Defense Mechanisms Involving Fc-Dependent Functions of Immunoglobulin A and Their Subversion by Bacterial Immunoglobulin A Proteases

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INTRODUCTION

Immunoglobulin A (IgA) is produced by many species, including humans, in quantities exceeding those of all other immunoglobulin classes combined. In humans, most IgA is secreted onto the vast (~400 m²) area of mucosal surfaces, becoming the principal mediator of humoral immunity at these sites. Large amounts of IgA are also produced in the bone marrow, but its rapid catabolism relative to that of IgG results in serum levels lower than those of IgG (26, 46). While serum levels of IgA mature only slowly over 15 years, the concentrations of IgA in external secretions may reach adult levels in as little as 4 to 6 weeks (22). In addition to differences in ontogeny and cellular origin, the secretary and serum IgA systems appear to be independent with respect to the molecular properties of the IgA produced, the distribution of the two IgA subclasses, antigen specificities, and functions (26, 47). IgA in serum occurs primarily in monomeric form with a pronounced predominance of IgA subclass 1 (IgA1). In contrast, secretory IgA (S-IgA) occurs as dimeric molecules to which the carbohydrate-rich secretory component (SC) is attached. The distribution of IgA1 and IgA2 in external secretions reflects the proportions of plasma cells in the corresponding tissues, with an increase in the proportion of IgA2 (31, 47). However, recent observations indicate that there are notable differences between different anatomical sites. While IgA2 cells may account for up to 60% of total S-IgA in the colon, the proportions in nasopharyngeal tissues are more like those in the bone marrow (32, 47). The predominance of IgA1 in nasopharyngeal secretions is important because most pathogens that produce IgA1 proteases colonize that area (see below).

Appreciation and understanding of the immunological role of the IgA system have been hampered by the relatively normal health status of many IgA-deficient individuals in Western populations. However, this implied unimportance of IgA might not be true: complete absence of IgA in both serum and secretions is rare, and the compensatory role of secretory IgM in replacing S-IgA (7) in deficient patients is not fully appreciated. Yet, even without taking the compensatory role of secretory IgM into account, increased incidences of a number of pathologic conditions such as respiratory tract infections and atopic and autoimmune diseases have been associated with selective IgA deficiency (2). In communities lacking modern standards of hygiene, subnormal mucosal protection due to IgA deficiency may have much more serious effects.

Another obstacle to understanding the significance of the IgA system has been the difficulties encountered in defining the effector functions mediated by the Fc part of the molecule. In contrast to plasma immunoglobulins, S-IgA functions in environments that differ greatly in pH, salt, protein, and lipid (milk) concentrations and in the presence of endogenous or microbial proteolytic enzymes. External secretions are generally deficient in complement components and in fully functional phagocytes. Consequently, those who evaluated the biological significance of antibodies of different isotypes by the criteria of complement activation or opsoni-
TABLE 1. Biological functions of IgA and their dependency on the Fcα region

| Function                                      | Dependency on Fcα |
|-----------------------------------------------|-------------------|
| S-IgA                                         |                   |
| Inhibition of microbial adherence to surfaces | +                 |
| Agglutination of microorganisms               |                   |
| Reduction of hydrophobicity and negative charge| +                 |
| Blockage of microbial adhesions               |                   |
| Neutralization of viruses                     |                   |
| Neutralization of toxins and enzymes          |                   |
| Inhibition of antigen penetration through mucosal surfaces | + |
| Occlusive defense properties                  |                   |
| Mediation of monocyte-dependent bactericidal activity | + |
| Antibody-dependent cellular cytotoxicity      | +                 |
| Enhancement of activity of some nonspecific antibacterial factors in secretions | + |
| Serum IgA                                      |                   |
| Anti-inflammatory activity                     |                   |
| Blockage of IgG-, IgM-, and IgE-mediated reactions: chemotaxis, phagocytosis, immune lysis, anaphylaxis, Arthus reactions | + |
| Hepatobiliary elimination of immune complexes (only in some animal species) | + |
| Mediation of monocyte-dependent bactericidal activity | + |
| Antibody-dependent cellular cytotoxicity      | +                 |

zation were unjustifiably but understandably disappointed by the performance of IgA. However, it is now clear that, instead, the particular polymeric configuration, ability to bind to SC, hydrophlicity, and charge, conferred by the Fc part of S-IgA, give this immunoglobulin isotype special mucosal defense properties. In addition, serum IgA and S-IgA may have unique functions in regulating immune effector mechanisms mediated by the delivery of null or negative signals by its Fc region. This review deals with Fc-mediated functions, with special emphasis on their role in the defense against infectious diseases (Table 1) and with the possibility that certain bacteria may cause temporary local deficiencies in the defense system.

DIRECT EFFECTOR FUNCTIONS OF S-IgA

Inhibition of Microbial Adherence and Colonization

The ability of S-IgA antibodies to inhibit mucosal colonization of humans and animals has been demonstrated in vivo with several species of microorganisms (1). Investigations of the mechanisms underlying this ability have confirmed that S-IgA antibodies exert a direct inhibitory effect on the adherence of microorganisms to host mucosal epithelial cells and to saliva-coated hydroxyapatite (simulating dental enamel) (1, 35, 58). Adherence of microorganisms to these surfaces may involve both nonspecific hydrophobic interactions and specific interactions involving adhesins on the microbial surface complementary to host surface receptors (1). Several studies indicate that S-IgA may interfere with both processes. Thus, the binding of S-IgA antibodies to naturally hydrophobic Escherichia coli and Salmonella typhimurium strains reduces their hydrophobicity (38). This effect, which is not shared by IgG and only partially shared by serum IgA (15), is undoubtedly due to the heavy glycosylation of the Fc-SC part of the S-IgA molecule. The significance of this property is supported by the observation that Fabα fragments on the surface of bacteria have little or no effect on their ability to accumulate on epithelial cells and saliva-coated hydroxyapatite in vitro (50, 58). The ability of S-IgA to block adhesins has been demonstrated with antibodies directed at specific structures such as fimbriae on gonococci and enterobacteria (69, 75).

Although the anti-adherence effect demonstrable in vitro is usually relatively modest, the effect of S-IgA in vivo is amplified by numerous other factors such as secretory glycoproteins and other nonimmune compounds in secretions, the continuous desquamation of the surface epithelium, and the intense competition between members of the mucosal flora (1, 64). While oral immunization with inactivated Vibrio cholerae results in only modest reductions in intestinal numbers of V. cholerae in monosodiumated rats, in conventional animals it results in a 10- to 30-fold decrease (64). Thus, a microorganism that is selectively disadvantaged by the specific effects of S-IgA is rapidly displaced from the competitive environment on mucosal and tooth surfaces.

Toxin and Enzyme Neutralization

Like other immunoglobulin isotypes S-IgA antibodies can neutralize microbial and other environmental toxins and enzymes by sterically blocking their binding to target cells or substrates without the requirement for the Fc region (21, 40). The toxin-neutralizing effect is particularly relevant in the gut and has been clearly demonstrated in both human and animal studies of immunity to cholera and other diseases caused by enterotoxin-producing bacteria (11, 28).

The firm establishment of Streptococcus mutans on tooth surfaces can be inhibited by salivary antibodies directed at S. mutans glycosyltransferases, which catalyze the synthesis of extracellular polysaccharides required for the accumulation of the bacterium (42, 66). An additional example of enzyme-neutralizing S-IgA antibodies, which may be important in host-parasite relationships, consists of those found in secretions with the ability to inhibit bacterial IgA1 proteases (21; see below).

Virus Neutralization

Extensive clinical experience with the human oral poliovirus vaccine and several peroral or intranasal virus vaccines applied in veterinary medicine has clearly demonstrated the protective effect of the mucosal immune system against respiratory and enteric viral infections (63). Although cellular immune reactions are involved, it is evident that S-IgA antibodies play a decisive role in this protection (53). It has been assumed that neutralizing antibody prevents entry of virus into susceptible cells by sterically blocking association with cellular receptors. However, recent in vitro studies on antibody-mediated neutralization of influenza virus and transmissible gastroenteritis virus failed to detect a significant inhibition of virus attachment by S-IgA, IgA, or IgG antibody preparations, although antibodies of all of these isotypes caused virtually complete loss of virus infectivity (52, 72). In fact, in the case of transmissible gastroenteritis virus, neutralizing S-IgA antibodies, but not IgG antibodies, increased the number of virions attached to host cells (52). It is possible that the measured number of attached virions represents the net effect of antibody-mediated inhibition of attachment and an enhanced indirect attachment of antibody-induced aggregates of neutralized viruses.
This dual effect of S-IgA and other secretory agglutinins is known from studies of the interaction of oral streptococci with tooth surfaces (35), and the larger size of complexes formed with S-IgA than with monomeric IgA and IgG would support this explanation. Whether such differences also explain the observation that influenza virus neutralized with S-IgA is unable to enter host cells in contrast to viruses neutralized by monomeric IgA or IgG (72) remains to be elucidated.

Inhibition of Antigen Absorption

Immune exclusion has been postulated as a distinctive function of IgA (68). Extensive studies have demonstrated that prior enteral exposure to alimentary antigens diminishes the absorption of subsequent doses of the same substances in immunologically reactive form (3, 79). Presumably, binding of soluble antigens, including antigens and toxins released from microorganisms, to S-IgA antibodies forms macromolecular complexes that are readily swept out of the intestinal tract. The function of S-IgA in sparing the internal milieu from an excessive circulating antigenic load and from potentially damaging immune complexes that can occur when a systemic (IgG) antibody response is mounted to the absorbed antigen is revealed by individuals deficient in IgA (14).

INDIRECT EFFECTOR FUNCTIONS OF IgA

Interactions of IgA with Innate Humoral Defense Factors

Complement. The ability of both serum and S-IgA to activate complement has been examined by numerous investigators, using various experimental systems and with different results. Several initial reports established the inability of IgA to activate complement by the classical pathway (26), although aggregated preparations of isolated Fc, fragments can do so (12, 29). Subsequent studies revealed that artificially aggregated polyclonal or monoclonal serum IgA and S-IgA activate the alternative complement pathway. This is also the case with immune precipitates of both murine and rat monoclonal IgA antibodies and corresponding antigen (56, 60). However, the complement activation induced by IgA immune complexes proceeds with consumption of C3 but little of C5, and C3b does not become covalently bound to the complex (56). Thus, probably little or no C5a, a major anaphylatoxic, chemotactic, and inflammatory peptide (13), is released. Furthermore, the terminal lytic complex is probably also not assembled efficiently. These findings may reconcile the apparently conflicting observations that, although complement components such as C3 may be consumed, the biological consequences normally mediated by bound C3b (opsonization), released C5a (inflammation), and final binding of C8 and C9 (lysis) are not manifested (24, 26, 62). It was recently reported that human IgA bound to erythrocytes coated with complement-nonbinding mouse monoclonal IgG1 antibodies to human IgA induces complement-mediated hemolysis (27). Although the alternative pathway was implicated, possibly the mouse IgG1 offered an available site for the covalent binding of C3b in this somewhat unphysiological model, so that hemolysis could proceed.

Support for the inability of IgA to induce the usual biological consequences of complement activation, unless present in an unphysiological aggregated form, comes from another line of important observations. Thus, IgA antibodies can inhibit complement-dependent IgM- or IgG-mediated bactericidal or hemolytic reactions in vitro as well as the Arthur reaction in mice (24, 62, 63). Polymeric IgA is more effective than monomeric IgA with the same antibody specificiticy. Detailed studies of the inhibitory mechanisms revealed that inhibition of IgG-mediated bacteriolysis is competitive whereas inhibition of IgM-mediated bacteriolysis is noncompetitive and dependent on the IgA/target cell ratio (24). On this basis, it has been hypothesized that aberrantly high serum IgA antibody levels may induce susceptibility to invasive infections such as meningococcal meningitis by blocking the bactericidal effect of IgM (24).

Lactoferrin, lactoperoxidase, and lysozyme. IgA in various forms appears able to potentiate the effect of some of the nonspecific antibacterial factors in exocrine secretions. Thus, IgA antibodies against the iron-binding molecules on bacterial surfaces exert a powerful bacteriostatic effect in synergy with iron-unsaturated lactoferrin. This synergism has been shown for enteric bacteria including E. coli, Pseudomonas aeruginosa, and Legionella pneumophila (4, 20). Part of the lactoferrin in secretions is covalently bound to S-IgA (80), but whether this is important for the synergistic effect is not known.

The activity of lactoperoxidase-H2O2-SCN− against S. mutans is enhanced by human myeloma IgA1 and IgA2 proteins, or S-IgA (73), but not by IgG or IgM. Apparently, the ability of IgA proteins to bind lactoperoxidase, presumably via the Fc region, stabilizes the enzymatic and antimicrobial activity. Further studies with other bacterial species are necessary for the generalization of this potentially important observation.

Early reports suggested that purified human colostral IgA, like IgG and IgM, lyases E. coli in the presence of complement and lysozyme, but these results were not substantiated (25). The contamination of IgA preparations with traces of highly active IgM may account for this apparent discrepancy.

Mucin. Mucin has been shown to possess structures mimicking the receptor sites for microorganisms on epithelial cells that facilitate trapping and subsequent disposal of pathogens (1). It has been suggested that S-IgA adds a specific element to this protective activity by being incorporated into the mucus layer on mucosal surfaces (5). This interpretation was supported by the observation that salmonellae become “mucophilic” when coated with S-IgA (39). The recent demonstration that the impaired ability of spermatozoa to penetrate human cervical mucus when coated with S-IgA is restored by incubation with IgA protease (9) suggests that the Fc·SC region is important for that property.

However, the molecular nature of mucin-IgA interactions is poorly understood, and binding of the two has been difficult to demonstrate experimentally with purified components (R. Crowther, S. Lichtman, J. Forstner, and G. Forstner, Fed. Proc. 44:691, 1985).

IgA-Dependent Cell-Mediated Effector Functions

IgA of various molecular properties and origins can interact with functionally diverse cells, including B and T lymphocytes, NK cells, cells of the monocyte/macrophage lineage, polymorphonuclear neutrophils (PMN), various epithelial cells, hepatocytes, and possibly erythrocytes (46). The physicochemical properties of the IgA receptor molecules on these cells have not been determined, except for SC or polyclonoglobulin receptor, which is expressed on certain epithelial cells and hepatocytes and is involved in
selective transport of polymeric IgA or IgM into external secretions (8, 49).

**Phagocytosis.** Expression of Fcγ receptors on monocytes and PMN from human peripheral blood is enhanced by incubation with myeloma or S-IgA (17). However, the role of IgA in the various effector functions of these cells is unclear. Most early investigators observed that human IgA has an inhibitory effect on phagocytosis, bactericidal activity, and chemotaxis by PMN (30, 51, 77, 81, 82, 84). The effect on phagocytosis is observed with both antigen-specific IgA, which may compete with IgG for antigenic determinants on the target, and polymeric myeloma IgA, suggesting a direct interaction with the phagocytic cell via Fcγ receptors (16, 78).

In other studies, IgA antibodies were shown to promote phagocytosis by human oral, but not blood, PMN and to be able to enhance the opsonizing effects of suboptimal quantities of IgG antibodies (16). IgA-mediated phagocytosis was also demonstrated in vitro with mouse lung alveolar macrophages (59). A heat-stable opsonic activity for yeasts in sera from liver disease patients has been surprisingly traced to IgA antibody to yeast cell mannan (83), a finding that needs confirmation in other systems. Finally, it was recently demonstrated that human serum IgA and S-IgA bind to Staphylococcus aureus and induce phagocytosis and the associated respiratory burst in human neutrophils (23). However, since IgA was possibly bound to cell wall protein A, it remains to be shown whether similar results will be obtained with other bacteria.

Inhibition of chemotaxis has been observed mainly with polymeric myeloma IgA or monomeric IgA complexed with the low-molecular-weight glycoprotein termed HC and depends on Fc (44, 65, 77). A recent study indicates, however, that all molecular forms of IgA have this effect (65). The inhibitory effect is seen in the presence of maximal chemotaxin-induced chemotaxis, whereas the opposite effect may be seen in the presence of small amounts of a chemotaxin. Furthermore, the various forms of IgA are capable of increasing the random migration of PMN (chemokinesis) (65).

Collectively, the available information strongly suggests a potential modulating effect of IgA on phagocytes in inflammatory sites, mainly depending on the interaction of IgA with Fcγ receptors on the cells. Although there are still unclear points, it appears that IgA either does not promote or blocks phagocytosis by phagocytes from the circulation. The biological significance of the opsonizing effect of S-IgA observed in vitro is uncertain, since functional phagocytes are generally present only in low numbers in external secretions rich in S-IgA.

**Antibody-dependent cell-mediated cytotoxicity.** Both IgG and IgA induce monocyte-mediated antibacterial activity against group C meningococci (37). Although the mechanisms are not clear and phagocytosis may be involved, this activity is independent of complement, is antigen specific, and depends on Fcγ (37). Likewise, S-IgA from milk and IgG from serum effectively promote the clearance of Giardia muris by peritoneal neutrophils and monocytes in mice (30).

Human and murine T lymphocytes in concert with IgA or IgG may display antimicrobial activity against gram-negative bacteria (70, 71). The activity of lymphocytes from the gut-associated lymphoid tissues and from mesenteric but not popliteal lymph nodes could be specifically increased by incubation with S-IgA (70).

**Hepatobiliary transport.** In those animal species (notably, rats, mice, and rabbits) that have SC expressed on the sinusoidal surfaces of liver parenchymal cells, polymeric IgA is transported from serum to bile by a receptor (SC)-mediated vesicular transcellular mechanism (76). Furthermore, antigens, including bacterial polysaccharides and absorbed food antigens, complexed with polymeric IgA antibodies can also be eliminated (10, 55, 61). This exact mechanism does not appear to operate in humans, because SC is not expressed on human hepatocytes.

**ANTI-INFLAMMATORY AND SHIELDING EFFECTS OF IgA**

The preceding discussion illustrates some conflicting properties of IgA in complement- and cell-mediated effector functions. However, the consensus is that IgA is relatively ineffective or directly antagonistic compared with IgG or IgM in such systems. Where all isotypes of immunoglobulins and cell-mediated immune mechanisms are present, it seems that the role of IgA antibody is to mitigate the inflammatory side effects of other immune effector systems.

The importance of this regulatory role of IgA, particularly at mucosal surfaces, is revealed by experiments showing increased absorption of a bystander antigen through oral or intestinal epithelia when another antigen is complexed with an inflammatory isotype of antibody such as IgG or IgE (6, 36, 74). IgA antibodies may also abrogate anaphylactic and Arthus-type reactions (63). Conceivably, submucosal IgA secreted by the resident plasma cells, as well as S-IgA in the lumen, will contribute to these effects. In other situations, however, the results may be undesirable, such as the exacerbation of infections by interference with complement-dependent antibacterial mechanisms (24, 51) or the blocking of cell-mediated antitumor immunity (41, 54).

**INTERFERENCE WITH IgA-MEDIATED DEFENSE MECHANISMS BY BACTERIAL IgA PROTEASES**

Even though the functional properties of Fcγ are inadequately understood, to carry out all of its ascribed functions, S-IgA must retain its integrity in the enzymatically hostile environment on mucosal surfaces. While this stability is, in part, ensured by S-IgA antibodies having neutralizing activity against microbial proteolytic enzymes, the special conformation of the S-IgA molecule makes it considerably more resistant than serum immunoglobulins, including monomeric IgA, to common microbial and intestinal enzymes (26, 45). However, this resistance of S-IgA does not apply to the extracellular IgA-specific proteases released by several medically important bacteria and which cleave human IgA of one or both subclasses. Recent evidence suggests that such bacterial IgA proteases may cause temporary functional deficiencies in the mucosal immune system and lead to blocking of other immune factors.

The biological significance of the IgA proteases in host-parasite relationships is strongly suggested by their association with certain human infectious diseases that take place at or originate from mucosal surfaces (33, 50, 57). Most notable, all three principal causes of bacterial meningitis (Haemophilus influenzae, Neisseria meningitidis, Streptococcus pneumoniae) produce IgA1 proteases. Closely related non-pathogenic Haemophilus and Neisseria species lack similar enzyme activity. IgA protease activity is also a characteristic of important causes of vaginal and urinary tract infections, such as the gonococcus, and Ureaplasma urealyticum (33, 50, 57). Among the several hundred species of bacteria encountered in the human oral cavity, it is remarkable that...
the two streptococcal species, *S. sanguis* and *S. mitior*, that initiate plaque formation on teeth and a group of anaerobic gram-negative rods, which may be implicated in the pathogenesis of periodontal diseases, produce IgA proteases (33, 50, 57).

An observation of potentially great significance is that some members of the family *Enterobacteriaceae* are capable of cleaving IgA (43, 48). This activity has been detected only in fresh isolates from feces and urinary tract infections and is rapidly lost upon subcultivation of the bacteria. Similar strains from culture collections have not disclosed IgA-cleaving activity, nor has it been possible to restore the lost IgA-cleaving activity; the molecular basis for this unusual pattern is unknown (43, 48). Similar ephemeral IgA-cleaving activity was recently demonstrated in *Veillonella* sp. isolated from subgingival plaque of patients with periodontal diseases (18). These findings suggest that some microorganisms originally found to lack IgA protease activity on examination of collection strains should be reexamined with fresh isolates.

The majority of the IgA proteases cleave only IgA molecules, because the susceptible site is one of the prolyl-seryl or prolyl-threonyl peptide bonds in the heavily glycosylated duplicated sequence, -Pro-Ser-Thr-Pro-Pro-Thr-Pro-Ser-, present in the hinge region of IgA1 but absent from IgA2 (33, 50, 57). Despite extensive screening, no substrate other than the human α1 chain and IgA from gorillas and chimpanzees has been found (33, 50, 57). The recently described enzyme from an intestinal isolate of *Clostridium ramosum* (19) is unique in attacking both IgA1 and IgA2 of the A2m(1) allotype, which is characteristic of the Caucasian race. The site of cleavage for this protease is the prolyl-valyl peptide bond common to the two chains between the CH1 domain and the hinge region. In any case, the result of IgA protease activity is the release of intact monomeric Fab and Fc (or Fc2, SC) fragments.

IgA proteases are not susceptible to physiological protease inhibitors, and their ability to function in vivo has been amply demonstrated. Thus, fragments suggestive of IgA protease activity (Fab, Fc, Fc2–SC) have been observed in intestinal fluids, in vaginal secretions from women with gonococcal infection, in cerebrospinal fluid from patients with *H. influenzae* meningitis, and in nasopharyngeal secretions from certain children. However, like other microbial enzymes, IgA proteases may be inhibited by neutralizing antibodies, and such antibodies have been demonstrated in sera and secretions of patients after infection with IgA1 protease-producing bacteria (21). The use of neutralizing antibodies to compare IgA1 proteases from different bacterial species has disclosed remarkable antigenic heterogeneity among the enzymes even within single species, such as *H. influenzae*, which has at least 15 different antigenic types of IgA1 proteases (33).

Cleavage of IgA in the hinge region may conceivably interfere with all functions associated with the Fc part of the molecule. This may allow bacteria to colonize and penetrate mucosal membranes provided that they possess the additional required virulence factors. Of central importance for understanding the pathogenic function of IgA1 proteases is that the released intact Fab fragments retain full antigen-binding capacity (40). Being monovalent, these Fab fragments are unable to induce agglutination of bacteria and, furthermore, are ineffective in inhibiting bacterial adherence (50, 58). More important, Fab, fragments bound to surface epitopes will protect the bacterium from the immune system by blocking access of intact antibody molecules of the same or other isotypes and of immunocompetent cells. On this

![Diagram](image)

**FIG. 1.** Hypothetical model for invasive infection due to IgA1 protease-producing bacteria (34).
basis, we have recently proposed the following hypothetical model for invasive infection due to IgA1 protease-producing bacteria (34).

Acquisition of H. influenzae serotype b, N. meningitidis, or S. pneumoniae and the subsequent temporary nasopharyngeal colonization, as it occurs in the majority of infants and children, results in the concurrent induction of S-IgA antibodies to bacterial surface antigens and neutralizing antibodies to the IgA1 protease excreted by the bacteria (21, 34). This situation does not allow the bacteria to become coated with Fab fragments, and the induced immune response confers protection from invasive disease and from subsequent attacks by the same bacteria. The susceptibility of occasional individuals to invasive disease is the result of preexisting IgA1 antibodies in secretions and sera against surface antigens of the pathogen. These antibodies are induced by prior mucosal contact with cross-reacting microorganisms and, therefore, do not include inhibiting antibodies against the IgA1 protease of the pathogen. As a result, the pathogen is able to protect itself by binding Fab antibody fragments, and the resulting efficient evasion of the immune system may allow the bacteria to penetrate the mucosal barrier and cause systemic infection (Fig. 1). Although supported by several hitherto unexplained in vivo observations (34), further studies are required for the evaluation of this hypothesis. The exquisite specificity of IgA1 proteases for human IgA1 may explain why humans are the only host naturally susceptible to infection with H. influenzae, S. pneumoniae, and the two pathogenic Neisseria species but, in addition, has the important consequence that animal studies of these mechanisms are impossible.

The extensive cleavage of S-IgA detected in nasopharyngeal secretions of certain individuals suggests that cleavage is not restricted to antibodies against the protease-excreting bacteria. The protease excreted by minor components of the flora at a mucosal surface may be accommodated by the host organism, by either an increased local production of S-IgA or enzymoneutralizing antibodies in the secretions. However, increased numbers of bacteria excreting an IgA1 protease not previously encountered may conceivably result in temporary local impairment of the mucosal immune barrier. This expands the group of diseases in which IgA proteases may be significant, because extensive cleavage of S-IgA may not only promote the establishment of other potentially pathogenic microorganisms, but also facilitate the penetration of microbial and other antigens or allergens. The demonstration of a significantly increased incidence of S-IgA cleavage in nasopharyngeal secretions from children with a history of atopic diseases as compared with normal controls is of interest in this context (67). Although not necessarily a primary event in the development of an atopic condition, IgA protease-induced impairment of the immune barrier of mucosal membranes may conceivably perpetuate the allergic disease. Since several intestinal bacteria may produce IgA proteases, studies of the association of such bacteria with inflammatory bowel diseases and malabsorption conditions are of immediate interest.

The production of IgA proteases, possibly by a much wider range of bacteria colonizing mucosal areas than is currently recognized, underscores the importance of S-IgA in regulating the composition of the mucosal flora. Furthermore, study of the effects of IgA cleavage in various immune systems may yield further insights into the functions of IgA.

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