LECTURE

Immunology of the Human Gastrointestinal Tract in Health and Disease—A Brief Review

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Introduction

Two decades ago it was shown that the major immunoglobulin (Ig) present in human exocrine secretions is a polymeric (mainly dimeric) IgA covalently bound to an epithelial glycoprotein of about 80 kD, now called the secretory component (SC). Pentameric IgM is likewise actively enriched in most exocrine fluids and is associated with SC, though not in a covalently stabilized complex.

More IgA is translocated to the gut lumen every day (~40 mg/kg) than the total daily production of IgG (~30 mg/kg). The secretion of IgA into one meter of small intestine amounts to 0.78 g/day, which is approximately the same output as from a lactating human breast. It is surprising that this dominating role of the gastrointestinal tract in humoral immunity is still poorly appreciated.

External transport of secretory immunoglobulins

Three findings explain the selective translocation of polymeric Ig (pIg) into exocrine fluids: (a) preferential local production; (b) J-chain-expressing capacity of pIg-producing immunocytes; and (c) SC-mediated epithelial transport (Fig. 1). Human

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Fig. 1 Model for SC-mediated epithelial transport of IgA and IgM. [1] Synthesis and core glycosylation (—) of transmembrane SC in rough endoplasmic reticulum (RER) of epithelial cell. [2] Terminal glycosylation (●—) in Golgi complex. [3] Phosphorylation (⊕) at some later step. [4] Complexing of SC with J-chain-containing dimeric IgA and pentameric IgM on basolateral cell membrane. [5] Endocytosis of complexes and excess of SC. [6] Transcytosis of vesicles. [7] Cleavage and release of SIgA, SIgM, and free SC. The cleavage mechanism and the fate of the cytoplasmic tail of transmembrane SC are unknown (?). During the external translocation, covalent stabilization of the IgA-SC complexes regularly occurs (two disulphide bridges indicated in SIgA), whereas an excess of free SC in the secretion serves to stabilize the non-covalent IgM-SC complex (dynamic equilibrium indicated for SIgM).

hepatocytes lack SC and the human liver, therefore, cannot act as an efficient "IgA pump" in contrast to the rat liver which shows a remarkable capacity for transport of dimeric IgA from blood to bile.

The J chain of pIg and the epithelial SC represent the "lock and key" in the glandular transport of secretory IgA (SIgA) and SIgM (Fig. 1). It has recently been shown that SC is synthesized as a transmembrane protein of about 95 kD and constitutes the actual pIg surface receptor. Complexing between ligand and receptor in the plasma membrane is followed by endocytosis; the completed SIgA and SIgM molecules are then translocated in cytoplasmic vesicles through the epithelial cell to the

gland lumen along with an excess of free SC.

Production and external transport of these two secretory immunoglobulins (SIgA and SIgM) depend on fascinating interactions of the B-cell system with glandular and mucosal epithelia. The fact that this complex cooperation between such different cell types has been preserved and become more elaborate during phylogeny, suggests that the secretory immune system is of protective significance.

Function of luminal antibodies

The main function of SIgA is to exert immune exclusion; that is, by intimate cooperation with innate nonspecific defense factors, it dampens down penetration of soluble antigens and inhibits epithelial colonization of bacteria and viruses (Fig. 2). SIgM may exert a similar protective function, especially in selective IgA deficiency when its synthesis is markedly increased in the intestinal mucosa.

Leakage of IgG into exocrine fluids is enhanced by mucosal irritation (Fig. 2). Although IgG should not be considered as an SIg, it may contribute to immune exclusion—especially in the respiratory tract where it is less easily subjected to proteolytic

Fig. 2 Schematic representation of the three main components of mucosal immune defense: immune exclusion, immune regulation and immune elimination. Antigen stimulation in mucosa-associated lymphoid tissue provides "first signals" to B cell which migrate to secretory sites *via* lymph and peripheral blood. "Second signals" (dashed heavy arrow) induce local proliferation and terminal differentiation of the extravasated B cells. Most plasma cells generated in this way produced J-chain-containing polymeric IgA, which is translocated to the lumen as stabilized secretory IgA. Also some IgM is actively transported by the secretory epithelial cells, whereas small amounts of IgG normally reach the lumen by passive diffusion (dashed thin arrow).

degradation than in the intestinal juice. However, by activating complement, IgG antibodies may at the same time be phlogistic and accelerate mucosal penetration of antigens. IgG may thus contribute to persistent immunopathology in mucosal disease. The same is true for IgE antibodies which may be carried into mucous membranes and secretions by mast cells and cause their degranulation with local histamine release. Traces of IgD may likewise be found in the secretions but without obvious biological significance.

Regulation of mucosal immunity

Regulation of mucosal immunity takes place both in organized mucosa-associated lymphoepithelial structures, such as the Peyer's patches, and adjacent to the glands in the lamina propria (Fig. 2). Antigen is primarily taken up by the former structures through the follicle-associated epithelium (FAE) which contains "membrane (M) cells" designed for sampling and inward transport. Antigen is presented to sub- and intra-epithelial T lymphocytes by dendritic antigen-presenting cells (APC) after being pro-

Fig. 3 Number of IgA-, IgM- and IgG-producing cells in various segments of normal human gastrointestinal mucosa. The counts are based on a "tissue unit" which constitutes a 6- μ m thick and a 500- μ m wide mucosal block extending from the muscularis mucosae to the lumen. The percentage class distribution of the immunocytes is indicated above the columns. Data from the author's laboratory.

cessed by subepithelial macrophages, or it may be subjected to direct presentation by epithelial cells. Both APC and FAE express major histocompatibility complex (MHC) class II (HLA-DR) molecules, which are required for an appropriate antigen-presenting function. T cells thus subjected to class II-restricted stimulation, release immunoregulatory factors which act on other lymphocytes in the microenvironment.

B cells that in this way receive their "first signals" become activated, migrate through lymph and peripheral blood, and are finally seeded into distant secretory tissues including the gut lamina propria. Here "second signals"—modulated by various elements expressing MHC class II determinants and by regulatory T lymphocytes—cause terminal maturation of B cells to Ig-producing plasma cells, mainly of the IgA class (Fig. 3). Regardless of Ig class, most of the mucosal immunocytes normally belong to clones of a particular maturation stage that is compatible with J-chain expression. The obvious functional goal of this immunoregulatory development is generation of SC-binding pIg locally where external transport through SC-positive epithelium readily can take place (Fig. 1).

This transport may be upregulated by immunoregulatory cytokines such as interferon- γ (IFN- γ) and tumour necrosis factor- α (TNF- α) which are released from activated T lymphocytes and macrophages, respectively. Both IFN- γ and TNF- α have been shown to stimulate the expression of SC. External translocation of pIg may thus be adjusted to the increased local production of polymeric IgA and IgM associated with an enhanced mucosal immune response.

Alterations of mucosal immunity in gut disease

In various gut diseases, local Ig production is altered both with regard to class and subclass. There is a disproportionate increase of IgG-producing cells, especially in inflammatory bowel diseases and chronic gastritis (Fig. 4). Local production of IgG1 is particularly marked in ulcerative colitis. Conversely, the Crohn lesion contains relatively more IgG2 cells than the former lesion.

In both diseases there is a marked change from local IgA2 to IgA1 formation, and less of the IgA is of the polymeric variety as shown by markedly decreased J-chain production. Along with topically decreased epithelial expression of SC, these immunoregulatory alterations are unfavourable for local secretory immunity. However, the consequences are still uncertain because the total number of mucosal IgA-producing cells in the inflamed colonic mucosa is increased at least two times (Fig. 4). The dramatic local overproduction of IgG and individual variations in IgG-subclasses may be of more pathogenetic significance.

In celiac disease secretory immunity is clearly enhanced—both in terms of the local production of IgA and IgM polymers and the epithelial expression of SC. The latter feature may be particularly intensified by IFN- γ released from numerous intraepithelial

Fig. 4 Alterations in local immunocyte populations as indicated by numeric increase per mucosal "tissue unit" in lesions of various gut diseases compared with normal counterparts. Immunocyte isotype distributions are indicated above the columns. Data from the author's laboratory.

T lymphocytes. This remarkable preservation of secretory immunity may explain the reversibility of the coeliac lesion.

Break of "oral tolerance" to gluten and other dietary or microbial antigens is apparently involved in the pathogenesis of coeliac and inflammatory bowel disease (Fig. 5). Enhanced expression of epithelial MHC class II determinants may to some extent explain that intraepithelial T4 ("helper") cells become unduly activated and stimulate local overproduction of IgG and induction of delayed type hypersensitivity. Perhaps the initial event in the break of tolerance is an epithelial virus infection in genetically susceptible individuals.

Allergic (atopic) gut disease in terms of food intolerance seems to be related to a slow postnatal development of SIgA immunity; but there is apparently no consistent increase of IgE-producing cells in the mucosal lesions. However, an increased number of IgE-bearing mucosal mast cells is a common finding in these patients.

Fig. 5 Hypothetical scheme for induction and abrogation of orally induced tolerance which normally affords down-regulation of both delayed type hypersensitivity (DTH) and IgG and IgE production. Left: Presentation to T8 ("suppressor/cytotoxic") cells of antigen that has been processed by epithelial cell or by specialized mucosal macrophage, or normal epithelial antigen presentation, results in regulatory signals conducive to suppression. Right: When there is a break in the epithelial lining (e.g. virus infection), undue stimulation of antigen-presenting cells, or aberrant epithelial expression of MHC class II determinants with ensuing enhanced presentation of luminal antigens, the result is overstimulation of T4 ("helper") cells. This gives rise not only to increased production of dimeric IgA, but also to excessive IgG and IgE responses and DTH.

Conclusions

Humoral immunity at gastrointestinal surfaces depends on complex interactions between the B-cell system and the gut epithelium. The most important factors in this cooperation are the J chain, polymeric IgA, SC, and probably epithelial MHC class II determinants. The obvious biological significance of the striking J-chain expression shown by mucosal immunocytes is that J-chain-containing IgA (and IgM) polymers are generated locally and become readily available for SC-mediated external transport. This important functional goal, in terms of clonal differentiation, may explain that J chain is also commonly expressed by B cell normally terminating in the mucosa with IgG (or IgD) production; these immunocytes may be considered a "spin-off" from immature memory clones that through isotype switching were on their way to IgA expression. SC-mediated glandular transport of locally produced IgA (and IgM) is in fact the only

efficient way of providing human gastrointestinal juice with protective antibodies because the human liver does not act as an "IgA pump".

Both the B-cell system and the mucosal epithelium show immunoregulatory alterations in various gut diseases. Local Ig production is altered with regard to class and subclass, and J-chain expression is variably depressed. The secretory epithelium may show enhanced or reduced SC, and the expression of MHC class II determinants is often significantly upregulated. Lack of immunoregulatory homeostasis in genetically susceptible individuals may explain the pathogenesis of various gut diseases.

For further details and complete referencing, the readers are referred to the following reviews and experimental articles:

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