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Human Fc Receptors: Critical Targets in the Treatment of Autoimmune Diseases and Transplant Rejections

Elena Ivan, Adriana Ioana Colovai

ABSTRACT: The receptors for the Fc region of immunoglobulins (FcR) are members of the immunoglobulin superfamily. They are expressed on various hematopoietic cells and constitute a link between humoral and cell-mediated immunity. The activation and downmodulation of immune responses are controlled by signals from activating and inhibitory FcR, expressed on the surface of immune cells. The signaling regions, defined as immunoreceptor-tyrosine-based activation motif and immunoreceptor-tyrosine-based inhibitory motif, are contained within the cytoplasmic domain of FcR or of the adaptor proteins associated with FcR. Activating and inhibitory FcR are usually coexpressed on the surface of the same cell and coengaged by the same ligand, functioning in concert to keep a balanced immune response. Impairment of the functional balance between activating and inhibitory FcR leads either to hyperactivity to foreign and self antigens or to unresponsiveness as seen in many autoimmune diseases and infections. Pathologic conditions in which immunoglobulin–FcR interactions play a major role, as well as the outcome of treatment with intravenous immunoglobulin and monoclonal antibodies, may be influenced by targeting FcR. *Human Immunology 67, 479–491 (2006).* © American Society for Histocompatibility and Immunogenetics, 2006. Published by Elsevier Inc.

KEYWORDS: Fc receptors; immunoglobulin-like transcripts; immunoreceptor-tyrosine-based activation motif; immunoreceptor-tyrosine-based inhibitory motif; autoimmune diseases

ABBREVIATIONS

ADCC	antibody-dependent cell-mediated cytotoxicity
APCs	antigen-presenting cells
FcR	receptor(s) for Fc region of Ig
FcRn	neonatal Fc receptor for IgG
HLA	human leukocyte antigen
IFN	interferon
IL	interleukin
ILT	immunoglobulin-like transcript(s)
ITAM	immunoreceptor-tyrosine-based activation motif
ITIM	immunoreceptor-tyrosine-based inhibitory motif
KIR	killer cell immunoglobulin-like receptor(s)
LAIR	leukocyte-associated immunoglobulin-like receptor(s)
MHC	major histocompatibility complex
PIgR	polymeric IgA/m receptor
PIR	paired immunoglobulin-like receptor(s)

NOMENCLATURE

Fc receptors (FcR) are the receptors for the Fc regions of immunoglobulins. They belong to several families of molecules. Most human and murine FcR are members of the immunoglobulin superfamily; some belong to lectin families. FcR exist as membrane receptors and as soluble molecules, produced by alternative splicing of FcR transcripts or by proteolysis of membrane receptors [1].

FcRs are defined by their specificity for immunoglobulin isotypes: FcγR bind IgG, FcαR bind IgA, FcεR bind IgE, FcμR bind IgM, and FcδR bind IgD. Structurally distinct receptors are distinguished by a Roman numeral, based on historical precedent; for example, FcγR has three groups: FcγRI, FcγRII, and FcγRIII. Within the same group, distinct genes that are structurally related are denoted by letters such as A, B, and C. The alternative spliced transcripts derived from a single gene are designated a1, a2, b1, b2, b3, and so on. The protein subunit is indicated by a Greek letter placed at the end of the name, for example, FcεRIα, FcεRIγ [1, 2]. Leukocyte FcγR are divided into three groups, FcγRI (CD64), FcγRII (CD32), and FcγRIII (CD16), encompassing at least 12 isoforms (Table 1).

A family of Fc receptor homologs have been identified through homology searching of the mouse and human genomes. These genes, which are located in humans on chromosome 1, as are some other FcR genes, share

From the Department of Pathology, Columbia University, New York, NY, USA.

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TABLE 1 Genetic characteristics of leukocyte FcγRs

Receptor	Genes	Chromosomal location	Isoforms
FcγRI (CD64)	FcγRIA, -B and -C	1q21	Ia, Ib1, Ib2, Ic
FcγRII (CD32)	FcγRIIA, -B and -C	1q23-24	IIa1, IIa2, IIb1 IIb2,IIb3, IIc
FcγRIII (CD16)	FcγRIIIA and -B	1q23	IIIa, IIIb
FcγRIV (mouse)	FcγRIV	1q23-24	
FcεRI	FcεRI	1q23	
FcεRII (CD23)	FcεRII	19p13.3	
FcαRI (CD89)	FcαRI	19q13.2-13.4	FcαRIa1,a2
Fcα/μR	Fcα/μR	1q32.1	
FcRn	FcRn	19q13.3	
pIgR	pIgR	1q31-41	
FcRH	FcRH1-6	1q21	

genomic structure and sequences with classic FcR genes. Their biological function is still unknown.

GENES AND STRUCTURE

The remarkable diversity of FcR gene products is generated at various levels. Leukocyte FcγR are encoded by eight genes, located on the long arm of chromosome 1. The FcεRI gene also maps to chromosome 1 (Table 1). FcγR are single α-chain glycoproteins characterized by two (FcγRII and FcγRIII) or three (FcγRI) N-terminal extracellular immunoglobulin-like domains (ligand-binding domains), a transmembrane region, and an intracellular tail with a C terminus (Figure 1). FcγR bind the lower hinge region of IgG. Because FcγR bind asymmetrically only one IgG molecule, they are unable to trigger cell activation spontaneously unless crosslinked by multiple ligands. Different patterns of glycosylation of IgG–Fc also influence the affinity and functional activity of FcγR [3, 4].

The FcγRI group contains three genes—FcγRIA, FcγRIB, and FcγRIC—that generate four different transcripts: FcγRa, FcγRb1, FcγRb2, and FcγRc. FcγRIa protein has high affinity for monomeric IgG, due to the presence of three extracellular ligand-binding domains. FcγRIb1 and FcγRIc transcripts contain stop codons in

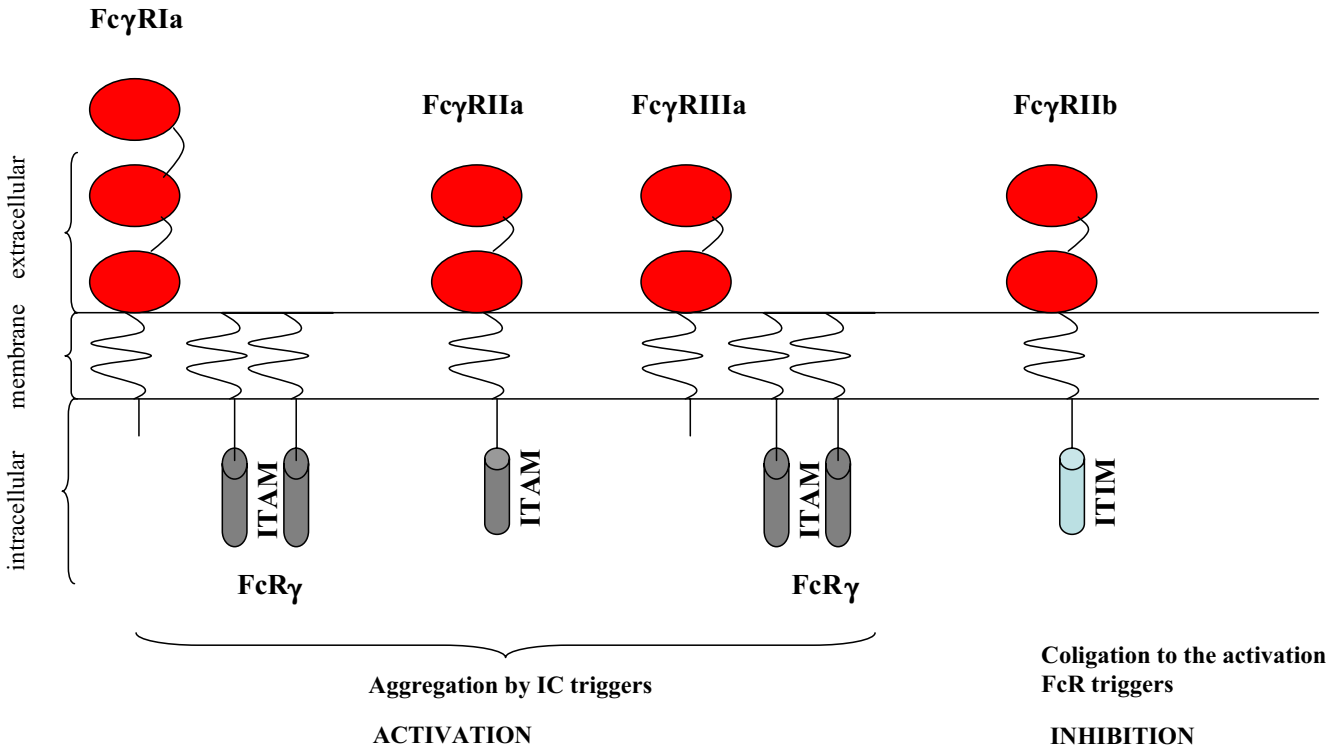

FIGURE 1 Schematic model for activating and inhibitory FcγR.