Annu. Rev. Cell Dev. Biol. 1996. 12:181–220

Fc RECEPTORS AND THEIR INTERACTIONS WITH IMMUNOGLOBULINS

*Malini Raghavan and Pamela J. Bjorkman**
Division of Biology 156-29, and *Howard Hughes Medical Institute, California Institute of Technology, Pasadena, California 91125

KEY WORDS: immunoglobulin gene superfamily, structure, binding, transcytosis, effector functions

---

ABSTRACT

Receptors for the Fc domain of immunoglobulins play an important role in immune defense. There are two well-defined functional classes of mammalian receptors. One class of receptors transports immunoglobulins across epithelial tissues to their main sites of action. This class includes the neonatal Fc receptor (FcRn), which transports immunoglobulin G (IgG), and the polymeric immunoglobulin receptor (pIgR), which transports immunoglobulin A (IgA) and immunoglobulin M (IgM). Another class of receptors present on the surfaces of effector cells triggers various biological responses upon binding antibody-antigen complexes. Of these, the IgG receptors (FcγR) and immunoglobulin E (IgE) receptors (FcϵR) are the best characterized. The biological responses elicited include antibody-dependent, cell-mediated cytotoxicity, phagocytosis, release of inflammatory mediators, and regulation of lymphocyte proliferation and differentiation. We summarize the current knowledge of the structures and functions of FcRn, pIgR, and the FcγR and FcϵRI proteins, concentrating on the interactions of the extracellular portions of these receptors with immunoglobulins.

CONTENTS

1081-0706/96/1115-0181$08.00

INTRODUCTION

Immunoglobulin (Ig) molecules consist of two copies of a variable Fab region that contains the binding site for antigen, and a relatively constant Fc region that interacts with effector molecules such as complement proteins and Fc receptors (FcRs) (Figure 1). Receptors for the Fc domain of Ig molecules form crucial components of immune defense by (*a*) facilitating specialized transport of antibody molecules to regions of the body where they are needed, (*b*) forming the crucial link between antigen binding by Igs and effector responses such as inflammation and the regulation of antibody production, and (*c*) controlling the lifetime of Ig molecules in serum.

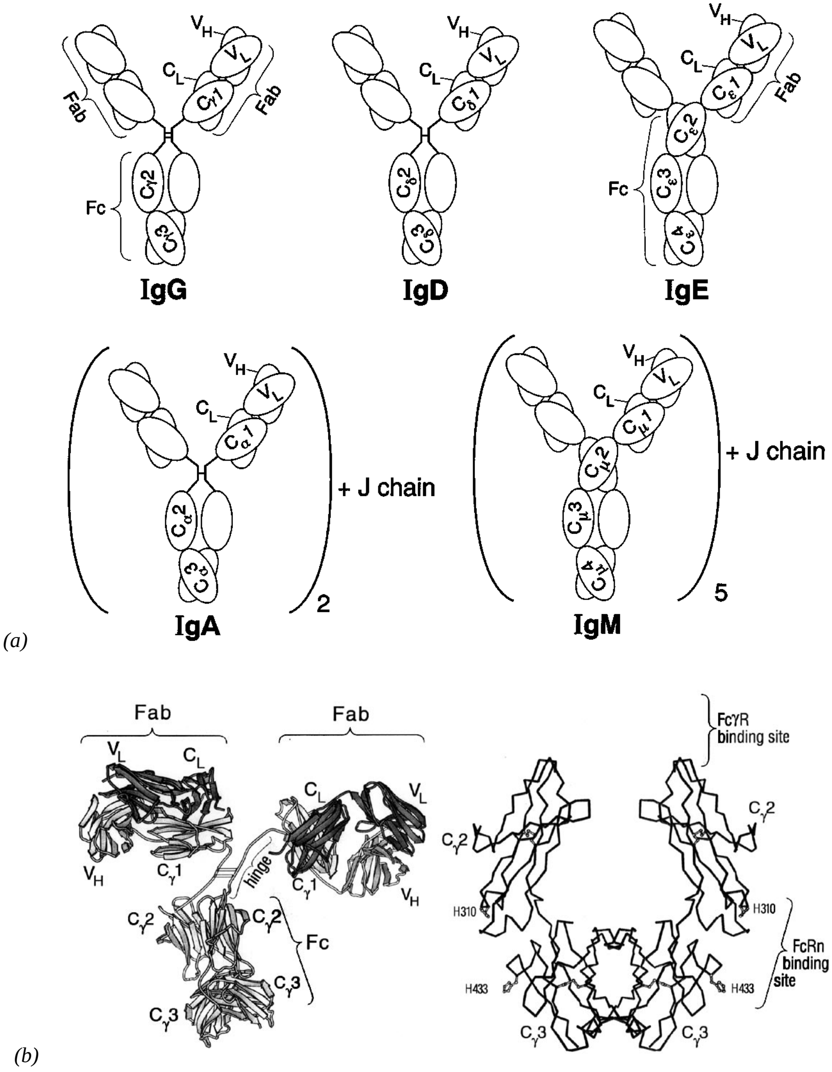
There are five isotypes of Igs in mammals: IgA, IgD, IgE, IgG, and IgM (Figure 1*a*). Particular Fc receptors are usually specific for only one or two of the Ig isotypes. FcγR and FcRn proteins are specific for IgG, and FcϵR proteins are specific for IgE. The polymeric immunoglobulin receptor (pIgR) recognizes dimeric[1] IgA and pentameric IgM. Other Fc receptors specific for

---

[1] Throughout this review, monomeric Ig refers to an Ig molecule consisting of two identical heavy chains and two identical light chains arranged into two Fab arms and a single Fc region (Figure 1). Thus dimeric IgA contains the four Fab arms and two Fc regions contributed from two IgA molecules.

⟶

Figure 1 Antibody structures. (*a*) Schematic representations of the structures of the five Ig isotypes. Variable and constant domains are represented by ovals. The Fc regions of the IgE and IgM isotypes contain an extra constant domain ($C_\epsilon 2$ and $C_\mu 2$, respectively) that replaces the hinge of the other Ig isotypes. The dimeric form of IgA and the pentameric form of IgM include an additional 15-kDa polypeptide called the J chain. However, some antibody-producing cells secrete a hexameric IgM that lacks the J chain (Randall et al 1992). (*b*) Three-dimensional structures of IgG and the Fc fragment. *Left:* ribbon diagram of the structure of an intact IgG (Harris et al 1992). The hinge region is disordered in the crystals, thus its location and the location of the disulfide bonds linking the two heavy chains (indicated as horizontal lines) are approximate. *Right:* carbon-α trace from the crystal structure of the Fc fragment (Deisenhofer 1981). The space between the two Cγ2 domains is filled with carbohydrate residues. The residues within the lower hinge region that define the binding site for the FcγR receptors are disordered in this structure. Fc histidine residues implicated in the pH-dependent interaction with FcRn (Burmeister et al 1994a, Kim et al 1994, Raghavan et al 1994, 1995a) are highlighted as sidechains with the residue name and number. Figures were prepared from coordinates available from the PDB (1FC2 for Fc) or provided by the authors (intact Ig coordinates obtained from A McPherson).


Fab
V_H
C_L
V_L
$C_\gamma 1$
Fab
Fc
$C_\gamma 2$
$C_\gamma 3$
IgG
V_H
C_L
V_L
$C_\delta 1$
$C_\delta 2$
$C_\delta 3$
IgD
V_H
C_L
V_L
$C_\varepsilon 1$
Fab
Fc
$C_\varepsilon 2$
$C_\varepsilon 3$
$C_\varepsilon 4$
IgE
V_H
C_L
V_L
$C_\alpha 1$
$C_\alpha 2$
$C_\alpha 3$
2
+ J chain
IgA
V_H
C_L
V_L
$C_\mu 1$
$C_\mu 2$
$C_\mu 3$
$C_\mu 4$
+ J chain
5
IgM
(a)
Fab
Fab
V_L
C_L
C_L
V_L
V_H
$C_\gamma 1$
hinge
$C_\gamma 1$
V_H
$C_\gamma 2$
$C_\gamma 2$
Fc
$C_\gamma 3$
$C_\gamma 3$
FcγR binding site
$C_\gamma 2$
$C_\gamma 2$
H310
H310
FcRn binding site
H433
H433
$C_\gamma 3$
$C_\gamma 3$
(b)

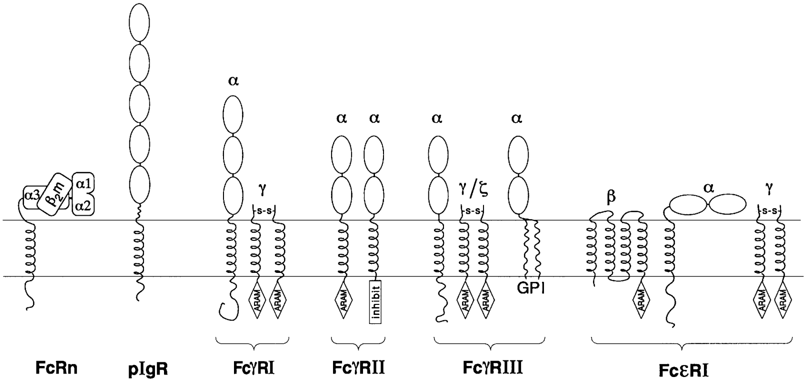


Figure 2 Schematic representation of the structures of the Ig superfamily FcRs. The Ig C1-set domains in FcRn are indicated by rectangles; V-like domains in the other FcRs are depicted as ovals. Greek letter names are written above the subunits. The Ig-binding domains of the FcγRs and FcϵRI are the α domains. Protein transmembrane regions are indicated as helices, and the glycophosphatidyl inositol anchor of FcγRIIIB is labeled GPI. ARAMs located in the cytoplasmic domains are indicated as diamonds, and the inhibitory motif of FcγRIIB is indicated as a rectangle. FcRn and FcϵRI are depicted in their lying-down orientations relative to the membrane, based on experimental data described in the text. The orientations of the other receptors with respect to the membrane are unknown (adapted from Figure 1 in Ravetch 1994).

IgA (Maliszewski 1990), IgM (Ohno et al 1990), and IgD (Sjoberg 1980) have been reported, but these receptors have not been extensively investigated and are not discussed in this review. Instead, we focus on the well-characterized Fc receptors that are members of the Ig superfamily: FcRn, pIgR, the FcγRs, and FcϵRI (Figure 2), concentrating on the extracellular regions of these receptors that are involved in ligand binding.

Ig superfamily members are defined as molecules that contain domains with sequence similarity to the variable or constant domains of antibodies (Williams & Barclay 1988). On the basis of sequence and structural similarities, Ig superfamily member domains are divided into three sets: C1, C2, and V-like (Williams & Barclay 1988). The C1 set includes antibody constant and topologically equivalent domains. FcRn is the only FcR that is a member of the Ig superfamily by virtue of containing constant or C1-set domains. C2 and V-like, the other Ig superfamily domains, are common building blocks of cell adhesion molecules (Wagner & Wyss 1994, Vaughn & Bjorkman 1996), which are structurally similar to the other FcRs discussed in this review. The V-like set includes domains that have a folding topology closely related to Ig variable domains. The C2 set has a slightly different organization of β-strands compared with the C1 and V-like sets (Figure 3). Many Ig superfamily domains were initially classified as C2 based primarily upon the number of residues separating the cysteines that form a disulfide bond in the folded domain structure. Indeed, the Ig-like domains in the FcγRs and in FcϵRI were classified as C2 and, in some cases, modeled as such (Sutton & Gould 1993, Hibbs et al 1994, Hulett & Hogarth 1994). Recent studies by Chothia and colleagues (Harpaz & Chothia 1994) suggest that some of the original classifications of Ig superfamily domains need to be reconsidered in light of recent crystal structures of Ig superfamily members (for reviews, see Harpaz & Chothia 1994, Wagner & Wyss 1994, Vaughn & Bjorkman 1996). We have therefore examined the sequences of the FcRs, taking the new structural information into account. We used consensus sequences for V-like and C2 domains obtained from structure-based sequence alignments to classify the FcR domains (Vaughn & Bjorkman 1996). Our analysis indicates that the Ig-like domains within pIgR, the FcγRs, and FcϵRI share features more in common with the V-like set than with the C2 set (Table 1).

Although crystal structures of the Fc binding regions of any of the receptors except FcRn (Burmeister et al 1994a) are not available, the structures of V-like and C2 domains in cell adhesion molecules (e.g. CD4, CD2, VCAM-1; Ryu et al 1990, Wang et al 1990, Jones et al 1992, 1995) can be used as approximate models for the three-dimensional structures of pIgR, the FcγRs, and FcϵRI. The extracellular domains of these FcRs consist of two or more Ig-like domains arranged in tandem, a domain organization in common with many cell adhesion molecules including those for which three-dimensional structures are available. As a framework for mutagenesis studies to map the interaction site on the receptors, we present topology and ribbon diagrams for the structures of Ig superfamily domains (Figure 3). Structural information about the immunoglobulin ligands of the Fc receptors is more complete: crystal structures of the IgG Fc fragment (Deisenhofer 1981) and of an intact IgG (Harris et al 1992) are available (Figure 1*b*) and can be used for interpretation of interaction site mapping studies.

Using these structural models as guides, we explore both the common features and the differences in the way that the FcRs interact with their ligands and discuss evidence showing that some of the Fc regions are less symmetric in solution that one might assume from the IgG Fc crystal structure. We also refer to the many excellent reviews covering topics not explored in detail, including the heterogeneity of the FcγR and FcϵR transmembrane and intracellular regions, the functional roles of different cytoplasmic domains, and FcR-mediated signaling.

Table 1 Alignment of FcR sequences with structure-based sequence alignments of V-like and C2 domains

```
strands                       A′      B                 C        D         E             F                G
V-like consensus                  Gxx*x*xC            *xW         +*      Lx*xx*xxxDx#xYxC               *x*x*
FcγRI     (domain 1)  ISLQPPWVSVFQEETVTLHCEVLHL--PGSSSTQWFLNGTATQTST----PSYRITSASVNDSGEYRCQRGL-----SGRSDPIQLEIHRGW
FcγRII    (domain 1)  LKLEPPWINVLQEDSVTLTCQGARS--PESDSIQWFHNGNLIPTHTQ---PSYRFK-ANNNDSGEYTCQTGQ-----TSLSDPVHLTVLSEW
FcγRIII   (domain 1)  VFLEPQWYSVLEKDSVTLKCQGAYS--PEDNSTQWFHNESLISSQA----SSYFIDAATVNDSGEYRCQTNL-----STLSDPVQLEVHIGW
FcεRI     (domain 1)  VSLDPPWNRIFKGENVTLTCNGNNF--FEVSSTKWFHNGSLSEETN----SSLNIVNAKFEDSGETKCQHQQ-----VNESEPVTLEVFSDW
C2 consensus                           *xCx*          *x*               +x*x*x         *xCx*
strands                     A           B               C     C′           E             F                G

strands                       A′      B                 C        D         E             F                G
V-like consensus                  Gxx*x*xC            *xW         +*      Lx*xx*xxxDx#xYxC               *x*x*
FcγRI     (domain 2)  LLLQVSSRVFTEGEPLALRCHAWKD--KLVYNVLYYRNG--KAFKFFHWNSNLTILKTNISHNGTYHCSGM---GKHRYTSAGISVTVK
FcγRII    (domain 2)  LVLQTPHLEFQEGETIMLRCHSWKD--KPLVKVTFFQNG--KSQKFSRLDPTFSIPQANHSHSGDYHCTGN--IGYTLFSSKPVTITVQ
FcγRIII   (domain 2)  LLLQAPRWVFKEEDPIHLRCHSWKN--TALHKVTYLQNG--KDRKYFHHNSDFHIPKATLKDSGSYFCRGL--VGSKNVSSETVNITIT
FcεRI     (domain 2)  LLLQASAEVVMEGQPLFLRCHGWRN--WDVYKVIYYKDG--EALKYWYENHNISITNATVEDSGTYYCTGK--VWQLDYESEPLNITVI//
C2 consensus                           *xCx*          *x*               +x*x*x         *xCx*
strands                     A           B               C     C′           E             F                G

strands                       A′      B                 C        D         E             F                G
V-like consensus                  Gxx*x*xC            *xW         +*      Lx*xx*xxxDx#xYxC               *x*x*
FcγRI     (domain 3)    //SVTSPLLEGNLVTLSCETKLLLQRPGLQLYFSFYMGSKTLRGRNTSSEYQILTARREDSGLYWCEAATEDGNVLKRSPELELQVL
C2 consensus                           *xCx*          *x*               +x*x*x         *xCx*
strands                     A           B               C     C′           E             F                G
```

Consensus sequences derived from a structure-based sequences alignment (Vaughn & Bjorkman 1996) are presented above (V-like) or below (C2) each domain sequence (adapted from the human sequences presented in Kochan et al 1988, Allen & Seed 1989). The alignment for the V-like consensus sequences was obtained after superposition of the available three-dimensional structures of V-like domains [CD2 domain 1, CD4 domains 1 and 3, telokin, V_H and V_L from a Fab, CD8, and VCAM-1 domain1; (Davis & Metzger 1983, Ryu et al 1990, Wang et al 1990, Holden et al 1992, Jones et al 1992, 1995, Leahy et al 1992, Brady et al 1993, Bodian et al 1994)] were superimposed to identify structurally corresponding residues. The alignment for the C2 consensus sequences was obtained after superposition of CD4 domains 2 and 4, CD2 domain 2, and VCAM-1 domain 2 (Ryu et al 1990, Wang et al 1990, Jones et al 1992, 1995, Brady et al 1993) (see Vaughn & Bjorkman 1996 for details). The consensus sequences are meant for comparison with FcR sequences and are not derived from the FcR sequences themselves. Consensus primary sequence patterns are identified by the one-letter code or symbols; *indicates a hydrophobic amino acid; + represents a basic amino acid, # indicates a Gly, Ala, or Asp; and an x indicates any amino acid. The approximate locations of the centers of β-strands are indicated by the letter name of the strand above or below the sequences. Gaps in one sequence compared with the others are represented by dashes and slashes indicate a missing portion of sequence. Residues implicated in Ig binding are underlined (mapping studies for FcγRII: Hulett et al 1995; mapping studies for FcγRIII: Hibbs et al 1994; FcϵRI mapping studies reviewed in Hulett & Hogarth 1994). The individual FcR domain sequences do not exactly match either V-like or C2 domain consensus sequences, but all the domains share some common features with the V-like domains. Some of the features that distinguish V-like domains from C2 domains are a β-turn connecting strand A$'$ to B, usually identifiable at the primary sequence level by a glycine seven residues before the first of the cysteines in the characteristic disulfide bond, and a distinguishing sequence motif in the vicinity of the E to F loop (the tyrosine corner) that includes a tyrosine two residues prior to the second cysteine (Harpaz & Chothia 1994).

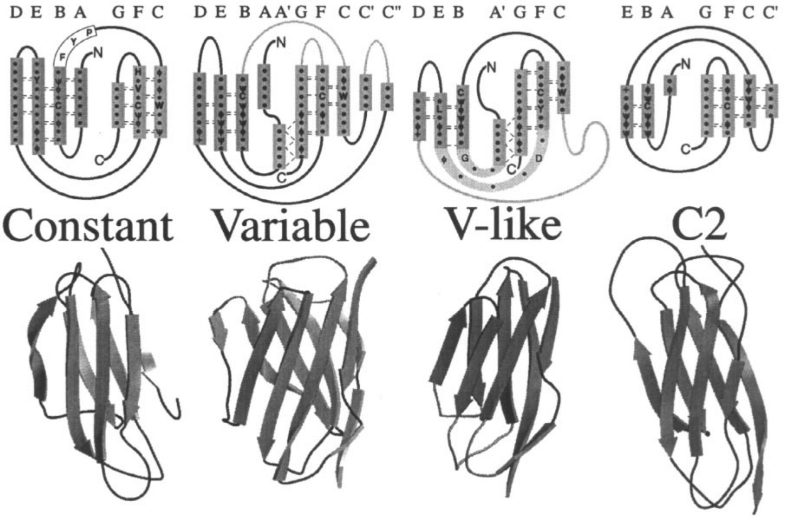


Figure 3 Structures of the Ig superfamily domains. Topology (*top*) and ribbon (*bottom*) diagrams are presented for each fold. β-strands are identified by letters in the topology diagrams. In the topology diagrams, the β-sheet containing strands A, B, and E is dark grey and the sheet containing strands G, F, and C is light grey. In the ribbon diagrams, the A-B-E containing β-sheet is in front of the G-F-C containing sheet. Amino acids that have equivalent positions in all structures of the domain type are indicated by a solid circle; by the one-letter code if the identity of the amino acid is conserved; by ϕ for hydrophobic residues; or by the symbol ψ for hydrophilic residues. β-sheet hydrogen bonding is indicated by dashed lines. Regions of irregular secondary structure are indicated by open rectangles. The antigen-binding loops in the Ig variable domain are B to C (CDR1), C′ to C″ (CDR2), and F to G (CDR3). Loops that are structurally conserved in V-like domains (A′ to B and E to F loops; see consensus sequence in Table 1) are thick. Ribbon diagrams were prepared from coordinates available from the PDB (7fab for Ig constant and variable domains) or provided by the authors (VCAM-1 coordinates from EY Jones for V-like and C2 domains) (adapted from Figure 3 in Vaughn & Bjorkman 1996).

FcRs IN ANTIBODY TRANSPORT

Transfer of maternal IgG molecules from the mother to the fetus or infant is a mechanism by which mammalian neonates acquire humoral immunity to antigens encountered by the mother. Passive acquisition of antibody is important to the neonate during the immediate time after birth when its immune system is not yet fully functional. The protein responsible for the transfer of IgG is called FcRn, for FcR neonatal (Rodewald & Kraehenbuhl 1984, Simister & Rees 1985). Here the word neonatal derives from the initial discovery of the receptor in the gut of suckling rats on the apical surface of intestinal epithelial cells (Jones & Waldman 1972). Maternal IgG in ingested milk is bound by the receptor, transported across the gut epithelium in a process called transcytosis (Mostov & Simister 1985), and then released into the bloodstream from the basolateral surface (Rodewald & Kraehenbuhl 1984). There is a net pH difference between the apical (pH 6.0–6.5) and basolateral (pH 7.0–7.5) sides of intestinal epithelial cells (Rodewald & Kraehenbuhl 1984). This pH difference facilitates the efficient unidirectional transport of IgG, because FcRn binds IgG at pH 6.0–6.5 but not at neutral or higher pH (Rodewald & Kraehenbuhl 1984, Simister & Mostov 1989b, Raghavan et al 1995a).

Recent studies have shown that FcRn is also expressed in the fetal yolk sac of rats and mice (Roberts et al 1990, Ahouse et al 1993) and in the human placenta, where it is thought to transfer maternal IgG to the fetus (Story et al 1994, Simister & Story 1996). In addition, FcRn is expressed on the canalicular cell surface of adult rat hepatocytes, where it could bind IgG in bile and potentially function to provide communication between bile and parenchymal immune cells (Blumberg et al 1995). In this case, the proposed model for FcRn function is to transport antibody-antigen complexes from bile to the parenchyma. Antigen-presenting cells in parenchyma would process the antigens and present them to T cells, which would then stimulate local B cells to secrete antigen-specific antibodies that are transported back into the bile by unknown mechanisms (Blumberg et al 1995). Thus FcRn appears to be used for transport of IgG in sites other than the intestine, and in adult animals as well as neonates. Human placental FcRn, FcRn from rat fetal yolk sac, and FcRn from rat hepatocytes all show the same pH-dependent interaction with IgG that is observed with the intestinal FcRn, i.e. IgG binding at pH 6.0–6.5 but not at neutral or basic pH (Roberts et al 1990, Story et al 1994, Blumberg et al 1995). This feature of the FcRn molecule may have evolved to facilitate IgG release from the receptor at the slightly basic pH of blood. Because a pH gradient does not exist across the placenta or the mammalian yolk sac, it is thought that FcRn binds IgG intracellularly, in acidic vesicles that are targeted to the cell surface where IgG is released upon exposure to the pH environment of blood (Roberts et al 1990, Story et al 1994, Simister & Story 1996).

In addition to these transport functions, current evidence suggests that FcRn is the catabolic receptor that controls the lifetime of Igs in serum. For example, mutant Fc fragments that show impaired FcRn binding in vitro and that are deficient for transcytosis in neonatal mice also have abnormally short serum half lives (Kim et al 1994, Popov et al 1996). Furthermore, murine IgG1 is degraded significantly faster in mice that are deficient in the FcRn light chain (β2-microglobulin; β2 m) (Ghetie et al 1996, Junghans & Anderson 1996, EJ Israel, D Wilsker & NE Simister, manuscript in preparation). Because the pH of serum is not permissive for IgG binding by FcRn, the postulated model for the catabolic receptor function of FcRn is that IgG is sequestered by FcRn in acidic intracellular vesicles and subsequently rereleased into serum.

Transport of other classes of Ig in the adult mammal occurs using different mechanisms. In order to confer specific protective functions at diverse sites, the Ig isotypes are distributed differently throughout the body, necessitating specific transport in some instances. The transport of IgA from the circulation into secretions has been well studied. IgA is found in epithelial secretions such as the lumen of the gut, the salivary and tear glands, respiratory secretions, and breast milk, where the neutralizing capacity of IgA molecules forms the first line of defense against entering pathogens (Underdown & Schiff 1986, Childers et al 1989, Kerr 1990, Hanson & Brandtzaeg 1993). IgA is synthesized by plasma cells beneath the basement membranes of surface epithelia. Subsequent to synthesis, the IgA molecules must cross the epithelial cell barrier to enter into secretions. Transcytosis of IgA across polarized epithelial cells first involves the binding of IgA to pIgR proteins on the basolateral surface (reviewed in Kraehenbuhl & Neutra 1992, Mostov 1994). pIgR-IgA complexes are internalized and sorted into endosomes destined for the apical surface. At the apical surface, pIgR is cleaved and the extracellular portion of the receptor is released into secretions as a complex with IgA. This complex, called secretory IgA, protects against pathogens in the digestive, respiratory, and genital tracts.

The structures of FcRn and pIgR and how they interact with their respective Ig molecules are now discussed.

FcRn

FcRn is a type I membrane glycoprotein that acts as a specific receptor for the IgG isotype (Jones & Waldman 1972). Reported values of the equilibrium association constant (K_A) range from $\approx 2 \times 10^7$ M^{-1} for the interaction of monomeric IgG with isolated microvilli membranes from neonatal rat intestine (Wallace & Rees 1980) to $\approx 5 \times 10^7$ M^{-1} for the interaction between purified soluble rat FcRn and monomeric IgG (Raghavan et al 1995b). This rather high affinity ensures that FcRn can efficiently transport unliganded IgG, which is the most useful form of Ig for the newborn, although transport of antigen-antibody complexes has also been observed (Abrahamson et al 1979). Unlike the other known FcRs, which are presumed to have monomeric extracellular Ig-binding regions, FcRn is a heterodimer. The FcRn light chain is β2m (Simister & Rees 1985), the same light chain that is associated with class I major histocompatibility complex (MHC) molecules (Figure 4*a*). Molecular cloning of the FcRn heavy chain revealed additional similarity to class I MHC molecules rather than to any of the other FcRs (Simister & Mostov 1989a). The heavy chains of both FcRn and class I MHC molecules consist of three extracellular domains, α1, α2, and α3, followed by a transmembrane region and a short cytoplasmic sequence

(Simister & Mostov 1989a, Bjorkman & Parham 1990) (Figure 4*a*). Although the extracellular region of FcRn and class I MHC molecules exhibits low but significant sequence similarity (22–30% identity for the $\alpha1$ and $\alpha2$ domains; 35–37% for the $\alpha3$ domain), the transmembrane and cytoplasmic regions of the two types of proteins show no detectable sequence similarity (Simister & Mostov 1989a). MHC class I molecules have no reported function as Ig receptors; instead they bind and present short peptides to T cells (Townsend & Bodmer 1989). The similarity at the primary, tertiary, and quaternary structure levels between FcRn and class I MHC molecules suggests that they share a common ancestor, in spite of their apparently unrelated immunological functions.

THREE-DIMENSIONAL STRUCTURE OF FcRn The crystal structure of rat FcRn confirmed that the overall fold is very similar to that of class I MHC molecules, such that the $\alpha1$ and $\alpha2$ domains form a platform of eight anti-parallel β-strands topped by two long α-helices, and the $\alpha3$ and $\beta2$m domains are β-sandwich structures similar to antibody constant or C1-set domains (Figure 4*a*) (Burmeister et al 1994a). Although the two α-helices that form the sides of the MHC peptide-binding groove are present in FcRn, they are closer together than their MHC counterparts, rendering the FcRn groove incapable of binding peptides, consistent with earlier biochemical studies (Raghavan et al 1993). To date, the FcRn counterpart of the MHC peptide-binding groove has not been implicated in any FcRn binding function.

FcRn DIMERIZATION A dimer of FcRn heterodimers (hereafter referred to as the FcRn dimer) mediated by contacts between the $\alpha3$ and $\beta2$m domains was observed in three different crystal forms of FcRn (Burmeister et al 1994a) (Figure 4*b*). Because of the 2:1 binding stoichiometry between FcRn and IgG (Huber et al 1993), it was suggested that the FcRn dimer could represent a receptor dimer induced by IgG binding (Burmeister et al 1994a,b). In the absence of IgG, FcRn is predominantly monomeric in solution at μM concentrations (Gastinel et al 1992); thus it was assumed that the high protein concentrations required for crystallization could induce formation of the FcRn dimer in the absence of IgG. If the observed dimer functions in IgG binding at the cell surface, each FcRn heterodimer would be aligned with its longest dimension roughly parallel to the plane of the membrane ("lying down") (Figure 5*b*), in contrast to the "standing up" orientation generally assumed for class I MHC molecules (as shown in Figure 4*a*).

The biological relevance of crystallographically observed dimers or oligomers is a question often encountered in structural biology, because crystal packing can induce protein multimers that are not found under physiological conditions. Several lines of evidence, including the observation that the

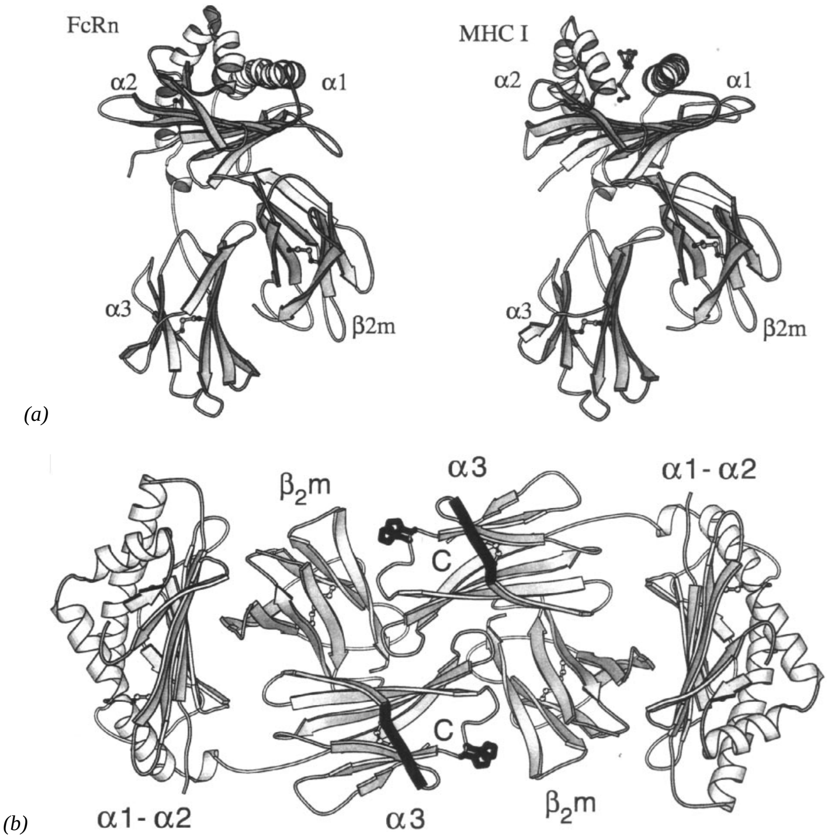


Figure 4 FcRn structure. (*a*) Ribbon diagrams of the structure of FcRn and a class I MHC molecule. Both are shown in the standing-up orientation believed to be relevant for the interactions of class I molecules with T-cell receptors. (*b*) Structure of the FcRn dimer observed in crystals of FcRn alone (Burmeister et al 1994a) and crystals of a 2:1 complex between FcRn and Fc (Burmeister et al 1994b). FcRn residues identified by site directed mutagenesis to affect the affinity of the FcRn interaction with IgG are highlighted (His 250 and His 251, dark sidechains; residues 219–224, dark loop; Raghavan et al 1994). The C-termini of the truncated FcRn heavy chains are labeled C. The FcRn dimer is believed to be oriented on the cell membrane as shown in Figure 5*b* (a 90° rotation about the horizontal axis from this view), so that in this orientation, the membrane is presumed to be parallel to and below the plane of the paper. This view of the dimer corresponds to the view in Figure 6*a*.

same dimer was observed in cocrystals of a complex between rat FcRn and Fc (Burmeister et al 1994b), indicate that the crystallographically observed FcRn dimer is not a crystal packing artifact. The crystal structure of the FcRn-Fc complex was solved at low resolution (4.5–6 Å) because the crystals diffracted poorly. However, the cocrystal structure confirmed the 2:1 FcRn-Fc binding stoichiometry, and the high resolution structures of FcRn (Burmeister et al 1994a) and Fc (Deisenhofer 1981) were used to deduce the mode of interaction between the two proteins. The cocrystal structure showed that the edge of the $\alpha 1$-$\alpha 2$ domain platform and the N-terminal portion of $\beta 2$m contact Fc at the interface between the C$\gamma 2$ and C$\gamma 3$ domains. The FcRn-binding site on Fc overlaps with the binding site for fragment B of protein A (Deisenhofer 1981), as predicted from previous mutagenesis and inhibition studies (Kim et al 1994, Raghavan et al 1994). Because FcRn is structurally distinct from the other FcRs, parallels between the FcRn-IgG interaction and the interaction of Igs with other FcRs are unlikely. Indeed, the binding site on Fc for most other FcRs (lower hinge region and top of the C$\gamma 2$ domain, see below; Figure 1*b*) does not overlap with the binding site for FcRn. The finding that FcRn interacts with a different portion of the Fc region than that contacted by the other FcRs can be rationalized by the observation that at least some of the pH dependence of the FcRn interaction with IgG arises from titration of Fc histidines at the FcRn binding site (Figure 1*b*; see below).

TWO DIFFERENT 2:1 FcRn-Fc COMPLEXES The interpretation of the cocrystal structure is complicated by the packing in the cocrystal, which creates two distinct 2:1 FcRn-Fc complexes, only one of which incorporates the FcRn dimer. The first 2:1 complex (the lying-down complex; Figure 5*a,b*) incorporates the same FcRn dimer observed in the crystals of FcRn alone. In this complex, the receptor dimer binds a single Fc molecule asymmetrically, with most of the contacts involving one molecule of the dimer (Burmeister et al 1994b). The second 2:1 FcRn-Fc complex (the standing-up complex; Figure 5*c*) does not involve the receptor dimer. Instead, Fc binds symmetrically between two FcRn molecules that are oriented with their long axes perpendicular to the membrane. Both 2:1 complexes are built from the same 1:1 FcRn-Fc building block (compare Figures 5*a* and *c*).

Information from the crystal structure alone could not resolve the issue of which of these two 2:1 complexes is physiologically relevant: the standing-up complex, the lying-down complex, or both. However, it was argued that intact IgG would be sterically prohibited from binding to cell surface FcRn in the standing-up complex because of collisions between the Fab arms and the membrane surface (Burmeister et al 1994b). In addition, biochemical studies established that the lying-down complex involving the FcRn dimer is required

(a)

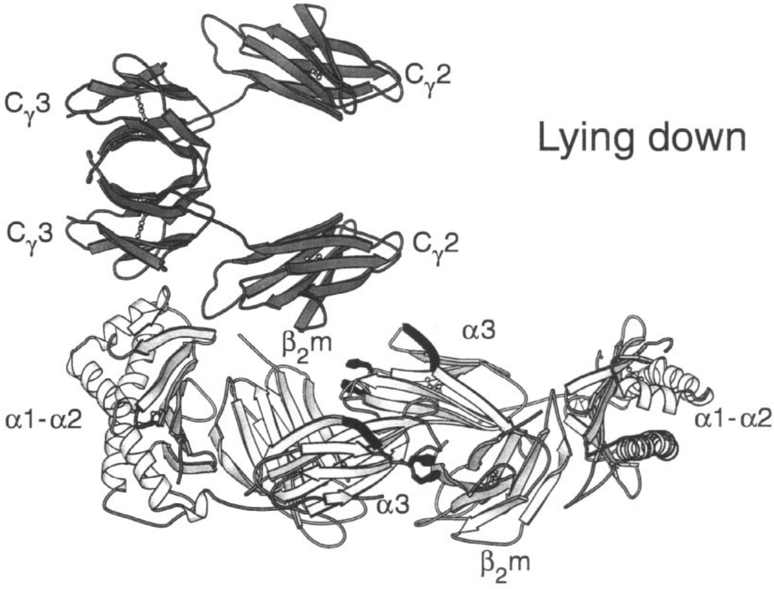


Figure 5 Two different 2:1 FcRn-Fc complexes observed in the crystals of FcRn bound to Fc (Burmeister et al 1994b). FcRn residues identified by site-directed mutagenesis to affect the affinity of the FcRn interaction with IgG are highlighted (His 250 and His 251, dark sidechains; residues 219–224, dark loop; Raghavan et al 1994). (*a*) Lying-down 2:1 complex involving the FcRn dimer. The Fc molecule interacts asymmetrically with the receptor dimer so that most of the contacts involve one of the FcRn molecules. Contacts are predicted between the N-terminal portion of the Cγ2 domain and the partner FcRn molecule, in the vicinity of FcRn heavy chain residues 219–224 (loop, shown in bold). His 250 and His 251 (highlighted) are predicted to exert their effect on the interaction with IgG by modulating the formation of the FcRn dimer, which is required for high-affinity binding of IgG (Raghavan et al 1995b). (*b*) View of the lying-down 2:1 complex rotated by 30° about the horizontal axis with respect to the orientation shown in *a*. The plane of the membrane for cell surface FcRn is horizontal. No steric hindrance between intact IgG and the membrane is expected in this orientation, as the two Fab arms of IgG could project out of the plane of the paper and into the plane of the paper. (*c*) The standing-up 2:1 complex oriented so that the plane of the membrane for cell surface FcRn is horizontal. Steric hindrance between the Fab arms of intact IgG and the membrane is predicted for this complex. In addition, neither of the regions indicated by site-directed mutagenesis to affect IgG binding affinity (histidines 250 and 250, highlighted; loop, comprising residues 219–224, bold) (Raghavan et al 1994) are at the Fc interface or any other protein-protein interface.

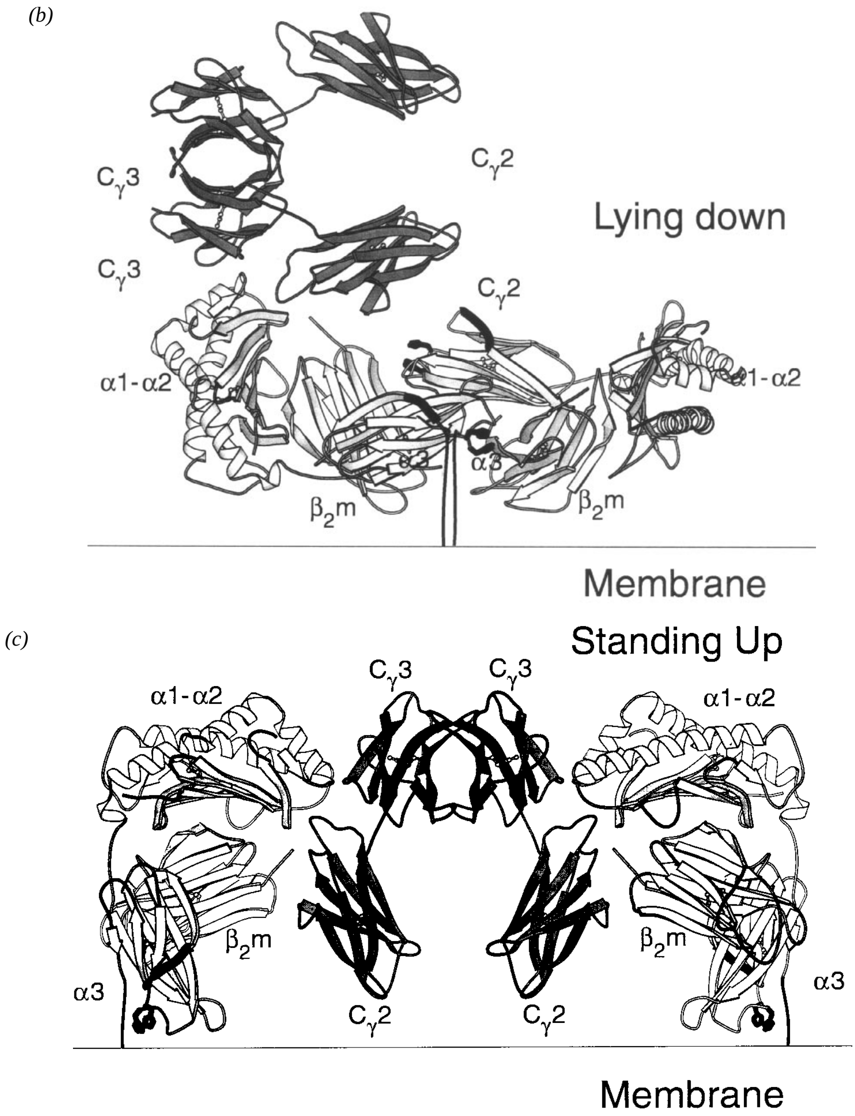


Figure 5 (*Continued*)

for high-affinity binding of IgG. The mutation of two histidine residues located at the FcRn dimer interface (Figures 4*b*, 5*a,b*) reduced the binding affinity for IgG (Raghavan et al 1994). These histidines are distant from the IgG-binding site and cannot directly contact Fc; thus their effect on IgG affinity is hypothesized to be an indirect result of modulating the formation of the FcRn dimer, which is predicted to have a higher affinity for IgG than an FcRn monomer. The prediction that the FcRn dimer has a higher IgG-binding affinity than an FcRn monomer was directly tested in biosensor studies using oriented coupling of FcRn molecules. These studies showed high-affinity IgG binding when FcRn was immobilized on a biosensor chip in an orientation facilitating dimerization, but an affinity reduction of over 100-fold when FcRn dimer formation was hindered (Raghavan et al 1995b). Examination of the predicted contacts between Fc and the two FcRn molecules in the lying-down 2:1 complex lends support to the idea that dimerization of FcRn results in an increased affinity for IgG, in that contacts between Fc and the second FcRn molecule are predicted in the regions near residues 219 and 245 of the $\alpha 3$ domain of FcRn and residues 272 and 285 in the $C\gamma 2$ domain of Fc (Burmeister et al 1994b) (Figure 5*a*). Site-directed mutagenesis confirmed that alteration of residues in the region of residue 219 of the FcRn heavy chain affected IgG binding affinity (Raghavan et al 1994) (Figure 5*a,b*).

Thus the available evidence suggests that FcRn dimerization is indeed involved in IgG binding and that the lying-down 2:1 complex is physiologically relevant for the binding of intact IgG by FcRn molecules at the cell surface. The crystallographic and biochemical results raise the possibility that FcRn functions like many other cell surface receptors in which ligand-induced dimerization is required for downstream signal transduction (Heldin 1995) which, in this case, would initiate the endocytosis of IgG-FcRn complexes. However, the lying-down 2:1 FcRn-Fc complex does not take advantage of the twofold symmetry of the Fc homodimer, because the FcRn binding site on one of the Fc polypeptide chains is not used (Figure 5*a,b*). Both binding sites are utilized in the cocrystals because the standing-up and lying-down complexes coexist to form an oligomeric ribbon with an overall stoichiometry of two receptors per Fc (Figure 6). If both complexes exist in the cocrystals, could both complexes form in vivo?

We recently proposed a model in which IgG-induced dimerization of FcRn followed by the creation of networks that include both the standing-up and lying-down 2:1 FcRn-IgG complexes (Figure 6) signals the initiation of transcytosis in vivo (Burmeister et al 1994b). This model requires that networks of FcRn-IgG complexes are formed between parallel adjacent membranes separated by $\approx$170 Å (Figure 6*b*). The requirement for closely spaced parallel adjacent membranes

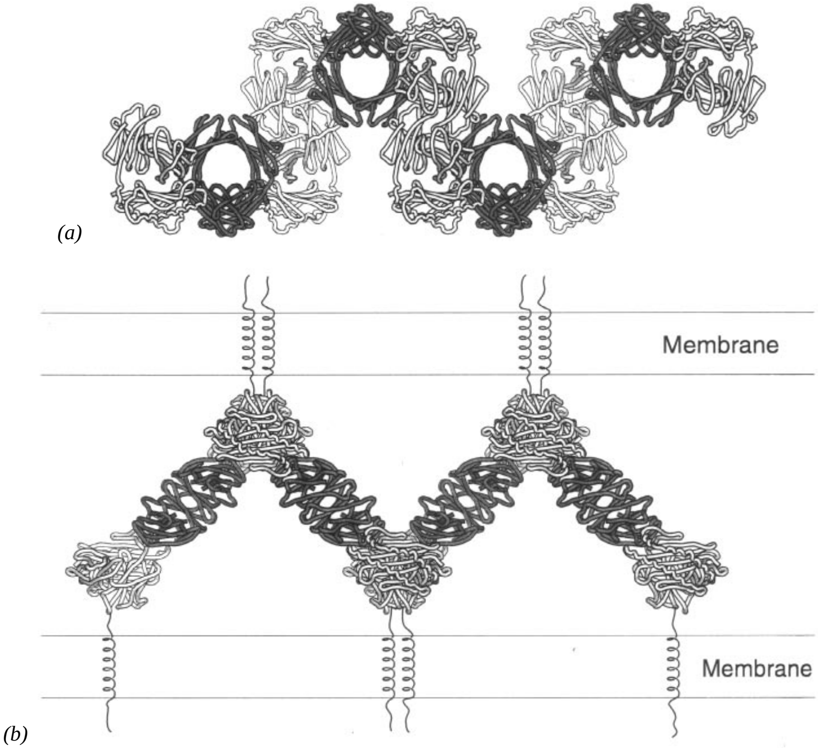


Figure 6 Network of FcRn-Fc complexes observed in the cocrystals (Burmeister et al 1994) as a model for the formation of higher order oligomers upon binding of IgG to cell surface FcRn. FcRn is grey and Fc is black. (*a*) Top view illustrating the simultaneous formation of lying-down and standing-up FcRn-Fc complexes. If this network is formed under physiological conditions, each FcRn dimer would be associated with a membrane parallel to the plane of the paper: the left-most dimer is associated with a membrane below the plane of the paper, the central dimer with a membrane above the plane of the paper, and the right-most dimer is again associated with a membrane below the plane of the paper. (*b*) Side view, rotated by 90° about the horizontal axis from the view in *a*. The FcRn dimers are seen looking down their long axes (vertical in *a*). Existence of this network under physiological conditions would require two parallel membranes separated by 160 to 170 Å (Burmeister et al 1994b). Adjacent microvilli membranes in the brush borders of neonatal rat epithelial cells can be separated by as little as 200 Å (Rodewald 1973), consistent with the possibility that networks of 2:1 FcRn-IgG complexes form between adjacent microvilli membranes.

is fulfilled in the microvilli of the brush border epithelial cells (Rodewald 1973) where FcRn is expressed and functions, but the bridging of adjacent membranes by IgG bound to FcRn dimers remains to be demonstrated. However, recent evidence suggests that both Fc binding sites are required for FcRn function in vivo, in that a hybrid Fc heterodimer containing one functional and one disrupted FcRn binding site is not transcytosed efficiently into the bloodstream of newborn mice (Kim et al 1994). The same hybrid Fc heterodimer was found to bind with normal affinity to mouse FcRn immobilized on a biosensor chip (Popov et al 1996). This latter observation was interpreted as support for a 1:1 binding stoichiometry between mouse FcRn and IgG (Popov et al 1996) but is also consistent with a 2:1 stoichiometry involving the FcRn dimer and the utilization of only one FcRn binding site on the Fc molecule (Figure 5*a*,*b*). In combination with the previously described results, these experiments suggest that the lying down FcRn-Fc 2:1 complex is necessary, but not sufficient, for transcytosis of IgG, and that both 2:1 complexes are relevant for FcRn function in vivo.

We have argued that the bridging of FcRn dimers on two adjacent membranes by IgG molecules is a prerequisite for transcytosis. However, when we prepare FcRn-Fc complexes at μM concentrations in solution, size exclusion chromatography suggests that the predominant species is a 2:1 receptor-Fc complex, rather than a higher-order multimer (AH Huber, L Sanchez & PJ Bjorkman, unpublished data). It is possible that higher-order multimers appear only under special circumstances of high local protein concentrations, i.e. in the cocrystal (mM concentration) or when FcRn dimers are constrained to adjacent membranes separated by the optimal distance for bridging by IgGs. One explanation for this involves the idea that the Fc region of IgG is asymmetric, such that only one of the FcRn-binding sites is in an optimal conformation for receptor binding. As a precedent for this idea, the Fc region of IgE is strongly bent both in solution and when bound to its receptor (reviewed in Baird et al 1993) and thus only one of the FcϵRI binding sites on the IgE Fc appears to be accessible (discussed in FcϵRI section; reviewed by Sutton & Gould 1993). There is evidence that IgG is also bent in solution (Baird et al 1993), and the FcRn binding sites might therefore be in slightly different conformations on both polypeptide chains. The low resolution of the cocrystal structure and the disorder of the N-terminal portion of the Cγ2 Fc domain (Burmeister et al 1994b) prevent the use of this crystal structure to determine whether Fc is bent when bound to FcRn. However, it is clear that in the crystals both FcRn-binding sites on Fc interact with an FcRn molecule, so one must assume that any Fc bending that occurs does not completely occlude either of the FcRn binding sites under the conditions of high protein concentration in the cocrystal.

pH DEPENDENCE OF THE FcRn-Fc INTERACTION To function as an efficient unidirectional transporter of IgG molecules, FcRn must bind IgG with high affinity prior to and during transcytosis and release intact IgG molecules at the end point of transport. As mentioned above, release of IgG from FcRn occurs rapidly upon exposure to environments of neutral pH such as the blood. Indeed, the affinity of FcRn for IgG is relatively stable between pH 5 and 6, then drops steeply by over two orders of magnitude as the pH is raised from 6.0 to 7.0 (Raghavan et al 1995a). The dramatic pH dependence of FcRn binding to IgG is unusual for protein-protein interactions. Histidine residues are likely candidates for effecting such pH-dependent affinity changes because the imidazole side chain usually deprotonates over the pH range of 6.0 to 7.0. Mutagenesis (Kim et al 1994), inhibition studies (Raghavan et al 1994), and the FcRn-Fc cocrystal structure (Burmeister et al 1994b) implicate conserved histidines at the interface of the Cγ2 and Cγ3 domains. A biosensor pH dependence assay was used to analyze the role of histidine residues in Fc and FcRn in the affinity transition (Raghavan et al 1995a). These studies suggest that the lying-down 2:1 FcRn-IgG complex is destabilized at neutral or basic pH values by titration of IgG histidine residues located at the IgG-FcRn interface (IgG His 310 and His 433; Figure 1*b*) as well as FcRn histidines located at the FcRn-FcRn dimer interface (FcRn His 250 and His 251; Figures 4*b*, 5*a*,*b*) (Raghavan et al 1995a). Thus an intricate molecular network of interactions has evolved to facilitate the binding and release of IgG by FcRn, a situation quite different from pIgR-mediated transport of IgA, where a proteolytic cleavage step is utilized to release IgA into secretions (see below). The advantage conferred upon the FcRn transporter system is that the same receptor molecule can be used for multiple rounds of transport.

pIgR

pIgR is so called because of its ability to transport polymeric Ig molecules: IgA and IgM (Brandtzaeg 1981). Serum IgA is produced in the bone marrow in a primarily monomeric form, whereas the IgA in secretions, the product of local synthesis at mucosal surfaces, is associated with a protein called the J chain and is primarily dimeric (Kerr 1990) (Figure 1*a*). The J chain is not required for IgA dimerization, but it appears to have a role in maintaining dimer stability (Hendrickson et al 1995). IgM is found in both pentameric and hexameric forms; only the pentameric form includes the J chain (Randall et al 1992). pIgR transports the dimeric form of IgA and the pentameric form of IgM (Brandtzaeg 1981). It is not known if IgM hexamers are transported by pIgR.

pIgR TRANSPORT After synthesis, pIgR transits from the endoplasmic reticulum to the Golgi and then to the *trans*-Golgi network, where the receptor is specifically targeted to the basolateral membrane of epithelial cells (reviewed in Mostov 1994). The basolateral targeting signal is contained in a 17-amino acid sequence of the cytoplasmic domain immediately C-terminal to the predicted transmembrane region (Casanova et al 1991). IgA binding occurs at the basolateral surface. Binding of IgA to pIgR stimulates transcytosis to the apical side of the cell, but some transcytosis of unliganded pIgR occurs constitutively (Song et al 1994). The direction of pIgR transcytosis, from the basolateral to apical side of the cell, is opposite to the direction of FcRn transcytosis, consistent with the opposite functions of the two receptors: pIgR to deposit Ig into secretions such as milk and FcRn to retrieve Ig from ingested milk.

In the transcytotic pathway, pIgR and pIgR-Ig complexes are first internalized into endosomes. Targeting of endosomes containing pIgR and pIgR-Ig complexes to the apical surface is thought to involve the same sorting signals and proteins required for basolateral targeting from the *trans*-Golgi network (Aroeti & Mostov 1994). At the apical surface, the extracellular portion of pIgR is cleaved at a site near the transmembrane sequence, and the extracellular portion of pIgR (called secretory component; SC) is released either alone or as a complex with IgA. The protease(s) involved in cleavage have not been characterized, but multiple C-terminal residues have been identified on SC, implying cleavage by multi- or nonspecific protease(s) (Eiffert et al 1984). Because pIgR is cleaved during the transcytosis process, it is used for only a single round of transport.

The cleavage of pIgR and formation of the SC-IgA complex confer enhanced resistance to proteolysis in the protease-rich mucosal environment (Underdown & Dorrington 1974). Once SC-IgA complexes are released into secretions, target microorganisms are efficiently cross-linked because dimeric IgA contains a total of four antigen-binding sites. The resulting large particles show retarded movement to the mucosal surface and can therefore be trapped in the mucus and cleared (Underdown & Schiff 1986, Kraehenbuhl & Neutra 1992). SC-IgA may also function by binding to microorganisms so as to prevent their interactions with the epithelia. In addition, SC-IgA can participate in direct killing of pathogens by facilitating the interaction of an antibody-bound microorganism with Fcα receptor-bearing macrophages and neutrophils in the mucosal surfaces (Underdown & Schiff 1986).

pIgR STRUCTURE pIgR is a glycosylated type I membrane protein containing an extracellular domain of about 629 amino acids, a single transmembrane region, and a cytoplasmic domain of 103 amino acids, with a total molecular weight of 100,000–105,000 (Mostov et al 1984). The extracellular portion is organized into five homologous domains that most closely resemble V-like domain members of the Ig superfamily (Mostov et al 1984) (Figure 2). The structure of pIgR is therefore very different from that of FcRn, the previously discussed FcR involved in Ig transport. As is the case for most FcRs, the extracellular portion of pIgR consists of multiple Ig-like domains arranged in tandem (Figure 2).

THE pIgR-Ig INTERACTION The derived affinity of interaction between SC and polymeric IgM is high: reported values for the K_A are $\approx 6 \times 10^8$ M^{-1} to 2×10^9 M^{-1} for the human SC-IgM interaction (Goto & Aki 1984). The binding of IgA to pIgR involves noncovalent interactions as well as covalent interactions thought to stabilize the complex (Mestecky & McGhee 1987); thus SC remains complexed to IgA in the mucosal environment to provide protection from proteolysis. By contrast to human SC-Ig complexes, some rabbit SC-Ig complexes are noncovalent (Knight et al 1975). The reported K_A values for the rabbit SC-IgA interaction are $\approx 1 \times 10^8$ M^{-1} (Kühn & Kraehenbuhl 1979), indicating tight binding even in the absence of covalent interactions.

Several pieces of evidence suggest that the N-terminal (membrane distal) Ig domain of pIgR is the primary determinant of the noncovalent interaction of pIgR with IgA (Frutiger et al 1986, Bakos et al 1991, Coyne et al 1994). It was originally demonstrated that a proteolytic fragment containing pIgR domain 1 could bind to IgA (Frutiger et al 1986). Site-directed mutagenesis of sequences in the regions predicted to encompass the B to C, C′ to C″, and F to G loops of domain 1 resulted in a significant reduction or nearly complete abrogation of IgA binding, suggesting that the binding site for IgA includes the counterparts of the antigen-binding loops in Ig variable domains (Coyne et al 1994) (Figure 3). In addition, the human SC-pIgR interaction involves a covalent interaction between Cys 311 of the Cα2 domain of one IgA heavy chain and Cys 467 of domain 5 of SC (Fallgreen-Gebauer et al 1993). Thus the binding interactions of pIgR involve the tip of domain 1, as well as domain 5, which are predicted to be separated by 150 to 170 Å if the five Ig-like domains in pIgR are aligned in a strictly end-to-end fashion with no significant kinks between domains (based on measurements of the Ig-like domains in crystal structures of CD4, CD2, and VCAM-1; Ryu et al 1990, Wang et al 1990, Jones et al 1992, 1995, Brady et al 1993). By contrast, the Fc region of IgA would be no more than 60 Å in length. This information suggests either that pIgR contacts both Fc regions in the IgA dimer or that it is significantly bent, or a combination of both possibilities.

There are little available data concerning the location of the sites on the IgA dimer or the IgM pentamer that determine their interactions with pIgR. Inhibition studies using monoclonal antibodies have suggested that regions of the Cα2 and Cα3 domains of IgA are involved in interactions with SC (Geneste et al 1986), although the contribution of residues 381–411 of the Cα3 domain was ruled out in studies of pIgR binding by an IgA molecule lacking these residues (Switzer et al 1992). It has been suggested that the pIgR binding site on IgA and IgM involves the J chain (Brandtzaeg & Pyrdz 1984), but the involvement of the J chain in pIgR binding is controversial (see Mestecky & McGhee 1987). Recent work using transport assays with pIgR-transfected Madin-Darby canine kidney (MDCK) cells showed impaired transport of IgA isolated from mice lacking the J chain (Hendrickson et al 1995), but this result does not distinguish between the possibility that pIgR directly contacts the J chain or that the IgA structure is altered in the absence of the J chain. The reported 1:1 stoichiometry of the SC-IgA interaction [one molecule of SC associated with one $(IgA)_2$-J chain complex] (Goto & Aki 1984, Mestecky & McGhee 1987) could be interpreted as consistent with the idea that SC interacts with the J chain. However, more structural and biochemical information will be required to understand the complete molecular details of the pIgR-Ig complexes.

FcRs IN ANTIBODY-MEDIATED EFFECTOR RESPONSES

FcRs for IgG and IgE are present on the surfaces of several accessory cells of the immune system. These receptors, designated FcγRs for those that bind IgG, and FcϵRs for those that bind IgE, interact with antibody-antigen complexes to activate various biological responses. Here we review the functions of the FcγR and FcϵR proteins and discuss the various forms of each type of receptor and how they are thought to interact with their Ig ligands.

Effector responses mediated by FcγRs include phagocytosis, endocytosis, antibody-dependent cell-mediated cytotoxicity (ADCC), the release of mediators of inflammation, and the regulation of B cell activation and antibody production (reviewed in Unkeless et al 1988, van de Winkel & Anderson 1991). Phagocytosis involves the engulfing of microbial particles, internalization into acidified cytoplasmic vesicles called phagosomes, and fusion of phagosomes with lysosomes, upon which lysosomal enzymes destroy the microbe (Silverstein et al 1989, CL Anderson et al 1990). The process of phagocytosis is distinguished from endocytosis by the size of the particle that is internalized and degraded, with phagocytosis referring to ingestion of particles of 1 μM or greater in diameter (Silverstein et al 1977). FcγRs mediate the internalization of smaller IgG-antigen complexes via endocytosis, which enhances the efficiency of antigen presentation by class II MHC molecules (Amigorena et al 1992b). In addition, FcγRs present on cells such as natural killer cells mediate interactions with antibody-coated target cells, resulting in the destruction of target cells by ADCC (reviewed in Unkeless et al 1988, van de Winkel & Anderson 1991).

On mast cells, the receptor for IgE, FcϵRI, binds monomeric IgE with high affinity. Upon cross-linking of the IgE by interaction with multivalent antigens, inflammatory responses are activated. These responses include the release of histamines, serotonin, and leukotrienes, resulting in fluid accumulation and the influx of cells and proteins to contain infection (Beaven & Metzger 1993, Sutton & Gould 1993, Ravetch 1994).

Molecular cloning of the genes encoding the FcγR and FcϵR proteins revealed the existence of three major classes of FcγRs (FcγRI, FcγRII, FcγRIII) and two classes of FcϵRs (FcϵRI and FcϵRII). The Ig-binding portions of FcγRI, FcγRII, FcγRIII, and FcϵRI (the α chains) are members of the Ig gene superfamily, all type I transmembrane proteins containing an extracellular region with two or more Ig-like domains and a polypeptide or lipid anchor in the membrane (Figure 2) (reviewed in Ravetch & Kinet 1991, Burton & Woof 1992, Hulett & Hogarth 1994). The extracellular regions of the FcγR and FcϵRI receptors show significant sequence similarity to each other: 70–98% sequence identity within the FcγRs and about 40% sequence identity between the FcγRs and FcϵRI (reviewed in Ravetch & Kinet 1991, Ravetch 1994). FcϵRII, a type II integral membrane protein containing a C-terminal extracellular region that includes a C-type lectin domain (Kikutani et al 1986), is not a member of the Ig superfamily and is not included in this discussion of the Ig superfamily FcRs.

The α subunits of many of the Ig superfamily FcRs are found in multiple forms (Ravetch et al 1986, Stuart et al 1989, Qiu et al 1990, Ernst et al 1992; reviewed in Ravetch & Kinet 1991, Fridman et al 1992, Hulett & Hogarth 1994). In the mouse, single genes encode each of the three classes of FcγR, whereas in humans, three FcγRI, three FcγRII, and two FcγRIII genes have been identified (reviewed in Ravetch 1994, Hulett & Hogarth 1994). Figure 2 shows the isoforms of the FcγRs discussed in this review. Differences in the cytoplasmic domains of the two FcγRII isoforms result in important functional differences (see below). The two FcγRIII isoforms differ in their membrane anchorage; one isoform is anchored to the membrane with a polypeptide chain, and the second isoform is anchored to the cell surface with a glycophosphatidyl inositol (GPI) linkage (Ravetch & Perussia 1989) (Figure 2). In addition to the membrane-bound form of FcRs, soluble versions generated by alternative splicing of the transmembrane exon or by proteolysis of membrane-bound forms are found in the circulation (Fridman 1991, Galon et al 1995). The soluble forms of FcRs may play an immunoregulatory role by interfering with the functions of their membrane bound counterparts (Fridman 1991, Galon et al 1995).

The ligand-binding domains of some FcRs are associated in the membrane with other proteins that are required for receptor assembly and signaling. The

α chains of FcϵRI and FcγRI associate with an integral membrane protein called the γ chain (Perez-Montfort et al 1983, Ra et al 1989, Ernst et al 1993, Scholl & Geha 1993). The γ chain is homologous to the ζ chain, a protein originally identified as essential for the assembly and signaling of the T-cell receptor-CD3 complex (Weissman et al 1989). Both γ and ζ chains associate with FcγRIII (Hibbs et al 1989, Lanier et al 1989). The cytoplasmic domains of γ and ζ chains share a common tyrosine-containing sequence motif called the antigen receptor activation motif (ARAM) (Reth 1989, Weiss & Littman 1994), ITAM (Cambier 1995), TAM (Samelson & Klausner 1992), or the ARH1 motif (Cambier 1992). In FcR signaling, as observed for signaling via the T and B cell receptors (Weiss & Littman 1994), the ARAM motifs associate with Src family protein tyrosine kinases that are activated upon receptor cross-linking to initiate a cascade of signal transduction events (Keegan & Paul 1992, Lin et al 1994).

We now review current knowledge about the structures of FcγRI, FcγRII, FcγRIII, and FcϵRI; their affinities and specificities for Ig; and binding domains interactions, and we discuss recent insights into the biological responses elicited by each receptor.

FcγRI

FcγRI is expressed on the surfaces of neutrophils, monocytes, granulocytes and macrophages (van de Winkel & Anderson 1991, Hulett & Hogarth 1994). Three human FcγRI genes have been identified, one encoding a transmembrane receptor with three Ig-like domains (Figure 2), and two encoding soluble receptors with three Ig-like domains. Alternative splicing of one of the soluble receptor genes results in an mRNA for a transmembrane receptor with two Ig-like domains (Ernst et al 1992). Of these isoforms, expression of only the transmembrane receptor with three Ig-like domains (FcγRIA) has been demonstrated. This receptor binds monomeric IgG with high affinity with reported K_A values ranging from 2×10^9 M^{-1} (for the binding of human IgG1 to human monocyte-like U937 cells expressing endogenous FcγRI; Shopes et al 1990) to 5×10^9 M^{-1} (for the binding of human IgG1 to COS cells transfected with human FcγRI; Allen & Seed 1989). Human IgG3 binds with an affinity comparable to human IgG1, but human IgG4 and human IgG2 bind more weakly (Allen & Seed 1989). The unique role of FcγRI compared with the low-affinity receptors FcγRII and FcγRIII may lie in the capability of FcγRI to trigger effector responses at low IgG concentrations, which are typical of early immune responses in vivo (Shen et al 1987).

The α chains of human and murine FcγRI consist of three extracellular Ig-like domains that show features most closely resembling the V-like set (Figure 2, Table 1), a transmembrane region, and a cytoplasmic domain (Allen & Seed

1989, Sears et al 1990, Ernst et al 1992). The α chain associates on cell surfaces with a γ homodimer (Ernst et al 1993) (Figure 2). Although transfection studies in COS cells show that the γ chain is not required for stable cell surface expression of FcγRI (Ernst et al 1993), macrophages derived from γ chain knockout mice do not bind murine IgG2a, which suggests that γ is required for FcγRI function in vivo (Takai et al 1994).

FCγRI FUNCTIONS FcγRI mediates ADCC, endocytosis, and phagocytosis in vitro (Shen et al 1987, CL Anderson et al 1990, Davis et al 1995). Despite the ability of FcγRI to bind monomeric IgG with high affinity, signals for endocytosis/degradation and phagocytosis are transduced by FcγRI only upon receptor cross-linking (Davis et al 1995). Although association of FcγRI with monomeric IgG results in internalization, the receptor-IgG complexes are rapidly recycled to the cell surface (Harrison et al 1994). Cross-linking of receptors at the cell surface also promotes internalization, but instead of being recycled, the receptor-ligand complexes are retained in intracellular compartments and subsequently degraded (Mellman & Plutner 1984, Harrison et al 1994). Internalization and degradation of cross-linked FcγRI-IgG-antigen complexes could lead to the enhanced presentation of peptide antigens on class II MHC molecules, as described for FcγRIII-immune complex interactions (Amigorena et al 1992b). However, because antigens associated with monomeric IgG bound to FcγRI are not degraded, FcγRI may not have a role in the enhancement of presentation of antigens with single epitopes.

FCγRI-IGG INTERACTION FcγRI contains an extra Ig-like domain in its extracellular portion compared with the lower-affinity receptors FcγRII and FcγRIII (Figure 2). The first two extracellular domains of FcγRI share greater sequence similarity with the two extracellular domains of FcγRII and FcγRIII than does the third domain, which suggests that the third domain is responsible for some of the interactions that confer high-affinity binding upon FcγRI (Allen & Seed 1989). Studies with mutant and chimeric FcRs demonstrate that removal of the third domain of murine FcγRI abrogates high-affinity binding to monomeric IgG, although domains 1 and 2 on their own retain a weak affinity for IgG. Linking FcγRI domain 3 to domains 1 and 2 of FcγRII does not confer high-affinity binding of monomeric IgG to FcγRII (Hulett et al 1991). Thus regions of FcγRI in addition to domain 3 are required for high-affinity binding of monomeric IgG (Hulett & Hogarth 1994).

The interaction sites on IgG for human FcγRI have been mapped in several studies that measured the binding of IgG and chimeric Igs to FcγRI expressed on U937 cells. Domain swap experiments involving chimeric IgGs constructed from different subtypes and chimeric IgE-IgG molecules identified the Cγ2 domain of IgG as an interaction site for FcγRI (Shopes et al 1990, Canfield & Morrison 1991). Mutagenesis studies showed that residues 234–237 of the lower hinge region as well as residue 331 in the Cγ2 domain of IgG are important (Duncan et al 1988, Canfield & Morrison 1991, Lund et al 1991) (Figure 1*b*). The binding sites for the closely related low affinity FcγRs (FcγRII and FcγRIII) have been mapped to a similar region of IgG, and FcϵRI appears to bind to an analogous place on the IgE Fc region (Hulett & Hogarth 1994; see below). Asn 297 of the Cγ2 domain is a conserved N-linked glycosylation site in IgG molecules. Alteration of the carbohydrate structure reduced the binding affinity of human FcγRI for IgG1 by four- to sixfold (Wright & Morrison 1994), implying involvement of carbohydrate in the receptor binding, either by direct interaction with the receptor, or by indirectly affecting the Fc conformation.

The Ig-binding domains of the FcγRs and FcϵRI proteins are generally assumed to be monomeric, based on analogy to similar Ig superfamily structures including CD4, CD2, and VCAM-1 (Ryu et al 1990, Wang et al 1990, Jones et al 1992, 1995). Indeed, FcγRI has been shown to bind only a single IgG molecule (O'Grady et al 1986), consistent with, but not conclusively demonstrating, the supposition that it is a monomer. However, all Ig Fc regions are dimers composed of two identical polypeptide chains (Figure 1*b*), each of which could theoretically interact with a single FcR to produce a 2:1 receptor-Ig stoichiometry. However, only one of two binding sites on IgG is utilized in the interaction with FcγRI (Koolwijk et al 1989), implying a 1:1 receptor-IgG stoichiometry. This issue is explored in more detail in the sections on FcγRIII and FcϵRI when other measurements of receptor-Ig stoichiometry are discussed.

FcγRII

FcγRII is very widely distributed among cells of the immune system (van de Winkel & Anderson 1991, Hulett & Hogarth 1994). Unlike FcγRI, which binds unaggregated IgG with high affinity, FcγRII binds monomeric IgG with low to undetectable affinity (estimated $K_A < 1 \times 10^7\ M^{-1}$ for human FcγRII binding to IgG; Hulett & Hogarth 1994). Under physiological conditions, the low affinity of FcγRII for monomeric IgG ensures that this receptor (and FcγRIII) interact only with IgG that has been aggregated by binding to multivalent antigens.

Although the γ chain is not required for FcγRII expression, γ has been observed in association with the α chain of human FcγRII (Masuda & Roos 1993). In mice, γ chain knockouts are impaired for the FcγRII-mediated phagocytic function of macrophages, although the expression levels of FcγRII are normal (Takai et al 1994). These results suggest that γ may be required to elicit biological responses associated with murine FcγRII (Takai et al 1994), consistent with the absence of an ARAM motif in murine FcγRII.

FCγRII ISOFORMS AND FUNCTION The α chains of human and murine FcγRII contain two extracellular Ig-like domains connected to a transmembrane and cytoplasmic region (Figure 2). The sequences of the two domains show characteristics of Ig V-like domains (Table 1), although they have been previously classified and modeled as C2 domains (Hulett & Hogarth 1994). Three human genes and one murine FcγRII gene have been identified (Ravetch et al 1986, Brooks et al 1989, Stuart et al 1989) encoding multiple transcripts that differ primarily in their cytoplasmic tails (Ravetch & Kinet 1991).

The FcγRII proteins exemplify how distinct biological responses can be elicited by differences in the cytoplasmic domains of receptors that have common extracellular ligand-binding domains (Ravetch 1994). The murine FcγRII gene has two transcripts, β1 and β2 (or b1 and b2). β1 contains a 46-amino acid insertion in the cytoplasmic region (Ravetch et al 1986) that prevents efficient FcγRIIβ1-mediated endocytosis (Miettinen et al 1989). B lymphocytes preferentially express the β1 isoform of FcγRII and are thus deficient in FcγRII-mediated endocytosis and enhancement of peptide antigen presentation by class II MHC molecules (Amigorena et al 1992a). This is thought to be important in order to limit B cell stimulation by T cells to antigens for which the B cell is specific; i.e. those internalized because of binding to the B cell receptor, rather than those internalized via IgG binding to FcγRII (Amigorena et al 1992a).

Both in vitro and in vivo studies have shown that FcγRII acts as a negative regulator of immune complex–triggered activation (Muta et al 1994, Daeron 1995, Takai et al 1996). On B lymphocytes, cross-linking of FcγRIIβ1 and membrane bound Ig by complexes of antigen and soluble antibody modulates B cell activation (Amigorena et al 1992a, Muta et al 1994), providing a feedback mechanism for regulation of B cell stimulation at high soluble antibody concentrations. In vitro reconstitution studies suggest that FcγRII can also inhibit FcϵRI-triggered activation of mast cells (Daeron 1995). Recent studies of FcγRII-deficient mice confirmed that FcγRII functions in vivo as an inhibitory receptor for both B cells and mast cells (Takai et al 1996). FcγRII-deficient mice display elevated Ig levels and demonstrate decreased thresholds for mast cell activation induced by FcγRIII (Takai et al 1996). The FcγRII isoforms that mediate these inhibitory functions do not contain ARAM motifs, and their cytoplasmic regions are indicated as "inhibit" in Figure 2. Both the murine β1 and β2 isoforms inhibit B-lymphocyte activation (Amigorena et al 1992a), as does the human homologue FcγRIIB (Ravetch 1994) [this protein has also been referred to as FcγRIIb (Brooks et al 1989) or FcγRIIC (Stuart et al 1989, Ravetch 1994)]. Other human FcγRII proteins contain the ARAM motifs in their cytoplasmic domains, which allows these receptors to mediate conventional cellular activation upon receptor cross-linking (indicated as ARAM in Figure 2).

FcγRII-IgG INTERACTION Unlike pIgR, which mainly uses its N-terminal Ig-like domain for interactions with IgA, most of the direct binding interactions between FcγRII and IgG involve the second domain of this receptor (Hulett & Hogarth 1994). Residues 154–161, 109–116, and 130–135 of the second Ig-like domain have been implicated in ligand binding (Hulett et al 1995) (*underlined* in Table 1). When these regions were modeled onto the structure of a Ig superfamily C2 domain (Hulett et al 1995), they corresponded to the F to G, B to C, and C′ to E loops (Figure 3). All three loops are predicted to be on the upper portion of the second domain, at the interface with the bottom of the first domain (Hulett et al 1995). The IgG binding site is therefore thought to involve the domain 1-domain 2 interface, with the first domain being required for stabilization of the regions of the second domain that interact with IgG (Hulett et al 1995).

The binding site on IgG for human FcγRII involves the same region of the IgG molecule as does the binding site for FcγRI; mutagenesis results implicate residues 234 to 237 of the lower hinge region adjacent to the Cγ2 domains (Lund et al 1991). Removal of the carbohydrate residues between the two Cγ2 domains also affects the ability of FcγRII to bind IgG (Walker et al 1989). Taken together with results mapping the FcϵRI-IgE interface to analogous regions on both the receptor and Ig ligand, the idea that the related IgG and IgE FcRs employ similar modes of interaction seems reasonable (Hulett & Hogarth 1994; see below).

FcγRIII

FcγRIII is expressed on macrophages, neutrophils, and mast cells and is the only FcR found on natural killer cells (van de Winkel & Anderson 1991, Hulett & Hogarth 1994). Like FcγRII, FcγRIII is classified as a low-affinity receptor for IgG. The Fc fragment of IgG binds human FcγRIII with a K_A value of 1.7 × 10^5 M^{-1} (Ghirlando et al 1995).

FcγRIII ISOFORMS AND FUNCTION Two human FcγRIII α chain genes have been identified, FcγRIIIA and FcγRIIIB, both encoding proteins containing an extracellular portion of 180 amino acids with two Ig-like domains (Ravetch & Perussia 1989). The Ig-like domains show sequence characteristics of Ig V-like domains (Table 1) although they were previously classified and modeled as C2 domains (Hibbs et al 1994). The most significant difference between FcγRIIIA and FcγRIIIB is that FcγRIIIA encodes a protein with a polypeptide transmembrane region and a cytoplasmic domain of 25 amino acids, whereas

FcγRIIIB encodes a protein that is anchored to the membrane by a glycophosphatidyl inositol linkage (Ravetch & Perussia 1989) (Figure 2). The FcγRIIIA and FcγRIIIB receptors have different cellular distributions, with FcγRIIIA found on macrophages, natural killer cells, and mast cells, whereas FcγRIIIB is expressed mainly on neutrophils (van de Winkel & Anderson 1991, Hulett & Hogarth 1994). By contrast to the human system, a single murine FcγRIII isoform expressed on macrophages and natural killer cells consists of two extracellular Ig domains and a polypeptide membrane linkage (previously called FcγRIIa; Ravetch et al 1986).

The α chain of murine FcγRIII associates with the γ chain (Kurosaki & Ravetch 1989), whereas human FcγRIIIA α associates with γ (Hibbs et al 1989) as well as ζ chains (in natural killer cells) (P Anderson et al 1990, Lanier et al 1989). The γ and ζ chains protect the α chain from degradation in the endoplasmic reticulum, and the absence of associated γ or ζ chains results in a reduction in cell surface expression of the transmembrane FcγRIII (Kurosaki & Ravetch 1989, Ra et al 1989). The in vivo role of FcγRIII in mediating ADCC was examined by studying γ-deficient mice. Natural killer cells from γ-deficient mice cannot mediate ADCC because of the absence of cell surface FcγRIII (Takai et al 1994).

In addition to its role in ADCC, in vitro experiments demonstrated that FcγRIII functions in endocytosis and phagocytosis (van de Winkel & Anderson 1991, Amigorena et al 1992b, Daeron et al 1994, Nagarajan et al 1995). Murine FcγRIIIA mediates rapid internalization of antibody-antigen complexes and enhances the efficiency of antigen presentation. Tyrosines in the ARAM motif of the γ subunit are required for signaling the internalization (Amigorena et al 1992b) and phagocytosis of antibody-coated erythrocytes (Daeron et al 1994). Transfection experiments in Chinese hamster ovary (CHO) cells showed that FcγRIIIA, when co-expressed with the γ chain, mediates phagocytosis of IgG-coated erythrocytes (Nagarajan et al 1995). By contrast, CHO cells expressing FcγRIIIB alone can bind IgG-coated erythrocytes, but not mediate their phagocytosis, suggesting that the lipid-linked FcγRIIIB does not deliver a phagocytic signal in CHO cells (Nagarajan et al 1995). However, it has been suggested that FcγRIIIB can work synergistically with FcγRII to enhance responses such as phagocytosis (Edberg et al 1992, Edberg & Kimberly 1994).

FCγRIII-IgG INTERACTION Similar to results described for FcγRI and FcγRII, the IgG-binding site of FcγRIII is thought to primarily involve the second Ig domain (the membrane proximal domain) (Hibbs et al 1994). When the results of mutagenesis and binding studies were mapped onto a model of this domain as a C2-set domain, the C to C$'$ loop was identified as the major site of IgG interaction, with contributions from the B to C and E to F loops (Hibbs et al 1994) (*underlined* in Table 1). The authors concluded that the FcγRIII interaction site lies on the portion of domain 2 that is furthest from domain 1 because of the positions of two of the three implicated loops (C to C′ and E to F, at the bottom of a C2 domain; Figure 3). By contrast, mutagenesis studies implicate the opposite portion of domain 2 of FcγRII in the interaction with IgG (Hulett & Hogarth 1994) (see above). Further work will be required to resolve whether the modes of FcγRIII and FcγRII interactions with IgG are different.

The interaction site on IgG for FcγRIII involves the same region of the IgG molecule as does the binding site for FcγRI and FcγRII, the lower hinge region just N-terminal to the Cγ2 domain (Jefferis et al 1990, Morgan et al 1995) (Figure 1*b*), but regions within the Cγ3 domain might also be involved (Gergely & Sarmay 1990).

Recent analytical ultracentrifugation experiments demonstrated that the stoichiometry of the FcγRIII-IgG interaction is 1:1 (Ghirlando et al 1995). A steric hindrance mechanism is one explanation for the observation that only one receptor binds per homodimeric Fc region, i.e. the binding of the first receptor to IgG hinders binding of the second. The location of the FcγR binding site on the lower hinge, where the two Cγ2 domains are in close spatial proximity, is consistent with this idea. The authors use thermodynamic data in support of a conformational change mechanism to explain the occupancy of only one of the two available sites on the Fc homodimer, whereby the binding of the first receptor molecule induces a conformational change that renders the second binding site on Fc nonfunctional (Ghirlando et al 1995). The exact details of the interaction of FcγRIII and the other FcγRs with IgG await the appropriate crystal structures. However, the currently available studies of the interactions of IgGs with the FcγRs and FcRn, and IgE with FcϵRI (see below), hint that these interactions are not as symmetric as might be initially assumed given the twofold symmetry of the IgGFc fragment in the crystal structure (Deisenhofer 1981) (Figure 1*b*).

FcϵRI

FcϵRI is a high-affinity receptor, binding to monomeric IgE with an equilibrium constant of $\approx 1 \times 10^{10}$ M^{-1} (Beavil et al 1993). IgE is present in very low concentrations in human serum (5–300 ng/ml), and the high-affinity binding permits a dramatic amplification of IgE-antigen interactions (Sutton & Gould 1993). Upon being cross-linked by the binding of IgE to a multivalent antigen, FcϵRI mediates a variety of allergic and inflammatory responses (Metzger 1991, Sutton & Gould 1993). Mast cells in tissues and basophils in blood express FcϵRI and are thought to be the cells principally responsible for an allergic response. Allergic reactions commonly begin with the production of IgE in response to pollen, cat dander, or other environmental antigens.

Receptor cross-linking triggered by the binding of these multivalent allergens to cell surface IgE-FcϵRI complexes results in the degranulation of cells and the release of stored mediators of inflammation, including histamine, serotonin, and leukotrienes (Metzger 1991, Sutton & Gould 1993). Recent in vivo studies confirm the importance of FcϵRI in the allergic response, in that the disruption of the FcϵRI α chain gene in mice resulted in a failure of the mice to mount anaphylactic responses (Dombrowicz et al 1994). The more beneficial role of FcϵRI is thought to involve the immune defense against parasites (Janeway & Travers 1994). Mast cell release of inflammatory mediators caused by cross-linking of FcϵRI through IgE binding of multivalent antigen induces smooth muscle contractions, with the result that mast cell degranulation results in protective responses such as vomiting, coughing, and sneezing that can help in expelling an invading organism (Janeway & Travers 1994).

FCϵRI STRUCTURE FcϵRI occurs on cell surfaces as a complex of four polypeptide chains: a ligand binding or α chain, a β chain, and a disulfide-linked γ chain homodimer (Blank et al 1989) (Figure 2). The α chain consists of two extracellular Ig-like domains, a single transmembrane sequence, and a cytoplasmic domain of about 20 to 31 amino acids (Kinet et al 1987, Metzger 1991). Although the Ig-like domains of FcϵRI were classified and modeled as C2-type domains (Sutton & Gould 1993; reviewed in Hulett & Hogarth 1994), we believe they share more similarity with V-like domains (Table 1). The β chain is predicted to contain four membrane-spanning domains, with the amino and carboxy termini being located on the cytoplasmic side (Kinet et al 1988).

FCϵRI-IGE INTERACTION Chimeric FcϵRI-FcγRIIIA and chimeric rodent-human FcϵRI were used to demonstrate that substitution of the second FcϵRI α chain extracellular domain (the membrane proximal domain) resulted in a loss of IgE binding (Mallamaci et al 1993, Robertson 1993). Further mutagenesis studies identified four regions in domain 2 as being important for interaction with IgE: residues 93–104, 111–125 and 129–137, and 154–161 (Mallamaci et al 1993, Hulett & Hogarth 1994) (*underlined* in Table 1). When the results of these studies were mapped onto a C2 set-based model of domain 2, the IgE interaction site was situated primarily in the portion of domain 2 near the interface with domain 1: the F to G, C$'$ to E, and B to C loops, and contributions from the B and C strands (Table 1) (Sutton & Gould 1993, Hulett & Hogarth 1994). Although the main site of IgE interaction involves the second FcϵRI domain, the observation that a mutant FcϵRI α chain containing only the second extracellular domain binds with lower affinity than the two-domain protein suggests that regions in the first domain are required for high-affinity binding (Robertson 1993).

The binding site on IgE for FcϵRI has been mapped to the interface between the $C_\epsilon 2$ and $C_\epsilon 3$ domains (Helm et al 1988, Weetall et al 1990, Nissim et al 1993), primarily involving residues of the $C_\epsilon 3$ domain, based upon the studies of the binding of chimeric rodent-human IgE molecules to rodent and human FcϵRI (Nissim et al 1993), and numerous other studies (Beavil et al 1993, Hulett & Hogarth 1994). Because the IgE heavy chain contains an extra domain, $C_\epsilon 2$, in the region corresponding to the IgG hinge (Figure 1*a*), the $C_\epsilon 2$-$C_\epsilon 3$ interface may be analogous to the IgG hinge-Cγ2 interface identified as the binding site of the FcγRs.

Fluorescence resonance energy transfer measurements demonstrated that IgE in solution is bent, such that the average end-to-end distance between the Fab and Fc segments is only 75 Å rather than the 180 Å predicted for a planar Y-shaped IgE structure (Baird et al 1993). Fluorescence energy transfer studies were also used to compare the conformation of IgE alone and IgE when bound to FcϵRI. The receptor-bound IgE was also bent, with an average end-to-end distance between the Fab and Fc segments of about 71 Å (Baird et al 1993). The bending of IgE should result in an asymmetric structure of the homodimeric IgE Fc region, such that only one of the two polypeptide chains of the Fc provides a binding site for FcϵRI. Indeed, the observed stoichiometry of the IgE-FcϵRI interaction is 1:1 (Robertson 1993), consistent with the idea that the bent region of IgE presents one concave and one convex surface, with the receptor site occluded on the concave surface (Baird et al 1993, Sutton & Gould 1993). Further analysis of the spectroscopic studies suggests that the Fc region of FcϵRI-bound IgE lies parallel to the membrane, based on measurements of the distances between the fluorophores on IgE and a fluorophore in the membrane (Baird et al 1993). This information implies a lying-down orientation for cell surface FcϵRI (Figure 2), reminiscent of the lying-down orientation proposed for the FcRn dimer (Burmeister et al 1994a,b) (Figure 5*a,b*). Because of the similarities in the predicted interfaces of the FcγR-IgG and the FcϵRI-IgE complexes, and the sequence similarities between the FcγRs and FcϵRI, a lying-down orientation on the membrane may be a common feature of many FcRs.

CONCLUSIONS

Most FcRs that are members of the Ig superfamily have related structures consisting of two or more Ig-like domains arranged in tandem, a domain organization shared by many cell adhesion molecules. FcRn, a heterodimer with an overall structural similarity to class I MHC molecules, is structurally distinct from the other Ig superfamily FcRs reviewed here (pIgR, the FcγRs, and FcϵRI). There are several common elements in the interactions of the adhesion molecule-like FcRs with Ig, which usually are not features of the interaction of FcRn with IgG.

First, the binding site on IgG for all the FcγRs involves the hinge and the hinge-proximal portion of the Cγ2 domain. The binding site for FcϵRI is at the $C_\epsilon 2$-$C_\epsilon 3$ interface, an analogous location on the IgE molecule. By contrast, FcRn binds to IgG at a different site, the interface between the Cγ2 and Cγ3 domains, where Fc histidine residues mediate part of the pH-dependent interaction between FcRn and IgG.

A second common feature of the FcγRs and FcϵRI is a 1:1 receptor-Ig stoichiometry in the case of FcγRI, FcγRIII, and FcϵRI, which suggests asymmetry in the Fc regions of receptor-bound Igs, such that one receptor binding site on the Fc homodimer is inaccessible. Strong evidence suggests that the IgE Fc region is bent, which may contribute to the inaccessibility of the second receptor binding site on IgE molecules. Biophysical studies also suggest that the Fc region of IgG is bent and can therefore bind asymmetrically to the FcγR receptors, which may explain the observation that only one of the two sites at the hinge-proximal end of the Cγ2 domain is available for interaction with FcγRI and FcγRIII. By contrast, both sites at the Cγ2-Cγ3 domain interface of IgG are accessible for interaction with FcRn in the crystals of FcRn bound to Fc; thus bending of IgG does not occlude either of the sites in this region of Fc at the high protein concentrations found in the crystals.

Another common feature of some of the adhesion molecule-like FcRs is the use of the membrane-proximal domain (domain 2 of FcγRII, FcγRIII, and FcϵRI; domain 3 of FcγRI) as the primary Ig-binding site, with possible contributions from the membrane distal domain(s). By contrast, pIgR binds to IgA primarily with its N-terminal domain, which is more typical of the interactions of adhesion molecules such as CD2, CD4, and ICAM-1 with their ligands. Because FcRn is so different structurally from the other FcRs, its interactions with IgG bear no resemblance to the Ig interactions of either pIgR or the other FcRs. The IgG-binding site is on the edge of the α1 and α2 domain platform, with contributions from the β2m subunit. This mode of interaction also does not resemble the ways that MHC proteins interact with any other molecules, including peptides, T-cell receptors and coreceptors, or superantigens.

Finally, in what appears to be the only common feature of Ig interaction between FcRn and the other Ig superfamily FcRs, a lying-down orientation was proposed for cell surface FcϵRI and FcRn. The orientations of the remaining receptors on the membrane are unknown, but the similarities in sequence and domain organization between FcϵRI and the FcγRs suggests this orientation may be relevant for the other receptors as well.

A more complete understanding of FcR-Ig interaction awaits high-resolution crystal structures of the adhesion molecule-like receptors in complex with their Fc ligands. In the absence of these structures, models of the FcγR and FcϵRI domains were constructed using the available Ig-like domain structures from cell adhesion molecules. Our analysis of the sequences of the FcγR and FcϵRI domains suggests that they have many features in common with V-like domains, although they had been classified as members of the C2 set. V-like and C2 domains differ primarily in the region between the C and E strands, which includes a region mapped as an Ig interaction site for some of these receptors. Further studies are required to resolve this issue, which promise to be of great interest owing to the recent advances in the understanding of the physiological functions of these receptors.

ACKNOWLEDGMENTS

We thank Dan Vaughn and Bob Turring for help with figures, Neil Simister and Sally Ward for communicating results prior to publication and for helpful discussions, Sherie Morrison and Dan Vaughn for helpful discussions, and Dan Vaughn and Luis Sanchez for critical reading of the manuscript. MR was supported by a fellowship from the Cancer Research Institute. PJB is supported by the Howard Hughes Medical Institute and a Camille and Henry Dreyfuss Teacher Scholar Award. Ribbon diagrams were prepared using MOLSCRIPT (Kraulis 1991).

Literature Cited

Abrahamson DR, Powers A, Rodewald R. 1979. Intestinal absorption of immune complexes by neonatal rats: a route of antigen transfer from mother to young. *Science* 206:567–69

Ahouse JJ, Hagerman CL, Mittal P, Gilbert DJ, Copeland NG, et al. 1993. Mouse MHC class-I like Fc receptor encoded outside the MHC. *J. Immunol.* 151:6076–88

Allen JM, Seed B. 1989. Isolation and expression of functional high affinity Fc receptor cDNAs. *Science* 243:378–80

Amigorena S, Bonnerot C, Drake JR, Choquet D, Hunziker W, et al. 1992a. Cytoplasmic domain heterogeneity and functions of IgG Fc receptors in B lymphocytes. *Science* 256:1808–12

Amigorena S, Salamero J, Davoust J, Fridman WH, Bonnerot C. 1992b. Tyrosine-containing motif that transduces cell activation signals also determines internalization and antigen presentation via type III receptors for IgG. *Nature* 358:337–41

Anderson CL, Shen L, Eicher DM, Wewers MD, Gill JK. 1990. Phagocytosis mediated by three distinct Fcγ receptor classes on human leukocytes. *J. Exp. Med.* 171:1333–45

Anderson P, Caligiuri M, O'Brien C, Manley T, Ritz J, Schlossman SF. 1990. Fcγ receptor type III (CD16) is included in the ζNK receptor complex expressed by human natural killer cells. *Proc. Natl. Acad. Sci. USA* 87:2274–78

Aroeti B, Mostov KE. 1994. Polarized sorting of the polymeric immunoglobulin receptor in the exocytic and endocytic pathways is controlled by the same amino acids. *EMBO J.* 13:2297–304

Baird B, Zheng Y, Holokwa D. 1993. Structural mapping of IgE-FcϵRI, an immunoreceptor complex. *Acc. Chem. Res.* 26:428–34

Bakos M-A, Kurosky A, Goldblum RM. 1991. Characterization of a critical binding site for human polymeric Ig on secretory component. *J. Immunol.* 147:3419–26

Beaven MA, Metzger H. 1993. Signal transduction by Fc receptors: the FcϵRI case. *Immunol. Today* 14:222–26

Beavil AJ, Beavil RL, Chan CMW, Cook JPD, Gould HJ, et al. 1993. Structural basis of the IgE-FcϵRI interaction. *Biochem. Soc. Trans.* 21:968–72

Bjorkman PJ, Parham P. 1990. Structure, function and diversity of class I major histocompatibility complex molecules. *Annu. Rev. Biochem.* 90:253–88

Blank U, Ra C, Miller L, Metzger H, Kinet JP. 1989. Complete structure and expression in transfected cells of high affinity IgE receptor. *Nature* 337:187–89

Blumberg RS, Koss T, Story CM, Barisani D, Polischuk J, et al. 1995. A major histocompatibility complex class I-related Fc receptor for IgG on rat hepatocytes. *J. Clin. Invest.* 95:2397–402

Bodian DL, Jones EY, Harlos K, Stuart DI, Davis SJ. 1994. Crystal structure of the extracellular region of the human cell adhesion molecule CD2 at 2.5 Å resolution. *Structure* 2:755–66

Brady RL, Dodson EJ, Dodson GG, Lange G, Davis SJ, et al. 1993. Crystal structure of domains 3 and 4 of rat CD4: relation to the NH_2-terminal domains. *Science* 260:979–83

Brandtzaeg P. 1981. Transport models for secretory IgA and secretory IgM. *Clin. Exp. Immunol.* 44:221–32

Brandtzaeg P, Pyrdz H. 1984. Direct evidence for an integrated function of J chain and secretory component in epithelial transport of immunoglobulins. *Nature* 311:71–73

Brooks DG, Qiu WQ, Luster AD, Ravetch JV. 1989. Structure and expression of human IgG FcγRII(CD32). *J. Exp. Med.* 170:1369–85

Burmeister WP, Gastinel LN, Simister NE, Blum ML, Bjorkman PJ. 1994a. The 2.2 Å crystal structure of the MHC-related neonatal Fc receptor. *Nature* 372:336–43

Burmeister WP, Huber AH, Bjorkman PJ. 1994b. Crystal structure of the complex between the rat neonatal Fc receptor and Fc. *Nature* 372:379–83

Burton DR, Woof JM. 1992. Human antibody effector functions. *Adv. Immunol.* 51:1–85

Cambier JC. 1992. Signal transduction by T- and B-cell antigen receptors: converging structures and concepts. *Curr. Opin. Immunol.* 4:257–64

Cambier JC. 1995. Antigen and FcR signaling—the awesome power of the immunoreceptor tyrosine-based activation motif (ITAM). *J. Immunol.* 155:3281–85

Canfield SM, Morrison SL. 1991. The binding affinity of human IgG for its high affinity Fc receptor is determined by multiple amino acids in the CH2 domain and is modulated by the hinge region. *J. Exp. Med.* 173:1483–91

Casanova JE, Apodaca G, Mostov KE. 1991. An autonomous signal for basolateral sorting in the cytoplasmic domain of the polymeric immunoglobulin receptor. *Cell* 66:65–75

Childers NK, Bruce MG, McGhee JR. 1989. Molecular mechanisms of immunoglobulin A defense. *Annu. Rev. Microbiol.* 43:503–36

Coyne RS, Siebrecht M, Peitsch MC, Casanova JE. 1994. Mutational analysis of polymeric immunoglobulin receptor/ligand interactions. *J. Biol. Chem.* 269:31620–25

Daeron M. 1995. Regulation of high affinity IgE receptor-mediated mast cell activation by murine low affinity IgG receptors. *J. Clin. Invest.* 95:577–85

Daeron M, Malbec O, Bonnerot C, Latour S, Segal DM, Fridman W. 1994. Tyrosine-containing activation motif-dependent phagocytosis in mast cells. *J. Immunol.* 152:783–92

Davies DR, Metzger H. 1983. Structural basis of antibody function. *Annu. Rev. Immunol.* 1:87–117

Davis W, Harrison PT, Hutchinson MJ, Allen JM. 1995. Two distinct regions of FcγRI initiate separate signaling pathways involved in endocytosis and phagocytosis. *EMBO J.* 14:432–41

Deisenhofer J. 1981. 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* 20:2361–70

Dombrowicz D, Flamand V, Brigman KK, Koller BH, Kinet J-P. 1994. Abolition of anaphylaxis by targeted disruption of the high affinity immunoglobulin E receptor α chain gene. *Cell* 75:969–76

Duncan AR, Woof JM, Partridge LJ, Burton DR, Winter G. 1988. Localization of the binding site for the human high-affinity Fc receptor on IgG. *Nature* 332:563–64

Edberg JC, Kimberly RP. 1994. Modulation of

Fcγ and complement receptor function by the glycosyl-phosphatidylinositol-anchored form of FcγRIII. *J. Immunol.* 1994:5826–35

Edberg JC, Salmon JE, Kimberly RP. 1992. Functional capacity of Fcγ receptor III (CD16) on human neutrophils. *Immunol. Res.* 11:239–51

Eiffert H, Quentin E, Decker J, Hillemeir S, Hufschmidt M, et al. 1984. Die Primärstruktur der menschlichen freien Sekretkomponente und die Anordnung der Disulfidbrucken. *Hoppe-Seyler's Z. Physiol. Chem.* 365:1489

Ernst LK, Duchemin A-M, Anderson CL. 1993. Association of the high affinity receptor for IgG (FcγRI) with the γ subunit of the IgE receptor. *Proc. Natl. Acad. Sci. USA* 90:6023–27

Ernst LK, van de Winkel JGJ, Chiu I, Anderson CL. 1992. Three genes for the human high affinity Fc receptor encode four different transcription products. *J. Biol. Chem.* 267:15692–700

Fallgreen-Gebauer E, Gebauer W, Bastian A, Kratzin HD, Eiffert H, et al. 1993. The covalent linkage of secretory component to IgA-structure of IgA. *Hoppe-Seyler's Z. Biol. Chem.* 374:1023–28

Fridman W. 1991. Fc receptors and immunoglobulin binding factors. *FASEB J.* 5:2684–90

Fridman WH, Bonnerot C, Daeron M, Amigorena S, Teillaud J-L, Sautes C. 1992. Structural bases of Fcγ receptor function. *Immunol. Rev.* 125:49–76

Frutiger S, Hughes GJ, Hanly WC, Kingzette M, Jaton JC. 1986. The amino-terminal domain of rabbit secretory component is responsible for noncovalent binding to immunoglobulin A dimers. *J. Biol. Chem.* 261:16673–81

Galon J, Bouchard C, Fridman WH, Sautes C. 1995. Ligands and biological activities of soluble Fcγ receptors. *Immunol. Lett.* 44:175–81

Gastinel LN, Simister NE, Bjorkman PJ. 1992. Expression and crystallization of a soluble and functional form of an Fc receptor related to class I histocompatibility molecules. *Proc. Natl. Acad. Sci. USA* 89:638–42

Geneste C, Iscaki S, Mangalo R, Pillot J. 1986. Both Fcα domains of human IgA are involved in in vitro interaction between secretory component and dimeric IgA. *Immunol. Lett.* 13:221–26

Gergely J, Sarmay G. 1990. The two binding site models of human IgG binding Fcγ receptors. *FASEB J.* 4:3275–83

Ghetie V, Hubbard JG, Kim J-K, Lee Y, Ward ES. 1996. Abnormally short serum half-lives of IgG in β2-microglobulin-deficient mice. *Eur. J. Immunol.* 26:690–96

Ghirlando R, Keown MB, Mackay GA, Lewis MS, Unkeless MS, Gould HJ. 1995. Stoichiometry and thermodynamics of the interaction between the Fc fragment of human IgG1 and its low-affinity receptor FcγRIII. *Biochemistry* 34:13320–27

Goto Y, Aki K. 1984. Interaction of the fluorescence-labeled secretory component with human polymeric immunoglobulins. *Biochemistry* 23:6736–44

Hanson A, Brandtzaeg P. 1993. The discovery of secretory IgA and the mucosal immune system. *Immunol. Today* 14:416–17

Harpaz Y, Chothia C. 1994. Many of the immunoglobulin superfamily domains in cell adhesion molecules and surface receptors belong to a new structural set which is close to that containing variable domains. *J. Mol. Biol.* 238:528–39

Harris LJ, Larson SB, Hasel KW, Day J, Greenwood A, McPherson A. 1992. The three-dimensional structure of an intact monoclonal antibody for canine lymphoma. *Nature* 360:369–72

Harrison PT, Davis W, Norman JC, Hockaday AR, Allen JA. 1994. Binding of monomeric immunoglobulin G triggers FcγRI-mediated endocytosis. *J. Biol. Chem.* 269:24396–402

Heldin C-H. 1995. Dimerization of cell surface receptors in signal transduction. *Cell* 80:213–23

Helm B, Marsh P, Vercelli D, Padlin E, Gould H, Geha R. 1988. The mast cell binding site on human immunoglobulin E. *Nature* 331:180–83

Hendrickson BA, Conner DA, Ladd DJ. 1995. Altered hepatic transport of immunoglobulin A in mice lacking the J chain. *J. Exp. Med.* 182:1905–11

Hibbs ML, Selvaraj P, Carpen O, Springer TA, Kuster H, et al. 1989. Mechanisms for regulating expression of membrane isoforms of FcγRIII (CD16). *Science* 246:1608–11

Hibbs ML, Tolvanen M, Carpen O. 1994. Membrane-proximal Ig-like domain of FcγRIII (CD16) contains residues critical for ligand binding. *J. Immunol.* 152:4466–74

Holden HM, Ito M, Hartshorne DJ, Rayment I. 1992. X-ray structure determination of telokin, the C-terminal domain of myosin light chain kinase, at 2.8 Å resolution. *J. Mol. Biol.* 277:840–51

Huber AH, Kelley RF, Gastinel LN, Bjorkman PJ. 1993. Crystallization and stoichiometry of binding of a complex between a rat intestinal Fc receptor and Fc. *J. Mol. Biol.* 230:1077–83

Hulett MD, Hogarth PM. 1994. Molecular basis of Fc receptor function. *Adv. Immunol.* 57:1–127

Hulett MD, Osman N, McKenzie IFC, Hogarth PM. 1991. Chimeric Fc receptors identify functional domains of murine FcγRI. *J. Immunol.* 142:1863–68

Hulett MD, Witort E, Brinkworth RI, McKenzie IFC, Hogarth PM. 1995. Multiple regions of human FcγRII (CD32) contribute to the binding of IgG. *J. Biol. Chem.* 270:21188–94

Janeway CA, Travers P. 1994. The immune system in health and disease. In *Current Biology* 8:33–34. London: Current Biology/New York: Garland

Jefferis R, Lund JJP. 1990. Molecular definition of interaction sites on human IgG for Fc receptors (huFcγR). *Mol. Immunol.* 27:1237–40

Jones EA, Waldman TA. 1972. The mechanism of intestinal uptake and transcellular transport of IgG in the neonatal rat. *J. Clin. Invest.* 51:2916–27

Jones EY, Davis SJ, Williams AF, Harlos K, Stuart DI. 1992. Crystal structure at 2.8 Å resolution of a soluble form of the cell adhesion molecule CD2. *Nature* 360:232–39

Jones EY, Harlos K, Bottomley MJ, Robinson RC, Driscoll PC, et al. 1995. Crystal structure of an integrin-binding fragment of vascular cell adhesion molecule-1 at 1.8 Å resolution. *Nature* 373:539–44

Junghans RP, Anderson CL. 1996. The protection receptor for IgG catabolism is the β2-microglobulin-containing neonatal intestinal transport receptor. *Proc. Natl. Acad. Sci. USA* 93:5512–16

Keegan A, Paul WE. 1992. Multichain immune recognition receptors: similarities in structure and signaling pathways. *Immunol. Today* 13:63–68

Kerr MA. 1990. The structure and function of human IgA. *Biochem. J.* 271:285–96

Kikutani H, Inui S, Sato R, Barsumain EL, Owaki H, et al. 1986. Molecular structure of human lymphocyte receptor for immunoglobulin E. *Cell* 47:657–65

Kim J-K, Tsen M-F, Ghetie V, Ward ES. 1994. Localization of the site of the murine IgG1 molecule that is involved in binding to the murine intestinal Fc receptor. *Eur. J. Immunol.* 24:2429–34

Kinet JP, Blank U, Ra C, Metzger H, Kochan J. 1988. Isolation and characterization of cDNAs coding for the beta subunit of the high affinity receptor for immunoglobulin E. *Proc. Natl. Acad. Sci. USA* 85:6483–87

Kinet JP, Metzger H, Hakimi J, Kochan J. 1987. A cDNA presumptively coding for the alpha subunit of the receptor with high affinity for immunoglobulin E. *Biochemistry* 26:4605–10

Knight KL, Vetter ML, Malek TR. 1975. Distribution of covalently-bound and non-covalently bound secretory component on subclasses of rabbit secretory IgA. *J. Immunol.* 115:595–98

Kochan J, Pettine LF, Hakimi J, Kishi K, Kinet JP. 1988. Isolation of the gene coding for the α subunit of the human high affinity IgE receptor. *Nucleic Acid Res.* 16:3584

Koolwijk P, Spierenburg GT, Frasa H, Boot JHA, van de Winkel JGJ, Bast BJEG. 1989. Interaction between hybrid mouse monoclonal antibodies and the human high-affinity IgG FcR, huFcγRI, on U937: involvement of only one of the mIgG heavy chains in receptor binding. *J. Immunol.* 143:1656–62

Kraehenbuhl J-P, Neutra MR. 1992. Transepithelial transport and mucosal defense II: secretion of IgA. *Trends Cell Biol.* 2:134–38

Kraulis PJ. 1991. MOLSCRIPT: a program to produce both detailed and schematic plots of protein structures. *J. Appl. Crystallogr.* 24:946–50

Kühn L, Kraehenbuhl J-P. 1979. Interaction of rabbit secretory component with rabbit IgA dimer. *J. Biol. Chem.* 254:11066–71

Kurosaki T, Ravetch JV. 1989. A single amino acid in glycosyl phosphatidylinositol attachment domain determines the membrane topology of FcγRIII. *Nature* 326:292–95

Lanier LL, Yu G, Phillips JH. 1989. Coassociation of CD3ζ with a receptor (CD16) for IgG Fc on human natural killer cells. *Nature* 342:803–5

Leahy DJ, Axel R, Hendrickson WA. 1992. Crystal structure of a soluble form of the human T cell coreceptor CD8 at 2.6 Å resolution. *Cell* 68:1145–62

Lin C, Shen Z, Boros P, Unkeless JC. 1994. Fc receptor mediated signal transduction. *J. Clin. Immunol.* 14:1–13

Lund J, Winter G, Jones PT, Pound JD, Tanaka T, et al. 1991. Human FcγRI and FcγRII interact with distinct but overlapping sites on human IgG. *J. Immunol.* 147:2657–62

Maliszewski CR. 1990. Expression cloning of a human Fc receptor for IgA. *J. Exp. Med.* 172:1665–72

Mallamaci MA, Chizzonite R, Griffin M, Nettleton M, Hakimi J, et al. 1993. Identification of sites on the human FcϵR1α subunit which are involved in binding human and rat IgE. *J. Biol. Chem.* 268:22076–83

Masuda M, Roos D. 1993. Association of all three types of FcγR (CD64, CD32 and CD16) with a γ chain homodimer in cultured human monocytes. *J. Immunol.* 151:6382–88

Mellman I, Plutner H. 1984. Internalization and degradation of macrophage Fc receptors bound to polyvalent immune complexes. *J. Cell Biol.* 98:1170–77

Mestecky J, McGhee JR. 1987. Immunoglobulin A (IgA): molecular and cellular interactions involved in IgA biosynthesis and immune response. *Adv. Immunol.* 40:153–245

Metzger H. 1991. The high affinity receptor for IgE on mast cells. *Clin. Exp. Allergy* 21:269–79

Miettinen HM, Rose JK, Mellman I. 1989. Fc receptor isoforms exhibit distinct abilities for coated pit localization as a result of cytoplasmic domain heterogeneity. *Cell* 58:317–27

Morgan A, Jones ND, Nesbitt AM, Chaplin L, Bodmer MW, Emtage JS. 1995. The N-terminal end of the CH2 domain of chimeric human IgG1 and anti-HLA-DR is necessary for C1q, FcγRI and FcγRIII binding. *Immunology* 86:319–24

Mostov KE. 1994. Transepithelial transport of imunoglobulins. *Annu. Rev. Immunol.* 12:63–84

Mostov KE, Friedlander M, Blobel G. 1984. The receptor for trans-epithelial transport of IgA and IgM contains multiple immunoglobulin-like domains. *Nature* 308:37–43

Mostov KE, Simister NE. 1985. Transcytosis. *Cell* 43:389–90

Muta T, Kurosaki T, Misulovin Z, Sanchez M, Nussenzweig MC, Ravetch JV. 1994. A 13-amino acid motif in the cytoplasmic domain of FcγRIIB modulates B-cell signalling. *Nature* 368:70–73

Nagarajan S, Chesla S, Cobern L, Anderson P, Zhu C, Selvaraj P. 1995. Ligand binding and phagocytosis by CD16 (Fcγ receptor III) isoforms. *J. Biol. Chem.* 270:25762–70

Nissim A, Schwarzbaum S, Siraganian R, Eshhar Z. 1993. Structural mapping of IgE-FcϵRI, an immunoreceptor complex. *J. Immunol.* 150:428–34

O'Grady JH, Looney RJ, Anderson CL. 1986. The valence for ligand of the human mononuclear phagocyte 72 kD high-affinity IgG Fc receptor is one. *J. Immunol.* 137:2307–10

Ohno T, Kubagawa H, Sanders SK, Cooper MD. 1990. Biochemical nature of an Fcμ receptor on human B-lineage cells. *J. Exp. Med.* 172:1165–75

Perez-Montfort R, Kinet JP, Metzger H. 1983. A previously unrecognized subunit of the receptor for immunoglobulin E. *Biochemistry* 22:5722–28

Popov S, Hubbard JG, Kim J-K, Ober B, Ghetie V, Ward ES. 1996. The stoichiometry and affinity of murine Fc fragments with the MHC class I-related receptor, FcRn. *Mol. Immunol.* In press

Qiu WQ, De Bruin D, Brownstein BH, Pearse R, Ravetch JV. 1990. Organization of the human and mouse low affinity FcγR genes: duplication and recombination. *Science* 248:732–35

Ra C, Jouvin M-H, Blank U, Kinet JP. 1989. A macrophage Fcγ receptor and the mast cell receptor for IgE share an identical subunit. *Nature* 341:752–54

Raghavan M, Bonagura VR, Morrison SL, Bjorkman PJ. 1995a. Analysis of the pH dependence of the neonatal Fc receptor/immunoglobulin G interaction using antibody and receptor variants. *Biochemistry* 34:14649–57

Raghavan M, Chen MY, Gastinel LN, Bjorkman PJ. 1994. Investigation of the interaction between the class I MHC-related Fc receptor and its immunoglobulin G ligand. *Immunity* 1:303–15

Raghavan M, Gastinel LN, Bjorkman PJ. 1993. The Class I MHC-related Fc receptor shows pH-dependent stability differences correlating with immunoglobulin binding and release. *Biochemistry* 32:8654–60

Raghavan M, Wang Y, Bjorkman PJ. 1995b. Effects of receptor dimerization on the interaction between the class I MHC related Fc receptor and immunoglobulin G. *Proc. Natl. Acad. Sci. USA* 92:11200–4

Randall TD, Brewer JW, Corley RB. 1992. Direct evidence that J-chain regulates the polymeric structure of IgM in antibody-secreting B-cells. *J. Biol. Chem.* 267:18002–7

Ravetch JV. 1994. Fc receptors: rubor redux. *Cell* 78:553–60

Ravetch JV, Kinet J-P. 1991. Fc receptors. *Annu. Rev. Immunol.* 9:457–92

Ravetch JV, Luster AD, Weinshank R, Kochan J, Pavlovec A, et al. 1986. Structural heterogeneity and functional domains of murine immunoglobulin G Fc receptors. *Science* 234:718–25

Ravetch JV, Perussia B. 1989. Alternative membrane forms of FcγRIII(CD16) on human natural killer cells and neutrophils. *J. Exp. Med.* 170:481–97

Reth M. 1989. Antigen receptor tail clue. *Nature* 338:383–84

Roberts DM, Guenthert M, Rodewald R. 1990. Isolation and characterization of the Fc receptor from fetal yolk sac of the rat. *J. Cell Biol.* 111:1867–76

Robertson MW. 1993. Phage and *Escherichia coli* expression of the human high affinity immunoglobulin E receptor α-subunit ectodomain. *J. Biol. Chem.* 268:12736–43

Rodewald R. 1973. Intestinal transport of antibodies in the newborn rat. *J. Cell Biol.* 58:189–211

Rodewald R, Kraehenbuhl J-P. 1984. Receptor-mediated transport of IgG. *J. Cell Biol.* 99:159-64s

Ryu S-E, Kwong PD, Truneh A, Porter TG, Arthos J, et al. 1990. Crystal structure of an HIV-binding recombinant fragment of human CD4. *Nature* 348:419–26

Samelson LE, Klausner RD. 1992. Tyrosine kinases and tyrosine-based activation motifs. Current research on activation via the T cell antigen receptor. *J. Biol. Chem.* 267:24913–16

Scholl PR, Geha RS. 1993. Physical association between the high affinity IgG receptor (FcγRI) and the gamma subunit of the high affinity IgE receptor (FcϵRI γ). *Proc. Natl. Acad. Sci. USA* 90:8847–50

Sears DW, Osman N, Tate B, McKenzie IFC, Hogarth PM. 1990. Molecular cloning and expression of the mouse high affinity receptor for IgG. *J. Immunol.* 144:371–78

Shen L, Guyre PM, Fanger MW. 1987. Polymorphonuclear leukocyte functions triggered through the high affinity Fc receptor for monomeric IgG. *J. Immunol.* 139:534–38

Shopes B, Weetall M, Holowka D, Baird B. 1990. Recombinant human IgG1-murine IgE chimeric Ig. Construction, expression and binding to Fcγ receptors. *J. Immunol.* 145:3842–48

Silverstein SC, Greenberg S, DiVirgillo F, Steinberg TH. 1989. Phagocytosis. In *Fundamental Immunology,* ed. WE Paul, 703–720. New York: Raven

Silverstein SC, Steinman RM, Cohn ZA. 1977. Endocytosis. *Annu. Rev. Biochem.* 46:669–722

Simister NE, Mostov KE. 1989a. Cloning and expression of the neonatal rat intestinal Fc receptor, a major histocompatibility complex class I antigen homolog. *Cold Spring Harbor Symp. Quant. Biol.* LIV:571–80

Simister NE, Mostov KE. 1989b. An Fc receptor structurally related to MHC class I antigens. *Nature* 337:184–87

Simister NE, Rees AR. 1985. Isolation and characterization of an Fc receptor from neonatal rat small intestine. *Eur. J. Immunol.* 15:733–38

Simister NE, Story CM. 1996. Fcγ receptors in human placenta. In *Human IgG Fc Receptors,* ed. JGJ van de Winkel, PJA Capel, pp. 25–38. Landes

Sjoberg O. 1980. Presence of receptors for IgD on human T and non-T lymphocytes. *Scand. J. Immunol.* 11:377–82

Song WX, Bomsel M, Casanova J, Vareman JP, Mostov K. 1994. Stimulation of transcytosis of the polymeric immunoglobulin receptor by dimeric IgA. *Proc. Natl. Acad. Sci. USA* 91:163–66

Story CM, Mikulska JE, Simister NE. 1994. MHC class I-like Fc receptor cloned from human placenta. *J. Exp. Med.* 180:2377–81

Stuart S, Simister NE, Clarkson SB, Kacinski BK, Shapiro M, Mellman I. 1989. Human IgG Fc receptor (hFcγRII; CD32) exists as multiple isoforms in macrophages, lymphocytes and IgG-transporting placental epithelium. *EMBO J.* 8:3657–66

Sutton BJ, Gould HJ. 1993. The human IgE network. *Nature* 366:421–28

Switzer IC, Loney GM, Yang DS, Underdown BJ. 1992. Binding of secretory component to protein 511, a pIgA mouse protein lacking 36 amino acid residues of the Cα3 domain. *Mol. Immunol.* 29:31–35

Takai T, Li M, Sylvestre D, Clynes R, Ravetch JV. 1994. FcRγ deletion results in pleiotrophic effector cell defects. *Cell* 76:519–29

Takai T, Ono M, Hikida M, Ohmori H, Ravetch JV. 1996. Augmented humoral and anaphylactic responses in FcγRII-deficient mice. *Nature* 379:346–49

Townsend A, Bodmer H. 1989. Antigen recognition by class I-restricted T lymphocytes. *Annu. Rev. Immunol.* 7:601–24

Underdown BJ, Dorrington KJ. 1974. Studies on the structural and conformational basis for the relative resistance of serum and secretory IgA to proteolysis. *J. Immunol.* 112:949–59

Underdown BJ, Schiff JM. 1986. Immunoglobulin A: strategic defense at the mucosal surface. *Annu. Rev. Immunol.* 4:389–417

Unkeless JC, Scigliano E, Freedman JH. 1988. Structure and function of human and murine receptors for IgG. *Annu. Rev. Immunol.* 6:251–81

van de Winkel JGJ, Anderson CL. 1991. Biology of human immunoglobulin G Fc receptors. *J. Leukocyte Biol.* 49:511–24

Vaughn DE, Bjorkman PJ. 1996. The (Greek) key to structures of neural adhesion molecules. *Neuron* 16:261–73

Wagner G, Wyss DF. 1994. Cell surface adhesion receptors. *Curr. Opin. Struct. Biol.* 4:841–51

Walker MR, Lund J, Thompson KM, Jefferies R. 1989. A glycosylation of human IgG1 and IgG3 monoclonal antibodies can eliminate recognition by human cells expressing FcγRI and/or FcγRII receptors. *Biochem. J.* 259:1347–53

Wallace KH, Rees AR. 1980. Studies on the immunoglobulin G Fc fragment receptor from neonatal rat small intestine. *Biochem. J.* 188:9–16

Wang J, Yan Y, Garrett TPJ, Liu J, Rodgers DW, et al. 1990. Atomic structure of a fragment of human CD4 containing two immunoglobulin-like domains. *Nature* 348:411–19

Weetall M, Shopes B, Holowka D, Baird B. 1990. Mapping the site of interaction between murine IgE and its high affinity receptor with chimeric Ig. *J. Immunol.* 145:3849–54

Weiss A, Littman DR. 1994. Signal transduction by lymphocyte antigen receptors. *Cell* 76:263–74

Weissman AM, Baniyash M, Hou D, Samuelson LE, Burgess WH, Klausner RD. 1989. Molecular cloning of the ζ chain of the T cell antigen receptor. *Science* 239:1018–21

Williams AF, Barclay AN. 1988. The immunoglobulin superfamily-domains for cell surface recognition. *Annu. Rev. Immunol.* 6:381–405

Wright A, Morrison SL. 1994. Effect of altered CH2-associated carbohydrate structure on the functional properties and in vivo fate of chimeric mouse-human immunoglobulin G1. *J. Exp. Med.* 180:1087–96

Annual Review of Cell and Developmental Biology
Volume 12, 1996

CONTENTS