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Recognition of Immunoglobulin A1 by Oral Actinomyces and Streptococcal Lectins

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***Actinomyces naeslundii* and *Streptococcus gordonii*, oral bacteria that possess Gal/GalNAc- and sialic acid-reactive lectins, respectively, were adherent to immobilized secretory immunoglobulin A (IgA) and two IgA1 myeloma proteins but not to two IgA2 myeloma proteins. Apparently, O-linked oligosaccharides at the hinge region of the IgA1 heavy chain are receptors for lectin-mediated adhesion of these bacteria.**

Lectin-like adhesins are present on a number of bacteria that colonize the oral cavity. For example, galactose (Gal)- and *N*-acetylgalactosamine (GalNAc)-reactive type 2 fimbriae of *Actinomyces naeslundii* recognize both Galβ1-3GalNAc and GalNAcβ1-3Gal of streptococcal cell wall polysaccharides and mammalian cell glycoconjugates (6, 8, 25). In addition, sialic acid-binding adhesins of viridans streptococci such as *Streptococcus gordonii* interact with erythrocytes and sialic acid-containing macromolecules including salivary mucins (13, 18, 22, 24, 28).

Secretory immunoglobulin A (S-IgA) is another salivary component that is a potential receptor molecule for bacterial lectins. The two subclasses of IgA differ in glycosylation. The IgA1 heavy chain contains five O-linked oligosaccharides, all at the hinge region (3), and two N-linked oligosaccharides (2), one in the CH2 domain near the hinge region and the other near the C-terminal end of the α1 chain. In contrast, the IgA2 heavy chain lacks O-linked but has four or five N-linked oligosaccharides distributed within the three constant region domains (26, 36). These oligosaccharides are implicated in the interactions of S-IgA with certain microorganisms. Thus, the ability of colostral S-IgA to inhibit adhesion of *Helicobacter pylori* to gastric epithelial cells was markedly reduced by the action of α-L-fucosidase on S-IgA (14). S-IgA also inhibited mannose-sensitive adhesion of type 1 piliated *Escherichia coli* and, in addition, initiated lectin-dependent agglutination of this bacterium (40). Both effects were attributed to mannose-rich N-linked oligosaccharides of IgA2.

Two oral bacteria, *A. naeslundii* and *S. gordonii*, have now been examined for lectin-mediated recognition of S-IgA and myeloma proteins of each IgA subclass. *A. naeslundii* WVU45 (7) and *S. gordonii* DL1 (18) were cultured from frozen stocks in complex medium as previously described (18). Bacteria were harvested from overnight cultures, washed twice in Hanks balanced salt solution (BioWhittaker, Walkersville, Md.), and adjusted to a turbidity of 260 Klett units, equivalent to approximately 2×10^9 bacteria per ml as determined with a Petroff-Hausser bacteria counter. Bacteria were biotin labeled by mixing 0.9 ml of bacteria in Hanks balanced salt solution with 0.1 ml of dimethyl sulfoxide containing 0.1 mg of NHS-LC-Biotin (Pierce, Rockford, Ill.). Labeling of actinomyces was performed in the presence of 100 mM lactose to protect lectin binding sites. Following 1 h of incubation at room temperature with occasional mixing, labeled bacteria were washed three times in Hanks balanced salt solution to remove free NHS-LC-Biotin. Samples of IgA included S-IgA (60% S-IgA1, 40% S-IgA2) purified from pooled colostrum of three donors (15); two IgA1 myeloma proteins, referred to as Cap (Organon Teknika Corp., Durham, N.C.) and Ath-1 (Athens Research and Technology, Athens, Ga.); and two IgA2 myeloma proteins, Ath-2 (Athens Research and Technology) and Fel, which was generously provided by J. Mestecky (University of Alabama, Birmingham). Serial threefold dilutions of each IgA were prepared, and 1-μl volumes containing from 1 μg to approximately 1 ng of protein were applied to nitrocellulose. Membranes were blocked for 4 h in Tris-buffered saline (0.15 M NaCl, 20 mM Tris HCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, and 0.02% sodium azide, pH 7.8) containing 5% bovine serum albumin (Sigma Chemical Co., St. Louis, Mo.) prior to the addition of biotinylated bacteria to a final concentration of approximately 5×10^8 per ml in the same buffer. Following overnight incubation at 4°C, membranes were washed to remove unbound bacteria and developed with avidin-D-alkaline phosphatase (Vector, Burlingame, Calif.) to detect adhesion (33).

As shown in Fig. 1A, *A. naeslundii* and *S. gordonii* bound to 0.3 μg of immobilized S-IgA and each IgA1 myeloma protein but not to the same amount of either IgA2 myeloma. Adhesion of actinomyces was observed to as little as 12 ng of S-IgA, 12 ng of one IgA1 myeloma protein (Ath-1), and 4 ng of the other (Cap). In contrast, adhesion to 1 μg of each IgA2 myeloma protein was negligible (results not shown). The IgA samples contained similar amounts of total carbohydrate as evidenced by the extent of labeling observed on a duplicate membrane that was subjected to oxidation with 10 mM sodium metaperiodate for 30 min at room temperature in the dark, reaction with biotin hydrazide, and development with avidin-D-alkaline phosphatase (16, 38) (Fig. 1B, CHO). *S. gordonii* was more adherent to the IgA1 myeloma proteins than to S-IgA. This was evident both from the extent of bacterial adhesion to 0.3 μg of these proteins (Fig. 1A) and from the minimum amounts of the immobilized IgAs required for adhesion; 37 ng of S-IgA and 1 ng of either IgA1 myeloma protein. These results may well reflect a difference in the sialic acid content of the IgA preparations. Thus, 0.3 μg of either IgA1 myeloma protein was

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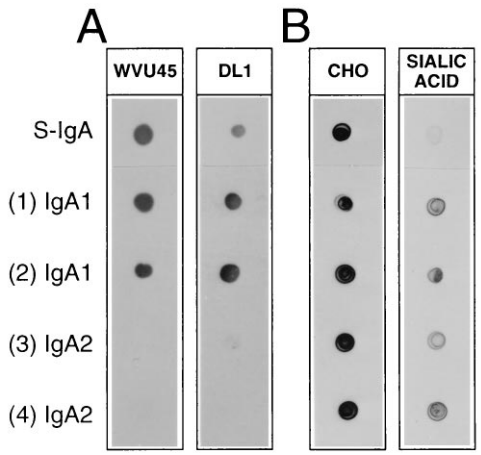

FIG. 1. Lectin-mediated adhesion of *A. naeslundii* and *S. gordonii* to immobilized human IgA. Samples containing 0.3 μg of purified human S-IgA, IgA1 myeloma proteins Ath-1 (1) and Cap (2), or IgA2 myeloma proteins Fel (3) and Ath-2 (4) were spotted on nitrocellulose. (A) Membranes were overlaid with biotinylated *A. naeslundii* (WVU45) or *S. gordonii* (DL1), washed, and developed with avidin-D-alkaline phosphatase to detect adherent bacteria. (B) Membranes were incubated with 10 or 1 mM sodium metaperiodate to oxidize total carbohydrate (CHO) or sialic acid, respectively, prior to reaction with biotin hydrazide and subsequent development with avidin-D-alkaline phosphatase.

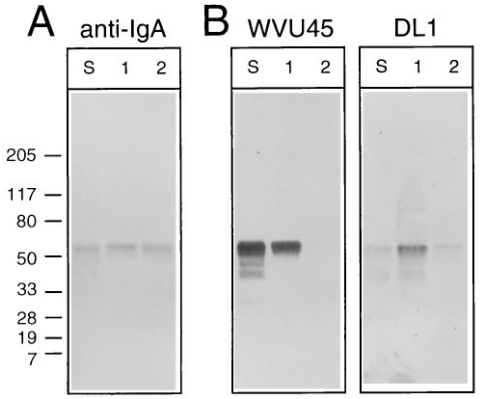

FIG. 2. Detection of IgA heavy chain by immunoblotting and bacterial overlay. Samples containing 2 μg of human S-IgA (S), IgA1 myeloma protein Ath-1 (1), or IgA2 myeloma protein Ath-2 (2) were reduced, separated by SDS-PAGE, and transferred to nitrocellulose. Membranes were overlaid with goat anti-human IgA followed by peroxidase-conjugated donkey anti-goat IgG (A) or biotinylated *A. naeslundii* (WVU45) or *S. gordonii* (DL1) (B), washed, and developed with avidin-D-alkaline phosphatase to detect adherent bacteria. The positions of molecular mass markers (in kilodaltons) are indicated on the left.

labeled to a greater extent than 0.3 μg of S-IgA on a duplicate membrane that was incubated with 1 mM sodium metaperiodate for 30 min at 4°C to selectively oxidize sialic acid prior to biotin hydrazide labeling and development with avidin-D-alkaline phosphatase (16, 38) (Fig. 1B, sialic acid). Bacterial overlays were also performed following treatment of additional duplicate membranes with 0.04 U of sialidase (type X neuraminidase from *Clostridium perfringens*; Sigma) per ml overnight at 37°C. The adhesion of *S. gordonii* was reduced by sialidase treatment as indicated by an increase in the amounts of S-IgA and IgA1 myeloma proteins required for adhesion of this species to the sialidase-treated membranes. This increase was 3-fold for S-IgA, 9-fold for IgA1 myeloma Cap, and at least 200-fold for IgA1 myeloma Ath-1 (results not shown). In contrast, adhesion of *A. naeslundii* to S-IgA and the IgA1 myeloma proteins was similar on sialidase-treated and untreated membranes.

Bacterial adhesion to dissociated S-IgA as well as IgA1 and IgA2 myeloma proteins was also examined. Samples were reduced, separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), and transferred to nitrocellulose. The heavy chain of each sample was detected as a band at approximately 55 kDa with affinity-purified goat anti-human IgA α-chain-specific antibody and peroxidase-conjugated affinity-purified donkey anti-goat IgG (Jackson ImmunoResearch Laboratories, Inc., West Grove, Pa.) (Fig. 2A). *A. naeslundii* bound to the heavy chains of S-IgA and an IgA1 myeloma (Ath-1) but not to the IgA2 myeloma (Ath-2) heavy chain (Fig. 2B, WVU45). *S. gordonii* also adhered strongly to the IgA1 myeloma heavy chain. However, weak interactions with the S-IgA and IgA2 myeloma heavy chains were detected (Fig. 2B, DL1). A spontaneous mutant of *A. naeslundii* WVU45 lacking Gal/GalNAc-reactive type 2 fimbriae (7) and each of three streptococcal strains lacking sialic acid lectin activity did not bind to any IgA heavy chains (results not shown). The three streptococci included two heterologous strains of *S. gordonii*, M5 and ATCC 10558, that did not interact with sialic acid-containing receptors of erythrocytes as detected by bacterial hemagglutination (18) and a spontaneous mutant of *S. gordonii* DL1 that failed to hemagglutinate but exhibited all other known adhesive properties of the parent strain (35).

The structural specificity of lectin-mediated adhesion was examined by bacterial overlay of nitrocellulose membranes spotted with decreasing concentrations of fetuin, asialo-fetuin, and neoglycoproteins prepared by conjugation of oligosaccharides to bovine serum albumin (Sigma) or human serum albumin (Accurate Chemical and Scientific Corp., Westbury, N.Y.). Adhesion of *A. naeslundii* WVU45 was greater to asialofetuin than to fetuin, indicating that the presence of terminal sialic acid blocks recognition of subterminal galactose by the actinomyces lectin (17). Of the neoglycoproteins examined, the lowest amounts (10 ng) detected by *A. naeslundii* were those with Galβ1-3GalNAc and GalNAcβ1-3Gal termini (Fig. 3A).

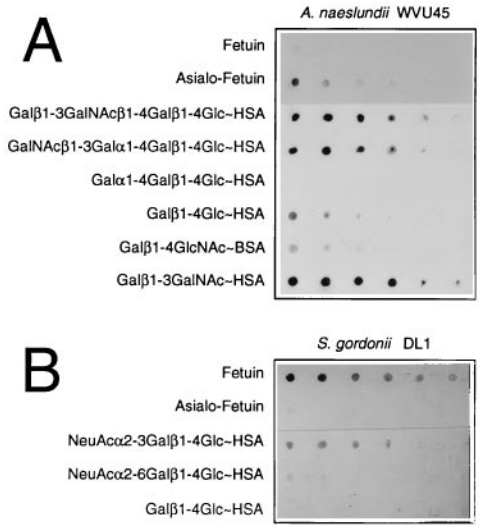

FIG. 3. Specificity of lectin-mediated adhesion of *A. naeslundii* and *S. gordonii*. Serial threefold dilutions of glycoproteins and neoglycoproteins, containing from 1 μg to 4 ng per μl, were spotted on nitrocellulose. Membranes were overlaid with biotinylated *A. naeslundii* WVU45 (A) or biotinylated *S. gordonii* DL1 (B), washed, and developed with avidin-D-alkaline phosphatase to detect adherent bacteria. HSA, human serum albumin; BSA, bovine serum albumin.

By comparison, approximately 100 ng of neoglycoproteins with either Galβ1-4Glc or Galβ1-4GlcNAc termini were required for adhesion while a neoglycoprotein with Galα1-4Gal termini was not recognized at amounts up to 1 μg. In view of these findings, the specificity of actinomyces for IgA1 resembles that of jacalin (21, 32), a plant lectin, and most likely depends on recognition of O-linked Galβ1-3GalNAc at the hinge region of the IgA1 heavy chain. In contrast, greater reactivity of the *Ricinus communis* and *Abrus precatorius* agglutinins with IgA1 than with IgA2 was previously attributed to binding of Gal in N-linked chains of IgA1 (41).

S. gordonii DL1 bound to fetuin, a glycoprotein with both α2-3- and α2-6-linked *N*-acetylneuraminic acid (NeuAc) termini (34), but not to asialo-fetuin (Fig. 3B). A neoglycoprotein with terminal NeuAcα2-3Galβ1-4Glc was also recognized whereas those with NeuAcα2-6Galβ1-4Glc or Galβ1-4Glc were not. Results from a previous study of sialic acid-binding streptococcal lectins (28) indicated that NeuAcα2-3Galβ1-4Glc was from 2 to 10 times less inhibitory than NeuAcα2-3Galβ1-3GalNAc, an oligosaccharide that is O-linked in many glycoproteins including fetuin (34). In the current study, immobilized fetuin and the IgA1 myelomas were recognized similarly, on a weight basis, by *S. gordonii*. Significantly, α2-3-linked sialic acid was identified on O-linked oligosaccharides from the hinge region of S-IgA1 (29, 30) and on one IgA1 myeloma protein (12) but was not present on the short O-linked chains of another IgA1 myeloma protein (3). In contrast, the sialic acid of N-linked oligosaccharides of IgA1 was entirely α2-6-linked (2). The oligosaccharides of IgA2 are also N-linked (36, 40) and, therefore, presumably possess α2-6-linked sialic acid termini like the similar N-linked oligosaccharides of J chain (4) and secretory component (27). Assuming that these patterns of glycosylation extend to the S-IgA and IgA myeloma proteins used in the present study, the presence of α2-3-linked sialic acid on O-linked oligosaccharides of IgA1 may account for the selective recognition of this subclass by *S. gordonii* DL1. Further studies are needed to examine this possibility.

Although *A. naeslundii* WVU45 and *S. gordonii* DL1 were adherent to nanogram amounts of IgA1 immobilized on nitrocellulose, these bacteria did not agglutinate in the presence of up to 20 μg of soluble IgA1 or IgA2 myeloma proteins per ml. Streptococci or actinomyces, adsorbed to wells of microtiter plates, also failed to bind soluble myeloma proteins (10 μg/ml) as detected by enzyme-linked immunosorbent assay (ELISA) (10) utilizing peroxidase-conjugated goat anti-human α chain (Jackson ImmunoResearch). Similarly, immobilized actinomyces failed to bind soluble S-IgA. The detection of lectin-mediated adhesion of actinomyces and streptococci to immobilized IgA1 but not binding of soluble IgA1 is consistent with the hypothesis that the lectins of these bacteria can recognize surface-associated receptors in the presence of salivary macromolecules that are potential inhibitors of adhesion (6, 9). Lectin-mediated bacterial adhesion in a secretory environment such as the oral cavity may depend on the expression of many low-affinity lectin sites that are spatially separated on the bacterial surface to an extent that permits multivalent binding of oligosaccharide receptor structures that are presented on a cell or tissue surface but not on soluble macromolecules. Thus, the failure of bacteria to bind soluble IgA1 may reflect a spatial arrangement of lectin sites that prevents simultaneous binding of multiple O-linked oligosaccharides at the hinge region of individual IgA1 molecules. Whereas soluble IgA1 myeloma proteins did not agglutinate oral actinomyces or streptococci, soluble S-IgA2 and IgA2 myeloma proteins reacted with the mannose-sensitive type 1 fimbriae of *E. coli*, resulting in agglutination of the bacteria and prevention of adhesion to colonic epithelial cells (40). In the present study, *S. gordonii* agglutinated in the presence of 5 μg of S-IgA per ml and also reacted with 0.5 μg of S-IgA per ml as detected by ELISA. These reactions most likely detect antistreptococcal antibodies that are present in colostral S-IgA (39) and bind streptococcal epitopes with an affinity that is much greater than the affinity of the streptococcal lectin for the carbohydrate moiety of IgA1. While antistreptococcal antibodies may have contributed to the adhesion of *S. gordonii* DL1 to undenatured S-IgA (Fig. 1A), it is clear that the adhesion of streptococci to the IgA1 myelomas, like those of actinomyces with the IgA1 myelomas and S-IgA, reflected the activities of the bacterial lectins.

The above considerations suggest that S-IgA1 immobilized on oral surfaces may promote lectin-mediated adhesion of viridans streptococci and actinomyces. These bacteria are colonizers of the tooth surface, and indeed, the adhesion of *Streptococcus sanguis* to saliva-treated hydroxyapatite, an interaction that is mediated by sialic acid-binding adhesins (18, 22, 24, 28), is increased by the presence of S-IgA in the acquired pellicle (23). S-IgA also coats bacteria in saliva and dental plaque (1, 5, 11), thereby providing potential receptors for lectin-mediated interbacterial adhesion. The presence of such receptors may be enhanced by the preferential production of S-IgA1 to specific oral microbial antigens (26) or, conversely, diminished by bacterial enzymes such as IgA proteases (19, 31) and glycosidases (20, 37, 42). Further studies are needed to determine the extent to which conditions within the oral environment favor the utilization of secretory antibodies as receptors for lectin-mediated bacterial adhesion.

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