6
Biological Functions of IgA

Michael W. Russell[1]

6.1. Introduction: The Enigma of IgA

Immunoglobulin A (IgA) is the most enigmatic of immunoglobulins. It is by far the most abundant of human Igs, being present in the blood plasma at concentrations approximating 2–3mg/mL, as well as the dominant isotype in most secretions where its output amounts to some 5–8g/day in adults. Furthermore, its evolutionary origins appear to precede the synapsid–diapsid divergence in tetrapod phylogeny (>300 million years ago) because it is present in both mammals and birds and therefore possibly also in reptiles (reviewed in

[1] Department of Microbiology and Immunology, University at Buffalo, Buffalo, NY 14214, USA.

Peppard et al., 2005); an IgA-like molecule has now been identified in a lizard (Deza et al., 2007). Yet IgA remains inadequately understood, at least with respect to its biological functions. In part this reflects its molecular heterogeneity (Russell et al., 1992) as well as its occurrence in two distinct physiological compartments: the systemic circulation and the mucosal secretions. As detailed in Chapter 1 of this volume, IgA in humans and the anthropoid apes occurs in two subclasses (IgA1 and IgA2) as well as in monomeric, polymeric (dimeric and higher), and secretory forms. Secretory IgA (SIgA) predominates in mucosal secretions, where its activities in the protection of these surfaces against colonization and invasion by pathogens and against injurious toxins are relatively well understood. However, the functions of circulating "serum" IgA remain poorly understood. Despite the metabolic cost involved in synthesizing IgA, which implies that there should be a significant physiological benefit derived from producing it, IgA is also the most readily dispensable isotype, as revealed by IgA deficiency. This is the most common form of primary immunodeficiency occurring in up to 1:400 individuals of Caucasian origin (although less frequently in other populations); yet, affected individuals are usually not severely immunocompromized (Chapter 13). Consideration of all these facts reveals that much about IgA remains perplexing.

Nevertheless, specific IgA antibodies, particularly in mucosal secretions, have been documented to provide significant protection against a variety of toxins, viruses, bacteria, and protozoa in both humans and experimental animal models (Tables 6.1 and 6.2) (reviewed in Russell and Kilian, 2005) (see Chapters 7 and 8). Conventional concepts of SIgA neutralizing toxins and enzymes, inhibiting the adherence of microorganisms to mucosal surfaces, and facilitating their clearance in the mucus layer remain essentially valid. SIgA is well adapted to mucosal protection, because its abundant carbohydrate chains render it hydrophilic and negatively charged. In addition, the secretory component (SC) of SIgA has been shown to protect it from proteolysis (Crottet and Corthésy, 1998), thereby prolonging its survival within enzymatically hostile environments such as the intestinal tract. This is consistent with models showing SC folded around the juxtaposed Fc domains of two IgA monomers that are held together partly by the J-chain polypeptide (Royle et al., 2003), based on computerized predictions derived from other Ig structures and solution studies (Chapter 1). However, a crystallographic model of SIgA, or even of its Fc_2.J.SC segment, is not yet available to confirm this.

6.2. Biological Properties of IgA

6.2.1. Heterogeneity of IgA in Relation to Function

In considering the biological functions of IgA, one should keep in mind that IgA is the most heterogeneous of immunoglobulins, occurring in several molecular forms, subclasses, allotypes, and probably glycoforms, although

Table 6.1. Selected examples demonstrating the role of IgA antibody in protective immunity *in vivo*.

Tract	Pathogen	Finding	Ref.
Respiratory	Influenza virus	IgA > IgG protects mice	Renegar and Small (1991)
	Influenza virus	Increased susceptibility in immunized IgA-KO mice	Arulanandam et al. (2001)
	S. pyogenes	SIgA > IgG protects mice	Bessen and Fischetti (1988)
	S. pneumoniae	Human IgA2 > IgA1 protects mice against lethal infection	Janoff et al. (2002)
	Shigella flexneri	SIgA > IgA protects mice	Phalipon et al. (1995, 2002)
Intestinal	Reovirus	IgA mAb protects mice against peroral infection	Kraehenbuhl & Neutra (1992)
	Rotavirus	Reduced protection in orally immunized J-chain–KO mice	Schwartz-Cornil et al. (2002)
	Vibrio cholerae *S. typhimurium*	pIgA protects mice against oral challenge (backpack tumor models)	Winner et al. (1991) Michetti et al. (1992)
	E. coli	Increased frequency of *E. coli* strains in IgA-deficient humans	Friman et al., 2002
	Cholera toxin	Reduced protection in orally immunized J chain-KO mice	Lycke et al. (1999)
	Giardia	IgA protects mice	Langford et al. (2002)
	Cryptosporidium	pIgA protects neonatal mice	Enriquez and Riggs (1998)
Genital	*Chlamydia*	IgA mAb protects mice	Pal et al. (1997)
Ocular	*Acanthamoeba*	pIgA protects hamsters	Leher et al. (1999)

Table 6.2. Selected examples of IgA antibody-dependent protective activities *in vitro*.

Pathogen	Finding	Ref.
Influenza virus	pIgA/SIgA > mIgA inhibit hemagglutination inhibition	Renegar et al. (1998)
Sendai and Measles virus	pIgA mAbs inhibit infection in polarized pIgR-expressing cells	Mazanec et al. (1992); Yan et al. (2002)
S. pneumoniae	IgA opsonizes (human PMN)	Janoff et al. (1999), van der Pol et al. (2000)
Neisseria meningitidis	p/mIgA opsonizes (human PMN)	Vidarsson et al. (2001)
Streptococcus mutans	SIgA > mIgA = IgG inhibits adherence to saliva-coated hydroxyapatite	Hajishengallis et al. (1992)
Salmonella enterica	IgA inhibits adhesion/invasion of polarized Hep-2 cells	Iankov et al. (2002)
Clostridium difficile toxin	pIgA > mIgA = IgG neutralizes	Stubbe et al. (2000)
Shigella flexneri LPS	pIgA inhibits NF-κB activation in polarized mouse epithelial cells	Fernandez et al. (2003)

the latter have been little explored. These patterns of heterogeneity also differ between species, implying that its functions might differ in subtle ways also. Most notably, humans along with our close relatives, the great apes, have evolved a novel subclass, IgA1, which has an extended proline-rich and O-glycosylated hinge region (Chapter 1). IgA1 circulates in human blood plasma at a relatively high concentration (2–3mg/mL) and in predominantly monomeric form. In contrast, most other eutherian mammals that have been investigated possess only one IgA isotype that is structurally more akin to IgA2 and that is predominantly dimeric and circulates at concentrations around 0.2 mg/mL, similar to the concentration of human IgA2. Quite what the physiological significance of this difference between humans and other mammals represents is uncertain, but the implication is that the "extra" abundance of monomeric (m) IgA1 fulfills an additional function that remains largely unknown. Steady-state concentrations of Igs in plasma, however, give a misleading impression, because they do not take into account the half-lives of the different isotypes. Whereas IgG has an average circulating half-life of ~21 days, that of IgA1 is 5.9 days and that of IgA2 is 4.5 days (Morell et al., 1973). These authors estimated the synthetic rate of plasma IgA1 as 24 mg/kg/day and that of IgA2 as 4.3 mg/kg/day, whereas for IgG it was ~30 mg/kg/day. Given that IgG consists of four subclasses, it is therefore probable that IgA1 is the most abundantly produced circulating Ig isotype in humans!

Antibody specificities for proteins and polysaccharides have been reported to be differently distributed between the subclasses, such that antibodies to carbohydrates are often preferentially expressed as IgA2; however, the distinction is not absolute (Mestecky and Russell, 1986). Otherwise, few clear functional differences have emerged, as both isotypes bind SC and are represented in SIgA and both bind the IgA Fc receptor on myeloid cells equally. A major difference is that IgA1, but not IgA2, is susceptible to cleavage by bacterial IgA1 proteases (see Sect. 6.2.4), but as these enzymes thereby disrupt its structure and function, the advantage of possessing IgA1 is difficult to grasp and it seems more likely that pathogens have exploited this weakness in human IgA1.

Further heterogeneity arises from the existence of at least two, possibly three (or more), allotypes of human IgA2, which appear to represent constant region domain-swap variants between IgA1 and IgA2 (Chintalacharuvu et al., 1994). Different glycoforms arise from the differential occurrence of N-glycosylation sites between subclasses and allotypes, as well as the presence of O-linked glycans in the hinge region of IgA1 (Mattu et al., 1998). In addition, structural analysis of the N-linked glycans in myeloma proteins has revealed considerable sequence variation, which might also occur in normal IgA (Endo et al., 1994). Because glycans can interact with lectinlike receptors and modulate interactions with Fc receptors and complement components, it is likely that subtle variations in glycosylation affect the functional properties of IgA in ways that have yet to be examined in detail. A particular example, however, is that defective glycosylation of IgA1 might be responsible for IgA nephropathy (Chapter 13).

Some other mammals also possess multiple IgA subclasses. The Lagomorphs (rabbits and their allies) have genes for 13 IgA subclasses, most of which are

expressed, although not equally, but their physiological significance remains a mystery (Knight and Rhee, 2005). Limited genetic data also suggest the presence of multiple IgA subclasses in the monotremes and marsupials (Peppard et al., 2005).

Although in humans polymeric (p) IgA constitutes only about 5–10% of total plasma IgA, several studies have shown that the initial serum IgA component of a systemic immune response is pIgA, followed by mIgA (reviewed in Russell et al., 1992). As discussed in Section 6.2.3.2, pIgA is better able to cross-link Fcα receptors on phagocytes and might therefore be advantageous in protection against infection. Otherwise, the functional significance of this, and the maturation of the response toward mIgA, is uncertain. Other studies have revealed that individual IgA-secreting cells first produce pIgA and later mIgA (Moldoveanu et al., 1984). The long-term production of circulating IgA is probably due to plasma cells in bone marrow, which mainly secrete mIgA1 (Hijmans, 1987).

6.2.2. Functions of SIgA at Mucosal Surfaces

6.2.2.1. Inhibition of Adherence

Just as it has become clear that colonizing microorganisms, whether pathogenic or commensal, must adhere to host tissue surfaces, so also has it been recognized that an important function of antibody-mediated defense of the mucosae is the inhibition of microbial adherence. It can readily be envisaged that any isotype of antibody having specificity for microbial adherence epitopes would inhibit their interactions with host receptors. However, SIgA is particularly well suited to this role because of its extensive glycosylation (accounting for 20% by weight), which confers hydrophilicity and negative charge on the molecule. SC, which contains 22% carbohydrate, contributes much of this property to SIgA. The macromolecular bulk of SIgA (400 kDa for dimeric forms) might also be important. Comparative studies of IgG, serum mIgA or pIgA, and SIgA antibodies of the same specificity for antigen have revealed the superiority of the latter in inhibiting adherence of different organisms to host surfaces (Hajishengallis et al., 1992; Phalipon et al., 2002) (see Chapter 8). Even if SIgA antibodies are not specific for adhesin antigens or epitopes, covering the surface of a microbe with a hydrophilic shell might be able to repel attachment of microbes to the surface. Agglutination of microbes is facilitated by the multiple valency (4 in the case of dimers) of SIgA, and this might promote their removal in the mucus stream.

The carbohydrate residues on SIgA might also enable it to inhibit adherence of microorganisms independently of its antibody activity, by binding to carbohydrate-specific adhesins on bacteria. For example, certain strains of *Escherichia coli* possessing mannose-specific type 1 pili can be agglutinated especially by IgA2, which carries mannose-rich glycans, and, as a result, inhibited from adherence to epithelial cells (Wold et al., 1990). In some cases it might be necessary for sialic acid or other terminal residues to be removed to

expose the interactive sugar residues (Royle et al., 2003). However, the extent to which these interactions function *in vivo* to inhibit adherence, or conversely to promote it depending on the size of aggregates formed, has been debated (Friman et al., 1996; Liljemark et al., 1979). An interesting if controversial example is represented by *Streptococcus pneumoniae*, which has been proposed to exploit its ability to bind SC to enhance epithelial cell invasion by inducing retrograde reuptake of SC (Brock et al., 2002; Zhang et al., 2000).

6.2.2.2. Interaction with Mucus

An old concept for the biological function of SIgA at mucosal surfaces is that SIgA is arrayed on the surface of the mucus layer to form a kind of immunological "flypaper," allowing entrapped microbes to be swept along with the mucus flow. As appealing as this idea might be, supporting experimental evidence is only tentative. Interactions of SIgA with mucins, possibly involving the mucinlike hinge region of IgA1, or even the formation of disulfide bonds have been proposed (Clamp, 1977), but other more recent studies indicate that SIgA diffuses freely through mucus (Saltzman et al., 1994). Coating of microorganisms with SIgA antibodies reduces their hydrophobicity and facilitates their entrapment in mucus (Edebo et al., 1985; Magnusson and Stjernström, 1982; Phalipon et al., 1995). SIgA is associated with high-molecular-weight fractions of saliva that also contain mucins, and binding of SIgA to mucin MG2 has been described (Biesbrock et al., 1991). Interestingly, when spermatozoa are coated with SIgA, their ability to penetrate cervical mucus is impaired, but treatment with IgA1 protease to remove the Fc and SC regions restores this ability (Bronson et al., 1987). It is likely that cross-linked complexes formed by polyvalent SIgA interfere with sperm mobility, but this is alleviated when IgA1 protease cleaves SIgA1 to monovalent Fab fragments.

6.2.2.3. Neutralization of Toxins, Enzymes, and Viruses

Numerous examples of enzyme and toxin neutralization by SIgA antibodies have been described, including cholera and other enterotoxins (Johnson et al., 1995; Lycke et al., 1987; Stubbe et al., 2000), bacterial neuraminidase, hyaluronidase, or chondroitin sulfatase (Fukui et al., 1973), the glycosyltransferases of *Streptococcus mutans* and *Streptococcus sobrinus*, which are involved in dental caries development (Smith et al., 1985), and bacterial IgA1 proteases (Reinholdt and Kilian, 1995). In some instances, it has been demonstrated that pIgA antibodies, or divalent $F(ab')_2$ fragments of IgA, are more effective than equivalent mIgA or IgG antibodies (Johnson et al., 1995; Norrby-Teglund et al., 2000). This implies that neutralization involves more than simply the blockade of substrate binding or induction of a conformational change that affects enzyme or toxic activity, because this would be independent of isotype, the presence of the Fc region, or molecular conformation. In contrast, the monovalent Fab fragments of IgA1 antibodies to bacterial IgA1 proteases retain inhibitory activity (Gilbert et al., 1983).

Secretory IgA antibodies have been well documented to neutralize a wide variety of viruses. Although in many instances this might be due to inhibition of the binding and uptake of virus by cell receptors, viral replication can be inhibited in various ways, including inhibition of viral uncoating and other intracellular replicative processes depending on the epitope specificity, isotype, and concentration of antibody and the virus and cells involved (Armstrong and Dimmock, 1992; Castilla et al., 1997; Liew et al., 1984). Again, pIgA and SIgA antibodies might be more effective than mIgA—for example, in inhibition of hemagglutination by influenza virus (Renegar et al., 1998). However, pIgA antibodies to gp340 that neutralize the infectivity of Epstein-Barr virus (EBV) for B-cells (via complement receptor CR2) promote infection of colonic carcinoma cells via pIgR, at least in unpolarized cells *in vitro* (Sixbey and Yao, 1992). On the other hand, polarized epithelial cells transport pIgA-complexed EBV from the basal to the apical surface without becoming infected by the virus, both *in vitro* and *in vivo* (Gan et al., 1997). Likewise, IgA antibodies to gp120 might neutralize human immunodeficiency virus (HIV) infection of T-cells (Burnett et al., 1994), whereas IgA antibodies enhance HIV infection of FcαR-expressing monocytes (Janoff et al., 1995; Kozlowski et al., 1995). SIgA or plasma IgA from HIV-1-exposed but uninfected individuals is especially effective in inhibiting the uptake and transcytosis of HIV-1 in epithelial cells (Devito et al., 2000). SIgA antibodies to the ELDKWA epitope of gp41 have been shown to prevent epithelial cell uptake of HIV-1 (Alfsen et al., 2001; Matoba et al., 2004). pIgA antibodies to gp41 can reexport virus to the apical surface of pIgR-expressing epithelial cells (Bomsel et al., 1998), in a process resembling the removal of absorbed antigens (Kaetzel et al., 1991) (see Chapter 7). Furthermore, it is possible for viruses to be neutralized within epithelial cells by pIgA antibodies during their pIgR-mediated transcytosis (Mazanec et al., 1992). For this to occur, vesicles containing replicating virus must interact with the vesicles that carry pIgA across the epithelial cells, and evidence of this has been obtained both *in vitro* and *in vivo* (Feng et al., 2002; Huang et al., 1997; Mazanec et al., 1995; Ruggeri et al., 1998; Yan et al., 2002) (see Chapter 7). In a similar way, the ability of *Shigella* lipopolysaccharide (LPS) to activate nuclear factor (NF-κB) within epithelial cells can be inhibited by pIgA antibody during its pIgR-mediated transcellular transport (Fernandez et al., 2003). The extent to which these mechanisms operate under natural conditions will depend on the presence of IgA antibody-secreting cells of appropriate specificity in the lamina propria adjacent to the site of the viral invasion or LPS uptake. Moreover, as pIgA is transported largely through cells in intestinal crypts, it might not encounter viruses or LPS entering through M-cells or the villi.

6.2.2.4. Inhibition of Antigen Penetration

Uptake of food antigens in the intestine can be inhibited by SIgA antibodies previously developed in response to them (Walker et al., 1972). It has been proposed that this mechanism can be exploited to inhibit the absorption of

environmental toxins or carcinogens (Silbart and Keren, 1989). Likewise, absorption of antigen from the airway is inhibited by the simultaneous administration of IgA antibody (Stokes *et al*., 1975). IgA-deficient subjects show increased absorption of food antigens and formation of circulating immune complexes (Cunningham-Rundles et al., 1981), which might predispose them to greater environmental antigenic challenge as well as increased susceptibility to atopic allergies or autoimmune disease (Stokes et al., 1974). However, more recent studies have shown that allergic patients have increased levels of not only allergen-specific IgE antibodies but also IgA, including SIgA, and IgG antibodies, which are not normally detectable in healthy individuals (Benson et al., 2003; Peebles et al., 2001; Reed et al., 1991). It has been proposed that cleavage of potentially protective IgA1 antibodies by bacterial IgA1 proteases might contribute to this finding (Kilian et al., 1995).

The mechanisms responsible for immune exclusion by SIgA are probably similar to those described earlier, including hydrophilicity, agglutination, and mucus entrapment. It is also possible that the pIgR-mediated transport of pIgA by enterocytes serves to reexport absorbed antigens that become complexed with pIgA antibody in the lamina propria (see Chapter 7). A similar process has been described for the hepatobiliary transport and elimination of antigens complexed to pIgA antibodies (see Sect. 6.2.3.3).

In contrast to the above, it has been proposed that SIgA antibodies can facilitate the uptake of reovirus through the M-cells of Peyer's patches and thereby enhance the mucosal immune response to it (Weltzin et al., 1989) (see Chapter 9). This, however, is difficult to reconcile with another report that describes inhibition of reovirus infection of M-cells by SIgA antibodies (Silvey et al., 2001). Lectinlike IgA receptors on murine M-cells, distinct from pIgR or the asialoglycoprotein receptor, might be responsible, and selective binding of human IgA2 was described (Mantis et al., 2002).

6.2.2.5. Interaction with Innate Defense Factors

Most mucosal secretions contain numerous innate defense factors that are highly effective in killing or inhibiting a broad range of microorganisms (Russell et al., 2005), offering ample opportunity for synergism with SIgA antibodies. Although it has been speculated that SIgA antibodies might target these factors to specific microbes, there is scant molecular evidence for such interactions. The classic example of a SIgA antibody interacting with complement and lysozyme to lyse *E. coli* (Adinolfi et al., 1966) unfortunately proved difficult to reproduce, and it is now thought that undetected contaminants were responsible for the observed effect. The bacteriostatic synergy of lactoferrin and SIgA antibodies (Stephens et al., 1980; Funakoshi et al., 1982) is possibly due to antibody-mediated inhibition of alternative mechanisms of iron acquisition; covalent complexes between lactoferrin and SIgA have been reported (Watanabe et al., 1984). Myeloma IgA1 and IgA2 proteins enhance the ability of lactoperoxidase-H_2O_2-SCN^- to inhibit *S. mutans* metabolism, but this was attributed to

stabilization of enzyme activity (Tenovuo et al., 1982). The interaction of SIgA with human secretory leukocyte protease inhibitor has been postulated to have a role in intrauterine defense (Hirano et al., 1999).

6.2.3. Functions of IgA Within the Tissues and Circulation

6.2.3.1. Interactions of IgA with the Complement System

The question of whether IgA activates complement has generated some controversy (reviewed in Russell and Kilian, 2005). It is accepted that IgA does not activate the classical complement pathway (CCP), as IgA molecules do not contain a C1q-binding motif. Statements commonly found in many texts that IgA activates the alternative complement pathway (ACP), however, should be examined by reference to the primary literature and careful consideration of the conditions under which the experiments were performed. Numerous reports describe activation of the ACP by heat-aggregated, chemically cross-linked, or denatured human serum IgA, colostral SIgA, or myeloma proteins or by artificial recombinant IgA antibody constructs produced in transfected cell lines and complexed to haptenated antigen (Boackle et al., 1974; Götze and Müller-Eberhard, 1971; Hiemstra et al., 1988; Valim and Lachmann, 1991). In contrast, human monoclonal and polyclonal IgA antibodies physiologically complexed with antigen do not activate the ACP (Colten and Bienenstock, 1974; Imai et al., 1988; Römer et al., 1980; Russell and Mansa, 1989). However, the same IgA antibodies might activate the ACP when bound to a hydrophobic surface, chemically cross-linked or deglycosylated (Nikolova et al., 1994a; Russell and Mansa, 1989; Zhang and Lachmann, 1994). Interestingly, ACP activation by aggregated IgA depends on the Fc (or Fc.SC) region instead of Fab, which is responsible for ACP activation by IgG (Nikolova et al., 1994a). In heat-aggregated mixtures of human IgG and IgA, C3b fixation by the ACP depends on the proportion of IgG, and C3b becomes covalently coupled to the IgG component (Waldo and Cochran, 1989). Mouse, rat, or rabbit IgA antihapten antibodies complexed with haptenated proteins activate the ACP (Pfaffenbach et al., 1982; Rits et al., 1988; Schneiderman et al., 1990). However, comparison of mouse monoclonal antibodies of different isotypes in studies of complement-mediated solubilization of immune complexes showed that whereas IgM and IgG complexes fix C4 and C3, IgA complexes do not (Stewart et al., 1990). Several factors might contribute to all of these conflicting results. IgA purified by procedures involving exposure to denaturing conditions might be conformationally altered. Recombinant IgA proteins produced in hybridoma or transfectoma cells are often abnormally or incompletely glycosylated. Moreover, heavily haptenated proteins themselves can activate the ACP. Nevertheless, it remains possible that differences in amino acid sequence as well as glycosylation between human and animal IgA result in subtle but important functional differences, including their ability to activate the ACP.

Numerous studies have shown that IgA antibodies can effectively interfere with complement activation mediated by other antibody isotypes. The exacerbation of meningococcal infection in some patients was attributed to the presence of IgA antibody to the capsular polysaccharide which inhibited IgG or IgM antibody-dependent complement-mediated lysis of *Neisseria meningitidis* (Griffiss et al., 1975). Similar findings have been made on the bacteriolysis of *Brucella abortus* (Hall et al., 1971), immune hemolysis of erythrocytes, and the Arthus reaction (Russell-Jones et al., 1980, 1981). Human monoclonal and polyclonal IgA1 antibodies inhibit IgG antibody-dependent CCP activation *in vitro* (Nikolova et al., 1994b; Russell et al., 1989). Interestingly, IgA1 protease-generated Fabα fragments of IgA antibodies also inhibit these IgG- and complement-mediated processes (Jarvis and Griffiss, 1991; Russell et al., 1989). However, the lysis of *N. meningitidis* by IgA antibody to outer membrane proteins (in contrast to antibody to capsular polysaccharide) through a mechanism requiring C1q remains unexplained (Jarvis and Griffiss, 1989; Jarvis and Li, 1997). Some of the most definitive evidence is provided by experiments using recombinant human monoclonal antibodies against meningococcal porin: Whereas IgG antibodies mediated complement-dependent bacteriolysis, IgA with identical antigen-binding domains not only failed to do so but also blocked IgG-dependent bacteriolysis (Vidarsson et al., 2001).

A third pathway of complement activation has been described involving lectins such as the mannose-binding lectin (MBL), which structurally resembles C1q and binds to terminal mannose, fucose, or *N*-acetylglucosamine residues in the presence of calcium. MBL-associated serine proteases, MSP-1 and MSP-2, which are homologous to C1r and C1s, similarly cleave C4 and the remainder of the classical pathway then follows (Møller-Kristensen et al., 2003). pIgA (but not mIgA) can bind MBL and initiate this pathway (Roos et al., 2001). Although the full physiological significance of the lectin pathway has yet to be elucidated, it might explain some of the controversy surrounding complement activation by IgA.

It can be generally concluded that native human IgA antibodies when complexed with antigens have little to no ability to activate complement by either the CCP or ACP. Within the mucosae, where IgA is abundant, the ability to resist complement activation and the consequent inflammatory reactions might help to maintain the integrity of the mucosal barrier. However, some findings remain to be explained, and it is possible that significant differences exist between IgA from humans and other species. In addition, it has been well demonstrated that denatured, conformationally altered, deglycosylated, or chemically modified IgA can activate the ACP. Whether equivalent changes can occur in IgA due to abnormal synthesis or even microbial attack and thereby initiate activation of complement and consequent pathological lesions is an interesting speculation. Support for this notion, however, might be found in IgA nephropathy, in which it is proposed that defective glycosylation of IgA1 leads to its deposition in the renal glomeruli and activation of the ACP (see Chapter 13).

6.2.3.2. Interactions of IgA with Leukocytes (Fig. 6.1)

6.2.3.2.1. Neutrophils and Macrophages

Several early studies, mostly using myeloma IgA proteins or colostral SIgA, indicated that IgA was inhibitory to phagocytosis, bactericidal activity, or chemotaxis by neutrophils or macrophages (reviewed in Kilian et al., 1988).

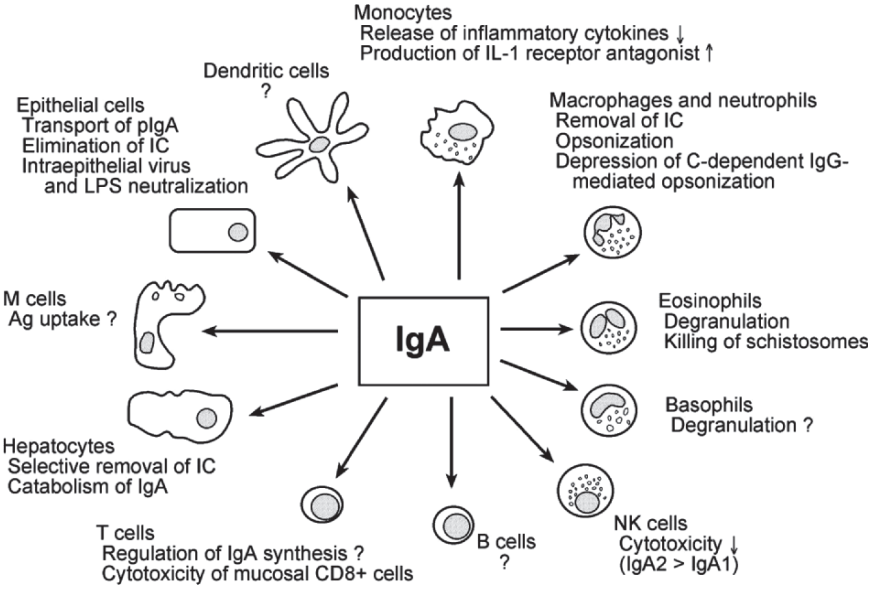

FIG. 6.1. Interactions of IgA with various cell types. Human cells of the myeloid lineage (neutrophils, eosinophils, monocytes, and macrophages) express FcαRI (CD89) through which they can be activated by serum IgA, especially in polymeric form or when aggregated or complexed with antigen. Binding of SIgA (at least by neutrophils) requires Mac-1 as a coreceptor. Expression of FcαRI varies according to the cell type, its state of differentiation or activation, and location. Signal transduction and hence cellular responses depend on association of FcαRI with FcRγ chain. Eosinophils bind and respond especially well to SIgA (or SC), but the nature of the receptor is not clear. Basophils are also reported to degranulate in response to SIgA. Fcα/μR occurs on T- and B-lymphocytes, but its physiological function remains uncertain. The interaction of IgA with NK cells mighty be mediated by lectinlike receptors for carbohydrate determinants. DCs variably express FcαRI or another receptor for IgA, but their response to IgA is controversial. Epithelial cells, including hepatocytes of certain nonprimate animal species, express pIgR, which binds pIgA and thereby transports it to the apical surface where it is released as SIgA. Antigens complexed to pIgA antibodies can be similarly transported by hepatocytes into bile or by intestinal epithelial cells into the gut lumen. pIgA antibodies might also be able to interfere with intracellular viral replication or inhibit responses to LPS within epithelial cells. Enterocytes and M-cells are also reported to bind IgA by other, possibly lectinlike, receptors. Serum IgA is catabolized by hepatocytes, probably after uptake mediated by the asialoglycoprotein receptor. For further details, see text. Reproduced with permission from Russell and Kilian (2005), © Elsevier Inc.

However, it is now known that a receptor for the Fc of IgA, FcαR (CD89), is expressed on myeloid cells and can mediate phagocytosis and other cellular responses to complexed IgA (reviewed in Monteiro and van de Winkel, 2003) (see Chapter 4). The level of expression of FcαR varies between cell types and their activation state. For example, FcαR is upregulated on gingival exudative neutrophils (Fanger et al., 1983; Yuan et al., 2000) but is absent from macrophages isolated from the gut mucosa (Smith et al., 2001). Several activating agents such as phorbol esters, bacterial LPS, or even IgA itself, as well as tumor necrosis factor (TNF)-α, interleukin (IL)-8, and granulocyte monocyte-colony stimulating factor (GM-CSF) enhance the surface expression of FcαR on neutrophils, whereas interferon (IFN)-γ and transforming growth factor (TGF)-β downregulate it (Gessl et al., 1994; Hostoffer et al., 1994; Maliszewski et al., 1985; Nikolova and Russell, 1995; Reterink et al., 1996; Weisbart et al., 1988; Shen et al., 1994). pIgA is more effective than mIgA in cross-linking FcαR (Stewart et al., 1994); indeed, plasma mIgA concentrations are sufficient to saturate FcαR, but in the absence of cross-linking, the cells are not triggered. Association of FcαR with the common FcRγ chain is necessary for signal transduction (Honorio-França et al., 2001; Van Egmond et al., 1999), but its expression varies between different cell types, their state of activation or differentiation, and location (Hamre et al., 2003). In the absence of the signaling FcRγ chain, IgA might be taken up and recycled without inducing inflammatory responses (Launay et al., 1999). Binding of SIgA appears to require Mac-1 (CD11b/CD18) as an accessory receptor (Van Spriel et al., 2002). Thus, numerous factors are involved in determining whether myeloid cells respond to IgA. It is remarkable that mice lack a CD89 homologue, implying that differences exist in the physiological functions of IgA in mice and humans. However, it has been found that galectin-3 can substitute as an IgA receptor, at least in mediating IgA antibody-dependent protection against *Mycobacterium tuberculosis* in a mouse model (Reljic et al., 2004).

Several studies have reported that polyclonal human serum IgA or monoclonal IgA antibodies can promote phagocytic uptake and killing of bacteria such as *S. pneumoniae* or *N. meningitidis* by human neutrophils *in vitro* (Janoff et al., 1999; Van der Pol et al., 2000; Vidarsson et al., 2001). Dependence on complement was variable in these experiments and its precise role is unclear: Nonclassical pathways and complement receptors CR1 or CR3 were implicated, and preactivation of neutrophils by C5a diminished the dependence on complement. IgA-mediated protection against infection has been shown *in vivo* using transgenic mice that express human FcαR, presumably involving opsono-phagocytic mechanisms (Hellwig et al., 2001; Van der Pol et al., 2000; Van Egmond et al., 2000).

In contrast to opsono-phagocytic activation, reports that IgA could downregulate the inflammatory response of LPS-stimulated human monocytes (Wolf et al., 1994, 1996) provoked renewed interest in the concept of IgA as an anti-inflammatory isotype. However, subsequent studies revealed FcαR-dependent signal transduction through Src-family kinases, similar to the pathways induced by other γ-chain-dependent Fc receptors (Gulle et al., 1998). In human alveolar macrophages, pIgA or SIgA downregulates the respiratory burst

induced by LPS through inhibition of the ERK1/2 pathway but enhance the response to phorbol ester in association with ERK1/2 phosphorylation and enhance TNF-α release by an ERK1/2-independent mechanism (Ouadrhiri et al., 2002). Studies on the partitioning of ligand-bound FcαRI into membrane lipid rafts with recruitment of tyrosine kinases have suggested that there are temporally regulated signaling events associated with IgA binding (Lang et al., 2002).

6.2.3.2.2. Eosinophils and Basophils

The interaction of IgA with other types of granulocyte (i.e., eosinophils and basophils) and hence its role in defense against parasites and in allergic reactions deserve more attention. A highly glycosylated isoform of FcαRI is found on eosinophils (Decot et al., 2005; Monteiro et al., 1993), and SIgA strongly stimulates the degranulation of these cells (Abu-Ghazaleh et al., 1989). IgA also mediates the killing of schistosomes by eosinophils (Dunne et al., 1993; Grezel et al., 1993). A distinct 15-kDa receptor for SIgA and SC was described on eosinophils (Lamkhioued et al., 1995) although its function and significance remain uncertain. However, an immunoregulatory role has been suggested as SIgA can inhibit IL-2 and IFN-γ secretion and induce that of IL-10 by eosinophils (Woerly et al., 1999). IgA antibodies were long ago shown to inhibit IgE-mediated hypersensitivity (Ishizaka et al., 1963; Russell-Jones et al., 1981). In contrast, the more recent finding that SIgA can induce basophil degranulation (Iikura et al., 1998) suggests a possible role in allergic reactions.

6.2.3.2.3. Lymphocytes

The presence of IgA receptors on lymphocytes has been somewhat controversial, and despite several earlier reports of IgA binding by T- or B-cells, no receptors were defined. However, it is possible that the receptor for IgA and IgM (FcαμR) recently found on human and murine lymphocytes accounts for some of those observations (reviewed in Shibuya and Honda, 2006). The transferrin receptor (CD71) also serves as a receptor for IgA1 on B-cells and epithelial cells (Moura et al., 2001). The ability of natural killer (NK) cells to bind IgA, especially IgA2, might be carbohydrate dependent (Komiyama et al., 1986; Mota et al., 2003), but the physiological significance of the cellular inhibition that resulted is uncertain. It currently remains unclear whether IgA has direct functional effects on lymphocytes.

6.2.3.2.4. Dendritic Cells

FcαR has been found on human interstitial dermal and gingival dendritic cells (DCs) as well as monocyte-derived DCs *in vitro*, but not on Langerhans cells (Geissmann et al., 2001). Triggering of monocyte-derived DCs with pIgA complexes induces their functional activation, endocytosis of the complexes, and the production of IL-10, suggesting that interstitial DCs might be able to take up and process IgA-opsonized antigens (Pasquier et al., 2004). Conversely, Heystek et al. (2002) found that FcαR expression was greatly diminished upon differentiation of monocytes into DCs, whereas monocyte-

derived DCs bound SIgA independently of FcαR but were not activated as a result. These authors suggested that immature DCs might serve to modulate immune responses to SIgA-complexed antigens at mucosal surfaces. As it has become clear that DCs represent highly variable and plastic types of cell, their expression of receptors for and responses to IgA might also be highly variable and dependent on the precise type of DC, their location, and state of maturity or activation. If intestinal DCs, which protrude into the lumen between the epithelial cells (Mowat, 2005; Rimoldi and Rescigno, 2005), express IgA receptors, then it might be speculated that intestinal IgA antibodies will influence the immune responses initiated by these cells.

6.2.3.3. Interactions of IgA with Epithelial Cells (Fig. 6.1)

Polymeric IgA, along with IgM, interacts with mucosal epithelial cells that express pIgR on their basolateral surfaces. As a result, pIgA is endocytosed and transported apically to be released into the lumen covalently coupled to SC as SIgA (see Chapter 3). In addition to serving as the mechanism for producing SIgA, this process has other functional consequences, some of which have already been discussed when considering the functions of SIgA at mucosal surfaces. The finding that certain animal species, among them rats, mice, and rabbits, have pIgR expressed on hepatocytes that can therefore transport pIgA directly from the blood into bile led to the demonstration that pIgA antibodies can mediate elimination of bound antigens from the circulation by hepatobiliary transport (Peppard et al., 1981; Russell et al., 1981; Socken et al., 1981). This has been proposed as a means of noninflammatory disposal of complex microbial antigens that cannot be broken down in mammalian tissues, or of food antigens absorbed in the intestine (Brown et al., 1984; Russell et al., 1983). However, as human hepatocytes do not express pIgR, this process does not occur in humans (Tomana et al., 1988). Nevertheless, other receptors, such as the asialoglycoprotein receptor, which mediates the uptake of desialylated glycoproteins for catabolism by the liver (Mestecky et al., 1991), and possibly also membrane galactosyltransferase, might contribute to a functionally similar transport process on a smaller scale (Tomana et al., 1993). A portion of desialylated IgA, together with any bound antigen, taken up by these receptors might become missorted into the biliary secretory pathway instead of the lysosomal degradative pathway (Schiff et al., 1984, 1986).

6.2.4. Counteraction of IgA by Bacterial IgA Proteases

One measure of the significance of IgA in protection of the mucosae in humans might be the frequency with which bacterial pathogens have developed countermeasures specific for human IgA. A classic example of this is IgA1 protease, which is expressed by numerous significant human mucosal pathogens but not by closely related nonpathogenic species (Table 6.3). Other species of bacteria produce IgA-binding proteins that have been proposed to interfere with

Table 6.3. Bacterial IgA1 proteases.

Homology group	Species	Enzyme type	Cleavage site	
I	*Haemophilus influenzae*	Serine protease	P231-S232	(type 1)
			P235-T236	(type 2)
	H. influenzae biogroup aegyptius		P235-T236	
	H. aegyptius		P231-S232	
	H. parahaemolyticus		P235-T236	
	Neisseria meningitidis		P237-S238	(type 1)
			P235-T236	(type 2)
	N. gonorrhoeae		P237-S238	(type 1)
			P235-T236	(type 2)
II	*Streptococcus pneumoniae*	Metalloprotease	P227-T228	
	S. sanguis		P227-T228	
	S. gordonii		P227-T228	
	S. oralis		P227-T228	
	S. mitis		P227-T228	
	Gemella haemolysans		P227-T228	
?	*Prevotella* sp	Cysteine protease	P223-S224	
?	*Capnocytophaga* sp	Metalloprotease	P223-S224	
?	*Ureaplasma urealyticum*	Serine protease	P235-T236	

functional protective mechanisms exerted by IgA antibodies, although these are not well understood (Kilian and Russell, 2005).

Molecular characterization of the IgA1 proteases and their catalytic mechanisms has revealed three distinct classes of enzyme: serine proteases (*Haemophilus, Neisseria, Ureaplasma*), metalloproteases (*Streptococcus, Capnocytophaga*), and cysteine proteases (*Prevotella*), as well as several different genetic origins (Table 6.3). This means that the same unique enzymatic activity has evolved independently as many as five times in bacterial phylogeny. Yet, all IgA1 proteases show the same effect of cleaving human IgA1 specifically at one or other of the proline-serine or proline-threonine bonds in the hinge region, yielding Fabα and Fcα fragments, which are not further degraded by these enzymes. mIgA, pIgA, and SIgA forms are all susceptible to cleavage, and the Fabα fragments retain antigen-binding activity (Mansa and Kilian, 1986). Apart from the homologous IgA1 proteins of other anthropoid apes (Cole and Hale, 1991; Qiu et al., 1996), no other species of IgA, or human IgA2, is cleaved by these proteases. Investigation of the role of IgA1 proteases as virulence factors is hampered by this exquisite specificity, which precludes the use of conventional animal models. Moreover, many of the bacteria that produce them are exclusively human pathogens. However, indirect inferential evidence suggests that IgA1 proteases contribute to the virulence of the organisms that produce them. One hypothetical mechanism (Kilian and Reinholdt, 1987) concerns the three species implicated in bacterial meningitis, *Haemophilus influenzae, Neisseria meningitidis,* and *S. pneumoniae*, which all produce IgA1 proteases. IgA1 anticapsular antibodies, which might occur in primary infections of children as a result of prior exposure to cross-reacting antigens, are cleaved by IgA1 protease to Fabα fragments,

which facilitate instead of preventing invasion of the organisms. Moreover, these Fabα fragments block access of other functionally intact antibodies of the same or different isotype. However, if the IgA1 protease elicits an inhibitory antibody response against itself concomitant with the induction of anticapsular IgA1 antibodies, then protection might be achieved. Several items of evidence lend indirect support to this hypothesis. The IgA1 proteases particularly of *H. influenzae* and to a lesser extent of *N. meningitidis* show extensive antigenic variation, which permits escape from antibody-mediated inhibition (Lomholt et al., 1995). Fabα fragments have been shown to be ineffective in inhibiting adherence, and to inhibit complement activation mediated by IgG antibodies (and resultant bacteriolysis) to the same antigen (Hajishengallis et al., 1992; Janoff et al., 2002; Jarvis and Griffiss, 1991; Reinholdt and Kilian, 1987; Russell et al., 1989; Tyler and Cole, 1998). In addition, adherence of *S. pneumoniae* to epithelial cells is enhanced in the presence of IgA1 antibodies to capsular polysaccharide that have been cleaved by IgA1 protease (Weiser et al., 2003). Analysis of virulence genes in *S. pneumoniae* has also revealed an association of the *iga* gene with pathogenicity in a mouse model, even though murine IgA is not susceptible to cleavage by IgA1 protease, suggesting the possibility of additional activities of IgA1 protease (Polissi et al., 1998). However, it is possible that a paralogous "*iga*" gene was involved in the observed association (Kilian and Russell, 2005).

6.3. IgA and Homeostasis

Immunoglobulin A has long been thought of as a benign form of antibody that lacks the dramatic functional activities commonly associated with other isotypes. Its relatively noninflammatory nature is undoubtedly important at mucosal surfaces where the immune system is continuously exposed to an abundance of microorganisms both pathogenic and harmless, as well as foreign macromolecules. IgA antibodies can form immune complexes with antigens without necessarily eliciting inflammatory reactions that can inflict collateral damage on the host tissues (Brandtzaeg and Tolo, 1977) (see Chapter 10). Yet, it has become clear that IgA can mediate potent responses in cells that possess receptors for it. Key to understanding the physiological role of IgA is the recognition that it is heterogeneous in structure, comprising monomeric, polymeric, and secretory forms, two subclasses (in humans), and possibly several glycoforms. Moreover, these variants are differentially distributed in two distinct compartments (the systemic circulation and mucosal secretions) and are produced with different temporal kinetics. In addition, the expression of cellular IgA receptors is subject to regulation. SIgA probably has little opportunity to interact with either complement or phagocytes at mucosal surfaces, because leukocytes quickly disintegrate in the hypotonic environment of most secretions and a fully functional complement system is not usually present. However, if the mucosal barrier is breached, microorganisms will

become exposed to an environment dominated by submucosal pIgA secreted by resident plasma cells as well as SIgA. Infiltrating neutrophils expressing FcαR will be capable of responding to IgA-opsonized organisms and thereby providing immune defense, but the IgA might also afford damage-limiting capability by regulating inflammatory responses. In this connection, it is noteworthy that inflammatory bowel diseases appear to involve increased IgG relative to IgA production in the affected tissues (Baklien et al., 1977).

Observations that preexisting mucosal antibody responses can interfere with the use of live bacterial or viral vectors for the delivery of mucosal vaccines (e.g., Attridge et al., 1997; Roberts et al., 1999; Svennerholm et al., 1981) have suggested that SIgA antibody might regulate the initiation of the immune response. This has been demonstrated in infant mice suckled on immune foster mothers: The neonates' antibody responses to reovirus were suppressed by maternal milk antibodies (Kramer and Cebra, 1995). It is likely that the low level of mucosal antibodies elicited by commensal bacteria prevents overstimulation of the immune system without actually eliminating harmless organisms that are desirable for host survival (Shroff et al., 1995). IgA antibodies to human leukocyte antigen (HLA) class I have been reported to promote the survival of kidney allografts (Koka et al., 1993), but the mechanism underlying this apparent suppression of immune responsiveness is not known. It seems likely that further work on the interaction of SIgA with epithelial cells, M-cells, or DCs will elucidate these observations.

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References

Abu-Ghazaleh, R. I., Fujisawa, T., Mestecky, J., Kyle, R. A., and Gleich, G. J. (1989). IgA-induced eosinophil degranulation. *J. Immunol*. 142:2393–2400.

Adinolfi, M., Glynn, A. A., Lindsay, M., and Milne, C. M. (1966). Serological properties of γA antibodies to *Escherichia coli* present in human colostrum. *Immunology* 10:517–526.

Alfsen, A., Iniguez, P., Bouguyon, E., and Bomsel, M. (2001). Secretory IgA specific for a conserved epitope on gp41 envelope glycoprotein inhibits epithelial transcytosis of HIV-1. *J. Immunol*. 166:6257–6265.

Armstrong, S. J., and Dimmock, N. J. (1992). Neutralization of influenza virus by low concentrations of hemagglutinin-specific polymeric immunoglobulin A inhibits viral fusion activity, but activation of the ribonucleoprotein is also inhibited. *J. Virol*. 66:3823–3832.

Arulanandam, B. P., Raeder, R. H., Nedrud, J. G., Bucher, D. J., Le, J. H., and Metzger, D. W. (2001). IgA immunodeficiency leads to inadequate Th cell priming and increased susceptibility to influenza virus infection. *J. Immunol*. 166:226–231.

Attridge, S. R., Davies, R., and LaBrooy, J. T. (1997). Oral delivery of foreign antigens by attenuated *Salmonella*: Consequences of prior exposure to the vector strain. *Vaccine* 15:155–162.

Baklien, K., Brandtzaeg, P., and Fausa, O. (1977). Immunoglobulins in jejunal mucosa and serum from patients with adult coeliac disease. *Scand. J. Immunol*. 12:149–159.

Benson, M., Reinholdt, J., and Cardell, L. O. (2003). Allergen-reactive antibodies are found in nasal fluids from patients with birch pollen-induced intermittent allergic rhinitis, but not in healthy controls. *Allergy* 58:386–392.

Bessen, D., and Fischetti, V. A. (1988). Passive acquired mucosal immunity to group A streptococci by secretory immunoglobulin A. *J. Exp. Med*. 167:1945–1950.

Biesbrock, A. R., Reddy, M. S., and Levine, M. J. (1991). Interaction of a salivary mucin-secretory immunoglobulin A complex with mucosal pathogens. *Infect. Immun*. 59:3492–3497.

Boackle, R. J., Pruitt, K. M., and Mestecky, J. (1974). The interactions of human complement with interfacially aggregated preparations of human secretory IgA. *Immunochemistry* 11:543–548.

Bomsel, M., Heyman, M., Hocini, H., Lagaye, S., Belec, L., Dupont, C., and Desgranges, C. (1998). Intracellular neutralization of HIV transcytosis across tight epithelial barriers by anti-HIV envelope protein dIgA or IgM. *Immunity* 9:277–287.

Brandtzaeg, P., and Tolo, K. (1977). Mucosal penetrability enhanced by serum-derived antibodies. *Nature* 266:262–263.

Brock, S. C., McGraw, P. A., Wright, P. F., and Crowe, J. E. (2002). The human polymeric immunoglobulin receptor facilitates invasion of epithelial cells by *Streptococcus pneumoniae* in a strain-specific and cell type-specific manner. *Infect. Immun*. 70:5091–5095.

Bronson, R. A., Cooper, G. W., Rosenfeld, D. L., Gilbert, J. V., and Plaut, A. G. (1987). The effect of an IgA1 protease on immunoglobulins bound to the sperm surface and sperm cervical mucus penetrating ability. *Fertil. Steril*. 47:985–991.

Brown, T. A., Russell, M. W., and Mestecky, J. (1984). Elimination of intestinally absorbed antigen into the bile by IgA. *J. Immunol*. 132:780–782.

Burnett, P. R., VanCott, T. C., Polonis, V. R., Redfield, R. R., and Birx, D. L. (1994). Serum IgA-mediated neutralization of HIV type 1. *J. Immunol*. 152:4642–4648.

Castilla, J., Sola, I., and Enjuanes, L. (1997). Interference of coronavirus infection by expression of immunoglobulin G (IgG) or IgA virus-neutralizing antibodies. *J. Virol*. 71:5251–5258.

Chintalacharuvu, K. R., Raines, M., and Morrison, S. L. (1994). Divergence of human α-chain constant region gene sequences. A novel recombinant α2 gene. *J. Immunol*. 152:5299–5304.

Clamp, J. R. (1977). The relationship between secretory immunoglobulin A and mucus. *Biochem. Soc. Trans*. 5:1579–1581.

Cole, M. F., and Hale, C. A. (1991). Cleavage of chimpanzee secretory immunoglobulin A by *Haemophilus influenzae* IgA1 protease. *Microb. Pathog*. 11:39–46.

Colten, H. R., and Bienenstock, J. (1974). Lack of C3 activation through classical or alternate pathways by human secretory IgA antiblood group A antibody. *Adv. Exp. Med. Biol*. 45:305–308.

Crottet, P., and Corthésy, B. (1998). Secretory component delays the conversion of secretory IgA into antigen-binding competent F(ab'): A possible implication for mucosal defense. *J. Immunol*. 161:5445–5453.

Cunningham-Rundles, C., Brandeis, W. E., Pudifin, D. J., Day, N. K., and Good, R. A. (1981). Autoimmunity in selective IgA deficiency: relationship to anti-bovine

protein antibodies, circulating immune complexes and clinical disease. *Clin. Exp. Immunol*. 45:299–304.

Decot, V., Woerly, G., Loyens, M., Loiseau, S., Quatannens, B., Capron, M., and Dombrowicz, D. (2005). Heterogeneity of expression of IgA receptors by human, mouse, and rat eosinophils. *J. Immunol*. 174:628–635.

Devito, C., Broliden, K., Kaul, R., Svensson, L., Johansen, K., Kiama, P., Kimani, J., Lopalco, L., Piconi, S., Bwayo, J. J., Plummer, F., Clerici, M., and Hinkula, J. (2000). Mucosal and plasma IgA from HIV-1-exposed uninfected individuals inhibit HIV-1 transcytosis across human epithelial cells. *J. Immunol*. 165:5170–5176.

Deza, F. G., Espinel, C. S., and Beneitez, J. V. (2007). A novel IgA-like immunoglobulin in the reptile *Eublepharis macularius. Dev. Comp. Immunol*. 31:596–605.

Dunne, D. W., Richardson, B. A., Jones, F. M., Clark, M., Thorne, K. J. I., and Butterworth, A. E. (1993). The use of mouse/human chimaeric antibodies to investigate the roles of different antibody isotypes, including IgA2, in the killing of *Schistosoma mansoni* schistosomula by eosinophils. *Parasite Immunol*. 15:181–185.

Edebo, L., Richardson, N., and Feinstein, A. (1985). The effects of binding mouse IgA to dinitrophenylated *Salmonella typhimurium* on physicochemical properties and interaction with phagocytic cells. *Int. Arch. Allergy Appl. Immunol*. 78:353–357.

Endo, T., Mestecky, J., Kulhavy, R., and Kobata, A. (1994). Carbohydrate heterogeneity of human myeloma proteins of the IgA1 and IgA2 subclasses. *Mol. Immunol*. 31:1415–1422.

Enriquez, F. J., and Riggs, M. W. (1998). Role of immunoglobulin A monoclonal antibodies against P23 in controlling murine *Cryptosporidium parvum* infection. *Infect. Immun*. 66:4469–4473.

Fanger, M. W., Goldstine, S. N., and Shen, L. (1983). Cytofluorographic analysis of receptors for IgA on human polymorphonuclear cells and monocytes and the correlation of receptor expression with phagocytosis. *Mol. Immunol*. 20:1019–1027.

Feng, N. G., Lawton, J. A., Gilbert, J., Kuklin, N., Vo, P., Prasad, B. V. V., and Greenberg, H. B. (2002). Inhibition of rotavirus replication by a non-neutralizing rotavirus VP6-specific IgA mAb. *J. Clin. Invest*. 109:1203–1213.

Fernandez, M. I., Pedron, T., Tournebize, R., Olivo-Marin, J. C., Sansonetti, P. J., and Phalipon, A. (2003). Anti-inflammatory role for intracellular dimeric immunoglobulin A by neutralization of lipopolysaccharide in epithelial cells. *Immunity* 18:739–749.

Friman, V., Adlerberth, I., Connell, H., Svanborg, C., Hanson, L.-Å., and Wold, A. E. (1996). Decreased expression of mannose-specific adhesins by *Escherichia coli* in the colonic microflora of immunoglobulin A-deficient individuals. *Infect. Immun*. 64:2794–2798.

Friman, V., Nowrouzian, F., Adlerberth, I., and Wold, A. E. (2002). Increased frequency of intestinal *Escherichia coli* carrying genes for S fimbriae and haemolysin in IgA-deficient individuals. *Microb. Pathog*. 32:35–42.

Fukui, Y., Fukui, K., and Moriyama, T. (1973). Inhibition of enzymes by human salivary immunoglobulin A. *Infect. Immun*. 8:335–340.

Funakoshi, S., Dot, T., Nakajima, T., Suyama, T., and Tokuda, M. (1982). Antimicrobial effect of human serum IgA. *Microbiol. Immunol*. 26:227–239.

Gan, Y. J., Chodosh, J., Morgan, A., and Sixbey, J. W. (1997). Epithelial cell polarization is a determinant in the infectious outcome of immunoglobulin A-mediated entry by Epstein-Barr virus. *J. Virol*. 71:519–526.

Geissmann, F., Launay, P., Pasquier, B., Lepelletier, Y., Leborgne, M., Lehuen, A., Brousse, N., and Monteiro, R. C. (2001). A subset of human dendritic cells expresses

IgA Fc receptor (CD89), which mediates internalization and activation upon cross-linking by IgA complexes. *J. Immunol*. 166:346–352.

Gessl, A., Willheim, M., Spittler, A., Agis, H., Krugluger, W., and Boltz-Nitulescu, G. (1994). Influence of tumor-necrosis factor-α on the expression of Fc IgG and IgA receptors, and other markers by cultured human blood monocytes and U937 cells. *Scand. J. Immunol*. 39:151–156.

Gilbert, J. V., Plaut, A. G., Longmaid, B., and Lamm, M. E. (1983). Inhibition of microbial IgA proteases by human secretory IgA and serum. *Mol. Immunol*. 20:1039–1049.

Götze, O., and Müller-Eberhard, H. J. (1971). The C3-activator system: An alternative pathway of complement activation. *J. Exp. Med*. 134:90s–108s.

Grezel, D., Capron, M., Grzych, J.-M., Fontaine, J., Lecocq, J.-P., and Capron, A. (1993). Protective immunity induced in rat schistosomiasis by a single dose of the Sm28GST recombinant antigen: Effector mechanisms involving IgE and IgA antibodies. *Eur. J. Immunol*. 23:454–460.

Griffiss, J. M., Broud, D., and Bertram, M. A. (1975). Bactericidal activity of meningococcal antisera. Blocking by IgA of lytic antibody in human convalescent sera. *J. Immunol*. 114:1779–1784.

Gulle, H., Samstag, A., Eibl, M. M., and Wolf, H. M. (1998). Physical and functional association of FcαR with protein tyrosine kinase Lyn. *Blood* 91:383–391.

Hajishengallis, G., Nikolova, E., and Russell, M. W. (1992). Inhibition of *Streptococcus mutans* adherence to saliva-coated hydroxyapatite by human secretory immunoglobulin A (SIgA) antibodies to cell surface protein antigen I/II: reversal by IgA1 protease cleavage. *Infect. Immun*. 60:5057–5064.

Hall, W. M., Manion, R. E., and Zinneman, H. H. (1971). Blocking serum lysis of *Brucella abortus* by hyperimmune rabbit immunoglobulin A. *J. Immunol*. 107:41–46.

Hamre, R., Farstad, I. N., Brandtzaeg, P., and Morton, H. C. (2003). Expression and modulation of the human immunoglobulin A Fc receptor (CD89) and the FcR γ chain on myeloid cells in blood and tissue. *Scand. J. Immunol*. 57:506–516.

Hellwig, S. M. M., Van Spriel, A. B., Schellekens, J. F. P., Mooi, F. R., and Van de Winkel, J. G. J. (2001). Immunoglobulin A-mediated protection against *Bordetella pertussis* infection. *Infect. Immun*. 69:4846–4850.

Heystek, H. C., Moulon, C., Woltman, A. M., Garonne, P., and van Kooten, C. (2002). Human immature dendritic cells efficiently bind and take up secretory IgA without induction of maturation. *J. Immunol*. 168:102–107.

Hiemstra, P. S., Biewenga, J., Gorter, A., Stuurman, M. E., Faber, A., Van Es, L. A., and Daha, M. R. (1988). Activation of complement by human serum IgA, secretory IgA and IgA1 fragments. *Mol. Immunol*. 25:527–533.

Hijmans, W. (1987). Circulating IgA in humans. *Adv. Exp. Med. Biol*. 216B:1169–1174.

Hirano, M., Kamada, M., Maegawa, M., Gima, H., and Aono, T. (1999). Binding of human secretory leukocyte protease inhibitor in uterine cervical mucus to immunoglobulins: Pathophysiology in immunologic infertility and local immune defense. *Fertil. Steril*. 71:1108–1114.

Honorio-França, A. C., Launay, P., Carneiro-Sampaio, M. M. S., and Monteiro, R. C. (2001). Colostral neutrophils express Fcα receptors (CD89) lacking γ chain association and mediate noninflammatory properties of secretory IgA. *J. Leuk. Biol*. 69:289–296.

Hostoffer, R. W., Krukovets, I., and Berger, M. (1994). Enhancement by tumor necrosis factor-α of Fcα receptor expression and IgA-mediated superoxide generation and killing of *Pseudomonas aeruginosa* by polymorphonuclear leukocytes. *J. Infect. Dis*. 170:82–87.

Huang, D. S., Emancipator, S. N., Lamm, M. E., Karban, T. L., Blatnik, F. H., Tsao, H. M., and Mazanec, M. B. (1997). Virus-specific IgA reduces hepatic viral titers *in vivo* on mouse hepatitis virus (MHV) infection. *Immunol. Cell Biol*. 75(Suppl. 1):A12.

Iankov, I. D., Petrov, D. P., Mladenov, I. V., Haralambieva, I. H., and Mitov, I. G. (2002). Lipopolysaccharide-specific but not anti-flagellar immunoglobulin A monoclonal antibodies prevent *Salmonella enterica* serotype enteritidis invasion and replication within Hep-2 cell monolayers. *Infect. Immun*. 70:1615–1618.

Iikura, M., Yamaguchi, M., Fujisawa, T., Miyamasu, M., Takaishi, T., Morita, Y., Iwase, T., Moro, I., Yamamoto, K., and Hirai, K. (1998). Secretory IgA induces degranulation of IL-3-primed basophils. *J. Immunol*. 161:1510–1515.

Imai, H., Chen, A., Wyatt, R. J., and Rifai, A. (1988). Lack of complement activation by human IgA immune complexes. *Clin. Exp. Immunol*. 73:479–483.

Ishizaka, K., Ishizaka, T., and Hornbrook, M. M. (1963). Blocking of Prausnitz-Küstner sensitization with reagin by normal human β_{2A} globulin. *J. Allergy* 34: 395–403.

Janoff, E. N., Fasching, C., Orenstein, J. M., Rubins, J. B., Opstad, N. L., and Dalmasso, A. P. (1999). Killing of *Streptococcus pneumoniae* by capsular polysaccharide-specific polymeric IgA, complement, and phagocytes. *J. Clin. Invest*. 104:1139–1147.

Janoff, E. N., Rubins, J. B., Fasching, C., Plaut, A., and Weiser, J. N. (2002). Inhibition of IgA-mediated killing of *S. pneumoniae* (Spn) by IgA1 protease (IgA1P). *Mucosal Immunol. Update* 10:Abst 2839.

Janoff, E. N., Wahl, S. M., Thomas, K., and Smith, P. D. (1995). Modulation of human immunodeficiency virus type 1 infection of human monocytes by IgA. *J. Infect. Dis*. 172:855–858.

Jarvis, G. A., and Griffiss, J. M. (1989). Human IgA1 initiates complement-mediated killing of *Neisseria meningitidis. J. Immunol*. 143:1703–1709.

Jarvis, G. A., and Griffiss, J. M. (1991). Human IgA1 blockade of IgG-initiated lysis of *Neisseria meningitidis* is a function of antigen-binding fragment binding to the polysaccharide capsule. *J. Immunol*. 147:1962–1967.

Jarvis, G. A., and Li, J. (1997). IgA1-initiated killing of *Neisseria meningitidis*: requirement for C1q and resistance to IgA1 protease. *Immunol. Cell Biol*. 75(Suppl. 1):A12.

Johnson, S., Sypura, W. D., Gerding, D. N., Ewing, S. L., and Janoff, E. N. (1995). Selective neutralization of a bacterial enterotoxin by serum immunoglobulin A in response to mucosal disease. *Infect. Immun*. 63:3166–3173.

Kaetzel, C. S., Robinson, J. K., Chintalacharuvu, K. R., Vaerman, J.-P., and Lamm, M. E. (1991). The polymeric immunoglobulin receptor (secretory component) mediates transport of immune complexes across epithelial cells: A local defense function for IgA. *Proc. Natl. Acad. Sci. USA* 88:8796–8800.

Kilian, M., Husby, S., Høst, A., and Halken, S. (1995). Increased proportions of bacteria capable of cleaving IgA1 in the pharynx of infants with atopic disease. *Pediatr. Res*. 38:182–186.

Kilian, M., Mestecky, J., and Russell, M. W. (1988). Defense mechanisms involving Fc-dependent functions of immunoglobulin A and their subversion by bacterial immunoglobulin A proteases. *Microbiol. Rev*. 52:296–303.

Kilian, M., and Reinholdt, J. (1987). A hypothetical model for the development of invasive infection due to IgA1 protease-producing bacteria. *Adv. Exp. Med. Biol*. 216B:1261–1269.

Kilian, M., and Russell, M. W. (2005). Microbial evasion of IgA functions. In: Mestecky, J., Bienenstock, J., Lamm, M. E., Mayer, L., Strober, W., and McGhee, J. R. (eds.), *Mucosal Immunology*. Elsevier/Academic Press, Amsterdam, pp. 291–303.

Knight, K. L., and Rhee, K.-J. (2005). Organization and expression of genes encoding IgA heavy chain, polymeric Ig receptor, and J chain. In: Mestecky, J., Bienenstock, J., Lamm, M. E., Mayer, L., Strober, W., and McGhee, J. R. (eds.), *Mucosal Immunology,* 3rd ed. Academic Press/Elsevier, San Diego, pp. 183–194.

Koka, P., Chia, D., Terasaki, P. I., Chan, H., Chia, J., Ozawa, M., and Lim, E. (1993). The role of IgA anti-HLA class I antibodies in kidney transplant survival. *Transplantation* 56:207–211.

Komiyama, K., Crago, S. S., Itoh, K., Moro, I., and Mestecky, J. (1986). Inhibition of natural killer cell activity by IgA. *Cell. Immunol*. 101:143–155.

Kozlowski, P. A., Black, K. P., Shen, L., and Jackson, S. (1995). High prevalence of serum IgA HIV-1 infection-enhancing antibodies in HIV-infected persons: masking by IgG. *J. Immunol*. 154:6163–6173.

Kraehenbuhl, J.-P., and Neutra, M. R. (1992). Molecular and cellular basis of immune protection of mucosal surfaces. *Physiol. Rev*. 72:853–879.

Kramer, D. R., and Cebra, J. J. (1995). Role of maternal antibody in the induction of virus specific and bystander IgA responses in Peyer's patches of suckling mice. *Int. Immunol*. 7:911–918.

Lamkhioued, B., Gounni, A. S., Gruart, V., Pierce, A., Capron, A., and Capron, M. (1995). Human eosinophils express a receptor for secretory component. Role in secretory IgA-dependent activation. *Eur. J. Immunol*. 25:117–125.

Lang, M. L., Chen, Y. W., Shen, L., Gao, H., Lang, G. A., Wade, T. K., and Wade, W. F. (2002). IgA Fc receptor (FcαR) cross-linking recruits tyrosine kinases, phosphoinositide kinases and serine/threonine kinases to glycolipid rafts. *Biochem. J*. 364:517–525.

Langford, T. D., Housley, M. P., Boes, M., Chen, J. Z., Kagnoff, M. F., Gillin, F. D., and Eckmann, L. (2002). Central importance of immunoglobulin A in host defense against *Giardia* spp. *Infect. Immun*. 70:11–18.

Launay, P., Patry, C., Lehuen, A., Pasquier, B., Blank, U., and Monteiro, R. C. (1999). Alternative endocytic pathway for immunoglobulin A Fc receptors (CD89) depends on the lack of FcRγ association and protects against degradation of bound ligand. *J. Biol. Chem*. 274:7216–7225.

Leher, H., Zaragoza, F., Taherzadeh, S., Alizadeh, H., and Niederkorn, J. Y. (1999). Monoclonal IgA antibodies protect against *Acanthamoeba* keratitis. *Exp. Eye Res*. 69:75–84.

Liew, F. Y., Russell, S. M., Appleyard, G., Brand, C. M., and Beale, J. (1984). Cross protection in mice infected with influenza A virus by the respiratory route is correlated with local IgA antibody rather than serum antibody or cytotoxic T cell reactivity. *Eur. J. Immunol*. 14:350–356.

Liljemark, W. F., Bloomquist, C. G., and Ofstehage, J. C. (1979). Aggregation and adherence of *Streptococcus sanguis*: role of human salivary immunoglobulin A. *Infect. Immun*. 26:1104–1110.

Lomholt, H., Poulsen, K., and Kilian, M. (1995). Antigenic and genetic heterogeneity among *Haemophilus* and *Neisseria* IgA1 proteases. *Adv. Exp. Med. Biol*. 371A:599–603.

Lycke, N., Eriksen, L., and Holmgren, J. (1987). Protection against cholera toxin after oral immunization is thymus-dependent and associated with intestinal production of neutralizing IgA antitoxin. *Scand. J. Immunol*. 25:413–419.

Lycke, N., Erlandsson, L., Ekman, L., Schön, K., and Leanderson, T. (1999). Lack of J chain inhibits the transport of gut IgA and abrogates the development of intestinal antitoxic protection. *J. Immunol*. 163:913–919.

Magnusson, K.-E., and Stjernström, I. (1982). Mucosal barrier systems. Interplay between secretory IgA (SIgA), IgG and mucins on the surface properties and association of salmonellae with intestine and granulocytes. *Immunology* 45:239–248.

Maliszewski, C. R., Shen, L., and Fanger, M. W. (1985). The expression of receptors for IgA on human monocytes and calcitriol-treated HL-60 cells. *J. Immunol*. 135:3878–3881.

Mansa, B., and Kilian, M. (1986). Retained antigen-binding activity of Fabα fragments of human monoclonal immunoglobulin A1 (IgA1) cleaved by IgA1 protease. *Infect. Immun*. 52:171–174.

Mantis, N. J., Cheung, M. C., Chintalacharuvu, K. R., Rey, J., Corthésy, B., and Neutra, M. R. (2002). Selective adherence of IgA to murine Peyer's patch M cells: Evidence for a novel IgA receptor. *J. Immunol*. 169:1844–1851.

Matoba, N., Magerus, A., Geyer, B. C., Zhang, Y., Muralidharan, M., Alfsen, A., Arntzen, C. J., Bomsel, M., and Mor, T. S. (2004). A mucosally targeted subunit vaccine candidate eliciting HIV-1 transcytosis-blocking Abs. *Proc. Natl. Acad. Sci. USA* 101:13584–13589.

Mattu, T. S., Pleass, R. J., Willis, A. C., Kilian, M., Wormald, M. R., Lellouch, A. C., Rudd, P. M., Woof, J. M., and Dwek, R. A. (1998). The glycosylation and structure of human serum IgA1, Fab, and Fc regions and the role of N-glycosylation on Fcα receptor interactions. *J. Biol. Chem*. 273:2260–2272.

Mazanec, M. B., Coudret, C. L., and Fletcher, D. R. (1995). Intracellular neutralization of influenza virus by immunoglobulin A anti-hemagglutinin monoclonal antibodies. *J. Virol*. 69:1339–1343.

Mazanec, M. B., Kaetzel, C. S., Lamm, M. E., Fletcher, D., and Nedrud, J. G. (1992). Intracellular neutralization of virus by immunoglobulin A antibodies. *Proc. Natl. Acad. Sci. USA* 89:6901–6905.

Mestecky, J., Lue, C., and Russell, M. W. (1991). Selective transport of IgA: cellular and molecular aspects. *Gastroenterol. Clin. North Amr*. 20:441–471.

Mestecky, J., and Russell, M. W. (1986). IgA Subclasses. *Monogr. Allergy* 19:277–301.

Michetti, P., Mahan, M. J., Slauch, J. M., Mekalanos, J. J., and Neutra, M. R. (1992). Monoclonal secretory immunoglobulin A protects mice against oral challenge with the invasive pathogen *Salmonella typhimurium. Infect. Immun*. 60:1786–1792.

Moldoveanu, Z., Egan, M. L., and Mestecky, J. (1984). Cellular origins of human polymeric and monomeric IgA: intracellular and secreted forms of IgA. *J. Immunol*. 133:3156–3162.

Møller-Kristensen, M., Thiel, S., Hansen, A. G., and Jensenius, J. C. (2003). On the site of C4 deposition upon complement activation via the mannan-binding lectin pathway or the classical pathway. *Scand. J. Immunol*. 57:556–561.

Monteiro, R. C., Hostoffer, R. W., Cooper, M. D., Bonner, J. R., Gartland, G. L., and Kubagawa, H. (1993). Definition of immunoglobulin A receptors on eosinophils and their enhanced expression in allergic individuals. *J. Clin. Invest*. 92:1681–1685.

Monteiro, R. C., and van de Winkel, J. G. J. (2003). IgA Fc receptors. *Annu. Rev. Immunol*. 21:177–204.

Morell, A., Skvaril, F., Noseda, G., and Barandun, S. (1973). Metabolic properties of human IgA subclasses. *Clin. Exp. Immunol*. 13:521–528.

Mota, G., Manciulea, M., Cosma, E., Popescu, I., Hirt, M., Jensen-Jarolim, E., Calugaru, A., Galatiuc, C., Regalia, T., Tamandl, D., Spittler, A., and Boltz-Nitulescu, G. (2003). Human NK cells express Fc receptors for IgA which mediate signal transduction and target cell killing. *Eur. J. Immunol*. 33:2197–2205.

Moura, I. C., Centelles, M. N., Arcos-Fajardo, M., Malheiros, D. M., Collawn, J. F., Cooper, M. D., and Monteiro, R. C. (2001). Identification of the transferrin receptor as a novel immunoglobulin (Ig)A1 receptor and its enhanced expression on mesangial cells in IgA nephropathy. *J. Exp. Med*. 194:417–425.

Mowat, A. M. (2005). Dendritic cells and immune responses to orally administered antigens. *Vaccine* 23:1797–1799.

Nikolova, E. B., and Russell, M. W. (1995). Dual function of human IgA antibodies: Inhibition of phagocytosis in circulating neutrophils and enhancement of responses in IL-8-stimulated cells. *J. Leuk. Biol*. 57:875–882.

Nikolova, E. B., Tomana, M., and Russell, M. W. (1994a). The role of the carbohydrate chains in complement (C3) fixation by solid-phase-bound human IgA. *Immunology* 82:321–327.

Nikolova, E. B., Tomana, M., and Russell, M. W. (1994b). All forms of human IgA antibodies bound to antigen interfere with complement (C3) fixation induced by IgG or by antigen alone. *Scand. J. Immunol*. 39:275–280.

Norrby-Teglund, A., Ihendyane, N., Kansal, R., Basma, H., Kotb, M., Andersson, J., and Hammarström, L. (2000). Relative neutralizing activity in polyspecific IgM, IgA, and IgG preparations against group A streptococcal superantigens. *Clin. Infect. Dis*. 31:1175–1182.

Ouadrhiri, Y., Pilette, C., Monteiro, R. C., Vaerman, J. P., and Sibille, Y. (2002). Effect of IgA on respiratory burst and cytokine release by human alveolar macrophages: Role of ERK1/2 mitogen-activated protein kinases and NF-κB. *Am. J. Respir. Cell. Mol. Biol*. 26:315–332.

Pal, S., Theodor, I., Peterson, E. M., and De la Maza, L. M. (1997). Monoclonal immunoglobulin A antibody to the major outer membrane protein of the *Chlamydia trachomatis* mouse pneumonitis biovar protects mice against a chlamydial genital challenge. *Vaccine* 15:575–582.

Pasquier, B., Lepelletier, Y., Baude, C., Hermine, O., and Monteiro, R. C. (2004). Differential expression and function of IgA receptors (CD89 and CD71) during maturation of dendritic cells. *J. Leuk. Biol*. 76:1134–1141.

Peebles, R. S., Hamilton, R. G., Lichtenstein, L. M., Schlosberg, M., Liu, M. C., Proud, D., and Togias, A. (2001). Antigen-specific IgE and IgA antibodies in bronchoalveolar lavage fluid are associated with stronger antigen-induced late phase reactions. *Clin. Exp. Allergy* 31:239–248.

Peppard, J., Orlans, E., Payne, A. W., and Andrew, E. (1981). The elimination of circulating complexes containing polymeric IgA by excretion in the bile. *Immunology* 42:83–89.

Peppard, J. V., Kaetzel, C. S., and Russell, M. W. (2005). Phylogeny and comparative physiology of IgA. In: Mestecky, J., Bienenstock, J., Lamm, M. E., Mayer, L., Strober, W., and McGhee, J. R. (eds.), *Mucosal Immunology*. Elsevier/Academic Press, Amsterdam, pp. 195–210.

Pfaffenbach, G., Lamm, M. E., and Gigli, I. (1982). Activation of the guinea pig alternative complement pathway by mouse IgA immune complexes. *J. Exp. Med*. 155:231–247.

Phalipon, A., Cardona, A., Kraehenbuhl, J. P., Edelman, L., Sansonetti, P. J., and Corthésy, B. (2002). Secretory component: A new role in secretory IgA-mediated immune exclusion *in vivo*. *Immunity* 17:107–115.

Phalipon, A., Kaufmann, M., Michetti, P., Cavaillon, J. M., Huerre, M., Sansonetti, P., and Kraehenbuhl, J. P. (1995). Monoclonal immunoglobulin A antibody directed against serotype-specific epitope of *Shigella flexneri* lipopolysaccharide protects against murine experimental shigellosis. *J. Exp. Med*. 182:769–778.

Polissi, A., Pontiggia, A., Feger, G., Altieri, M., Mottl, H., Ferrari, L., and Simon, D. (1998). Large-scale identification of virulence genes from *Streptococcus pneumoniae*. *Infect. Immun*. 66:5620–5629.

Qiu, J., Brackee, G. P., and Plaut, A. G. (1996). Analysis of the specificity of bacterial immunoglobulin A (IgA) proteases by a comparative study of ape serum IgAs as substrates. *Infect. Immun*. 64:933–937.

Reed, C. E., Bubak, M., Dunnette, S., Blomgren, J., Pfenning, M., Wentz-Murtha, P., Wallen, N., Keating, M., and Gleich, G. J. (1991). Ragweed-specific IgA in nasal lavage fluid of ragweed-sensitive allergic rhinitis patients: increase during the pollen season. *Int. Arch. Allergy Appl. Immunol*. 94:275–277.

Reinholdt, J., and Kilian, M. (1987). Interference of IgA protease with the effect of secretory IgA on adherence of oral streptococci to saliva-coated hydroxyapatite. *J. Dent. Res*. 66:492–497.

Reinholdt, J., and Kilian, M. (1995). Titration of inhibiting antibodies to bacterial IgA1 proteases in human serum and secretions. *Adv. Exp. Med. Biol*. 371A:605–608.

Reljic, R., Crawford, C., Challacombe, S., and Ivanyi, J. (2004). Mouse monoclonal IgA binds to the galectin-3/Mac-2 lectin from mouse macrophage cell lines. *Immunol. Lett*. 93:51–56.

Renegar, K. B., Jackson, G. D. F., and Mestecky, J. (1998). *In vitro* comparison of the biologic activities of monoclonal monomeric IgA, polymeric IgA, and secretory IgA. *J. Immunol*. 160:1219–1223.

Renegar, K. B., and Small, P. A. (1991). Passive transfer of local immunity to influenza virus infection by IgA antibody. *J. Immunol*. 146:1972–1978.

Reterink, T. J. F., Levarht, E. W. N., Klar-Mohamad, N., Van Es, L. A., and Daha, M. R. (1996). Transforming growth factor-beta 1 (TGF-β1) down-regulates IgA Fc-receptor (CD89) expression on human monocytes. *Clin. Exp. Immunol*. 103:161–166.

Rimoldi, M., and Rescigno, M. (2005). Uptake and presentation of orally administered antigens. *Vaccine* 23:1793–1796.

Rits, M., Hiemstra, P. S., Bazin, H., Van Es, L. A., Vaerman, J.-P., and Daha, M. R. (1988). Activation of rat complement by soluble and insoluble rat IgA immune complexes. *Eur. J. Immunol*. 18:1873–1880.

Roberts, M., Bacon, A., Li, J. L., and Chatfield, S. (1999). Prior immunity to homologous and heterologous *Salmonella* serotypes suppresses local and systemic anti-fragment C antibody responses and protection from tetanus toxin in mice immunized with *Salmonella* strains expressing fragment C. *Infect. Immun*. 67:3810–3815.

Römer, W., Rothke, U., and Roelcke, D. (1980). Failure of IgA cold agglutinin to activate C. *Immunobiology* 157:41–46.

Roos, A., Bouwman, L. H., van Gijlswijk-Janssen, D. J., Faber-Krol, M. C., Stahl, G. L., and Daha, M. R. (2001). Human IgA activates the complement system via the mannan-binding lectin pathway. *J. Immunol*. 167:2861–2868.

Royle, L., Roos, A., Harvey, D. J., Wormald, M. R., van Gijlswijk-Janssen, D., Redwan, E.-R. M., Wilson, I. A., Daha, M. R., Dwek, R. A., and Rudd, P. M. (2003). Secretory IgA N- and O-glycans provide a link between the innate and adaptive immune systems. *J. Biol. Chem*. 278:20,140–20,153.

Ruggeri, F. M., Johansen, K., Basile, G., Kraehenbuhl, J.-P., and Svensson, L. (1998). Antirotavirus immunoglobulin A neutralizes virus *in vitro* after transcytosis through epithelial cells and protects infant mice from diarrhea. *J. Virol*. 72:2708–2714.

Russell, M. W., Bobek, L. A., Brock, J. H., Hajishengallis, G., and Tenovuo, J. (2005). Innate humoral defense factors. In: Mestecky, J., Bienenstock, J., Lamm, M. E., Mayer, L., Strober, W., and McGhee, J. R. (eds.), *Mucosal Immunology*. Elsevier/ Academic Press, Amsterdam, pp. 73–93.

Russell, M. W., Brown, T. A., and Mestecky, J. (1981). Role of serum IgA: Hepatobiliary transport of circulating antigen. *J. Exp. Med* 153:968–976.

Russell, M. W., Brown, T. A., Claflin, J. L., Schroer, K., and Mestecky, J. (1983). IgA-mediated hepatobiliary transport constitutes a natural pathway for disposing of bacterial antigens. *Infect. Immun*. 42:1041–1048.

Russell, M. W., and Kilian, M. (2005). Biological activities of IgA. In: Mestecky, J., Bienenstock, J., Lamm, M. E., Mayer, L., Strober, W., and McGhee, J. R. (eds.), *Mucosal Immunology*. Academic Press, San Diego, pp. 267–289.

Russell, M. W., Lue, C., van den Wall Bake, A. W. L., Moldoveanu, Z., and Mestecky, J. (1992). Molecular heterogeneity of human IgA antibodies during an immune response. *Clin. Exp. Immunol*. 87:1–6.

Russell, M. W., and Mansa, B. (1989). Complement-fixing properties of human IgA antibodies. Alternative pathway complement activation by plastic-bound, but not specific antigen-bound, IgA. *Scand. J. Immunol*. 30:175–189.

Russell, M. W., Reinholdt, J., and Kilian, M. (1989). Anti-inflammatory activity of human IgA antibodies and their Fabα fragments: Inhibition of IgG-mediated complement activation. *Eur. J. Immunol*. 19:2243–2249.

Russell-Jones, G. J., Ey, P. L., and Reynolds, B. L. (1980). The ability of IgA to inhibit the complement-mediated lysis of target red blood cells sensitized with IgG antibody. *Mol. Immunol*. 17:1173–1180.

Russell-Jones, G. J., Ey, P. L., and Reynolds, B. L. (1981). Inhibition of cutaneous anaphylaxis and Arthus reactions in the mouse by antigen-specific IgA. *Int. Arch. Allergy Appl. Immunol*. 66:316–325.

Saltzman, W. M., Radomsky, M. L., Whaley, K. J., and Cone, R. A. (1994). Antibody diffusion in human cervical mucus. *Biophys. J*. 66:508–515.

Schiff, J. M., Fisher, M. M., and Underdown, B. J. (1984). Receptor-mediated biliary transport of immunoglobulin A and asialoglycoprotein: Sorting and missorting of ligands revealed by two radiolabeling methods. *J. Cell. Biol*. 98:79–89.

Schiff, J. M., Huling, S. L., and Jones, A. L. (1986). Receptor-mediated uptake of asialoglycoprotein by the primate liver initiates both lysosomal and transcellular pathways. *Hepatology* 6:837–847.

Schneiderman, R. D., Lint, T. F., and Knight, K. L. (1990). Activation of the alternative pathway of complement by twelve different rabbit-mouse chimeric transfectoma IgA isotypes. *J. Immunol*. 145:233–237.

Schwartz-Cornil, I., Benureau, Y., Greenberg, H., Hendrickson, B. A., and Cohen, J. (2002). Heterologous protection induced by the inner capsid proteins of rotavirus requires transcytosis of mucosal immunoglobulins. *J. Virol*. 76:8110–8117.

Shen, L., Collins, J. E., Schoenborn, M. A., and Maliszewski, C. R. (1994). Lipopolysaccharide and cytokine augmentation of human monocyte IgA receptor expression and function. *J. Immunol*. 152:4080–4086.

Shibuya, A., and Honda, S. (2006). Molecular and functional characteristics of the Fcα/μR, a novel Fc receptor for IgM and IgA. *Springer Semin. Immunopathol*. 28:377–382.

Shroff, K. E., Meslin, K., and Cebra, J. J. (1995). Commensal enteric bacteria engender a self-limiting humoral mucosal immune response while permanently colonizing the gut. *Infect. Immun*. 63:3904–3913.

Silbart, L. K., and Keren, D. F. (1989). Reduction of intestinal carcinogen absorption by carcinogen-specific secretory immunity. *Science* 243:1462–1464.

Silvey, K. J., Hutchings, A. B., Vajdy, M., Petzke, M. M., and Neutra, M. R. (2001). Role of immunoglobulin A in protection against reovirus entry into murine Peyer's patches. *J. Virol*. 75:10,870–10,879.

Sixbey, J. W., and Yao, Q. (1992). Immunoglobulin A-induced shift of Epstein-Barr virus tissue tropism. *Science* 255:1578–1580.

Smith, D. J., Taubman, M. A., and Ebersole, J. L. (1985). Salivary IgA antibody to glucosyltransferase in man. *Clin. Exp. Immunol*. 61:416–424.

Smith, P. D., Smythies, L. E., Mosteller-Barnum, M., Sibley, D. A., Russell, M. W., Merger, M., Sellers, M. T., Orenstein, J. M., Shimada, T., Graham, M. F., and Kubagawa, H. (2001). Intestinal macrophages lack CD14 and CD89 and consequently are down-regulated for LPS- and IgA-mediated activities. *J. Immunol*. 167:2651–2656.

Socken, D. J., Simms, E. S., Nagy, B. R., Fisher, M. M., and Underdown, B. J. (1981). Secretory component-dependent hepatic transport of IgA antibody-antigen complexes. *J. Immunol*. 127:316–319.

Stephens, S., Dolby, J. M., Montreuil, J., and Spik, G. (1980). Differences in inhibition of the growth of commensal and enteropathogenic strains of *Escherichia coli* by lactotransferrin and secretory immunoglobulin A isolated from human milk. *Immunology* 41:597–603.

Stewart, W. W., Johnson, A., Steward, M. W., Whaley, K., and Kerr, M. A. (1990). The effect of antibody isotype on the activation of C3 and C4 by immune complexes formed in the presence of serum: Correlation with the prevention of immune precipitation. *Mol. Immunol*. 27:423–428.

Stewart, W. W., Mazengera, R. L., Shen, L., and Kerr, M. A. (1994). Unaggregated serum IgA binds to neutrophil FcαR at physiological concentrations and is endocytosed but cross-linking is necessary to elicit a respiratory burst. *J. Leuk. Biol*. 56:481–487.

Stokes, C. R., Soothill, J. F., and Turner, M. W. (1975). Immune exclusion is a function of IgA. *Nature* 255:745–746.

Stokes, C. R., Taylor, B., and Turner, M. W. (1974). Association of house-dust and grass-pollen allergies with specific IgA antibody deficiency. *Lancet* 2:485-488.

Stubbe, H., Berdoz, J., Kraehenbuhl, J. P., and Corthésy, B. (2000). Polymeric IgA is superior to monomeric IgA and IgG carrying the same variable domain in preventing *Clostridium difficile* toxin A damaging of T84 monolayers. *J. Immunol*. 164:1952–1960.

Svennerholm, A. M., Hanson, L. A., Holmgren, J., Jalil, F., Lindblad, B. S., Khan, S. R., Nilsson, A., and Svennerholm, B. (1981). Antibody responses to live and killed poliovirus vaccines in the milk of Pakistani and Swedish women. *J. Infect. Dis*. 143:707–711.

Tenovuo, J., Moldoveanu, Z., Mestecky, J., Pruitt, K. M., and Mansson-Rahemtulla, B. (1982). Interaction of specific and innate factors of immunity: IgA enhances the antimicrobial effect of the lactoperoxidase system against *Streptococcus mutans*. *J. Immunol*. 128:726–731.

Tomana, M., Kulhavy, R., and Mestecky, J. (1988). Receptor-mediated binding and uptake of immunoglobulin A by human liver. *Gastroenterology* 94:762–770.

Tomana, M., Zikan, J., Moldoveanu, Z., Kulhavy, R., Bennett, J. C., and Mestecky, J. (1993). Interactions of cell-surface galactosyltransferase with immunoglobulins. *Mol. Immunol*. 30:265–275.

Tyler, B. M., and Cole, M. F. (1998). Effect of IgA1 protease on the ability of secretory IgA1 antibodies to inhibit the adherence of *Streptococcus mutans. Microbiol. Immunol*. 42:503–508.

Valim, Y. M. L., and Lachmann, P. J. (1991). The effect of antibody isotype and antigenic epitope density on the complement-fixing activity of immune complexes: A systematic study using chimaeric anti-NIP antibodies with human Fc regions. *Clin. Exp. Immunol*. 84:1–8.

Van der Pol, W. L., Vidarsson, G., Vilé, H. A., Van de Winkel, J. G. J., and Rodriguez, M. E. (2000). Pneumococcal capsular polysaccharide-specific IgA triggers efficient neutrophil effector functions via FcαRI (CD89). *J. Infect. Dis*. 182:1139–1145.

Van Egmond, M., Van Garderen, E., Van Spriel, A. B., Damen, C. A., Van Amersfoort, E. S., Van Zandbergen, G., Van Hattum, J., Kuiper, J., and Van de Winkel, J. G. J. (2000). FcαRI-positive liver Kupffer cells: Reappraisal of the function of immunoglobulin A in immunity. *Nature Med*. 6:680–685.

Van Egmond, M., Van Vuuren, A. J. H., Morton, H. C., Van Spriel, A. B., Shen, L., Hofhuis, F. M. A., Saito, T., Mayadas, T. N., Verbeek, J. S., and Van de Winkel, J. G. J. (1999). Human immunoglobulin A receptor (FcαRI, CD89) function in transgenic mice requires both FcR γ chain and CR3 (CD11b/CD18). *Blood* 93:4387–4394.

Van Spriel, A. B., Leusen, J. H. W., Vilé, H., and Van de Winkel, J. G. J. (2002). Mac-1 (CD11b/CD18) as accessory molecule, for FcαR (CD89) binding of IgA. *J. Immunol*. 169:3831–3836.

Vidarsson, G., van der Pol, W.-L., van den Elsen, J. M. H., Vilé, H., Jansen, M., Duijs, J., Morton, H. C., Boel, E., Daha, M. R., Corthésy, B., and Van de Winkel, J. G. J. (2001). Activity of human IgG and IgA subclasses in immune defense against *Neisseria meningitidis* serogroup B. *J. Immunol*. 166:6250–6256.

Waldo, F. B., and Cochran, A. M. (1989). Mixed IgA-IgG aggregates as a model of immune complexes in IgA nephropathy. *J. Immunol*. 142:3841–3846.

Walker, W. A., Isselbacher, K. J., and Bloch, K. J. (1972). Intestinal uptake of macromolecules: effect of oral immunization. *Science* 177:608–610.

Watanabe, T., Nagura, H., Watanabe, K., and Brown, W. R. (1984). The binding of human milk lactoferrin to immunoglobulin A. *FEBS Lett*. 168:203–207.

Weisbart, R. H., Kacena, A., Schuh, A., and Golde, D. W. (1988). GM-CSF induces human neutrophil IgA-mediated phagocytosis by an IgA Fc receptor activation mechanism. *Nature* 332:647–648.

Weiser, J. N., Bae, D., Fasching, C., Scamurra, R. W., Ratner, A. J., and Janoff, E. N. (2003). Antibody-enhanced pneumococcal adherence requires IgA1 protease. *Proc. Natl. Acad. Sci. USA* 100:4215–4220.

Weltzin, R., Lecia-Jandris, P., Michetti, P., Fields, B. N., Kraehenbuhl, J. P., and Neutra, M. R. (1989). Binding and transepithelial transport of immunoglobulins by intestinal M cells: Demonstration using monoclonal IgA antibodies against enteric viral proteins. *J. Cell Biol*. 108:1673–1685.

Winner, L., Mack, J., Weltzin, R., Mekalanos, J. J., Kraehenbuhl, J.-P., and Neutra, M. R. (1991). New model for analysis of mucosal immunity: intestinal secretion of specific monoclonal immunoglobulin A from hybridoma tumors protects against *Vibrio cholerae* infection. *Infect. Immun*. 59:977–982.

Woerly, G., Roger, N., Loiseau, S., Dombrowicz, D., Capron, A., and Capron, M. (1999). Expression of CD28 and CD86 by human eosinophils and role in the secretion of type 1 cytokines (interleukin 2 and interferon γ): Inhibition by immunoglobulin A complexes. *J. Exp. Med*. 190:487–495.

Wold, A., Mestecky, J., Tomana, M., Kobata, A., Ohbayashi, H., Endo, T., and Svanborg Edén, C. (1990). Secretory immunoglobulin A carries oligosaccharide receptors for *Escherichia coli* type 1 fimbrial lectin. *Infect. Immun*. 58:3073–3077.

Wolf, H. M., Fischer, M. B., Pühringer, H., Samstag, A., Vogel, E., and Eibl, M. M. (1994). Human serum IgA downregulates the release of inflammatory cytokines (tumor necrosis factor-α, interleukin-6) in human monocytes. *Blood* 83:1278–1288.

Wolf, H. M., Hauber, I., Gulle, H., Samstag, A., Fischer, M. B., Ahmad, R. U., and Eibl, M. M. (1996). Anti-inflammatory properties of human serum IgA: Induction of IL-1 receptor antagonist and FcαR (CD89)-mediated down regulation of tumor necrosis factor-α (TNF-α) and IL-6 in human monocytes. *Clin. Exp. Immunol*. 105:537–543.

Yan, H. M., Lamm, M. E., Björling, E., and Huang, Y. T. (2002). Multiple functions of immunoglobulin A in mucosal defense against viruses: an *in vitro* measles virus model. *J. Virol*. 76:10972–10979.

Yuan, Z. N., Gjermo, P., Helgeland, K., and Schenk, K. (2000). Fcα receptor I (CD89) on neutrophils in periodontal lesions. *J. Clin. Periodontol*. 27:489–493.

Zhang, J. R., Mostov, K. E., Lamm, M. E., Nanno, M., Shimida, S., Ohwaki, M., and Tuomanen, E. (2000). The polymeric immunoglobulin receptor translocates pneumococci across human nasopharyngeal epithelial cells. *Cell* 102:827–837.

Zhang, W., and Lachmann, P. J. (1994). Glycosylation of IgA is required for optimal activation of the alternative complement pathway by immune complexes. *Immunology* 81:137–141.