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REVIEW ARTICLE

The structure and function of human IgA

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INTRODUCTION

IgA is present in normal human serum at about one-fifth of the concentration of IgG. However, it is catabolized around five times faster than IgG and therefore the rates of synthesis of the two immunoglobulins must be similar [1]. IgA is the most abundant immunoglobulin in secretions. Secretory IgA (sIgA) is the product of local synthesis at the mucosal surfaces which are the main source of antigenic material for the body. In mucosal tissue, IgA synthesis far exceeds that of other classes. As a result, in man, more IgA is produced than all other immunoglobulin classes combined. In contrast to other immunoglobulins, human IgA displays a unique heterogeneity in its molecular forms, each with a characteristic distribution in various body fluids [2]. Human IgA occurs in two isotypic forms, IgA1 and IgA2, with IgA2 existing as two allotypic variants IgA2m(1) and IgA2m(2). Each of these forms is found in various degrees of aggregation.

Although the importance of IgA in mucosal secretions is well established, it is now clear that in humans much of the IgA is secreted directly into the blood and never reaches the mucosal surfaces [3]. Serum IgA is predominantly monomeric IgA1 which is produced in the bone marrow, while in external secretions most of the locally produced IgA is polymeric with a relative increase in the proportion of IgA2 [4, 5]. The lymphocytes which produce monomeric or polymeric IgA, IgA1 or IgA2 are characteristically distributed in various lymphoid and nonlymphoid tissues. The differential interaction of monomeric and polymeric IgA molecules with various cells leads to their selective distribution in body fluids and possibly to differences in their effector functions. Secretory and serum IgA are therefore molecules with different biochemical and immunochemical properties produced by cells with different organ distributions.

Table 1. Distribution of IgA and IgG in serum and secretions

Abridged and modified from [1, 2, 4, 6]. Abbreviation: n.d., not determined.

Fluid	Concentration (mg/100 ml) IgG	IgA	Polymeric IgA (%)	Ratio IgA1/IgA2
Serum	1230	328	13	89:11
Colostrum	10	1234	96	65:35
Whole saliva	4.9	30.4	96	63:37
Jejunal fluid	34	27.6	95	70:30
Colonic fluid	86	82.7	n.d.	35:65
Hepatic bile	18.2	10.5	65	74:26
Nasal fluid	5.8	25.7	n.d.	95: 5
Bronchial	1.8	n.d.	82	67:33

The high concentration of monomeric serum IgA is unique to man, most laboratory animals having much lower concentrations of serum IgA which is predominantly polymeric [6]. Various methods of immunization can induce an immune response of serum and/or secretory IgA [7, 8]. Although most of the serum IgA is monomeric, recent studies indicate that specific serum IgA antibodies induced by either mucosal or systemic immunizations with microbial or dietary antigens can appear first in the dimeric form [9, 10]. The synthesis of IgA and its control has been the main subject of other reviews [5, 11, 12] and therefore it will not be covered here in detail. This review will concentrate on the structure of the different species of IgA and on biochemistry of their interactions with other proteins, both humoral and cellular, which are pertinent to the effector functions of the molecule.

In spite of its abundance, relatively little is known about the functions of IgA. The biochemical characterization of the different forms of IgA, the improvement in methods of purification and the availability of monoclonal antibodies against each isotype has allowed a reappraisal of the immunology of these proteins. Recent research suggests a more active role in immunity than previously considered. Serum IgA had been shown to prevent activation of the complement system and to inhibit phagocytosis, chemotaxis and antibody-dependent cellular cytotoxicity [13–15]. These results suggested that the predominant role of serum IgA was the removal of antigenic substances without the generation of an inflammatory response. However, more recent work has shown that IgA can activate complement and will efficiently trigger cell-mediated events [16–18].

The idea of a passive role for serum IgA in immunity was reinforced by the observation that IgA deficiency is relatively common and is not usually associated with markedly impaired resistance to infection [19]. There is however, compelling evidence for an important role for secretory IgA in immunity [20–22]. Furthermore, serum IgA levels are frequently raised in rheumatic diseases and in other autoimmune diseases as well as in liver disease and persistent infections such as bacterial endocarditis and AIDS [23–25]. Elevated IgA levels are associated with rises in serum polymeric IgA, circulating IgA-containing immune complexes and IgA rheumatoid factor. Immune complexes containing IgA have been suggested to be pathogenic in these and other diseases such as IgA nephropathy, a common cause of kidney failure [26, 27].

THE STRUCTURE OF IgA

Monomeric IgA comprises two heavy and two light chains, the light chains being the same as those found in other immunoglobulins. Electron microscopy suggests the common Y-shaped structure [28]. The heavy or α chain has a molecular mass of

Abbreviations used: ADCC, antibody-dependent cellular cytotoxicity; BSA, bovine serum albumin; IgA-R, IgA receptor; IgA-BF, soluble IgA binding factor; LPS, lipopolysaccharide; SC, secretory component; sIgA, secretory IgA; dIgA, dimeric IgA; pIgA, polymeric IgA.

around 60 kDa, slightly larger than that of IgG because of its heavier glycosylation. Like the heavy chains of IgG and IgD, it is made up of four domains, a variable domain and three constant domains; C_H1, C_H2 and C_H3. IgA is more negatively charged than most of the IgG, having β mobility on electrophoresis.

Human serum IgA occurs mainly in the monomeric, 160 kDa, 6.5–7.0 S form. A small amount of serum IgA is found in polymeric forms, usually dimers, linked by disulphide bonds and by an additional, cysteine-rich polypeptide termed J chain (16 kDa). Monomeric IgA is also found in most secretions, but the dimeric (11 S) form predominates. Higher aggregation states, particularly tetramers, are also found in some secretions. The polymeric secretory IgA comprises not only IgA and J chain but also a heavily glycosylated protein called secretory component (SC), which is complexed with the IgA during the secretion process. It is part of a cell surface polymeric Ig receptor which mediates the transcytosis of polymeric IgA and IgM across the epithelial cell barrier (see below). SC and J chain are both disulphide-linked to the Fc region of the IgA, although not to one another.

The amino acid sequences of IgAs from man, mouse and rabbit have been determined or deduced [29–34]. They show around 50% homology. Although all of the intradomain disulphide bonds appear to be conserved, some cysteines, probably involved in interchain disulphide bonds, are not. The *C*-terminus of the α chain, like that of the μ chain, extends 18 amino acids relative to that of other heavy chains, with a penultimate cysteine residue which is linked to J chain in polymeric forms [35]. In monomeric forms, this penultimate cysteine can apparently form a disulphide bond with the homologous cysteine on the other α chain, another cysteine in the other α chain or occasionally with other, non-immunoglobulin proteins, such as albumin or α_1-antitrypsin. In dimeric forms the individual monomers are linked by disulphide bonds utilizing this penultimate cysteine residue. The other cysteine which makes up this pair is the subject of some debate, but it is probably Cys-311 on the C_H2 domain [36]. It is possible that studies on myelomas which show greater tendency to polymerize might not reflect the normal situation.

Human IgA1 and IgA2 heavy chains differ in only 22 amino acids, predominantly due to a deletion in IgA2 of 13 amino acids in the hinge region (Fig. 1). The hinge region of IgA1 is composed of an unusual repeating sequence rich in proline, serine and threonine, the serines carrying *O*-linked sugars. The lack of this region in IgA2 makes it resistant to the action of a number of bacterial proteinases which cleave IgA1 in the hinge region and

			IgA2	
	Residue	IgA1[a]	A2m(1)[b]	A2m(2)[c]
CH1 domain	133	Cys	Asp	Asp
	136	Gln	Pro	Pro
	137	Pro	Gln	Gln
	143	Ile	Val	Val
	166	Gly	Asn GlcNAc-X	Asn GlcNAc-X
	197	Leu	Pro	Pro
	198	Ala	Asp	Asp
	211	Asn	Asn	Asn GlcNAc-X
	212	Pro	Pro	Ser
	221	Pro	Pro	Arg
Hinge region	223	Pro		
	224	Ser GalNAc		
	225	Thr		
	226	Pro		
	227	Pro		
	228	Thr		
	229	Pro		
	230	Ser GalNAc-Gal	Deletion	
	231	Pro		
	232	Ser GalNAc-Gal		
	233	Thr		
	234	Pro		
	235	Pro		
	236	Thr	Pro	Pro
	238	Ser GalNAc-Gal	Pro	Pro
	240	Ser GalNAc-Gal	Pro	Pro
	263	Asn GlcNAc-X	Asn GlcNAc-X	Asn GlcNAc-X
CH2	277	Val	Ala	Ala
	319	Lys	Glu	Glu
	327	Tyr	His	His
	330	Ser	Leu	Leu
	337	Thr	Asn GlcNAc-X	Asn GlcNAc-X
	338	Leu	Ile	Ile
	339	Ser	Thr	Thr
CH3	411	Phe	Phe	Tyr
	428	Asp	Asp	Gln
	458	Val	Val	Ile
	459	Asn GlcNAc-X	Asn GlcNAc-X	Asn GlcNAc-X
	467	Val	Val	Ala

Fig. 1. Differences in the amino acid sequence and carbohydrate structure of the C-regions of the human α_1 and two allotypes of α_2 chains

Residues are numbered according to sequence determined for the α chain of IgA1 Bur [29]. Sequences are those of [a] IgA1 Bur, [b] IgA2 Lan [30], [c] IgA2 But [31].

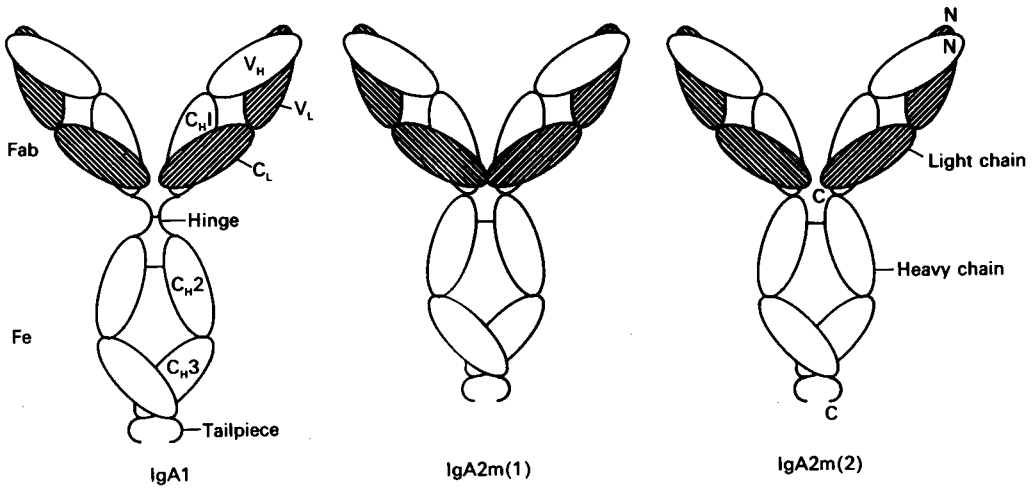


Fig. 2. Structures of monomeric IgA1, IgA2m(1) and IgA2m(2)

These theoretical models are based on the known structure of IgG. They show unpaired C_H2 domains held apart by carbohydrate. The linear extensions or tailpieces at the *C*-termini of the heavy chains are also glycosylated. IgA1 has an extended, glycosylated, hinge region which is absent from the IgA2 allotypes. Heavy chains can be linked by disulphide bonds between C_H2 domains, C_H3 domains and between cysteines at the hinge/C_H2 boundary. In IgA2m(1) the terminal cysteines of each light chain (hatched) are disulphide bonded, whereas in IgA1 and IgA2m(2) they are linked to cysteines in the V_H/C_H1 boundary.

are thought to be important in the pathogenicity of the bacteria. The allotypic variants of IgA2, IgA2m(1) and IgA2m(2), differ in important respects [37]. A2m(1) molecules lack the disulphide bond between the heavy and light chains, allowing the two light chains to be linked to each other. Under denaturing conditions, the molecule therefore splits into heavy chain and light chain dimers. The A2m(2) allotype has the usual interchain disulphide bond. The A2m(1) α chain is a hybrid between A1 and A2m(2) in that the C_H3 domain is identical to that in α1 whereas the C_H1 and C_H2 are identical to α2m(2). Both forms of IgA2 lack the hinge region (Fig. 2).

The amino acid sequences of human and murine J chain have been determined [38]. It has eight cysteine residues, six in intrachain disulphide bonds. In polymeric IgA, two J chain cysteines are usually disulphide-linked to the penultimate cysteines of α chains. In some IgA molecules, a second disulphide bond to a cysteine residue in the C_H2 domain has been demonstrated. The exact nature of the interaction between the α chain and J chain has not been elucidated. Although it has been shown that most molecules of secretory dimeric IgA contain one molecule of J chain [39], it is not clear whether all serum dimeric IgA contains J chain. Some studies [40] have shown polymeric IgA myelomas with an average of two J chains per dimer, but others which lack J chain have also been reported [41].

SC is produced by epithelial cells lining the mucosal surface, unlike the IgA and J chain which are synthesized in mucosal lymphocytes. SC is found in secretions complexed to IgA (or IgM) and also as a free glycoprotein. It has been shown to stabilize markedly the structure of secretory IgA and to increase its resistance to proteolysis [42]. SC is somewhat heterogeneous, with molecular masses reported from 50 to 90 kDa. It is heavily glycosylated with *N*-linked sugars. The amino acid sequence of SC from rabbit and human has been determined [43, 44]. Human SC contains 20 cysteine residues. Although it confers marked stability to secretory IgA, in its free form, it is remarkably susceptible to proteolysis.

The detail of the interaction between SC and IgA remains controversial. Most of the secretory IgA contains two IgA monomers, one J chain and one SC which are covalently linked to the α chains. The antigenic determinants of J chain appear to

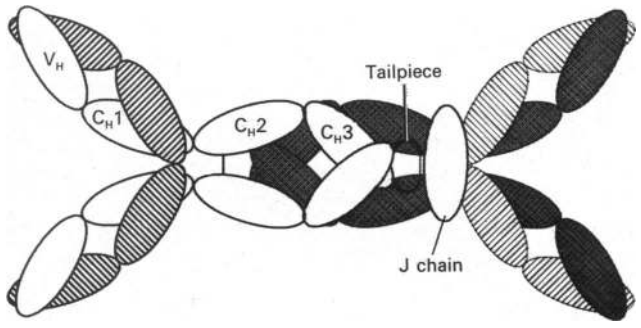


Fig. 3. Structure of dimeric IgA

This theoretical model [5, 47] of dimeric IgA2m(1) shows the Fc regions crossed over with J chain linked to the tailpiece cysteine residues of one pair of heavy chains (unhatched). These heavy chains are linked by cysteine residues in the C_H2 domains to the tailpiece cysteines of the other pair of heavy chains (cross-hatched).

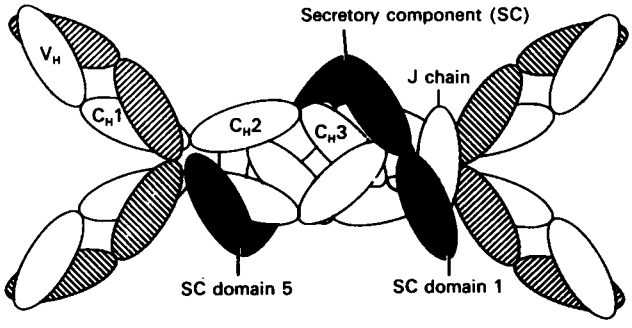


Fig. 4. Structure of secretory IgA

This theoretical model of secretory IgA2m(1) shows secretory component (dark shading) interacting with C_H2 and C_H3 domains of both pairs of heavy chains. The fifth domain of the secretory component is disulphide-linked to the C_H2 domain of one of the IgA monomers.

be buried within the structure, and since SC does not bind to monomeric IgA it appears that J chain is involved in the binding. The affinity of SC for polymeric IgA is rather high (K_a 10^8 M^{-1}). SC is linked by disulphide bonds to the α chain, probably to Cys-299 and/or Cys-301 of the C_H2 domain [32]. Immunochemical studies [45] have suggested that both the C_H2 and C_H3 domains of the IgA are equally and independently involved in the interaction with SC (Fig. 4). However, IgA proteases cleaving at the hinge region or between the C_H2 and C_H3 domains will cleave secretory IgA, albeit slower than serum IgA [37, 46]. Several different IgA Fc receptors will also bind to both monomeric and secretory forms of IgA. Taken together, these results suggest that, contrary to some earlier models (47) of the structure of secretory IgA, much of the Fc region might be exposed.

THE GLYCOSYLATION OF IgA

IgA1 contains two potential *N*-linked glycosylation sites and five *O*-linked sites in the hinge region. IgA2 lacks these *O*-linked sugars, but IgA2m(1) has two extra *N*-linked sites, one each in the C_H1 and C_H2 domains. The A2m(2) allotype has a further potential *N*-linked site in the C_H1 domain. The *O*-linked sugars found in a serum myeloma IgA1 are simple, one site having only *N*-acetylgalactosamine and four others having galactosyl-(β1–3)-*N*-acetylgalactosamine residues [48]. The *O*-linked sugars isolated from milk sIgA appear to be more complex and heterogeneous, containing sialic acid, fucose and *N*-acetylglucosamine [49, 50]. The *N*-linked sugars of serum and secretory IgA are complex and variable in structure [51]. Both J chain and SC are also glycosylated, J chain (8% carbohydrate) with a single *N*-linked chain, SC (22% carbohydrate) with five to seven chains, making sIgA a relatively heavily glycosylated molecule. It is generally accepted that SC confers marked stability on the sIgA and this might be due to the carbohydrate. It has been proposed that mannose-specific bacterial adhesins might interact with IgA2, both serum and secretory, through these *N*-linked sugars [52]. The interaction of the asialoglycoprotein receptor with the carbohydrate chains of IgA will be discussed later.

The purification of IgA and separation of IgA1 and IgA2 have been greatly facilitated by the availability of a lectin, jacalin, purified from the seed of the jackfruit (*Atrocarpus* spp.), which has specificity for galactose residues such as those on the hinge region of IgA1 [53]. Jacalin binds to serum or sIgA1 but does not recognize IgG, IgM or IgA2 of either allotype [54, 55]. The lectin has been used extensively for the affinity purification of IgA1, although care must be taken since there does appear to be heterogeneity in the jacalin preparations from different sources, some binding only to serum and sIgA1 whilst others show weaker but significant binding to IgA2 [56–58]. Jacalin does not bind to mouse, rat, pig, goat, horse, cow or dog IgA [59, 60]. Although the lectin is of considerable value in the purification of human IgA1 it is not totally specific, recognizing other serum and also cell-surface proteins. The interaction with IgA is unaffected by bivalent metal ions or by many detergents, although it is inhibited by denaturing agents. Jacalin has an apparent molecular mass of 40–50 kDa and is a tetramer comprised of two distinct types of polypeptide chain [61, 62]. Since serum and sIgA1 bind with similar affinity it appears that the hinge region of IgA1 is readily accessible in both species.

THE SECRETION OF IgA AND THE ROLE OF THE POLY(Ig) RECEPTOR

Most IgA is produced by mucosal lymphocytes as J-chain-associated dimers. These dimers are bound rapidly by a polymeric-immunoglobulin receptor present on the surface of epithelial cells lining the mucosal surfaces. This poly(Ig) receptor, which has a molecular mass of 100 kDa, is the precursor of SC. It is a member of the immunoglobulin superfamily, comprising five immunoglobulin-like domains, a 23-amino-acid membrane-spanning region and a 103-amino-acid cytosplasmic tail [44]. After synthesis, the receptor is specifically directed to the basolateral membrane of the epithelial cells. Here, the receptor binds polymeric IgA with high affinity and transcytoses the ligand to the luminal surface where it is cleaved by one or more proteinases to release the IgA with associated SC. The remaining membrane-bound 20 kDa fragment is further degraded intracellularily. Transcytosis of the receptor, which does not depend on ligand binding, occurs with a $t_{\frac{1}{2}}$ of 30 min [63]. Unbound receptor appears to be cleaved to release free SC found in secretions. The transcytosis in specific vesicles has been studied extensively and reviewed recently [5, 64].

Study of rabbit SC, which is highly heterogeneous in terms of molecular mass and glycosylation, has suggested that the first *N*-terminal domain of SC is necessary and sufficient for efficient non-covalent binding to dimeric IgA [65]. Immunochemical studies using a large panel of monoclonal antibodies against human SC showed that most SC-related epitopes on sIgA appear to be generated by the physical interaction of SC with dimeric IgA, whereas most epitopes on free SC are masked or altered by this interaction [66]. These results are consistent with the marked decrease in sensitivity of the SC to proteases which occurs on binding to IgA, suggesting marked changes in the conformation of the receptor after binding.

In rodents the poly(Ig) receptor is expressed on the sinusoidal surface of hepatocytes and the liver plays a key role in the translocation of IgA into the upper gastrointestinal tract [5, 64]. Polymeric forms of IgA are efficiently transported from the circulation into the bile, possibly transporting IgA-bound antigens at the same time. In man and in some other animals this mechanism does not appear to function [67, 68], although it has recently been shown that human hepatocytes do express some poly(Ig) receptor [69]. It is well established that the liver does play an important role in the IgA system even in man. Liver disease is frequently associated with marked elevations in the serum IgA levels and in increased serum polymeric IgA [70]. Although human biliary epithelial cells do express the receptor which can effect limited secretion of pIgA into bile, most of the biliary pIgA is synthesized locally in biliary tract plasma cells [71].

IgA interactions with hepatocytes can also be mediated by the asialoglycoprotein receptor or hepatic binding protein [72]. This lectin, which recognizes the *O*-linked sugars of IgA and other proteins after desialylation, is found on the hepatocytes of most animals including man. In rodents, both the poly(Ig) receptor and the asialoglycoprotein receptor can bind polymeric serum IgA. Whereas polymeric mouse IgA is taken up via the poly(Ig) receptor (SC), for quantitative delivery to bile, when polymeric human IgA is presented as a ligand in the rat, it is recognized both by secretory component and by the asialoglycoprotein receptor, possibly being first captured from blood by the asialoglycoprotein receptor and then switching to the poly(Ig) receptor during transport, implying that the two receptors briefly share a common intracellular compartment. Apart from this early compartment, there is remarkable selectivity in the intracellular traffic of these vesicles since IgA bound to the asialoglycoprotein receptor in the same cells is transported not to the luminal surface but to an intracellular compartment where it is degraded in lysosomes [73]. The role of this hepatic lectin in man remains to be clarified, although it is well documented that it can bind both serum and secretory IgA1 [74, 75,].

BINDING OF IgA TO SERUM AND SECRETED PROTEINS

The penultimate cysteine residue at the *C*-terminus of monomeric serum IgA is available for complexing with other serum proteins with a similar free SH- group. Amongst the proteins which have been shown to be complexed in this way are albumin, α_1-proteinase inhibitor (α_1-antitrypsin) and the heterogeneously charged (HC)-protein, which is related to α_1-microglobulin. These complexes appear to be a common component of IgA myeloma sera [76] although their significance is not known. Complexes of α_1-proteinase inhibitor and IgA of all classes have been found in myeloma sera [77, 78]. Since α_1-antiproteinase is a potent inhibitor of leucocyte elastase and thus an important regulator of inflammation, it is interesting that the IgA-inhibitor complex has also been detected in the sera of patients with rheumatoid arthritis [79].

HC-protein is a heterogeneously charged low-molecular-mass protein of unknown function first isolated from human urine. It is found in serum at aroung 40 mg/l, half of which is complexed with IgA [80]. The low-molecular-mass form in serum appears to be identical in amino acid sequence to the urinary protein, although its charge heterogeneity is less pronounced. The HC protein is not found in IgA-deficient plasma nor is it found associated with other proteins in normal or myeloma sera. It appears to be associated almost exclusively with monomeric IgA, even in plasma containing predominantly dimeric IgA myelomas [81, 82]. On SDS gels the plasma high-molecular-mass protein HC appears to be made up of four polypeptide chains: two light immunoglobulin chains, one IgA α chain, and one chain with of approx. 90 kDa having both α-chain and protein HC antigenic determinants, although some reports suggest the 90 kDa component to lack IgA epitopes.

Both HC-protein and its IgA complex are inhibitors of the directed (chemotactic) but not the random migration of neutrophils [83]. Concentrations of HC-protein and its IgA complex producing significant inhibition of the chemotaxis are found to occur in plasma from healthy and diseased individuals as well as in synovial fluid from patients with rheumatoid arthritis, suggesting that HC-protein and its IgA complex play physiological roles in the regulation of the inflammatory response. In addition to these serum proteins shown to bind to the free SH group of monomeric IgA, a recent report [84] suggests an association between fibronectin and IgA in patients with primary IgA nephropathy. Complexes are able to bind collagens I, II, and IV through the collagen-binding site of the fibronectin. In colostrum and milk, the bacteriostatic effect of sIgA *in vitro* has been shown to be increased in the presence of the iron-binding proteins lactoferrin and transferrin [85, 86], some of the lactoferrin being covalently bound to sIgA [87].

BACTERIAL IgA RECEPTORS AND PROTEIN A

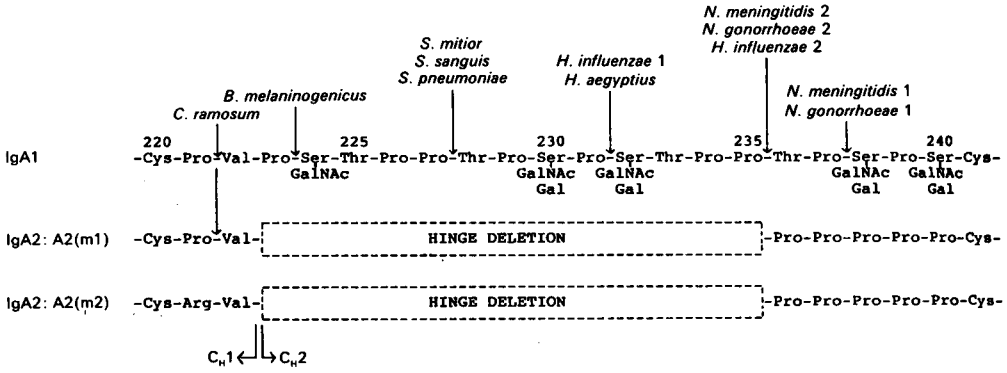
Since IgA is the major immunoglobulin at mucosal surfaces, it is not unexpected that pathogenic bacteria have evolved mechanisms by which to evade the effects of these antibodies. One mechanism utilized by some streptococci involves a cell-surface receptor which recognizes the Fc region of IgA. This receptor, found on group A strains of certain M types, plays an important role as a virulence factor for these micro-organisms because of its anti-phagocytic activity [88, 89]. The IgA receptor is found together with IgG receptors on some strains but others express only receptors for IgA. In group B strains of various serotypes, the receptor is a 130 kDa detergent-extractable protein which recognizes monomeric or polymeric IgA but not IgM or IgG [90]. IgA receptors from several group A strains have been purified and cloned [91, 92]. They are similar but not identical. The gene coding for the receptor is closely linked to that of the fibrinogen receptor, which is probably an M protein.

Protein A, the classical IgG-binding protein of staphylococci, has also been shown to bind to some IgA molecules. Although first reports [93] suggested that human colostral IgA and IgA myelomas could be separated into Protein A reactive and non-reactive forms, possibly corresponding to IgA2 and IgA1, subsequent work [94] suggested that this was an oversimplification with different IgA1 myelomas binding to different extents from 1% to 84%. Binding appears to be generally greater with predominantly polymeric myelomas and the binding site resides in the Fab region, probably in the C_H1 domain. In contrast to IgG, the Fc region does not contain a binding site [95]. The significance of this binding *in vivo* has not been studied.

BACTERIAL IgA PROTEINASES

Another method of evasion of the immune system is the secretion by a limited number of highly pathogenic bacteria of proteinases with marked specificity for IgA1. These bacteria include important pathogens of mucosal surfaces such as *Neisseria gonorrhoeae*, *N. meningitidis*, *Haemophilus influenzae* and *Streptococcus pneumoniae*. Since other related, but non-pathogenic, species of the same bacterial genera do not produce IgA proteinases, the production of these enzymes may be associated with the virulence of the organisms [96, 97]. The IgA proteinases produced by these bacteria are characterized by their extremely narrow substrate specificity, being able to cleave only IgA1 from humans, some apes and gorillas. The enzymes cleave the heavy chain of IgA1 at Pro-Ser or Pro-Thr bonds within the hinge region to yield intact Fab and Fc fragments. This segment is not present in IgA2, which is thereby resistant (Scheme 1).

Although inhibitor studies suggest these IgA proteinases to be metalloenzymes, gene cloning has shown them to be highly



Scheme 1. The hinge region of human IgA1 and IgA2 allotypes A2(m1) and A2(m2) showing the cleavage sites of bacterial IgA proteinases

complex and unusual bacterial proteinases. Sequencing of the gene for the IgA proteinase from *N. gonorrhoeae* shows the secreted form of the enzyme to be a 105 kDa protein derived from a 169 kDa precursor molecule by autoproteolytic cleavage at sites in the precursor which are similar to the target site in IgA1. Since consensus sequences of the specific cleavage sites are found in a number of relevant human proteins, the proteinase may have other natural substrates besides IgA1 [98, 99].

Different strains of *H. influenzae* produce three distinct types of IgA proteinases that cleave different peptide bonds within the IgA1 hinge region. Most serotypes have a single gene except for serotype f strains which produce two proteinases. There appears to be considerable homology between the proteinase genes of the various serotypes. Interestingly, three strains without detectable IgA1 protease activity appear to have proteinase genes [100, 101]. Cloning of the gene from serotype b shows that the enzyme also has strong homology with the proteinase from *N. gonorrhoeae*, both having precursors which undergo similar processing on secretion [102]. The gene for the IgA proteinase from the oral bacterium, *Streptococcus sanguis*, has also been cloned [103]. It does not hybridize with chromosomal DNA of gram-negative bacteria that excrete IgA proteinase or *S. pneumoniae*, although the IgA proteinases of these two streptococcal species cleave the identical peptide bond in the human IgA1 heavy-chain hinge region.

In addition to these classical IgA proteinases, a number of other species have been shown to secrete proteinases which cleave IgA. Some of these enzymes have the characteristic limited specificity, whilst others have broader specificity. A survey of gram-negative bacteria isolated from patients with urinary tract infections showed many (seven genera, eight species) to hydrolyse myeloma IgA but not IgG, IgM or secretory IgA [104]. Some of the proteinases responsible for this hydrolysis were dissimilar in the specificity of their IgA cleavage sites. We have shown that many species of *Proteus*, a common pathogen of the urinary tract, produce an EDTA-sensitive proteinase which cleaves secretory and serum IgA1 and IgA2 outside the hinge region [105]. The purified 50 kDa enzyme has rather broad substrate specificity, cleaving not only the two isotypes of IgA but also IgG and a limited number of non-immunoglobulin proteins such as secretory component, casein and bovine serum albumin [46].

Only one other IgA proteinase has been shown to cleave both IgA1 and IgA2 selectively. This is secreted by a strain of *Clostridium ramosum* associated with ulcerative colitis [106]. This enzyme cleaves a Pro-Val bond found just before the hinge region in the α chains of IgA1 and the IgA2m(1) allotype, but not in IgA2m(2) where it is Arg-Val. The proteinase, like most IgA proteinases, is sensitive to EDTA [107]. Other bacterial pathogens shown to produce proteolytic enzymes capable of degrading IgG as well as IgA include some species of the periodontal pathogens *Bacteriodes* and *Capnocytophaga* [108, 109]. However, many of these species degrade IgA1, IgA2 and IgG extensively, yielding fragments too small to be detectable by electrophoresis.

It is interesting that these proteinases are resistant to plasma proteinase inhibitors such as α_1-proteinase inhibitor and even α_2-macroglobulin [110]. However, it appears that the enzymes produced by *H. influenzae*, *S. pneumoniae*, *N. gonorrhoeae* and *N. meningitidis*, but not by *C. ramosum*, can be inactivated by specific enzyme-neutralizing antibodies present in serum or sIgA preparations [111]. Although the pathological significance of these proteinases has not been firmly established, it is remarkable that the three major causes of meningitis all secrete IgA proteinases [96]. The presence of Fab and Fc fragments and detectable IgA proteinase activity in secretions of patients infected with IgA-proteinase-producing bacteria suggests that these proteinases are produced and are active *in vivo*. These enzymes are valuable tools for the biochemist seeking to correlate the inadequately defined functions of IgA with its structure.

THE INTERACTION OF IgA WITH COMPLEMENT

The activation of complement by IgA remains a confusing and controversial subject. Compared with IgM and IgG, IgA is a poor activator of complement. However, there is important debate about how (in)efficiently IgA activates complement, with contradictory evidence resulting from the use of different assays and different sources of IgA and complement. Assays which use IgA antibodies recognizing erythrocyte antigens or antigens absorbed onto erythrocytes have generally produced negative results, suggesting that IgA-dependent complement-mediated cytolysis or microbial killing is of limited immunological importance. The activation of complement by immune complexes is of greater significance when considering the pathogenesis of diseases associated with IgA immune complexes. It is well established that a major function of the complement system is the maintenance in solution of immune complexes or antibody–antigen aggregates. If IgA-containing complexes do not activate complement then these complexes could become insoluble and thus have considerable pathogenic potential.

There is general agreement that aggregated IgA or IgA antibody–antigen aggregates do not activate the classical pathway. The Fc fragments of some myeloma IgAs appear to activate through C1 even though the intact myelomas do not [112]. Several reports have shown that IgA antibodies will inhibit the activation of the classical pathway by IgG or IgM antibodies recognizing the same antigen [13, 113]. This has been interpreted to suggest that serum IgA might limit the activation of complement by bacteria entering the circulation from mucosal sites and therefore direct the micro-organisms into macrophages and away from polymorphonuclear leukocytes, allowing removal and processing of antigen whilst limiting the inflammatory response [114]. A recent report [115] from the same laboratory, which shows that specific human IgA1 antibodies are able to kill *N. meningitidis* through activation of the classical pathway, suggests that further work is needed in this area.

There is evidence from several laboratories that the alternative pathway of a number of species is activated by aggregated IgA. This observation, first reported in 1971 [116] means that the significance of the inhibitory effects of IgA must be interpreted with caution since these experiments were usually carried out at low serum concentration where activation of the alternative pathway is not achieved. More recent studies [16] have shown both subclasses of serum and secretory IgA to activate the alternative pathway when bound to glutaraldehyde-coated microtitre plates. Activation also occurred with $F(ab')_2$ and $F(abc)_2$ but not Fab or Fc fragments, indicating the need for aggregation of the Fab region but not the presence of the hinge or Fc region. The significance of these results has, however, been questioned by a second study which showed that although IgA antibodies bound directly to plastic could activate the alternative pathway, when bound through antigen they could not [117].

Activation of the alternative pathway of human complement has also been demonstrated by the lysis of erythrocytes coated with a monoclonal mouse IgG1 against IgA when incubated with human serum in the presence of aggregated human IgA [118]. The activation of complement by IgA from other species has been studied in more detail and shown to be a complex issue dependent on the system used, the state of aggregation of the IgA and the source of complement. Some of these studies are summarised in Table 2. The results suggest that the alternative pathway is less easily activated in human serum than in most other species.

Table 2. Activation of complement by IgA

Abbreviations used: HS, GPS, MS, RS, human, guinea pig, mouse or rat serum; CP, classical pathway; AP, alternative pathway; RBC, red blood cell; TNP, trinitrophenyl; DNP, dinitrophenyl; BSA, bovine serum albumin; PC, phosphorylcholine; KLH, keyhole limpet haemocyanin.

IgA species and source	Complement	Assay	Result	Reference
Human				
Anti-human RBC	HS or GPS	Haemolytic	CP−	Several, reviewed
Myeloma, heat-aggregated	GPS	Complement fixation	CP−	in [112]
Myeloma, heat-aggregated	HS	CH50, C1, C3	CP−	[112]
Fc regions, heat-aggregated	HS		CP+	
Myeloma, chemically aggregated	HS	Factor B	AP+	[119]
Secretory or myeloma, heat aggregated	HS	CH50, C1, C3–9	AP+/CP−	[120]
Secretory or myeloma, heat aggregated	HS	C4, C3–C9	AP+/CP−	[121]
Serum IgA; anti-IgA (IgA chemically aggregated)	HS	Haemolytic, CH50	AP+	[118]
Serum, secretory A1, A2 solid phase	HS	C3, C4, P	AP+	[16]
Myeloma, solid phase	HS	C3	AP+/CP−	[117]
Myeloma-antigen solid phase	HS	C3	AP−/CP−	
Mouse				
Myeloma anti-TNP:TNP-SRBC or TNP-BSA	GPS	Several	CP−	Several, reviewed in [124]
Myeloma anti-TNP:DNP-BSA	HS	C3a, C4a release	CP−	[122]
		Solubilization	AP−	
Myeloma anti-DNP:DNP-BSA, anti-PC:PC-KLH	MS	Solubilization	AP+	[123]
Monoclonal anti-PC:PC-BSA	HS	C2, C4, C5, B, C3–9	AP−	[124]
	MS		AP−	
	GPS		AP+	
	HS, MS. GPS		CP−	
Rat				
Monoclonal heat aggregated	RS	C1, CH50	AP+	[16]
Monoclonal anti-DNP:DNP-BSA	RS	C3, solubilization	AP+	[125*a*–*c*]

IgA nephropathy is one of the commonest causes of kidney disease, and appears to be the result of a buildup of IgA-containing immune complexes in the kidney. Extensive study of this disease has led to important insights into the role of complement in the interaction of IgA-containing complexes. The sera of patients with IgA nephropathy and other IgA immune complex-associated diseases frequently contain IgA 'immune complexes' detectable by the complement (C3)-dependent assays [126]. Although some reports suggest these complexes to be small, other studies [127] have shown the complexes to contain IgA, IgG, and C3 with C3 fragments associated only with the IgG.

Rifai and colleagues have shown that heat-aggregated human IgG, but not IgA, mixed with normal human serum causes C3 activation. In mixed aggregates, there was a linear decrease in C3 activation as the percentage of IgA increased. When naturally occurring human IgA immune complexes and covalently cross-linked human IgA oligomers were added to fresh normal human serum both failed to activate complement [128]. Furthermore, the same aggregates upon injection into mice resulted in intense glomerular deposition of IgA but no C3. Collectively, these findings suggest that neither soluble nor renal-localized human IgA complexes activate complement. However, the same authors subsequently [129] showed that large chemically cross-linked IgA oligomers prepared with purified IgA of different specificity, when injected simultaneously with antigen, deposited to a similar amount in glomeruli but had markedly different amounts of C3 associated. These results suggest that the activation of complement by IgA immune complexes can be highly dependent on the nature of the antigen and on the presence of IgG in the complex.

IgA RECEPTORS ON HUMAN GRANULOCYTES

Although IgG Fc receptors on phagocytic cells and other leucocytes have been extensively studied in recent years [130], IgA receptors (IgA-R) have received relatively little attention. Nevertheless, the direct binding of IgA to human neutrophils, monocytes and macrophages has been clearly demonstrated by several techniques. A recent report suggests the presence of an IgA receptor on eosinophils [131]. A large number of studies have shown aggregated IgA to stimulate or inhibit a variety of neutrophil functions. The neutrophil receptor was first demonstrated by Fanger and colleagues by using rosetting techniques [132, 133]. They also showed that the expression of the receptor on blood neutrophils was apparently enhanced by overnight incubation with IgA. Oral neutrophils expressed more receptors per cell than neutrophils in blood and were capable of phagocytosing target cells coated with IgA alone. In functional studies, IgA-R appeared to co-operate with receptors for IgG in enhancing the phagocytosis of target cells coated with IgG and IgA.

Other studies have also shown that the expression of these receptors can be controlled by external factors. GM-CSF and G-CSF, but not IL-3, have been shown to induce a change from low- to high-affinity neutrophil IgA-R receptors within 30 min, a change which is associated with the development of IgA-mediated phagocytosis [134]. The human promyelocytic leukaemia cell line HL-60, which does not express IgA-R, can be induced to do so by treatment of with the differentiating agent calcitriol. Again, these cells are capable of ingesting IgA-coated erythrocyte targets [135].

Several early studies, using mainly animal serum IgA, human myeloma IgA or human colostral secretory IgA, showed that IgA did not opsonise erythrocytes [136, 137], cells or micro-organisms [138–140] for phagocytosis by human neutrophils. Other studies [14] suggested that normal serum and sIgA could inhibit the binding and phagocytosis of yeast. This inhibition, which was enhanced by heat aggregation of the IgA, was apparently due to the binding of the IgA to the neutrophil. Aggregated IgA has also

been shown to inhibit other neutrophil functions. An inhibitor of neutrophil chemotaxis found in the serum of patients with liver disease or IgA nephropathy has been identified as polymeric IgA [15, 141, 142].

Human IgA myeloma proteins have been shown to inhibit the chemotaxis and chemotactic peptide-induced chemiluminescence of neutrophils [143]. This inhibition is mediated by the Fc part of the molecule and potentiated by heating and aggregation. The binding and phagocytosis of aggregated IgA has been demonstrated in several laboratories [144, 145], both *in vitro* where the rate of uptake of aggregated IgA myeloma proteins and subsequent release of granule enzymes is similar to that of IgG aggregates, and *in vivo* where IgA immune complexes have been detected in neutrophils isolated from patients with IgA nephropathy [146, 147].

We have studied the interaction of serum IgA with neutrophils using several different systems. Whilst investigating the ability of pathological sera to opsonise yeast we identified a heat-stable opsonic activity in the sera of patients with liver and inflammatory bowel disease which was due to IgA anti-(yeast mannan) antibody [17]. Using an assay for yeast phagocytosis in which both yeast and neutrophils are kept in suspension, IgA showed greater opsonic activity than IgG anti-mannan antibody. If yeast and neutrophils were allowed to settle, IgA and IgG were equally efficient opsonins. IgA antibodies are at least as efficient as IgG in causing the degranulation of neutrophils as measured by enzyme release or by triggering of the respiratory burst. Similar effects have also been observed for IgA-opsonized *S. aureus* [18].

Neutrophils will bind to IgA–Sepharose or IgG–Sepharose, but not to BSA–Sepharose, and this binding elicits a similar respiratory burst and degranulation response. We have used IgA–Sepharose to purify the IgA-R from human neutrophils by affinity chromatography of detergent-solubilized membrane extracts [148]. The receptor, identified initially from radiolabelled cell membrane proteins, but more recently by silver staining of the purified protein, appeared on SDS gels as a diffuse band corresponding to a protein of M_r 50–70 kDa. Using IgG–Sepharose under identical conditions, IgG FcγRII could be isolated. When judged by the amount of radioactivity or protein recovered, the amount of IgA-R purified was similar to that of the FcRγII receptor. The amount of IgA-R recovered was less than the amount of FcRγIII which could be precipitated from the same neutrophil extract using CD16 monoclonal antibodies. Since in our experiments the low affinity of the FcRγIII receptor prevented purification on the IgG–Sepharose resin, it appeared that the affinity of IgA-R for IgA must be similar to that of FcRγII for IgG.

After elution from the IgA–Sepharose affinity columns with 0.5 M-acetic acid, upon neutralization IgA-R rebound specifically to IgA– but not to IgG– or BSA–Sepharose. The binding of receptor to IgA–Sepharose was blocked by IgA1 or IgA2 in both monomeric and secretory forms but not by IgG or IgM. This confirmed, directly, earlier reports on the specificity of the receptor showing IgA1 and IgA2 to be equally efficient in their capacity to inhibit rosette formation [145, 149, 150]. Our results suggest the affinity of the receptor for IgA is 5×10^7 M^{-1} [151]. We have also shown recently [151a] that when coated onto microtitre plates, serum or sIgA of either subclass or IgG are able to elicit similar levels of lucigenin-enhanced chemiluminescence from neutrophils. Although the binding site on IgA has not been fully determined, several studies have suggested a site on the Fc region. Since a IgA half-molecule lacking the C_H3 domain is also recognized, it appears that it is the C_H2 domain which is involved in binding to the receptor [149].

Taken together, these results demonstrate the presence on phagocytic cells of specific IgA-R with at least equal affinity and in similar amounts to the functional IgG Fc receptors (Table 3). IgA aggregated artificially or by binding to antigen will elicit similar responses to those elicited by aggregated IgG, suggesting that serum IgA might indeed play a role in defence against infection and in the generation of inflammation. These observations are not necessarily in conflict with earlier papers suggesting an inhibitory role for IgA. The opsonic activity of IgA (or IgG) alone is much less than that of complement. Therefore IgG, by activating complement efficiently, will be detected in serum as a far more powerful opsonin than IgA, which activates complement poorly. As a result, IgA antibodies competing with IgG will appear to inhibit opsonization. In the absence of complement, either as a result of depletion by immune complexes or in secretions where levels of complement are low, the importance of IgA as an opsonin might be increased.

Table 3. Comparison of the properties of neutrophil Fc receptors

Data on the IgA receptor are taken from [151, 155] where the data on IgG Fc receptors are also reviewed.

	IgA-R	FcγRII	FcγRIII
Molecular mass (kDa)	50–70	40	50–70
Polypeptide mass (kDa)	32–36	30–35	30
Membrane linkage	Transmembrane	Transmembrane	GPI
Molecules per cell	10^4	10^4	2×10^5
Specificity	IgA IgA1 = IgA2 = sIgA1 = sIgA2	IgG IgG1 = IgG3 > IgG2, IgG4	IgG IgG1 = IgG3 > IgG2, IgG4
Affinity for monomer Ig (M^{-1})	5×10^7	$< 10^6$	$< 10^6$

IgA RECEPTORS ON MONOCYTES AND MACROPHAGES

IgA receptors have also been identified on human monocytes, macrophages and related cells by immunofluorescence and by rosetting with IgA-sensitized cells [143, 152, 153]. Peripheral blood monocytes and alveolar macrophages have been demonstrated to ingest IgA-coated particles and bacteria [154]. Recently, Monteiro *et al.* [155] have isolated an IgA-R from human monocytes and related cell lines which was similar to that found on neutrophils. Receptors recognizing human IgA have also been detected in heterologous systems using macrophages and macrophage-related cells from mouse, rat and rabbit. In mouse, a subpopulation of alveolar macrophages (around 20%) express the receptor although this value increases along with an increase in ligand density on stimulation *in vitro* or *in vivo* [156] coincident with an increase in phagocytic activity.

The significance of IgA-R on these cells remains unclear. Ward and colleagues in a series of papers [157–159] have studied the interaction of lung macrophages and neutrophils with IgA and IgG immune complexes. They have shown that when IgA is instilled into the airways of rats and antigen injected intravenously, acute lung injury occurs, which is dependent on antigen and directly proportional to the amount of IgA. Lung injury related to IgA-containing immune complexes is complement-dependent but neutrophil-independent, whereas similar lung pathology due to IgG complexes is complement- and

neutrophil-dependent. *In vitro*, rat lung interstitial and alveolar macrophages incubated with IgA or IgG immune complexes produce similar amounts of superoxide in a dose-dependent manner. In contrast, peripheral blood neutrophils respond to IgG immune complexes but not to IgA immune complexes; monocytes respond to neither. The results suggest that in the rat, IgG immune complex lung injury is primarily neutrophil-mediated, wheras IgA complex lung injury is predominantly macrophage-mediated.

It has been widely suggested that macrophages might also be involved in the clearance of IgA-containing immune complexes. Evidence in humans is limited but studies have been made in mice [160]. The rapid phase of removal of large IgA aggregates involves the clearance by the liver with an insignificant amount ending up in the bile. Heavy polymers of dIgA or mIgA predominantly localize in Kupffer cells [161, 162], a subpopulation of which express IgA-R [163]. Although these results point to a role for the reticuloendothelial system in generation of inflammation and the removal of IgA immune complexes, the mechanism remains unclear. Other studies [164] on the *in vitro* binding, internalization and degradation of IgA immune complexes (IC) by resident rat peritoneal macrophages suggest that the asialoglycoprotein receptor is involved. Although there is little information concerning the role of IgA-R on mononuclear phagocytes in the killing of micro-organisms, a recent study demonstrated the phagocytosis of erythrocytes and release of superoxide triggered by IgA [165]. Human monocytes have been described to have ADCC activity [166, 167]. Of particular significance is the observation that a human monoclonal anti-pneumococcal IgA produced from an EBV-transformed cell line induces direct killing and increases the phagocytosis of these bacteria by mouse macrophages *in vitro* although the antibody does not fix complement [168].

IgA RECEPTORS ON LYMPHOCYTES AND THE CONTROL OF THE IgA RESPONSE

IgA-R have been detected on subpopulations of T cells, B cells and also non-T non-B cells of several species both in the circulation and in lymphoid tissues, especially the gut-associated lymphoid tissue [153, 169–171]. The percentage of lymphocytes expressing IgA-R is usually low but can be increased upon activation either by culturing overnight with IgA or by mitogenic stimulation in the absence of IgA. Several reports have suggested an increase in the number of lymphocytes bearing IgA-R in diseases associated with raised serum IgA or IgA immune complexes, such as IgA nephropathy [172] or Crohns disease [173]. IgA-R can also be induced by aggregated IgA purified from the sera of patients with IgA nephropathy [174].

Human T cells increase their expression of IgA-R on stimulation with concanavalin A or phytohaemagglutinin [169, 175]. Human B cells activated with *S. aureus*, anti-IgM antibodies or *E. coli* LPS also show increased numbers of IgA-R positive cells [175, 177]. The induction of IgA-R expression on peripheral blood T cells, T cell lines and clones by IgA depends on the concentration and state of aggregation of the IgA, with polymeric or secretory IgA being effective, but not serum IgA, IgG or IgM [178, 179]. T cell lines and T cell clones derived from tonsils respond better than those established from peripheral blood. The induction of receptor expression, which is found with both $CD4^+$ and $CD8^+$ T cell clones, is dependent on protein and RNA synthesis but not on DNA synthesis.

The exact function of IgA-R on lymphocytes is not known, nor is it known whether this receptor is related to IgA-R on phagocytic cells. The receptors on B and T cells are involved in the isotype-specific immune regulation, although the mechanism remains unclear. IgA production seems to be regulated at several points during B cell differentiation by $IgA\text{-}R^+$ T cells or products released from these cells involving the switch of isotype-uncommitted B cells as well as post-switch expansion of IgA-committed B cells [180]. Most of the detailed functional studies on lymphocyte IgA-R have been carried out in mice [181, 182]. In one extensively studied murine system, Kiyono and colleagues [183–185] have demonstrated that $IgA\text{-}R^+$ antigen-specific T cell clones derived from Peyers patches are able to increase the numbers of surface IgA^+ but not surface IgA^- B cells by release of an IgA-binding factor (IgA BF). Preincubation of T helper cell clones with excess monomeric or dimeric IgA blocks the IgA response, whereas $F(ab')_2$ fragments of IgA, free α chain and IgA molecules with C_H3 deletions have no effect. The IgA BF appears to be a soluble form of the IgA receptor since affinity chromatography of supernatants from $IgA\text{-}R^+$ T cell lines results in the binding of IgA-promoting activity to IgA (but not to IgM or IgG). The activity is recoverable upon elution. High concentrations of this soluble factor suppress T-dependent IgA responses, while optimal levels enhance this isotype response.

The suppression of IgA production by $IgA\text{-}R^+$ positive cells or products derived from these cells has also been studied in several laboratories. An $IgA\text{-}R^+$ murine T cell hybridoma stimulated with IgA has been shown to induce the release of IgA-BF which suppresses the response of mouse spleen cells in the presence of pokeweed mitogen [185]. In a human system, IgA-BF isolated from either mononuclear cell suspensions or monoclonal $IgA\text{-}R^+$ B cell lines selectively depresses the maturation of B cells into IgA plasma cells and the proliferation of a surface IgA^+ B cell line [187]. $IgA\text{-}R^+$ human T cells pre-incubated with aggregated IgA have been shown to selectively suppress the ability of pokeweed mitogen-stimulated B cells to produce IgA [188].

The nature of the IgA receptor and IgA-BF has been studied extensively by Yodoi and colleagues [189–194] using a murine T cell hybridoma, T2D4, shown to express a trypsin-sensitive receptor for IgA. The cells bind IgA in a dose-dependent manner, resulting in increased expression of IgA-R and secretion of an IgA-BF. This factor competitively inhibits the binding of IgA to T2D4 cells and specifically suppresses IgA but not IgG nor IgM responses of pokeweed mitogen-stimulated spleen cells. A subpopulation of murine spleen cells activated with concanavalin A, after 18 h preculture with IgA, can also be induced to express IgA-R and to release the same IgA-BF. The IgA-BF is a 56 kDa glycoprotein which binds to IgA-bearing but not to IgG-bearing myelomas, indicating that it interacts with B cells bearing IgA to suppress their differentiation.

A similar suppressive IgA-BF is also produced by a human natural killer (NK)-like cell line (YT), indicating these cells may also be involved in the regulation of the class-specific antibody responses and suggesting that, in human as well as murine systems, T- and NK-cells have the capacity to co-express multiple class-specific Fc receptors and to produce the corresponding immunoglobulin binding factors. Studies on an IgE-binding factor and Fc receptors for IgE on T cells have shown that both are specifically enhanced or up-regulated by IgE [194]. While the IgE receptor expression is abnormally enhanced in diseases with elevated serum IgE, disregulation of IgA receptor is associated with diseases involving elevated IgA such as IgA nephropathy. Interestingly, it has recently been suggested that 'autoimmune' young NZB mice produce an IgA-BF that has aberrant biological activity when compared to IgA-BF produced from $IgA\text{-}R^+$ T cells of BALB/c mice [195]. Although the IgA receptor and binding factor have not yet been fully characterized, a recent, as yet unconfirmed, report has suggested that the murine lymphocyte IgA-R might be serologically related to secretory component [196].

CONCLUDING REMARKS

It is clear that IgA is able to bind to a variety of soluble and cell bound proteins. In many cases the full significance of these interactions has still to be elucidated. There is ample evidence that immunity to infection at mucosal surfaces is mediated by IgA. There is increasing evidence that serum IgA might also play a role in immunity although this has yet to be determined. Selective deficiency of IgA is one of the most frequent immunodeficiencies although these deficiencies are seldom complete [197]. This deficiency can be associated with a number of autoimmune diseases, recurrent infections and atopy, but not all deficients are symptomatic [19]. Nevertheless, there is increasing evidence that many leucocytes have receptors for IgA and binding of IgA to these receptors triggers a variety of effector functions. The control of mucosal IgA synthesis and secretion is complex and here again IgA receptors appear to play an important role.

The importance of IgA in the pathogenesis of certain diseases is an area of special interest. IgA-containing immune complexes are found in the serum and tissues of patients with a number of different diseases and a polyclonal increase in serum IgA is associated with others. Although there has been extensive research into these diseases a detailed understanding of the immunological role of IgA can only come from better characterization of the specific IgA receptors and elucidation of the structures of the different forms of IgA.

Note added in proof

A cDNA for a human myeloid IgA receptor has recently been isolated (C. R. Maliszewski, personal communication). The cDNA encodes a protein of approximately 30 kDa which has six potential *N*-glycosylation sites. The protein is a member of the immunoglobulin superfamily, homologous to known IgG and IgE receptors.

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