Mucosal Immunity: Role of Gut-Associated Lymphoid Tissue (GALT) in IgA Response

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INTRODUCTION

Mucosal immunity is a unique form of immune response that is primarily located in the mucosal surfaces of the body. It is characterized by the presence of specialized immune cells and tissues, such as the gut-associated lymphoid tissue (GALT), which play a crucial role in the immune response against antigens present in the mucosal environment. GALT is an organized lymphoid tissue situated along the mucosal surfaces of the gut, respiratory, and genitourinary tracts, and it constitutes an important part of the mucosal immune system.

GALT is composed of several distinct components, including Peyer's patches, M cells, and other lymphoid aggregates. Peyer's patches are oval, lymphoid nodules in the lamina propria of the intestinal mucosa, and they are rich in immune cells, including B cells, T cells, and macrophages. M cells are specialized epithelial cells that are present in the gut-associated lymphoid tissue and are capable of capturing antigens from the luminal side of the gut epithelium and transporting them into the underlying lymphoid tissue. This process facilitates the activation and differentiation of immune cells, leading to the production of antibodies and other immune effector molecules.

Key Words: mucosal immune system - IgA - Peyer's patch - M cells - oral immunization.
INTRODUCTION

A protective local end mucosal immune system seems to function independently of systemic immunity. The concept of local immunity was initially proposed by Bernadini in 1919 (cir. Brandtzæg, 1989), that rabbits after being immunized orally with killed Shigella bacilli, were protected against fatal dysentery irrespective of the serum antibody titer. In 1922 the human mucosal immunity was first reported by Davies (cir. Brandtzæg, 1989) that bacterial agglutinins could appear in dysentery stools several days earlier than in the blood. The molecular basis for local immune system was established when Tomasi et al. (1965) confirmed that external secretions contain a unique immunoglobulin (Ig), which is called secretory IgA (slgA). This antibody which is the predominant Ig class in human external secretions provides specific immune protection for the mucosal surfaces (McGhee & Mestecky, 1995; Helmarow et al., 1992).

BIOLOGICAL SIGNIFICANCE OF THE MUCOSAL IMMUNE SYSTEM

The role of secretory IgA in protection against infections is illustrated by the fact that most infectious agents enter the host via the mucous membranes (McGhee & Mestecky, 1990; Hanson & Brandtzæg, 1993). For instance, the great majority of the 40,000 children under the age of five years that die every year has been due to mucosal infections in the respiratory and gastrointestinal tracts (UNICEF, 1992). In addition, the protection for the breastfed infants provided by slgA in milk has been demonstrated for cholera, enteroaggregative E. coli (ETEC) and Campylobacter infections. Moreover, breast feeding is 18-fold better at protecting neonatal sepsicaemia when compared to infants who are not breast-fed and the risk of dying from diarrhoea in infancy is almost 24 times higher without breast feeding compared with exclusive breast feeding (UNICEF, 1992). These illustrate the importance of mucosal immunity for the well being of the young as well as the adult.

CONTRIBUTIONS OF GALT TO THE MUCOSAL IMMUNITY

The mucosal surface of the gut has an enormous exposure area to exogenous agents including microorganisms, toxins, enzymes and dietary antigens. It is not surprising, therefore, that mucosal tissue is equipped with local immune system capable in mounting and effecting a wide variety of immunologic reactions.

The intestine contains the so-called gut-associated lymphoid tissue (GALT) (Beutler & Belus, 1984), which represents the largest immunological organ of the body. More than 80% of all immunoglobulin (Ig) producing cells (approximately $10^6$ $m^{-1}$ Ig-producing cells) are found along the gut mucosa. These cells produce more slgA (5-100 mg/kg body weight/day) (Brandtzæg, 1989; Mestecky et al., 1991). Although GALT is frequently associated with Peyer's patch(es) (PP), its name designates for all lymphoid cells and structures along the gut mucosa (Sosenko et al., 1990; Sosenko, 1992). This includes lymphocytes within the epithelium (intraepithelial lymphocytes, IEL), lamina propria, isolated lymphoid follicles, appendix, and colonic lymphoid patches (Sosenko et al., 1993). In addition, the gut-draining mesenteric lymph nodes (MLN) are considered to be part of GALT (Gebbers & Gebbers, 1992).
STRUCTURAL AND FUNCTIONAL FEATURES OF PP

Peyer's Patch, an organized lymphoepithelial structure, comprises B cell-dependent follicles, interfollicular T cell-dependent areas, and follicle-associated epithelium (FAE) overlying the dome of lymphoid nodules (FIGURE 1). The FAE is characterized by the presence of modified epithelial cells, called M (membranous/microfold) cells, located interproximately among absorptive cells of the lymphoid follicles.

![Schematic drawing of Peyer's patch and its compartments. Note: the follicle-associated epithelium (FAE) with M cell (see inset); VE = villous epithelial; IF = interfollicular T cell area; LP = lamina propria; F = follicle; AG = antigen, IEL = intraepithelial lymphocytes; HEV = high endothelial venule.](image)

M cells are unique both in morphology and functional properties (Sneller & Strober, 1986; Tron, 1991). Unlike the absorptive epithelial cells, these cells have small numbers and short microvilli, a poorly developed glycocalyx, remarkable cytoplasmic processes, few lysosomes, and low acid phosphatase content. These special structures of M cells are instrumental for the transmucosal transport of potentially antigenic materials from the gut lumen. M cells are ideal gateways for the presentation of enteric antigens to the underlying immunocompetent cells of the lymphoid nodules. In addition to lymphoid cell populations, nonlymphoid accessory cells as macrophages and interdigitating dendritic cells (IDC) are found in the dome and T cell areas, respectively.

It is generally agreed that the induction for IgA immune reactions occurs in the PP (Dibbgen et al., 1989; Björke & Brandtzaeg, 1990; Weinstein & Cebra, 1991). In addition, this lymphoid organ serves as a source for IgA plasma cell precursors that populate mucosal surfaces of the body (Weiss-Carrington et al., 1987; Björke & Brandtzaeg, 1990). Luminal antigens will be taken up by M cells, and are subsequently processed by the dome macrophages and presented to Tg (CD4^+ cells) which in turn activate B cells. The expression of membrane (mIg) bearing B cells in the PP germinal centers (GC) undergoes switching, i.e. from mlgM/mIgD B cells to mlgA B cells with the help of Tg (Twitch), follicular dendritic cells (FDC) and interleukin (IL-4). This preference for switching to mlgA B cells is likely due to the local microenvironment within PP GC (Cebra et al., 1991; Weinstein & Cebra, 1991). Committed B- and T-cells will then...
leave the PP, migrate to MLN, and enter the blood circulation through the thoracic duct. These B cells expand, undergo proliferation and differentiation, and home to the effector sites, i.e., in the gut lamina propria and migrate to remote mucosal tissues. These cells mature to become IgA plasma cells, and produce IgA antibodies in the secretions, such as salivary, tears, milk, gut- and vaginal washings. The final specific maturation of IgA B cells is influenced by IL-5 and IL-6 (McGhee et al., 1989; McGhee & Mestecky, 1994). The migration of specifically primed T and B cells from GALT and then homing to the mucosa (mucosa-associated lymphoid tissue, MALT) and the external secretions, is an important basis for mucosal immunity (Brandizzi, 1989). The concept of a common mucosal immune system is illustrated in FIGURE 2.

FIGURE 2 - Concept of common mucosal immune system. The initial induction of the immune response occurs in the GALT following a luminal antigen sampling by M cells. Antigen- sensitized, precursor IgA B cells and CD4+ T cells leave via effenter lymphatics and migrate to the mesenteric lymph nodes (MLN), into thoracic duct (TD) and to the blood circulation. Migrating cells enter and homing to the effector sites for production and transport of pIgA into mucosal surfaces or secretions. The pIgA, with J-chain associated with SC on the basolateral side of the epithelial cells, is endocytosed, transported across the cytoplasm, and trafficked to the apical membrane (McGhee & Mestecky, 1990).

MECHANISMS FOR IgA TRANSPORT

As other Ig isotypes, IgA is composed of four polypeptides chain subunits: two α heavy chains and two light chains (either κ or λ) forming two identical antigen-combining sites. Each α heavy chain has one variable region domain and three constant region domains. A distinctive feature of IgA is its ability to form polymers by means of having a special constant region (Cα) terminal extension with an extra cysteine residue, which can participate in cross linking monomeric subunits together via disulfide bridges. While IgA monomer is found in the circulation, IgA polymers are produced by plasma
cells locally in the tissue. Polymeric (lgA) usually occurs in dimers (11 S) (Chilkers et al., 1989; Mostecky et al., 1991). The polymerization occurs as these two monomeric forms are joined together by a small glycoprotein (MW 15 kD), called joining (J)-chain. The J-chain that enables lgA to bind to membrane secretory component (SC), is synthesized in the cytoplasm of B cells at various stages of differentiation and in plasma cells. lgA antibodies containing J-chain could increase the avidity for antigen. The SC is a transport secretory antibody (sIgA and also sIgM), because it protects the polymeric form against proteolytic enzymes. Molecular structure of SC comprises a single polypeptide chain folded into five immunoglobulin-like domains, which shares sequence homology with Ig light-chain variable regions. The secretory component also contains large amounts of carbohydrates, in which the function(s) is not yet known, possibly involved in the interaction of SC with pIgA.

Transport of pIgA into secretions is mediated by SC. The SC is synthesized by and expressed on the surfaces of epithelial cells in the gastrointestinal and respiratory tracts, acinar and ductal cells in the gastrointestinal and expressed on the surfaces of epithelial cells, in the gastrointestinal and respiratory tracts, acinar and ductal cells in the acinar tissue, and cells lining the ureters. In the small intestine, SC is found primarily in the columnar cells of the crypts on the surface of epithelial cells. It should be noted that in rats, mice, and rabbits, SC is also expressed on the hepatocyte membrane and constitutes an additional receptor and transport mechanisms for the secretion of pIgA into bile. This transport mechanism is not seen in human, because SC is not produced in the hepatocytes (Mostecky et al., 1986). IgA that is found in human bile is synthesized locally in minor cryptic areas of the liver in the vicinity of large hepatic ducts, and thus, it is not transported from the blood (Chilkers et al., 1989). In the crypts of epithelial cells, the transmembrane form of SC is synthesized on the rough endoplasmic reticulum (RER) and then moves through the cells to the Golgi apparatus, where terminal glycosylation occurs. Finally, SC is translocated to the basolateral side of the cell, and is then inserted into the membrane. The processed SC molecule as a receptor is about 100 kD, whereas SC forms in secretions as a cleavage product is 71-75 kD. The pIgA with J-chain bound by SC at the cell surface is internalized into vesicles and transported to the cell apex. The vesicles fuse with the membrane, and the entire complex (only small SC portion remains on cell membrane) is released as sIgA (FIGURE 2). Proteolytic cleavage is thought to be the mechanism of release. However, the site of cleavage on SC molecule and the mechanism responsible are at present unknown.

**BIOLGICAL ACTIVITIES OF SIGA**

IgA shares with other antibody isotypes the ability to interact with an enormous spectrum of antigens of viral, bacterial and parasitic origin with a high degree of specificity. IgA in external secretions occurs predominantly in dimeric or trimeric forms (with four or eight antigen-binding sites, respectively), and thus, displays greater avidity than monomeric IgA. The pIgA has been shown to neutralize viruses more efficiently than monomeric IgA (Taylor & Dineson, 1983), and its multivalent also enables IgA polymers to interact with bacteria better than corresponding monomers. In addition to viruses, sIgA antibodies also neutralize other biologically active antigens such as bacterial toxins and enzymes (Kilian et al., 1988). For example, studies on celiac disease in a rat model have shown that specific IgA antibody efficiently prevents the dehydrogenase secretory effects of cholera toxin in the intestine. It was proposed that IgA...
may allow *Vibrio cholerae* to be present without causing disease until the organism is cleared by other immune and non-immune mechanisms. Some organisms, e.g. *certain Streptococci, Neisseria, Haemophilus, Chlamydia*, are able to counteract the effects of IgA by producing specific IgA proteases (in general, IgA proteases resistant). These enzymes cleave IgA in the hinge region into one Fab and two Fc residues. It is not clear whether cleavage of IgA by these proteases is sufficient to inhibit the protective effects of IgA, because human myeloma IgA molecules of known antigen activity were not significantly inactivated by IgA proteases from several organisms. Besides direct actions of sIgA against pathogens (direct killing, agglutination, neutralization), invasion of mucosal sites. The role of antibodies in immune exclusion has been well documented that, antibody-coated bacteria cannot attach the epithelial cells. Previous enteric exposure to foreign soluble antigens diminishes the absorption of the same but not mucosal immune activity owing to the presence of specific sIgA antibodies (Kilian et al., 1988, Meghee & Montecchi, 1990). Through this immune exclusion mechanism, IgA limits further absorption of undegraded antigenic material and the formation of potentially harmful circulating immune complexes that contain predominantly IgG antibodies. Among the best evidence for immune exclusion is mucosal immunity to *Vibrio cholerae*, which produces an interleukin that binds to a porcine IL-6 receptor (IR) on intestinal epithelial cells, sIgA antibodies purified from serum and colostrum of Indian patients convalescing from cholera inhibited adherence of *Vibrio cholerae* to sections of rabbit intestinal tissue (Majumdar & Olson, 1981; Majumdar & Gone, 1982). However, antiadherence activity of sIgA from colostrum of Swedish women (cholera is not endemic in Sweden) was absent. This in contrast to sIgA collected from colostrum of Indian women which has a high antiadherence activity against cholera.

**CONCLUSION**

Although sIgA is quite versatile and has been able to adapt the invasive challenge of the mucosal ecosystem, its optimal effects might require interactions with other specific and non-specific host defence factors. For instance, interactions with mucosal phagocytes, lymphocytes involved in the antibody-dependent cell-mediated cytotoxicity (ADCC) with CD8, CD11 or CD18 T cell subsets, should not be ruled out. In addition, as the initiation of an IgA response occurs in PIP, it would be beneficial if oral immunization and vaccination could be targeted to the GALT in order to obtain an optimal mucosa-binding carriers, such as cholera B subunit, biodegradable microparticles or live vectors, by using mucosal adjuvants.

**REFERENCES**


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