The human IgA–Fcα receptor interaction and its blockade by streptococcal IgA-binding proteins

J. M. Woof

Department of Molecular and Cellular Pathology, University of Dundee Medical School, Ninewells Hospital, Dundee DD1 9SY, U.K.

Abstract

IgA plays a key role in immune defence of the mucosal surfaces. IgA can trigger elimination mechanisms against pathogens through the interaction of its Fc region with FcαRs (receptors specific for the Fc region of IgA) present on neutrophils, macrophages, monocytes and eosinophils. The human FcαR (CD89) shares homology with receptors specific for the Fc region of IgG (FcγRs) and IgE (FceRIα), but is a more distantly related member of the receptor family. CD89 interacts with residues lying at the interface of the two domains of IgA Fc, a site quite distinct from the homologous regions at the top of IgG and IgE Fc recognized by FcγR and FcεRI respectively. Certain pathogenic bacteria express surface proteins that bind to human IgA Fc. Experiments with domain-swap antibodies and mutant IgAs indicate that binding of three such proteins (Sir22 and Arp4 of Streptococcus pyogenes and β protein of group B streptococci) depend on sites in the Fc interdomain region of IgA, the binding region also used by CD89. Further, we have found that the streptococcal proteins can inhibit interaction of IgA with CD89, and have thereby identified a mechanism by which a bacterial IgA-binding protein may modulate IgA effector function.

The role of human IgA in immunity

Human IgA is the most abundant antibody class in the body. The daily production of IgA, estimated to be of the order of 65 mg/kg, far exceeds that of the other antibody classes combined [1]. IgA is an important serum antibody, but perhaps plays its most important role as the major Ig in the seromucous secretions that bathe mucosal surfaces such as those of the tracheobronchial, gastrointestinal and genito-urinary tracts. These tracts represent major potential sites of invasion due to their enormous surface area. Hence secretory IgA offers a critical first line of defence against many invading pathogens. There is also growing acceptance that serum IgA acts as an important second line of defence against micro-organisms that have breached the mucosal defences [2].

Human IgA structure

Two subclasses of human IgA, termed IgA1 and IgA2, are present in both serum and secretory forms, though at different proportions in the two locations. Both subclasses display the typical antibody configuration of two heavy chains and two light chains arranged into two identical Fab arms, responsible for antigen binding, separated from a single Fc region by a flexible region known as the hinge. The Fc region mediates the effector function of the antibody, designed to bring about the destruction of the target recognized as foreign by the Fab arms. For IgA, a critical effector mechanism is that triggered by interaction of its Fc region with the Fcα receptor (the receptor specific for the Fc region of IgA, FcαR; CD89), present on neutrophils, monocytes, macrophages, eosinophils and certain other cells [3].

No X-ray crystallography data are currently available for human IgA, but recent work using X-ray and neutron scattering has shed light on the likely conformation adopted by human IgA1 [4]. The antibody appears to have an ‘average’ ‘T’-shaped structure in which the tips of the Fab arms are spaced at 23 nm apart. This suggests that IgA1 is able to bind to two antigen molecules separated by a much greater distance than those within the comparatively more limited reach (13–16 nm) of IgG. This capability may be advantageous in the recognition of certain pathogens, particularly if, as in some bacteria, they express repeated antigenic structural motifs spaced along their surface.

Human FcαR

Human FcαR (CD89) displays homology to the receptors specific for the Fc region of IgG (FcγR,
FCyRII and FCyRIII and to the high-affinity receptor specific for the Fc region of IgE (FCzR). All have evolved as members of the Ig gene superfamily, and possess usually two or, in the case of FCyRII, three extracellular Ig-like domains responsible for ligand binding. FCzR is the least closely related member of this family and is in fact encoded on chromosome 19q13.4 within the so-called leukocyte receptor cluster, which encodes many natural killer cell inhibitory receptors (KIRs) and Ig-like transcripts (ILTs), rather than on chromosome 1q32.3 like the other Fc receptors. The ligand-binding α chain of FCzR has two extracellular Ig-like domains, and associates via its transmembrane region with a disulphide-bonded homodimer of the γ subunit, found as the signalling component of many Fc receptors. Signalling motifs in the intracellular region of the γ chains are important triggers for many of the effector mechanisms of the receptor. These immunoreceptor tyrosine-based activation motifs (ITAMs), typically Tyr-Xaa-Xaa-Leu-Xaa,-Tyr-Xaa-Xaa-Leu (where Xaa is any amino acid, become phosphorylated following receptor cross-linking and serve as sites promoting signalling-complex formation [5].

Interaction of IgA and the human FCzR

The interaction site on FCzR for IgA has been localized to the apical F-G region of the first (membrane-proximal) domain of the two extracellular domains of the receptor through a series of site-directed mutagenesis experiments [6]. In particular, residues Tyr-35 and Arg-82 have been implicated in the interaction, with contributions also from Tyr-81 and Arg-52 [7].

Turning to IgA, a range of mutagenesis experiments has been informative in localization of the interaction site for FCzR. Mutant antibodies in which CH3 domains of the IgA Fc were exchanged between human IgA1 and human IgG1 were found to be unable to bind FCzR, indicating a requirement for both domains in FCzR recognition [8,9]. A number of IgAs, each with a point substitution within two loops lying at the interface between the CH2 and CH3 domains were found either to no longer bind the receptor or to display substantially reduced affinity [8,9]. Further, their reduced abilities to trigger neutrophil respiratory bursts via the receptor mirrored these reductions in affinity [9]. Thus the two loops (Leu-257–Gly-259 in the CH2 domain and Pro-440–Phe-443 in the CH3 domain) have been identified as playing a critical role in FCzR binding and triggering (Figure 1).

This site contrasts markedly with the equivalent site on IgG for FCyRI and that on IgE for FcERI, despite the fact that both receptors and ligands share considerable homology. On IgG, the sites for FCyRI, FCyRII and FCyRIII occupy distinct but overlapping sites at the hinge-proximal end of the CH2 domain [10−12], whilst in IgE the site for FcERI lies in the equivalent position at the top of the CH3 domain [13]. One can speculate that the alternative arrangement of the Fc relative to the Fab arms seen in the average T-shape of IgA1 may provide reduced accessibility to the N-terminus of the Fc and may have thereby favoured evolution of an FCzR site at the interdomain region of the Fc.

Figure 1

Molecular model of human IgA1 [4]

The model highlights in black the residues in the Fc region essential for FCzR binding (heavy chain on the right) and streptococcal IgA-BP interaction (heavy chain on the left). For clarity, only one of each site is shown, but equivalent sites exist on each heavy chain.

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Figure 2
A simplified view of a possible mechanism by which Sir22 IgA-BP might interfere with IgA-mediated clearance of group A streptococci

An IgA molecule specific for surface antigens on a group A streptococcal cell is shown binding to two antigen molecules through its Fab arms. The IgA-binding region of the Sir22 protein is simultaneously interacting with the interdomain region in the IgA Fc, thereby blocking access to the same region by the FcαR on an adjacent neutrophil.

Streptococcal IgA-binding proteins (IgA-BPs)
A number of pathogenic bacteria express proteins on their surfaces that bind to the Fc regions of IgA or IgG. Important examples of the IgG-binding proteins are staphylococcal Protein A and streptococcal Protein G, both used very widely as valuable laboratory tools to isolate or detect IgG. Despite their wide use, their biological function remains unclear.

IgA-BPs have been described in many strains of group A streptococci (Streptococcus pyogenes) and group B streptococci [14–16]. Both of these are important human pathogens. Group A streptococci commonly cause acute sore throat and skin infections and may also cause a life-threatening toxic-shock syndrome. Moreover, infections with group A streptococci may be followed by rheumatic fever or acute glomerulonephritis, causing heart and kidney damage, respectively. IgA-BPs expressed by this bacterium include proteins Arp4 [16] and Sir22 [17], members of the M protein family, a group of coiled-coil proteins implicated in virulence. Group B streptococci are the most common cause of life-threatening bacterial infection in newborn babies, which are infected by their mothers during late pregnancy or childbirth. Certain group B streptococcal strains express an IgA-BP, unrelated to those of S. pyogenes, termed β protein [18].

Interaction of IgA with streptococcal IgA-BPs
Experiments with domain-swap antibodies and mutant IgAs have shown that Arp4, Sir22, β protein and a 50-amino acid peptide derived from Sir22 bind to similar sites between the two Fc domains [19]. In particular, residues Leu-257, Pro-440 and Phe-443 are predicted to play key roles in binding to the IgA-BP. Importantly, these streptococcal proteins appear to share the same interaction site on IgA as human FcαR (Figure 1).

Inhibition of IgA effector function by streptococcal IgA-BPs
An investigation into the ability of Sir22 and Arp4 to influence the binding of IgA to human FcαR on neutrophils revealed that the streptococcal IgA-BPs were able to inhibit IgA binding to FcαR [19]. Moreover, the same effect was seen with the Sir22-derived peptide but not with a control peptide, indicating that the effect was specific. Further, Arp4 was found capable of inhibiting a neutrophil respiratory burst triggered by binding of IgA to FcαR [19].
Mechanism for blockade of IgA function

Taken together, the above results indicate that the streptococcal proteins can block the binding of FcαR by IgA and, in the case tested (Arp4), can also inhibit FcεR triggering. Thus the streptococcal IgA-BPs may be capable of perturbing IgA function during a bacterial infection. Figure 2 illustrates one possible mechanism by which such disruption to IgA function might be achieved. Here, an IgA molecule specific for a surface antigen on a group A streptococcal cell binds via antigen-binding sites at the tips of the Fab arms. The IgA-binding region of the Sir22 molecule, which extends some distance out from the cell surface, may then engage the Fc region of the IgA molecule. Access to the same Fc site by FcαR on an approaching neutrophil is thus prevented. The outcome is that the bacterium evades the elimination processes that would normally be triggered via FcαR ligation. After many years of uncertainty over the pathogenic role of bacterial IgG-binding proteins such as Proteins A and G, the mechanism described here may offer new insights into the possible advantages that Ig-binding proteins may afford pathogenic bacteria.

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References


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