

Leading article

Intestinal IgA: novel views on its function in the defence of the largest mucosal surface

The intestine is undoubtedly the most misunderstood and under-appreciated lymphoid organ in the body. Yet, in the eyes of mucosal immunologists, the gut exemplifies finely tuned, extensively interacting populations of cells and their products involved in innate and specific defence of the body's largest surface area, a surface exposed to the heaviest burden of environmental antigens. As the largest lymphoepithelial organ, it contains cells that absorb, process, and present antigen, B and T cells of various types, and antibody producing cells.¹ Every day intestinal plasma cells produce more antibodies than do all other lymphoid organs (spleen, lymph nodes, and the bone marrow) combined.² Although the remarkable dominance of IgA producing cells in the intestine and of IgA in the intestinal fluid has been known for decades, fine details of the migration or "homing" of IgA plasma cell precursors, their terminal differentiation, the mechanisms mediating and regulating the selective transepithelial transport of IgA, and the functional advantages of this molecule in the gut continue to emerge with impressive rapidity.

One feature unique to the mucosal immune system is the crucial role of epithelial cells of various morphological forms and phenotypes in mucosal defences.³ Functional interdependence of epithelial and lymphoid cells in the intestine has been amply documented. In addition to production of inflammatory cytokines (e.g. interleukin (IL) 8 and macrophage inflammatory protein (MIP) 1 α and anti-inflammatory cytokines (e.g. transforming growth factor (TGF) β and IL-10), epithelial cells are also a source of cytokines that regulate the terminal differentiation of arriving lymphocytes into IgA producing plasma cells (e.g. TGF- β , IL-6, IL-10).³ Lymphocytes resident in the lamina propria and in the intraepithelial compartment, mostly of T cell lineage, participate directly and indirectly in the protection of the mucosa,⁴ and provide stimuli (e.g. interferon (IFN) γ) for the maintenance of epithelial health⁵ and expression of the epithelial receptor that selectively transports locally produced polymeric IgA (pIgA) into the intestinal lumen.⁶⁻⁸ Due to this intimate epithelial-lymphoid cell collaboration, the final product—secretory IgA (S-IgA)—is delivered onto the mucosal surfaces of the human gut in huge quantities, 3–5 g of S-IgA/day!⁹ IgA is the most heterogeneous of human immunoglobulins, as it occurs in multiple molecular forms (monomeric (m), polymeric, and secretory) and subclasses (IgA1 and IgA2) which are distributed differently between the circulatory and mucosal immune systems.⁹⁻¹⁰ IgA antibodies may therefore have different functional properties depending upon their molecular form as well as their location. Functional advantages of S-IgA over other immunoglobulin isotypes include its multi-valency (4–8 antigen binding sites) which enhances its effectiveness over mIgA by at least an order of magnitude.¹¹ Furthermore, S-IgA is characteristically resistant to proteolytic enzymes due to the unique primary structure of its α chains and a putatively protective effect of the epithelial polymeric immunoglobulin receptor (pIgR), whose major extracellular fragment, secretory

component (SC), remains covalently associated with pIgA after its transcytosis through epithelial cells.⁶⁻⁸ Most importantly, IgA displays strong anti-inflammatory properties mediated by several mechanisms (see later).

The protective effect of antigen specific S-IgA in the intestinal lumen depends on its ability to inhibit the absorption of soluble and particulate antigens by forming intraluminal immune complexes,¹² to neutralise biologically active antigens (e.g. toxins and viruses) and to interfere with microbial adherence to epithelial cells. In addition to this specific antibody dependent function, abundant glycans on the Fc region of the molecule can aggregate enterobacteria carrying type 1 fimbriae, due to interaction of mannose binding fimbrial lectin and high mannose type glycan side chains of IgA.¹³ As a result, IgA coated bacteria are prevented from adhering to epithelial cells expressing analogous mannose rich glycans on their luminal surfaces without the need for specific antibody activity.

However, commensal microorganisms endogenous to the intestinal lumen are also coated with IgA.¹⁴ The apparent contradiction between the earlier described role of S-IgA in immune exclusion of pathogenetic microorganisms, and the fact that the normal intestinal microbiota remains relatively stable despite the IgA coating, may be reconciled by the existence of two functionally distinct "types" of S-IgA antibodies, produced by two separate B cell populations. The so called B-1 (formerly Ly1+ or CD5+) lymphocytes whose origin has been traced, in the mouse, to the peritoneal cavity and which contribute importantly to the lamina propria IgA plasma cells, produce less specific, perhaps polyreactive, "natural" antibodies which may actually play a role in the maintenance of the normal intestinal microbiota. Pathogenetic microorganisms, however, which stimulate the immune system after invasion through the Peyer's patch M cells,¹⁵ stimulate locally present conventional B-2 cells that are then disseminated to the lamina propria of the gut, mature into IgA plasma cells, and produce specific IgA antibodies with high affinity for the pathogen, thereby leading to its exclusion. The existence of a similar functional dichotomy of S-IgA antibodies in humans has not been investigated. Nevertheless, the presence of IgA1 and IgA2 subclasses with subtle structural and functional differences⁹⁻¹⁰ including sensitivity to bacterial proteases and notable differences in the distribution of mannose rich glycan chains,¹³ should provide fertile ground for such studies. Indeed, it is tempting to speculate that IgA2 antibodies, which are associated with specificity for common structural microbial antigens (e.g. lipopolysaccharides (LPS) and polysaccharides), are resistant to bacterial proteases, carry mannose rich glycans,

Abbreviations used in this paper: IL, interleukin; TGF, transforming growth factor; MIP, macrophage inflammatory protein; IFN, interferon; SC, secretory component; LPS, lipopolysaccharide; pIgA, polymeric IgA; pIgR, polymeric immunoglobulin receptor; mIgA, monomeric IgA; S-IgA, secretory IgA; Ag, antigen; TNF, tumour necrosis factor.

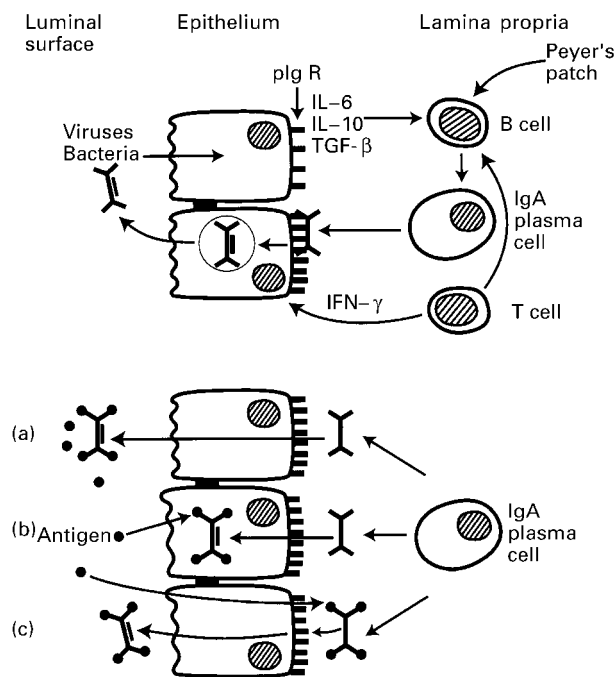


Figure 1 Examples of interactions of epithelial cells with lymphocytes in mucosal defence. Viruses and bacteria which invade epithelial cells stimulate production of several pro- and anti-inflammatory cytokines; some of them (e.g. IL-6, IL-10, and TGF- β) participate in differentiation of arriving B cells into IgA producing plasma cells.³ Mucosal T cells of Th1 lineage which are abundant in the intestinal lamina propria produce, among other cytokines, IFN- γ which upregulates the expression of pIgR on epithelial cells, thus facilitating transepithelial transport of pIgA onto the luminal surface.⁷ S-IgA can interact with luminal antigens (Ag) and inhibit their absorption by epithelial cells (a). Antigens which escape such luminal exclusion (e.g. viruses)^{24,25} encounter transported pIgA within the epithelial cells resulting in intracellular neutralisation (b). Antigens which penetrate the epithelial barrier interact with pIgA in the lamina propria and are eliminated as Ag-pIgA complexes by the pIgR dependent mechanism (c).²⁵

and are produced mainly in the most extensively colonised lower intestinal tract, are functionally analogous to murine B-1 cell products. Saliva and colostrum from normal humans contain polyreactive S-IgA antibodies that recognise a variety of autoantigens and several bacterial antigens.¹⁶ It has been proposed that these are products of B-1 cells, constituting part of the “natural antibody” repertoire that is encoded in the germline, and that such antibodies protect the mucosal surfaces prior to the generation of specific antibodies from conventional B-2 cells after exposure to nominal antigens. Although these polyreactive S-IgA antibodies may be of low affinity for antigen, the presence of 4–8 antigen binding sites on S-IgA results in high functional avidity.

The density of IgA producing plasma cells in the intestinal lamina propria is much reduced in animals kept in a germ-free environment and on an antigen-free diet; exposure to bacterial antigen results in a prompt infiltration of the gut with IgA plasma cells.¹⁴ What are the probable interactions involved in such a dramatic response? A picture begins to emerge which comprises hitherto unsuspected, multifaceted, and complementary interactions between the mucosal microbiota, epithelial cells, B and T cells, and their products—bacteriokines and chemokines.¹⁷ Viruses and bacteria, particularly those which invade epithelial cells, provide potent stimuli for the epithelial cell production of inflammatory cytokines responsible for the influx of phagocytic cells (e.g. IL-8, MIP1 α).³ Perhaps in parallel, cytokines with anti-inflammatory properties and also having the concurrent ability to promote differentiation of arriving precursors of IgA plasma cells (TGF- β ,

IL-10, and IL-6), are produced by stimulated epithelial cells,³ resulting in their terminal maturation and secretion of IgA with anti-inflammatory properties. However, epithelial–lymphocyte interactions are not restricted to lymphocytes of the B cell lineage; lamina propria and intraepithelial T cells interact with epithelial cells and vice versa, resulting in regulation of T cell proliferation.¹⁸

The well documented protective function of S-IgA has been exploited in passive immunisation with preformed antibodies. Ingestion of breast milk containing S-IgA antibodies induced by natural exposure of the maternal mucosal immune system to microbial antigens protects the gastrointestinal tract of newborns, whose mucosal immune system has not yet matured and thus is not able to respond to microorganisms, such as those causing diarrhoeal diseases.¹⁹ Practical use has been made of the anti-inflammatory property of IgA in the feeding of an IgA rich (70% IgA) immunoglobulin preparation to low birth weight infants to prevent necrotising enterocolitis.²⁰ To extend such passive immunisation to adults, ingestion of immunoglobulins (mostly IgG) obtained from milk of immunised cows or from eggs of immunised chickens has been tried. In more sophisticated approaches, genes encoding the component chains of S-IgA—that is, heavy, light, and J chains, and also SC, have been expressed in transgenic plants,²¹ insect cells,²² or mammalian cells.²³ Such molecular engineering of human S-IgA antibodies with specificity for a desired antigen may be useful for passive protection and treatment of microbial diarrhoeal diseases, and also in the prevention of infectious diseases of the respiratory and genital tracts, exploiting the functional advantages of homologous human S-IgA over cow or chicken IgG.

A novel principle of IgA mediated mucosal defence involving intraepithelial interactions between pIgA and antigen has been demonstrated in vitro (fig 1).^{24,25} In these studies, pIgA with antiviral activity internalised by the basolateral pIgR effectively neutralised a virus infecting the epithelial cells through the apical surface. Apparently, the transcytotic route of pIgA intercepts the pathways involved in virus assembly, resulting in intracellular neutralisation. In addition, elimination of non-infectious antigens in the form of antigen–IgA immune complexes transported across epithelial cells by pIgR has been demonstrated.²⁵ The existence of this attractive mechanism for protection in vivo needs to be established. Because almost all intestinal pIgA antibodies are produced locally by subepithelial plasma cells rather than from the circulatory pool, it is unlikely that the density of plasma cells producing pIgA of needed specificity would be high enough to provide generalised protection of all infectable epithelial cells. Even during a vigorous immune response, usually less than 1% of immunoglobulin secreting cells produce antibodies specific for a given antigen. Furthermore, the epithelial cells that participate most efficiently in the translocation of pIgA are located in the crypts, not the villi, of the small intestine; expression of pIgR on epithelial cells is diminished and ultimately lost during their migration from the crypt to the villus.²⁶ Lastly, with the exception of rotaviruses which infect villus epithelial cells, most viruses (e.g. poliovirus, reovirus, coxsackie virus, HIV, and adenoviruses) appear to invade through M cells¹⁵ which do not express pIgR.²⁶ It could be argued that pIgA from plasma might be internalised by epithelial cells. However, this is unlikely in humans because only small quantities (~1–2%) of total intestinal S-IgA are derived from the circulation.^{7,27} This is apparently due to several factors, such as the size of pIgA and the diminished diffusion of large molecules (including IgM) from plasma into extravascular spaces through the capillaries, and the effective competition of locally

produced pIgA with plasma derived pIgA, which is normally a minor component of human plasma.⁷ However, in species in which pIgA is the dominant form in plasma (e.g. rats, rabbits, and mice), this mechanism of intracellular neutralisation is likely to be effective at mucosal surfaces, particularly of the respiratory tract.²⁸ Interestingly, in these species but not in humans, hepatocytes also express pIgR and are involved in selective transport of pIgA from the circulation into the bile and ultimately to the gut fluid, thus reinforcing mucosal protection of the gut by plasma derived pIgA.²⁹ In addition, small molecular mass immune complexes composed of an antigen and corresponding pIgA can be eliminated by such hepatobiliary transport.^{7, 30}

Although S-IgA mediated inhibition of epithelial absorption of antigens is quite effective, small quantities of undigested antigens, mostly of food origin, are found in the circulation despite the presence of corresponding S-IgA antibodies in the gut.³¹ What are the consequences of the formation of antigen-IgA immune complexes that are not eliminated by the epithelial pathway and remain in the tissue? The non-inflammatory nature of IgA¹² is probably of great importance for the maintenance of the integrity of mucosal surfaces and submucosae. Inflammation is a physiological response, involving numerous cells and effector molecules, to damage inflicted by infectious or non-infectious agents, and may be important in the initiation of the immune response in generating "second signals" to lymphocytes. It is also a consequence of immune effector mechanisms in combatting infection, as collateral tissue damage even greater than that caused by the pathogens themselves can ensue. Thus inflammation is both beneficial and necessary, but failure of, or interference with, the homeostatic mechanisms that regulate it may result in chronic inflammatory disease.

The concept that IgA antibodies represent an anti-inflammatory type of antibody is exemplified by the findings that intact, native human IgA antibodies fail to activate complement when complexed with antigen,³² and that they interfere with complement activation by IgM and IgG antibodies.^{33, 34} Close examination of the frequently cited ability of IgA to activate the alternative complement pathway reveals that this is largely due to artificial aggregation or conformational alteration of IgA induced by heat, deposition on hydrophobic surfaces, chemical cross-linking or modification, aberrant synthesis (including glycosylation), or denaturation during purification.¹²

Phagocytes express the receptor for IgA (FcαR, CD89), which is capable of mediating phagocytosis and transducing signals for oxidative metabolism and granule release.³⁵ FcαR is a heterogeneous receptor that is variably glycosylated in different cells, and although it is constitutively expressed on monocytes, neutrophils and eosinophils, it is upregulated on neutrophils by certain cytokines, such as tumour necrosis factor (TNF) α or IL-8, which enhance the cells' ability to ingest IgA opsonised particles.^{36, 37} This may have functional significance within mucosal tissues such as in the gut, by enabling the cells to function effectively in the IgA rich environment of the mucosa, particularly when incipient bacterial invasion induces the epithelial cells to produce IL-8 or TNF-α which in turn recruit and activate neutrophils. It will be interesting to determine whether such activated phagocytes respond to IgA in the same way, or not, as cells reacting to IgG and C3b, as it is clearly important that, in defending the mucosa against the threat of bacterial invasion, collateral damage to the mucosa itself be controlled, lest the situation be aggravated. It is therefore significant that IgA downregulates the production of TNF-α and IL-6, and upregulates the production of IL-1

receptor antagonist in LPS stimulated monocytes,³⁸ and that the intracellular signal transducing events are different from those induced through IgG receptors.³⁹ However, tissue macrophages express FcαR variably, and it seems to be absent from human intestinal lamina propria resident macrophages.⁴⁰ As these cells also lack CD14,⁴¹ it is tempting to speculate that such adaptations are significant in modifying the responses of resident macrophages to IgA and LPS, which are abundant in the intestinal microenvironment.

The possibility that IgA antibodies, especially mIgA that predominates in humans, could have a role in regulating immune responses deserves to be re-examined. We have postulated that IgA antibodies might suppress immune responses in inflammatory foci, particularly when the threat posed by a pathogen declines after its successful disposal.⁴² These considerations could be relevant to chronic inflammatory diseases, such as inflammatory bowel disease, in which there seems to be a failure of the homeostatic mechanisms that regulate mucosal immune responses. In these conditions, an antigen or pathogen may be the initiating cause of inflammation, even though its identity is unknown. However, breakdown of the homeostatic mechanisms, possibly by microbial intervention, perpetuates the immune response-inflammation cycle that results in chronic tissue damage instead of resolution and repair. In these circumstances, measures designed to enhance the IgA component of the immune response could have an ameliorating effect.

Thus a picture is beginning to emerge of how mIgA contributes to the maintenance of health. Whereas S-IgA exerts antimicrobial defence on the mucosal surfaces, and pIgA may have a similar role within the epithelial cells, circulating mIgA instead seems to act more as a regulator of immunity and of collateral inflammatory damage. In regard to effector mechanisms, IgA antibodies can interfere with complement activation and modulate phagocytic function, and thus perhaps also downregulate ongoing immune responses by modifying the activities of antigen processing cells.⁴² These effects of IgA are counterbalanced by the antimicrobial defence mediated by IgM and IgG antibodies and by phagocytic cells. Two points arise from these considerations: enhancing the development of IgA antibodies may be beneficial in chronic inflammatory diseases; and the pathogenetic mechanisms through which microorganisms interfere with the functions of IgA and create an environment more favourable to their survival at the expense of the host deserve more attention.

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