FcγRs in Health and Disease

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Abstract Genetic defects affecting the humoral immune response and especially the production of antibodies of the immunoglobulin G (IgG) isotype result in a heightened susceptibility to infections. Studies over the last years have demonstrated the crucial role of Fc-receptors for IgG (FcγRs) widely expressed on innate immune effector cells in mediating the protective function of IgG. During the last years, additional ligands interacting with FcγRs as well as additional receptors binding to IgG glycosylation variants have been identified. In this review, we discuss how the interaction of these different ligands with classical and novel Fcγ-receptors influences the immune response and which strategies microorganisms have developed to prevent them.

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1 Introduction

Apart from physical barriers, cells of the innate immune system, including mast cells, neutrophils, monocytes, and macrophages represent one of the first lines of defense against pathogenic microorganisms. Armed with a multitude of receptors, such as the Toll-like receptor family, recognizing danger and pathogen associated molecular patterns (DAMPs and PAMPs), they are able to recognize microorganisms directly and thereby prevent an overwhelming infection (Iwasaki and Medzhitov 2010). In the absence of adaptive immunity, however, many infections cannot be cleared, emphasizing the importance of the interplay between the two arms of the immune system. Antibodies, the hallmark of the adaptive immune response, are essential in providing protection against recurrent infections (Ballow 2002). While low affinity antibodies of the IgM isotype are characteristic for the early immune response, antibodies of the IgG subclass dominate the later response and are typically of higher affinity and exquisite specificity for the respective target antigen. Genetic defects affecting the production of high affinity IgG antibodies often result in a heightened susceptibility to microbial infections emphasizing the protective role of this isotype (Ballow 2002). Studies performed in mouse model systems over the last decade have led to the conclusion that the underlying mechanism of this protective activity of IgG, which consists of four different subclasses in mice (IgG1, IgG2a/c, IgG2b, IgG3) and humans (IgG1–IgG4), is the recruitment and activation of innate immune effector cells via receptors specific for the IgG Fc (fragment crystallizable) domain (Fcγ-receptors, FcγR) (Hogarth 2002; Nimmerjahn and Ravetch 2008b; Takai 2002). Depending on the effector cell, crosslinking of these receptors results in cell degranulation, release of different cytokines/chemokines, phagocytosis, or antibody dependent cellular cytotoxicity (ADCC). Thus, Fc-receptors provide the link between the high specificity of the adaptive immune system and the powerful effector functions of cells of the innate immune system and target these proinflammatory activities to sites of infection or healthy tissues during autoimmune disease (Hogarth 2002; Nimmerjahn and Ravetch 2008b; Takai 2002). In contrast to the early IgM dominated immune response, which largely depends on the activation of the classical complement pathway, marking microorganisms for phagocytosis via complement receptors or initiation of bacterial lysis through the generation of lytic membrane attack complexes, activation of the complement pathway is not essential for IgG mediated effector functions, although it can enhance the activity of certain IgG subclasses (Azeredo da Silveira et al. 2002; Carroll 2004; Clynes and Ravetch 1995; Nimmerjahn and Ravetch 2005; Ravetch and Clynes 1998; Sylvestre et al. 1996; Uchida et al. 2004). While this proinflammatory activity of IgG is desirable in the case of an infection, it leads to severe tissue and organ damage if directed toward healthy tissues during autoimmune disease (Hogarth 2002; Nimmerjahn and Ravetch 2008b; Takai 2002). Several factors, including the individual IgG subclass and the antibody glycosylation pattern, can influence the quality and strength of this interaction (Nimmerjahn and Ravetch 2006). Besides IgG, other molecules such as members of the evolutionary conserved pentraxin family can bind to FcγRs

(Marnell et al. 2005; Woof and Burton 2004). More recently, it was shown that certain antibody glycosylation variants can bind to other cell surface receptors belonging to the family of C-type lectins unrelated to the family of classical FcγRs (Anthony et al. 2008a, b; Kaneko et al. 2006b; Nimmerjahn and Ravetch 2008a). This review summarizes our current understanding of how the interaction of these different ligands with cellular FcγRs is regulated and how this might help develop novel therapeutic avenues for the optimization of antimicrobial and the amelioration of autoreactive antibody responses.

2 The Family of Canonical Fcγ-Receptors

FcγRs are a conserved family of glycoproteins that belong to the IgG superfamily and are comprised of a ligand binding a-subunit consisting of two or three C2-type extracellular domains (Fig. 1). In mice, monkeys, humans and other mammalian species the family of FcγRs is comprised of several activating (FcγRIA, IIA, IIC, IIIA in humans; FcγRI, III, IV in mice) and one inhibitory (FcγRIIB) member (Hogarth 2002; Nimmerjahn and Ravetch 2008b; Takai 2002; Willcocks et al. 2009). Whereas the inhibitory FcγR has an immunoreceptor tyrosine based inhibitory motif (ITIM) in its cytosolic domain, the majority of activating FcγRs have to

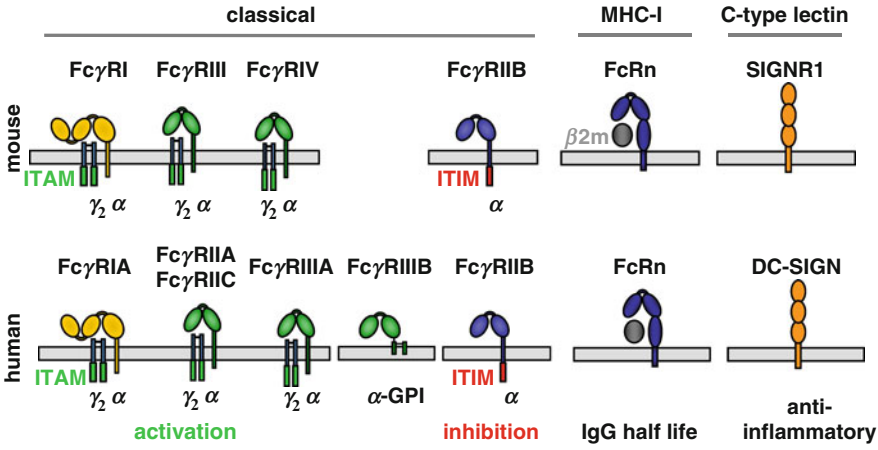

Fig. 1 The extended family of mouse and human Fcγ-receptors. In mice and humans the family of classical FcγRs consists of several activating and one inhibitory member. In addition, humans have a GPI-linked FcγR (FcγRIIIB) exclusively expressed on neutrophils. The neonatal FcRn is responsible for IgG half life in mice and humans and belongs to the family of major histocompatibility class I (MHCI) molecules. More recently, mouse SIGNR1 and its human orthologue DC-SIGN joined the family of IgG binding proteins with a selective specificity for IgG glycoforms rich in terminal sialic acid residues (see text for further details)

associate with signaling adaptor proteins containing immunoreceptor tyrosine based activation motifs (ITAM) such as the FcR common γ-chain (γ-chain). In humans and monkeys, there are some exceptions to this rule as FcγRIIA and FcγRIIC have an ITAM in their cytosolic domain and do not require signaling adaptor molecules for cell surface expression and functionality (Fig. 1) (Willcocks et al. 2009). Besides these differences in signal transduction, the other distinguishing feature among the family members is the affinity and specificity for the different IgG subclasses. In analogy to the high affinity Fc-receptor for IgE (FcεR), there is one high affinity receptor for IgG (FcγRI or CD64), which has nanomolar affinity for select IgG subclasses (IgG2a/c in mice; IgG1/3 in humans) and is saturated in the presence of serum IgG on cells such as monocytes in the blood. All the other receptors have a low to medium affinity in the micromolar range and can only bind to IgG if present in the form of immune complexes (ICs) (Nimmerjahn and Ravetch 2008b). Structural analysis of human IgG together with FcγRIIIA showed that IgG–FcgR binding occurs in a one to one ratio and that the sugar side chains of IgG and FcγRs are critically involved in this binding (Ferrara et al. 2006; Mimura et al. 2001; Radaev et al. 2001; Sondermann et al. 2000). FcγRs are expressed on the majority of innate immune effector cells such as basophils, eosinophils, mast cells, monocytes, macrophages, NK cells and neutrophils. Among these cell lineages, monocytes and macrophages express the broadest repertoire of activating FcγRs (I, III, and IV), whereas neutrophils express FcγRIII and IV, and NK cells selectively express FcγRIII. In addition, dendritic cells (DCs) essential for the initiation of adaptive immune responses, and B cells do express FcγRs. Early studies have also identified FcγR expression on some T cell populations although the role of these receptors for T cell activity or development is unclear and requires further analysis (Anderson and Grey 1974; Leclerc et al. 1977; Stout and Herzenberg 1975). A hallmark of this receptor family is the coexpression of activating and inhibitory receptors on the majority of innate immune effector cells and DCs. Thus, the simultaneous triggering of activating and inhibitory signaling pathways sets a threshold for cell activation and regulates cellular effector functions. Indeed, deletion of the inhibitory FcγRIIB resulted in heightened IgG dependent proinflammatory reactions, DC maturation and antigen presentation *in vivo* (Boruchov et al. 2005; Dhodapkar et al. 2005; Kalergis and Ravetch 2002; Nimmerjahn and Ravetch 2008b; Takai et al. 1996). An exception to this rule is NK cells which solely express FcγRIIIA (CD16) in humans and FcγRIII in mice. Recently, a small subpopulation of NK cells has been shown to express FcγRIIB, although the functional role of this NK cell subset remains to be established (Dutertre et al. 2008). B cells do not express activating FcγRs, but express the inhibitory Fc-receptor, which regulates positive signals initiated via the B cell receptor. The importance of FcγRIIB on B cells was demonstrated by the development of autoantibodies and a severe autoimmune disease similar to human systemic lupus erythematosus (SLE) in mice deficient for this receptor (Baerenwaldt and Nimmerjahn 2008; Bolland and Ravetch 1999, 2000; Daeron and Lesourne 2006; Ravetch and Lanier 2000; Takai 2002; Takai et al. 1996).

Based on genomic localization and sequence similarity in the extracellular portion, orthologous receptors can be identified between mice and humans (Hirano et al. 2007; Nimmerjahn and Ravetch 2006). Thus, the high affinity receptors FcγRIA/FcγRI and the low affinity receptors FcγRIIB cluster in the same group (Fig. 1). Similarly, human FcγRIIIA/mouse FcγRIV and human FcγRIIA/mouse FcγRIII share a high level of sequence homology in their extracellular domains (Nimmerjahn and Ravetch 2006). Despite this similarity caution should be taken in a one to one transfer of data obtained in mouse models to the human system as the ligands (the IgG subclasses) and the cellular expression pattern of some of the receptors differ between mice and humans. Thus, human FcγRI binds two IgG subclasses (IgG1and IgG3) with high affinity whereas mouse FcγRI only binds IgG2a/c with nanomolar affinity. Similarly, mouse FcγRIV (not expressed on NK cells) has the capacity to recognize IgE whereas human FcγRIIIA (expressed on NK cells) does not (Hirano et al. 2007; Mancardi et al. 2008). Moreover, humans express several allelic variants of the low affinity receptors FcγRIIA and FcγRIIIA which greatly differ in their affinity for the different IgG subclasses (Bruhns et al. 2009; Ravetch and Nimmerjahn 2008). Thus, human IgG2 binds only to an FcγRIIA variant carrying a histidine at position 131 (FcγRIIA-131H) whereas the allele carrying an arginine allele (FcγRIIA-131R) has a very low affinity for this IgG subclass. Similarly, FcγRIIIA with a valine residue at position 158 (FcγRIIIA-158V) has a much higher affinity for IgG1 and IgG3 than its allelic counterpart with a phenylalanine residue (FcγRIIIA-158F) at this position. Studies with human patient cohorts suggest that these differences in affinity impact the outcome of therapeutic success with antitumor antibodies, for example (Cartron et al. 2002; Weng et al. 2004; Weng and Levy 2003). To mimic these allelic differences in the future, novel mouse models carrying these allelic variants of the human FcγRs will be essential. Nonetheless, classical mouse models have been and will continue to be detrimental for deciphering the role of the family of FcγRs for antibody activity in infection and autoimmunity which will be discussed in the following paragraphs.

3 Regulation of IgG Activity *In Vivo*

Given the crucial role of FcγRs for IgG mediated effector functions, several studies have addressed the issue about which activating FcγRs were involved in mediating the activity of the individual IgG subclasses. *In vitro* studies indicated that IgG1 can only bind to FcγRIII, IgG2a/c can bind to all activating FcγRs and IgG2b binds to FcγRIII and FcγRIV. IgG3, in contrast, did not bind with significant affinity to any of the known FcγRs in C57BL/6 mice, although binding to an FcγRI allele in NOD mice was described (Gavin et al. 1998). Consistent with these in vitro data, IgG1 activity was abrogated in mouse strains deficient in FcγRIII (Hazenbos et al. 1996; Meyer et al. 1998; Nimmerjahn and Ravetch 2005, 2006). In contrast, the situation for IgG2a/c and IgG2b is more complicated: in some model systems the activity of

these subclasses was abrogated in FcγRIII knockout animals whereas in others it was not. In models of IgG2b dependent platelet depletion, B cell depletion, and nephrotoxic nephritis, for example, blockade of FcγRIV function prevented platelet and B cell depletion and kidney inflammation (Hamaguchi et al. 2006; Kaneko et al. 2006a; Nimmerjahn et al. 2005; Nimmerjahn and Ravetch 2005). In the case of IgG2b dependent autoimmune hemolytic anemia (AIHA), acute glomerular inflammation and IC induced lung inflammation, both FcγRIII and FcγRIV were essential for the activity of this IgG subclass (Baudino et al. 2008; Giorgini et al. 2008; Syed et al. 2009). For IgG2a/c a similar picture emerges as for IgG2b with additional contributions of the high affinity Fc-receptor depending on the system model used (Baudino et al. 2008; Bevaart et al. 2006; Ioan-Facsinay et al. 2002; Otten et al. 2008). Together with the aforementioned correlation of allelic variants of FcγRIIA and FcγRIIIA with the activity of therapeutic antibodies in human cancer patients this indicates that the low affinity FcγRs are critical for IgG dependent effector functions in mice and humans.

While these studies confirmed the crucial role of FcγRs for IgG activity they did not explain another observation that was made in several *in vivo* model systems of autoimmunity and infection, suggesting that the different IgG subclasses have a different activity *in vivo*. Using IgG subclass switch variants of platelet or red blood cell (RBC) specific antibodies it was demonstrated that IgG2a/c and IgG2b were superior to the other IgG subclasses in mediating phagocytosis of opsonized platelets or RBCs compared to IgG1 and IgG3, respectively (Fossati-Jimack et al. 2000; Nimmerjahn et al. 2005; Nimmerjahn and Ravetch 2005). Similarly, IgG2a/c mediated depletion of B cells, syngeneic melanoma cells, and T cell lymphomas was far more efficient compared to antibodies with an IgG1 Fc-fragment, for example, consistent with earlier results obtained in vitro (Kaminski et al. 1986; Kipps et al. 1985; Lambert et al. 2004; Nimmerjahn and Ravetch 2005; Uchida et al. 2004). Further confirming this observation glomerular inflammation induced by IgG subclass switch variants was most severe for the IgG2a/c subclass followed by IgG2b and a much weaker activity of IgG1 (Giorgini et al. 2008). Similarly, antimicrobial antibodies of the IgG2a/c subclass yielded enhanced protection from the development of poliomyelitis following infection with lactate dehydrogenase elevating virus or enhanced phagocytosis of opsonized *Cryptococcus neoformans* (Markine-Goriaynoff and Coutelier 2002; Schlageter and Kozel 1990). A possible explanation for this hierarchy of activities was afforded by the affinities of the different IgG subclasses toward their triggering activating and inhibitory FcγR pairs. Thus, IgG1 has a higher affinity for the inhibitory FcγRIIB than toward the activating FcγRIII, resulting in a high threshold for activation. In contrast, IgG2a/c and IgG2b have a much higher affinity for the activating FcγRIV than for the inhibitory FcγR, thus being less influenced by cotriggering. Consistent with this in vitro data, deletion of the inhibitory FcγRIIB most strongly enhances the activity of IgG1 in models of platelet depletion and tumor cell destruction (Nimmerjahn and Ravetch 2005). Of note, this affinity based model of IgG subclass activity can be influenced by several factors, including the varying FcγR repertoire of individual innate immune effector cells and DCs and cytokines that can alter the ratio of

activating to inhibitory FcγR expression. Thus, TH1-type cytokines, LPS, and the anaphylatoxin C5a have been shown to increase activating FcγR expression (Nimmerjahn and Ravetch 2008b; Schmidt and Gessner 2005). In contrast, TH2-signature cytokines such as IL4 had the opposite effect, with the exception of B cells where IL4 was suggested to downmodulate expression of FcγRIIB (Nimmerjahn and Ravetch 2006). Apart from the expression level of the individual FcγRs, recent studies have highlighted the role of the sugar side-chain of IgG which is attached to the asparagine 297 (N297) residue in the IgG heavy chain in modulating the affinity to activating FcγRs which will be discussed in the next chapter.

4 Influence of Antibody Glycosylation and Novel Fcγ-Receptors

All immunoglobulin isotypes are glycoproteins with a varying amount of sugar side chains attached to the protein backbone. In contrast to IgM, IgA, and IgE which contain multiple exposed sugar side chains, the IgG associated sugar domain is constrained by the groove formed by the two individual IgG heavy chains (Nimmerjahn and Ravetch 2008b). Deletion of this sugar domain results in an altered conformation and severely impaired binding to cellular FcγRs and diminished activation of the complement pathway (Shields et al. 2001). Compared to the homogeneous composition of the sugar domain of the other Ig isotypes the IgG associated sugar moiety is heterogeneous. Thus, in a healthy individual more than 30 different IgG glycosylation variants can be detected in the serum of mice and humans (Arnold et al. 2007). This heterogeneity stems from variable additions of terminal and branching sugar residues such as sialic acid, galactose, *N*-acetylglucosamine and fucose. Interestingly, this glycosylation pattern of serum IgG changes during active autoimmune disease in mice and humans where glycoforms rich in terminal sialic acid and galactose residues were diminished (Bond et al. 1990; Kaneko et al. 2006b; Mizuochi et al. 1990; Nimmerjahn and Ravetch 2008a). A similar change in serum IgG glycosylation pattern was observed with older age, whereas during pregnancy IgG glycoforms rich in terminal sialic acid and galactose residues were increased and correlated with remission of disease (Arnold et al. 2007; Rook et al. 1991; van de Geijn et al. 2009). Although the function of this altered glycosylation pattern is not fully understood, recent evidence points toward an important role of differential IgG glycosylation in modulation of IgG activity (Jefferis 2009). The absence of the branching fucose residue, for example, results in a selective increase of affinity of IgG subclasses to human FcγRIIIA and its mouse orthologue FcγRIV (Nimmerjahn and Ravetch 2005; Shields et al. 2002; Shinkawa et al. 2003). This increased affinity results in enhanced *in vivo* activity as demonstrated by the ability to prevent tumor growth in various model systems (Nimmerjahn and Ravetch 2007a). In contrast, the presence of high levels of terminal sialic acid residues diminished the affinity of human and mouse IgG for the family of classical FcγRs, consistent with a lower proinflammatory activity (Anthony et al. 2008a; Kaneko et al. 2006b; Scallon et al. 2007). Importantly,

however, sialic acid rich IgG glycovariants not only display reduced proinflammatory activity, as a result of the diminished binding to classical FcγRs, but they actually gained an active anti-inflammatory activity of IgG, which was able to suppress the proinflammatory activity of other autoantibodies (Anthony et al. 2008a, b; Kaneko et al. 2006b; Nimmerjahn and Ravetch 2007b). This finding might explain the long known anti-inflammatory activity of infusion of high doses of pooled serum IgG from several thousands of donors (IVIg therapy), which has been in use for nearly three decades as an efficient symptomatic treatment of different human autoimmune diseases, including thrombocytopenia, rheumatoid arthritis and chronic inflammatory demyelinating polyneuropathy (Nimmerjahn and Ravetch 2008a). A recent study identified SIGNR-1 (specific ICAM3 grabbing nonintegrin related 1) and its human orthologue DC-SIGN (dendritic cell specific ICAM3 grabbing nonintegrin) as cellular receptors that can specifically bind to IgG glycovariants containing high levels of terminal sialic acid residues. Consistent with this in vitro binding, IVIg lost its anti-inflammatory activity in SIGNR-1 knockout mice in a model of rheumatoid arthritis (Anthony et al. 2008b). During the steady state SIGNR-1 expression is most dominant on splenic marginal zone macrophages characterized by expression of another cell surface receptor called MARCO (macrophage receptor with collagenous structure) (Fig. 2). Consistent with an important function of this SIGNR-1 positive splenic macrophage population, splenectomized mice, mice with a disturbed splenic structure or osteopetrotic op/op mice lacking this macrophage subpopulation were no longer protected by IVIg (Anthony et al. 2008b; Bruhns et al. 2003). Thus, in analogy to the family of Toll-like receptors which can recognize microbial as well as self ligands, these studies highlight the dual function of receptors such as SIGNR1 and DC-SIGN in recognition of microbial and self ligands. Further studies showed that IVIg infusion changes the threshold for innate immune effector cell activation through ICs through an upregulation of the inhibitory FcγRIIB and a downregulation of activating FcγRs in different mouse model systems and in patients with chronic inflammatory demyelinating polyneuropathy (Fig. 2) (Bruhns et al. 2003; Kaneko et al. 2006a, b; Samuelsson et al. 2001; Tackenberg et al. 2009). It is tempting to speculate that pathogens, such as HIV and *Mycobacterium tuberculosis*, which bind to DC-SIGN use this anti-inflammatory pathway to escape an initial immune response. Besides the important function of sialic acid residues, it has been proposed that the additional lack of galactose residues, which exposes the mannose rich core sugar structure, would result in the capacity to activate the lectin pathway of complement activation via mannan binding lectin (MBL) and thereby enhance the proinflammatory activity of this so called IgG-G0 glycovariant (lacking terminal sialic acid and galactose residues) (Malhotra et al. 1995). However, recent *in vivo* studies using MBL1/2 knockout animals could not confirm these previous in vitro observations and rather suggest that IgG glycoforms with or without galactose are still fully dependent on cellular FcγRs and do not gain proinflammatory activity through the MBL pathway of complement activation (Nimmerjahn et al. 2007).

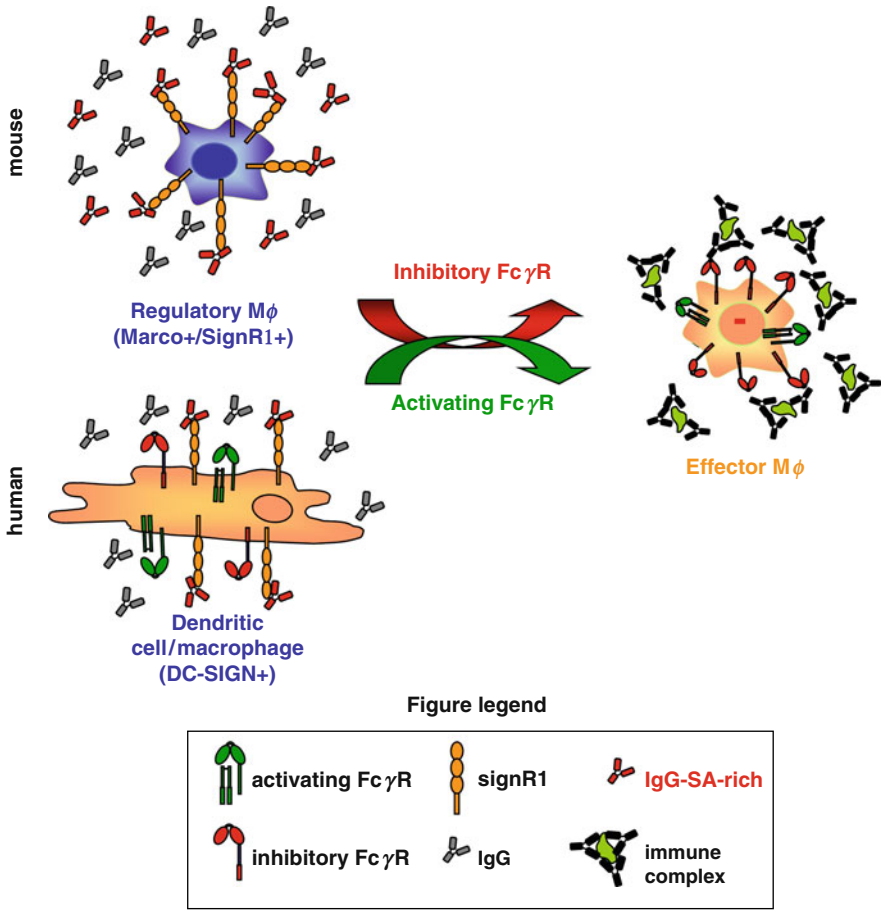

Fig. 2 Model for the anti-inflammatory activity of IgG. Immunoglobulin G glycovariants rich in terminal sialic acid residues (SA-rich IgG) loose affinity for classical FcγRs but gain the capacity to bind to C-type lectin receptors such as mouse SIGNR1 and human DC-SIGN. Binding of SA-rich IgG to splenic resident MARCO positive macrophages heightens the threshold for innate immune effector cell activation by upregulation of inhibitory FcγRIIB expression and lowering expression of activating FcγRs. In humans, DC-SIGN positive dendritic cells or macrophages might be involved in the IgG dependent anti-inflammatory pathway

5 Role of FcγRs for Infection

A role for IgG antibodies in the prevention of infection is demonstrated by the heightened susceptibility of patients with hypogammaglobulinemia or hyper-IgM syndrome to recurrent infections with encapsulated bacteria, viruses and with some protozoan infections (Ballow 2002; Wood 2009). Major efforts have been undertaken to identify broadly neutralizing antibodies capable of protecting the host from

infection with a wide range of microorganisms (especially highly pathogenic viruses such as influenza and HIV) from the same or different species (Karlsson Hedestam et al. 2008; Walker and Burton 2008). One general issue with respect to many human pathogens is that they do not infect mice. Therefore, one has to rely on in vitro model systems and readouts to evaluate the capacity of pathogen specific antibodies to prevent infection of host cells. Such an approach may be severely biased by the choice of target cells used in such an assay. For example, HIV infects both T cells and myeloid cells, of which only the latter cell lineage expresses FcγRs. In screening for neutralizing antibodies by using T cells as a readout one selectively screens for antibodies preventing the interaction of viral ligands with cellular receptors such as CD4 expressed on T cells, which would be solely dependent on the specificity (the F(ab)2 fragment) of the antibody. By doing so one might miss a potential role for the antibody Fc-fragment and FcγRs in antibody mediated protection from a productive infection or viral replication (Fig. 3). Along these lines, it was recently demonstrated that different cell lines used for in vitro neutralization assays with antibodies specific for the anthrax toxin express different

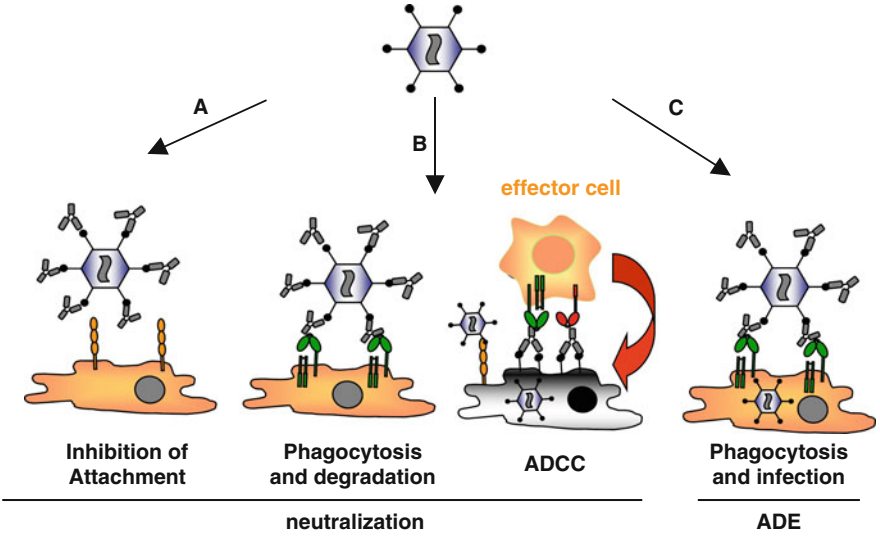

Fig. 3 Pathways of IgG dependent pathogen neutralization or enhancement of infection. Pathogen specific IgG can either block infection (neutralization) of host cells (A, B) or lead to antibody dependent enhancement (ADE) of pathogen infectivity (C). (A) Binding of IgG to the surface of bacterial or viral receptors essential for the attachment to host cells blocks pathogen entry and prevents an infection. This mechanism of neutralization is solely dependent on the specificity of the antibody and independent of the Fc-fragment. (B) Opsonized pathogens or pathogen specific IgG binding to infected cells results in pathogen clearance via phagocytosis and destruction of the microorganism in acidic endosomal/lysosomal vesicles or to killing of infected host cells by effector cells via antibody dependent cell-mediated cytotoxicity (ADCC). (C) For some opsonized microorganisms FcγR dependent uptake results in enhanced infection of target cells instead of degradation in lysosomal vesicles (see text for further details)

levels of FcγRs and that toxin neutralization was more efficient in the cell line expressing higher levels of FcγRs (Verma et al. 2009). Moreover, blocking FcγRs impaired IgG dependent anthrax toxin neutralization in this in vitro assay. Thus, in vitro neutralization assays should screen for both, FcγR dependent and independent mechanisms of neutralization to ensure the highest level of predictability for *in vivo* functionality. The importance of ADCC or other FcγR dependent pathways for inhibition of viral replication and spread (also referred to as antibody dependent cell-mediated viral inhibition; ADCVI) *in vivo* have only recently become appreciated. Thus, γ-chain deficient mice lacking the activity of all activating FcγRs were more susceptible to influenza virus infection due to reduced phagocytosis and ADCC dependent killing of infected cells (Fig. 3) (Huber et al. 2001). Along the same lines, the capacity of immune serum to trigger ADCC in vitro has been associated with protection from HIV infection in some (but not all) studies and nonneutralizing antibodies (as defined by classical in vitro assays) were able to inhibit HIV replication in human macrophages in vitro (Florese et al. 2006; Gomez-Roman et al. 2005; Holl et al. 2006a). More recently it was demonstrated that the protective activity of the broadly neutralizing HIV specific antibody b12 directed against the CD4 binding site of gp120 mediates its activity at least in part via engaging activating FcγRs but not the complement pathway *in vivo* (Hessell et al. 2007). Several studies have addressed the role of individual activating FcγRs for this antiviral activity and have suggested that especially FcγRIA and FcγRIIA were involved in conferring protection (David et al. 2006; Forthal and Moog 2009; Holl et al. 2004, 2006b; Perez-Bercoff et al. 2003). Apart from a simple ADCC and phagocytosis followed by destruction of antibody bound virus in endosomal/lysosomal vessicles, other mechanisms such as FcγR dependent induction of transcription factors are discussed to be involved in inhibition of virus infection and replication (Bergamaschi et al. 2009). Although more studies are necessary to elucidate the molecular pathways involved in FcγR dependent protection from virus infection, the available data suggest a critical involvement of IgG-Fc dependent pathways in parallel to the IgG-F(ab)2 dependent interference with virus binding to cellular receptors (Fig. 3).

Consistent with the results obtained for HIV and influenza, antibody dependent phagocytosis of *Bordetella pertussis* was enhanced via FcγRs but not via complement receptor 3 (CR3) in mouse models *in vivo* and with human effector cells in vitro (Hellwig et al. 2001; Rodriguez et al. 2001). With respect to parasitic infections, mice deficient in activating FcγRs were less efficient in clearing microfilariae of *Brugia malayi* and showed a decreased antibody mediated phagocytosis of *Plasmodium bergei* and enhanced susceptibility to infection in this murine malaria model (Gray and Lawrence 2002; Yoneto et al. 2001). Confirming the role of the inhibitory FcγRIIB in setting a threshold for cell activation, mice deficient in the inhibitory FcγR were more efficient in the phagocytosis of bacteria and showed enhanced resistance to infection with *Plasmodium chabaudi chabaudi*, *Staphylococcus aureus* and *Streptococcus pneumoniae* (Clatworthy and Smith 2004; Clatworthy et al. 2007; Gjertsson et al. 2002). Another line of evidence for an involvement of FcγRs in antibacterial responses in humans comes from IgG

subclass deficiencies. An IgG2 deficiency, for example, predisposes to infections with microorganisms such as *Haemophilus influenzae* (causing upper respiratory tract infections and pneumonia), *S. pneumoniae* (causing pneumonia, peritonitis and meningitis) and *Nisei meningitides* (causing meningitis and septicemia) (Ballow 2002; Pathan et al. 2003). IgG2 is a poor activator of the complement pathway and selectively binds the FcγRIIA-131H allele (Ravetch and Nimmerjahn 2008). Supporting a role for this activating FcγR in phagocytosis of opsonized bacteria of these species, it was demonstrated that humans with the low affinity FcγRIIA-131R allele had a higher susceptibility to invasive pneumococcal disease and higher risk for fulminant meningococcal septic shock (Bredius et al. 1994; Fijen et al. 2000; Rodriguez et al. 1999; Willcocks et al. 2009; Yee et al. 2000; Yuan et al. 2003). Moreover, neutrophils of FcγRIIA-131H donors were more efficient in phagocytosing opsonized bacteria in vitro (Fijen et al. 2000; Pathan et al. 2003; Rodriguez et al. 1999). Consistent with this finding murine IgG1 antibodies against cell wall components of *S. pneumoniae*, which cannot activate the complement pathway, could protect mice from lethal infection (Briles et al. 1984a, b). Taken together, there is evidence that FcγRs are involved in antibody dependent control at least of certain bacterial and viral infections in mice and humans. For genetic association studies in humans, larger patient cohorts will be essential to provide convincing evidence as some of the current studies show contradicting results (Smith et al. 2003). Of note, FcγRs are not only involved in protection from microbial infections but can also be responsible for promoting susceptibility of the host, a phenomenon that has been termed antibody mediated enhancement (ADE) of infection (Fig. 3). Thus, *Leishmania major* infection of susceptible mouse strains is severely impaired in γ-chain knockout animals (Kima et al. 2000; Padigel and Farrell 2005). Similar results have been obtained for many viruses including HIV and members of the dengue virus family (Brouwer et al. 2004; Littaua et al. 1990; Loke et al. 2002; Takeda et al. 1988) . Despite this FcγR dependent effect of ADE, this does not preclude the use of neutralizing antibodies to block virus infection. Thus, dengue virus specific IgG was efficient in protecting animals from infection if used in an aglycosyl form which can no longer interact with cellular FcγRs (Balsitis et al. 2010).

6 Microbial Immune Escape Mechanisms Targeting the IgG–FcγR Interaction

Further evidence that the interaction of antimicrobial antibodies with FcγRs is of importance is provided by the fact that several viruses and bacteria have developed strategies to interfere with this interaction. Prime examples are protein A (*S. aureus*) and protein G (*Streptococcus spec.*) which immobilize IgG to inactivate its effector functions (Langone 1982). Herpes simplex virus (HSV) as well as cytomegalovirus express viral FcγRs which compete with cellular FcγRs for IgG

binding and thereby prevent direct virus recognition and detection of infected cells through innate immune effector cells (Atalay et al. 2002; Dubin et al. 1991; Frank and Friedman 1989; Sprague et al. 2008). As demonstrated for gp68 of human cytomegalovirus (HCMV), viral FcγRs bind to IgG independent of the N297 attached sugar moiety, which is crucial for binding to cellular FcγRs. In contrast to classical FcγRs which bind to IgG in the CH2/hinge domain in a one to one ratio, HCMV gp68 binds IgG more closely to the CH3 domain with nanomolar affinity and in a two to one stoichiometry (Sprague et al. 2008). More recently, several secreted glycosidases and proteases derived from *Streptococcus pyogenes* with a high specificity for the IgG attached sugar moiety or the IgG Fc-fragment have been identified (Collin and Olsen 2001; Johansson et al. 2008). Thus, Endoglycosidase S (EndoS) efficiently cleaves the N297-attached sugar moiety after the first *N*-acetylglucosamine residue, which results in a decreased binding to cellular FcγRs. In a variety of models of IgG dependent autoimmune disease, injection of purified EndoS resulted in decreased autoantibody activity and reduced tissue damage, suggesting that EndoS might help *S. pyogenes* to inactivate the antimicrobial activity of IgG (Albert et al. 2008; Allhorn et al. 2008; Nandakumar et al. 2007a). Interestingly, EndoS treatment showed an IgG subclass specific activity and was not able to impair the activity of the most potent subclass IgG2a/c (Albert et al. 2008). In contrast, the protease Ide S efficiently cleaves the IgG Fc-fragment of all human IgG subclasses and of mouse IgG2a/c, resulting in inactivation of (auto) antibody activity in vitro and *in vivo* (Johansson et al. 2008; Nandakumar et al. 2007b). Taken together, pathogenic microorganisms have evolved several mechanisms to escape the potent effector pathways initiated through the IgG Fc-fragment. These studies may provide the basis to develop not only novel antimicrobial therapies, but also be helpful to limit the destructive potential of autoantibodies during autoimmune disease (Allhorn and Collin 2009; Nandakumar and Holmdahl 2008).

7 Other Ligands for Fcγ-Receptors

Apart from IgG, there is evidence that other proteins unrelated to IgG can bind to FcγRs and use the potent effector functions initiated via these receptors. The most prominent examples are members of the pentraxin superfamily which are evolutionary conserved proteins with a multimeric cyclic structure (Agrawal et al. 2009). Two members of this family, C-reactive protein (CRP) and serum amyloid P (SAP), have been shown to bind to human and mouse FcγRs (Bharadwaj et al. 1999, 2001; Lu et al. 2008; Marjon et al. 2009; Thomas-Rudolph et al. 2007). Whereas these proteins are present only in minute amounts in the serum in the steady state they become greatly upregulated during inflammatory responses such as microbial infections. Similar to antimicrobial antibodies, CRP and SAP can directly bind to a variety of pathogens including bacteria, fungi and viruses marking them for phagocytosis by neutrophils and macrophages of the host (Agrawal et al. 2009; Marnell et al. 2005). Besides the activation of the classical complement pathway

through these pentraxins a role of FcγRs in the CRP dependent phagocytosis of microorganism was suggested by in vitro studies with FcγR expressing cell lines and more recently by a cocrystal structure of SAP together with FcγRIIA, demonstrating that CRP and SAP can bind to the low affinity FcγRIIA and FcγRIIB and to the high affinity FcγRI (Bharadwaj et al. 1999, 2001; Lu et al. 2008). Although the relevance of this binding for the phagocytosis of CRP opsonised microorganisms *in vivo* remains to be established it was recently demonstrated that FcγR dependent uptake of CRP opsonised *S. pneumoniae* enhances the immune response against this microorganism (Thomas-Rudolph et al. 2007). In addition to this antimicrobial function CRP has also been shown to have an anti-inflammatory activity which seems to be dependent on cellular FcγRs. Thus, mice deficient in FcγRs are not protected from lethal LPS challenge, nephrotoxic nephritis and ITP by injection of human CRP. For the latter two autoimmune models it has been shown that FcγRI was crucial for this CRP dependent suppression of autoimmune disease although the exact mechanism of this activity requires further studies (Marjon et al. 2009; Rodriguez et al. 2007).

8 Conclusions

Work over the last years has highlighted the central importance of FcγRs in mediating the proinflammatory activity of IgG. By setting a threshold for innate immune effector cell activation activating and inhibitory FcγRs modulate the strength of the immune response and prevent an unwanted activation of the immune system which might result in destruction of healthy tissues. The identification of novel IgG glycosylation variants involved in the long known but poorly understood anti-inflammatory activity of IgG was an important step toward a more complete picture of the underlying mechanism of this activity. It is tempting to speculate that molecules such as SIGNR-1 which have the capacity to recognize pathogens directly during an infection might have another function during the steady state and help to maintain the immune system in a resting state. The immune escape mechanisms which have been developed by different microorganisms are as complex as these novel pathways responsible for IgG effector functions. It is a safe assumption that many more microbial molecules that target the IgG–FcγR interaction will be identified in future studies, which might not only be useful for fighting microbial infections but also for the development of novel strategies to interfere with the deleterious activities of IgG during autoimmune disease.

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References

Agrawal A, Singh PP, Bottazzi B, Garlanda C, Mantovani A (2009) Pattern recognition by pentraxins. Adv Exp Med Biol 653:98–116

Albert H, Collin M, Dudziak D, Ravetch JV, Nimmerjahn F (2008) *In vivo* enzymatic modulation of IgG glycosylation inhibits autoimmune disease in an IgG subclass-dependent manner. Proc Natl Acad Sci USA 105:15005–15009

Allhorn M, Collin M (2009) Sugar-free antibodies–the bacterial solution to autoimmunity? Ann NY Acad Sci 1173:664–669

Allhorn M, Olin AI, Nimmerjahn F, Collin M (2008) Human IgG/Fc gamma R interactions are modulated by streptococcal IgG glycan hydrolysis. PLoS One 3:e1413

Anderson CL, Grey HM (1974) Receptors for aggregated IgG on mouse lymphocytes: their presence on thymocytes, thymus-derived, and bone marrow-derived lymphocytes. J Exp Med 139:1175–1188

Anthony RM, Nimmerjahn F, Ashline DJ, Reinhold VN, Paulson JC, Ravetch JV (2008a) Recapitulation of IVIG anti-inflammatory activity with a recombinant IgG Fc. Science 320:373–376

Anthony RM, Wermeling F, Karlsson MC, Ravetch JV (2008b) Identification of a receptor required for the anti-inflammatory activity of IVIG. Proc Natl Acad Sci USA 105:19571–19578

Arnold JN, Wormald MR, Sim RB, Rudd PM, Dwek RA (2007) The impact of glycosylation on the biological function and structure of human immunoglobulins. Annu Rev Immunol 25:21–50

Atalay R, Zimmermann A, Wagner M, Borst E, Benz C, Messerle M, Hengel H (2002) Identification and expression of human cytomegalovirus transcription units coding for two distinct Fcgamma receptor homologs. J Virol 76:8596–8608

Azeredo da Silveira S, Kikuchi S, Fossati-Jimack L, Moll T, Saito T, Verbeek JS, Botto M, Walport MJ, Carroll M, Izui S (2002) Complement activation selectively potentiates the pathogenicity of the IgG2b and IgG3 isotypes of a high affinity anti-erythrocyte autoantibody. J Exp Med 195:665–672

Baerenwaldt A, Nimmerjahn F (2008) Immune regulation – Fc gamma RIIB – regulating the balance between protective and autoreactive immune responses. Immun Cell Biol 86:482–484

Ballow M (2002) Primary immunodeficiency disorders: antibody deficiency. J Allergy Clin Immunol 109:581–591

Balsitis SJ, Williams KL, Lachica R, Flores D, Kyle JL, Mehlhop E, Johnson S, Diamond MS, Beatty PR, Harris E (2010) Lethal antibody enhancement of dengue disease in mice is prevented by Fc modification. PLoS Pathog 6:e1000790

Baudino L, Nimmerjahn F, Azeredo da Silveira S, Martinez-Soria E, Saito T, Carroll M, Ravetch JV, Verbeek JS, Izui S (2008) Differential contribution of three activating IgG Fc receptors (FcgammaRI, FcgammaRIII, and FcgammaRIV) to IgG2a- and IgG2b-induced autoimmune hemolytic anemia in mice. J Immunol 180:1948–1953

Bergamaschi A, David A, Le Rouzic E, Nisole S, Barre-Sinoussi F, Pancino G (2009) The CDK inhibitor p21Cip1/WAF1 is induced by FcgammaR activation and restricts the replication of human immunodeficiency virus type 1 and related primate lentiviruses in human macrophages. J Virol 83:12253–12265

Bevaart L, Jansen MJ, van Vugt MJ, Verbeek JS, van de Winkel JG, Leusen JH (2006) The high-affinity IgG receptor, FcgammaRI, plays a central role in antibody therapy of experimental melanoma. Cancer Res 66:1261–1264

Bharadwaj D, Stein MP, Volzer M, Mold C, Du Clos TW (1999) The major receptor for C-reactive protein on leukocytes is fcgamma receptor II. J Exp Med 190:585–590

Bharadwaj D, Mold C, Markham E, Du Clos TW (2001) Serum amyloid P component binds to Fc gamma receptors and opsonizes particles for phagocytosis. J Immunol 166:6735–6741

Bolland S, Ravetch JV (1999) Inhibitory pathways triggered by ITIM-containing receptors. Adv Immunol 72:149–177

Bolland S, Ravetch JV (2000) Spontaneous autoimmune disease in Fc(gamma)RIIB-deficient mice results from strain-specific epistasis. Immunity 13:277–285

Bond A, Cooke A, Hay FC (1990) Glycosylation of IgG, immune complexes and IgG subclasses in the MRL-lpr/lpr mouse model of rheumatoid arthritis. Eur J Immunol 20:2229–2233

Boruchov AM, Heller G, Veri MC, Bonvini E, Ravetch JV, Young JW (2005) Activating and inhibitory IgG Fc receptors on human DCs mediate opposing functions. J Clin Invest 115:2914–2923

Bredius RG, Derkx BH, Fijen CA, de Wit TP, de Haas M, Weening RS, van de Winkel JG, Out TA (1994) Fc gamma receptor IIa (CD32) polymorphism in fulminant meningococcal septic shock in children. J Infect Dis 170:848–853

Briles DE, Forman C, Hudak S, Claflin JL (1984a) The effects of idiotype on the ability of IgG1 anti-phosphorylcholine antibodies to protect mice from fatal infection with Streptococcus pneumoniae. Eur J Immunol 14:1027–1030

Briles DE, Forman C, Hudak S, Claflin JL (1984b) The effects of subclass on the ability of anti-phosphocholine antibodies to protect mice from fatal infection with Streptococcus pneumoniae. J Mol Cell Immunol 1:305–309

Brouwer KC, Lal RB, Mirel LB, Yang C, van Eijk AM, Ayisi J, Otieno J, Nahlen BL, Steketee R, Lal AA, Shi YP (2004) Polymorphism of Fc receptor IIa for IgG in infants is associated with susceptibility to perinatal HIV-1 infection. AIDS 18:1187–1194

Bruhns P, Samuelsson A, Pollard JW, Ravetch JV (2003) Colony-stimulating factor-1-dependent macrophages are responsible for IVIG protection in antibody-induced autoimmune disease. Immunity 18:573–581

Bruhns P, Iannascoli B, England P, Mancardi DA, Fernandez N, Jorieux S, Daeron M (2009) Specificity and affinity of human Fcgamma receptors and their polymorphic variants for human IgG subclasses. Blood 113:3716–3725

Carroll MC (2004) The complement system in regulation of adaptive immunity. Nat Immunol 5:981–986

Cartron G, Dacheux L, Salles G, Solal-Celigny P, Bardos P, Colombat P, Watier H (2002) Therapeutic activity of humanized anti-CD20 monoclonal antibody and polymorphism in IgG Fc receptor FcgammaRIIIa gene. Blood 99:754–758

Clatworthy MR, Smith KG (2004) FcgammaRIIb balances efficient pathogen clearance and the cytokine-mediated consequences of sepsis. J Exp Med 199:717–723

Clatworthy MR, Willcocks L, Urban B, Langhorne J, Williams TN, Peshu N, Watkins NA, Floto RA, Smith KG (2007) Systemic lupus erythematosus-associated defects in the inhibitory receptor FcgammaRIIb reduce susceptibility to malaria. Proc Natl Acad Sci USA 104:7169–7174

Clynes R, Ravetch JV (1995) Cytotoxic antibodies trigger inflammation through Fc receptors. Immunity 3:21–26

Collin M, Olsen A (2001) Effect of SpeB and EndoS from Streptococcus pyogenes on human immunoglobulins. Infect Immun 69:7187–7189

Daeron M, Lesourne R (2006) Negative signaling in Fc receptor complexes. Adv Immunol 89: 39–86

David A, Saez-Cirion A, Versmisse P, Malbec O, Iannascoli B, Herschke F, Lucas M, Barre-Sinoussi F, Mouscadet JF, Daeron M, Pancino G (2006) The engagement of activating FcgammaRs inhibits primate lentivirus replication in human macrophages. J Immunol 177:6291–6300

Dhodapkar KM, Kaufman JL, Ehlers M, Banerjee DK, Bonvini E, Koenig S, Steinman RM, Ravetch JV, Dhodapkar MV (2005) Selective blockade of inhibitory Fcgamma receptor enables human dendritic cell maturation with IL-12p70 production and immunity to antibody-coated tumor cells. Proc Natl Acad Sci USA 102:2910–2915

Dubin G, Socolof E, Frank I, Friedman HM (1991) Herpes simplex virus type 1 Fc receptor protects infected cells from antibody-dependent cellular cytotoxicity. J Virol 65:7046–7050

Dutertre CA, Bonnin-Gelize E, Pulford K, Bourel D, Fridman WH, Teillaud JL (2008) A novel subset of NK cells expressing high levels of inhibitory FcgammaRIIB modulating antibody-dependent function. J Leukoc Biol 84:1511–1520

Ferrara C, Stuart F, Sondermann P, Brunker P, Umana P (2006) The carbohydrate at FcgammaR-IIIa Asn-162. An element required for high affinity binding to non-fucosylated IgG glycoforms. J Biol Chem 281:5032–5036

Fijen CA, Bredius RG, Kuijper EJ, Out TA, De Haas M, De Wit AP, Daha MR, De Winkel JG (2000) The role of Fcgamma receptor polymorphisms and C3 in the immune defence against Neisseria meningitidis in complement-deficient individuals. Clin Exp Immunol 120:338–345

Florese RH, Van Rompay KK, Aldrich K, Forthal DN, Landucci G, Mahalanabis M, Haigwood N, Venzon D, Kalyanaraman VS, Marthas ML, Robert-Guroff M (2006) Evaluation of passively transferred, nonneutralizing antibody-dependent cellular cytotoxicity-mediating IgG in protection of neonatal rhesus macaques against oral SIVmac251 challenge. J Immunol 177:4028–4036

Forthal DN, Moog C (2009) Fc receptor-mediated antiviral antibodies. Curr Opin HIV AIDS 4:388–393

Fossati-Jimack L, Ioan-Facsinay A, Reininger L, Chicheportiche Y, Watanabe N, Saito T, Hofhuis FM, Gessner JE, Schiller C, Schmidt RE, Honjo T, Verbeek JS, Izui S (2000) Markedly different pathogenicity of four immunoglobulin G isotype-switch variants of an antierythrocyte autoantibody is based on their capacity to interact *in vivo* with the low-affinity Fcgamma receptor III. J Exp Med 191:1293–1302

Frank I, Friedman HM (1989) A novel function of the herpes simplex virus type 1 Fc receptor: participation in bipolar bridging of antiviral immunoglobulin G. J Virol 63:4479–4488

Gavin AL, Tan PS, Hogarth PM (1998) Gain-of-function mutations in FcgammaRI of NOD mice: implications for the evolution of the Ig superfamily. EMBO J 17:3850–3857

Giorgini A, Brown HJ, Lock HR, Nimmerjahn F, Ravetch JV, Verbeek JS, Sacks SH, Robson MG (2008) Fc gamma RIII and Fc gamma RIV are indispensable for acute glomerular inflammation induced by switch variant monoclonal antibodies. J Immunol 181:8745–8752

Gjertsson I, Kleinau S, Tarkowski A (2002) The impact of Fcgamma receptors on Staphylococcus aureus infection. Microb Pathog 33:145–152

Gomez-Roman VR, Patterson LJ, Venzon D, Liewehr D, Aldrich K, Florese R, Robert-Guroff M (2005) Vaccine-elicited antibodies mediate antibody-dependent cellular cytotoxicity correlated with significantly reduced acute viremia in rhesus macaques challenged with SIVmac251. J Immunol 174:2185–2189

Gray CA, Lawrence RA (2002) A role for antibody and Fc receptor in the clearance of Brugia malayi microfilariae. Eur J Immunol 32:1114–1120

Hamaguchi Y, Xiu Y, Komura K, Nimmerjahn F, Tedder TF (2006) Antibody isotype-specific engagement of Fcgamma receptors regulates B lymphocyte depletion during CD20 immunotherapy. J Exp Med 203:743–753, Epub 2006 Mar 6

Hazenbos WL, Gessner JE, Hofhuis FM, Kuipers H, Meyer D, Heijnen IA, Schmidt RE, Sandor M, Capel PJ, Daeron M, van de Winkel JG, Verbeek JS (1996) Impaired IgG-dependent anaphylaxis and Arthus reaction in Fc gamma RIII (CD16) deficient mice. Immunity 5:181–188

Hellwig SM, van Oirschot HF, Hazenbos WL, van Spriel AB, Mooi FR, van De Winkel JG (2001) Targeting to Fcgamma receptors, but not CR3 (CD11b/CD18), increases clearance of *Bordetella pertussis*. J Infect Dis 183:871–879

Hessell AJ, Hangartner L, Hunter M, Havenith CE, Beurskens FJ, Bakker JM, Lanigan CM, Landucci G, Forthal DN, Parren PW, Marx PA, Burton DR (2007) Fc receptor but not complement binding is important in antibody protection against HIV. Nature 449:101–104

Hirano M, Davis RS, Fine WD, Nakamura S, Shimizu K, Yagi H, Kato K, Stephan RP, Cooper MD (2007) IgEb immune complexes activate macrophages through FcgammaRIV binding. Nat Immunol 8:762–771

Hogarth PM (2002) Fc receptors are major mediators of antibody based inflammation in autoimmunity. Curr Opin Immunol 14:798–802

Holl V, Hemmerter S, Burrer R, Schmidt S, Bohbot A, Aubertin AM, Moog C (2004) Involvement of Fc gamma RI (CD64) in the mechanism of HIV-1 inhibition by polyclonal IgG purified from infected patients in cultured monocyte-derived macrophages. J Immunol 173:6274–6283

Holl V, Peressin M, Decoville T, Schmidt S, Zolla-Pazner S, Aubertin AM, Moog C (2006a) Nonneutralizing antibodies are able to inhibit human immunodeficiency virus type 1 replication in macrophages and immature dendritic cells. J Virol 80:6177–6181

Holl V, Peressin M, Schmidt S, Decoville T, Zolla-Pazner S, Aubertin AM, Moog C (2006b) Efficient inhibition of HIV-1 replication in human immature monocyte-derived dendritic cells by purified anti-HIV-1 IgG without induction of maturation. Blood 107:4466–4474

Huber VC, Lynch JM, Bucher DJ, Le J, Metzger DW (2001) Fc receptor-mediated phagocytosis makes a significant contribution to clearance of influenza virus infections. J Immunol 166:7381–7388

Ioan-Facsinay A, de Kimpe SJ, Hellwig SM, van Lent PL, Hofhuis FM, van Ojik HH, Sedlik C, da Silveira SA, Gerber J, de Jong YF, Roozendaal R, Aarden LA, van den Berg WB, Saito T, Mosser D, Amigorena S, Izui S, van Ommen GJ, van Vugt M, van de Winkel JG, Verbeek JS (2002) FcgammaRI (CD64) contributes substantially to severity of arthritis, hypersensitivity responses, and protection from bacterial infection. Immunity 16:391–402

Iwasaki A, Medzhitov R (2010) Regulation of adaptive immunity by the innate immune system. Science 327:291–295

Jefferis R (2009) Glycosylation as a strategy to improve antibody-based therapeutics. Nat Rev Drug Discov 8:226–234

Johansson BP, Shannon O, Bjorck L (2008) IdeS: a bacterial proteolytic enzyme with therapeutic potential. PLoS One 3:e1692

Kalergis AM, Ravetch JV (2002) Inducing tumor immunity through the selective engagement of activating Fcgamma receptors on dendritic cells. J Exp Med 195:1653–1659

Kaminski MS, Kitamura K, Maloney DG, Campbell MJ, Levy R (1986) Importance of antibody isotype in monoclonal anti-idiotype therapy of a murine B cell lymphoma. A study of hybridoma class switch variants. J Immunol 136:1123–1130

Kaneko Y, Nimmerjahn F, Madaio MP, Ravetch JV (2006a) Pathology and protection in nephrotoxic nephritis is determined by selective engagement of specific Fc receptors. J Exp Med 203:789–797, Epub 2006 Mar 6

Kaneko Y, Nimmerjahn F, Ravetch JV (2006b) Anti-inflammatory activity of immunoglobulin G resulting from Fc sialylation. Science 313:670–673

Karlsson Hedestam GB, Fouchier RA, Phogat S, Burton DR, Sodroski J, Wyatt RT (2008) The challenges of eliciting neutralizing antibodies to HIV-1 and to influenza virus. Nat Rev Microbiol 6:143–155

Kima PE, Constant SL, Hannum L, Colmenares M, Lee KS, Haberman AM, Shlomchik MJ, McMahon-Pratt D (2000) Internalization of Leishmania mexicana complex amastigotes via the Fc receptor is required to sustain infection in murine cutaneous leishmaniasis. J Exp Med 191:1063–1068

Kipps TJ, Parham P, Punt J, Herzenberg LA (1985) Importance of immunoglobulin isotype in human antibody-dependent, cell-mediated cytotoxicity directed by murine monoclonal antibodies. J Exp Med 161:1–17

Lambert SL, Okada CY, Levy R (2004) TCR vaccines against a murine T cell lymphoma: a primary role for antibodies of the IgG2c class in tumor protection. J Immunol 172:929–936

Langone JJ (1982) Protein A of Staphylococcus aureus and related immunoglobulin receptors produced by streptococci and pneumococci. Adv Immunol 32:157–252

Leclerc JC, Plater C, Fridman WH (1977) The role of the Fc receptor (FcR) of thymus-derived lymphocytes. I. Presence of FcR on cytotoxic lymphocytes and absence of direct role in cytotoxicity. Eur J Immunol 7:543–548

Littaua R, Kurane I, Ennis FA (1990) Human IgG Fc receptor II mediates antibody-dependent enhancement of dengue virus infection. J Immunol 144:3183–3186
Loke H, Bethell D, Phuong CX, Day N, White N, Farrar J, Hill A (2002) Susceptibility to dengue hemorrhagic fever in vietnam: evidence of an association with variation in the vitamin d receptor and Fc gamma receptor IIa genes. Am J Trop Med Hyg 67:102–106
Lu J, Marnell LL, Marjon KD, Mold C, Du Clos TW, Sun PD (2008) Structural recognition and functional activation of FcgammaR by innate pentraxins. Nature 456:989–992
Malhotra R, Wormald MR, Rudd PM, Fischer PB, Dwek RA, Sim RB (1995) Glycosylation changes of IgG associated with rheumatoid arthritis can activate complement via the mannose-binding protein. Nat Med 1:237–243
Mancardi DA, Iannascoli B, Hoos S, England P, Daeron M, Bruhns P (2008) FcgammaRIV is a mouse IgE receptor that resembles macrophage FcepsilonRI in humans and promotes IgE-induced lung inflammation. J Clin Invest 118:3738–3750
Marjon KD, Marnell LL, Mold C, Du Clos TW (2009) Macrophages activated by C-reactive protein through Fc gamma RI transfer suppression of immune thrombocytopenia. J Immunol 182:1397–1403
Markine-Goriaynoff D, Coutelier JP (2002) Increased efficacy of the immunoglobulin G2a subclass in antibody-mediated protection against lactate dehydrogenase-elevating virus-induced polioencephalomyelitis revealed with switch mutants. J Virol 76:432–435
Marnell L, Mold C, Du Clos TW (2005) C-reactive protein: ligands, receptors and role in inflammation. Clin Immunol 117:104–111
Meyer D, Schiller C, Westermann J, Izui S, Hazenbos WL, Verbeek JS, Schmidt RE, Gessner JE (1998) FcgammaRIII (CD16)-deficient mice show IgG isotype-dependent protection to experimental autoimmune hemolytic anemia. Blood 92:3997–4002
Mimura Y, Sondermann P, Ghirlando R, Lund J, Young SP, Goodall M, Jefferis R (2001) Role of oligosaccharide residues of IgG1-Fc in Fc gamma RIIb binding. J Biol Chem 276:45539–45547
Mizuochi T, Hamako J, Nose M, Titani K (1990) Structural changes in the oligosaccharide chains of IgG in autoimmune MRL/Mp-lpr/lpr mice. J Immunol 145:1794–1798
Nandakumar KS, Holmdahl R (2008) Therapeutic cleavage of IgG: new avenues for treating inflammation. Trends Immunol 29:173–178
Nandakumar KS, Collin M, Olsen A, Nimmerjahn F, Blom AM, Ravetch JV, Holmdahl R (2007a) Endoglycosidase treatment abrogates IgG arthritogenicity: Importance of IgG glycosylation in arthritis. Eur J Immunol 37:2973–2982
Nandakumar KS, Johansson BP, Bjorck L, Holmdahl R (2007b) Blocking of experimental arthritis by cleavage of IgG antibodies *in vivo*. Arthritis Rheum 56:3253–3260
Nimmerjahn F, Ravetch JV (2005) Divergent immunoglobulin G subclass activity through selective Fc receptor binding. Science 310:1510–1512
Nimmerjahn F, Ravetch JV (2006) Fcgamma receptors: old friends and new family members. Immunity 24:19–28
Nimmerjahn F, Ravetch JV (2007a) Antibodies, Fc receptors and cancer. Curr Opin Immunol 19:239–245
Nimmerjahn F, Ravetch JV (2007b) The antiinflammatory activity of IgG: the intravenous IgG paradox. J Exp Med 204:11–15
Nimmerjahn F, Ravetch JV (2008a) Anti-inflammatory actions of intravenous immunoglobulin. Annu Rev Immunol 26:513–533
Nimmerjahn F, Ravetch JV (2008b) Fc gamma receptors as regulators of immune responses. Nat Rev Immunol 8:34–47
Nimmerjahn F, Bruhns P, Horiuchi K, Ravetch JV (2005) FcgammaRIV: a novel FcR with distinct IgG subclass specificity. Immunity 23:41–51
Nimmerjahn F, Anthony RM, Ravetch JV (2007) Agalactosylated IgG antibodies depend on cellular Fc receptors for *in vivo* activity. Proc Natl Acad Sci USA 104:8433–8437
Otten MA, van der Bij GJ, Verbeek SJ, Nimmerjahn F, Ravetch JV, Beelen RH, van de Winkel JG, van Egmond M (2008) Experimental antibody therapy of liver metastases reveals functional redundancy between Fc gammaRI and Fc gammaRIV. J Immunol 181:6829–6836

Padigel UM, Farrell JP (2005) Control of infection with Leishmania major in susceptible BALB/c mice lacking the common gamma-chain for FcR is associated with reduced production of IL-10 and TGF-beta by parasitized cells. J Immunol 174:6340–6345

Pathan N, Faust SN, Levin M (2003) Pathophysiology of meningococcal meningitis and septicaemia. Arch Dis Child 88:601–607

Perez-Bercoff D, David A, Sudry H, Barre-Sinoussi F, Pancino G (2003) Fcgamma receptor-mediated suppression of human immunodeficiency virus type 1 replication in primary human macrophages. J Virol 77:4081–4094

Radaev S, Motyka S, Fridman WH, Sautes-Fridman C, Sun PD (2001) The structure of a human type III Fcgamma receptor in complex with Fc. J Biol Chem 276:16469–16477

Ravetch JV, Clynes RA (1998) Divergent roles for Fc receptors and complement *in vivo*. Annu Rev Immunol 16:421–432

Ravetch JV, Lanier LL (2000) Immune inhibitory receptors. Science 290:84–89

Ravetch JV, Nimmerjahn F (2008) Fc receptors. In: Paul WE (ed) Fundamental immunology, 5th edn. Lippincott-Raven, Philadelphia, pp 684–705

Rodriguez ME, van der Pol WL, Sanders LA, van de Winkel JG (1999) Crucial role of FcgammaRIIa (CD32) in assessment of functional anti-Streptococcus pneumoniae antibody activity in human sera. J Infect Dis 179:423–433

Rodriguez ME, Hellwig SM, Hozbor DF, Leusen J, van der Pol WL, van de Winkel JG (2001) Fc receptor-mediated immunity against Bordetella pertussis. J Immunol 167:6545–6551

Rodriguez W, Mold C, Kataranovski M, Hutt JA, Marnell LL, Verbeek JS, Du Clos TW (2007) C-reactive protein-mediated suppression of nephrotoxic nephritis: role of macrophages, complement, and Fcgamma receptors. J Immunol 178:530–538

Rook GA, Steele J, Brealey R, Whyte A, Isenberg D, Sumar N, Nelson JL, Bodman KB, Young A, Roitt IM et al (1991) Changes in IgG glycoform levels are associated with remission of arthritis during pregnancy. J Autoimmun 4:779–794

Samuelsson A, Towers TL, Ravetch JV (2001) Anti-inflammatory activity of IVIG mediated through the inhibitory Fc receptor. Science 291:484–486

Scallon BJ, Tam SH, McCarthy SG, Cai AN, Raju TS (2007) Higher levels of sialylated Fc glycans in immunoglobulin G molecules can adversely impact functionality. Mol Immunol 44:1524–1534

Schlageter AM, Kozel TR (1990) Opsonization of *Cryptococcus neoformans* by a family of isotype-switch variant antibodies specific for the capsular polysaccharide. Infect Immun 58:1914–1918

Schmidt RE, Gessner JE (2005) Fc receptors and their interaction with complement in autoimmunity. Immunol Lett 100:56–67

Shields RL, Namenuk AK, Hong K, Meng YG, Rae J, Briggs J, Xie D, Lai J, Stadlen A, Li B, Fox JA, Presta LG (2001) High resolution mapping of the binding site on human IgG1 for Fc gamma RI, Fc gamma RII, Fc gamma RIII, and FcRn and design of IgG1 variants with improved binding to the Fc gamma R. J Biol Chem 276:6591–6604

Shields RL, Lai J, Keck R, O'Connell LY, Hong K, Meng YG, Weikert SH, Presta LG (2002) Lack of fucose on human IgG1 N-linked oligosaccharide improves binding to human Fcgamma RIII and antibody-dependent cellular toxicity. J Biol Chem 277:26733–26740, Epub 2002 May 1

Shinkawa T, Nakamura K, Yamane N, Shoji-Hosaka E, Kanda Y, Sakurada M, Uchida K, Anazawa H, Satoh M, Yamasaki M, Hanai N, Shitara K (2003) The absence of fucose but not the presence of galactose or bisecting *N*-acetylglucosamine of human IgG1 complex-type oligosaccharides shows the critical role of enhancing antibody-dependent cellular cytotoxicity. J Biol Chem 278:3466–3473, Epub 2002 Nov 8

Smith I, Vedeler C, Halstensen A (2003) FcgammaRIIa and FcgammaRIIIb polymorphisms were not associated with meningococcal disease in Western Norway. Epidemiol Infect 130:193–199

Sondermann P, Huber R, Oosthuizen V, Jacob U (2000) The 3.2-A crystal structure of the human IgG1 Fc fragment-Fc gammaRIII complex. Nature 406:267–273

Sprague ER, Reinhard H, Cheung EJ, Farley AH, Trujillo RD, Hengel H, Bjorkman PJ (2008) The human cytomegalovirus Fc receptor gp68 binds the Fc CH2-CH3 interface of immunoglobulin G. J Virol 82:3490–3499

Stout RD, Herzenberg LA (1975) The Fc receptor on thymus-derived lymphocytes. I. Detection of a subpopulation of murine T lymphocytes bearing the Fc receptor. J Exp Med 142:611–621

Syed SN, Konrad S, Wiege K, Nieswandt B, Nimmerjahn F, Schmidt RE, Gessner JE (2009) Both FcgammaRIV and FcgammaRIII are essential receptors mediating type II and type III autoimmune responses via FcRgamma-LAT-dependent generation of C5a. Eur J Immunol 39:3343–3356

Sylvestre D, Clynes R, Ma M, Warren H, Carroll MC, Ravetch JV (1996) Immunoglobulin G-mediated inflammatory responses develop normally in complement-deficient mice. J Exp Med 184:2385–2392

Tackenberg B, Jelcic I, Baerenwaldt A, Oertel WH, Sommer N, Nimmerjahn F, Lunemann JD (2009) Impaired inhibitory Fc gamma receptor IIB expression on B cells in chronic inflammatory demyelinating polyneuropathy. Proc Natl Acad Sci USA 106:4788–4792

Takai T (2002) Roles of Fc receptors in autoimmunity. Nat Rev Immunol 2:580–592

Takai T, Ono M, Hikida M, Ohmori H, Ravetch JV (1996) Augmented humoral and anaphylactic responses in Fc gamma RII-deficient mice. Nature 379:346–349

Takeda A, Tuazon CU, Ennis FA (1988) Antibody-enhanced infection by HIV-1 via Fc receptor-mediated entry. Science 242:580–583

Thomas-Rudolph D, Du Clos TW, Snapper CM, Mold C (2007) C-reactive protein enhances immunity to Streptococcus pneumoniae by targeting uptake to Fc gamma R on dendritic cells. J Immunol 178:7283–7291

Uchida J, Hamaguchi Y, Oliver JA, Ravetch JV, Poe JC, Haas KM, Tedder TF (2004) The innate mononuclear phagocyte network depletes B lymphocytes through Fc receptor-dependent mechanisms during anti-CD20 antibody immunotherapy. J Exp Med 199:1659–1669

van de Geijn FE, Wuhrer M, Selman MH, Willemsen SP, de Man YA, Deelder AM, Hazes JM, Dolhain RJ (2009) Immunoglobulin G galactosylation and sialylation are associated with pregnancy-induced improvement of rheumatoid arthritis and the postpartum flare: results from a large prospective cohort study. Arthritis Res Ther 11:R193

Verma A, Ngundi MM, Meade BD, De Pascalis R, Elkins KL, Burns DL (2009) Analysis of the Fc gamma receptor-dependent component of neutralization measured by anthrax toxin neutralization assays. Clin Vaccine Immunol 16:1405–1412

Walker BD, Burton DR (2008) Toward an AIDS vaccine. Science 320:760–764

Weng WK, Levy R (2003) Two immunoglobulin G fragment C receptor polymorphisms independently predict response to rituximab in patients with follicular lymphoma. J Clin Oncol 21:3940–3947, Epub 2003 Sep 15

Weng WK, Czerwinski D, Timmerman J, Hsu FJ, Levy R (2004) Clinical outcome of lymphoma patients after idiotype vaccination is correlated with humoral immune response and immunoglobulin G Fc receptor genotype. J Clin Oncol 22:4717–4724, Epub 2004 Oct 13

Willcocks LC, Smith KG, Clatworthy MR (2009) Low-affinity Fcgamma receptors, autoimmunity and infection. Expert Rev Mol Med 11:e24

Wood P (2009) Primary antibody deficiency syndromes. Ann Clin Biochem 46:99–108

Woof JM, Burton DR (2004) Human antibody-Fc receptor interactions illuminated by crystal structures. Nat Rev Immunol 4:89–99

Yee AM, Phan HM, Zuniga R, Salmon JE, Musher DM (2000) Association between FcgammaRIIa-R131 allotype and bacteremic pneumococcal pneumonia. Clin Infect Dis 30:25–28

Yoneto T, Waki S, Takai T, Tagawa Y, Iwakura Y, Mizuguchi J, Nariuchi H, Yoshimoto T (2001) A critical role of Fc receptor-mediated antibody-dependent phagocytosis in the host resistance to blood-stage Plasmodium berghei XAT infection. J Immunol 166:6236–6241

Yuan FF, Wong M, Pererva N, Keating J, Davis AR, Bryant JA, Sullivan JS (2003) FcgammaRIIA polymorphisms in *Streptococcus pneumoniae* infection. Immunol Cell Biol 81:192–195