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MINIREVIEW

Diversity of Antibody-Mediated Immunity at the Mucosal Barrier

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Although over 90% of all human infections begin at a mucosal site (respiratory, gastrointestinal, urogenital, or ocular), the total number of infections occurring in the population is relatively low. This is in part the result of the secretion of a complex array of local and systemically produced immunoglobulins (Igs). Since the time of Pasteur (37), when immunization by the oral route was first described, and the identification of a special mucosal immune system by Besredka (7), considerable progress in understanding secretory immunity in humans has been achieved. Mechanisms of induction, synthesis, translocation, and activity of secretory immunoglobulin A (S-IgA) antibodies are now well established, as extensively reviewed in a recent book (46). However, while it would be more effective to block infections at the mucosa by using specific mucosal vaccines, the only such vaccine commercialized for human use is the oral polio vaccine (53). This delay in commercialization is due to the necessity of optimizing safety and efficacy which are related to a number of factors such as the requirements for persistent antigens (Ags) which linger on mucosal surfaces, for highly effective mucosal adjuvants, and for live mucosal vaccine vectors with harmless colonizing properties. Present efforts have focused on the study of both mucosal adjuvants, mainly cholera toxin and its derivatives, and immunogens such as encapsulated molecules, DNA, and recombinant microorganisms. Alternatively, an understanding of additional aspects of antibody-mediated immunity in secretions may enable us to develop new methods of local protection against pathogens. We present here those immune mechanisms known to be used by the host to block infection at the mucosal surface and discuss their respective importance and limitations.

Ag-INDUCED MUCOSAL S-IgA

The importance of the mucosal immune system was quickly realized after the discovery that S-IgA is the most abundant isotype of antibody in secretions and the elucidation of its unique structural properties. S-IgA is the major isotype in the human digestive tract and milk, as evidenced by both Ig levels and the presence of Ig-producing cells (17). Its structure (38) affords the molecule resistance to most proteases and increases its functional affinity for corresponding Ags. Unlike serum IgA, which is highly sensitive to proteases, the Fc region of S-IgA is wrapped within a secretory component (SC) molecule, which renders the associated chains protease resistant. In addition, the hinge region of IgA is either absent in the IgA2 subclass or replaced by a pseudo-hinge structure with low flexibility, which is also protected from many enzymes by the presence of special carbohydrate chains (35). The functional capacity of the S-IgA molecule is increased by its dimeric and even tetrameric status, as demonstrated for other polymeric Igs (29). It has been clearly established that the secretory immune system is compartmentalized and independent from the systemic immune system (33). Current evidence indicates that Ags penetrate the epithelial layer through "microfold" cells (M cells) (44), located in specialized areas covering mucosa-associated lymphoid tissues (MALT), where they trigger an immune response. The activated cells undergo a circulating cycle via blood and lymph where they mature and reach the "high" endothelial veinules (HEV) and then disperse to areas of the subepithelial stroma. It has been found that cells of the secretory system often, but not always, tend to migrate toward their tissue of origin (17). In the stroma, these Ig-producing cells synthesize polymeric IgA covalently linked with a joining (J) chain required for Ig binding to the transmembrane precursor of SC (19), called the polymeric Ig receptor (pIgR) (41). The pIgR is initially localized to the basolateral surfaces of epithelial cells and allows active transcytosis of IgA through the epithelium and its release into the lumen as S-IgA after cleavage of the ectoplasmic domain of the pIgR. Covalent disulfide bridges between IgA and the pIgR appear during transport. This well designed system ultimately leads to "immune exclusion" on the mucosal surface (57), i.e., preventing the entry of new pathogens through the mucosal barrier. In addition, transcytosis results in "immune elimination" (15), which consists of the active transport of IgA-bound pathogens from either the stroma (31) or the epithelium into the digestive lumen where they are ultimately released (36). During the transcytosis, IgA not only allows the active transport of the pathogens but also can inactivate them before release into the lumen. The efficacy of this system as a first immune barrier to infection depends on the presence of pathogen-specific antibodies before the first encounter with the pathogen. Problems arise because the Ag-mediated primary mucosal immune response peaks at day 21 after pathogen entry (21).

Ag-INDUCED SERUM-DERIVED S-IgA

In rodents and lagomorphs, serum IgA is primarily polymeric in nature and is eliminated in the gut by active transport from the serum to the bile through hepatocytes. In these animals, the poly-Ig receptor is present both in epithelial and liver cells, causing the gut contents to become enriched with serum-derived IgA with a structure identical to that of mucosal S-IgA,

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including its covalently bound SC. This pathway, called the hepatic pump (22), does not exist in humans but does exist in many current laboratory animals, such as mice, rats, and rabbits. These antibodies can be useful in hepatic bile and intestinal fluids, but they are serum derived and their induction differs from that of a true mucosal response. Similar to milk S-IgA, which is passively transferred from the maternal breast to the infant digestive tract during lactation, serum-derived S-IgA can provide immune exclusion of pathogens but not immune elimination, which requires local synthesis and transcytosis of the IgA complex. This difference from locally synthesized S-IgA could explain the improved protection against *Salmonella typhimurium* in mice vaccinated by the oral route, compared with that of mice inoculated parenterally. The corresponding S-IgA antibodies of the latter animals are serum derived and thus present only in the gut lumen; therefore, the animals cannot eliminate the pathogen from the lamina and the epithelium (2).

POLYREACTIVE S-IgA NATURAL ANTIBODIES

In mice, important variations in B-cell lineages and their subepithelial or MALT location have recently been described. B cells in the Peyer's patches belong to the B2 type, whereas those in the lamina propria are mostly B1, suggesting that a large proportion of gut effector B cells are unrelated to the MALT (42). This duality has been recently confirmed in mice with a deletion of the interleukin-5 receptor α chain in which MALT-independent mucosal B1 cells are selectively reduced (28). Interestingly, B1 cells, which usually exhibit the CD5 marker, are known to synthesize polyreactive antibodies. First described in humans, these polyclonal and monoclonal antibodies (24, 27) have the capacity to bind several epitopes, especially from unrelated self Ags. The structural reason for this unique specificity remains undetermined. However, it is known that these polyreactive antibodies are frequently encoded by germline genes with no, or only a few, phenotypic changes (4, 23). Concerning S-IgA, it has recently been shown that human colostrum and saliva contain large amounts of polyreactive antibodies, each recognizing both self and microbial Ags (50), which likely act to complement Ag-induced S-IgA. These pre-existing antibodies are capable of making initial contact with entering pathogens by acting as a first barrier to infection, particularly against primary insults. Moreover, by recognizing self Ags, these antibodies could eliminate fragments of autologous components, thus preventing their recirculation and the possible induction of pathogenic autoimmunity. However, the efficiency of natural antibodies is limited by their specificity, which, in many respects, is poorly adapted to local pathogens. At variance with Ag-induced S-IgA, it was previously hypothesized (10) that natural antibodies fail to detect key molecules of pathogenicity, such as toxins and adhesins, but rather act in immediate immunity, functioning solely to decrease the local burden of entering pathogens.

SERUM-DERIVED MUCOSAL IgG

In addition to responses to inflammation and transient increases in mucosal permeability (48, 49), serum IgG can also translocate towards the lumen by a physiological mechanism associated with the normal catabolism of Igs. Early studies using radiolabeled IgG molecules injected intravenously in humans demonstrated that IgG is released by the liver towards the bile and gut lumen (59). It has now been shown that IgG remains uncleaved in human bile but is degraded by proteases into Fab fragments during its migration along the gut (51). The Fab fragments from serum-derived IgG retain their Ag-binding activity with no loss of affinity—at least for hyperimmune antibodies—as demonstrated with stool Fab antitoxins. Interestingly, maternal IgG, which translocates through the placenta to the fetal serum, is also released from fetal blood into the intestinal lumen via the liver and bile (51). These antibodies are detected at high levels in the meconium and the infant's stools, leading to passive protection of the intestine mainly during the first week of life when autologous S-IgA has not yet been formed and released and when digestive protection is provided solely by maternal colostrum and milk. The protective power of these serum-derived Fab fragments differs from that of S-IgA since they can neither agglutinate nor opsonize Ags. However, they can exhibit antitoxin, antiadhesin, and even antivirus activities. The activity of uncleaved IgG with relation to its Fab fragments has resulted in conflicting reports, reviewed by Dimmock (25), which vary according to the system used in the investigation. The interest in IgG stems from its well-known property of high-level and long-lasting strong immunological response, high affinity, and immune memory.

LOCALLY SYNTHESIZED Ag-INDUCED IgG

The possibility of locally synthesized IgG, different from its serum counterpart, has been suggested by the observed higher specific activity of local IgG during intestinal infections (34). In addition, regional variations in the percentages of cells producing different Ig subclasses have been reported in different mucosae in both normal and IgA-deficient subjects (45). An independent local synthesis has also been proposed during AIDS (5) where elevated anti-human immunodeficiency virus-specific activities have been found in saliva and vaginal secretions compared with those in autologous serum. Recently, we examined the specificity pattern of antibodies to streptococcal Ags by using a computer-assisted immunoblotting method and found that IgG purified from secretions exhibits an antibody pattern different from that of autologous serum IgG (6). Moreover, this pattern varies according to the source of the secretion, demonstrating the compartmentalization of the IgG response in secretions. This regionalization has now been confirmed by the observation of different specificities and neutralizing activities of autologous serum and colostrum IgG in human immunodeficiency virus-positive women (4a). It appears, therefore, that mucosal IgG-positive B cells participate in specific local immune protection, which is in agreement with the previous observation of intracellular synthesis of a J chain by these cells (9). Although it is too soon to know, some of the main functions of local IgG could be to specifically control mucosal invasion of pathogens, to complement the activity of locally synthesized S-IgA, and to participate in IgA-dependent transcytosis of subepithelial immune complexes (31). One can imagine that local IgG and polymeric IgA could simultaneously be bound to a pathogen in the stroma, the first isotype functioning to neutralize the particle and the second driving the transcytosis of the complex to its ultimate release in the lumen. Further studies will be required to delineate the importance of local IgG in preventing infections and to identify methods to increase its level in secretions.

OTHER ISOTYPES

IgM is an isotype already present in primitive vertebrates. It is a minor component of Igs in human secretions in terms of both isotype percentage and antibody activity. However, in IgA-deficient subjects, the lack of a switch mechanism from IgM to the IgA isotype leads to a large increase of both mu-

TABLE 1. Proposed differential properties of antibodies in mucosae and secretions

Isotype and source[a]	Resistance to current proteases	Level of intrinsic affinity	Adaptation to local pathogens	Immune elimination[b]	Degree of agglutination	Neutralization of pathogenic factors
Mucosal S-IgA						
Ag-induced local Abs	Yes	Medium	Yes	+++	++	Yes
Milk Abs	Yes	Medium	Variable	−	++	Variable
Serum-derived Abs[c]	Yes	Medium	Variable	−	++	Variable
Natural local Abs	Yes	Variable	No	+++	++	No
Mucosal IgG						
From liver catabolism	No	High	Variable	−	+	Yes
From tissue diffusion	No	High	Variable	pIg-dependent	+	Yes
Intraluminal Fab fragments	Yes	High	Variable	−	−	Yes
Ag-induced local Abs	No	High	Yes	pIg-dependent	+	Yes
Mucosal S-IgM						
Ag-induced local Abs	No	Low	Yes	+	+++	Yes
Natural local Abs	No	Low	No	+	+++	No

[a] Abs, antibodies.
[b] During transcytosis of Ig as polymeric IgA or pentameric IgM (pIg).
[c] In rodents and lagomorphs.

cosal IgM-producing cells and S-IgM in secretions, as originally observed by Brandtzaeg et al. (18). IgM exhibits useful agglutinating activities, but in contrast to S-IgA, the SC binding is not covalent and does not provide resistance against enzymatic cleavage. Moreover, despite similar affinities for SC and comparable levels of transcytosis, the low diffusion rate of IgM leads to an external transfer that is overall 6- to 12-fold-lower than that of dimeric IgA (43), thus impairing immune elimination. IgD is extremely fragile and cannot be detected in secretions. However, an increased percentage of IgD-producing cells in the nasal mucosa is positively correlated with disease in IgA-deficient subjects (16). The IgE isotype is also very sensitive to enzymatic degradation and has been considered a good protective agent against parasites (20). While IgE is involved in digestive allergies, it could also augment absorption of food by inducing a low level of local vasodilatation during transit. Conversely, IgE is also able to increase the local concentration of antibodies of other isotypes (56). Its role in preventing parasitic infection is significant, as suggested by the number of mast cells in the lamina propria which can be activated by the gut protein Fv (Ig-variable fragment-binding protein) (47).

FACTORS FAVORING Ig ACTIVITIES

In certain situations, such as those in axenic animals, where synthesis of S-Igs is deeply depressed but not fully abolished, the defect may be restored by simply establishing bacterial colonization (40). Under these conditions the secretory immune response and induction of immune oral tolerance are modified (39), but the presence of natural antibodies has been observed. It is thus obvious that microbial products may exert positive and important changes in the activity of the secretory immune system in that such microbial molecules can directly increase the activity of Igs. The affinity of mucoproteins for Igs favors the carriage of secretory immune complexes with the mucus flow. More specifically, endogenous protein Fv plays the role of coreceptor for S-IgA in the gut lumen (13). Protein Fv is a 175-kDa sialoglycoprotein that is resistant to most proteases. It can bind the V_H domain of human Ig (14) provided it belongs to the V_H3 family (54, 55), i.e., the V_H clan 3 in animals (11). The molecule's six valences bind S-IgA and its fragments to form a large nonimmune complex (12), called an immune fortress. While these complexes increase both the agglutinating properties of Igs and the titer of natural antibodies, their major role in humans is to maintain, and even increase, the polymeric status of S-IgA despite its cleavage in the colonic lumen. The release of protein Fv is favored by infections such as human viral hepatitis (13) and colonization of axenic rats with normal human flora organisms (3).

FACTORS IMPAIRING SOME Ig ACTIVITIES

Proteolytic cleavage of endoluminal Igs by endogenous digestive enzymes occurs with IgG, S-IgM, IgD, and IgE, leading to Fab fragments. In contrast, S-IgA is relatively resistant to these proteases but can be sensitive to a group of microbial enzymes, mostly restricted to the IgA1 subclass (32). Proteolytic degradation of Igs abolishes their agglutinating properties and dramatically decreases their functional affinity. However, fragments from high-affinity antibodies may not be greatly affected in their recognition properties, as observed with Fabγ antitoxins isolated from human stools which can display an affinity constant as high as 1.6×10^{11} M^{-1} (51).

In addition to antimicrobial or antiself activities, natural antibodies can display anti-idiotypic activities against other natural antibodies. These properties were first described in adult and fetal sera (1, 30), where IgM can inhibit autologous and maternal autoreactive IgG, respectively. More recently, similar observations have been reported in human amniotic fluid where fetal IgA inhibits the autoreactivity of maternally derived IgG (52). This observation is of interest because amniotic fluid can be considered a secretion since it is mainly released from fetal urine and is located outside maternal and fetal bodies. In this fluid, the autoantibody activity of maternal IgG is potentially harmful towards the fetus and it is the fetal monomeric IgA which provides protection against an autoimmune reaction. In contrast, maternal Ag-induced IgG is not affected and remains capable of protecting the fetus against infection.

CONCLUSION

Recognition of the complexity of the secretory immune system (Table 1) extends the domain of these immune defenses to

additional pathways. An overall examination of these mechanisms demonstrates that they are both complementary and cumulative, explaining why the lack of S-IgA in individuals with IgA deficiencies does not, in most cases, lead to infections. It is likely that these pathways have been acquired progressively and developed, or lost, according to local factors, often depending on the presence of proteolytic enzymes in the animal species. In agreement with a recent hypothesis (10), we propose that primitive immune defenses against the entry of pathogens were first provided by polyreactive natural antibodies of the S-IgM isotype. The polyreactivity and transcytosis of these antibody ancestors can be reasonably predicted, since both SC (26) and IgM are present in primitive vertebrates, while the J chain has been detected even in invertebrates (58). The sensitivity of S-IgM to enzymatic cleavage and its poor avidity, which is further reduced after digestion, may have led to its replacement by S-IgA, a protease-resistant molecule with higher intrinsic affinity. The release of serum-derived IgG from the liver during the catabolism pathway and the transcytosis of S-IgA by the hepatic pump in rodents and lagomorphs have enabled digestive tract immunity to gain the help of antigen-induced "à la carte antibodies," with a much higher affinity associated with their Ag-driven selection process (10). However, the release of serum-derived Ag-induced antibodies by the IgA-pump in rodents and lagomorphs and by IgG catabolism in most vertebrates is mainly adapted to systemic and not to local pathogens. The final wave of the mucosal immune system must have been the development of Ag-induced local responses, including the major S-IgA-associated system and the proposed local IgG-associated system, which provide local antibodies in response to local pathogens. The notion of regionally adapted responses to local pathogens is derived from the presence of compartmentalized antibody patterns in these two systems. Perhaps the reason that both isotypes coexist in different proportions in secretions is associated with their relative properties: IgA is more active in immune exclusion (8) and is protease resistant, whereas local IgG could have features complementary to these, such as elevated and long-lasting response, high affinity, and immune memory.

Delineation of the different immune pathways leading to antibodies found in secretions will provide a better understanding of the early defense mechanisms mounted by humans against the entry of pathogens. The compartmentalization of both S-IgA and local IgG is in agreement with new approaches taken in mucosal immunization which consider the site of inoculation an important factor for the induction of immunity against a specific pathogen (17). Finally, understanding the specificities of local IgG and S-IgA and their kinetics of induction and anamnestic reactions, in combination with an awareness of the invasive properties of each pathogen, will reveal new strategies for the development of vaccination procedures at the level of the human mucosae.

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