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Decreased Expression of Mannose-Specific Adhesins by *Escherichia coli* in the Colonic Microflora of Immunoglobulin A-Deficient Individuals

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Most *Escherichia coli* isolates can express type 1 fimbriae with mannose-specific adhesins. These adhesins bind to the oligosaccharide chains of secretory immunoglobulin A (IgA). Thus, in addition to specific antibody activity, secretory IgA possesses a broad reactivity with bacteria expressing type 1 fimbriae. The absence of secretory IgA in colonic secretions, as seen in IgA deficiency, might therefore alter the ability of type 1-fimbriated *E. coli* to colonize the large intestines of these individuals. In the present study, 10 *E. coli* isolates from each of 17 IgA-deficient and 17 age-matched control individuals were assessed for the carriage of the *fim* gene cluster by DNA-DNA hybridization and for the expression of type 1 fimbriae by hemagglutination of guinea pig erythrocytes. The contribution of type 1-fimbria-mediated adherence to HT-29 colonic cells was also analyzed. The proportion of *fim*$^+$ *E. coli* isolates was lower in IgA-deficient than in control individuals (74 versus 94%, $P < 0.05$), as was the proportion of isolates expressing type 1 fimbriae in vitro (69% versus 85%, $P < 0.05$). The median mannose-sensitive adherence to HT-29 cells was lower for isolates from IgA-deficient individuals than from the controls (9 versus 26 bacteria per cell, $P < 0.05$). Isolates expressing type 1 fimbriae showed lower adherence to HT-29 cells when they were derived from IgA-deficient individuals than when they were derived from control individuals (15 versus 27 bacteria per cell, $P < 0.05$). The results suggest that the interaction of type 1 fimbriae with secretory IgA contributes to the large intestinal colonization by these bacteria.

The human large intestine is the major ecological niche for *Escherichia coli*. The most commonly expressed adhesin in this species is the mannose-sensitive adhesin of type 1 fimbriae (6). Type 1 fimbriae are encoded by the *fim* gene cluster, in which the *fimA* gene encodes the major structural fimbrial subunit and *fimH* encodes the adhesin which is interspersed along the fimbrial shaft and at the tip (16). Despite the ubiquitous occurrence of type 1 fimbriae and the fact that these were the first bacterial adhesins to be discovered (5, 7), their functional significance has been much debated. Although some studies suggest a role for type 1 fimbriae in experimental urinary tract infection in mice and rats (8, 14), their role in human pathogenicity has not been clearly defined (12, 22, 28).

FimH recognizes terminal Manα1→3Manβ exposed on N-linked oligosaccharides on glycoproteins. Such receptor sequences are found on a variety of epithelial cells (5, 9, 20, 32) and on neutrophils and macrophages (2, 3). Terminal mannose residues with receptor activity occur also on secreted glycoproteins such as urinary Tamm-Horsfall glycoprotein (21) and secretory immunoglobulin A (IgA) (30). While all IgA molecules are glycosylated, the largest amount of mannose occurs on IgA2 that predominates in the large intestine (31). The interaction between secretory IgA and type 1-fimbriated *E. coli* agglutinates the bacteria and prevents them from attaching to a mannose-containing receptor on colonic epithelial cells (30). Secretory IgA might provide receptor sites for type 1-fimbriated strains that enhance colonization or might increase the turnover of type 1-fimbriated strains by inhibiting their adherence. In either case, the lack of intestinal secretory IgA in individuals with IgA deficiency would be expected to influence the intestinal persistence of type 1-fimbriated bacteria.

The aim of the present study was to compare the occurrence of the *fim* genotype and the expression of type 1 fimbriae between *E. coli* isolates from IgA-deficient individuals and healthy controls.

MATERIALS AND METHODS

Subjects. Seventeen individuals with selective IgA deficiency were included in the study. IgA deficiency was defined as a serum IgA level of less than 0.05 g/liter in the presence of IgM, IgG, and IgG1 through IgG4 above the lower limit of the normal range: 0.5, 7.0, 4.22, 1.17, 0.41, and 0.01 g/liter, respectively (13, 23). Six of the IgA-deficient individuals had a history of frequent respiratory tract infection, but none of them had apparent signs of infection at the time of the study. One of these patients had systemic lupus erythematosus, and another suffered from hypothyroidism. Eleven of the IgA-deficient individuals were healthy blood donors who had been diagnosed at screening. Seventeen age-matched individuals with a normal level of serum immunoglobulins served as a control group. None of the individuals in the study had been treated with antibiotics for at least 3 months preceding sampling of the rectal flora. The characteristics of the IgA-deficient and control individuals are shown in Table 1.

Sixteen of the 17 IgA-deficient individuals were investigated for the presence of IgA at the mucosal level by either of two methods. Nine had been previously analyzed for the presence of IgA-secreting cells in the small intestinal mucosa by using the enzyme-linked immunospot assay and compared with a control group of 21 persons, none of whom participated in the present study (10). Another 7 IgA-deficient individuals and 10 persons in the control group were assayed for the presence of secretory IgA in saliva by using enzyme-linked immunosorbent assay (see below). As shown in Table 1, all tested IgA-deficient individuals lacked secretory IgA in the saliva or had very few, if any, IgA-producing cells in the duodenal mucosa.

Informed consent was obtained from all individuals, and the study was approved by the Ethics Committee of the Medical Faculty of Göteborg University.

Quantification of secretory IgA in saliva. Unstimulated whole saliva was collected and stored at −70°C until analyzed. Polyvinyl chloride plastic plates (Dynatech, Alexandria, Va.) were coated with 2.8 mg of rabbit anti-human α-chain F(ab′)$_2$ fragment (Dakopatts A/S, Glostrup, Denmark) per liter and incubated with saliva samples appropriately diluted in phosphate-buffered saline (PBS) with 0.05% Tween 20. Rabbit anti-human secretory component conju-

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TABLE 1. Characteristics of IgA-deficient and control individuals

Characteristic	Value for subject group	
	IgA deficient	Control
No.	17	17
Age (yr)		
Median	39	42
Range	20–66	23–62
Sex (female/male)	12/5	14/3
Serum IgA concn (g/liter)		
Median	<0.05	2.4
Range		0.6–4.8
Saliva secretory IgA concn (mg/liter)		
Median	<0.02[a]	51[b]
Range		21–160[b]
No. of intestinal mucosa IgA-secreting cells (per 10^6 mononuclear cells)		
Median	0[c,d]	20,400[c,e]
Range	0–350[c,d]	2,600–54,000[c,e]

[a] Seven individuals tested.
[b] Ten individuals tested.
[c] Data from previous study (10).
[d] Nine individuals tested in previous study.
[e] Twenty-one individuals not included in the present study.

gated to alkaline phosphatase (Dako A/S, Glostrup, Denmark) was used for detection, and 1 g of *p*-nitrophenylphosphate per liter (Sigma, St. Louis, Mo.) in diethanolamine buffer, pH 9.8, was used for development of the reaction. The enzyme-substrate reaction was recorded at 405 nm, and calculations were made from a standard curve by using a human milk sample with a known concentration of secretory IgA.

Sampling of rectal bacterial flora and species identification. A sample of the rectal flora was obtained with a cotton-tipped culture swab which was inserted 4 cm into the anal canal of each study subject. The swab was put in sealed tubes with modified Stuart's transportation medium and brought directly to the laboratory. The swab was streaked onto a modified Conradi-Drigalski agar plate, a selective medium for Gram negative facultative anaerobes (27). The inoculum was spread with a sterile platinum loop in a three-step manner and cultivated aerobically overnight at 37°C. The last 10 free-lying colonies were picked, tested for purity by subculture on a Conradi-Drigalski agar plate, and transferred to stab agar culture. A selection of 10 colonies gives a possibility greater than 99.5% of including the dominant enterobacterial strain (18).

E. coli and other members of the family *Enterobacteriaceae* were identified by biotyping with the API 20 E system (Triolab AB, Mölndal, Sweden).

Hemagglutination properties of the bacteria. Each bacterial isolate was cultured once on Conradi-Drigalski agar, to check the purity, and thereafter passaged three times in static Luria broth in order to maximize the expression of type 1 fimbriae (5). After the last passage, the bacteria were suspended at 5×10^9/ml in PBS. One drop of bacterial suspension was mixed on a microscope slide with one drop of a 3% suspension of human or guinea pig erythrocytes either in PBS or in PBS with 2.5% α-methyl-D-mannoside (Sigma). Agglutination was determined by the naked eye after gentle tilting of the slide for 3 min. An agglutination of guinea pig erythrocytes in the absence but not in the presence of α-methyl-D-mannoside was defined as mannose sensitive. An agglutination of human erythrocytes in the presence and absence of α-methyl-D-mannoside was defined as mannose resistant. Isolates agglutinating neither human nor guinea pig erythrocytes were considered hemagglutination negative. As control strains, the transformant *E. coli* strains 506 MS (type 1 fimbriated) and 506 P (hemagglutination negative) were included (11).

DNA probes and DNA-DNA hybridizations. A 10-kb *Hin*dIII-*Sty*I fragment containing the *fim* gene cluster from the recombinant plasmid pPKLO4 (15) was used as a specific probe for the *fim* DNA sequences.

Individual bacterial strains were taken from overnight cultures on tryptic agar plates (Difco, Detroit, Mich.), spotted on a Hybond N+ filter (Amersham, Solna, Sweden), placed on a tryptic soy agar plate, and cultured for 4 h at 37°C. The filters were soaked in 1.5 M NaCl–0.5 M NaOH for 7 min and neutralized in 1.5 M NaCl–0.5 M Tris (pH 7.2) twice for 3 min. The filters were rinsed in 2× SSC (2× SSC is 0.3 M NaCl–0.03 M sodium citrate) and dried.

The filters were prehybridized at 62°C for 2 to 4 h in 2× SSC–1% sodium dodecyl sulfate (SDS)–1% skim milk (Difco)–0.1 mg of freshly denatured (95°C, 5 min) herring sperm DNA (Sigma) per ml. The DNA probe was labeled with [^{32}P]dCTP by using the MultiPrime DNA labeling kit (Amersham), and 0.1 to 0.5 μg of freshly denatured probe DNA per ml was added to the prehybridization solution. Hybridization was carried out at 62°C for 16 to 18 h, and the filters were washed twice in 2× SSC–0.1% (wt/vol) SDS for 5 min at room temperature and twice in 0.1× SSC–0.1% (wt/vol) SDS for 15 min at 62°C. Radioactive label was detected by exposure to Kodak X-Omat film at −70°C for 24 to 48 h.

Attachment to human colonic epithelial cells. Each isolate was tested for its capacity to adhere to human colonic epithelial cells of the HT-29 cell line (32). After three passages in static Luria broth, the bacteria were suspended at 5×10^9/ml in Hanks' balanced salt solution (HBSS), and 0.1 ml of this suspension was mixed with 0.1 ml of HT-29 cells at 5×10^6/ml in HBSS. Either 0.3 ml of HBSS or 0.3 ml of HBSS with 2.5% α-methyl-D-mannoside was added, and the mixture was incubated for 30 min at 4°C with end-over-end rotation. The cells were washed and fixed with neutral buffered formalin, and at least 40 epithelial cells were assessed for the presence of adherent bacteria by microscopy (×500 magnification; Nikon Optiphot with interference contrast equipment; Bergström Instruments AB, Göteborg, Sweden). In each experiment, isolates from one IgA-deficient and one control individual were tested. Adherence was assessed by one person, who was unaware of the identity of the individuals from whom the bacteria derived. The adhesion of each isolate was expressed as the mean number of adherent bacteria per cell. The mannose-sensitive adherence was calculated by subtracting the number of bacteria adhering in the presence of α-methyl-D-mannoside (mannose-resistant adherence) from the number of bacteria adhering in the absence of α-methyl-D-mannoside (total adherence). The type 1-fimbriated strain *E. coli* 506 MS and the adhesin-negative strain *E. coli* 506 P were included as control strains in each adhesion experiment (11).

Statistical evaluation. For hemagglutination and *fim* gene carriage, the percentage of *E. coli* isolates expressing a certain hemagglutination pattern, or hybridizing with *fim* gene probe, in each individual constituted the unit of measurement, and the Mann-Whitney U test was used for comparing the two groups. For adherence to HT-29 cells, the mean adherence of all *E. coli* isolates from one individual constituted the unit of measurement, and the Mann-Whitney U test was used for testing significance.

RESULTS

Frequency of different enterobacterial species. All bacterial isolates were typed by using API 20 to establish their enterobacterial species identity. Only 2 of 17 IgA-deficient individuals and 1 of 17 control individuals yielded any other members of the *Enterobacteriaceae* than *E. coli* among the 10 isolates. These three individuals contributed one, three, and two colonies each of non-*E. coli Enterobacteriaceae* (one *Proteus vulgaris*, three *Citrobacter freundii*, one *Klebsiella oxytoca*, and one *Kluyvera* sp., respectively). All further analyses were based only on the *E. coli* isolates.

The API pattern was also used to assess the heterogeneity of the *E. coli* flora in a single individual. In roughly half of the cases (8 of 17 of the IgA-deficient and 10 of 17 of the control individuals) all *E. coli* isolates from one individual yielded identical API patterns, indicating that they derived from a single *E. coli* strain. Assuming that each API pattern represented a single *E. coli* strain, means of 1.7 *E. coli* strains per individual in the IgA-deficient group and 1.6 *E. coli* strains per individual in the control group were found. Thus, according to this crude measure of strain identity, there was no major difference in *E. coli* diversity between the groups.

Type 1 fimbrial expression and *fim* genotype. Expression of type 1 fimbriae was detected as mannose-sensitive agglutination of guinea pig erythrocytes. In each individual, the percentage of all isolates expressing type 1 fimbriae was calculated, and the mean frequencies of type 1-fimbriated isolates in the two groups were compared. Type 1-fimbriated isolates accounted for 69% of the *E. coli* from the IgA-deficient group, compared with 85% of the *E. coli* from the control group ($P = 0.031$) (Table 2). There was no difference in the frequency of mannose-resistant hemagglutination or in the hemagglutination-negative phenotype between the two groups (Table 2).

One isolate of *E. coli* may express several adhesins. As is evident from Table 3, the fractions of *E. coli* expressing only mannose-sensitive adhesins were similar in IgA-deficient and control individuals. In contrast, the IgA-deficient individuals tended to have more isolates expressing only mannose-resistant adhesins than the control group ($P = 0.07$) (Table 3). These isolates seemed to have replaced those expressing a

TABLE 2. Hemagglutination pattern and carriage of *fim* gene in *E. coli* isolates from IgA-deficient and control individuals[a]

Subject	% of isolates with hemagglutination pattern			*fim* gene positive (% of isolates)
	Mannose sensitive	Mannose resistant	Negative	
IgA deficient	69[b]	40	10	74[c]
Control	85	38	11	94

[a] Agglutination was tested by using 3% suspensions of human and guinea pig erythrocytes in the absence or presence of 2.5% α-methyl-D-mannoside. Mannose-sensitive agglutination denotes agglutination of guinea pig erythrocytes in the absence but not in the presence of α-methyl-D-mannoside. Mannose-resistant agglutination denotes agglutination of human erythrocytes in the absence and presence of α-methyl-D-mannoside. "Negative" indicates no agglutination with human or guinea pig erythrocytes. Carriage of the *fim* gene was detected by colony hybridization. There were 17 subjects in each group.
[b] $P = 0.031$ (Mann-Whitney U test) compared with control values.
[c] $P = 0.019$ (Mann-Whitney U test) compared with control value.

combination of mannose-sensitive and mannose-resistant adhesins, which were more common in the control group (Table 3).

To assess whether the decreased frequency of type 1-positive *E. coli* isolates in IgA-deficient individuals was due to a lack of the *fim* gene, the *fim* genotype was defined by DNA-DNA hybridization by using a probe internal to the *fim* gene cluster. Thirty isolates of 336 could not be screened because they had died during storage; these were equally distributed between IgA-deficient and control individuals. *fim*-positive isolates accounted for 94% of *E. coli* isolates in the control group, compared with 74% of *E. coli* isolates in the IgA-deficient group ($P = 0.019$) (Table 2).

The expression of type 1 fimbriae, as evidenced by hemagglutination, was analyzed as a function of the *fim* genotype. Type 1 fimbriae were expressed by 81% of the *fim*-positive isolates from IgA-deficient and 86% of the isolates from control individuals (not significant).

Mannose-sensitive adherence to HT-29 cells. The *E. coli* isolates from IgA-deficient and control individuals were tested for adherence to HT-29 colonic epithelial cells. The attachment was analyzed in the presence or absence of the receptor analog α-methyl-D-mannoside. Adherence sensitive to α-methyl-D-mannoside was attributed to type 1 fimbriae, whereas residual adherence was attributed to other adhesins.

The mean mannose-sensitive adherence of all isolates in one individual was calculated and compared between IgA-deficient and control individuals. The mannose-sensitive adherence values were 9 bacteria per cell as a median for *E. coli* from the IgA-deficient group and 26 bacteria per cell as a median for *E. coli* from the control group ($P < 0.05$) (Fig. 1).

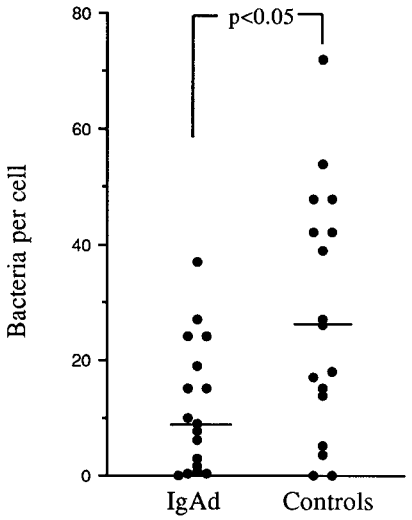

FIG. 1. Mannose-sensitive adherence to HT-29 cells of all *E. coli* isolates recovered from IgA-deficient (IgAd) individuals and healthy controls. Each circle denotes the mean value for all *E. coli* isolates obtained from one individual. The bar indicates the median for each group.

The mannose-sensitive adherence was then analyzed for only those *E. coli* isolates that expressed type 1 fimbriae or possessed the *fim* gene (Fig. 2). The mean mannose-sensitive adherence of all isolates from one individual exhibiting mannose-sensitive hemagglutination or possessing the *fim* gene constituted the unit of observation. Type 1-fimbriated isolates from the IgA-deficient group adhered in lower numbers to HT-29 cells (median, 15 bacteria per cell) than the type 1-positive isolates from control group (median, 27 bacteria per cell) ($P < 0.05$). A similar difference was observed between the

TABLE 3. Frequency of *E. coli* isolates from IgA-deficient and control individuals expressing different combinations of adhesins[a]

Subject	% of isolates with hemagglutination pattern			
	MS only	MRMS	MR only	Negative
IgA deficient	50	19[b]	21[c]	10
Control	51	34	4	11

[a] Agglutination was tested by using 3% suspensions of human and guinea pig erythrocytes in the absence or presence of 2.5% α-methyl-D-mannoside. Mannose-sensitive (MS) agglutination denotes agglutination of guinea pig erythrocytes in the absence but not in the presence of α-methyl-D-mannoside. Mannose-resistant (MR) agglutination denotes agglutination of human erythrocytes in the absence and presence of α-methyl-D-mannoside. "Negative" indicates no agglutination with human or guinea pig erythrocytes. There were 17 subjects in each group.
[b] $P = 0.26$ (Mann-Whitney U test) compared with control value.
[c] $P = 0.07$ (Mann-Whitney U test) compared with control value.

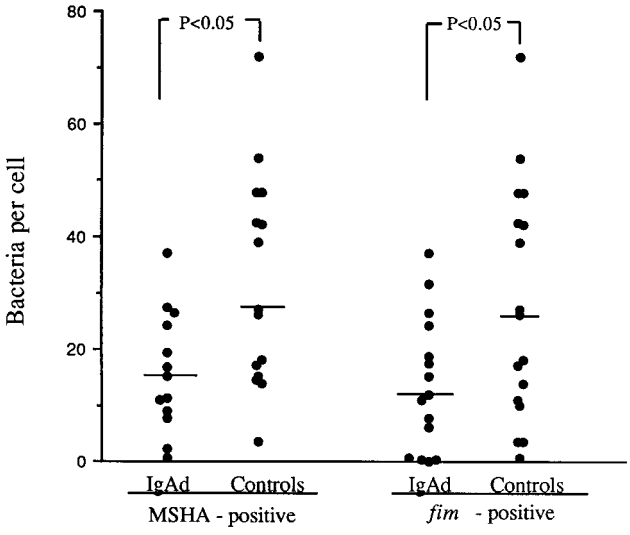

FIG. 2. Mannose-sensitive adherence to HT-29 cells of *E. coli* isolates expressing mannose-sensitive adhesins, as evidenced by hemagglutination (MSHA-positive), or possessing the *fim* gene, as evidenced by hybridization (*fim*-positive). Each circle denotes the mean value for the *E. coli* isolates obtained from one IgA-deficient (IgAd) or control individual. The bar indicates the median for each group.

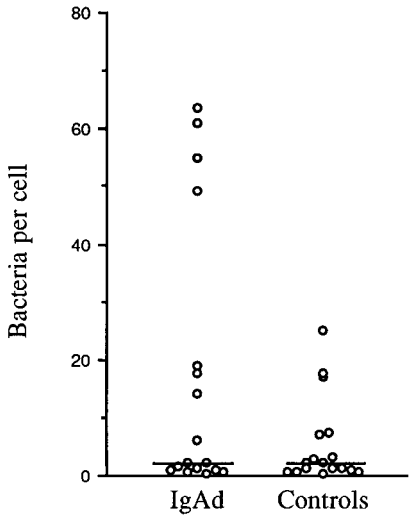

FIG. 3. Mannose-resistant adherence to HT-29 cells of all *E. coli* isolates recovered from IgA-deficient (IgAd) individuals and healthy controls. Each circle denotes the mean value for all *E. coli* isolates obtained from one individual. The bar indicates the median for each group.

fim-positive isolates from the IgA-deficient and control groups (11 versus 26 bacteria per cell, $P < 0.05$).

Since the value for the mannose-sensitive adherence was obtained by subtracting the mannose-resistant adherence from the total adherence, the mannose-sensitive adherence may be underestimated for isolates that also express mannose-resistant adherence. Therefore, the adherence of isolates expressing exclusively mannose-sensitive hemagglutination, but not mannose-resistant hemagglutination, was separately analyzed. The difference in mannose-sensitive adherence between isolates from IgA-deficient and control individuals was confirmed in this analysis (16 versus 39 bacteria per cell, $P < 0.05$).

The adherence mediated by mannose-resistant interactions is shown in Fig. 3. While there was no significant difference in the overall levels of mannose-resistant adherence between IgA-deficient and control individuals, four individuals in the IgA-deficient group but none in the control group showed a very high level of mannose-resistant adherence of their *E. coli* isolates: >40 bacteria per cell on average. Altogether 36 of 166 isolates from the IgA-deficient group but only 1 of 168 isolates from the control group displayed mannose-resistant adherence of >40 bacteria per cell.

DISCUSSION

E. coli type 1 fimbriae bind in a mannose-sensitive manner to secretory IgA (30). The interaction has been attributed to the recognition by type 1 fimbriae of terminal mannose residues on the heavy chains of the IgA dimer and on the secretory component (30). The binding is independent of the antibody activity of IgA; type 1 fimbriae aggregate myeloma IgA proteins with unknown specificity. The results of the present study demonstrate a difference in carriage of type 1-fimbriated *E. coli* between IgA-deficient individuals and healthy controls, suggesting that the interaction between type 1 fimbriae and IgA is of ecological importance in the human large intestine.

IgA deficiency is the most common primary immunodeficiency; it occurs at a frequency of about 1 in 600 individuals (13). IgA-deficient individuals lack circulating monomeric IgA and do not secrete IgA dimers among mucosal epithelial cells. IgA deficiency predisposes the individual to respiratory tract infections and is associated with an increased risk for autoimmune disorders. Infection by *Giardia lamblia* with subsequent chronic diarrhea (33) and enteropathies such as celiac disease and ulcerative colitis are also associated with IgA deficiency (1, 13). Despite this, most IgA-deficient individuals remain healthy.

Many IgA-deficient individuals have increased levels of IgG- and IgM-containing plasma cells in the intestinal mucosa (10, 19, 25). Since IgM can bind the secretory component and be transported across the epithelial lining of the mucosal surface (4), it might be expected to replace IgA as a receptor for type 1 fimbriae. However, although IgM is even more heavily glycosylated than IgA (26), it is more easily degraded within the intestinal lumen (24), and its oligosaccharide chains are not as efficient as receptors for *E. coli* mannose-specific adhesins as those of IgA (30). Secretion of IgM across the colonic mucosa is therefore unlikely to fully compensate for the lack of IgA receptors for type 1 fimbriae.

The bulk of the type 1-fimbriated flora remained despite IgA deficiency. The colonic mucosa contains mannosylated glycoproteins other than secretory IgA with receptor activity for type 1 fimbriae. Binding to such receptor structures may account for the high frequency of type 1-fimbriated bacteria in the IgA-deficient individuals. However, the type 1-fimbriated isolates from IgA-deficient individuals had significantly decreased adherence to colonic epithelial cells compared with type 1-fimbriated isolates from control individuals. This suggested that IgA may also influence the level of type 1 fimbrial expression by *E. coli*. Type 1-fimbriated *E. coli* strains that colonize IgA-deficient individuals may first down-regulate their adhesin expression and eventually lose their *fim* genes.

In humans, the degree of expression of type 1 fimbriae by *E. coli* in the colonic microflora in situ is unknown. Since *E. coli* strains represent only 0.1 to 1% of the colonic bacterial population, they have to be enriched by culture on selective media, which depress the expression of type 1 fimbriae (6). In streptomycin-treated mice, however, *E. coli* colonizing the large intestine expresses substantially more type 1 fimbriae than after cultivation in Luria broth (17). An interaction between secretory IgA and *E. coli* does occur in the human intestine; a majority of colonic *E. coli* bacteria are coated with IgA (29).

Secretory IgA can prevent attachment of type 1-fimbriated bacteria to epithelial cells in three ways: (i) through a lectin-carbohydrate interaction between the mannose-specific adhesins and secretory IgA carbohydrate; (ii) through an interaction between antifimbrial antibodies and the fimbriae or adhesins; and (iii) through an antigen-antibody interaction with other surface antigens, e.g., lipopolysaccharides, leading to agglutination. All these mechanisms could reduce adherence to epithelial cells. Our previous results indicate that the lectin-carbohydrate interaction accounts for 75 to 99% of all agglutinating activity of secretory IgA against type 1-fimbriated *E. coli* in vitro (reference 30 and unpublished results). It has previously been assumed that the presence of an agglutinating and antiadhesive molecule such as secretory IgA would disfavor the colonization of bacteria interacting with this molecule. The results of this study are not consistent with this notion. In contrast, the IgA-deficient individuals had reduced carriage of type 1-fimbriated bacteria. This observation suggests that secretory IgA plays the role of a receptor in the mucous layer of the large intestine of normal individuals and that the absence of IgA results in the loss of this function in IgA-deficient individuals. Studies that address the fimbrial expression and the receptor repertoire at the site of colonization are required to resolve these questions.

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