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Functions of the Fc Receptors for Immunoglobulin G

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INTRODUCTION

Fc receptors for immunoglobulin G (FcγR) are essential links between the humoral and cellular components of the immune response. They bind the constant Fc region of an antibody molecule which at the same time binds with its antigen-specific Fab portion to cellbound or soluble antigen. FcγR in humans are expressed in a variety of cell types derived from bone marrow, such as monocytes, macrophages, neutrophils, and platelets. In these cells they trigger different cellular functions that are correlated to the defense of foreign or altered structures. These include antibody dependent cellular cytotoxicity (ADCC), release of mediators and reactive oxygen species, phagocytosis, and other effector functions. Other FcγR functions are the transport of immunoglobulin G across the human placenta from the mother to the fetus and, as demonstrated recently, the regulation of IgG plasma concentration.

Human FcγR are members of the immunoglobulin supergene family. Three different receptor classes for IgG have been described: FcγRI (CD64), FcγRII (CD32), and FcγRIII (CD16). Each receptor class exists in different isoforms. The FcγRIa, which is expressed mainly on mononuclear phagocytes, binds soluble and complexed IgG with high affinity. The low-affinity FcγRIIa, the receptor with the widest cellular distribution, binds IgG only after specific binding to an antigen and in complexes, respectively. The low-affinity FcγRIII exists in two different forms, the transmembrane FcγRIIIa which is expressed on macrophages and NK-cells and the glycosyl-phosphatidylinositol-anchored FcγRIIIb which is restricted to neutrophils.

The neonatal FcR (FcRn) differs from the FcγRI, II, and III in several ways. This receptor first described for neonatal rats shows high homology with MHC class I antigens. It is located on rat and mouse intestinal epithelial cells and mediates the transfer of immunoglobulin from milk to the blood and thus helps the newborn animal to acquire passive immunity. In humans, the FcRn is expressed in the syncytiotrophoblast of the placenta, in fetal and adult intestine, and in vascular endothelial cells.

Besides the mammalian FcγR, receptors specific for immunoglobulin also are known from microorganisms. Surface receptors from *Staphylococcus aureus*, termed protein A, as well as receptors from different group G streptococci in vitro are used to purify IgG. The biological importance of these IgG receptors and that of parasite and virus-associated Fc receptors is not entirely understood.

HUMAN FCG RECEPTORS: EXPRESSION, STRUCTURE, AND SIGNAL TRANSDUCTION

Human Fcγ Receptor I (huFcgRI)

The human FcγRI (huFcγRI) is constitutively expressed on monocytes and macrophages with about 2×10^4 copies/cell (1). Hofbauer cells in the stroma of the human placenta also carry FcγRI (2–5). Receptor density on neutrophils may be enhanced by IFN-γ or G-CSF from $< 2 \times 10^3$ copies/cell to 1×10^4 copies/cell (6). Three genes code for FcγRI: FcγRIA, Fcγ RIB, and FcγRIC, mapped on chromosome 1q21.1 (7,8). From the three FcRγI gene transcripts only FcγRIa has been detected in the form of a translated membrane protein on hematopoietic cells. The 72 kDa glycoprotein is comprised of three extracellular domains, a membrane spanning region, and a cytoplasmic region. It is the only receptor binding complex as well as monomeric IgG with high affinity (10^8–10^9 M^{-1}, Table 1) (9). This is attributed to the third extracellular domain, which is lacking in all other human FcγR (10). The FcγRIb1 and FcγRIc lack the transmembrane region due to a stop codon in the exon encoding the third extracellular domain and therefore, these presumably exist as soluble proteins. The FcγRIb2 isoform, which lacks the third domain, binds IgG complexes but not monomeric IgG (11). This knowledge comes from transfection experiments; however, no such protein has been demonstrated on the membrane of hematopoietic cells. Domain two also participates in IgG bind-

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TABLE 1. General characteristics of human IgG Fc receptors

	FcγRI	FcγRII	FcγRIII	FcRn
Molecular weight	72 kDa	40 kDa	50-80 kDa	41–50 kDa
Transcripts	Ia, Ib, Ic	IIa-R131, IIa-H131 IIb1, IIb2, IIb3, IIc	IIIa, IIIb-NA1, IIIb-NA2	FcRn
Association	Ia: γ chain	IIa: γ chain	IIIa: γ chain, ξ chain IIIb: GPI anchor	β_2m
Copies/cell	~ 2×10^4	~ $3–6 \times 10^4$ (neutrophiils)	IIIb: $1–2 \times 10^5$	
Affinity	Ia: $10^8–10^9$ M^{-1}	< $10^7 M^{-1}$	IIIa: ~ $3 \times 10^7 M^{-1}$ IIIb: < $10^7 M^{-1}$	$2–10 \times 10^7 M^{-1}$ (pH dependent)
Isotype specificity	hulgG3 > 1 > 4	IIa-R131: hulgG3 > 1 mulgG1 > 2a > 2b IIa-H131: hulgG3 > 1 > 2 mlgG2a > 2b IIb: hulgG3 > 1 > 4	hulgG3 = 1	hulgG1 = 2 > 3 > 4

ing, but domain three is critical to the high-affinity binding of monomeric IgG. On the IgG molecule, the C 2 domain is involved in monocyte FcR binding (1) (Figure 1). FcγRIa specifically binds huIgG3, huIgG1, and huIgG4 with decreasing affinity. Until now, no allelic variation has been reported for FcγRI. Four members of a Belgian family lack this receptor due to a single nucleotide exchange leading to a termination codon (12,13).

Signal transduction by FcγR follows a cascade of events which is common to many other immune system receptors such as the T-cell receptor and the B-cell receptor. An early critical event is tyrosine phosphorylation (10) which is associated with an immunoreceptor tyrosine activation motif (ITAM), a consensus motif usually consisting of two YxxL sequences separated by 7 amino acids (14,15). Crosslinking of the receptor is followed by binding of Src family protein tyrosine kinase (PTK) to the ITAM leading to an activation of the Src family PTKs and ITAM tyrosine phosphorylation (16,17). The next step is translocation or association of Syk family members with phosphorylated ITAM (16,17) which is followed by activation of phospholipase C (PLC) and phosphatidylinositol-3 (PI-3). Further steps are activation of protein kinase C (PKC) and Ca^{2+} release from intracellular stores. The activation process may lead to degranulation, mediator release, or phagocytosis.

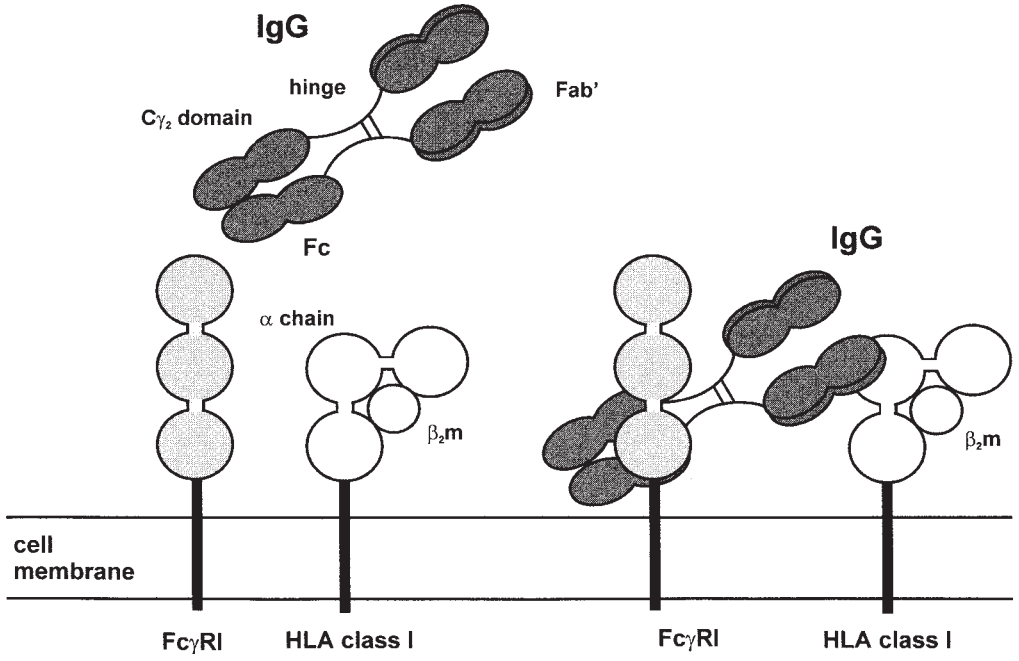

Fig. 1. Model describing the IgG-FcγR interaction. The Fab part of an antibody (here, HLA class-I specific) binds to the HLA antigen while the Fc part of the same antibody molecule binds to the FcγRI involving the $C\gamma_2$ domain of the IgG molecle and the extracellular domains three and two of the FcγRI. This illustration shows the special case of a three-molecule complex in that HLA antigen and FcγR reside on the membrane of the same receptor cell.

The FcγRIa is associated with the FcR chain signaling unit (10,18) which is a disulfid-linked homodimer containing two ITAMs that was first described in association with the IgE receptor (14,15). Crosslinking of the FcγRI by antibody or ligand activates a series of tyrosine kinases including members of both the Src family kinases ($p59^{Hck}$) and $p72^{Syk}$, PLCγ1 and PLCγ2 (19).

Human Fcγ Receptor II (huFcγRII)

The human FcγRII exhibits the broadest cellular distribution among all FcγR. It is expressed on monocytes, macrophages, neutrophils, eosinophils, basophils, B cells, platelets, dendritic cells, and Langerhans cells (9,20). Monocytes and neutrophils carry about $3–6 \times 10^4$ copies/cell (6). Additionally, FcγRII is expressed on blood vessel endothelial cells and Hofbauer stromal cells of the placenta (2–5). In contrast to FcγRI it binds IgG with low affinity ($< 10^7$ M^{-1}) only in complexes but not in monomeric form (9). The second extracellular domain is directly involved in IgG Fc binding but the first domain also is required for optimal ligand binding (21,22). Three different FcγRII genes located on chromosome 1q23-24 encode six glycoprotein isoforms (see Table 1) of 40 kDa each (20, 23–25). The isoforms are highly homologous in their extracellular regions but differ in their cytoplasmic regions (26). The FcγRIIA gene encodes the transmembrane receptor molecule FcγRIIa1 with a 76-amino-acid cytoplasmic portion. The FcγRIIa2, on the other hand, is a soluble molecule found in plasma because it has no transmembrane region (27). The FcγRIIA gene shows allelic variation due to single base exchanges that cause amino acid exchanges. Most important for phenotypic variation is position 131 in which histidine and arginine alternatively can be found (28). FcγRIIa-His131 is the only form that binds huIgG2 efficiently, while FcγRIIa-Arg131 is the exclusive receptor binding mIgG1. FcR IIa-His131 binds huIgG3, huIgG1, and huIgG2 with decreasing affinity, while FcγRIIa-Arg131 only binds huIgG3 and huIgG1 (9, 28–30) (see Table 1). In the Caucasian population, the FcγRIIA gene frequencies range between 0.50 and 0.57 for the His131 gene and between 0.43 and 0.5 for the Arg131 gene (31–33). We determined the phenotype frequencies in the German population as being 33.5% for FcγRIIa-Arg131 negative individuals (low responder for mIgG1) and 66.5% for FcγRIIa-Arg131 positive individuals (high responder for mIgG1) (34). Tax et al. (35) calculated 70% high responders and 30% low responders from experiments with antibody-induced T-cell proliferation in the Caucasian population. Interestingly, the frequencies in Japanese differ from those values, in that only about 39% carry the FcγRIIa-Arg131 gene (Arg/Arg131 and Arg/His131) but 94% are positive for the His131 gene (His/His131 and Arg/His) (32). An additional polymorphism at position 27 without effect on the binding of human or mouse IgG isoforms (36) and a glutamine to lysine exchange at position 127 in an FcγRIIa-Arg131 homozygous individual have been described (37). In the latter case the cells of this individual bound both huIgG2 and mIgG1 in contrast to individuals homozygous for FcγRIIa-Arg131 and -Gln127.

The FcγRIIb1, IIb2, and IIb3 isoforms are encoded by the FcγRIIB gene and differ only in some amino acids (27) The FcγRIIb1 and IIb2 isoforms are identical except for a 19-amino-acid insert in the cytoplasmic region of FcγRIIb1. FcγRIIb3 lacks 21 nucleotides coding for the signal peptide of FcγRIIb2. The FcγRIIb molecules are preferentially expressed on monocytes and macrophages but also reside on B cells (38). The FcγRIIb1 molecule interacts well with huIgG3 and huIgG1 and less well with IgG4 complexes (39). The FcγRIIC gene codes for a protein that is intracellularly homologous to FcγRIIa and that extracellularly resembles the FcγRIIb form, due to an unequal crossover between the FcγRIIA and IIB genes (40). FcγRIIC transcripts have been detected on the membrane of B cells and myelomonocytic cells (38) but the cellular expression of FcγRIIc has not been studied in detail to date.

All FcγRII forms consist of two extracellular domains and all but FcγRIIa2 have a cell membrane and a cytoplasmic region. FcγRIIa1 and IIc contain a unique ITAM copy in their cytoplasmic tail (20) that is critical for Ca^{2+} mobilization, tyrosine phosphorylation, and phagocytosis, but not for immune complex internalization (41–43). This and other functions such as cytokine release and antigen presentation may be mediated by association of the FcγRIIa with an FcR γ chain unit (44). While cytokine release and antigen presentation can be triggered much more effectively by the FcR γ chain ITAM, the FcγRIIa ITAM seems to be much more effective in phagocytosis (42). This ITAM of FcγRIIa is structurally distinct from most other ITAMs in that it consists of 12 amino acids separating the YxxL repeat in contrast to 7 amino acids in the γ- and ξ-chains (20). Engangement of FcγRIIa is followed by tyrosine phosphorylation of many cellular proteins including the receptor itself (45). Different Src family kinases and PTK $p72^{syk}$ associate to FcγRIIa upon crosslinking. Further activation processes follow similar mechanisms as described for FcγRIa (16). The FcγR IIb1 and IIb2 isoforms are the only receptors with a cytoplasmic inhibition motif (ITIM = immunoreceptor tyrosine-based inhibition motif) (42). In B cells this motif inhibits the receptor-mediated Ig production and in phagocytic cells it seems to inhibit the FcγRIIa-mediated phagocytosis (46).

Human Fcγ Receptor III (hu FcγRIII)

In humans FcγRIII is encoded by two genes, FcγRIIIA and FcγRIIIB, located on chromosome 1q23-24 (20,23). The two different gene products, FcγRIIa and FcγRIIIb, share high homology in their two extracellular domains, but completely differ in their transmembrane and cytoplasmic regions (47).

FcγRIIIa which is expressed on NK cells, macrophages and subsets of monocytes and T cells, is a cell-type-specific glycosylated transmembrane protein of 42–72 kDa in monocytes and 57–58 kDa in NK cells (48). Additionally, FcγRIIIa has been detected in Hofbauer cells of the placenta while expression on the syncytiotrophoblast remains unclear (2–5,49). The FcγRIIIa binds monomeric and complexed huIgG1 and huIgG3 with moderate affinity ($3 \times 10^7 M^{-1}$) but not IgG2 and IgG4 (50). For efficient cell-surface expression, the hu FcγRIIIa on NK cells requires association to small transmembrane polypetides such as FcR γ2 or ζ2 homodimers or γ-ζ heterodimers while FcγRIIIa on macrophages associates only with FcR γ chain homodimers (51). Crosslinking of FcγRIIIa on NK cells induces phosphorylation of the FcR ζ chain (52) and association of the Src-family PTK $p56^{Lck}$ which triggers tyrosine phosphorylation of PI-3 kinase, PLCγ1 and PLCγ2 (53). On macrophages FcγRIIIa crosslinking also leads to rapid tyrosine phosphorylation of $p72^{Syk}$ (16).

In contrast, FcγRIIIb does not contain any transmembrane or cytoplasmic region. The receptor molecule, which is restricted to polymorphonuclear neutrophils (PMN), is anchored to the cell membrane by glycosyl-phosphatidylinositol (GPI) (54) without association with FcR γ or ζ chains. It is the most abundant of all FcγR with $1–2 \times 10^5$ copies/PMN (6). FcγRIIIb binds complexed huIgG1 and IgG3 with low affinity ($< 10^7 M^{-1}$) (see Table 1) (55–57). Both, FcγRIIIa and FcγRIIIb use the second domain for ligand binding (58). Two allogeneic FcγRIIIB genes differ by five base substitutions which are followed by four amino-acid exchanges in the extracellular portion of the receptor (47,59). The corresponding polymorphic glycoproteins, termed neutrophil antigens 1 (NA1) and 2 (NA2), show different molecular masses in SDS-PAGE ranging from 50–65 kDa for NA1 to 65–80 kDa for NA2 due to two glycosylation sites in NA1 and four in NA2 (60). An additional mutation of the NA2 form has been described which is characterized by an Ala78Asp substitution and is termed SH (61). Some individuals are reported who lack the FcγRIIIb due to total loss of the FcγRIIIB gene and at least partial loss of the FcγRIIC gene (62–64). There is no evidence for any disease association with FcγRIIIb deficiency.

Soluble forms of both FcγRIIIa and IIIb have been reported. The products of proteolytic cleavage of the membrane forms are found in saliva, synovial and seminal fluid, serum, and plasma. The majority of the plasma form seems to be mainly derived from neutrophils, as individuals deficient in FcγRIIIb only have minor concentrations of soluble FcγRIII, which then has to come from FcγRIIIa on NK cells (65).

Neonatal Fcγ Receptor (FcRn)

The neonatal FcR was first isolated from the intestine of fetal rats (66); it was subsequently isolated from mice where it is expressed in the yolk sac in late gestation and in epithelial cells of the intestine of suckling neonates (67). It mediates the transport of maternal IgG from the uterine lumen to the amniotic fluid from which it may be taken up by the fetus, while in the neonate, FcRn may mediate the transport of IgG from milk through the intestine. In humans, FcRn has been detected in the syncytiotrophoblast of the placenta (2,68,69) as well as in fetal and adult intestine (70) and different vascular endothelia (71). The FcRn gene has been mapped to the human chromosome 19q13.3 (71). Structurally, FcRn differs extremely from the FcγRI, II and III. It is a heterodimer consisting of two chains, an MHC class I-like transmembrane 41–50-kDaα chain that is associated with β2m (66). The crystal structure has been achieved for the rat FcRn (73,74). The extracellular region of the α chain is comprised of three Ig-like domains homologous to MHC class I, a transmembrane, and a cytoplasmic region. The counterpart of the MHC peptide-binding groove in FcRn is closed and the IgG Fc binding region is distinct from the MHC peptide binding site (73). The alpha 3 domain of FcRn seems to affect the affinity for IgG (75) while the binding site on the immunoglobulin Fc for FcRn is localized on the CH2-CH3 domain interface (75,76). FcRn binds IgG Fc in a 2:1 binding stoichiometry (74). All subclasses of IgG (huIgG1 = huIgG2 > huIgG3 < huIgG4) are bound with high affinity ($2–10 \times 10^7 M^{-1}$) in a pH-dependent manner (2,74). Optimum binding is achieved between pH 5 and 6.5 (68) and is attributed to three histidines present at the CH2-CH3 domain interface of Fc (75). It has been suggested that IgG is bound by FcRn in acidified endocytic vesicles either in the syncytiotrophoblast of the human placenta or in the rat yolk sac. IgG transport may be enabled by endosomes that thereafter release IgG into the plasma at neutral pH where FcRn is unable to bind IgG (2). Aside from its IgG transporter function, FcRn is believed to be involved in the regulation of serum IgG levels (77).

Placental Alkaline Phosphatase (PLAP) and Annexin II

PLAP is a GPI-linked protein present in high amounts on the apical surface of the syncytiotrophoblast and in the amniochorion of the placenta. The protein that has many allelic variants binds IgG with a low affinity of about $3 \times 10^5 M^{-1}$ (2). It was supposed to function in the endocytosis of IgG at physiological pH of the maternal blood (2,78). However, experiments with carcinoma cell lines transfected with the PLAP cDNA do not support this assumption (78). Another placental protein is the 40 kDa Annexin II found in abundance in the trophoblast and endothelial cells of the placenta (2,79). It has no membrane anchor and binds only immobilized aggregated IgG with low affinity. A role in transmission of IgG across the syncytiotrophoblast is possible, but seems unlikely.

Microbial Fc Receptors

The ability of some bacterial cell-surface proteins to bind IgG has been used for many years to purify IgG. Protein A is

found on the surface of most strains of *S. aureus* (80,81). It binds huIgG1, 2 and 4 with affinities between $1–3 \times 10^6$ M^{-1} and 4×10^7 M^{-1} at the CH2-CH3 domain (82–84) and consists of five IgG binding domains (85). Group G streptococci express protein G which binds all human IgG subclasses with high affinity (Ka = $2–6 \times 10^9$ M^{-1}) (82). The C-terminal part of the protein consists of three IgG-binding domains followed by a region that anchors the protein to the cell surface (86).

On their surface microorganisms have several host protein binding molecules which probably are important factors of virulence. The *S. aureus* protein A and the protein G from various streptococci bind firmly to the Fc portions of mainly immunoglobulin G from a range of mammalian species and compete with the host Fc receptors. In this way the immunoglobulin G Fc receptor-mediated cellular defense of the host is avoided by the invading microorganism (87,88).

PHYLOGENY AND ONTOGENY OF IGG AND FCγR

Immunoglobulin domain-like folded molecules that are members of the immunoglobulin (Ig) superfamily have been found in bacteria and throughout the invertebrate phyla (89). Ig-like domains with a C2-like strand in receptor molecules have been detected in sponges whose evolutionary paths diverged about 800 million years ago from that of other animals. The classical immunoglobulin molecules, however, with domains folded by disulphide-bound heavy and light chains appear only in vertebrates. The first known Ig isotype was IgM which is presently found in all ancient and modern fish (90–92). True IgG evolved very late; it is restricted to mammalia.

There is much less known about the phylogeny of Fc receptors (for review see 93). Cell-surface molecules binding to the Fc portion of IgG are reported for *S. aureus* and group G streptococci, but they are not related to the mammalian Fc receptors. The earliest forms of IgM in sharks bind to shark leukocytes (94) indicating that receptor molecules for Ig must have evolved early. However, nonmammalian Fc receptors are not characterized in detail. Development of FcγR-like structures early in evolution is possible as is the presence of unrelated molecules having Ig-binding properties. In mammalia however, FcγR have been cloned from many species. The mammalian FcγR consist of two to three immunoglobulin-like domains showing that FcγR and immunoglobulins are structurally related. The domain type used by the FcγR is considered to be evolutionarily older than that used by immunoglobulins, indicating that FcγR and immunoglobulins may have diverged very early on (93,95). Thus one can speculate that Fc receptor-like molecules evolved earlier than immunoglobulins and that these molecules presumably bound molecules other than Ig.

Experiments to detect the appearance of immunoglobulins and Fc receptors in ontogeny have been undertaken with chicken and mice. In both species FcγR develop earlier than immunoglobulins or immunoglobulin producing B cells (96–99).

FUNCTION OF FCγR

FcγR mediate different cellular functions upon crosslinking by ligand or specific antibody. These functions include phagocytosis of antibody-coated particles, pinocytosis of soluble ligands, antibody dependent cellular cytotoxicity (ADCC), cytokine release, superoxide production, and antigen presentation after the uptake of small immune complexes (Table 2). The initial step for antigen presentation is the uptake, processing, and MHC-restricted presentation of antigen to the T-lymphocyte. Blood monocytes and tissue macrophages usually are poor presenting cells for native antigens but become very effective in that IgG-captured antigen is recognized via membrane-bound FcγR (100). In contrast to endocytosis, processing, and presentation of small antigen particles, ADCC and phagocytosis intend to destroy IgG-coated cells. The phagocytic process may be divided into several steps: receptor-ligand binding, extension of pseudopods, internalization, and lysosomal fusion (101). The engulfment of particles requires the presence of IgG over the total circumference of the particle (bacteria, red blood cell, etc.) (102). Internalization into phagocytic vacuoles is a protein tyrosine kinase (PTK)-dependent mechanism. Only after these vacuoles have fused with lysosomes can the engulfed bacteria be killed efficiently.

FcγRI, II and III

FcγRI is the only receptor binding monomeric IgG (9). Its in-vivo functions have not been clarified in detail but it is assumed that the FcγRIa is saturated with IgG under serum conditions. This may hinder the binding of immune complexes

TABLE 2. Biological functions of human IgG Fc receptors

	FcγRI	FcγRIIa	FcγRIIb	FcγRIIIa	FcγRIIIb	FcRn
Endocytosis	+	+	–	+	–	–
Phagocytosis	+	+	–	+	–	–
ADCC	+	+	–	+	–	–
Superoxide production	+	+	–	+	–	–
Cytokine production	+	+	–	+	–	–
B cell down regulation	–	–	+	–	–	–
IgG transport through placenta	+[a]	+[a]	–	+[a]	?	+
IgG regulation	–	–	–	–	–	+

[a]Supposed function, mechanism unresolved.

but alternate functions such as antigen presentation may be triggered effectively. Additionally, FcγRI might mediate the passive sensitization ("arming") of human macrophages with IgG antibodies resulting in the in vivo destruction of unsensitized cells expressing the corresponding antigen (103). In vitro, numerous antibody-dependent functions have been described for the different FcγR (see Table 2).

Principally, all three major classes of FcγR are able to induce the phagocytosis of IgG-sensitized red blood cells (43,104) and ADCC (6,105) but there are different requirements concerning signal transduction, IgG subclasses, nature of the antigen and of the phagocytic cell. Concerning phagocytosis as an FcγR mediated function, engagement of both the FcγRI and the ITAM-containing FcR γ chain is necessary to induce phagocytosis while FcγRI alone is capable of endocytosing small immune complexes (106). In PMN, both FcγRIIa and the GPI-anchored FcγRIIIb induce actin filament assembly which is a prerequisite for motile behaviors such as phagocytosis (107). Monocyte interactions with IgG-coated red blood cells such as rosette formation, ADCC, phagocytosis, and oxygen generation are predominantly mediated by FcγRI in an IgG subclass-dependent manner (108,109). While huIgG3 anti-D is predominantly involved in monocyte binding and rosette formation with rbc (110), huIgG1 anti-D-coated rbc are the preferential phagocytosis targets (111). In contrast, in IFNγ-induced PMN, FcγRI-specific phagocytosis of huIgG3 anti-D rbc predominates that of huIgG1 anti-D rbc (112). FcγRIIa has a minor but clearly detectable phagocytosis capacity in monocytes and seems to be the main FcγR on PMN in mediating phagoytosis (30,112,113). In contrast to FcγRI, huIgG3 seems to be more effective in FcγRIIa-specific phagocytosis induction than huIgG1 (112–114). In most studies, FcγRIIIb on neutrophils does not directly mediate phagocytosis of IgG-coated particles or red cells (104), but contributes in actin filament assembly and primes FcγRII-dependent phagocytosis (107). One group however reports that FcγRIIIb on PMN is able to induce phagocytosis of IgG-coated rbc (115).

FcγRIa, IIa, and IIIa are each involved in the antibody-dependent cellular cytotoxicity (ADCC) (6,105). The FcγR-mediated killing of IgG-sensitized rbc is significantly enhanced after IFN incubation of monocytes and neutrophils. With regard to FcγR, this may be explained by an increased receptor expression. Effectiveness of cell lysis depends on the IgG subclasses and the cell types. While huIgG3 anti-D-coated rbc are preferentially lysed by monocytes after FcγRI interaction, huIgG1-coated rbc are the predominant target for FcγRIIIa on NK cells (116). HuIgG2 anti-D-coated rbc did not trigger cellular functions presumably due to the relatively inflexible huIgG2 anti-D molecule, while huIgG2 anti-A-coated rbc were lysed effectively via FcγRIIa on FcγRIIa-His131-positive cells (117).

Superoxide production may be induced by each class of FcγR. Reactive oxygen species may be induced either by binding of IgG-coated rbc (118), by crosslinking of two FcγR molecules (119), or by crosslinking of an FcγR molecule with another neighboring membrane protein by one antibody molecule (120). Monocytes release superoxide after incubation with IgG anti-D-coated rbc (118) while IFNγ-induced U937 cells produce superoxide after crosslinking of either FcγR I or FcγII by an FcγR-specific monoclonal antibody and addition of anti-mIg (119). IFN-primed monocytes demonstrate a respiratory burst in response to some monoclonal antibodies specific for FcγRII, CD13, CD14, and MHC class II (120). The underlying mechanism is the formation of a three-molecule complex in which the Fab portion of a membrane antigen specific antibody binds to this antigen while the Fc portion of the same antibody molecule binds simultaneously to the FcγR (compare Fig. 1). In IFN-stimulated PMN, superoxide release may be triggered by FcγRI (121) while in resting neutrophils FcγRII is essential for the IgG-induced respiratory burst (122,123). FcγRIIIb on neutrophils is essential for the binding of small immune complexes but this binding alone without the involvement of FcγRII does not induce the release of oxygen radicals (55).

Monocytes produce IL-8 in response to bacterial cell-wall products such as lipopolysaccharide but also do so after FcγRI crosslinking by immobilized IgG (124). Additionally, crosslinking of monocyte FcγR triggers IL-6 production, secretion of tumor necrosis factor (125,126), and production of monocyte chemoattractant protein-1 (MCP-1), which is involved in the recruitment of monocytes to compartments with immune complex deposition (127).

Effective antigen presentation after internalization through FcγR has been demonstrated in different myeloid cells. All three classes of FcγR enhance the presentation of IgG-complexed antigens (128) in an MHC-restricted manner although Gosselin et al. (129) demonstrated that human IgG1-enhanced presentation of tetanus toxoid is mediated by FcγR I and not by FcγRII on monocytes. The only exception is FcγRIIb1 on B cells that does not promote internalization of bound immune complexes (128). In B lymphocytes, specific membrane immunoglobulin binds antigen and leads to internalization, processing, and presentation.

Neonatal Fc Receptor

The FcRn is not only expressed in fetal and neonatal but also in adult tissues (70,71). In addition to its involvement in the transport of IgG from the mother to the fetus or through the intestine of the neonate, the FcRn also regulates plasma IgG levels. Recent evidence revealed that FcRn is the specific IgG "protection receptor" that has been postulated by Brambell et al. more than 30 years ago (71,77,130). After the uptake of antigen-bound IgG through the plasma membrane into acidified pinocytic vacuoles, the antigen is released and IgG may be bound by the protection receptor that redirects its transport to the circulation. Both the unbound antigen and

the Fc receptor would be directly catabolized in lysosomes. By this mechanism, the "neonatal gut transport receptor" would prevent IgG from entering degradative compartments such as lysosomes. High plasma IgG levels result in greater competition for FcRn binding, and therefore increased lysosomal degradation, whereas lower IgG levels would be upregulated by increased IgG release to the plasma. Recently in FcRn knock-out mice, evidence was shown that the FcRn is identical to the proposed "protection receptor" (71).

Placental Fc Receptors

FcγRI, II, and III as well as FcRn have been detected in the placenta. But the process of IgG transport through the placenta from mother to fetus is not entirely clear to date (2). On the way from the maternal blood to the fetal blood endothelium, the IgG molecules have to cross the syncytiotrophoblast which expresses FcRn, Annexin II, PLAP, and possibly FcγRIII. As FcRn binds IgG in a pH-dependent manner it cannot be responsible for the uptake of IgG at neutral pH from the maternal blood at the apical plasma membrane of the syncytiotrophoblast. PLAP is highly expressed on the apical surface of the syncytiotrophoblast (2) but its expression does not correlate with the IgG binding, internalization, and transcytosis (78). Initial IgG binding by Annexin II also seems unlikely due to the very low affinity for monomeric IgG (2,79). The presence of FcγRIII on the trophoblast seems to be mainly restricted to the first trimester while there are conflicting results concerning the term placenta (4,49). Additionally, neither FcγRIIIa nor FcγRIIIb bind huIgG2 and huIgG4 (50), both of which in fact cross the placenta even if IgG2 remains at lower levels in the umbilical vein than in the maternal peripheral blood (131). After the initial IgG uptake by a hitherto unknown process, FcRn may bind IgG in vesicles (e.g., endosomes) at acidic pH. Thereafter the vesicle membrane may fuse with the basolateral plasma membrane of the syncytiotrophoblast thus delivering IgG to the cell surface. There the IgG is released by FcRn at neutral pH into the stroma.

Maternal antibodies directed against paternal determinants of the fetus may lead to the formation of immune complexes which are bound by the Hofbauer cells of the stroma carrying FcγR I, II, and III (3,5,49). To reach the fetal blood circulation monomeric IgG from the stromal side of the syncytiotrophoblast has to cross the fetal vessel endothelium which expresses FcγRII as sole IgG receptor (5). However, FcγRII has a very low affinity for monomeric IgG; it does not bind huIgG4 and binds huIgG2 only in the FcγRIIa-His131 form. Therefore transport of IgG into the fetal blood vessels remains unresolved but, nevertheless, maternal antibodies transmitted to the fetal circulation are able to inhibit FcγR-mediated functions (132).

At least the human FcγRI and II are inhibited by antibodies with specificity to all HLA antigens that are expressed on effector cells (109,133–135). The inhibition has an impact on every FcR-expressing cell and frequently appears as a total abrogation of the FcR function. It is because of this marked in-vitro effect that we assume that the HLA-induced inhibition is biologically relevant. Indeed, we correspondingly found FcR inhibition in vivo, i.e., in monocytes of newborns whose mothers markedly produce antibodies to HLA of the neonate (132). This also demonstrates that, as was proven earlier in an animal model (136), the maternal antibodies pass the placental barrier and reach the corresponding HLA in the fetus. Since the FcR-mediated destruction of anti-D sensitized fetal red blood cells in hemolytic disease of the fetus and the newborn (HDN) is the main pathogenic factor, we hypothesized that, in cases of not only maternal anti-D but also maternal HLA antibodies, the latter can ameliorate the clinical course of HDN by inhibiting fetal and placental FcR (137) (Figs. 2 and 3). This hypothesis was independently confirmed in studies on mothers and their newborns with HDN (138,139). Our group came to the same conclusion in a multicenter study on more individuals without, in contrast to Dooren et al. (138) and Shepard et al. (139), selecting the cases by immunological criteria of the causative Rhesus antibodies. Contrary to the findings of Dorren et al. (138) and in agreement with those of Shepard et al. (139), we found that the ameliorating antibodies were primarily specific for HLA A, B, and C (140). Maternal HLA antibodies also could be protective against other detrimental antibodies of the mother, e.g., to fetal platelet antigens causing the fetal or neonatal alloimmune thrombocytopenia or passive autoimmune thrombocytopenia, and to neutrophil granulocyte antigens causing the respective

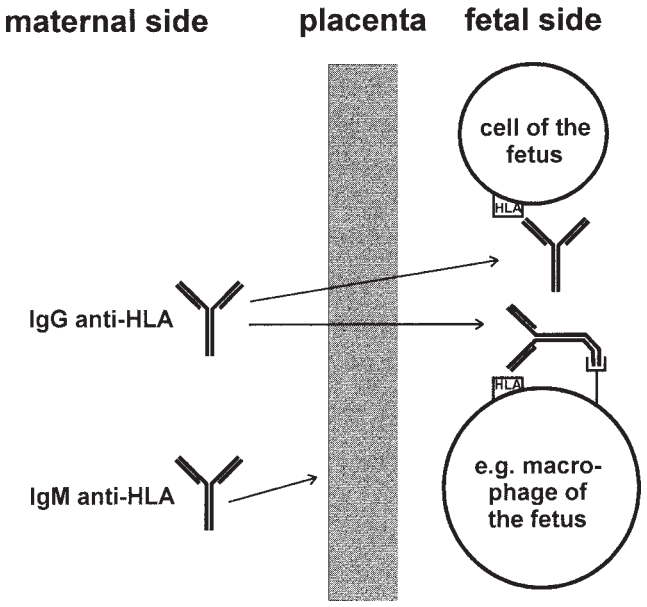

Fig. 2. Model of HLA-antibody induced fetal protection. Maternal IgG anti-HLA passes the placental barrier and sensitizes placental and fetal target cells. This causes Fc receptor blockade on the effector cells by formation of three-molecule complexes, thus preventing the Fc receptor-dependent injury to the target.

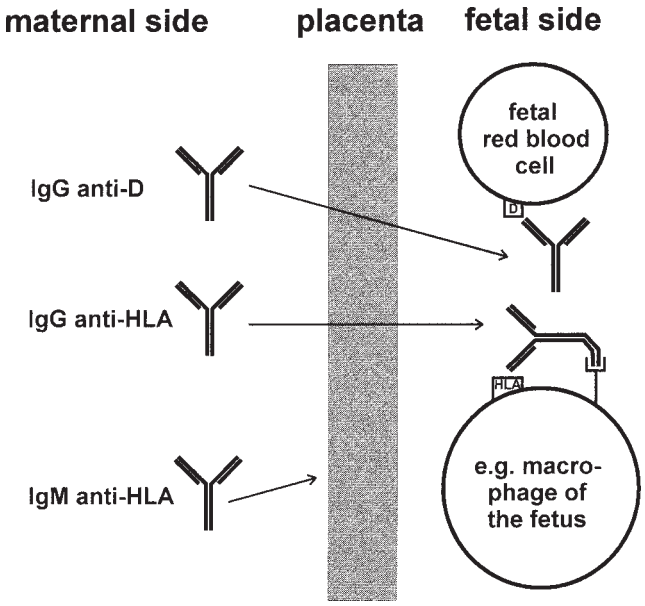

Fig. 3. Influence of HLA-antibodies in HDN. In the hemolytic disease of the fetus and newborn (HDN), maternal IgG-anti-D passes the placenta before parturition. The anti-D sensitizes fetal red blood cells which thereafter can be attacked by Fc receptor-bearing effector cells (severe courses of HDN). If the mother additionally produces an antibody specific for fetal HLA, then this antibody also passes the placenta and causes Fc receptor inhibition on the fetal effector cells, thus diminishing the Fc receptor-dependent injury to the red blood cells (mild courses of HDN).

alloimmune neutropenia of the child. Moreover, inhibition of fetal FcR by maternal HLA antibodies also could be the mechanism by which the fetus protects itself against the inherent injuring effect—considerable if directed to a transplanted allogeneic organ—of these HLA antibodies. Repeated allotypic attack of the mothers against their immunologically different offspring could ensure their negative selection, thus restricting the allotypic diversity in a species during the course of time. Therefore, the aforementioned protective mechanism of specific FcR inhibition may well contribute to the maintenance of allotypia in a species (109), thought to be essential for its survival during the co-evolution with pathogens that mimic host antigens to use the host's inability to recognize and attack self antigens (141).

ANTIBODY-MEDIATED INTERACTION OF DIFFERENT CELLBOUND MOLECULES INCLUDING FCγR

Cell-membrane proteins often exist as clusters or rafts within the membrane. Due to their proximity, these membrane proteins may act together in the induction of signalling and cellular functions. Not only transmembrane proteins but also GPI-anchored proteins occur in microdomains within the cell membrane as shown for decay-accelerating factor (DAF) and folate receptor (142,143). Cooperation between FcγR and different molecules has been deduced from functional studies. Complement receptor 3 (CR3; CD11b/CD18) interacts with FcγRIIIb. On neutrophils, FcγRIIIb and CR3 cocap after incubation with an appropriate antibody (144) and cooperate in the generation of respiratory burst (145). The latter process requires tyrosine phosphorylation of the intracellular activation motive of FcγRII in that ligation of CR3 on the adherent PMN surface leads to FcγRII association with the actin cytoskeleton while coligation of FcγRIIIb with CR3 is required for tyrosine phosphorylation of FcγRII. In contrast, another study has demonstrated the cooperation of FcγRIIIb with CR3 on fibroblast transfectants to mediate phagocytosis in the absence of FcγRII (146). FcγRIIa has been shown to functionally interact with the glycoprotein Ib-IX-V complex on platelets. Flow-cytometric-fluorescence energy transfer demonstrates a physical proximity of less than 10 nm between these receptors (147). Interaction of neighbored cell-bound molecules often is induced by crosslinking via antibodies. Crosslinking of FcγRIIIb on neutrophils with anti-FcγRIII $F(ab')_2$ enhances phagocytosis mediated by FcγRII (107) and co-ligation of FcγRII and FcγRIIIb results in a phagocytic response which is greater than that of either receptor alone or the sum of both (11). Engagement of two FcγRIIIb molecules and one FcγRIIa molecule by one anti-FcγRIII-specific monoclonal antibody 3G8, binding with its Fab portions to FcγRIIIb and with its Fc portion to FcγRIIa, induces a more effecient neutrophil activation than does the crosslinking of one of the receptors separately (148). FcγRIII-specific monoclonal antibodies and alloantisera significantly inhibit FcγRII-specific phagocytosis and in IFN-induced FcγRI expressing neutrophils also FcγRI specific phagocytosis by crosslinking different FcγR on the cell membrane (112,113). HLA antigens also seem to reside in close proximity to different FcγR on the surface of monocytes and neutrophils as HLA antibodies inhibit both FcγRI- and FcγRII-specific phagocytosis (112,113) albeit with a different immunoglobulin isotype-dependent impact on FcγRI and II (109).

Early experiments using FcγR-inhibiting antibodies to major histocompatibility (MHC) class-II antigens suggested that these antigens and FcγR are closely associated or identical (149). From further data it was concluded that antibodies to HLA class II (but not class I) inhibited the FcγR on lymphoid cells (150). Nusbacher et al. (151) observed that the granulocyte phagocytosis of opsonized red cells was specifically inhibited by antibodies to HLA class I. In a later study (152) murine monoclonal antibodies with specificity to various molecules on human cells inhibited the FcγR only if the antibody molecule was complete. The inhibition was abrogated if the monoclonal antibodies were employed as $F(ab')_2$ fragments. The authors concluded that inhibition was due to the formation of a three-component complex composed of antibody bound by its Fab portion to antigen and by its Fc fragment to an FcγR (compare Fig. 1). Our group found that heterologous and allogeneic antibodies with specificity to all MHC products are inhibitory to FcγRI and II on monocytes,

macrophages, B cells, and granulocytes, if these products are expressed on the cells (109,134,135). $F(ab')_2$ fragments of monoclonal HLA class I and II specific antibodies lost their inhibitory capacity (133). Class I-specific antibodies exert stronger inhibition than do class II-specific antibodies (109), which was confirmed by others measuring the inhibition of the FcγR-dependent cell activation using chemiluminiscence (153). HLA class-I antibodies are known to induce not only capping of class I but also cocapping of class-II antigens while class II-specific antibodies only induce capping of the corresponding class-II antigens (154). Subsequent to this, these antibodies induce endocytosis of the corresponding HLA antigens. Thus we assumed that the entire three-component complex, and possibly more constituents in the caps, are endocytosed and will be split in the lysosomes at pH 4–5. We also know that the bulk of HLA antigens are not degraded in the cell and recycle to the cell surface while the FcγR are catabolized in the cell (Fig. 4) (155). Because of this process and because the three-molecule complex is markedly compact through binding of the middle parts of both molecules, the FcR, and the MHC antibody, this can explain the strong inhibitory effect of MHC antibodies (Fig. 1). To date no factors other than IgG-HLA antibodies could be identified within an allogeneic system as inhibitors of the FcγR when analyzed by the monocyte immune phagocytosis inhibition (IPI; 155 and unpublished data) or a chemiluminescence test (156).

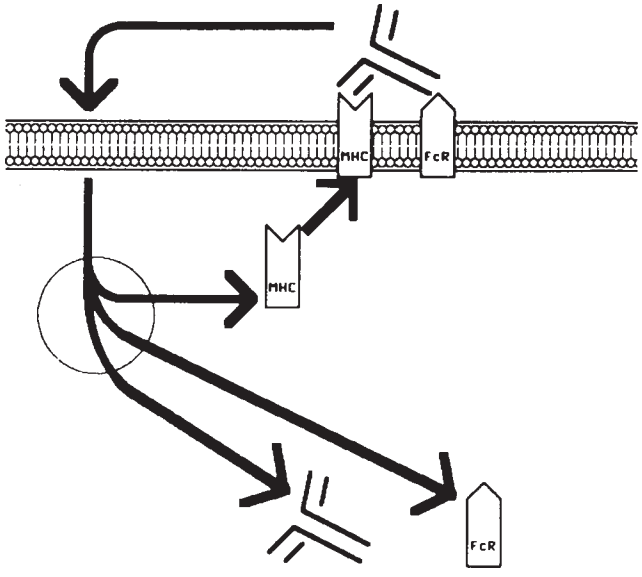

Fig. 4. Intracellular processing of internalized three-molecule complexes. Subsequent to the bipolar binding of the MHC antibody to the MHC antigen and to the Fc receptor the entire complex is moving laterally to patches or caps of the cell. Thereafter the complex is ingested and split into its constituents in the acidic lysosome. The antibody and the Fc receptor are finally degraded but the MHC antigen recycles to the cell surface enabling the cell to eliminate more Fc receptors. A long-lasting deficiency of Fc receptor function is the result (compare to reference 155).

Using granulocytes, clinically relevant auto- and alloantibodies to the neutrophil-specific antigens NA1 and NA2 also can inhibit FcR-dependent functions such as immune phagocytosis and cell activation in vitro (109,153). In in vivo animal models, however, these antibodies may act in the opposite way (157), and in patients where they can cause life-threatening transfusion-related lung injury (158), autoimmune neutropenia and materno-fetal incompatibility (fetal or neonatal alloimmune neutropenia).

CLINICAL IMPLICATIONS

FcγR and Disease Association

FcγR may be involved in disease in several ways. A number of reports deal with the association of certain FcγR polymorphic forms with different diseases. Additionally, complete deficiency of special receptors for IgG is under investigation. Furthermore, alloantibodies specific for epitopes on FcγR molecules influence cell function, as do antibodies directed against epitopes which are in close proximity to FcγR on the cell membrane. And lastly, FcγR-mediated functions are involved in alloimmune diseases of the fetus and the newborn.

FcγR may directly contribute in disease generation. Inflammatory mediators such as IFNγ or G-CSF enhance the expression of FcγRI on the neutrophil surface thus leading to an enhanced activation of monocytes and granulocytes (6) which may be one of the factors responsible for vasculitis following G-CSF therapy. In the case of idiopathic thrombocytic purpura (ITP), autoantibodies bound to the platelet surface are recognized and degraded by FcγR-bearing cells of the reticuloendothelial system in spleen and liver. It is generally accepted that this degradation provokes thrombocytopenia.

FcγRIIa exhibits two polymorphic forms in that the FcγRIIa-His131 form is the only FcγR that binds huIgG2 in complexed form while the FcγRIIa-Arg131 is unable to do so (29,30). Additionally significantly lower levels of IgG2 were found in the serum of individuals homozygous for the FcγRIIa-His131 form, suggesting increased turnover of IgG2 in these individuals (30). IgG2 is the main isotype produced in response to bacterial polysaccharides and encapsulated bacteria such as *Hemophilus influenzae* and *Streptococcus pneumoniae* (159). And indeed, FcγRIIa-His131 homozygous PMN phagocytosis of IgG2 opsonized bacteria is significantly higher than that of FcγRIIa-Arg131 homozygous cells (160,161). In 48 children with recurrent bacterial respiratory tract infections, the FcγRIIa-His/His131 type was less than half that observed in healthy adults (160). Comparable results were found in children with fulminant meningococcal septic shock (162) suggesting deficiency of FcγR-mediated defence against the implicated pathogens in FcγRIIa-Arg131 individuals.

Discussions regarding the correlation between FcγRIIa polymorphism and heparin-induced thrombocytopenia (HIT) are controversial. Antibodies against a complex of heparin

and platelet factor 4 (PF4) are thought to bind with the Fab portion to the heparin/PF4 complex and with the Fc portion to the FcγRIIa on the platelet membrane thus activating the platelets. Theoretically this crosslinking would be most significant, if the autoantibodies had the isotype huIgG2 and the FcγRIIa had the allotype His131. In these instances one would assume severe courses of the disease. Not all patients who generate heparin-dependent antibodies develop HIT. Most of the serum antibodies against the heparin/PF4 complex are of the IgG1 isotype alone or in combination with IgG2 or IgG3 (163). Some studies show an overrepresentation of the FcγRIIa-His/His131 genotype among HIT patients (164,165), others describe an overrepresentation of the FcγRIIa-Arg/Arg131 genotype especially among those HIT patients with thromboembolic complications (166) while others disprove any correlation between FcγRIIa polymorphism and HIT (167).

The influence of the FcγRIIa polymorphism on different autoimmunologic disorders has been investigated. For systemic lupus erythematosus (SLE) the FcγRIIa polymorphic form has been excluded as a genetic risk factor (168,169) although the polymorphism might influence the clinical manifestation and course of the disease (170). In myastenia gravis (MG) the FcγRIIa-His/His131 type was overrepresented in those patients with thymoma compared to other MG patients, while the FcγRIIIb NA1/NA1 genotype dominated in those patients with the most severe MG (171).

Monocytes from patients with hereditary hemochromatosis have a decreased antibody-mediated phagocytosis but this phenomenon cannot be attributed to a reduced level of FcγRI or II expression or to FcγRIIa polymorphism (172).

It is reported that autoantibodies directed against FcγRI, II, and III were found in sera of patients with different systemic autoimmune diseases such as SLE, Sjögren Syndrome, and progressive systemic sclerosis (173,174). The binding of these autoantibodies to the different FcγR-bearing cells might activate them and induce the release of oxygen radicals and soluble mediators. Binding to FcγRI could block the clearance of immune complexes.

Antineutrophil cytoplasmic antibodies (ANCA) are very often found in patients with systemic vasculitis, above all in Wegener's granulomatosis. Neutrophils of these patients express antigens as proteinase 3, elastase, and others on their cell surface which are normally located in intracellular granules (175). Dislocation of the antigens on the cell surface makes them accessible to the autoantibodies which can then activate the granulocytes by forming three-molecule complexes, including the antigen and FcγRIIa. This interaction induces degranulation and respiratory burst (176,177). However, no association between the FcγRIIa polymorphism and Wegener's granulomatosis with or without renal disease was found (178).

Autoantibodies with specificities for NA1 or NA2 on PMN were demonstrated in autoimmune neutropenia (179,180). The cause is clearance of the antibody coated PMN through FcγR on mononuclear phagocytes.

Soluble forms of FcγR I, II, and III have been described. Their biological role is unknown to date, but regulation of B-cell function and/or inhibition of immune complex activation of inflammatory cells have been discussed (181,182). Altered levels of soluble FcγRII and/or FcγRIII have been detected in patients with either rheumatoid arthritis and/or SLE, in patients with stage C chronic lymphocytic leukemia, and in sites of inflammation (183–186).

Some individuals with FcγR deficiencies have been described in the literature. Four members of one Belgian family lack the FcγRI due to a single nucleotide exchange leading to a termination codon. All family members are healthy (12,13). Individuals lacking FcγRIIIb due to a complete absence of the FcγRIIIB gene have been identified the world over (62–64,187). One individual suffered from SLE (187), while among 21 individuals only some suffered from repeated infections, and in two, autoimmune thyreoditis was present (62). Thus no precise disease association could be demonstrated. However, FcγRIIIb deficiency may lead to alloimmunization in pregnant women or transfused patients. The alloantibodies then may induce severe complications.

While on the one hand FcγR play an important role in the pathogenesis of autoimmune neutropenia, fetal or neonatal alloimmune neutropenia, and the transfusion-related acute lung injury, on the other hand they may be involved in the amelioration of materno-fetal incompatibilty by HLA antibodies in the hemolytic disease of the fetus or newborn. In this instance the FcR-mediated destruction of the sensitized red cells by FcR-bearing cells of the placenta and the fetus apparently can be prevented by maternal HLA antibodies passing the placenta to the child and abrogating FcR-mediated functions (Fig. 3) (137,140). The same mechanism could be observed in an entirely allogeneic animal model. Intravenous application of rabbit alloantibodies against MHC antigens of the recipient prolonged the circulatory survival of subsequent transfused rabbit red cells sensitized with rabbit blood-group antibodies with properties comparable to those of the human Rh-antibodies (188).

FcγR and Therapy

High doses of pooled IgG from the plasma of healthy donors are used for the therapy of autoimmune disorders, but the mechanism of action is not known. Therapeutic concentrations of exogenous IgG may block the FcγRI on phagocytes thus competing with the autoimmune antibodies for FcγR binding sites. But only FcγRI is able to bind monomeric IgG. Analogous to the mechanism mentioned in the preceding paragraph, we assume that the benefit of anti-D IgG for idiopathic thrombocytopenic purpura (ITP) might be due to the contaminating HLA but not to the D antibodies. The HLA antibodies abrogate the FcR activity in the patient. This can only

be true in polyclonal (as opposed to monoclonal) anti-D-IgG preparations. Indeed, there are indications that the latter are ineffective while, in some cases, polyclonal anti-D may be effective in D-negative patients (189,190). It has not yet been proven that pure anti-D-IgG without contaminating HLA antibodies (e.g., eluted from D-positive red cells or monoclonal anti-D) is effective as a Rh-prophylaxis in Rh-negative women. Similarly, the therapeutic effect of intravenous IgG in ITP also may be due to contaminating HLA antibodies which inhibit Fc receptors.

It is important to note that the intravenous application of HLA antibodies as a therapeutic tool is still quite speculative in nature. It might even be hazardous to prove the therapeutic effect of FcR-inhibiting HLA antibodies in humans: almost simultaneously (and based on the same hypothesis) the groups in Giessen and Amsterdam independently administered a human polyclonal HLA antibody preparation intravenously to volunteers. This resulted in a mild (191) and in a life-threatening interstitial lung edema (transfusion related acute lung injury, TRALI; 192). Whether the outcome is beneficial or detrimental could depend upon the antibody quantity relative to the recipients' body weight and on the specificity of the antibodies against the patients' HLA.

Another possible action of pooled IgG includes the regulatory properties of anti-idiotype antibodies but the mechanism has not been proved. Another possible therapy for autoimmune disease is based on the IgG level-regulating potential of FcRn. Agents reacting with the FcRn (antibodies, anti-sense nucleotides, etc.) could prevent the binding of autoantibodies to FcRn in endocytic vacuoles and their subsequent release into the plasma. This blockade of FcRn would induce degradation of ingested IgG molecules (193). Clinical trials using antibodies specific for different FcγR, anti-Rh antibodies, or bispecific antibodies are in progress in autoimmune disorders like ITP, in cancer, and in infectious diseases (for review see 194). These studies either use the FcR-blocking ability of antibodies (thus preventing degradation of target cells by FcR positive cells) or, in the case of bispecific antibodies, they bind with the tumor-specific "arm" to the tumor cell and with the FcR-specific "arm" to the FcγR-positive cell, mediating destruction of the tumor cell by phagocytosis or ADCC.

REFERENCES

1. Woof JM, Partridge LJ, Jeffris R, Burton DR. Localisation of the monocyte-binding region on human immunoglobulin G Molec Immunol 1986;23:319–330.
2. Simister NE, Story CM. Human placental Fc receptors and the transmission of antibodies from mother to fetus. J Reprod Immunol 1997;37:1–23.
3. Kristoffersen EK, Ulvestad E, Vedeler CA, Matre R. Fcγ receptor heterogeneity in the human placenta. Scand J Immunol 1990;31:561–564.
4. Kameda T, Koyama M, Matsuzaki N, Taniguchi T, Saji F, Tanizawa O. Localization of three subtypes of Fcγ receptors in human placenta by immunohistochemical analysis. Placenta 1991;12:15–26.
5. Sedmak DD, Davis DH, Singh U, van de Winkel JGJ, Anderson CL. Expression of IgG Fc receptor antigens in placenta and on endothelial cells in humans. An immunohistochemical study. Am J Pathol 1991;138:175–181.
6. Fanger MW, Shen L, Graziano RF, Guyre PM. Cytotoxicity mediated by human Fc receptors for IgG. Immunol Today 1989;10:92–99.
7. van de Winkel JGJ, Ernst LK, Anderson CL, Chiu IM. Gene organization of the human high affinity receptor for IgG, Fc RI (CD64). J Biol Chem 1991;266:13449–13455.
8. de Wit TPM, Suijkerbuijk RF, Capel RJA, van Kessel AG, van de Winkel JGJ. Assignment of three human high-affinity Fcγ receptor I genes to chromosome 1, band q21.1. Immunogenetics 1993;38:57–59.
9. van de Winkel JGJ, Capel PJA. Human IgG Fc receptor heterogeneity: molecular aspects and clinical implications. Immunol Today 1993; 14:215–221.
10. Hulett MD, Hogarth PM. Molecular basis of Fc receptor function. Adv Immunol 1994;57:1–127.
11. Porges AJ, Redecha PB, Doebele R, Pan LC, Salmon JE, Kimberly RP. Novel Fcγ receptor 1 family gene products in human mononuclear cells. J Clin Invest 1992;90:2101–2109.
12. Ceuppens JL, Baroja ML, van Vaeck F, Anderson CL. Defect in the membrane expression of high affinity 72-kD Fcγ receptors on phagocytic cells in four healthy subjects. J Clin Invest 1988;82:571–578.
13. van de Winkel JGJ, de Wit TPM, Ernst LK, Capel PJA, Ceuppens JL. Molecular basis for a familial defect in phagocyte expression of IgG receptor I (CD64). J Immunol 1995;154:2896–2903.
14. Reth M. Antigen receptor tail clue. Nature 1989;338:383–384.
15. Cambier JC. New nomenclature for the Reth motif (or ARH1/TAM/ARAM/YXXL). Immunol Today 1995;16:110–114.
16. Agarwal A, Salem P, Robbins KC. Involvement of $p72^{syk}$, a protein-tyrosine kinase, in Fcγ receptor signaling. J Biol Chem 1993; 268:15900–15905.
17. Kiener PA, Rankin BM, Burkhardt AL, et al. Cross-linking of Fcγ receptor I (FcγRI) and receptor II (FcγRII) on monocytic cells activates a signal transduction pathway common to both Fc receptors that involves the stimulation of p72 Syk protein tyrosine kinase. J Biol Chem 1993;268:24442–24448.
18. Ernst LK, Duchemin A-M, Anderson CL. Association of the high-affinity receptor for IgG (FcγRI) with the γ subunit of the IgE receptor. Proc Natl Acad Sci U S A 1993;90:6023–27.
19. Durden DL, Kim HM, Calore B, Liu Y. The FcγRI receptor signals through the activation of hck and MAP kinase. J Immunol 1995; 154:4039–4047,
20. Ravetch JV, Kinet J-P. Fc receptors. Annu Rev Immunol 1991; 9:457–492.
21. Hulett MD, McKenzie IFC, Hogarth PM. Chimeric Fc receptors identify immunoglobulin-binding regions in human FcγRII and FcγRI. Eur J Immunol 1993;23:640–645.
22. Hulett MD, Witort E, Brinkworth RI, McKenzie IF, Hogarth PM. Multiple regions of human FcγRII (CD32) contribute to the binding of IgG. J Biol Chem 1995;270:21188–21194.
23. Qiu WQ, de Bruin D, Brownstein BH, Pearse R, Ravetch JV. Organization of the human and mouse low-affinity FcγR genes: duplication and recombination. Science 1990;248:732–753.
24. Sammartino L, Webber LM, Hogarth PM, McKenzie IFC, Garson OM. Assignment of the gene coding for human FcRII (CD32) to bands q23q24 on chromosome 1. Immunogenetics 1988;28:380–381.
25. van de Winkel JGJ, Anderson CL. Biology of human immunoglobulin G Fc receptors. J Leuk Biol 1991;49:511–524.
26. Stuart SG, Simister NE, Clarkson SB, Kacinski BM, Shapiro M, Mellman I. Human IgG Fc receptor (hFcRII; CD32) exists as multiple isoforms in macrophages, lymphocytes and IgG-transporting placental epithelium. EMBO J 1989;8:3657–3666.
27. Brooks DG, Qiu WQ, Luster AD, Ravetch JV. Structure and expression of human IgG FcRII (CD32). J Exp Med 1989;170:1369–1385.

28. Warmerdam PAM, van de Winkel JGJ, Gosselin EJ, Capel PJA. Molecular basis for a polymorphism of human Fcγ receptor II (CD32). J Exp Med 1990;172:19–25.
29. Warmerdam PAM, van de Winkel JGJ, Vlug A, Westerdal NAC, Capel PJA. A single amino acid in the second Ig-like domain of the human Fcγ receptor II is critical for human IgG2 binding. J Immunol 1991; 147:1338–1343.
30. Parren PWHI, Warmdam PAM, Boeije LCM, et al. On the interaction of IgG subclasses with the low-affinity FcγRIIa (CD32) on human monocytes, neutrophils and platelets; analysis of a functional polymorphism to human IgG2. J Clin Invest 1992;90:1537–1546.
31. Flesch BK, Bauer F, Neppert J. Rapid typing of the human Fcγ receptor IIA polymorphism by polymerase chain reaction amplification with allele-specific primers. Transfusion 1998;38:174–176.
32. Osborne JM, Chaacko GW, Brandt JT, Anderson CL. Ethnic variation in frequency of an allelic polymorphism of human FcγRIIA determined with allele specific oligonucleotide probes. J Immunol Meths 1994; 173:207–217.
33. Reilly AF, Norris CF, Surrey S, et al. Genetic diversity in human Fc receptor II for immunoglobulin G: Fcγ receptor IIA ligand-binding polymorphism. Clin Diagnostic Lab Immunol 1994;1:640–644.
34. Schnackenberg L, Flesch BK, Neppert J. Linkage disequilibria between Duffy blood groups, FcγRIIa and FcγRIIIb allotypes. Exp Clin Immunogenet 1997;14:235–242.
35. Tax WJM, Hermes FFM, Willems RW, Capel PJA, Koene RAP. Fc receptors for mouse IgG1 on human monocytes: polymorphism and role in antibody-induced T cell proliferation. J Immunol 1984;133:1185–1189.
36. Tate BJ, Witort E, McKenzie IFC, Hogarth PM. Expression of the high responder/ non-responder human FcγRII. Analysis by PCR and transfection into FcR-COS cells. Immunol Cell Biol 1992;70:79–87.
37. Norris CF, Pricop L, Millard SS, et al. A naturally occurring mutation in FcγRIIA: a Q to K127 change confers unique IgG binding properties to the R131 allelic form of the receptor. Blood 1998;91:656–662.
38. Cassel DL, Keller MA, Surrey S, et al. Differential expression of FcγRIIA, FcγRIIB and FcγRIIC in hematopoietic cells: analysis of transcipts. Mol Immunol 1993;30:451–460.
39. Warmerdam PAM, van den Herik-Oudijk IE, Parren PWHI, Westerdaal NAC, van de Winkel JGJ, Capel PJA. Interaction of a human FcγRIIb1 (CD32) isoform with murine and human IgG subclasses. Int Immunol 1993;5:239–247.
40. Warmerdam PAM, Nabben NMJM, van de Graaf SAR, van de Winkel JGJ, Capel PJ. The human low affinity immunoglobulin G Fc receptor IIC gene is a result of an unequal crossover event. J Biol Chem 1992;268:7346–7349.
41. Odin JA, Edberg JC, Painter CJ, Kimberly RP, Unkeless JC. Regulation of phagocytosis and $[Ca^{2+}]_i$ flux by distinct regions of an Fc receptor. Science 1991;254:1785–1788.
42. van den Herik-Oudijk IE, Capel PJA, van der Bruggen T, van de Winkel JGJ. Identification of signalling motifs within human FcγRIIA and FcγRIIB isoforms. Blood 1995;85:2202–2211.
43. Indik ZK, Park J-G, Hunter S, Schreiber AD. The molecular dissection of Fcγ receptor mediated phagocytosis. Blood 1995;86:4389–4399.
44. Masuda M, Roos D. Association of all three types of FcγR (CD64, CD32, CD16) with a γ chain homodimer in cultured human monocytes. J Immunol 1993;151:6382–6388.
45. Huang MM, Indik ZK, Brass LF, Hoxie JA, Schreiber AD, Brugge JS. Activation of FcγRII induces tyrosine phosphorylation of multiple proteins including FcγRII. J Biol Chem 1992;267:5467–5473.
46. Hunter S, Indik ZK, Kim M-K, Cauley MD, Park J-G, Schreiber AD. Inhibition of Fcγ receptor-mediated phagocytosis by a nonphagocytic Fcγ receptor. Blood 1998;91:1762–1768.
47. Ravetch JV, Perussia B. Alternative membrane forms of FcγRIII (CD16) on human natural killer cells and neutrophils. J Exp Med 1989;170:481–497.
48. Edberg CJ, Barinsky M, Redecha PB, Salmon JE, Kimberly RP. FcγRIII expressed on cultured monocytes is a N-glycosylated transmembrane protein distinct from FcγRIII expressed on natural killler cells. J Immunol 1990;144:4729–4734.
49. Wainwright SD, Holmes CH. Distribution of Fcγ receptors on trophoblast during human placental development: an immunohistochemical and immunoblotting study. Immunology 1993;80:343–351.
50. Vance BA, Huizinga TWJ, Wardwell K, Guyre PM. Binding of monomeric human IgG defines an expression polymorphism of Fc gamma RIII on large granular lymphocyte/natural killer cells. J Immunol 1993;151:6429–6439.
51. Letourneur O, Kennedy ICS, Brini AT, Ortaldo JR, O'Shea JJ, Kinet JP. Characterization of the family of dimers associated with Fc receptors (FcγRI and FcγRIII). J Immunol 1991;147:2652–2656.
52. Vivier E, Morin P, O'Brien C, Druker B, Schlossman SF, Anderson P. Tyrosine phosphorylation of the FcγRIII (CD16): complex in human natural killer cells. J Immunol 1991;146:206–210.
53. Ting AT, Karnitz LM, Schoon RA, Abraham RT, Leibson PJ. Fcγ receptor activation induces the tyrosine phosporylation of both phospholipase C (PLC)- γ1 and PLC-γ2 in natural killer cells. J Exp Med 1992;176:1751–1755.
54. Selvaraj P, Rosse WF, Silber R, Springer TA. The major Fc receptor in blood has a phosphatidylinositol anchor and is deficient in paroxysmal nocturnal haemoglobinuria. Nature 1988;333:565–567.
55. Huizinga TW, Kerst M, Nuyens JH, et al. Binding characteristics of dimeric IgG subclass complexes to human neutrophils. J Immunol 1989;142:2359–2364.
56. Fleit HG, Wright SD, Unkeless JC. Human neutrophil Fcγ receptor distribution and structure. Proc Natl Acad Sci U S A 1982;79:3275–3279.
57. Anderson CL, Looney RJ. Human leukocyte IgG Fc receptors. Immunol Today 1986;7:264–266.
58. Hibbs ML, Tolvanen M, Carpén O. Membrane-proximal Ig-like domain of FcγRIII (CD16) contains residues critical for ligand binding. J Immunol 1994;152:4466–4474.
59. Ory PA, Goldstein IM, Kwoh EE, Clarkson SB. Characterization of polymorphic forms of FcRIII on human neutrophils. J Clin Invest 1989;83:1676–1681.
60. Huizinga TWJ, Kleijer M, Tetteroo PAT, Roos D, von dem Brone AEGKr. Biallelic neutrophil NA-antigen system is associated with a polymorphism on the phospho-inositol-linked Fcγ receptor III (CD16). Blood 1990;75:213–217.
61. Bux J, Stein EL, Bierling P, et al. Characterization of a new alloantigen (SH) on the human neutrophil Fc receptor IIIB. Blood 1997;89:1027–1034.
62. de Haas M, Kleijer M, van Zwieten R, Roos D, von dem Borne AEGKr. Neutrophil FcγRIIIb deficiency, nature, and clinical consequences: a study of 21 individuals from 14 families. Blood 1995;86:2403–2413.
63. Huizinga TWJ, Kuijpers RWAM, Kleijer M, et al. Maternal genomic neutrophil FcRIII deficiency leading to neonatal isoimmune neutropenia. Blood 1990;76:1927–1932.
64. Flesch BK, Achtert G, Bauer F, Neppert J. The NA "null" phenotype of a young man is caused by an FcγRIIIB gene deficiency while the products of the neighboured FcγRIIA and FcγRIIIA genes are present. Ann Hematol 1998;76:215–220.
65. de Haas M, Kleijer M, Minchinton RM, Roos D, von dem Borne AEGKr. Soluble FcγRIIIa is present in plasma and is derived from natural killer cells. J Immunol 1994;152:900–907.
66. Simister NE, Rees AR. Isolation and characterization of an Fc receptor from neonatal rat small intestine. Eur J Immunol 1985;15:733–738.
67. Ahouse JJ, Hagerman CL, Mittal P, et al. A mouse MHC class-I-like Fc receptor encoded outside the MHC. J Immunol 1993;152:6076–6088.
68. Story CM, Mikulska JE, Simister NE. A major histocompatibility com-

plex class I-like Fc receptor cloned from human placenta: possible role in transfer of immunoglobulin G form mother to fetus. J Exp Med 1994;180:2377–2381.
69. Leach JL, Sedmak DD, Osborne JM, Rahill B, Lairmore MD, Anderson CL. Isolation from human placenta of the IgG transporter, FcRn, and localization to the syncytiotrophoblast: implications for maternal-fetal antibody transport. J Immunol 1996;157:3317–3322.
70. Israel EJ, Taylor S, Wu Z, et al. Expression of the neonatal Fc receptor, FcRn, on human intestinal epithelial cells. Immunology 1997; 92:69–74.
71. Junghans RP, Anderson CL. The protection receptor for IgG catabolism is the β_1-microglobulin-containing neonatal intestinal transport receptor. Proc Natl Acad Sci U S A 1996;93:5512–5516.
72. Kandil E, Egashira M, Miyoshi O, Niikawa N, Ishibashi T, Kasahara M. The human gene encoding the heavy chain of the major histocompatibility complex class I-like Fc receptor (FCGRT) maps to 19q13.3. Cytogenet Cell Genet 1996;73:97–98.
73. Burmeister WP, Gastinel LN, Simister NE, Blum ML, Bjorkman PJ. Crystal structure at 2.2 Å resolution of the MHC-related neonatal Fc receptor. Nature 1994;372:336–343.
74. Burmeister WP, Huber AH, Bjorkman PJ. Crystal structure of the complex of rat neonatal Fc receptor with Fc. Nature 1994;372:379–383.
75. Raghavan M, Chen MY, Gastinel LN, Bjorkman PJ. Investigation of the interaction between the class I MHC-related Fc receptor and its immunoglobulin G ligand. Immunity 1994;1:303–315.
76. Medesan C, Radu C, Kim J-K, Ghetie V, Ward ES. Localization of the site of the IgG molecule that regulates maternofetal transmission in mice. Eur J Immunol 1996;26:2533–2536.
77. Ghetie V, Ward ES. FcRn: the MHC class I-related receptor that is more than an IgG transporter. Immunol Today 1997;18:592–598.
78. Stefaner I, Stefanescu A, Hunziker W, Fuchs R. Expression of placental alkaline phosphatase does not correlate with IgG binding, internalization and transcytosis. Biochem J 1997;327:585–592.
79. Kristoffersen EK. Human placental Fc gamma-binding proteins in the maternofetal transfer of IgG. APMIS 1996;104(Suppl)64:5–36.
80. Forsgren A, Sjöquist J. "Protein A" from *S. aureus.* I. Pseudo-immune reaction with human γ-globulin. J Immunol 1966;97:822–827.
81. Kronvall G, Seal US, Finstad J, Williams RC. Phylogenetic insight into evolution of mammalian Fc fragment of gamma G globulin using staphylococcal protein A. J Immunol 1970;104:140–147.
82. Åkerström B, Björck L. A physicochemical study of protein G, a molecule with unique immunoglobulin G-binding properties. J Biol Chem 1986;261:10240–10247.
83. Kronvall G, Quie PG, Williams RC. Quantitation of staphylococcal protein A: determination of equilibrium constant and number of protein A residues on bacteria. J Immunol 1970;104:273–278.
84. Deisenhofer J. Crystallographic refinement and atomic models of a human Fc fragment and its complex with fragment B of Protein A from *Staphylococcus aureus* at 2.9- and 2.8-Å resolution. Biochemistry 1981;20:2361–2370.
85. Moks T, Abrahmsen L, Nilsson B, Hellman U, Sjöquist J, Uhlén M. Staphylococcal protein A consists of five IgG-binding domains. Eur J Biochem 1986;156:637–643.
86. Guss B, Eliasson M, Olsson A, Uhlén M, Frej A-K, Jörnvall H, Flock J-I, Lindberg M. Structure of the IgG-binding regions of streptococcal protein G. EMBO J 1986;5:1567–1575.
87. Espersen F. Interactions between human plasma proteins and cell wall components of *Staphylococcus aureus.* Dan Med Mull 1987;34:59–69.
88. Foster TJ, McDevitt D. Surface-associated proteins of *Staphylococcus aureus*: their possible roles in virulence. FEMS Microbiol Lett 1994;118:199–205.
89. Schäcke H, Müller WEG, Gamulin V, Rinkevich B. The Ig superfamily includes members from the lowest invertebrates to the highest vertebrates. Immunol Today 1994;15:497–498.
90. Kobayashi K, Tomonaga S. The second immunoglobulin class commonly present in cartilaginous fish belonging to the order Rajiformes. Mol Immunol 1988;25:115–120.
91. Atanossov CL, Botev BA. Isolation and partial characterization of IgM-like immunoglobulins from the serum of carp (*Cyprinas carpio* L.), frog (*Rana ridibunda* Pall.) and tortoise (*Testudo graeca* Pall.). Comp Biochem Physiol 1988;89:737–741.
92. Rosenshein IL, Schluter SF, Marchalonis JJ. Conservation among the immunoglobulins of carcharhine sharks and phylogenetic conservation of variable region determinants. Vet Immunol Immunopathol 1986;12:13–20.
93. Sandor M, Lynch RG. A possible role of FcγR in hematopoietic cell development. In: van de Winkel JGJ, Capel PJA, editors. Human IgG Fc receptors. Heidelberg, Germany: Springer-Verlag; 1996. p 165–179.
94. Haynes L, Fuller L, McKinney EC. Fc receptor for shark IgM. Dev Comp Immunol 1988;12:561–571.
95. Williams FA, Barclay AN. The immunoglobulin superfamily-domains for cell surface recognition. Ann Rev Immunol 1988;6:381–405.
96. Novak JS, Lassila O, Vainio O, Granfors K, Toivanen P. IgG Fc receptor-bearing cells during early lymphoid cell development in the chicken. Cell Immunol 1982;74:198–203.
97. Lassilla O, Alanen A, Lefkovits I, Cooper MD, Pink JR. Immunoglobulin diversification in embryonic chicken bursae in individual bursal follicles. Eur J Immunol 1988;18:943–948.
98. Sandor M, Galone J, Takacs L, et al. An alternative Fcγ-receptor ligand: potential role in T-cell development. Proc Natl Acad Sci U S A 1994;91:12857–12861.
99. Nossal GJV, Pike BL. Studies on the differentiation of B lymphocytes in the mouse. Immunology 1973;25:33–45.
100. Manca F, Fenoglio D, Li Pira G, Kunkel A, Celada F. Effect of antigen/antibody ratio on macrophage uptake, processing and presentation to T cells of antigen complexed with polyclonal antibodies. J Exp Med 1991;173:37–48.
101. Lowry MB, Duchemin AM, Robinson JM, Anderson CL. Functional separation of pseudopod extension and particle internalization during Fc receptor-mediated phagocytosis. J Exp Med 1998;187:161–176.
102. Griffin FM Jr, Griffin JA, Leider JE, Silverstein SC. Studies on the mechanism of phagocytosis. I. Requirements for circumferential attachment of particle-bound ligands to specific receptors on the macrophage plasma membrane. J Exp Med. 1975;142:1263–1282.
103. Griffiths HL, Kumpel BM, Elson CJ, Hadley AG. The functional activity of human monocytes passively sensitized with monoclonal anti-D suggests a novel role for Fc gamma RI in the immune destruction of blood cells. Immunology 1994;83:370–377.
104. Anderson CL, Shen L, Eicher DM, Wewers Md, Gill JK. Phagocytosis mediated by three distinct Fcγ receptor classes on human leukocytes. J Exp Med 1990;171:1333–1345.
105. Graziano RF, Fanger MW. FcγRI and FcγRII on monocytes and granulocytes are cytotoxic trigger molecules for tumor cells. J Immunol 1987;139:3536–3541.
106. Davis W, Harrison PT, Hutchinson MJ, Allen JM. Two distinct regions of FcγRI initiate separate signalling pathways involved in endocytosis and phagocytosis. EMBO J 1995;14:432–441.
107. Salmon JE, Brogle N, Edberg JC, Kimberly RP. Fcγ receptor III induces actin polymerization in human neutrophils and primes phagocytosis mediated by FcγRII. J Immunol 1991;146:997–1004.
108. Kumpel BM, Hadley AG. Functional interactions of red cells sensitized by IgG1 and IgG3 human monoclonal anti-D with enzyme-modified human monocytes and FcR-bearing cell lines. Molec Immunol 1990;27:247–256,
109. Neppert J, Jungi TW. Antibodies to human major histocompatibility complex products inhibit Fcγ receptors types I and II. Transfusion Med 1996;6:125–131.
110. Dougherty GJ, Selvendran Y, Murdoch S, Palmer DG, Hogg N. The

human mononuclear phagocyte high-affinity Fc receptor, FcRI, defined by a monoclonal antibody, 10.1. Eur J Immunol 1987;17:1453–1459.
111. Hadley AG, Kumpel BM. Synergistic effect of blending IgG1 and IgG3 monoclonal anti-D in promoting the metabolic response of monocytes to sensitized red cells. Immunology 1989;67:550–552.
112. Flesch BK, Maass W, Neppert J. NA1/NA2 antisera inhibit FcRγI- but not FcγRII-mediated phagocytosis. Vox Sang 1998;75:247–252.
113. Flesch BK, Achtert G, Neppert J. Inhibition of monocyte and polymorphonuclear granulocyte immune phagocytosis by monoclonal antibodies specfic for FcγRI, II and III. Ann Hematol 1997;74:15–22.
114. Wiener E, Dellow RA, Mawas F, Rodeck CH. Role of FcγRIIa (CD32) in IgG anti-RhD-mediated red cell phagocytosis in vitro. Transfusion Med 1996;6:235–241.
115. Edberg JC, Kimberly RP. Modulation of Fcγ and complement receptor function by the glycosyl-phosphatidylinositol-anchored form of FcγRIII. J Immunology 1994;152:5826–5835.
116. Kumpel BM. In vitro functional activity of IgG1 and IgG3 polyclonal and monoclonal anti-D. Vox Sang 1997;72:45–51.
117. Kumpel BM, van de Winkel JGJ, Westerdaal NAC, Hadley AG, Dugoujon JM, Blancher A. Antigen topography is critical for interaction of IgG2 anti-red-cell antibodies with Fc gamma receptors. Br J Haematol 1996;94:175–183.
118. Hadley AG, Kumpel BM, Merry AH. The chemiluminescent response of human monocytes to red cells sensitized with monoclonal anti-Rh(D) antibodies. Clin Lab Haematol 1988;10:377–384.
119. Anderson CL, Guyre PM, Whitin JC, Ryan DH, Looney RJ, Fanger MW. Monoclonal antibodies to Fc receptors for IgG on human mononuclear phagocytes. J Biol Chem 1986;261:12856–12864.
120. MacIntyre EA, Roberts PJ, Jones M, et al. Activation of human monocytes occurs on cross-linking monocytic antigens to an Fc receptor. J Immunol 1989;142:2377–2383.
121. Akerley WL III, Guyre PM, Davis BH. Neutrophil activation through high-affinity Fcγ receptor using a monomeric antibody with unique properties. Blood 1991;77:607–615.
122. Huizinga TWJ, van Kemenade F, Koenderman L, Dolman KM, von dem Borne AEGKr, Tetteroo PAT, Roos D: The 40 KDa Fcγ receptor (FcγRII) on human neutrophils is essential for the IgG-induced respiratory burst and IgG-induced phagocytosis. J Immunol 1989;142:2365–2369.
123. Willis HE, Browder B, Feister AJ, Mohanakumar T, Ruddy S. Monoclonal antibody to human IgG Fc receptors. Cross-linking of receptors induces lysosomal enzyme release and superoxide generation by neutrophils. J Immunol 1988;140:234–239.
124. Marsh CB, Gadek JE, Kindt GC, Moore SH, Wewers MD. Monocyte Fcγ receptor cross-linking induces IL-8 production. J Immunol 1995;155:3161–3167.
125. Krutmann J, Kirnbauer R, Köck A, Schwarz T, Schöpf E, May LT, Sehgal PB, Luger TA. Crosslinking Fc receptors on monocytes triggers IL-6 production. J Immunol 1990;145:1337–1342.
126. Debets JMH, van de Winkel JGJ, Ceuppens JL, Dieteren IEM, Buurman WA. Cross-linking of both FcγRI and FcγRII induces secretion of tumor necrosis factor by human monocytes, requiring high affinity Fc-FcγR interactions. J Immunol 1990;144:1304–1310.
127. Marsh CB, Wewers MD, Tan LC, Rovin BH. Fcγ receptor cross-linking induces peripheral blood mononuclear cell monocyte chemoattractant protein-1 expression. J Immunol 1997;158:1078–1084.
128. Amigorena S. Internalization through receptors for immunoglobulin. In: Fridman WH, Sautès C, editors. Cell-mediated effects of immunoglobulins. New York: Springer Landes Bioscience; 1997. p 117–138.
129. Gosselin EJ, Wardwell K, Gosselin DR, Alter N, Fisher JL, Guyre PM. Enhanced antigen presentation using human Fc gamma receptor (monocyte/macrophage)-specific immunogens. J Immunol 1992;149:3477–3481.
130. Brambell FWR, Hemmings WA, Morris IG. A theoretical model of γ-globulin catabolism. Nature 1964;203:1352–1355.
131. Malek A, Sager R, Schneider H. Maternal-fetal transport of immunoglobulin G and its subclasses during the third trimester of human pregnancy. Am J Reprod Immunol 1994;32:8–14.
132. Neppert J, Mueller-Eckhardt G, Heine O. Reduced immune phagocytosis of monocytes from neonates whose mothers produce HLA antibodies. Vox Sang 1988;54:177–180.
133. Neppert J, Marquard F, Mueller-Eckhardt C. Murine monoclonal antibodies and human alloantisera specific for HLA inhibit monocyte phagocytosis of anti-D sensitized human red blood cells. Eur J Immunol 1985;15:559–563.
132. Neppert J. Insignificant immune phagocytosis inhibition (IPI) and cytotoxicity by the murine monoclonal HLA-DP antibody B7/21 tested on human monocytes and macrophages. Scand J Immunol 1986; 24:321–326.
135. Faust A, Neppert J. Detection of antibodies specific for HLA-A, B, C, DR, DQ and DP by the erythrocyte antibody rosette inhibition (EAI) and immune phagocytosis inhibition (IPI) tests. J Immunol Meths 1987;102:71–75.
136. Adeniyi-Jones SCA, Ozato K. Transfer of antibodies directed to paternal major histocompatibility class I antigens from pregnant mice to the developing fetus. J Immunol 1987;138:1408–1415.
137. Neppert J: Rhesus-Du and -D incompatibility in the newborn without haemolytic disease: immune phagocytosis inhibition? Vox Sang 1987;53:239.
138. Dooren MC, Kuijpers RWAM, Joekes EC, et al. Protection against immune haemolytic disease of newborn infants by maternal monocyte-reactive IgG alloantibodies (anti-HLA-DR). Lancet 1992; 339:1067–1070.
139. Shepard SL, Noble AL, Filbey D, Hadley AG. Inhibition of the monocyte chemiluminescent response to anti-D-sensitized red cells by FcγRI-blocking antibodies which ameliorate the severity of haemolytic disease of the newborn. Vox Sang 1996;70:157–163.
140. Neppert J, Witzleben-Schürholz E, Zupanska B, et al. High incidence of maternal HLA A, B and C antibodies associated with a mild course of haemolytic disease of the newborn. European J Haematol 1999;63:120–125.
141. Snell, GD. The H-2 locus of the mouse: observations and speculations concerning its comparative genetics and its polymorphism. Folia Biol (Praha) 1968;14:335–358.
142. Friedrichson T, Kurzschalia TV. Microdomains of GPI-anchored proteins in living cells revealed by crosslinking. Nature 1998;394:802–805.
143. Varma R, Mayor S. GPI-anchored proteins are organized in submicron domains at the cell surface. Nature 1998;394:798–801.
144. Zhou MJ, Todd III RF, van de Winkel JGJ, Petty HR. Cocapping of the leukoadhesin molecules complement receptor type 3 and lymphocyte function-associated antigen-1 with Fcγ receptor III on human neutrophils. J Immunol 1993;150:3030–3041.
145. Zhou M-J, Brown EJ. CR3 (Mac-1, $\alpha_M\beta_2$, CD11b/CD18) and FcγRIII cooperate in generation of a neutrophil respiratory burst: requirement for FcγRII and tyrosine phosphorylation. J Cell Biol 1994;125:1407–1416.
146. Krauss JC, Poo H, Xue W, Mayo-Bond L, Todd III RF, Petty HR. Reconstitution of antibody-dependent phagocytosis in fibroblasts expressing Fcγ receptor IIIB and the complement receptor type 3. J Immunol 1994;153:1769–1777.
147. Sullam PM, Hyun WC, Szöllösi J, Dong JF, Foss WM, López JA. Physical proximity and functional interplay of the glycoprotein Ib-IX-V complex and the Fc receptor FcγRIIA on the platelet plasma membrane. J Biol Chem 1998;273:5331–5336.
148. Vossebeld PJM, Homburg CHE, Roos D, Verhoeven AJ. The anti-FcγRIII mab 3G8 induces neutrophil activation via a cooperative action of FcγRIIIb and FcγRIIa. Int J Biochem Cell Biol 1997; 29:465–473.

149. Dickler HB, Sachs DH. Evidence for identity or close association of the Fc receptor of B lymphocytes and alloantigens determined by the *Ir* region of the *H-2* complex. J Exp Med 1974;140:779–796.
150. Solheim BG, Thorsby E, Moller E. Inhibition of the Fc receptor of human lymphoid cells by antisera-recognizing determinants of the HLA system. J Exp Med 1976;143:1568–1574.
151. Nusbacher J, MacPherson JL, Gore I Jr, Grinberg R. Inhibition of granulocyte erythrophagocytosis by HLA antisera. Blood 1979;53:350–357.
152. Kurlander RJ. Blockade of Fc receptor-mediated binding to U-937 cells by murine monoclonal antibodies directed against a variety of surface antigens. J Immunol 1983;131:140–147.
153. Bux J, Dickmann JO, Stockert U, Mueller-Eckhardt C. Influence of granulocyte antibodies on granulocyte function. Vox Sang 1993; 64:220–225.
154. Neppert J, Mueller-Eckhardt C. Monoclonal mouse antibodies to human MHC class I antigens cocap class II antigens. Tissue Antigens 1984;24:187–189.
155. Neppert J. Persistence and selectivity of the immune phagocytosis inhibition by major histocompatibility complex antibodies. Scand J Immunol 1987;26:737–743.
156. Shepard SL, Hadley AG. A chemiluminescence test for the detection of monocyte-binding Fcγ receptor (FcγR)-blocking antibodies; comparison with inhibition of red cell phagocytosis and lysis. Transfusion Med 1993;3(Suppl)1:99.
157. Seeger W, Schneider U, Kreusler B, et al. Reproduction of transfusion-related acute lung injury in an ex vivo lung model. Blood 1990;76:1438–1444.
158. Popovsky MA. Transfusion-related acute lung injury (TRALI). In: Popovsky MA, editor. Transfusion reactions. Bethesda: AABB Press; 1996. p 167–183.
159. Siber GR, Schur PH, Aisenberg AC, Weitzman SA, Schiffman G. Correlation between serum IgG-2 concentrations and the antibody response to bacterial polysaccharide antigens. N Engl J Med 1980;303:178–182.
160. Sanders LAM, van de Winkel JGJ, Rijkers GT, et al. Fcγ receptor IIa (CD32) heterogeneity in patients with recurrent bacterial respiratory tract infections. J Infect Dis 1994;170:854–861.
161. Bredius RGM, deVries CEE, Troelstra A, et al. Phagocytosis of *Staphylococcus aureus* and *Haemophilus influenzae* type B opsonized with polyclonal human IgG1 and IgG2 antibodies. Functional hFcγRIIA polymorphism to IgG2. J Immunol 1993;151:1463–1468.
162. Bredius RGM, Derkx BHF, Fijen CAP, et al. Fcγ receptor IIa (CD32) polymorphism in fulminant meningococcal septic shock in children. J Infect Dis 1994;170:848–853.
163. Denomme GA, Warkentin TE, Horsewood P, Sheppard JAI, Warner MN, Kelton JG. Activation of platelets by sera containing IgG1 heparin-dependent antibodies: an explanation for the predominance of the FcγRIIa "low responder" (his131) gene in patients with heparin-induced thrombocytopenia. J Lab Clin Med 1997;130:278–284.
164. Burgess JK, Lindeman R,Chesterman CN, Chong BH. Single amino acid mutation of Fc gamma receptor is associated with the development of heparin-induced thrombocytopenia. Br J Haematol 1995; 91:761–766.
165. Brandt JT, Isenhart CE, Osborne JM, Ahmed A, Anderson CL. On the role of platelet Fc gamma RIIa phenotype in heparin-induced thrombocytopenia. Thromb Haemost 1995;74:1564–1572.
166. Carlsson LE, Santoso S, Baurichter G, et al. Heparin-induced thrombocytopenia: new insights into the impact of the FcγRIIa-R-H131 polymorphism. Blood 1998;92:1526–1531.
167. Arepally G, McKenzie SE, Jiang XM, Poncz M, Cines DB. Fc gamma RIIA H/R 131 polymorphism, subclass specific IgG anti-heparin/platelet factor 4 antibodies and clinical course in patients with heparin-induced thrombocytopenia and thrombosis. Blood 1997;89:370–375.
168. Smyth LJC, Snowden N, Carthy D, Papasteriades C, Hajeer A, Ollier WER. FcγRIIa polymorphism in systemic lupus erythematosus. Ann Rheum Dis 1997;56:744–746.
169. Botto M, Theodoridis E, Thompson EM, et al. FcγRIIa polymorphism in systemic lupus erythematosus (SLE): no association with disease. Clin Exp Immunol 1996;104:264–268.
170. Manger K, Repp R, Spriewald BM, et al. Fcγ receptor IIa polymorphism in Caucasian patients with systemic lupus erythematosus: association with clinical symptoms. Arthritis Rheum 1998;41:1181–1189.
171. Raknes G, Skeie GO, Gilhus NE, Aadland S, Vedeler C. FcγRIIA and FcγRIIIB polymorphisms in myasthenia gravis. J Neuroimmunol 1998;81:173–176.
172. Moura E, Verheul AFM, Marx JJM. Evaluation of the role of Fc and complement receptors in the decreased phagoctosis of hereditary haemochromatosis patients. Scand J Immunol 1997;46: 399–405.
173. Boros P, Muryoi T, Spiera H, Bona C, Unkeless JC. Autoantibodies directed against different classes of FcγR are found in sera of autoimmune patients. J Immunol 1993;150:2018–2024.
174. Szegedi A, Boros P, Chen J, Kaffina M, Bona C, Unkeless JC. An FcγRIII (CD16)-specific autoantibody from a patient with progressive systemic sclerosis. Immunol Lett 1993;35:69–76.
175. Gross WL, Csernok E, Flesch BK.Classic anti-neutrophil cytoplasmic autoantibodies (cANCA), Wegeners autoantigen and their immunopathogenic role in Wegener's granulomatosis. J Autoimmun 1993;6:171–184.
176. Mulder AHL, Heeringa P, Brouwer E, Limburg PC, Kallenber CGM. Activation of granulocytes by anti-neutrophil cytoplasmic antibodies (ANCA): a FcγRII-dependent process. Clin Exp Immunol 1994; 98:270–278.
177. Porges AJ, Redecha PB, Kimberly WT, Csernok E, Gross WL, Kimberly RP. Anti-neutrophil cytoplasmic antibodies engage and activate human neutrophils via FcγRII. J Immunol 1994;153:1271–1280.
178. Edberg JC, Wainstein E, Wu J, et al. Analysis of FcγRII gene polymorphisms in Wegener's granulomatosis. Exp Clin Immunogenet. 1997;14:183–195.
179. Lalezari P, Khorshidi M, Petrosova M. Autoimmune neutropenia of infancy. J Pediatr 1986;109:764–769.
180. Bux J, Kissel K, Nowak K, Spengel U, Mueller-Eckhardt C. Autoimmune neutropenia: clinical and laboratory studies in 143 patients. Ann Hematol 1991;63:249–252.
181. Brunati S, Moncuit J, Fridman WH, Teillaud JL. Regulation of IgG production by suppressor Fc gamma RII+ T hybridomas. Eur J Immunol 1990;20:55–61.
182. Gavin AL, Wines BD, Powell MS, Hogarth PM. Recombinant soluble Fc gamma RII inhibits immune complex precipitation. Clin Exp Immunol 1995;102:620–625.
183. Ulvestad E, Matre R, Tonder O. IgG Fc receptors in sera from patients with Rheumatoid Arthritis and Systemic Lupus Erythematosus. Scand J Rheumatol Suppl 1988;75:203–209.
184. Hutin P, Lamour A, Pennec YL, et al. Cell-free Fc-gamma receptor III in sera from patients with systemic lupus erythematosus: correlation with clinical and biological features. Int Arch Allergy Immunol 1994;103:23–27.
185. Astier A, Merle-Beral H, de la Salle H, et al. Soluble Fcγ receptor, FcγRIIa2, is present in two forms in human serum and is increased in patients: with stage C chronic lymphocytic leukemia. Leuk Lymphoma 1997;26:317–326.
186. Fleit HB, Kobasiuk CD, Daly C, Furie R, Levy PC, Webster RO. A soluble form of FcγRIII is present in human serum and other body fluids and is elevated at sites of inflammation. Blood 1992;79:2721–2728.
187. Clark MR, Liu L, Clarkson SB, Ory PA, Goldstein IM. An abnormality of the gene that encodes neutrophil Fc receptor III in a patient with systemic lupus erythematosus. J Clin Invest 1990;86:341–346.

188. Faust A, Neppert J, Kissel K. Circulatory clearance of transfused antibody-sensitized red cells in an entirely allogenic rabbit model. Infusionstherapie 1994;21:260–264.
189. Neppert J, Witzleben-Schürholz E. Treatment of chronic autoimmune thrombocytopenic purpura with monoclonal anti-D; lack of efficiency due to absence of FcγR-inhibiting activity? Transfusion 1997;37:444–445.
190. Neppert J. International Forum. Treatment of patients with autoimmune thrombocytopenia (AITP) with intravenous IgG-anti-D. Vox Sang 1999;76:254.
191. Leger R, Palm S, Wulf H, Vosberg A, Neppert J. Transfusion-related lung injury with leukopenic reaction caused by fresh frozen plasma containing anti-NB1. Anesthesiology 1999;91:1529–1532.
192. Dooren MC, Ouwehand WH, Verhoeven AJ, von dem Borne AEGKr, Kuijpers RWAM: Adult respiratory distress syndrome after experimental intravenous γ-globulin concentrate and monocyte-reactive IgG antibodies. Lancet 1998;352:1601–1602.
193. Yu Z, Lennon VA. Mechanism of intravenous immune globulin therapy in antibody-mediated autoimmune diseases. N Engl J Med 1999; 340:227–228.
194. Deo YM, Graziano RF, Repp R, van de Winkel JGJ. Clinical significance of IgG Fc receptors and FcγR-directed immunotherapies. Immunol Today 1997;18:127–135.