 magnification. The reciprocal of the highest dilution giving visible agglutination was recorded as the agglutination titer. The specificity of inhibition was tested with glucose, fucose, galactose, *N*-acetyl-D-galactosamine, and *N*-acetyl-D-glucosamine (all from Sigma Chemical Co., St. Louis, Mo.) in parallel with methyl-α-D-mannoside.

Structural analysis of asparagine-linked oligosaccharides of IgA1 and IgA2 myeloma proteins. Thoroughly dried IgA1 myeloma protein (Car, 4.7 mg) and IgA2 myeloma protein (Fel, 3.5 mg) were suspended in 0.5 ml of anhydrous hydrazine and subjected to hydrazinolysis at 100°C for 9 h. Released oligosaccharides were N acetylated and purified as described previously (25, 28). One portion of the oligosaccharide fractions was reduced with NaB^3H_4 (0.4 mCi; New England Nuclear Corp., Boston, Mass.) to obtain tritium-labeled oligosaccharide mixtures. The rest was reduced with $NaBH_4$ (2 mg) for methylation analysis. All other experimental procedures were the same as described earlier (25, 28).

Inhibition of bacterial adhesion to human colonic carcinoma cell line HT-29. Adherence to human colonic cells was studied by using the human colonic carcinoma cell line HT-29 (34). The cells were detached by treatment with EDTA, and a single-cell suspension of 5×10^6 cells per ml in Hanks balanced salt solution was prepared. The cell suspension (0.1 ml) was mixed with an equal volume of the bacterial suspension at 5×10^9/ml in Hanks balanced salt solution, and with 0.3 ml of either Hanks balanced salt solution or immunoglobulins dissolved in this solution. The adhesion mixture was incubated with end-over-end rotation for 30 min at 4°C. After the incubation, 10 ml of cold PBS was added, and the cells were spun down, resuspended, and fixed with a few drops of neutral buffered Formalin (Histofix; Histolab, Goteborg, Sweden). The number of bacteria attached to at least 40 cells was determined, and the mean number of bacteria attached per cell was calculated.

RESULTS

Agglutination of mannose-specific bacteria by S-IgA and human gamma globulin. S-IgA and gamma globulin both agglutinated mannose-specific *E. coli* 506MS but not the homologous strain, 506MR (Table 1). Whereas most of the agglutination by S-IgA was inhibitible by mannose, the weak agglutinating activity of gamma globulin was not affected. S-IgA was separated by affinity chromatography on Jacalin into S-IgA1 and S-IgA2. Both subclasses of S-IgA strongly agglutinated 506MS. The greatest portion of the agglutination, especially that induced by S-IgA2, was reversible by mannose. Free secretory component, prepared from colostrum, did not agglutinate any of the strains.

TABLE 1. Agglutination of *E. coli* with or without mannose-specific lectins by polyclonal immunoglobulin preparations

Immunoglobulin preparation[a]	Agglutination titer		
	506MS with:		506MR
	PBS	Mannose	
S-IgA	128	2	<1
S-IgA1	64	4	<1
S-IgA2	128	2	<1
Free secretory component	<1	<1	<1
Gamma globulin	2	4	<1

[a] For methods of preparation and agglutination, see the text.

Agglutination of mannose-specific bacteria by myeloma proteins. To test the possibility that the mannose-sensitive part of the agglutination was due to an interaction between bacterial lectin and immunoglobulin carbohydrate, human myeloma proteins of different isotypes were tested for their abilities to agglutinate *E. coli* 506MS. Three of six IgA2 myeloma proteins agglutinated 506MS at high titers; the reactions were completely inhibited by mannose (Table 2). Other monosaccharides (glucose, galactose, fucose, *N*-acetyl-D-galactosamine, and *N*-acetyl-D-glucosamine) were inactive as inhibitors when tested with an IgA2 myeloma protein of high agglutinating titer (Fel). Three of the six polymeric IgA1 myeloma proteins were also active, but with lower titers than the IgA2 myeloma proteins. None of the IgA myeloma proteins agglutinated *E. coli* 506MR. Myeloma proteins of the IgG and IgM isotypes were also tested (data not shown). None of the IgG myeloma proteins agglutinated *E. coli* 506MS or 506MR. Of the six IgM myeloma proteins tested, three agglutinated 506MS in a mannose-sensitive manner, with titers of 8 to 16.

TABLE 2. Agglutination of mannose-sensitive and -resistant *E. coli* by myeloma proteins of IgA1 or IgA2 isotype

Immunoglobulin isotype (polymeric)[a]	Myeloma	Allotype	L chain type	Agglutination titer		
				506MS with:		506MR
				PBS	Mannose	
IgA2	Map	A2m(1)	κ	128	<1	<1
	Bil	A2m(1)	κ	256	<1	<1
	Fel	A2m(2)	λ	512	<1	<1
	Bel	A2m(2)	κ	<1	<1	<1
	Kur	A2m(2)	κ	<1	<1	<1
	Kaw	A2m(2)	λ	<1	<1	<1
IgA1	Car		κ	8	<1	<1
	Wms		κ	8	<1	<1
	Lay		κ	8	<1	<1
	Lat		κ	<1	<1	<1
	Xoc		κ	<1	<1	<1
	Ste		λ	<1	<1	<1

[a] For methods of preparation and agglutination, see the text.

TABLE 3. Structures and molar ratios of neutral (N), mono-(A1N), and disialylated (A2N) fractions of IgA1 and IgA2 myeloma proteins

	Oligosaccharide species	Per Cent Molar Ratio					
		IgA2 (Fel)			IgA1 (Car)		
		N	A1N	A2N	N	A1N	A2N
I.	Manα1→6 Manα1 / Manα1→3 Manα1 → Manβ1-4GlcNAcβ1-4GlcNAc	17.9	—	—	7.3	—	—
II.	GlcNAcβ1 (4), Fucα1 (6); GlcNAcβ1-2Manα1→6 / GlcNAcβ1-2Manα1→3 → Manβ1-4GlcNAcβ1-4GlcNAc	52.4	—	—	6.5	—	—
III.	GlcNAcβ1 (4), Fucα1 (6); GlcNAcβ1-2Manα1→6 / Galβ1-4GlcNAcβ1-2Manα1→3 → Manβ1-4GlcNAcβ1-4GlcNAc	—	4.8	—	3.1	4.9	—
IV.	Fucα1 (6); Galβ1-4GlcNAcβ1-2Manα1→6 / GlcNAcβ1-2Manα1→3 → Manβ1-4GlcNAcβ1-4GlcNAc	—	0.2	—	—	—	—
V.	Fucα1 (6); GlcNAcβ1-2Manα1→6 / Galβ1-4GlcNAcβ1-2Manα1→3 → Manβ1-4GlcNAcβ1-4GlcNAc	—	7.5	—	—	0.5	—
VI.	Fucα1 (6); Galβ1-4GlcNAcβ1-2Manα1→6 / Galβ1-4GlcNAcβ1-2Manα1→3 → Manβ1-4GlcNAcβ1-4GlcNAc	—	3.0	1.4	1.0	12.9	8.1
VII.	GlcNAcβ1 (4), Fucα1 (6); Galβ1-4GlcNAcβ1-2Manα1→6 / Galβ1-4GlcNAcβ1-2Manα1→3 → Manβ1-4GlcNAcβ1-4GlcNAc	—	—	0.2	6.6	9.7	4.2
VIII.	GlcNAcβ1-2Manα1→6 / GlcNAcβ1-2Manα1→3 → Manβ1-4GlcNAcβ1-4GlcNAc	1.7	—	—	—	—	—
IX.	GlcNAcβ1 (4); GlcNAcβ1-2Manα1→6 / GlcNAcβ1-2Manα1→3 → Manβ1-4GlcNAcβ1-4GlcNAc	4.0	—	—	1.3	—	—
X.	GlcNAcβ1 (4); GlcNAcβ1-2Manα1→6 / Galβ1-4GlcNAcβ1-2Manα1→3 → Manβ1-4GlcNAcβ1-4GlcNAc	—	0.2	—	6.6	4.0	—
XI.	Galβ1-4GlcNAcβ1-2Manα1→6 / GlcNAcβ1-2Manα1→3 → Manβ1-4GlcNAcβ1-4GlcNAc	2.3	—	—	—	—	—
XII.	GlcNAcβ1-2Manα1→6 / Galβ1-4GlcNAcβ1-2Manα1→3 → Manβ1-4GlcNAcβ1-4GlcNAc	—	0.8	—	—	1.9	—
XIII.	Galβ1-4GlcNAcβ1-2Manα1→6 / Galβ1-4GlcNAcβ1-2Manα1→3 → Manβ1-4GlcNAcβ1-4GlcNAc	—	0.8	1.4	1.5	12.3	5.4
XIV.	GlcNAcβ1 (4); Galβ1-4GlcNAcβ1-2Manα1→6 / Galβ1-4GlcNAcβ1-2Manα1→3 → Manβ1-4GlcNAcβ1-4GlcNAc	—	1.1	—	—	2.3	—
XIV.	Manα1→6 / Galβ1-4GlcNAcβ1-2Manα1→3 → Manβ1-4GlcNAcβ1-4GlcNAc	—	0.3	—	—	—	—

TABLE 4. Inhibition of mannose-sensitive and -resistant *E. coli* adhesion to human colonic epithelial cells by S-IgA and IgA2 myeloma protein (Fel)

Immunoglobulin preparation	Adhesion (mean no. of bacteria/cell)[a]	
	506MS	506MR
Control	68	45
S-IgA	<5	44
IgA2 myeloma protein (Fel)	<5	38
Gamma globulin	65	40

[a] When agglutinates were loosely associated with epithelial cells otherwise free of attached bacteria, cells were scored as negative. See the text for details on methods.

Structures of asparagine-linked oligosaccharides of IgA1 and IgA2 myeloma proteins. To clarify the different reactivities of IgA molecules with mannose-specific *E. coli*, the asparagine-linked oligosaccharides of an IgA1 myeloma protein with relatively low agglutinating activity (Car; agglutination titer, 8) and of an IgA2 myeloma protein with strong activity (Fel; titer, 512) were analyzed. Radioactively labeled oligosaccharide mixtures were separated into neutral (N), monosialylated (A1), and disialylated (A2) fractions by paper electrophoresis at pH 5.4. The percent molar ratios of the respective fractions were 34% N, 48% A1, and 18% A2 for IgA1 (Car) and 78% N, 19% A1, and 3% A2 for the IgA2 (Fel) myeloma proteins.

The neutral oligosaccharide fractions obtained for A1 and A2 after sialidase digestion (25, 28) were named A1N and A2N, respectively. Individual oligosaccharide structures (from each of the fractions N, A1N, and A2N) were elucidated by methylation analysis, serial lectin column chromatography, and sequential exoglycosidase digestion. The structures found and their percent molar ratios are shown in Table 3. Both IgA preparations contained complex types as well as high-mannose-type oligosaccharide chains, but the high-mannose type was more abundant in the IgA2 myeloma protein than in the IgA1 myeloma protein.

Inhibition of attachment to HT-29 colonic carcinoma cell line. The human colonic carcinoma cell line HT-29 expresses receptors for mannose-specific as well as for Galα1→4Galβ-specific *E. coli* (34). The abilities of S-IgA, IgA2 myeloma protein (Fel), and gamma globulin to inhibit the attachment of *E. coli* 506MS or 506MR were tested. The attachment of *E. coli* 506MS was inhibited by S-IgA and by the IgA2 myeloma protein (Table 4). The gamma globulin preparation did not inhibit the adhesion of either of the strains, although it induced visible agglutination of the type 1-fimbriated bacteria.

DISCUSSION

The present study demonstrates that S-IgA possesses carbohydrate receptors for the mannose-specific type 1 fimbrial lectin of *E. coli*.

Asparagine-linked oligosaccharides, especially those of the high-mannose type, have been proposed as the receptors for type 1 fimbriae (11, 26). Oligosaccharide chains of the high-mannose type were more abundant (18%) in the IgA2 myeloma protein (Fel), which strongly agglutinated mannose-specific *E. coli* (agglutination titer, 512), than in the IgA1 myeloma protein (Car), which had an agglutination titer of 8 (7.3% oligosaccharides of the high-mannose type). IgA2 myeloma proteins have been shown to differ from IgA1 myeloma proteins in glycosylation pattern. The difference can be seen both in total sugar composition (31) and in lectin-binding pattern when different plant lectins recognizing asparagine-linked oligosaccharide chains are used (A. E. Wold, unpublished data). In addition, IgA2 is more highly glycosylated than IgA1 (31, 32), which could explain the higher agglutinating activity of IgA2. Nevertheless, half of the myeloma proteins tested, whether of the IgA1 or the IgA2 subclass, lacked such activity, demonstrating the variability in glycosylation pattern between individual immunoglobulins (15, 25, 29). It should be noted that the high-mannose type of oligosaccharide has not previously been found in IgA1 (2).

Interestingly, only one type of high-mannose oligosaccharide was found, both in the IgA1 and the IgA2 myeloma proteins analyzed: Manα1-6(Manα1-3)Manα1-6(Manα1-3)Manβ1-4GlcNAcβ1-4GlcNAc (or Man_5 · GlcNAc · GlcNAc). Generally, as in the case of IgM (28), the high-mannose type oligosaccharides occur as a series of molecules: $(Man\alpha1\text{-}2)_{0\text{-}4}$ · Man_5 · GlcNAC · GlcNAc. Such terminal α1-2-linked mannose has been shown to weaken the binding of bacterial mannose-specific lectin (26) and may explain why myeloma proteins of the IgM isotype were not more active, although they are substituted with high-mannose oligosaccharide chains (28, 32).

In oligosaccharide chains of the complex type, the mannose is substituted with *N*-acetylglucosamine, galactose, and sialic acid, but truncated forms of oligosaccharide chains with mannose in the terminal positions are also formed because of incomplete glycosylation (25, 29). Short oligosaccharide chains with terminal mannose residues have, indeed, been isolated from secretory component (24). Although free secretory component did not agglutinate mannose-specific *E. coli*, it may have contributed to the agglutinating activity of S-IgA, since S-IgA1 was strongly active while polymeric IgA1 myeloma proteins were only weakly active or inactive. In addition, the J chain, which ties together immunoglobulin monomers in IgM and polymeric IgA, possesses one complex type of oligosaccharide chain and may add to the receptor activity of polymeric IgA and IgM (3).

The human large intestine is the major ecological niche for gram-negative enteric bacteria, many of which are able to express mannose-specific lectins (9). The colonic mucosa is also the site where IgA2-producing cells predominate over those secreting IgA1 (6, 16). Interaction between mannose-specific *E. coli* and IgA2 myeloma protein or S-IgA blocked bacterial binding to colonic epithelial cells. In contrast, IgG, which had antibody activity against type 1 fimbriae (as evidenced by a mannose-resistant agglutination of this type 1-fimbriated strain) was unable to interfere with attachment. Antibodies formed after vaccination or natural infection with fimbriated bacteria are mostly directed against the major structural protein of fimbriae rather than against the minor lectin component and consequently often do not interfere with attachment (1, 7). One major function of S-IgA in the intestine could, thus, be to agglutinate intestinal bacteria and prevent their attachment to host cells by providing receptor sites for bacterial lectins. By this mechanism, S-IgA would protect the host against a wide range of enterobacteria without any need for previous immunologic encounter.

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