

Chapter 2

Immunoglobulin A: Molecular Mechanisms of Function and Role in Immune Defence

Jenny M. Woof

Abstract Our immune system produces more immunoglobulin A (IgA) than all of the other antibody classes combined. Much of this synthesis is directed towards protection of the mucosal surfaces which form a vast and vulnerable interface with the environment. As the predominant immunoglobulin class at these surfaces, IgA is an important first line of defence. In addition, IgA is also a major serum immunoglobulin. Both monomeric IgA in serum and polymeric secretory forms of IgA mediate a wide range of protective functions through interaction with numerous receptors and other mediators. It is telling that in order to gain better opportunities for invasion, certain pathogens have evolved mechanisms to thwart IgA function. An improved understanding of this multifaceted immunoglobulin is likely to inform strategies for improved treatments for infections and other diseases.

Keywords Immunoglobulin A • Immune defence • IgA • IgA1 • IgA2 • Glycosylation • Dimeric IgA • IgA receptors

2.1 Introduction

IgA was first recognised as an immunoglobulin isotype at the end of the 1950s by Heremans and colleagues, when it became apparent that the carbohydrate-rich antibody species present in the β -globulin fraction of serum was distinct from the isotypes that had already been defined, namely, IgG and IgM (reviewed by Mestecky et al. 2005). Tomasi and co-workers shortly afterwards showed that IgA was present in a polymeric form in many external secretions (reviewed by Mestecky et al. 2005).

J.M. Woof, B.Sc. Ph.D (✉)

Division of Cancer Research, Medical Research Institute, Jacqui Wood Cancer Centre, Ninewells Hospital and Medical School, University of Dundee, James Arrott Drive, DD1 9SY Dundee, UK
e-mail: j.m.woof@dundee.ac.uk

Although in some secretions, e.g. those of the lower respiratory and female genital tracts, the level of IgG may at times be quite high and even exceed that of IgA, it is clear that IgA is the predominant antibody class in most external secretions of humans. Indeed, it is now known that the majority of the body's immunoglobulin production is directed towards the IgA class. In fact, the average human produces more IgA per day than all of the other antibody classes combined. Typically, over 60 mg IgA is produced per kg of body weight each day (Mestecky et al. 1986; Conley and Delacroix 1987). Most of this IgA is localised to the mucosal tissues, especially those of the gastrointestinal, respiratory and genitourinary tracts, where it is generated by the abundant plasma cells in the mucosal subepithelium (Conley and Delacroix 1987; Mestecky et al. 1991).

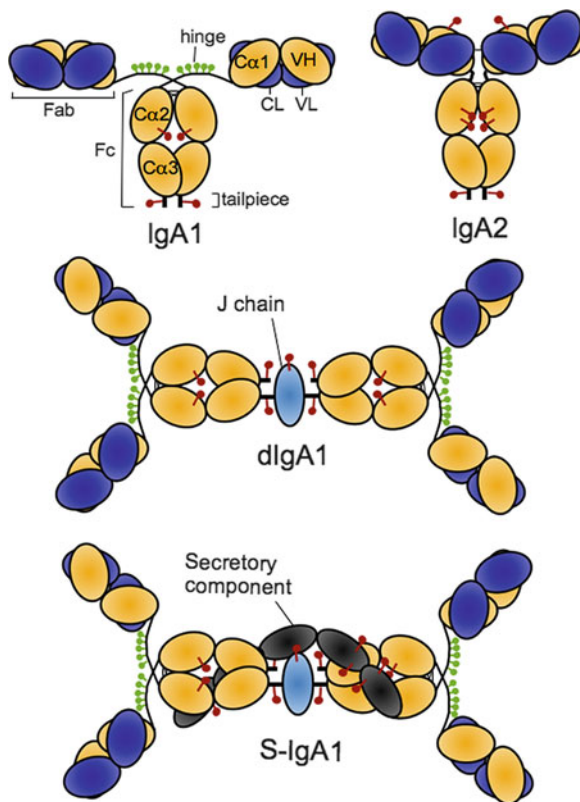
Considerable energy expenditure is presumably necessary to maintain such prolific IgA production. The maintenance of such high energy cost during human evolution suggests that IgA serves as a keystone of a mucosal immune defence system that is critical for survival. Mucosal surfaces have an immense collective surface area, typically 400 m² in the human adult (Childers et al. 1989). These surfaces are thus the main area of exposure to the environment and represent a key point of vulnerability to attack by pathogens. A highly effective system for their protection is clearly essential. IgA makes a critical contribution to this process, helping to prevent breaching of the mucosal surfaces by pathogens, while also having a role to play in the circulation (Woof and Russell 2011). This chapter will consider structure and functional aspects of both serum and secretory forms of IgA, concentrating chiefly on the human system.

2.2 Multiple Molecular Forms of IgA

In human serum, IgA is the second most prevalent immunoglobulin class after IgG. IgA is normally present at concentrations of 2–3 mg/ml, i.e. about one fifth that of IgG. Because it does not interact with FcRn, the receptor responsible for rescuing IgG from degradation, IgA has a much faster turnover than IgG, being metabolised about five times faster. Therefore, the relative concentrations and rates of metabolism suggest that the production rates of serum IgG and serum IgA are similar.

Serum IgA exists principally as a monomer with a molecular mass of approximately 170 kDa (Fig. 2.1). In marked contrast, for IgA in the mucosal secretions (secretory IgA, SIgA), the majority is in dimeric form (Fig. 2.1). Some higher molecular weight species, mainly trimers and tetramers, are also present. As mentioned above, SIgA is present in the secretions that bathe the respiratory, gastrointestinal and genitourinary tracts. It is also the predominant immunoglobulin in milk, colostrum, tears and saliva. As will be discussed in more detail later, SIgA is formed following the interaction of dimeric IgA, produced locally at mucosal sites, with the polymeric immunoglobulin receptor (pIgR) (Mostov et al. 1980). During transfer of the dimeric IgA-pIgR complex across the epithelium, the receptor is cleaved. The major cleavage product of the receptor, termed secretory component (SC), remains

Fig. 2.1 Schematic representation of the monomeric forms of human IgA1 and IgA2 and the dimeric (dIgA1) and secretory (SIgA1) forms of IgA1. Heavy chains are shown in gold and light chains in purple. J chain is shown in blue and secretory component in dark grey. O-linked sugars on the IgA1 hinge are shown in green, while N-linked oligosaccharides are shown in red



bonded to the IgA dimer on release into the mucosal secretions, serving as an integral component of SIgA (Fig. 2.1).

2.3 IgA Structure

2.3.1 Monomeric Unit

Similar to the other immunoglobulin classes, IgA molecules are based on a monomer unit comprising two heavy chains (in this case, α -chains) and two light chains. The latter are common to all immunoglobulin classes, while the α -heavy chains are unique to IgA and essentially define the antibody class. Each chain is folded up into a number of globular domains, four for the heavy chain (named from the N-terminus VH, Ca1, Ca2 and Ca3) and two for the light chain (known as VL and CL) (Fig. 2.1). A hinge region separates the Ca1 and Ca2 domains of the heavy chain.

All the domains fold up into essentially the same secondary architecture typical of all immunoglobulins, known as the immunoglobulin fold. The domains each

comprise around 110 amino acids and are arranged into two β -sheets, made up of antiparallel β -strands, which form a sandwich stabilised by a characteristic disulphide bond. In common with the other immunoglobulin classes, each domain is encoded by a separate exon. In humans but not all species, IgA is unusual in that the hinge is encoded by a region located at the 5' end of the C α 2 exon rather than having its own distinct exon or exons as is seen with IgG, for example.

At the C-terminus of the α -heavy chain of IgA, there is an 18 amino acid extension known as the tailpiece. This element is central to IgA's ability to polymerise. The IgA tailpiece shares close similarity to that present at the C-terminus of the IgM heavy chain. IgM is similarly capable of polymerisation, in its case primarily into pentamers. Tailpiece equivalents are lacking in IgG and IgE with the result that these antibodies exist solely as monomers.

Like other immunoglobulins, the heavy and light chains of IgA are arranged into two antigen-binding Fab regions that are linked through the hinge region to the Fc region (Fig. 2.1). This arrangement is stabilised through an extensive array of non-covalent interactions, primarily hydrogen bonds and van der Waals contacts, between paired domains from different polypeptide chains. Thus, in the Fab region, the VH domains pair closely with the VL domains and the C α 1 domains with the CL domains, while in the Fc region, the C α 3 domains of the two heavy chains are closely paired. Such close association between domains contributes to stability by removing substantial surface areas of the domains from contact with solvent. Some further stabilisation is contributed by interaction between neighbouring domains in the same polypeptide chain. An exception to the domain pairing is seen with the C α 2 domains, which do not form a close pair. Instead, the "interior" surfaces of these domains lie apart from each other but are partially removed from solvent exposure by N-linked oligosaccharides that are attached to these surfaces (see Sect. 2.3.3).

As in all antibody molecules, the paired VH and VL domains at the tips of the two Fab regions of IgA form the sites responsible for binding to antigen. In each case, the antigen-binding site itself is formed by the association of the three hypervariable loops or complementarity determining regions (CDRs) of the VH domain with the three CDRs of the VL domain. The precise three-dimensional conformation of the antigen-binding site formed through the coming together of these six loops at the tips of the VH and VL domains, unique for each different antibody, determines the specificity for antigen. Thus, binding of high affinity will only occur when the molecular structure of the antigen (or subcomponent of the antigen) is the exact three-dimensional complement of the antigen-binding site.

While the Fab arms dictate antigen binding, the Fc region is responsible for the effector function of the IgA molecule. IgA fulfils its role as an adaptor molecule by linking these two critical functions together, thereby enabling the immune system to trigger appropriate elimination processes (via effector function) once a foreign invader has been detected (via antigen binding). The effector mechanisms are mediated, in the main, through interaction of the IgA Fc region with a variety of specific receptors present on a range of different cell types. These include receptors that bind to the Fc region of IgA such as Fc α RI on phagocytes, Fc α / μ R present on some follicular dendritic cells, macrophages, plasma cells and Paneth cells, and pIgR on epithelial cells (discussed in detail in Sects. 2.3.5 and 2.7).

The X-ray crystal structure of the Fc region of human IgA1 has been determined in complex with the extracellular part of human Fc α RI (Herr et al. 2003) or with SSL7, an IgA-binding protein produced by *Staphylococcus aureus* (Ramsland et al. 2007). Overall, the structure is very similar to the equivalent regions of IgG or IgE. There are some key differences, however. These include the arrangement of the oligosaccharides, which is explored in Sect. 2.3.3, and the location of disulphide bridges between the heavy chains. In IgG, the two heavy chains are anchored to each other by disulphide bonds in the hinge region, but IgA differs in this regard. Instead, the bonds lie at the “top” of the C α 2 domains, tying the upper reaches of the two domains together (Fig. 2.1). Two such bonds link Cys242 with Cys299 in the opposite chain. Additional bonds, possibly between the two Cys241 residues or between Cys241 on one chain and Cys301 on the other, are presumed to exist although the truncated constructs used to obtain the X-ray crystal structures did not extend far enough to resolve these. There are no disulphide links between the hinge regions of IgA, which marks a sharp contrast to the situation in the IgG hinge region. The lack of disulphides in the IgA hinge means that on emerging from the globular C α 2 domains, the heavy chains are presumably relatively free to flex independently of each other. Thus, these different modes of anchoring the two heavy chains together likely have implications in terms of overall flexibility, reach of the Fab arms to distantly spaced antigens, and susceptibility of the hinge peptide to proteolysis.

2.3.2 IgA Subclasses

The number of IgA genes varies from species to species as will be discussed later (Sect. 2.5). In humans, two subclasses of IgA exist. Known as IgA1 and IgA2, they differ in their α -heavy chain constant regions which are encoded by separate C α genes. Although the differences between the subclasses relate to several specific amino acid differences throughout the length of their heavy chains, the most major differences are seen within the hinge region. The hinge region of IgA1 is much more extended than that of IgA2 due to an insertion event which has introduced two eight amino acid repeats, rich in proline, serine and threonine residues (Figs. 2.1 and 2.5). The IgA1 hinge is usually decorated with three to five O-linked oligosaccharides (Mattu et al. 1998; Royle et al. 2003) attached to particular serine and threonine residues. A small proportion (5–10 %) of molecules are reported to carry six O-linked sugars (Tarelli et al. 2004).

Two IgA2 allotypes, named IgA2m(1) and IgA2m(2), have been well characterised in humans (Fig. 2.2). Another IgA2 variant, presumed to be an allelic form, has also been described (Chintalacharuvu et al. 1994). Although the IgA2m(1) and IgA2m(2) allotypes differ at just six amino acid positions in their heavy chain constant regions, there is a significant difference in their arrangements of their inter-chain disulphide bridges. While in IgA2m(2), the usual disulphide links between heavy and light chains are present, these are generally lacking in IgA2m(1). In the latter allotype, the association of the heavy chains is stabilised via non-covalent interactions, and a disulphide bridge links the light chains to one another.

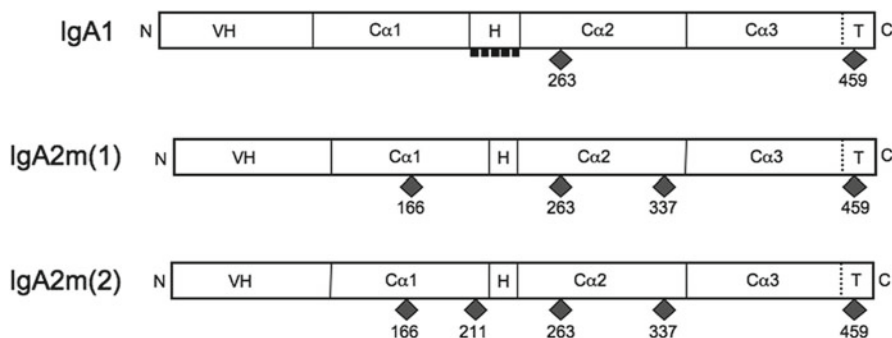


Fig. 2.2 Glycosylation of the heavy chains of human IgA1, IgA2m(1) and IgA2m(2). N-linked and O-linked oligosaccharides are depicted as grey diamonds and black squares, respectively. Attachment sites for N-linked oligosaccharides are numbered using Bur IgA1 numbering

The relative proportions of the human IgA subclasses vary between body compartments. In serum, IgA1 predominates with about 90 % of the IgA being of the IgA1 subclass. In the mucosal secretions, there tends to be a more even distribution of the two subclasses. Typical proportions are around 60 % IgA2 and 40 % IgA1, but there is considerable variability at different mucosal sites.

2.3.3 Glycosylation

N-linked oligosaccharides contribute quite a significant part of the total mass of IgA. In human IgA1, they account for 6–7 % of the mass, while in human IgA2, they make up 8–10 % of the mass (Tomana et al. 1976). Two N-linked sugars, attached at residue Asn263 in the Cα2 domain and Asn459 in the tailpiece, decorate each heavy chain of IgA1 (Fig. 2.2). Human IgA2 molecules possess these same oligosaccharides as well as additional ones, the number varying with allotype. Thus, IgA2m(1) has additional sugars attached to residues Asn166 in the Cα1 domain and Asn337 in the Cα2 domain, while IgA2m(2) has a further Cα1 domain sugar moiety attached at Asn 211 (Fig. 2.2).

Compositional analysis of the N-linked oligosaccharides of serum IgA1 and SIgA revealed the presence of a family of structures based principally around a biantennary mannosyl chitobiose core (Field et al. 1994; Mattu et al. 1998; Royle et al. 2003). A small proportion of the sugars are more branched, mainly as triantennary structures. Within this family, there is considerable variation in the level of fucosylation and the number and type of sugars (galactose and sialic acid) attached at the termini of the branches.

The Cα2 domains of IgA share a common feature with the equivalent Cγ2 domains of IgG and the Cε3 domains of IgE in that they are not closely paired and have N-linked oligosaccharides attached. However, there are important differences between IgA and these other isotypes in the attachment sites and

positions occupied by the glycans. In IgA, the glycans attached at Asn 263 lie over the outer surfaces of the C α 2 domain and, in the process, bury some 930 Å² of C α 2 domain surface area per Fc from solvent contact. They make contacts with the C α 3 domain too, burying a further 914 Å² of domain surface per Fc from solvent. In contrast, in IgG and IgE, the N-linked oligosaccharides are attached at a different point within the C γ 2 and C ϵ 3 domains and, in each case, occupy the interior of the Fc. Their contribution to stability through burying surface from solvent is therefore less, at around 1044 Å² per Fc for IgG and 900 Å² per Fc for IgE. Moreover, their oligosaccharides make no contacts with the C γ 3 or C ϵ 4 domains (the equivalents of the C α 3 domain).

As mentioned in Sect. 2.3.2, the IgA1 hinge carries a number (three to five, or in some cases six) of O-linked oligosaccharides attached at serine and threonine residues (Fig. 2.2). These sugars are much smaller and less complex than the N-linked glycans, comprising mainly N-acetyl galactosamine, galactose and sialic acid. The presence of the O-linked sugars may adjust the conformation adopted by the IgA1 hinge (Narimatsu et al. 2010). The impact of N- and O-linked glycosylation on the functions of IgA will be discussed further in later sections.

2.3.4 Dimeric IgA

As mentioned in Sect. 2.2, IgA has the capacity to polymerise, primarily into dimers. These comprise not just the two IgA monomer units but also one additional molecule of joining chain or J chain (Koshland 1985). This 15 kDa glycoprotein is highly conserved between species and is also involved in the polymerisation of IgM into pentamers. Seemingly unrelated to other known proteins, J chain contains eight cysteine residues and is rich in acidic amino acids. While the three-dimensional structure of J chain remains unsolved, folding models have been proposed. These include a two-domain structure, one of β -sheets followed by one of α -helices (Cann et al. 1982), and a single-domain model featuring a β -barrel structure similar to an immunoglobulin VL domain (Zikan et al. 1985). Following assignment of intra-chain disulphides (see below), another two-domain model emerged that predicted an N-terminal β -barrel domain linked to a second domain of both α -helices and β -strands (Frutiger et al. 1992).

Six of the J chain cysteines form intrachain disulphide bridges, while the remaining two, Cys14 and Cys68, form disulphide bridges to the monomer units of IgA. Specifically, Cys14 links to Cys471, the penultimate tailpiece residue in one of the heavy chains of one of the monomers, while Cys68 links to Cys471 in the tailpiece of one of the heavy chains of the other monomer (Bastian et al. 1992). Mutagenesis experiments showed that these cysteine residues on J chain and the IgA tailpiece were essential for dimer formation (Atkin et al. 1996; Krugmann et al. 1997). These linkages mediate an end-to-end arrangement of the two Fc regions that is consistent with the dimensions of the joined Fc regions as determined from electron microscopy images of dimeric IgA (Fig. 2.1).

The presence of other elements in J chain and IgA has also been shown to contribute to efficient dimer formation. These include the N-linked oligosaccharide attached to residue Asn459 of the tailpiece and the N-linked oligosaccharide which is attached to Asn48 of J chain (Atkin et al. 1996; Krugmann et al. 1997). The domains of the IgA Fc region also appear to contribute to polymerisation, with the presence of the C α 2 domain aiding the efficiency of dimerisation and that of the C α 3 domain impacting on the size of the polymer formed (Yoo et al. 1999).

2.3.5 Secretory IgA

As indicated in Sect. 2.2, the transport of IgA into the mucosal secretions to form SIgA is mediated by a specific receptor, the polymeric immunoglobulin receptor (pIgR). pIgR is expressed on the basolateral surface of epithelial cells that form the mucosal surface. A number of host and microbial factors contribute to the regulation of its expression (Johansen and Kaetzel 2011).

pIgR is composed of a single polypeptide with a large extracellular region (approximately 620 amino acids), a 23-residue transmembrane segment and an intracellular region of just over 100 amino acids (Kaetzel 2005). The extracellular portion is arranged into five immunoglobulin-like domains that show homology to immunoglobulin variable domains and are each stabilised by one or more internal disulphide bridges. The domains are designated 1–5 (D1–D5) from the N-terminus. There are seven N-linked oligosaccharides attached to the domains – two each to D1, D2 and D5 and one to D4. C-terminal to these domains, leading to the membrane, there lies a stretch of non-immunoglobulin-like polypeptide.

The transport process involves binding of dimeric IgA to the receptor at the basolateral surface (Fig. 2.3). The complex is then internalised and transported via vesicular compartments to the apical surface of the epithelial cell. The pIgR is cleaved at a site located between D5 and the cell membrane to release the major portion of the receptor as a fragment known as secretory component (SC). During transport, a disulphide bridge forms between SC and dimeric IgA so that upon release at the apical surface, SC remains as an integral part of the released IgA, now referred to as SIgA (Fig. 2.1).

pIgR binds only to polymeric immunoglobulins, i.e. to dimers (or larger polymers) of IgA and IgM, and not to IgG or IgE. Under experimental conditions, the receptor is able to transport both IgA and IgM polymers at similar rates. However, in the body, access of IgM to pIgR is likely hindered by slow diffusion rates of the pentamer from the circulation through the extracellular matrix and basement membrane. As a result, the transport of IgA dimers across the mucosal surfaces is favoured over that of the larger IgM (Natvig et al. 1997).

Binding between dimeric IgA and pIgR has been studied in some detail, and the elements critical for interaction have been defined. Domains D4 and D5 of pIgR appear to make some contribution to the affinity of the interaction, but it is D1–D3 that play the key roles (Norderhaug et al. 1999). D1, in particular, has a central role

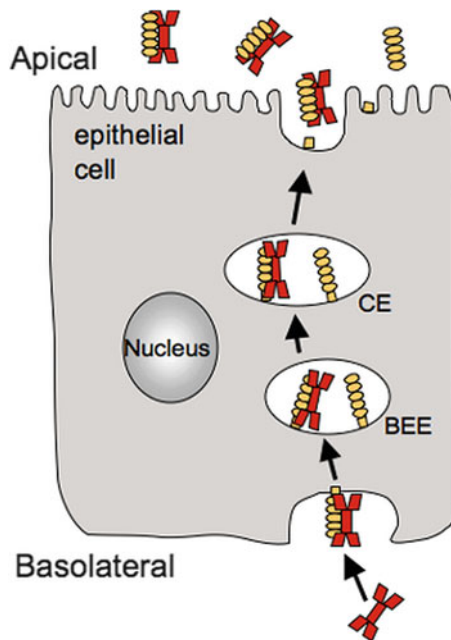


Fig. 2.3 *Receptor-mediated transport of IgA across the epithelial cell layer at mucosal surfaces.* Locally produced dimeric IgA binds to pIgR expressed on the basolateral surface of polarised epithelial cells. pIgR, either unoccupied or bound to dimeric IgA, undergoes endocytosis and is transported across the cell to the apical surface via various intracellular vesicles, including additional vesicular compartments not shown in this simplified diagram. pIgR is cleaved to yield SC which has become covalently linked to the IgA dimer, and the complex (SIgA) is released at the mucosal surface. Unoccupied receptor is also cleaved releasing free SC. BEE basolateral early endosome, CE common endosome

in binding to dimeric IgA, and loops at the end of this domain that occupy positions analogous to the complementarity determining regions (CDRs) that comprise the antigen-binding site in antibody variable domains have been shown to be critical for binding (Bakos et al. 1993; Coyne et al. 1994). The solved X-ray crystal structure for pIgR D1 confirmed that this domain adopts a structure similar to that of immunoglobulin variable domains (Hamburger et al. 2004). Residues in CDR1 (Thr27–Thr33) and CDR2 (Glu53 and Gly54) of D1 that had been implicated in dimeric IgA binding in mutagenesis studies were confirmed to lie close to each other in three-dimensional space.

D1 of pIgR interacts via non-covalent interactions with the Fc region of dimeric IgA. The C α 3 domain is central to this initial binding event (Hexham et al. 1999; Braathen et al. 2002). An exposed loop at the upper surface of the domain comprising residues 402–410 has been implicated (Hexham et al. 1999; White and Capra 2002). Close-lying residues Phe411, Val413, Thr414 and Lys377 appear also to be involved, as well as a stretch lying at the interface with the C α 2 domain consisting of residues Pro440–Ph443 (Lewis et al. 2005). From the available evidence, one can

conclude that, together, these motifs form a binding site for pIgR D1 lying essentially across the C α 2-proximal surface of the C α 3 domain. Once D1 has bound the C α 3 domain in the Fc region of dimeric IgA, a disulphide bond is formed between Cys467 of D5 of pIgR and a cysteine residue (Cys311) that lies on the exterior of the C α 2 domain of IgA (Fallgren-Gebauer et al. 1995; Underdown et al. 1977). In addition to these IgA-pIgR interactions, direct interactions between J chain and pIgR also contribute (Johansen et al. 2001).

2.4 Induction of IgA

2.4.1 Sites of IgA Production

The biosynthesis of mucosal IgA is completely distinct from that of circulating IgA. Serum IgA is produced in the bone marrow, principally in the form of monomeric IgA1. In contrast, SIgA is produced locally by plasma cells situated at mucosal surfaces. These cells are present in huge numbers, comprising about 80–90 % of all plasma cells in the body. For example, there are calculated to be approximately 10^{10} plasma cells per metre of adult human intestine (Brandtzaeg et al. 1999). The IgA produced by these cells is primarily polymeric as a result of the co-expression of IgA light and heavy chains and J chain, with neither IgA subclass predominating.

The mucosal plasma cells comprise a key part of a highly specialised mucosal immune system that functions largely independently of the systemic immune system. Unsurprisingly, as a result of these very different sites of production, different methods of immunisation can induce serum or secretory IgA responses or a combination of the two. For example, oral immunisation with microbial antigens induces SIgA responses in external secretions but only low serum IgA responses. Conversely, systemic immunisation with antigens that induce dominant IgA responses in plasma does not induce strong IgA responses in mucosal secretions.

The tissue compartments involved with induction of a mucosal IgA response consist of mucosa-associated lymphoid tissue (MALT). MALT is subdivided based on anatomical region, with gut-associated mucosal tissue (GALT) being the largest component. Such sites are specially adapted to generate precursors programmed for IgA production and are exposed to antigens arriving directly from mucosal surfaces. In short, they comprise B cell follicles, made up of a germinal centre of rapidly dividing B cells within a mantle zone of naive B cells, with intervening T cell zones and an array of antigen-presenting cells. These underlie specialised follicle-associated epithelium that contains microfold (M) cells which, aided by dendritic cells, transport exogenous antigenic material from the mucosal lumen to the immune cells below. Questions surrounding whether or not events initiating a human intestinal IgA mucosal response might occur outside GALT have persisted, but it seems likely that this is not the case (Spencer et al. 2012).

Following priming and expansion of mucosal B and T cells in MALT, these cells migrate to local and more distal mucosal effector sites, such as the lamina propria and epithelium of the intestine and respiratory tract. These homing responses are guided through coordinated expression of adhesion molecules, such as the integrin $\alpha 4 \beta 7$ which binds to its ligand MAdCAM-1 on endothelial cells, and certain chemokines and their receptors, such as CCL25 and its receptor CCR9 (Brandtzaeg and Johansen 2005; Macpherson et al. 2012).

2.4.2 *Class Switch Recombination to Generate IgA*

Induction of pathogen-specific mucosal IgA must occur against a background of constant antigenic challenge from food, environmental antigens and a multitude of commensal microorganisms (Macpherson et al. 2012). In fact, IgA induction is highly sensitive to the presence of commensal bacteria. In their absence, laboratory animals have very low levels of IgA, but IgA expression can be switched on by their introduction. This process requires limited sampling of commensal bacteria by intestinal dendritic cells which drives induction of IgA (Macpherson and Uhr 2004), a point which will be returned to below.

In order to produce IgA antibodies, B cells must undergo class switch recombination (CSR), a process involving DNA splicing such that the VDJ segment encoding the variable domain of the heavy chain becomes positioned just upstream of the C α constant region sequence. CSR is regulated by the specific cytokine milieu. In the case of CSR to IgA, transforming growth factor- β (TGF β) and interleukin 4 (IL-4) act to promote the switch, with IL-2 and IL-10 having synergistic effects and IL-5 and IL-6 enhancing secretion of IgA (Coffman et al 1989). The mechanism entails engagement of the TGF β receptor, which signals via SMAD2, SMAD3 and SMAD4 transcription factors in concert with RUNX3, another DNA binding factor. These bind specifically to promoter regions upstream of the initiation (I) α -exon (an initiation point specific to the IgA constant region), initiating transcription and opening the DNA structure. Thereafter, the DNA-editing enzyme activation-induced cytidine deaminase (AID) is able to initiate CSR specifically to IgA.

CSR is also regulated by nuclear factor κ B (NF κ B), through involvement at the I α locus and through AID induction. NF κ B can be activated by events following from the engagement of CD40 on B cells by CD40L on T cells or in a T cell-independent manner by the cytokines BAFF and APRIL which can be produced by GALT dendritic cells and trigger through specific receptors on B cells (Cerutti 2008). These two alternatives explain how induction of IgA CSR can potentially occur through both T-dependent and T-independent mechanisms.

Returning to the induction of protective IgA antibodies by commensal bacteria mentioned earlier, there are likely a number of mechanisms at play. One possibility is that dendritic cells present bacterial products derived from commensal sampling to B cells, thereby activating Toll-like receptors (TLRs). Through signalling cascades in the B cell, AID expression may then be induced. Microbial products may

also stimulate the release of BAFF and APRIL by dendritic cells, which will drive IgA class switching. Another mechanism that has been described involves the triggering of intestinal epithelial cells to release APRIL after they sense bacteria through TLRs (He et al. 2007). These various mechanisms undoubtedly have parts to play in the flexible and complex homeostasis of the mucosal immune system that is necessary to prevent excessive responsiveness to harmless commensals yet allow adequate responsiveness to more harmful microorganisms (Slack et al. 2012).

2.5 IgA in Other Species

2.5.1 *Evolutionary Considerations*

Studies by Vaerman and colleagues first demonstrated the presence of IgA in several mammals such as dog, cat, cow, sheep, goat, horse and pig (Vaerman et al 1969). It is now known by virtue of genetic sequence analysis and functional comparisons that IgA is present in all categories of mammals (placental, marsupials and monotremes) and also in birds.

The vast majority of mammals have a single IgA isotype. In other words, they possess a single C α gene encoding an IgA heavy chain constant region. The exceptions are humans, related primates and rabbits. Rabbits and related species (Lagomorpha) have a remarkable 13 C α genes (Burnett et al. 1989). Eleven of these are apparently expressed, although the level of each varies between different tissues (Spieker-Polet et al. 1993). The role of such a large number of subclasses remains an enigma but perhaps relates to the fact that rabbits have only a single IgG isotype, whereas many mammals that have a single IgA have several IgG subclasses.

Chimpanzees, gorillas and gibbons are like humans in that they have two C α genes encoding IgA1 and IgA2 subclasses (Kawamura et al. 1992). An equivalent of IgA1 is also present in orangutans, but they have lost their IgA2 equivalent. The dual C α genes have arisen through duplication of the entire immunoglobulin heavy chain constant region locus in the ancestor common to the apes after the point of divergence from the monkeys. In some species, subsequent deletion or silencing of some of the duplicated genes has occurred (Kawamura and Ueda 1992). The elongated hinge seen in all IgA1 molecules has seemingly evolved only recently in evolutionary terms due to an insertion event.

Allotypic variation in IgA is exemplified by the allotypes of human IgA2 (see Sect. 2.3.2), but it is clear that such diversification is exhibited in various mammalian species. For example, IgA in rhesus macaques shows allotypic variation, with notable allelic polymorphisms in the hinge region (Scinicariello et al. 2004). Allotypic variation has also been observed in the IgA of sooty mangabeys, pig-tailed macaques and baboons (Scinicariello et al. 2006; Rogers et al. 2008) with a high degree of hinge heterogeneity being a prominent feature. Interestingly, the six IgA allotypes in mice also have major differences in their hinge regions (Phillips-Quagliata 2002), while hinge variation is also evident in pig IgA allotypes (Navarro et al. 2000).

Based on analysis in a limited number of avian orders (those represented by chickens, ducks and pigeons), IgA in birds is somewhat unusual in that it lacks a hinge region and has four constant regions in its heavy chain (Mansikka 1992). The level of homology between chicken IgA and mammalian IgAs is around 35–37 %, consistent with evolution of IgA before the divergence of mammals and birds.

In lower vertebrate species that lack IgA, other immunoglobulin isotypes appear to undertake the functions of a mucosal antibody. In some, immunoglobulin analogous to IgM will fulfil this role, while in others, alternative isotypes have evolved independently for this purpose. For example, the external surfaces of amphibians seem to be protected by IgX (Du et al. 2012), while IgT serves as a mucosally active immunoglobulin in teleost fishes (Zhang et al. 2010).

2.5.2 Species-Dependent Variability in Mucosal Immunoglobulins

IgA plays a common role in protection of external surfaces in many species (Snoeck et al. 2006). However, there are some important differences between species in terms of the levels and distribution of immunoglobulin isotypes in mucosal secretions. For example, while IgA is the predominant antibody isotype in human colostrum and milk, the same is not true for all mammals. In cows, sheep, goats and horses, the main immunoglobulin isotype in milk and colostrum is IgG. These species lack the transplacental transport of IgG that occurs in humans, and hence, ingestion of colostral-derived IgG by newborn animals is essential for survival. After ingestion, the IgG is transported across the gut epithelium in an active process that occurs for the first 2–3 days of life.

Another distinction is seen between the IgA systems of humans and animals commonly used for experimental purposes (i.e. mice, rats and rabbits). In these species, the serum IgA, as well as that in secretions, is mainly in the form of J chain-containing dimers. Moreover, unlike humans, these species express significant levels of pIgR on their hepatocytes, which results in highly efficient transport of polymeric IgA from the circulation into the bile and thereafter into the intestinal secretions. As a result, the main source of SIgA in the gut lumen of these species is the bile.

2.6 Role in Immune Defence Against Infections

2.6.1 Neutralisation and Blocking Activity and Synergy with Innate Humoral Factors

Specific IgA antibodies have been demonstrated to provide effective protection against a range of invading pathogens including viruses, bacteria and protozoa and their products such as toxins (Russell and Kilian 2005; Mantis et al. 2011)

(see Fig. 2.4). By direct interaction through their antigen-binding sites, IgA molecules can neutralise the activity of pathogens such as viruses and prevent attachment to host cells. Biologically active toxins derived from plants or pathogens can similarly be neutralised. In a process sometimes referred to as immune exclusion, SIgA can diminish the absorption of antigens to mucosal surfaces. The polymeric nature of SIgA means that it is capable of binding with high avidity to antigenic substances because each molecule has multiple antigen-binding sites (four for dimeric SIgA, eight for tetrameric SIgA).

As well as this general protective role at mucosal surfaces, SIgA has a specific role to play in protection of the newborn. There is overwhelming evidence that SIgA in human colostrum and milk is important in this capacity, and it is established that breastfeeding decreases infant death from both respiratory and gastrointestinal infections (Hanson and Korotkova 2002). SIgA is present at high concentrations in human colostrum and milk (up to 12 mg/ml). It displays specificity for a wide variety of microbial pathogens and can neutralise viruses and toxins. The SIgA in milk most likely acts as a molecular “paint”, neutralising the effect of microorganisms by preventing adherence and other invasion processes.

Innate defence factors present in mucosal secretions may interact with SIgA to enhance immune protection. For example, salivary mucins have been reported to undergo non-covalent interactions with SIgA (Fig. 2.4). This is thought to help to concentrate the factors at the tissue-environment interface and enhance the ability of the components to agglutinate bacteria (Biesbrock et al. 1991). Similarly, synergy between SIgA and the antimicrobial effects of the lactoferrin and lactoperoxidase systems has been described (Stephens et al. 1980; Tenovuo et al. 1982; Watanabe et al. 1984).

2.6.2 Intracellular Neutralisation

In addition to the protective effects that SIgA can mediate after release into mucosal secretions, it has become apparent that it may fulfil defensive functions during its passage through the mucosal epithelium. Based on *in vitro* studies using models of polarised epithelial cells, specific dimeric IgA molecules undergoing pIgR-mediated transcytosis through the cells have been shown to be able to neutralise endocytosed bacterial lipopolysaccharide (LPS) that had been taken up at the apical surface. The LPS and dIgA colocalised within the apical recycling compartment of the cells, preventing the proinflammatory events that would normally be triggered by the LPS (Fernandez et al. 2003) (Fig. 2.4).

Using similar *in vitro* systems, dimeric IgA molecules directed against viral envelope undergoing epithelial transcytosis have been shown to block growth of Sendai virus following infection at the apical surface (Mazanec et al. 1992) (Fig. 2.4). Using analogous systems, similar inhibitory effects were found for influenza virus (Mazanec et al. 1995), measles virus (Yan et al. 2002), rotavirus (Feng et al. 2002; Corthésy et al. 2006) and human immunodeficiency virus (HIV) (Huang et al. 2005; Wright et al. 2006). It appears that the apical recycling endosomes are the key point of intersection of the IgA and viral proteins.

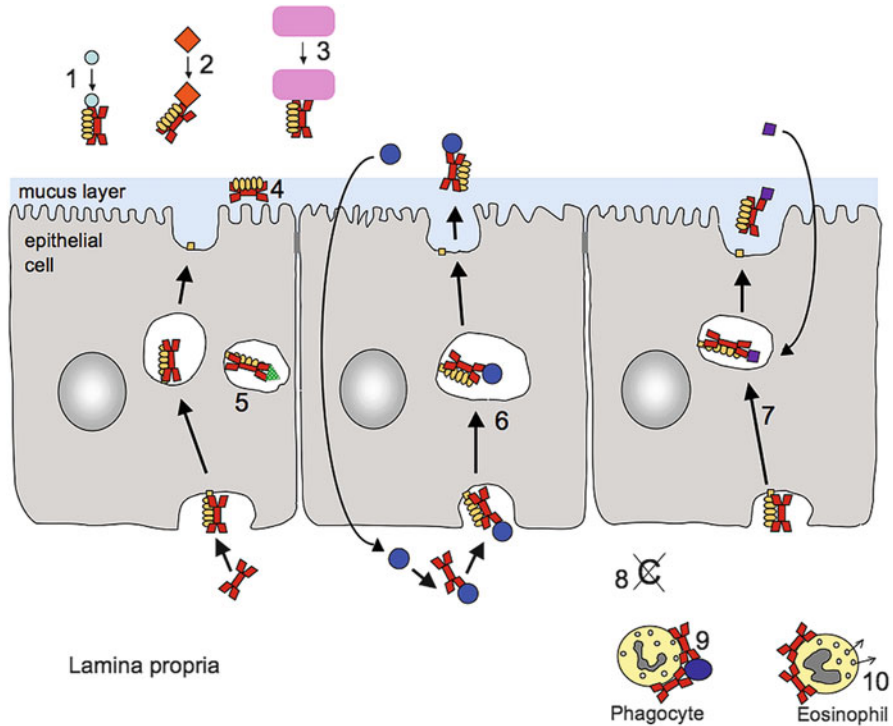


Fig. 2.4 *The roles of IgA in protection at mucosal surfaces.* 1 Inhibition of uptake of soluble or particulate antigens, 2 Neutralisation of biologically active toxins and viruses, 3 Inhibition of microbial adherence, 4 Enhancement of activities of innate humoral factors (e.g. mucin, lactoferrin, peroxidase system), 5 Intracellular neutralisation, 6 Elimination of immune complexes formed within the lamina propria, 7 Elimination of immune complexes formed within epithelial cells, 8 Inhibition of complement activation, 9 Antibody-dependent cell-mediated cytotoxicity and opsonisation, 10 Degranulation of eosinophils

Evidence that these *in vitro* observations may reflect *in vivo* capabilities has been derived from experiments in which systemically delivered IgA antibodies directed against an inner core protein of rotavirus were shown to prevent infection and cure existing infection in mice (Burns et al. 1996; Feng et al. 2002; Schwartz-Cornil et al. 2002).

2.6.3 Excretion of Antigenic Material Across Mucosal Epithelium

Remarkably, pIgR can transport dimeric IgA alone or in complex with antigen. Consequently, pIgR-mediated transport can deliver antigen-IgA immune complexes from tissues underlying the epithelium (such as the lamina propria) to the luminal surface of the epithelial cell barrier. This mechanism allows for removal and

excretion of soluble antigens, whether derived from microorganisms, diet or the environment (Kaetzel et al. 1991; Robinson et al. 2001) (Fig. 2.4). Virus particles that encounter specific dimeric IgA in the lamina propria, as well as immune complexes formed within epithelial vesicles, can be excreted via this same mechanism, thereby preventing the spread of infectious agents beyond the mucosal surfaces (Yan et al. 2002; Bomsel et al. 1998).

2.6.4 Glycan-Mediated Protective Activity

The N-linked oligosaccharides attached to IgA and SC impart to SIgA the capability for additional non-specific, innate responses to bacterial pathogens and certain of their products. These sugar moieties are able to bind to sugar-dependent receptors or fimbriae on bacterial surfaces and inhibit attachment to host mucosal surfaces (Wold et al. 1990; Ruhl et al. 1996). The demonstration of binding of SC to *Clostridium difficile* toxin A suggests that this is an additional means by which SIgA can recognise certain bacterial components (Dallas and Rolfe 1998) providing another way for SIgA to limit the effects of infection.

2.6.5 Interaction with Complement

IgA lacks the C1q binding motif necessary for binding of the first component of the classical complement pathway and thus is unable to activate this pathway. While this point is clear-cut, the ability of IgA to activate complement via the alternative pathway has been a subject of debate over the years. The consensus view that has emerged is that the reported activation of this pathway by IgA was most likely artefactual. Finally, SIgA has been reported to bind mannose-binding lectin and activate complement via the lectin pathway of complement activation (Roos et al. 2001). Further insights into the physiological significance of such activation are awaited since they may help resolve the controversy that has surrounded complement activation by IgA.

2.7 IgA Receptors

2.7.1 Host Receptors for IgA

In concert with the functions described in Sect. 2.6, IgA interacts with a range of host receptors present on different cell types to generate a variety of outcomes. Transport of IgA into mucosal secretions following interaction of dimeric IgA with

pIgR on epithelial cells has already been discussed (Sect. 2.3.5). Another important example is the IgA receptor Fc α RI, which mediates a variety of functions to help eliminate pathogenic invaders. The precise functions of other receptors, some characterised to a greater degree than others, are less clear. All demonstrate specificity for the α -heavy chain of IgA, although some, e.g. pIgR and Fc α / μ R, are seen to also interact with other immunoglobulin isotypes.

2.7.2 *Fc α RI*

Fc α RI, or CD89, is a member of a family of Fc receptors that falls within the much broader immunoglobulin gene superfamily (Bakema and van Egmond 2011a). However, it has key distinctions from the other Fc receptors in this group. Its gene lies in the leukocyte receptor cluster close to killer cell immunoglobulin-like receptors (KIR) and leukocyte immunoglobulin-like receptors on chromosome 19, quite unlike other Fc receptors such as the IgG-specific Fc γ R and the IgE-specific Fc ϵ RI, which are clustered on chromosome 1. Indeed, Fc α RI has closer amino acid similarity to the LRC members than to other immunoglobulin gene superfamily Fc receptors. It is a transmembrane glycoprotein with two immunoglobulin-like extracellular domains and a short cytoplasmic region that lacks any known signalling motifs. It associates via its transmembrane region with a dimer of the FcR- γ chain, a signalling chain that possesses two immunoreceptor tyrosine-based activation (ITAM) motifs within its cytoplasmic region. The globular extracellular domains of Fc α RI are positioned at an angle of approximately 90° to each other (Herr et al. 2003). Their relative orientation is very different from that of the extracellular domains of other Fc receptors (Herr et al. 2003; Woof and Burton 2004).

Fc α RI is expressed on neutrophils, monocytes, eosinophils, platelets and some macrophages and dendritic cells. It is also expressed on Kupffer cells in the liver where it is believed to play a role in mediating phagocytosis of pathogens that have entered the circulation and been opsonised by serum IgA (van Egmond et al. 2000).

Human Fc α RI binds equally well to human IgA1 and IgA2 and can engage both serum IgA and secretory IgA, although the outcomes may differ as discussed below. The sites of interaction on both Fc α RI and the Fc region of IgA have been defined, initially through mutagenesis analysis and subsequently through solving of the X-ray crystal structure of the complex of IgA1 Fc and the extracellular portion of the receptor (Wines et al. 1999; Wines et al. 2001; Carayannopoulos et al. 1996; Pleass et al. 1999; Herr et al. 2003). The hydrophobic core of the interaction essentially involves a region on the membrane distal domain of the receptor comprising Tyr53, Leu54, Phe56, Gly84 and His85 with contributions from Lys55, which interacts with the interface between the two domains of the IgA Fc region, comprising C α 2 residues Leu257 and Leu258 and C α 3 residues Met433, Leu441, Ala442, Phe443, and the aliphatic portion of Arg382. This mode of interaction is completely different from that of IgG with Fc γ R and IgE with Fc ϵ RI, despite considerable homology between both receptors and ligands (Woof and Burton 2004). The latter

receptors bind to regions lying at the “top” of the respective Fc regions, well away from this interdomain region.

Engagement of Fc α RI by IgA molecules clustered on the antigenic surface of a virus, bacterium or other foreign material can trigger an array of potent killing mechanisms. In the case of serum IgA, these processes include phagocytosis, release of activated oxygen species, cytokine release, degranulation and antibody-dependent cell-mediated cytotoxicity. While SIgA appears unable to trigger phagocytosis via Fc α RI, it can elicit a respiratory burst through the receptor on neutrophils in a manner dependent on the presence of the complement receptor CR3 (Mac-1, CD11b/CD18) (Stewart and Kerr 1990; van Spriel et al. 2002).

When Fc α RI molecules are effectively cross-linked by binding of IgA immune complexes or by engaging with IgA aggregated on an antigenic surface, they redistribute into detergent-insoluble lipid domains (Lang et al. 1999, 2001), where the Src kinase Lyn phosphorylates the ITAM motifs of the associated FcR- γ dimer. Subsequently, Syk, B lymphocyte kinase (Blk), phospholipase C- γ , Shc and growth factor receptor-bound protein 2 (Grb2) are recruited, and activation of multiple targets, such as PI3K, and a Grb2-containing multi-component adapter protein complex ensues. The GTPase Sos is then engaged and converts GDP-RAS to GTP-RAS, leading to activation of the Raf-1/MEK/MAP kinase and PI3-kinase pathways (reviewed by Bakema and van Egmond 2011a). Ultimately, this interlacing signalling cascade coordinates activation of transcription factors, gene expression and the archetypal mechanisms of pathogen elimination mentioned above – phagocytosis, respiratory burst and ADCC. Interestingly, some Fc α RI do not associate with FcR- γ chain dimer but are still able to bind IgA and endocytose IgA immune complexes, although the fate appears to be recycling rather than entry into the degradative pathway. Signalling via FcR- γ chain therefore does not seem essential for endocytosis (Launay et al. 1999). In another twist to the story, binding of monomeric ligand to Fc α RI has been demonstrated to trigger inhibitory rather than activatory signals via the FcR- γ chain ITAM leading to downregulation of events such as Fc γ R-mediated phagocytosis (Pasquier et al. 2005; Blank et al. 2009). This inhibitory signalling via ITAM, referred to as ITAMi, is suggested to have a role in the dampening of excessive immune complex-triggered responses.

2.7.3 *Fc α / μ R*

The expression profiles of Fc α / μ R, a receptor that binds both IgA and IgM, differ between humans and mice, suggesting that they play distinct roles in each species (Shibuya and Honda 2006). Little is known, as yet, about expression in other species. In humans, the receptor is found on follicular dendritic cells in tonsil (Kikuno et al. 2007) and on plasma cells, macrophages and Paneth cells in the lamina propria and intestinal germinal centres (Wang et al. 2009), locations that hint at a role in coordinating the immune response in mucosal tissues. However, the functional repertoire of the receptor remains to be elucidated.

The Fc α / μ R gene lies close to that of pIgR on human chromosome 1. There are other similarities with pIgR too. The N-terminal immunoglobulin-like domain of Fc α / μ R is homologous to D1 of pIgR, and they have been suggested to share structural similarities based on the presence of certain conserved residues (Hamburger et al. 2004). Of particular note, their CDR-like loops are similar. Since these regions in pIgR are believed to interact with dimeric IgA, Fc α / μ R may share similar ligand binding characteristics. In common with pIgR, Fc α / μ R interacts only with polymeric forms of IgA and IgM (Ghumra et al. 2009). However, unlike pIgR, the presence of J chain does not appear to be essential for binding (Yoo et al. 2011). A site at the C α 2-C α 3 domain interface of the IgA heavy chain, overlapping with those of Fc α RI and pIgR, has been shown to be critical for interaction with Fc α / μ R (Ghumra et al. 2009).

2.7.4 Other Receptors for IgA

Information on other receptors that bind IgA is more limited. These include the transferrin receptor (TfR or CD71), named for its involvement in iron metabolism, which appears to bind only to monomeric IgA1 possibly via the O-linked sugars of the hinge region (Moura et al. 2001). Another receptor that interacts with the oligosaccharide moieties of IgA, in this case the exposed terminal sugars on desialylated IgA, is the asialoglycoprotein receptor (ASGP-R) (Stockert et al. 1982). ASGP-R removes IgA molecules lacking sialic acid from the circulation and hence plays an important role in catabolism and regulation of IgA serum levels.

Another IgA-specific receptor has been described on intestinal M cells in both mice and humans (Mantis et al. 2002). Over the years, IgA has also been reported to bind to B cells, T cells and NK cells, but the precise identities of the receptors involved remain unresolved. Finally, one might mention the putative receptor for SC on eosinophils that may account in part for SIgA's particular ability to trigger degranulation of these cells (Lamkhioed et al. 1995).

2.8 Strategies Used by Pathogens to Perturb IgA Function

2.8.1 Advantages to Microorganisms of Circumventing IgA Function

Numerous pathogens including many that can cause serious disease have evolved mechanisms to specifically subvert the protection provided by IgA. Available evidence indicates that these mechanisms have frequently arisen independently in different organisms, suggesting that there is considerable evolutionary pressure to develop effective systems to attack IgA. Obviously, there are considerable benefits

for the organisms in question in terms of enhanced capability for colonisation and spread, particularly via mucosal invasion. Important examples include the production of proteases that cleave IgA into inactive fragments, the utilisation of IgA-binding proteins to competitively block interaction sites on IgA used by host Fc receptors and the use of proteins that can interact with pIgR to facilitate adherence and invasion at mucosal sites.

2.8.2 *IgA1 Proteases*

Certain bacterial pathogens produce proteases that specifically cleave IgA within the hinge region. The impact of the resulting release of the Fc region from the Fab portions has a dramatic effect on function. The Fab arms are still able to bind to bacterial antigens, but having done so, they lack the means to recruit the effector mechanisms that are normally evoked through the Fc region and hence are unable to trigger killing of the recognised bacteria. Moreover, their attachment prevents access of intact antibodies. Hinge cleavage is therefore an effective strategy to evade the protective functions of IgA.

The majority of IgA proteases cleave only IgA1. These so-called IgA1 proteases are produced by some important human pathogens that are associated with life-threatening infections (Kilian et al. 1996). For example, the principal causes of bacterial meningitis (*Neisseria meningitidis*, *Haemophilus influenzae* and *Streptococcus pneumoniae*) all secrete IgA1 proteases. Closely related but non-pathogenic *Neisseria* and *Haemophilus* species do not produce IgA1 proteases, underlining the noted association of these proteases with virulence (Polissi et al. 1998). IgA1 proteases are also produced by bacteria associated with vaginal and urinary tract infections, such as *Neisseria gonorrhoeae* and *Ureaplasma urealyticum*. Certain bacteria associated with disease in the oral cavity, notably *Streptococcus sanguis* and *Streptococcus mitis* known for their role in initiation of plaque formation, secrete IgA1 proteases also. The picture that emerges is that the microorganisms involved tend to colonise and even invade mucosal surfaces. Their production of IgA1 proteases presumably helps them establish a foothold within mucosal tissues.

All IgA1 proteases cleave C-terminal to one of the proline residues of the IgA1 hinge. The particular peptide bond cleaved in each case is indicated in Fig. 2.5. IgA2 lacks the susceptible hinge sequence and, therefore, is resistant to cleavage. The IgA1 proteases are remarkably specific and are known to cleave human IgA1 and the equivalents from gorillas and chimpanzees, but very few other substrates appear to exist. The structural requirements for effective substrate recognition and cleavage have been probed by mutagenesis (Senior et al. 2000; Batten et al. 2003; Senior and Woof 2005a). The susceptible bond must be suitably positioned relative to the Fc region for optimal cleavage (Senior and Woof 2005b). For some enzymes, structural elements within the C α 3 domain must be present for hinge cleavage to occur (Chintalacharuvu et al. 2003; Senior and Woof 2006). This finding, though

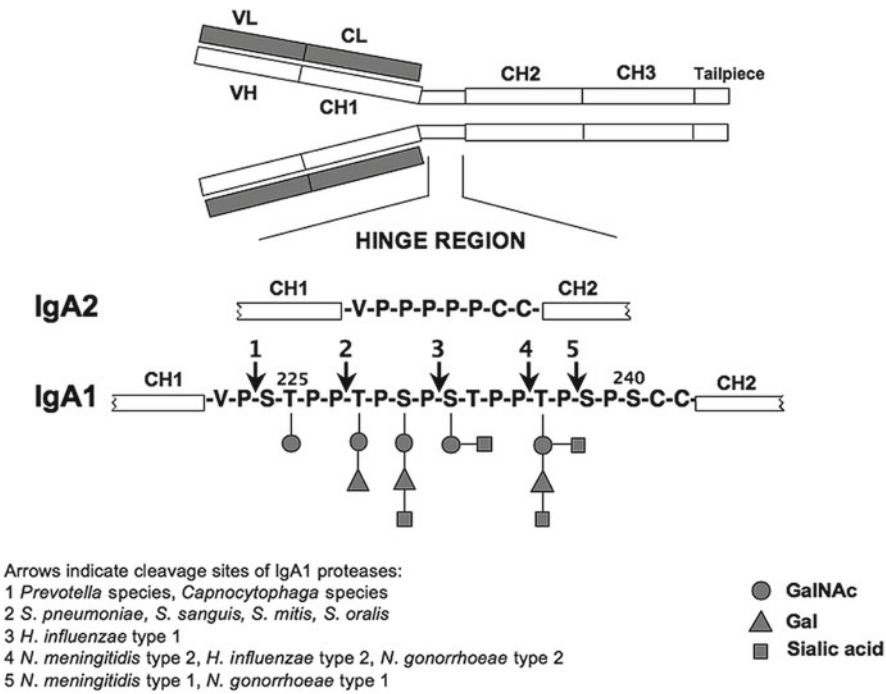


Fig. 2.5 Differences between the hinge regions of human IgA1 and IgA2. The amino acid sequences of the hinge regions are shown. Arrows above the IgA1 hinge sequence indicate the cleavage sites of particular IgA1 proteases. The O-linked oligosaccharides carried by the IgA1 hinge are indicated below the sequence

surprising, fits well with a model for IgA1-IgA1 protease interaction proposed on the basis of the solved crystal structure for an IgA1 protease from *H. influenzae* (Johnson et al. 2009). The model proposes that interactions between the IgA1 Fc region and a critical loop region of the protease hold the loop away from the active site, allowing access of the hinge peptide and subsequent cleavage. Therefore, IgA1 proteases appear to identify a substrate for cleavage through a combination of hinge sequence recognition and contextual recognition, at least in some cases.

2.8.3 IgA-Binding Proteins

IgA-binding proteins (IgA-BP) are known to be expressed by some important bacterial pathogens, including some streptococci and *Staphylococcus aureus*. Examples of these proteins in streptococci are Arp4 and Sir22 expressed on group A *streptococcus* (Frithz et al. 1989; Stenberg et al. 1994) and an unrelated protein known as β -protein that is expressed by group B *streptococcus* (Héden et al. 1991). Mutagenesis experiments showed that these IgA-BP all bind to the interdomain

region of IgA Fc, at a site overlapping with that for Fc α RI (Pleass et al. 2001). Importantly, the streptococcal IgA-BP inhibit both binding of IgA to Fc α RI and the subsequent triggering of killing mechanisms (Pleass et al. 2001). Simple blockade at this site therefore allows the bacteria to avoid those elimination processes normally triggered through Fc α RI.

In *Staphylococcus aureus*, a similar effect has been described, albeit mediated through a completely different IgA-BP called SSL7. The SSL7 toxin also binds to the interface between C α 2 and C α 3 and competitively inhibits Fc α RI binding (Wines et al. 2006; Ramsland et al. 2007). It appears that the evasion strategy of blocking immunoglobulin function by binding to the Fc interdomain region is a common one, used by a variety of bacterial species that infect different mammalian hosts (Lewis et al. 2008; Wines et al. 2012).

2.8.4 *Pneumococcal CbpA Binding to pIgR*

A surface protein of *Streptococcus pneumoniae* known as CbpA, PspC or SpsA has been shown to bind via a hexapeptide motif to domains D3–D4 of pIgR (Hammerschmidt et al. 2000; Lu et al. 2003; Elm et al. 2004). In vitro, in the absence of free SC or SIgA, the CbpA–pIgR interaction facilitates adherence of *S. pneumoniae* to epithelial cells and subsequent internalisation (Zhang et al. 2000). This co-opting of pIgR may therefore aid pneumococcal adherence to nasopharyngeal cells in vivo, leading to colonisation.

2.9 Potential of Therapeutic IgA Monoclonal Antibodies

Although monoclonal antibodies (mAbs) currently licenced for therapeutic use are all IgG-based, mAbs based on an IgA backbone may offer novel possibilities, given the unique structural and functional properties of this isotype (Dechant and Valerius 2001; Corth  sy 2003; Bakema and van Egmond 2011b). A number of studies, mostly early-stage investigations, have indicated that recombinant IgA mAbs directed against bacterial pathogens may offer a means to control or limit certain infections. For example, an IgA-based mAb targeting an adhesin protein on *Streptococcus mutans* as a means to control caries was found to limit oral recolonisation (Ma et al. 1998), and other IgA-based mAbs have shown promise against pathogens such as *S. pneumoniae*, *N. meningitidis*, *Bordetella pertussis* and *Mycobacterium tuberculosis* (van der Pol et al. 2000; Vidarsson et al. 2001; Hellwig et al. 2001; Balu et al. 2011). IgA-based or Fc α RI-directed approaches are also showing potential as novel cancer therapeutics (Stockmeyer et al. 2000; van Egmond et al. 2001; Dechant et al. 2002; Otten et al. 2005; Zhao et al. 2008; Lohse et al. 2011; Bakema et al. 2011). Future studies may reveal whether IgA mAbs can offer advantages in the physiological setting.

2.10 Concluding Remarks

IgA is marked out from the other antibody classes by its heterogeneity of form, its location within the body, its novel functions and the vast quantities that are produced each day. Historically, understanding of this complex antibody has lagged behind that of some of the other immunoglobulin isotypes, probably due to difficulties in isolation, compounded by species differences. However, there has been a resurgence of interest, and a clearer picture of IgA structure and function has emerged in recent years, spearheaded by advances in antibody engineering. Further research into IgA promises to open up new avenues for therapy and possibly also for improved vaccination strategies targeted to mucosal surfaces.

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