IgA antibody as a non-inflammatory regulator of immunity
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Introduction
In contrast with IgM and IgG, IgA antibodies are essentially non-inflammatory in their mode of action [1–3], a property that is probably of great importance for the maintenance of the integrity of mucosal surfaces as well as internal tissues. Inflammation is a complex and multifaceted process involving numerous lymphoid cells and immunological effector molecules, as well as cellular and non-cellular factors not normally regarded as part of the immune system, and is the physiological response of the body to damage inflicted by infectious or non-infectious agents. Recent thought has emphasized the role of inflammation in the initiation of the immune response, by inducing the generation of 'second signals' to lymphocytes [4,5], but inflammation is also a consequence of immune effector mechanisms in combating infection, as several products of the defence mechanisms have potent inflammatory effects. Thus inflammation is both beneficial and necessary, but because of its potential for inflicting tissue damage even greater than that caused by the direct action of pathogens, it must be regulated by homeostatic mechanisms. When these fail, inflammatory disease may result and persist. IgA is the most heterogeneous of human immunoglobulins, as it occurs in multiple...
molecular forms (monomeric, polymeric and secretory) and subclasses (1 and 2) which are distributed differently between the circulatory and mucosal immune systems [6]. IgA antibodies may therefore have different functional properties depending on their precise molecular constitution, as well as the circumstances of their action.

**IgA and complement**

The concept that IgA represents a ‘safe’ form of anti-inflammatory antibody [7] is exemplified by the findings that intact native human IgA antibodies fail to activate complement by either major pathway when complexed with antigen [8], and further that they powerfully interfere with complement activation by IgM and IgG antibodies [2,9]. The frequently cited ability of IgA to promote turnover of the alternative complement pathway (ACP) (reviewed in [3]) on close examination turns out to be due to artificial aggregation or conformational alteration of IgA induced by exposure to denaturing agents during purification, heat, deposition on hydrophobic surfaces, chemical cross-linking or modification, or aberrant synthesis. However, there may be pathological (rather than physiological) relevance in this, for example, in IgA nephropathy, where it appears that IgA1 deposited in the glomerular mesangium (where complement is activated) may be defective in the composition of its oligosaccharides particularly the O-linked glycans of the hinge region [10]. In particular, the cleavage of sialic acid, as well as other carbohydrate moieties, from IgA enhances its ability to promote ACP activation [11]. Although carbohydrate residues are important for ACP activation [12], terminal sialic acids inhibit ACP activation [13,14]. To the extent that opsonization of particular antigens by antibodies depends on complement fixation, thereby engaging C3 receptors on phagocytes, interference with complement activation by IgA antibodies also diminishes phagocytosis and the release of reactive oxygen intermediates [15].

**IgA and phagocytes**

However, phagocytes (including monocytes/macrophages, neutrophils and eosinophils) express FcζR, which, at least under certain circumstances, is capable of mediating phagocytosis and transducing signals for oxidative metabolism and granule release [15-20]. FcζR is a heterogeneous receptor that appears to be extensively and variably glycosylated depending in part on the cell type on which it is expressed [21,22], and its intracellular connections with signal-transducing systems are beginning to be elucidated [23]. Although FcζR is constitutively expressed on monococytes, neutrophils and eosinophils, it is up-regulated by certain cytokines. Exposure of neutrophils to tumor necrosis factor α (TNF-α) or interleukin (IL)-8 increases surface expression of FcζR and enhances their ability to respond to IgA-opsonized particles [15,24,25]. Tissue macrophages appear to express FcζR variably, and it is not known what regulates this expression, nor its functional significance [26]. In the case of neutrophils, which in their resting state appear to respond weakly if at all to IgA-complexed antigen, it can be speculated that enhanced expression of FcζR on exposure to inflammatory or chemotactic cytokines has functional significance within mucosal tissues such as the gut. IL-8 and TNF-α released by epithelial cells exposed to aggressive bacteria attract and activate neutrophils to a site of potential pathogenic challenge, and functional up-regulation of their FcζRs enables them to be effective phagocytes in the IgA-rich environment of the submucosa. It will be interesting to determine if such activated neutrophils respond to IgA in the same way, or not, as cells reacting to IgG and C3b, since it is clearly important that, in defending the mucosa against the threat of bacterial invasion, the collateral damage to the mucosa itself be strictly limited, or else the situation may be aggravated.

It is particularly noteworthy that IgA, especially secretory IgA (S-IgA), when coupled to agarose, is the most potent stimulus for eosinophil degranulation [18]. As eosinophils occur frequently in mucosal tissues and are implicated in defence against metazoan parasites, this may be an important effector activity of IgA [27,28]. However, further work is necessary in this area, especially using IgA (and S-IgA) antibodies complexed with antigens to model more closely the physiological situation.

With monocytes, an interesting picture is beginning to emerge. IgA has been shown to suppress the release of inflammatory cytokines (TNF-α and IL-6) by human monocytes exposed to lipopolysaccharide [29]. Furthermore IgA has recently been found to induce the expression and release of IL-1 receptor antagonist [30]. However, as IgA prepared from pooled donor serum was used, it is unclear if this effect was due to
the presence of IgA antibody to the stimulating lipopolysaccharide, or if it is dependent on the molecular form or aggregation of the IgA. It is noteworthy that an IgM monoclonal antibody (My-43) that cross-links FcεR was also capable of exerting these effects. Since circulating monocytes are naturally exposed in vivo to IgA, largely of the monomeric form, it seems likely that complexation, aggregation, or possibly the polymeric form of IgA would be necessary for these effects.

IgA and the regulation of immune response: an hypothesis

The inability of IgA immune complexes to fix C3b (as discussed above) provokes another hypothesis concerning the role of complement in the induction of immune responses. This has received recent attention in several papers describing the role of C3b in antigen processing by B-cells, which possess CD21, the receptor for C3dg (CR2) [31-34]. This receptor forms part of a complex comprising CD19, CD21 and other molecules connected to intracellular signal-transducing kinases [35]. Co-ligation of CR2 with the B-cell antigen receptor (surface immunoglobulin) greatly enhances the response to low concentrations of antigens that otherwise would not stimulate B-cells. In vivo, antigens become associated with C3dg, the ligand for CR2, by activation of complement and the covalent binding of C3b which is subsequently cleaved to C3dg. Such activation can occur through complexation of the antigen with its corresponding antibody of IgM or IgG isotypes, and consequent activation of the classical complement pathway, or possibly through antibody-independent activation of the ACP. As discussed above, IgA antibodies powerfully interfere with classical complement activation by IgG (and also by IgM [36]) and may also suppress activation of the ACP [37]. Thus, in the situation of an ongoing or secondary immune response, i.e. when B-cells become important as antigen-presenting cells and there are already antibodies present of the IgM or IgG isotype, complexation of the antigen with antibody further enhances the immunogenicity of the antigen to the extent that the immune complexes are able to fix complement [38,39] (Figure 1a). According to the present hypothesis, if IgA antibodies are also present, they will suppress C3b fixation by the immune complex and thereby diminish its ability to stimulate B-cells to respond to take up the complex, and present the processed antigen to cognate T-cells (Figure 1b). At one time, it was suggested that IgA immune complexes could be responsible for the development and maintenance of oral tolerance [40], although this was later reinterpreted as being due to other immunoglobulin isotypes, especially IgG1 which in mice, interestingly, is a weak activator of complement [41]. Furthermore,

**Figure 1**

Proposed model for suppression of B-cell signalling by antigen complexed with IgA antibody

In (a), antigen (Ag) is complexed with IgG which activates the classical complement pathway (CCP) resulting in the covalent association of C3b, which is subsequently cleaved to C3dg, with the complex. The B-cell recognizes antigen through its surface immunoglobulin (sig), and co-ligation of CR2 by C3dg enhances the signal transduction, which in turn leads to uptake, processing and presentation of the antigen as peptides associated with MHC class II molecules. In (b), the presence of IgA antibody in the immune complex interferes with the activation of complement so that C3b is not bound, and therefore the CR2 is not ligated. Recognition of the complex only through surface immunoglobulin results in a weak signal, unless antigen is present at much higher concentration.
the rapid clearance of circulating antigen by polymeric IgA by hepatobiliary transport in mice and rats was taken as evidence against a role for IgA in this [42-44].

Nevertheless, the possibility that IgA antibodies, particularly the monomeric form that predominates in humans especially in inflammatory foci, could have a role in regulating ongoing immunity deserves to be re-examined. We postulate that IgA antibodies should suppress immune responses in foci of inflammation, particularly when the threat posed by the presence of foreign antigen is declining after the successful disposal of the pathogen that produced it. Under these circumstances, it might be physiologically desirable to turn down the antibody-producing mechanism when only small amounts of antigen — too small to stimulate B-cells unless complexed with complement-fixing antibody — remain. Such considerations might have relevance with respect to chronic inflammatory diseases, such as periodontal disease, inflammatory bowel disease and possibly rheumatoid arthritis, in which there appears to be a failure of the homeostatic mechanisms that regulate immune responses. In these conditions, an antigen or pathogen may be the initiating cause of inflammation (even though its identity may remain unknown, as in rheumatoid arthritis, or variable and multiple, in the case of periodontal disease in which numerous dental plaque bacteria have been implicated). However, breakdown of the homeostatic mechanisms, possibly by microbial intervention, perpetuates the immune-response—inflammation cycle, which results in chronic connective tissue damage instead of resolution and repair. In these circumstances it could be that measures designed to enhance the IgA component of the immune response would have an ameliorating influence.

Recent clinical data provide tentative support for this, as elevated IgA concentrations in periodontal pocket fluid are associated with a better prognosis for resolution of periodontal disease [45].

Conclusion
Thus a picture is beginning to emerge of how serum IgA antibodies may contribute to the maintenance of health. It has been clear for a long time that, in general, serum IgA has little to do with protection against infection, a role fulfilled manifestly well by IgM and IgG antibodies which recruit the complement system and phagocytosis as potent anti-microbial effector mechanisms. Moreover, circulating IgA, even in its minority polymeric form, is not effectively transported on to mucosal surfaces (except for the remarkable hepatobiliary transport of polymeric IgA in rats, mice and certain other animals, but not in primates). Circulating IgA and S-IgA (the latter being the product of the mucosal immune system) are largely independent of each other, and there is little correlation of antibody levels between the two in humans. Whereas S-IgA exerts an anti-microbial defence function with respect to the mucosal surfaces, circulating IgA, which is predominantly monomeric, instead appears to act mainly as a regulator of immunity and the collateral inflammatory damage associated with it. This occurs at two possible levels: at the effector level, IgA antibodies interfere with complement activation and modulate phagocytic cell activities; at the inductive level, it may be speculated that IgA antibodies can down-regulate ongoing immune responses by modifying the activities of B-cells as secondary antigen-presenting cells. Clearly these activities of IgA will themselves need to be counterbalanced by the opposite tendencies of antimicrobial defence mediated by IgM and IgG antibodies and phagocytic cells, and the persistence of immune responses against aggressive antigens that have not been eliminated. Two consequences arise from such a view of the role of IgA in maintenance of health. Manipulation of immune responses to favour the development of IgA antibodies may have a beneficial effect on chronic inflammatory diseases, in which dysregulated immune responses perpetuate tissue damage. Consideration should be given to potential pathogenic mechanisms in which microorganisms might interfere with the regulatory activities of IgA and create an environment more favourable to their survival at the expense of the host.

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