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The Unexplored Roles of Human Serum IgA

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The roles of human serum IgA, in contrast to that of mucosal IgA, are relatively unexplored. Previous studies have shown that IgA mediates either pro- or anti-inflammatory effects in innate immune cells. Serum IgA has been shown to interact with many proteins and glycoproteins of which the functions and mechanisms are not fully characterized. Here, we present fresh perspectives into the roles of serum IgA, describing novel IgA–protein interactions, the importance of its glycosylation status in normal functions, and the plausible role of IgA as a driver and regulator of autoimmune diseases/immune overactivation. Other potential roles, including the regulation of cytokines, effector cell function, and homeostasis, are considered in view of the maintenance of immune function. We anticipate future research to uncover new anti-inflammatory or pro-inflammatory roles of human serum IgA in immune functions and dysfunctions, with implications on systemic lupus erythematosus (SLE).

Introduction

Humans produce two major forms of IgA, the monomeric serum IgA and the dimeric mucosal secretory IgA. The total amount of IgA produced far exceeds the combined total of all other antibody classes (Kerr, 1990). Monomeric serum IgA is relatively abundant, second to IgG, the most prevalent circulating antibody (Mestecky *et al.*, 1986). Monomeric serum IgA is produced by plasma cells in the bone marrow, marginal zone B cells, and B1 cells. However, the existence of B1 cells in humans remains controversial (Kerr, 1990; Cerutti *et al.*, 2013; Tangye, 2013). In contrast, the dimeric form of IgA is found mainly in secretions lining the mucosal surfaces, for example, in the gastrointestinal tract, the reproductive tracts, the respiratory epithelium, tears, saliva, and colostrum (Mestecky, 2005). Plasma cells present in the lamina propria of the mucosal surfaces produce polymeric IgA (pIgA), which are monomeric IgA antibodies joined together at the Fc region by a polypeptide called the J chain. pIgA then binds the polymeric immunoglobulin receptor (pIgR) present on the basolateral membrane of epithelial cells and is transported across the epithelium and onto the mucosal surfaces. The pIgR is cleaved to release the pIgA bound by a glycoprotein called the secretory component (SC) derived from the pIgR (Pabst, 2012). This form of dimeric IgA is termed the secretory IgA (sIgA). sIgA performs a plethora of functions, including immune exclusion of pathogens, toxins, or commensal bacteria from crossing the epithelial layer; neutralization of intracellular pathogens; antigen secretion; homeostasis of commensals, and downregulation of pro-inflammatory responses (Corthesy, 2013). Hence, sIgA mainly functions to prevent the invasion of pathogenic and commensal bacteria across the mucosal epithelial layer, thus preventing systemic infection while simultaneously maintaining a physiologically indispensable symbiotic relationship with commensal bacteria.

Hitherto, most of the research on IgA has focused on the mucosa. Literature that expound solely on serum IgA pales in comparison to that on mucosal IgA. Serum IgA receives cursory mention in most texts, before the focus shifts onto the more ''important'' roles of sIgA in mucosal immunity. This clearly indicates a lack of conclusive evidence or a consensus on functions of serum IgA. The noninflammatory functions of mucosal IgA probably influenced the perception on serum IgA as a neutralizing antibody with poor complement activating and opsonising ability. Pioneer studies into serum IgA largely agreed with this view. Serum IgA has the ability to downregulate the phagocytic ability of polymorphonuclear leukocytes (PMNs) (Wilton, 1978; Nikolova and Russell, 1995). It downregulates pro-inflammatory cytokines or upregulates anti-inflammatory cytokines released by peripheral blood mononuclear cells (PBMCs) (Wolf *et al.*, 1994, 1996; Olas *et al.*, 2005).

Serum from IgA myeloma patients was shown to inhibit chemotaxis and bactericidal activities of PMNs (Van Epps and Williams, 1976; Van Epps *et al.*, 1978). Subsequent studies revealed that this anti-inflammatory function was due to monomeric binding of serum IgA to the Fc alpha receptor (FcαRI), transmitting inhibitory signals through myeloid cells (e.g., monocytes, macrophages, dendritic cells, Kupffer cells, neutrophils, and eosinophils). However, in these studies, it was also found that crosslinking of the FcαRI resulting from IgA binding to pathogens or immune complex formation transmits activating signals leading to phagocytosis, respiratory burst, antibody-dependent cytotoxicity, increased antigen presentation, degranulation, and cytokine release by

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the abovementioned immune cells (Monteiro, 2010). It was suggested that inhibitory signals occur in the normal physiological state, when IgA titres are lower. During pathogenic infection, IgA binding to its antigen induces crosslinking of FcαRI, which activates immune effector cells to carry out their effector functions (Bakema and van Egmond, 2011). This explains the findings reported by van Egmond *et al.* (2000), where serum IgA-opsonised bacteria enabled clearance of the pathogen and resolution of the infection by liver Kupffer cells.

Other than binding the FcαRI, IgA has also been found to interact with the Fcα/μ receptors, asialoglycoprotein receptors (ASGP-R), transferrin receptors (CD71), SC receptors, and M-cell receptors. These interactions occur through binding of the IgA Fc region, the glycan chains, the J chain, or SC. The functional implications of these interactions (Stockert *et al.*, 1982; Mostov, 1994; Lamkhioued *et al.*, 1995; Shibuya *et al.*, 2000; Moura *et al.*, 2001; Mantis *et al.*, 2002; Bakema and van Egmond, 2011) have yet to be fully understood and warrant further research. Clearly, the view of serum IgA as a quiescent player in immunity is beginning to change and many more potential functions remain to be ascribed to serum IgA. A comprehensive examination of IgA function is beyond the scope of this article. Instead, here we convey novel perspectives on the potential emerging roles of serum IgA.

IgA Interacts with Other Serum Components

The C-terminal cysteine residue of IgA contains a reactive thiol group that allows covalent bonding with other serum proteins. IgA has been shown to bind through this manner to albumin, α1-antitrypsin, HC-protein, and fibronectin (Kerr, 1990). The IgA–α1-antitrypsin complex inhibits leukocyte elastase, while the IgA–HC complex inhibits directed chemotaxis of neutrophils, suggesting that certain serum IgA complexes can play an anti-inflammatory role (Mendez *et al.*, 1986; Dawes *et al.*, 1987). IgA–fibronectin complexes are present in some individuals suffering primary IgA nephropathy (Kerr, 1990). On the other hand, the bacteriostatic activity of secretory IgA (sIgA) in milk and colostrum has been shown to be increased with the presence of iron-carrier proteins, such as lactoferrin and transferrin, with some sIgA and lactoferrin being covalently bound together (Funakoshi *et al.*, 1982; Dolby and Stephens, 1983; Watanabe *et al.*, 1984). Pathogen-specific serum IgA may bind complement components to enhance chemotaxis or phagocytosis of immune cells. Possessing a reactive thiol group is deemed to confer IgA (both serum IgA and sIgA) with the potential to bind serum components, although some of the complexes may not necessarily be covalent in nature. In fact, it is conceivable that noncovalent interactions between serum IgA and other serum proteins could be more functionally meaningful.

Serum IgA Is a Potential Regulator of Immune Complex Formation and Immune Overactivation

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease in which auto-antibodies produced are directed against self-antigens (e.g., nuclear components), causing widespread immune complex deposition in various tissues in the body (Munoz *et al.*, 2005). IgG has been widely reported as the main player in such immune complexes (Kotzin, 1997; Boes *et al.*, 2000). Patients with SLE appear to suffer from chronic infection-inflammation condition (lowered serum pH levels) and altered levels of serum proteins, such as ficolins, and elevated levels of IgG and IgM (Boes *et al.*, 2000; Mathsson *et al.*, 2007). In addition, SLE patients exhibit poor clearance of immune complexes due to deficient serum complement components, such as C1, C2, and C4 (Truedsson *et al.*, 2007).

Persistent immune complexes induce widespread cytokine release by immune cells, causing a chronic inflammatory condition (Mathsson *et al.*, 2007). Such a condition exacerbates immune complex formation, setting up a vicious cycle that drives continuation of the disease state. The cause of SLE is multifactorial, involving genetics and the environment. It is hard to pin down a single factor as the major cause (Munoz *et al.*, 2005). Regardless of the cause of the disease, certain homeostatic factors would have been lost to allow the disease to progress. A recent discovery that IgG binds ficolin-associated bacteria (Panda *et al.*, 2013) motivated us to make a preliminary study of the immune complexes formed in SLE serum—to examine whether the H-ficolin and IgG are the molecular drivers of immune complex formation, and to tease out which regulatory homeostatic factors may be missing. Studying the immune complexes formed would also allow us to gain an insight on whether IgA is part of such immune complexes, and its potential role(s) in interaction with other serum proteins.

Preliminary studies (Leong *et al.*, 2014) on SLE serum, compared with normal healthy control serum, revealed that the pH was consistently lower, and that IgG levels are elevated in the SLE serum, which agree with earlier findings (Boes *et al.*, 2000; Mathsson *et al.*, 2007). On the other hand, the IgA levels appeared to be lower. Immune complexes in SLE were composed of IgG, mannose binding lectin, H-ficolin, and C-reactive protein whereas, in normal human serum, only IgG and H-ficolin were found in complex but were substantially lower than SLE serum. Interestingly, serum IgA was not found to be part of such immune complexes. These observations indicate that although IgA is present, although in relatively lower amounts in SLE serum, it does not participate in immune complexes, or at best probably forms unstable complexes under infection-inflammation conditions. Conceivably, serum IgA could act as one of the regulatory factors downregulated in SLE and its downregulation may contribute to the exacerbation of SLE. This provoked a further *in vitro* analysis of the interaction between IgA and H-ficolin in comparison with the more well-known IgG complex formation (Panda *et al.*, 2013, 2014). Comparison of the binding interaction between IgA–H-ficolin and IgG–H-ficolin (under normal or infection-inflammation conditions) showed that IgA had much higher affinity for H-ficolin under normal conditions (14-fold higher affinity compared with IgG–H-ficolin) but a drastically weaker affinity under infection-inflammation conditions (74-fold weaker affinity compared with IgG–H-ficolin). These preliminary observations suggest a potential reciprocal functional relationship between IgG and IgA, perhaps in competition for ficolin, to regulate immune complex formation.

In consideration of greater affinity of IgA for H-ficolin under normal condition, the native serum IgA plausibly competes against IgG for H-ficolin to pre-empt IgG–ficolin

immune complex formation and thereby maintains homeostasis. Under infection-inflammation conditions, IgA probably relinquishes its binding to H-ficolin (mechanism unknown), giving way to a greatly increased affinity of IgG for H-ficolin, which would result in the formation of IgG–ficolin complexes that facilitate effective opsonisation and phagocytosis of pathogens (Panda *et al.*, 2013).

At this juncture, it is worth considering selective IgA deficiency (sIgAD). Individuals with sIgAD are normally asymptomatic, although they show increased susceptibility to sinopulmonary and gastrointestinal infections. This has been mainly attributed to compensatory increase in other components, such as secretory IgM (IgM joined by the SC), at the mucosal surfaces or the increase in serum antibodies of other isotypes (Pereira *et al.*, 1997; Cunningham-Rundles, 2001; Saghafi *et al.*, 2008). These individuals also show increased susceptibility to autoimmune diseases (e.g., SLE and rheumatoid arthritis) and allergies, such as allergic conjunctivitis, rhinitis, urticarial, atopic eczema, food allergy, and bronchial asthma (Cunningham-Rundles, 2001; Wang *et al.*, 2011). Furthermore, such individuals possess auto-antibodies (30% harbor IgG antibodies directed against IgA), and deficiency in factors mediating class switching for IgA production, such as APRIL and BAFF (Cunningham-Rundles, 2001; Wang *et al.*, 2011). A parallel can thus be drawn with SLE patients who have lowered levels of IgA, which may compromise the regulation of IgG–immune complex formation, contributing to the exacerbation of the disease. This is also seen in sIgAD. IgA is thus a potential regulator of the immune complex formation and its reduced levels plausibly promote immune complex formation among other antibodies. However, the mechanisms in each case need to be fully explored.

Sugar Residues in Serum IgA: Impact on Its Interactions and Functions

Human serum contains two subclasses of IgA, namely, IgA1 and IgA2, with IgA1 being the dominant subclass ($\sim$84% IgA1 compared with $\sim$16% IgA2). The opposite is true at the mucosal surfaces (Conley and Delacroix, 1987). IgA is naturally glycosylated post-translationally. IgA1 bears two conserved N-linked glycan chains at the Fc region, on the CH2 and CH3 tailpiece. IgA2 can be further split into three allotypes: IgA2m(1), IgA2m(2), and IgA2(n). The IgA2m(1) contains two additional N-linked glycan chains at the CH1 and CH2 domains compared with IgA1. The IgA2m(2) and IgA2(n) each possesses one additional N-linked glycan in the CH1 domain in comparison to IgA1 and IgA2m(1) (Mattu *et al.*, 1998; Yarema, 2005). In addition, IgA1 is O-glycosylated at three to five sites at the hinge region. The hinge region is missing in all IgA2 allotypes and they are not O-glycosylated. The number and composition of glycan chains at the Fc region or hinge region can show considerable heterogeneity within individuals, as was demonstrated in myeloma patients (Pierce-Cretel *et al.*, 1981, 1989; Mestecky, 2005). The dichotomy of the predominance of the glycosylated forms of IgA1 and IgA2 isotypes in the serum and at the mucosal surfaces is an unsolved enigma worthy of further investigation. Thus far, evidence from studies suggests that (1) O-linked glycans present on IgA1 are required for uptake and catabolism by hepatocytes expressing the ASGP-R and (2) lack of a hinge region in IgA2 confers protection from antibody-cleaving proteases secreted by bacteria at the mucosal surface (Senior *et al.*, 2000; Mestecky, 2005).

Glycan chains on IgA have been reported to be important for interactions between IgA and pathogen or IgA and protein/glycoproteins. For example, removal of carbohydrate chains decorating sIgA or from the free SC resulted in its reduced ability to coat commensal bacteria (Mathias and Corthesy, 2011). Panda *et al.* (2014) showed that the immune complex between IgG and H-ficolin, which directs the pathogen for phagocytosis, was delineated to the glycosylated CH2–CH3 region of natural IgG Fc and the P-subdomain of ficolin FBG domain. IgA is the most heavily glycosylated isotype of antibodies (IgA1 possesses O-linked glycans at the hinge region and N-linked glycans at the CH2 and CH3 domains), and since H-ficolin is a lectin, it is conceivable that perhaps the glycan chains of IgA would contribute to the IgA–H-ficolin interaction. Indeed, enzymatic removal of the N-linked glycan chains completely abrogated IgA–H-ficolin interaction, and partial removal of glycan chains weakened the IgA–H-ficolin binding affinity (Leong *et al.*, 2014), which suggests that (1) the glycan chains of IgA are important for IgA and H-ficolin interaction, (2) the length of the carbohydrate chains determines the strength of binding to partner proteins, and (3) specific sugar residues are important for binding. However, the exact mechanism of such an interaction has not been characterized and it would be worth exploring.

It follows that glycan chains of IgA may be important for its interaction with other proteins, and thus, for carrying out its normal functions. The importance of its glycosylation is demonstrated most strikingly in the two immune complex diseases, IgA nephropathy and Henoch–Schönlein purpura. In these diseases, IgA is reportedly the major cause of immune complex formation. IgA nephropathy is caused by immune complexes involving IgA depositing in the kidney glomeruli (Wyatt and Julian, 2013). Henoch–Schönlein purpura is caused by immune complexes involving IgA depositing in small blood vessels (Roberts *et al.*, 2007). Patients suffering from such diseases have elevated levels of IgA and, importantly, exhibit aberrant glycosylation of IgA at the O-linked region. Apparently, inappropriate glycosylation of IgA causes conformational changes, leading to increased immune complex formation. Thus, such aberrantly glycosylated IgA antibodies are not only unable to carry out their normal functions but they become drivers of immune complex diseases.

IgG has been shown to be aberrantly glycosylated in SLE patients (Tomana *et al.*, 1992). However, thus far, there is no report on the glycosylation status of IgA in SLE patients, which warrants the need to study the glycosylation status of antibodies in SLE serum, in particular, IgA. Validating that SLE serum IgA is ''properly'' glycosylated would lend support to the observation that the low propensity of IgA to form immune complexes in SLE patients is attributable to (1) lowered pH due to chronic inflammatory conditions and/or (2) appropriate IgA glycosylation patterns. In such patients, it could be possible that only IgG shows inappropriate glycosylation, adding to the severity of the disease. In contrast, given the differences in antibody isotype trafficking, IgA could still be properly glycosylated. As mentioned before, in diseases like IgA nephropathy and Henoch–Schönlein

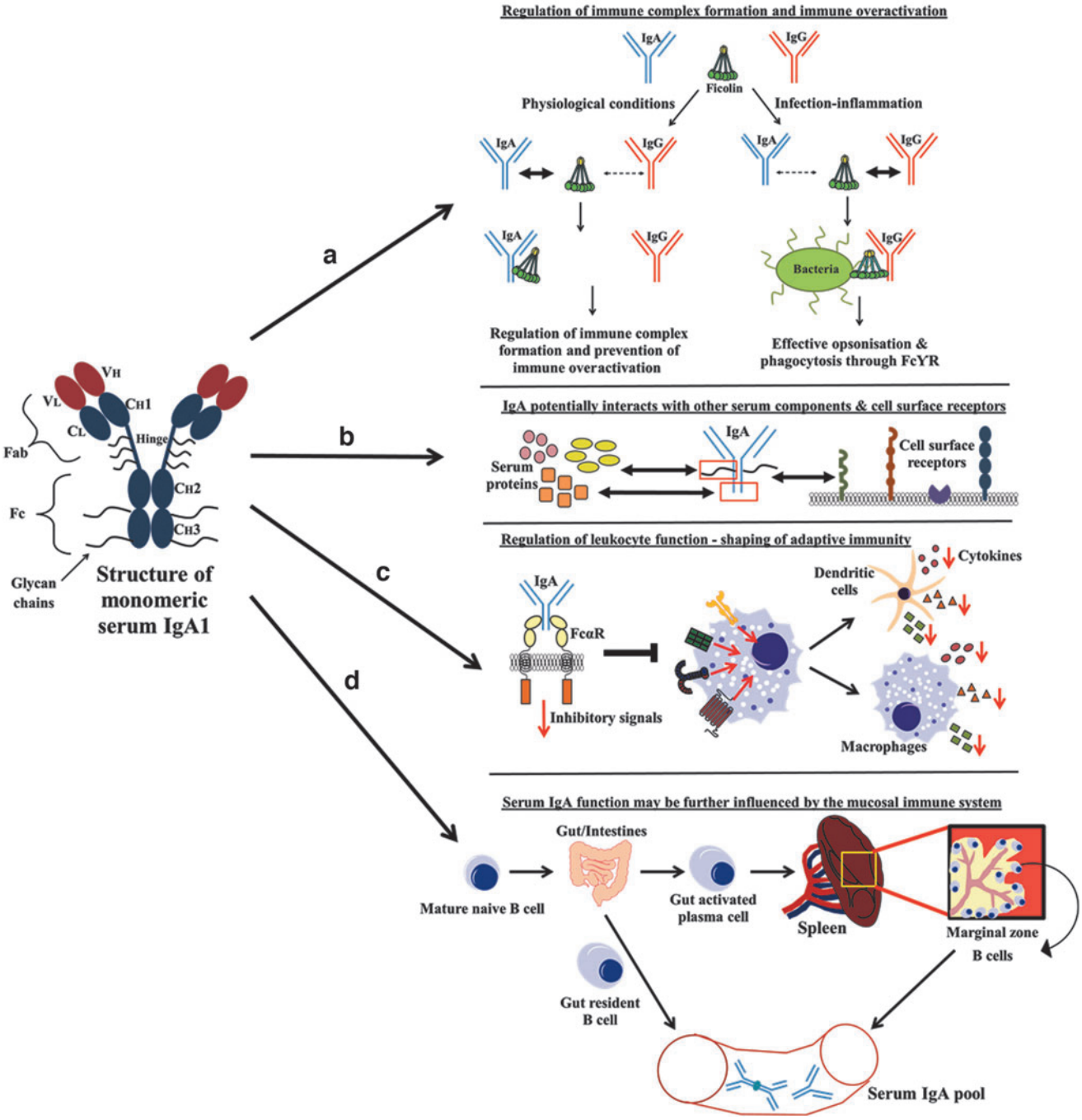

FIG. 1. Roles of serum IgA. Structure of monomeric serum IgA1 is shown on the *left*. **(a)** Role of serum IgA in regulating immune complex formation and immune overactivation (Panda *et al.*, 2013). **(b)** Serum IgA associates with serum proteins and cell surface receptors (through glycan chains present on various regions of the antibody) to effect various functions (Kerr, 1990). **(c)** Monovalent binding of FcαRI by monomeric serum IgA Fab transduces inhibitory signals that extend to other receptors, such as FcγR, FcεRI, TLR4, CCR2, and TNFR, and affects the activation threshold of innate immune cells. Local concentrations of serum IgA in various tissues thus affect the cytokines released by innate immune cells and play a role in the shaping of the adaptive immunity (Dewey, 1959; Fearon and Locksley, 1996; Kanamaru *et al.*, 2008; Pasquier *et al.*, 2005). **(d)** Mature naive B cells that are activated in the gut may home into the marginal zone of the spleen, contributing IgA antibodies that are specific for gut pathogens/commensal antigens to the serum IgA pool. Gut-resident B cells further contribute to the serum IgA pool in the form dimeric IgA (Vossenkamper *et al.*, 2013; Mestecky *et al.*, 1999). Figure is not drawn to scale.

purpura, inappropriate glycosylation of IgA, which causes conformational deviation, is the cause of IgA immune complex formation. Taken together, all sources of evidence seem to indicate that inappropriate glycosylation of IgA is sufficient for immune complex formation involving IgA. We hasten to add that elevated levels of IgA do not drive IgA immune complex formation (Mestecky and Tomana, 1997; Mestecky *et al.*, 2002).

Serum IgA Function May Be Further Influenced by the Mucosal Immune System

A proportion of serum IgA is derived from marginal zone B cells. Recent evidence suggests that naive B cells activated in the gut-associated lymphoid tissue may home in to the marginal zone of the spleen (Vossenkamper *et al.*, 2013). Therefore IgA, specific for commensal or pathogenic bacteria, produced by plasma cells in the marginal zone may be secreted into the bloodstream. These IgA antibodies may be playing the role of ''standby'' or ''backup'' antibodies to guard against systemic infection due to invasion across the mucosal epithelium. It has been shown that B-cells can be activated in a T-cell-independent manner; B cells respond to antigens, such as lipopolysaccharide and polysaccharides, of bacteria (Craxton *et al.*, 2003). The response of marginal zone B cells derived from the gut when they encounter such antigens and the impact on serum IgA levels is an area that remains unexplored. Showing that these cells do respond to gut microbiota would further affirm that marginal zone B cells can indeed be derived from the gut.

Humans are not equipped with the hepatobiliary transport system for secretion of sIgA into the bile and into the gut due to the lack of pIgR expression on hepatocytes, unlike in mice, chickens, and rabbits (Mestecky *et al.*, 1999). This further increases the amount of IgA in systemic circulation that is derived from the gut, which may explain the presence of up to 20% of serum IgA as dimers, trimers, or tetramers (Mestecky, 2005). The ASGP-R expressed by hepatocytes has been shown to be efficient in the uptake of both monomeric and polymeric forms of IgA (Tomana *et al.*, 1985). Whether or not a pathogen-specific pIgA is part of a system that involves clearance by the ASGP-R on hepatocytes has yet to be explored. Any additional physiological roles of these polymeric forms of IgA merit further investigation. Revelation of the two abovementioned scenarios would add to the understanding of the complexity of the relationship between the mucosal and systemic immune systems. Previous studies have shown that exposure to commensal or food antigens at mucosal surfaces is able to suppress or enhance systemic antibody responses and affects immune cell activation (with suppression being predominant); the response is dependent on factors such as species, genetics, age, dosage, and the physical form of the antigen (Mestecky *et al.*, 2005).

Serum-IgA-Mediated Regulation of Leukocyte Function: Shaping of Adaptive Immunity

Pasquier *et al.* (2005) showed that monovalent binding of FcαRI by monomeric IgA or anti-FcαRI Fab transduced inhibitory signals while crosslinking of FcαRI induced degranulation by human PBMCs. Local concentrations of plasma proteins have been shown to vary in different tissues in rats (Dewey, 1959). As such, local concentrations of IgA in various tissues are likely to be different and dependent on many physiological factors. How this affects the functions of immune cells in the tissue microenvironment before and during a pathogen challenge and the influence of the adaptive immune response is an interesting proposition. The key players being affected in shaping of the adaptive immune response to pathogens are the dendritic cells and macrophages, and the combinations of cytokines released by these cells determine the type of adaptive immune response (Fearon and Locksley, 1996). To illustrate, interleukin 12 released by dendritic cells and macrophages is important for directing the activation of naive CD4 T cells toward the T_h1 helper T cell subtype instead of the T_h2 subtype (Hsieh *et al.*, 1993).

The mechanisms of FcαRI-mediated inhibitory effects are unclear and are just beginning to be elucidated; it has been postulated that the degree and stability of oligomerization determines the duration or extent of activating or inactivating signals (Blank *et al.*, 2009). The inhibitory effects extend to other receptors, such as FcγR, FcεRI, TLR4, CCR2, and TNFR (Pasquier *et al.*, 2005; Kanamaru *et al.*, 2008). As such, whether or not changing levels of serum IgA affect the activation threshold of innate immune cells and the sensing of pathogens is an area worth exploring. The sensing of pathogens through innate pathogen-sensing receptors, such as Toll-like receptors (TLRs), induces combinations of cytokines by immune cells. Therefore, serum IgA, through its ability to inhibit other receptors, clearly has a role in the perturbation of the cytokine network crucial in shaping immune responses. But how the network is altered remains unanswered. The knowledge gained from further investigations on serum IgA and its cognate receptors would be vital if intravenous IgA were to be considered as an anti-inflammatory agent (Monteiro, 2010).

Perspectives

Humoral responses to primary and secondary pathogenic challenge are mainly geared toward the production of high-affinity IgG antibodies that efficiently resolves an infection (Cruse and Lewis, 2010). Nevertheless, it is conceivable that the immune system has evolved to attribute different functions to the various antibody isotypes. The frequency of antigen-specific IgA is low, and IgA performs its roles at the mucosal surfaces and serum mainly as an anti-inflammatory antibody that maintains homeostasis under normal conditions (Kerr, 1990). Under infection-inflammation conditions, serum IgA has the potential to strengthen an immune response and aid the resolution of an infection.

The revelation of IgG effector function and its potency in warding off infection has probably added to the mystery of serum IgA function. Now, with new discoveries being made, IgA should no longer be regarded as the ''silent housekeeper,'' but as a vital cog in the clockwork of the immune system. Figure 1 illustrates the roles of human serum IgA.

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The authors declare no competing financial interests exist.

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