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# Mouse and human FcR effector functions

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**Summary:** Mouse and human FcRs have been a major focus of attention not only of the scientific community, through the cloning and characterization of novel receptors, and of the medical community, through the identification of polymorphisms and linkage to disease but also of the pharmaceutical community, through the identification of FcRs as targets for therapy or engineering of Fc domains for the generation of enhanced therapeutic antibodies. The availability of knockout mouse lines for every single mouse FcR, of multiple or cell-specific—'à la carte'—FcR knockouts and the increasing generation of hFcR transgenics enable powerful *in vivo* approaches for the study of mouse and human FcR biology. This review will present the landscape of the current FcR family, their effector functions and the *in vivo* models at hand to study them. These *in vivo* models were recently instrumental in re-defining the properties and effector functions of FcRs that had been overlooked or discarded from previous analyses. A particular focus will be made on the (mis)concepts on the role of high-affinity IgG receptors *in vivo* and on results from antibody engineering to enhance or abrogate antibody effector functions mediated by FcRs.

Keywords: *Fc receptor, FcγR, mouse models, antibody-mediated disease, antibody-mediated therapy, high-affinity receptor*

## Mouse FcRs

Myeloid cells, B cells, and natural killer (NK) cells in the mouse are equipped with a variety of receptors that enable their interaction with monomeric or aggregated immunoglobulins, antigen–antibody immune complexes, and/or opsonized (antibody-coated) particles, cells, or surfaces. Most of these receptors bind the Fc portion of immunoglobulins (receptors for the Fc portion of immunoglobulins, FcR) in mice (*Fig. 1*), whereas other receptors bind to glycosylations present on (but not to amino acid residues of) the Fc portion of immunoglobulins, e.g. SIGNR1 and DC-SIGN. All these receptors endow mouse myeloid cells, NK cells, and B cells, but not T cells or platelets, with the capacity to interact directly with IgM, IgG, IgA, and/or IgE classes of immunoglobulins. Among the 10 FcRs expressed in mice, only half are receptors for a specific class of immunoglobulins, the other half possess a dual specificity (e.g. binding of IgM and IgA, or IgG and IgE).

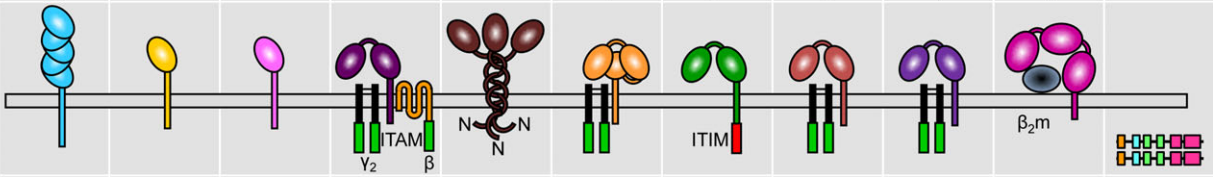
| Mouse FcRs | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Name** | **polyIgR** | **FcμR** | **Fcα/μR** | **FcεRI** | **FcεRII** | **FcγRI** | **FcγRIIB** | **FcγRIII** | **FcγRIV** | **FcRn** | **TRIM21** |
| ***Gene*** | *Pigr* | *Faim3* | *Fcamr* | *Fcer1a* | *Fcer2a* | *Fcgr1* | *Fcgr2b* | *Fcgr3* | *Fcgr4* | *Fcgrt* | *Trim21* |
| |   | | | | | | | | | | |
| **Alleles** | / | / | / | / | / | / | Ly17.1/ Ly17.2 | V, T, H | / | / | / |
| **IgM** | $1x10^8$ | $1x10^8$ | $3x10^{10}$ | – | – | – | – | – | – | – | $2x10^6$ |
| **IgG1** | – | – | – | – | – | – | $3x10^6$ | $3x10^5$ | – | **$8x10^6$** | + |
| **IgG2a** | – | – | – | – | – | **$3x10^7$** | $4x10^5$ | $7x10^5$ | **$3x10^7$** | + | + |
| **IgG2b** | – | – | – | – | – | $1x10^5$ | $2x10^6$ | $6x10^5$ | **$2x10^7$** | + | + |
| **IgG3** | – | – | – | – | – | +* | – | – | – | + | – |
| **IgE** | – | – | – | **$1x10^9$** | mo: $5x10^6$ tri: $1x10^8$ | – | $2x10^4$ | $2x10^4$ | $3x10^5$ | – | – |
| **IgA** | $1x10^9$ | – | $3x10^8$ | – | – | – | – | – | – | – | – |
| **Major role** | Ig transport | Activation? Endocytosis , IgM regulation | Phago/ Endocytosis | Activation | IgE regulation | Activation | Inhibition | Activation: ITAMi-inhibition | Activation | IgG recycling; transport. Ag pres. | Activation; proteasome viral degradation |
| B cell | – | + | + | – | + | – | + | – | – | – | + |
| T cell | – | – | – | – | – | – | – | – | – | – | + |
| NK cell | – | – | – | – | – | – | – | + | – | – | + |
| Mono/MΦ | – | – | – | – | – | +/– | + | + | + | + | + |
| Neutrophil | – | – | – | –↯ | – | – | + | + | + | + | + |
| DC | – | – | –/FDC+ | –↯ | +/– | +/- | + | + | – | + | + |
| Basophil | – | – | – | + | – | – | + | + | – | ? | + |
| Mast cell | – | – | – | + | – | – | + | + | – | ? | + |
| Eosinophil | – | – | – | – | – | – | + | + | – | ? | + |
| Platelet | – | – | – | – | – | – | – | – | – | – | ? |
| Endothelium | – | – | – | – | – | – | – | – | – | + | +/– |
| Epithelium | + | – | – | – | – | – | – | – | – | +/– | ? |
| Yolk sac | ? | ? | ? | ? | ? | ? | ? | ? | ? | + | ? |

**Fig. 1. Mouse Fc receptors (FcRs)**. Schematic representations of mouse FcRs in respect to the cell membrane (gray bar), in complex with their respective signaling subunits, i.e. β, FcRβ subunit; $\gamma_2$, FcRγ subunit dimer; $\beta_2$m, β-2 microglobulin. ITAM, immunoreceptor tyrosine-based activation motif; ITIM, immunoreceptor tyrosine-based inhibitory motif. TRIM21 is a cytoplasmic molecule. Alleles are identified by the name of the polymorphic/allelic variant. *Upper part*: Binding affinities for the various immunoglobulin subclasses are given as $K_A$ ($M^{-1}$); +, binding but no affinity value has been reported; high-affinity interactions with monomeric Ig are indicated in bold; −, no binding. *: under debate (280, 281). '*Ag pres.*': antigen presentation. ↯: during infections (211, 282). NB: the affinities of the monomeric (mo) and trimeric (tri) state of FcεRII are indicated. *Lower part*: Expression patterns of FcRs are summarized as follows: +, expression; +/−, expression on a subpopulation; ?, unknown. LSEC, liver sinusoidal cell.

## Mouse FcR ligands

Mice express one 'strict' IgM receptor (mFcμR), two receptors for both IgM and IgA (mPolyIgR and mFcα/μR), two 'strict' IgE receptors (mFcεRI and mFcεRII/mCD23), three 'strict' IgG receptors (mFcγRI, mFcRn, and mTRIM21), and three IgG and IgE receptors (mFcγRIIB, mFcγRIII, and mFcγRIV) (1) (*Fig.* 1). The affinity of the latter dual-specific receptors for IgG and IgE is so much in favor of IgG binding (≈2 log higher affinity) that most consider and describe mFcγRIIB, mFcγRIII, and mFcγRIV as IgG receptors. Nevertheless, one should keep in mind that their interaction with IgE is sufficient to induce biological consequences (2, 3). All FcRs bind immunoglobulins on the surface of the cells expressing them, except mFcRn (4) and mTRIM21 (5) that bind immunoglobulins once internalized (TRIM21: reviewed in 6). The association constants ($K_A$) of these Ig–FcR interactions range over 6 logs, from $3 \times 10^{10}$ $M^{-1}$ to $2 \times 10^4$ $M^{-1}$ (*Fig.* 1). Polymorphisms of mouse FcRs have been described for mFcγRIIB (Ly17.1 and Ly17.2 allele) (7, 8) and mFcγRIII (V, T, H alleles) (9). In

addition, mFcγRIIB exists as three splice variants that differ in the composition of their intracytoplasmic domain, i.e. mFcγRIIB1, mFcγRIIB1′, and mFcγRIIB2 (10). Consequences on affinity or specificity for immunoglobulin binding have not been reported for these polymorphic or splice variants. Independent of their measured affinity, FcRs are characterized additionally as either 'low-affinity' receptors that can only bind immunoglobulins when multimeric (present in an immune complex, aggregated, or opsonized) and 'high-affinity' receptors that can also bind free/monomeric immunoglobulin. Receptors for pentameric IgM and/or dimeric IgA (i.e. polyIgR, FcαR, Fcα/μR) escape this classification. High-affinity FcRs in mice are thus mFcεRI for IgE, mFcγRI for IgG2a (but not IgG2b or IgG3), mFcγRIV for IgG2a and IgG2b (but not for IgE), and mFcRn for all IgG subclasses. Due to the high circulating levels of IgG in mouse serum (≈6 mg/mL), it is expected that the binding sites of high-affinity IgG receptors are constitutively saturated by IgG *in vivo*, at least on circulating cells: the concept, beliefs, and *in vivo* evidence of biological functions associated to these high-affinity FcRs are discussed in section 'The (mis)concepts on high-affinity IgG receptors: FcγRI and FcγRIV' in this review.

## Mouse FcR functions

All mouse FcRs can induce diverse biological functions following binding of their ligand, mostly when the ligand is in a multimeric state (in an immune complex, opsonized, or aggregated) but also in some instances when monomeric. FcRs are thus sub-classified as 'activating', 'inhibitory', or 'routing/transport' receptors. Activating mFcRs are associated to signaling subunits that contain an immunoreceptor tyrosine-based activation motif (ITAM), which consists of the mandatory FcRγ subunit (*Fig. 1*) and in addition in mast cells and basophils the FcRβ subunit, or in NK cells the CD3ζ chain. Note: mFcμR and mFcα/μR have not been reported to associate with signaling subunits. These ITAM-containing structures allow these receptors, once aggregated by immune complexes, to activate signaling cascades via SRC family kinases and spleen tyrosine kinase (SYK) leading to cell activation, cytokine/chemokine production and cell migration (11–13). The 'inhibitory' mFcR, mFcγRIIB, contains another motif termed immunoreceptor tyrosine-based inhibition motif (ITIM) in its intracytoplasmic domain (14). This ITIM allows this receptor, once co-aggregated to activating FcRs by a common ligand, to recruit the inositol polyphosphate-5-phosphatase SHIP1 (15) that counteracts the signals mediated by activating FcRs (16, 17). Some mFcRs like mTRIM21 and mFcεRII (mCD23) are devoid of both ITAM and ITIM but have been reported to induce cell activation or cell inhibition through other mechanisms (5, 18–21), respectively. mPolyIgR, mFcμR, mFcα/μR, mFcRn, and mTRIM21 are considered as 'routing/transport' FcRs as their (apparent) main function consists of internalizing (endocytosis or phagocytosis), intracellular routing, transcytosis (by polarized cells), or recycling of immunoglobulins. Notably, internalization of immunoglobulins is a common role for all mFcRs; the only exceptions being mFcRn and mTRIM21 that bind immunoglobulins once already pinocytosed or endocytosed by other receptors, and the mFcγRIIB1 variant that induces capping of immune complexes on the cell surface (10, 14). Internalization and routing of antibodies by FcRs represents an essential mechanism for antigen processing/presentation by the immune system, as antibody-bound antigen is not dissociated from antibodies during these processes. It follows indeed that processing and presentation of antibody-bound antigen is considerably more efficient by antigen-presenting cells than that of free antigen (22–27). Remarkably, the repertoire of antigenic epitopes presented following antigen–antibody internalization differ depending on the type of mFcR mediating the internalization: when mFcγRIIB is involved a restricted set of T-cell epitopes is presented compared to when mFcγRIII is involved after immune complex internalization, probably due to cell activation concomitantly triggered by the latter receptor through the FcRγ chain (28) and the SYK kinase (29). Internalization of antigen–antibody complexes have been recently reviewed elsewhere (30).

The ability of FcRs to induce biological functions following interaction with immunoglobulins (i.e. activation, inhibition, internalization, routing, transport) depend on the molecular state of the ligands, whether monomeric, present in an immune complex, or opsonizing cells, viruses, or bacteria. Not only does the state of immunoglobulins dictate whether a given FcR can bind these immunoglobulins (high- versus low-affinity FcR) but it also dictates the nature of the biological response. Monomeric immunoglobulins are bound by mFcεRI, mFcγRI, mFcγRIV, and mFcRn. Although binding of monomeric IgG by mFcγRI and mFcγRIV has not been reported to lead to biological functions, binding of monomeric IgE to mFcεRI induces prolonged mast cell survival (31), and monomeric binding of IgG to mFcRn induces protection of IgG from catabolism, IgG recycling, and transport of IgG to tissue (4). Adding to the complexity, interactions that cannot be defined as 'binding' of the

low-affinity receptor mFcγRIII with monomeric IgG have been reported to lead to modification of homeostasis and of thresholds of activation, referred to as 'inhibitory ITAM (ITAMi)' signaling: an activating FcR complex containing ITAMs inducing inhibition instead of inducing cell activation (32). Multimeric immunoglobulins, however, trigger activating FcRs to mediate intracellular signaling leading to a diversity of cellular responses including phagocytosis, cell differentiation, cell migration, degranulation, secretion of mediators, antibody-dependent cellular cytotoxicity (ADCC), or proteasome addressing. It seems that most FcRs are triggered following interaction with multimeric immunoglobulins, whether presented in an immune complex with a soluble antigen or opsonized on a cell surface, virus, or bacteria; the induced biological consequence may be different, but FcRs are triggered in all these cases. mTRIM21, however, appears to discriminate, and selectively binds to opsonized particles (e.g. opsonized viruses), but not to immune complexes made of soluble antigen and antibodies (18, 20).

### Mouse FcR expression patterns

The portfolio of biological functions of each mFcR complex relies by definition on their intracytoplasmic signaling motives or on the signaling subunits (if any) they associate to. Nevertheless, the nature of the cell expressing a given mFcR will determine a selection of biological activities among this portfolio. Lymphocytes, myeloid cells, and non-hematopoietic cells (endothelial cells, smooth muscle cells, etc.) can therefore express the same receptor that will not trigger the same biological activities in each of these cell types. The expression of the various mFcRs is strikingly different among hematopoietic cells (*Fig. 1*) (*Note*: for expression and functions outside the hematopoietic system, reviewed in 33) Among the various mFcR expression patterns, we would like to highlight those of mFcγRs that do not make a consensus in the field. The expression of mFcγRI appears restricted to mouse tissue macrophages and monocyte-derived dendritic cells (DCs): no expression of this receptor on circulating cells has indeed been identified by us and others (34–36). Other groups have reported low to barely detectable expression of mFcγRI on circulating monocytes (37–39), which do not, in our view, represent functional levels of expression (for *in vivo* activity of mFcγRI, please refer to section 'Mouse FcR knockout models' and section 'The (mis)concepts on high-affinity IgG receptors: FcγRI and FcγRIV'). Inhibitory mFcγRIIB is highly expressed on B cells, monocytes/macrophages, mast cells, basophils, dendritic cells, and eosinophils, low on neutrophils, and absent on T and NK cells. mFcγRIII is highly expressed on monocytes/macrophages, mast cells, neutrophils, basophils, dendritic cells, and eosinophils, low on NK cells, and absent on T cells. mFcγRIV is highly expressed only on $Ly6C^{lo}$ monocytes, macrophages, and neutrophils, and absent on other cells, in particular on $Ly6C^{hi}$ monocytes (39); its expression on dendritic cells remains controversial (40, 41). The expression of most FcRs is positively (IFNγ, LPS, IL-4) and negatively (TGFβ) regulated by cytokines (42), but an additional level of control has been reveled recently. Cytokine stimulation of mFcγRI-expressing cells has indeed been reported to increase the capacity of this receptor to bind IgG immune complex, independent of surface expression levels (43) and termed inside-out signaling (reviewed in 44).

### Mouse FcR knockout models

The contribution of mFcRs to antibody-induced disease models or antibody-mediated immunotherapy models has been extensively studied in the last 20 years using FcR-deficient mice (1). $FcR\gamma^{-/-}$ mice that genetically lack expression of the ITAM-bearing FcRγ subunit (45) were exploited first because of their lack of surface expression of mFcεRI, mFcγRI, mFcγRIII, and mFcγRIV. Single FcR knockouts were thereafter systematically reported for all known mouse FcRs to study the specific role of the 'classical' FcRs or of the new family members: $mFc\varepsilon RI^{-/-}$ (46), $mFc\varepsilon RII^{-/-}$ (47), $mFc\gamma RI^{-/-}$ (37, 38), $mFc\gamma RIIB^{-/-}$ (48), $mFc\gamma RIII^{-/-}$ (49, 50), $mFc\gamma RIV^{-/-}$ (51), $mFcRn^{-/-}$ (52), $mTRIM21^{-/-}$ (53, 54), $mPolyIgR^{-/-}$ (55), $mFc\mu R^{-/-}$ (56, 57), and $mFc\alpha/\mu R^{-/-}$ (58) mice.

### Models: advantages and limitations

The contribution of mFcRs to infection and inflammation models are summarized in *Table 1*, and to antibody-mediated immunotherapy models in *Table 2*. These non-exhaustive data summaries highlight the broad range of contributions that could already be identified for mFcRs to both disease and therapy models. It has to be noted, nevertheless, that single FcR deficiencies may affect the expression of other FcRs, and that the conclusions drawn from the use of these knockout models may require caution. For example, $mFc\gamma RIIB^{-/-}$ and $mFc\gamma RIII^{-/-}$ mice, but not $mFc\gamma RI^{-/-}$ mice, exhibit increased expression of mFcγRIV compared to wildtype (wt) mice (51, 59, 60). The deficiency in FcRγ abrogates not only

***Table 1.*** **FcR knockout phenotypes in infection and inflammation models**

| Pathology model | Mouse | Phenotype |
|---|---|---|
| Infection | FcγRI$^{-/-}$ | • Impaired clearance of pathogenic bacteria (38)<br>• Resistance to *E. coli* infection (203)<br>• Impaired helminth larvae trapping (204) |
| | FcγRIIB$^{-/-}$ | • Increased resistance to *Mycobacterium tuberculosis* infection (205)<br>• Increased resistance to malaria infection (206)<br>• Increased bacterial clearance (207) |
| | FcγRIII$^{-/-}$ | Impaired *E. Coli* phagocytosis and facilitation of inflammation (208) |
| | FcγRIV$^{-/-}$ | N.T. |
| | FcRn$^{-/-}$ | Reduced anti-*Borrelia burgdorferi* antibody response and subsequent induction of Lyme arthritis (209) |
| | TRIM21$^{-/-}$ | Impaired protection from fatal viral infection (210) |
| | FcεRI$^{-/-}$ | • Increased resistance to experimental cerebral malaria (211)<br>• Increased helminth-induced liver pathology (212) |
| | FcεRII$^{-/-}$ | N.T. |
| | polyIgR$^{-/-}$ | Reduced resistance to mycobacterial infections (213) and to protozoan parasite infection (214) |
| | FcμR$^{-/-}$ | • Susceptibility to *Listeria monocytogenes* infection (56)<br>• Resistance to LPS-induced shock (56) |
| | Fcα/μR$^{-/-}$ | N.T. |
| Inflammation | FcγRI$^{-/-}$ | • Reduced Arthus reaction (37) and reverse Arthus reaction (215)<br>• Reduced mBSA-induced arthritis (38, 216)<br>• Reduced Ab-induced anemia (194): *contradicted by* (217) |
| | FcγRIIB$^{-/-}$ | • Increased Arthus reaction (218, 219) and immune complex-induced alveolitis (220)<br>• Increased collagen-induced arthritis (221–223) and mBSA-induced arthritis (216, 224)<br>• Development of Goodpasture's syndrome upon type IV collagen immunization (225)<br>• Enables induction of arthritis by human autoantibodies from arthritic patients (226)<br>• Spontaneous development of glomerulonephritis on the C57BL/6 background (227)<br>• Increased anti-glomerular basement membrane antibody-induced glomerulonephritis (228)<br>• Resistance to anti-Fas antibody-induced hepatotoxicity (229)<br>• Increased susceptibility to experimental autoimmune encephalomyelitis (230) |
| | FcγRIII$^{-/-}$ | • Reduced reverse Arthus reaction (49, 215, 218, 219)<br>• Reduced K/BxN arthritis (75, 76) and collagen-induced arthritis (231)<br>• Reduced skin vasculitis (232)<br>• Reduced Ab-induced anemia (59, 194, 217, 219, 233, 234) and abrogated IgG1-induced liver erythrophagocytosis (234)<br>• Reduced atopic dermatitis (235) and airway inflammation (236) |
| | FcγRIV$^{-/-}$ | • Reduced K/BxN arthritis (51)<br>• Impaired experimental nephrotoxic nephritis (51) |
| | FcRn$^{-/-}$ | • Impaired K/BxN arthritis (34, 237)<br>• Impaired bullous pemphigoid, pemphigus foliaceus, and Pemphigus vulgaris (238)<br>• Reduced experimental epidermolysis bullosa acquisita (239)<br>• Increased Ab-dependent rejection of allograft (157) |
| | TRIM21$^{-/-}$ | Severe tissue inflammation and development of SLE following injury (54) |
| | FcεRI$^{-/-}$ | • Reduced atopic dermatitis (235)<br>• Reduced airway hyperresponsiveness after aerosolized antigen exposure (240)<br>• Reduced intestinal inflammation following oral-challenge with allergen (241)<br>• Reduced allergic rhinitis (242)<br>• Impaired TNBS-induced colitis (243) |
| | FcεRII$^{-/-}$ | • Induction of allergic airway hyperresponsiveness following antigen sensitization (244)<br>• Reduced severity of collagen-induced arthritis (245) |
| | polyIgR$^{-/-}$ | Altered commensal flora and higher susceptibility to DSS-induced colitis (246, 247) |
| | FcμR$^{-/-}$ | Altered tolerance (57) |
| | Fcα/μR$^{-/-}$ | N.T. |

N.T., not tested.

the expression of mFcγRI, mFcγRIII, mFcγRIV, and mFcεRI but also the expression of macrophage-inducible C-type lectin (Mincle) (60) and of the osteoclast-associated receptor (OSCAR) (62), and contributes to the signal transduction of several other molecules. The phenotypes observed in FcRγ$^{-/-}$ mice might thus be partially or completely attributed to molecules not related to FcRs, or even be a complex consequence of multiple alterations among FcR and non-FcR molecules. Thus, the results obtained using FcRγ$^{-/-}$ mice have purposely not been integrated in *Tables 1 and 2*. The recent generation of mFcγR$^{null}$ mice (i.e. mFcγRI/IIB/III/IV quadruple-knockout mice), obtained by intercrossing of mFcγRI$^{-/-}$ mice with mFcγRIIB/III/IV$^{-/-}$ mice by several groups [Ravetch group (63); Verbeek group (Leiden University Medical Center, The Netherlands) and our group (unpublished)] finally allows investigators to address the role of full mFcγR-deficiency without the biases introduced by the deficiency in the FcRγ-subunit.

***Table 2.*** **FcR knockout phenotypes in antibody-base therapy models**

| Model | Mouse | Phenotype |
|---|---|---|
| Antibody-based therapy | FcγRI$^{-/-}$ | • Reduced antitumor mAb therapy of liver and lung metastatic melanoma (66, 195, 248)<br>• Reduced anti-CD20 mAb lymphoma depletion (249) |
| | FcγRIIB$^{-/-}$ | • Increased mAb-induced antitumor therapy (133, 249, 250)<br>• Impaired anti-inflammatory effects of intravenous immunoglobulin (IVIG) (76, 251–253)<br>• Enables anti-CD44 therapy of experimental thrombocytopenia (250) |
| | FcγRIII$^{-/-}$ | • Reduced mAb-induced antitumor therapy (66, 254)<br>• Impaired anti-inflammatory effects of intravenous immunoglobulin (IVIG) (32, 255–257) |
| | FcγRIV$^{-/-}$ | Impaired mAb-induced antitumor therapy (51) |
| | TRIM21$^{-/-}$ | N.T. |
| | FcRn$^{-/-}$ | • Reduced anti-influenza mAb therapy (258) or anti-serum therapy of HSV-2 (259)<br>• Impaired IVIG therapy of autoimmune skin blistering disease (238) |
| | FcεRI$^{-/-}$ | Impaired vaccine effect by IgE-loaded tumor cells (170) |
| | FcεRII$^{-/-}$ | N.T. |
| | polyIgR$^{-/-}$ | Protection against Influenza virus following intranasal vaccination (260) |
| | FcμR$^{-/-}$ | N.T. |
| | Fcα/μR$^{-/-}$ | N.T. |

N.T., not tested.

### Unexpected/unappreciated functions of mFcRs *in vivo*

*In vivo* studies exploiting mFcR-deficient mouse models did not just validate biological functions attributed to these receptors following *in vitro* studies, they also revealed unexpected or unappreciated functions of mFcRs *in vivo*. mFcεRI, for example does not only contribute to allergy and hypersensitivity reactions but also to clearance of pathogenic bacteria and Helminth larvae (***Table 1***) and to IgE-mediated antitumor vaccination (***Table 2***). The biological functions of mFcRn, an intracellular IgG receptor, that were mainly perceived to reside in IgG recycling and protection from catabolism have been broadened considerably using mFcRn$^{-/-}$ mice (and $\beta_2$-microglobulin$^{-/-}$ mice that also lack expression of mFcRn): it contributes to the transport of IgG, and therefore also of IgG autoantibodies, to tissues enabling autoimmune diseases on one hand and allowing antibody therapy on the other hand (reviewed in 4). The other transporter, mPolyIgR, has been involved in protection from infections and stability of the commensal flora through IgA/IgM transport to mucosa and exploited in mucosal vaccination protocols. Studies using mice deficient in mFcγRI, the high-affinity IgG2a receptor, or mFcγRIV, the high-affinity IgG2a and IgG2b receptor, have demonstrated their (unexpected?) roles *in vivo*, in disease and therapy: mFcγRI contribute to IgG2a-induced models of type I and II hypersensitivity (systemic anaphylaxis and experimental autoimmune hemolytic anemia, respectively), to collagen-induced arthritis and to reversed passive Arthus reaction, and also to the anti-melanoma and -lymphoma activity of antibodies; FcγRIV contribute to experimental nephrotoxic nephritis and autoimmune arthritis, and also to the anti-melanoma activity of antibodies. Because mFcγRI and mFcγRIV bind monomeric IgG2a (and mFcγRIV binds monomeric IgG2b), these receptors should be theoretically occupied *in vivo* and thus unavailable to participate in immediate antibody-mediated reactions (for discussion on these aspects, refer to the section 'The (mis)concepts on high-affinity IgG receptors: FcγRI and FcγRIV'). mFcγRIIB$^{-/-}$ mice revealed mFcγRIIB as a major negative regulator of inflammatory and hypersensitivity reactions in several autoimmune, allergic, and inflammatory models (reviewed in 17), whereas mFcγRIII$^{-/-}$ mice revealed mFcγRIII as a major activating IgG receptor, contributing predominantly to several models including Arthus reaction, passive cutaneous anaphylaxis (PCA), passive systemic anaphylaxis, and arthritis (summarized in ***Table 1 and 2***). The *in vivo* roles of mTRIM21, mFcμR, and mFcα/μR using recently generated deficient mice remain scarce but will certainly broaden rapidly.

The availability of single FcR-deficient mice allowed intercrossing of these mice to generate multiple FcR-deficient mice for 'classical' IgG receptors, e.g. mFcγRI/III$^{-/-}$, mFcγRIIB/III$^{-/-}$, mFcγRI/IIB/III$^{-/-}$ (64), or mFcγRI/IIB/III/IV$^{-/-}$ (mFcγR$^{null}$) mice (63), and also for 'classical' IgG and IgE receptors and a transporter, e.g. mFcγRI/IIB/III mFcεRI/II mFcRn sextuple knockout mice (34). The generation of these multiple FcR knockout mice has enabled the study of a particular FcR in the absence of the other FcRs. mFcγRI/IIB/III-triple knockout (3KO) mice, lacking three of

the four mFcγRs, were indeed described to retain the ability to develop collagen-induced arthritis following immunization with bovine collagen type II in Freund's adjuvant (64). Because these mice express only mFcγRIV as an activating IgG receptor, it was deduced that mFcγRIV contributes to CIA. These mice, nevertheless, express mFcεRI that may also contribute to CIA, as immunizations in Freund's adjuvant lead to antigen-specific IgG and also IgE production (60). The generation of mFcγRI/IIB/III$^{-/-}$ FcεRI/II$^{-/-}$ mice that do not express mFcγRs or mFcεRs other than mFcγRIV (5KO a.k.a. 'mFcγRIV-only') circumvented this potential issue: mFcγRIV could by itself induce arthritic inflammation in the passive K/BxN model of arthritis (34, 65). 'mFcγRIV-only' mice also developed lung inflammation following activation of alveolar macrophages in the presence of IgE immune complexes (3), and experimental autoimmune thrombocytopenia (60). Finally, studies using mFcγRI/IIB/IIIA$^{-/-}$ mFcεRI/II$^{-/-}$ mFcRn$^{-/-}$-sextuple knockout mice demonstrated that mFcγRIV-dependent induction of arthritis requires mFcRn, probably to transport pathogenic IgG2a and IgG2b antibodies to the joints and to protect these antibodies from degradation (34). mFcγRI$^{only}$ mice, i.e. mFcγRIIB/III/IV$^{-/-}$ generated through a single deletion of the locus encoding the three receptors, revealed the contribution of mFcγRI to antitumor antibody therapy (66). These laborious intercrossing efforts will presumably not be pursued further (at least not by our group) due to the genetic proximity of the genes encoding mFcγRIIB (*Fcgr2b*), mFcγRIV (*Fcgr4*), and mFcγRIII (*Fcgr3*): generation of mFcγRI/IIB/IV$^{-/-}$ (mFcγRIII$^{only}$) or mFcγRI/III/IV$^{-/-}$ (mFcγRIIB$^{only}$) mice is therefore unlikely and all things considered, not particularly worth generating. Indeed, mFcγRIII is the only activating receptor for mouse IgG1, suggesting that mouse IgG1-mediated disease/therapy models can mimic this situation using wildtype or mFcγRIIB$^{-/-}$ mice. Similarly, mFcγRIIB$^{only}$ mice can be mimicked using mFcRγ$^{-/-}$ mice (that still express this inhibitory receptor) even though this latter mouse model has severe limitations (see above).

### Cell-specific mFcR effector functions

Linking the phenotype induced by a particular FcR deficiency to the contribution of a specific cell population still represents a challenge in the field. The effect of given mFcR deficiencies may be correlated from the phenotype found in models of pathology (*Table 1*) and therapy (*Table 2*), with consequences observed on the major roles expected to be played by these mFcRs on particular cells, like DCs and macrophages. Macrophages from mFcγRI$^{-/-}$ mice were indeed reported for reduced endocytosis of IgG immune complexes, ADCC, and antigen presentation after antigen–antibody complex internalization (37, 38). DCs from mFcγRI$^{-/-}$, mFcγRIII$^{-/-}$, or mFcRn$^{-/-}$ mice have also been reported for reduced antigen presentation after antigen–antibody complex internalization (38, 67). Inversely, DCs from mFcγRIIB$^{-/-}$ mice enabled to demonstrate that IgG immune complexes internalized by this inhibitory receptor are not degraded but recycled to the cell surface for presentation to B cells (68). DCs from FcRγ$^{-/-}$ mice (23) and from mFcRn$^{-/-}$ mice (69) have been reported to be impaired in maturation and cross-presentation of exogenous antigens on MHC class I molecules. Altogether, the roles identified for activating mFcRs in the ability of DCs and macrophages to internalize, process, and present antigen to T cells, correlates with most phenotypes found in infectious and inflammatory models (*Table 1*), whereas their roles in mediating ADCC by macrophages correlate with results obtained in mAb-induced therapy models (*Table 2*). The negative regulation of cell activation, DC maturation, and antigen presentation by mFcγRIIB correlates also well with the involvement of macrophages in inflammatory, infectious, or therapy models, and the involvement of DCs in pathology models that rely on the induction of an adaptive immune response (i.e. immunization, infection).

Linking the phenotype induced by a particular FcR deficiency to the contribution of a specific cell population has recently been possible by the generation of cell-specific FcR-deficient mice. Indeed, FcγRIIB-floxed mice (FcγRIIB$^{fl/fl}$) have been generated and crossed to mice expressing the Cre recombinase specifically in B cells (CD19Cre$^{+}$) or in myeloid cells (CEBPαCre$^{+}$) mice. The resulting mice allowed demonstrating that mFcγRIIB on myeloid cells, rather than on B cells, contributes to the protection against nephrotoxic nephritis (70) and against collagen-induced arthritis (71). These first reports certainly open the way to the detailed understanding on the role of mFcRs on specific cell types that requires, nevertheless, the generation of additional mFcR-floxed mice and considerable breeding efforts to Cre-specific mouse lines.

### Specific antibodies to block mFcRs *in vivo*?

The extensive use of mFcγR-deficient mice will certainly continue for the analysis of mFcγR contribution to disease and therapy models as *in vivo* blocking of mFcγRs meets two

serious limitations. First, only mFcγRIII and mFcγRIV can be efficiently blocked *in vivo* using specific blocking mAbs clone 275003 (34, 60) and clone 9E9 (40), respectively. No blocking antibody against mFcγRI has been described so far. Blocking antibodies against mFcγRIIB exist (7, 72) but their use *in vivo* has recently been proposed to be hindered by their rapid elimination by internalization after target binding (73) that could (in our view) be related to the expression of this receptor on liver sinusoidal endothelium, representing 75% of mFcγRIIB in the mouse (74). Results obtained using anti-mFcγRIII and anti-mFcγRIV blocking antibodies in wt mice have shown that mFcγRIII and mFcγRIV both contribute to autoimmune thrombocytopenia, autoimmune arthritis, and systemic anaphylaxis. Using a combination of anti-mFcγRIII and anti-mFcγRIV mAbs revealed that these receptors are, together, responsible for an autoimmune arthritis and for a systemic anaphylaxis model (34, 40, 60). As double knockout mFcγRIII/IV$^{-/-}$ mice do not exist, the use of this cocktail of antibodies has proven more informative than the use of single FcR knockouts, while in agreement with previous reports using mFcγRIII$^{-/-}$ and mFcγRIV$^{-/-}$ mice (51, 75, 76). If mFcγRI-specific blocking antibodies become available, the use of a set of specific blocking anti-FcγR mAbs in wt mice should certainly become the method of choice to study mFcγR properties *in vivo*.

### Human FcR-transgenic models

Considerable differences exist between mouse and human FcRs in terms of their expression, their affinity for ligands but also their existence in both species. Like mice, humans express a single IgM receptor (hFcμR), two receptors for both IgM and IgA (hPolyIgR and hFcα/μR/CD351), and two IgE receptors (hFcεRI and hFcεRII/CD23). Unique to humans is the expression of an IgA-specific receptor, hFcαRI/CD89. Additionally, 10 IgG-binding receptors were identified in humans. Among them, six are classical IgG receptors (hFcγRI/CD64, hFcγRIIA/CD32A, hFcγRIIB/CD32B, hFcγRIIC/CD32C, hFcγRIIIA/CD16A, and hFcγRIIIB/CD16B), complemented by the two FcR-like receptors, hFcRL4/CD307d and hFcRL5/CD307e, that are homologous to hFcγRI and contain one or more Ig superfamily domains, and hFcRn and hTRIM21. Interestingly, with the exception of hFcRL4 that binds both human IgA and human IgG4 (and hIgG3?; to be confirmed) (77), human IgG receptors bind to IgG, but no other class of immunoglobulins (*Fig.* 2).

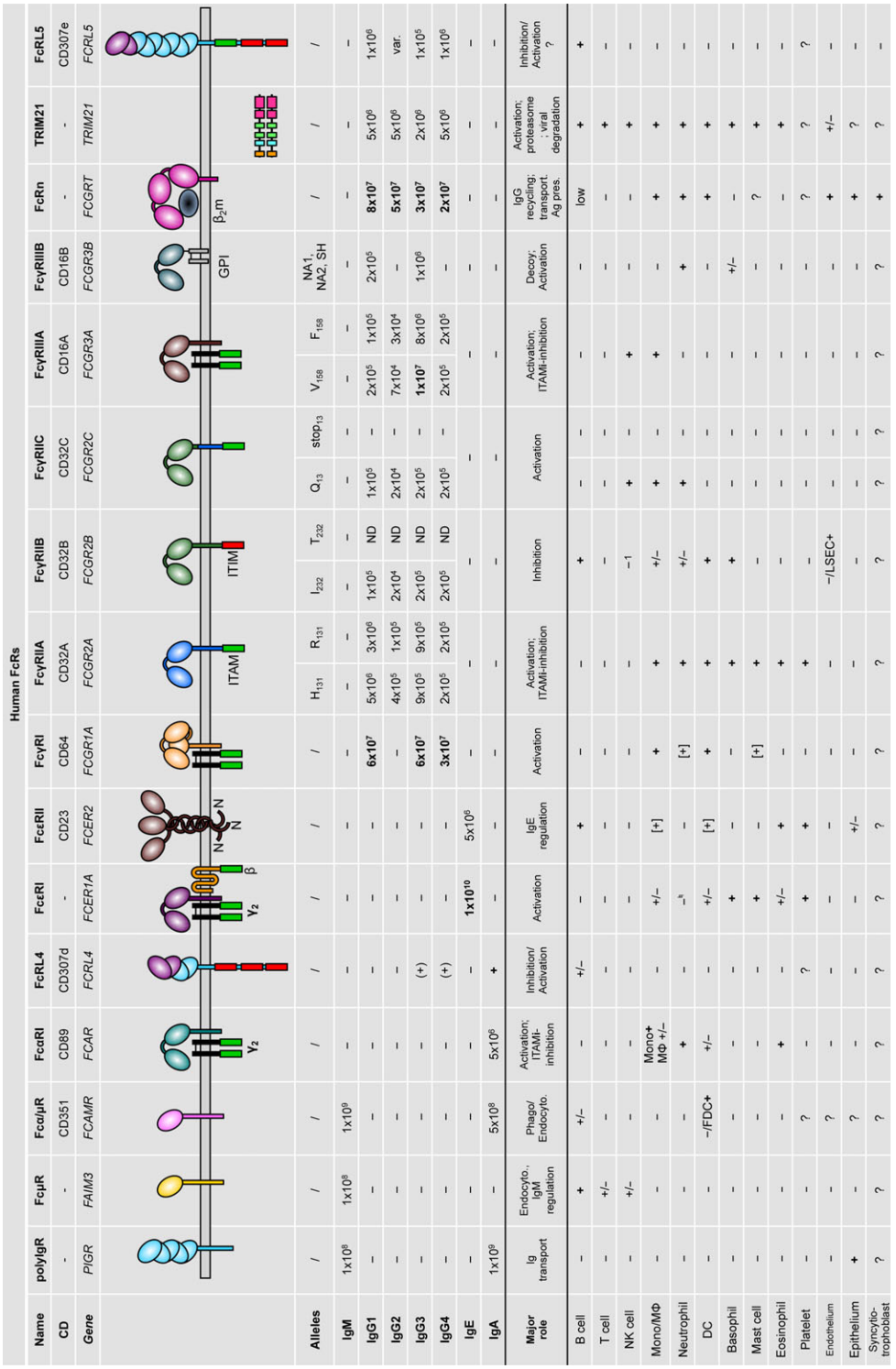
#### 'Non-classical' FcR expression – hFcRn, hPolyIgR, hTRIM21

Like in mice, hFcRn and hPolyIgR are transport or recycling receptors. hPolyIgR binds Ig at the basolateral surface of epithelial cells to transport Ig across the cell and secrete them at the apical surface (78). Similarly, expression of hFcRn allows vascular endothelial cells and intestinal epithelial cells to participate in IgG recycling, bidirectional IgG transport (from the circulation into the tissue and vice-versa), and allows placental syncytiotrophoblasts the passage of maternal IgG to the fetus (4). Besides its role in transporting and recycling IgG antibodies, hFcRn was also reported to transport IgG-bound antigens thus facilitating antigen presentation and subsequent immune responses (79) in dendritic cells, monocytes/macrophages (80), and neutrophils (81). hFcα/μR expression seems more restricted than its murine ortholog. It is hardly detectable on mononuclear cells in the blood, spleen, and bone marrow, but was identified on macrophages and follicular dendritic cells in tonsils and on macrophages in the lamina propria (82, 83), favoring the internalization of IgA and IgM and associated immune complexes (84). The intracellular receptor hTRIM21 is ubiquitously expressed, but it can be found increased or at the cell surface of epithelial cells and keratinocytes in autoimmune diseases (85). The expression of hFcRL4 and hFcRL5 is limited to B cells, with hFcRL5 being expressed on a variety of B-cell subsets (86) and hFcRL4 being restricted to a unique subset of tissue memory B cells (87, 88).

#### 'Classical' FcR expression – hFcαRs, hFcγRs, and hFcεRs

Until recently it was thought that biological functions of 'classical' IgG FcRs (hFcγRs) relied on their expression on hematopoietic cells, but several recent reports have challenged this notion (reviewed in 33). For instance, hFcγRI has been reported on sensory and motor neurons enabling the uptake of IgG from the surroundings and neurotransmitter release following hFcγRI triggering (89). hFcγRIIB is expressed on hippocampal neurons in healthy individuals, and its expression is increased in patients affected by Alzheimer's disease (90). hFcγRIIB is also highly expressed on liver endothelial sinuoid cells this expression has been linked to the clearance of small immune complexes from the circulation by the liver (74, 91).

Within the hematopoietic system hFcαRI, for which there is no mouse equivalent, is highly expressed on neutrophils and monocytes, but can also be detected on eosinophils,




| Name | polyIgR | FcμR | Fcα/μR | FcγRI | FcεRI | FcRL4 | FcεRII | FcγRI | FcγRIIA | | FcγRIIB | | FcγRIIC | | FcγRIIIA | | FcγRIIIB | FcRn | TRIM21 | FcRL5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CD | - | - | CD351 | CD89 | - | CD307d | CD23 | CD64 | CD32A | | CD32B | | CD32C | | CD16A | | CD16B | - | - | CD307e |
| Gene | *PIGR* | *FAIM3* | *FCAMR* | *FCAR* | *FCER1A* | *FCRL4* | *FCER2* | *FCGR1A* | *FCGR2A* | | *FCGR2B* | | *FCGR2C* | | *FCGR3A* | | *FCGR3B* | *FCGRT* | *TRIM21* | *FCRL5* |
| **Alleles** | / | / | / | / | / | / | / | / | $H_{131}$ | $R_{131}$ | $I_{232}$ | $T_{232}$ | $Q_{13}$ | $stop_{13}$ | $V_{158}$ | $F_{158}$ | NA1, NA2, SH | / | / | / |
| **IgM** | $1x10^8$ | $1x10^8$ | $1x10^9$ | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – |
| **IgG1** | – | – | – | – | – | – | – | **$6x10^7$** | $5x10^6$ | $3x10^6$ | $1x10^5$ | ND | $1x10^5$ | – | $2x10^5$ | $1x10^5$ | $2x10^5$ | **$8x10^7$** | $5x10^6$ | $1x10^6$ |
| **IgG2** | – | – | – | – | – | – | – | – | $4x10^5$ | $1x10^5$ | $2x10^4$ | ND | $2x10^4$ | – | $7x10^4$ | $3x10^4$ | – | **$5x10^7$** | $5x10^6$ | var. |
| **IgG3** | – | – | – | – | – | (+) | – | **$6x10^7$** | $9x10^5$ | $9x10^5$ | $2x10^5$ | ND | $2x10^5$ | – | **$1x10^7$** | $8x10^6$ | $1x10^6$ | **$3x10^7$** | $2x10^6$ | $1x10^5$ |
| **IgG4** | – | – | – | – | – | (+) | – | **$3x10^7$** | $2x10^5$ | $2x10^5$ | $2x10^5$ | ND | $2x10^5$ | – | $2x10^5$ | $2x10^5$ | – | **$2x10^7$** | $5x10^6$ | $1x10^6$ |
| **IgE** | – | – | – | – | – | – | **$1x10^{10}$** | $5x10^6$ | – | – | – | – | – | – | – | – | – | – | – | – |
| **IgA** | $1x10^9$ | – | $5x10^8$ | $5x10^6$ | + | + | – | – | – | – | – | – | – | – | – | – | – | – | – | – |
| **Major role** | Ig transport | Endocyto., IgM regulation | Phago/ Endocyto. | Activation: ITAMI-inhibition | Activation | Inhibition/ Activation | IgE regulation | Activation | Activation; ITAMI-inhibition | | Inhibition | | Activation | | Activation; ITAMI-inhibition | | Decoy; Activation | IgG recycling; transport. Ag pres. | Activation: proteasome ; viral degradation | Inhibition/ Activation ? |
| B cell | – | + | +/– | – | – | +/– | + | – | – | | + | | – | – | – | | – | low | + | + |
| T cell | – | +/– | – | – | – | – | – | – | – | | – | | – | – | – | | – | – | + | – |
| NK cell | – | +/– | – | – | – | – | – | – | – | | −1 | + | – | – | + | | – | – | + | – |
| Mono/MΦ | – | – | – | Mono+ MΦ +/– | +/– | – | [+] | + | + | | +/– | + | – | – | + | | – | + | + | – |
| Neutrophil | – | – | – | + | – | – | – | [+] | + | | +/– | + | – | – | – | | + | + | + | – |
| DC | – | – | –/FDC+ | +/– | – | +/– | [+] | + | + | | + | | – | – | – | | – | + | + | – |
| Basophil | – | – | – | – | – | + | – | – | + | | + | | – | – | – | | +/– | – | + | – |
| Mast cell | – | – | – | – | – | + | – | [+] | + | | – | | – | – | – | | – | ? | + | – |
| Eosinophil | – | – | – | + | – | +/– | + | – | + | | – | | – | – | – | | – | – | + | – |
| Platelet | – | – | ? | – | – | ? | + | – | + | | – | | – | – | – | | – | ? | ? | ? |
| Endothelium | – | – | ? | – | – | – | – | – | – | | –/LSEC+ | | – | – | – | | – | + | +/– | – |
| Epithelium | + | – | ? | – | – | – | +/– | – | – | | – | | – | – | – | | – | + | ? | – |
| Syncytio-trophoblast | ? | ? | ? | ? | ? | ? | ? | ? | ? | | ? | | ? | ? | ? | | ? | + | ? | – |

***Fig. 2.* Human Fc receptors (FcRs)**. Schematic representations of human FcRs in respect to the cell membrane (gray bar), in complex with their respective signaling subunits, i.e. β, FcεRIβ subunit; $\gamma_2$, FcεRIγ subunit dimer aka FcRγ; $\beta_2$m, β-2 microglobulin. ITAM, immunoreceptor tyrosine-based activation motif; ITIM, immunoreceptor tyrosine-based inhibitory motif. TRIM21 is a cytoplasmic molecule. Alleles are identified by the amino acid variant in the protein (e.g. $H_{131}$), or by the name of the allelic variant (NA1, NA2 or SH). *Upper part*: Binding affinities are indicated as $K_A$ ($M^{-1}$); high-affinity interactions with monomeric Ig are indicated in bold; +, binding but no affinity values available; −, no binding; (+) to be confirmed (77); ND, not determined. '*Ag pres.*': antigen presentation. *Lower part*: Expression patterns of FcRs are summarized as follows: +, expression; +/−, expression on a subpopulation; [+], inducible expression; ?, unknown. [1], detectable and functional expression in non-conventional *Fcgr2c*-Stop individuals (118) and on a rare subpopulation of $CD56^{dim}/FcγRII^{bright}$ NK cells (282). ♮: in asthmatic patients (283).

some macrophages, and dendritic cells (92, 93). hFcμR is predominantly expressed by adaptive immune cells, both B and T lymphocytes and, to a lesser extent, NK cells, but not by other hematopoietic cells (94, 95). hFcεRI expression in humans does not absolutely require the FcRβ subunit as in mouse and can therefore be found not only as an $\alpha\beta\gamma_2$ complex on mast cells and basophils but also as an $\alpha\gamma_2$ complex (96, 97) on eosinophils, dendritic cells, monocyte/macrophages, and platelets (98–101). hFcεRII/CD23 is predominantly expressed by B cells in healthy individuals; however, early reports suggested that hFcεRII may also be expressed by platelets (102), eosinophils (103), monocytes (104), dendritic cells (105), and some epithelial cells (106, 107). hFcεRII has important functions in the regulation of B-cell growth, their differentiation, and the production of IgE, and also in IgE-facilitated presentation of antigens to T cells and the bidirectional transport of IgE through epithelial cells (reviewed in 108). Opposing the barely detectable expression of mFcγRI in the mouse, hFcγRI in humans is constitutively expressed by monocytes/macrophages and some dendritic cells (109, 110) and inducibly expressed on neutrophils (111) and mast cells (112) under inflammatory conditions. hFcγRIIA is constitutively expressed on all myeloid cells (113, 114), including platelets (115), but is absent on lymphocytes. It is therefore the IgG receptor with the broadest expression on hematopoietic cells in humans. The inhibitory IgG receptor hFcγRIIB is expressed highly on B cells (116) and basophils and to a lesser extent on monocytes (117), tissue macrophages, and dendritic cells (116), but not on mast cells (114). No expression of hFcγRIIB can be found on NK cells, except in individuals carrying a rare deletion in the *FCGR2C–FCGR3B* locus allowing the expression of hFcγRIIB on NK cells (118). The expression of hFcγRIIC is restricted to NK cells (119), monocytes, and neutrophils (118) in individuals carrying the *FCGR2C*-ORF polymorphism that represent 20–25% of the population. The expression of hFcγRIIIA is restricted to NK cells and monocytes/macrophages. hFcγRIIIB is highly expressed only by neutrophils, but can be expressed at low levels by basophils (120).

### hFcR effector functions

In addition to their capacities to internalize, transport, and/or recycle antibodies and their bound antigens, human FcRs can further be subdivided into 'activating' or 'inhibitory' FcRs. Like mouse FcRs, activating human FcRs can be associated with an ITAM-containing signaling subunit (FcRβ, FcRγ), and inhibitory human FcRs can possess an ITIM in their intracytoplasmic domain. Unlike mouse FcRs, however, some activating human FcRs possess an ITAM in their intracytoplasmic domain (*Fig.* 2). Activating receptors in humans are thus (i) the FcεRIγ-chain-associated hFcεRI, hFcαRI, hFcγRI, and hFcγRIIIA, and (ii) the single chain hFcγRIIA, hFcγRIIC, and FcRL4 (121) that carry their own ITAM in their intracytoplasmic domains. Notably, despite the presence of an ITAM motif in the intracellular portion of FcRL5, no activatory signal was detected in a cross-ligation assay in human B cells (122); this may be explained by the presence of two ITIMs that may counteract/control the signals by the ITAM of FcRL5. In humans, indeed, two other FcRs than hFcγRIIB contain ITIMs and are therefore proposed to have inhibitory properties, namely, hFcRL4 and hFcRL5 (122, 123). Signaling cascades downstream of human FcR ITAM phosphorylation resemble in large parts the pathways described for mouse FcRs in section 'Mouse FcRs' and will therefore not be further discussed here.

Adding to the complexity, it has been recently described that triggering of hFcαRI or hFcγRIIA by monomeric Ig may result in a sub-optimal phosphorylation of the ITAM motif, termed ITAMi, resulting in the generation of inhibitory signal (13, 124, 125). The capacity of hFcRs to induce activating or inhibitory signals, seems however not exclusively determined by ITAM or ITIM motifs. Indeed, FcRs that lack both ITAM and ITIM may trigger cell activation (126, 127) by associating to other molecules capable of transmitting signals. Such an association has been described for hFcγRIIIB that interacts with integrins (128) and for hTRIM21 that can trigger cell activation by engaging the ubiquitination cascade and proteasomal degradation (5, 18–20, 129). Alternative splicing may also result in the generation of different isoforms of the same FcR that may thus possess different properties. For example, two different isoforms of hFcγRIIB exist in humans that differ in their antigen internalization and presentation properties (11): hFcγRIIB1 enables internalization but not antigenic epitope presentation (10) and hFcγRIIB2 enables both internalization and antigen presentation (25).

### Effector functions versus affinity for the ligand

The cellular response triggered by a given FcR not only depends on its expression and signaling capacities, but also depends on the ligand initiating the trigger. Several studies using surface plasmon resonance or flow cytometry on FcR-

expressing transfected cell lines (130–135) have helped to establish several different findings: (i) association constants ($K_A$) of Ig–FcR interactions range from 2 x $10^4$ $M^{-1}$ to 1 × $10^{10}$ $M^{-1}$. These observations are in agreement with the notion of 'high-' and 'low'-affinity FcRs: 'high-affinity' receptors can bind free/monomeric Ig and thus should be occupied *in vivo*; 'low-affinity' receptors can only bind Ig when present in an immune complex, aggregated, or opsonized. Low-affinity FcR are therefore expected to be unoccupied *in vivo* and available for Ig-dependent cellular reactions. *In vivo*, the high-affinity IgE receptor hFcεRI can indeed be 'sensitized' to a given antigen by injection of a specific IgE several hours before antigen challenge. These 'charged' hFcεRIs can then readily be aggregated by their specific antigen *in vivo* (136–140). The retention of antibodies by high-affinity hFcRs on specific cell types may be considered as a 'memory' that may last from hours to days following binding of the ligand, until recycling of the receptor or dissociation of the interaction. When it comes to high-affinity human IgG receptors, however, which should be similarly occupied by endogenous IgG *in vivo* and therefore unavailable for IgG-dependent reactions, this rule does not hold anymore (60, 141). This notion is thoroughly discussed in section 'The (mis)concepts on high-affinity IgG receptors: FcγRI and FcγRIV'.

The differences in the association or dissociation constants, or the abundance of the different immunoglobulin classes and subclasses, may account for different hFcR behavior *in vivo*. For instance, all human IgG receptors bind at least two IgG subclasses (1). Human IgG1 is bound by all IgG receptors with the exception of hFcRL4; IgG2 by all but hFcγRI, hFcγRIIIB, and hFcRL4; IgG3 by all IgG receptors (considering that IgG3 binding to hFcRL4 is confirmed); IgG4 by all but hFcγRIIIB (77, 135) (*Fig.* 2). The latter result has been a recent matter of debate as for a long time receptors for IgG4 remained elusive and as IgG4 was considered a neutral IgG isotype (142). This erroneous notion possibly accounts for the side effects observed using IgG4-based therapeutic antibodies: e.g. gemtuzumab (IgG4 anti-CD33) had to be withdrawn from the market (143), and TGN1412 (IgG4 anti-CD28) was ended following adverse events in the first trial. Unlike mouse FcRs, polymorphisms in the extracellular domain of hFcRs have been described that modify their affinity for ligands. In particular, polymorphisms of hFcγRIIA and hFcγRIIIA (1, 135) were reported to modify their capacity to trigger ADCC with important consequences for tumor immunotherapy (143–145), and also confers homozygous individuals with a greater susceptibility to develop certain autoimmune diseases (reviewed in 146).

### Existing models of hFcR-transgenic mice

Many important insights into human FcR biology have been obtained by analyzing hFcR-transgenic mice. In particular, these studies have highlighted the respective contributions of hFcRs, and the cells that express them, to antibody-mediated inflammatory and allergic diseases. Different transgenic mice expressing human FcRs under the control of their endogenous promoters have been developed throughout the past two decades: hFcεRI$^{tg}$ (147); hFcαRI$^{tg}$ (148, 149); hFcγRI$^{tg}$ (27), hFcγRIIA$^{tg}$ (150), hFcγRIIB$^{tg}$ (151), hFcγRIIIA$^{tg}$, and hFcγRIIIB$^{tg}$; (152) and hFcRn$^{tg}$ (52). Mice expressing hPolyIgR, hFcμR, hFcα/μR, hFcεRII, hFcRL4, hFcRL5, or hFcγRIIC have not yet been generated. Although hFcεRI$^{tg}$ and hFcγRIIA$^{tg}$ mice closely recapitulated human FcR expression, a number of transgenes did not reproduce the expected expression pattern once present in mice. For example, hFcαRI$^{tg}$ mice showed transgenic FcR expression on neutrophils as anticipated, but only on a subpopulation of monocytes (148). hFcαRI expression on macrophages isolated from the peritoneal cavity was absent under steady-state conditions, but could be induced following GM-CSF treatment (148, 153). hFcγRI on mouse neutrophils was found constitutively expressed in hFcγRI$^{tg}$ mice, whereas it is inducibly expressed on human neutrophils (154). Both hFcγRIIIA and hFcγRIIIB showed expression on spleen and circulating DCs, and hFcγRIIIA on eosinophils from hFcγRIIIA$^{tg}$ hFcγRIIIB$^{tg}$ mice (63). They are, however, not expressed on these cell populations in humans. Finally, hFcγRIIB$^{tg}$ mice display a significantly higher hFcγRIIB expression on mouse monocytes and granulocytes than on these cell types in humans (116).

While these transgenic mice helped to gain many important insights into the *in vivo* properties of human FcRs, conclusions on hFcR contribution to disease and therapy should be drawn with care. Indeed, analysis of results obtained in these mice is complicated by the fact that mouse immunoglobulins often cross-bind human receptors, possibly resulting in competition for IgG binding *in vivo* or in aggregation of receptors originating from different species. Furthermore, transgenic expression of a supplementary activating receptor in wt mice may unbalance the homeostasis of immune cell activation and inhibition and thus induce adverse reactions. This has been reported, e.g. in mice expressing the hFcγRIIA transgene on a wt background, which spontaneously develop an autoimmune phenotype

(155). To circumvent these difficulties, several studies have examined transgene function in mice deficient for various endogenous mouse FcRs. A relatively simple approach consists in the use of FcεRIγ$^{-/-}$ mice (FcRγ$^{-/-}$ mice; associated to various caveats: refer to section 'Models: advantages and limitations') that lack expression of endogenous activating FcRs (mFcεRI, mFcγRI, mFcγRIII, and mFcγRIV), in combination with transgenic expression of human FcRs that do not require the FcRγ subunit, such as hFcγRIIA (150). This approach is, however, restricted to the study of hFcγRIIA, hFcγRIIC, and hFcγRIIIB among hFcγRs, as hFcγRI, and hFcγRIIIA require the FcRγ subunit. Because FcRγ$^{-/-}$ mice still express endogenous mFcγRIIB, this background is not relevant for the expression of hFcγRIIB.

As an alternative, hFcRs were analyzed in mice in which the transgene replaced its mouse ortholog, e.g. hFcεRI was used to substitute for mFcεRI (147) and hFcRn for mFcRn (157). Furthermore, mice deficient for multiple mFcRs were generated by intercrossing single FcR knockouts for the study of hFcRs that may be in competition with endogenous mouse FcRs for ligand binding: mice deficient for mFcγRI/IIB/III were first reported (38), followed by mice deficient for mFcγRI/IIB/III and mFcεRI/II (3), and mice deficient for mFcγRI/IIB/III and mFcεRI/II and mFcRn (34). The role of hFcγRIIA (113, 158) or hFcγRI (141) in disease and therapy models could thus be described using these multiple deficient backgrounds. A disadvantage of these mice is that they still express mFcγRIV that might require blocking by specific blocking mAbs to address the role of the human transgene when IgG subclasses bind to both mFcγRIV and the human transgene. The generation of mice deficient for mFcγRI/IIB/III/IV, i.e. all mouse FcγRs, named mFcγR$^{null}$ (63) allows studying the properties of transgenically expressed hFcγRs without the interference of endogenous FcγRs, absence of FcRγ or usage of blocking mAbs.

To examine the role of hFcRs on a particular cell population or to overcome erroneous expression, specific promoter sequences were used to confer expression of the transgene to the cells of interest. To this aim, the CD11b promoter has been used to drive the expression of the hFcαRI transgene on neutrophils and monocytes/macrophages (149). Similarly, the human MRP8 promoter was used to generate mice that expressed hFcγRIIA and/or hFcγRIIIB exclusively on neutrophils and some monocytes (127). While this approach effectively permitted analysis of the effecter role of these hFcRs on the cells of interest, one has to keep in mind that expression levels and patterns might not accurately reflect human physiology. Other hFcγR-transgenic mice have been generated in later studies to evaluate the use of engineered antibody therapeutics to treat models of tumor (e.g. hFcγRIIIA (159)), allergy, and autoimmune pathologies [e.g. hFcγRIIB (160, 161)]. Finally, intercrossing of single transgenic mice together resulted in a mouse model expressing most hFcγRs, i.e. hFcγRI/IIA/IIB/IIIA/IIIB, but neither hFcγRIIC nor hFcRn (63).

### Understanding *in vivo* hFcR biology with the help of transgenic mice

The various human FcR-transgenic mice described above have been used in various disease and therapy models that are summarized in *Table* 3. Effector functions that could be identified are highlighted in this section.

*hFcRn$^{tg}$ mice*: confirming the important role of hFcRn as a transport and recycling receptor, hFcRn expression in FcRn$^{-/-}$ mice revealed that hFcRn prolongs the lifespan of human IgG (162) and albumin (52), enables capture and processing of luminal IgG-bound antigens favoring the adaptive immune response (79), and restores K/BxN arthritis in resistant mFcRn$^{-/-}$ mice (34).

*hFcαRI$^{tg}$ mice*: Two hFcαRI transgenic mouse strains have been generated that allowed to demonstrate that hFcαRI on neutrophils or Kupffer cells can trigger phagocytosis and ADCC. Although the FcRγ chain was required for receptor expression and the capacity of the receptor to trigger phagocytosis, complement receptor 3 (CR3) proved indispensable for hFcαRI-triggered ADCC and tumor cell killing (148, 163, 164). IgA-mediated antigen presentation was, however, inefficient in hFcαRI$^{tg}$ mice (165). Importantly, CD11b–hFcαRI$^{tg}$ mice were found to spontaneously develop nephropathy around 4 months of age that aggravated over time and was associated with mesangial IgA deposition, downregulation of hFcαRI, and the presence of circulating (IgA–soluble hFcαRI) complexes. Interestingly, both the transfer of serum-containing (IgA–soluble hFcαRI) complexes into RAG$^{-/-}$ mice as well as transfer of IgA from IgA nephropathy patients into CD11b–hFcαRI$^{tg}$–SCID mice were sufficient to trigger transient hematuria, mesangial IgA deposition and CD11b$^{+}$ cell infiltration in kidney glomeruli (149). Interestingly, induction of hFcαRI–ITAMi signaling in these mice could not only prevent renal inflammation but also other immunological and non-immunological disease models (166). To further elucidate the role of the IgA axis in nephropathy, CD11b–hFcαRI$^{tg}$ mice were crossed to mice producing human IgA to account for differences between IgA molecules in the two species, notably occurrence of O-glycosylation (167). These mice

***Table* 3. hFcR effector function identified using hFcR$^{tg}$ mouse models**

| Promoter | Expression | Strain | *In vivo* findings | Ref. |
|---|---|---|---|---|
| **CD89 (hFcαRI)** | | | | |
| hFcαRI | Neutrophils, subpopulation of monocytes, inducible on peritoneal macrophages Kupffer cells, DCs | C57 | hFcαRI allows IgA-dependent phagocytosis, ADCC | (148) |
| | | | hFcαRI bearing Kupffer cells phagocytose serum IgA-coated bacteria | (163) |
| | | | Inefficient antigen presentation via the IgA Fc receptor (FcαRI) on dendritic cells | (165) |
| CD11b | Neutrophils, monocytes/ macrophages | C57, SCID | hFcαRI contributes to IgA-dependent nephropathy | (149) |
| | | C57, Balb/c | FcαRI-ITAMi signaling prevents renal inflammation | (166) |
| | | αIKI mice | Transglutaminase is essential for IgA nephropathy development acting through IgA receptors | (167) |
| | | | Gluten component gliadin contributes to IgA nephropathy through induction of IgA1–shFcαRI complex formation | (168) |
| **hFcεRI** | | | | |
| hFcεRI | Mast cells, basophils, monocytes, DCs, Langerhans cells, eosinophils | mFcεRIα$^{-/-}$/C57B1/6 | hFcεRI is sufficient for IgE-PSA | (147) |
| | | mFcεRIα$^{-/-}$/Balb/c | Role of hFcεRI in antitumor IgE adjuvanticity | (170) |
| | | mFcεRIα$^{-/-}$/C57B1/6 | hFcεRI on cDCs and monocytes contributes to IgE clearance from the serum and rapid lysosomal degradation | (169) |
| **CD64 (hFcγRI)** | | | | |
| hCD64 | Monocytes, macrophages, DCs, neutrophils | FVB/N | hFcγRI triggered killing mediated via (bispecific) Abs (*in vitro*) | (171) |
| | | FVB/N | Immunization with an anti-hFcγRI mAb elicits enhanced Ab responses | (27) |
| | | FVB/N | hFcγRI-mediated binding and phagocytosis of opsonized RBC | (173) |
| | | Unknown | Antigen targeting to hFcγRI increased vaccination potency | (261) |
| | | FVB/N | Targeting of weak antigens to hFcγRI enhances immunogenicity | (262) |
| | | FVB/N | Anti-hFcγRI-Ricin A immunotoxin-mediated killing of skin macrophages resolves cutaneous inflammation | (263) |
| | | Wistar rats | Contribution of hFcγRI-expressing macrophages to arthritis | (264) |
| | | 5KO | hFcγRI is sufficient for K/BxN arthritis, thrombocytopenia, airway inflammation, and anaphylaxis (PSA and ASA) | (141) |
| **CD32A (hFcγRIIA)** | | | | |
| hCD32A | Monocytes, macrophages, neutrophils, eosinophils, basophils, mast cells, DCs, megakarocytes, platelets | C57BL/6 × SJL $F_1$ mice/FcRγ$^{-/-}$ | Immune thrombocytopenia can be induced via hFcγRIIA | (150) |
| | | FcγR$^{-/-}$ | Activating anti-platelet Abs induced thrombosis and shock in hFcγRIIA$^{tg}$/FcγR$^{-/-}$ mice | (176) |
| | | C57BL/J6 ± hPF4$^{tg}$ | Heparin-induced thrombocytopenia (HIT) depends on platelet activation via hFcγRIIA | (177) |
| | | C57BL/6 | hFcγRIIA$^{tg}$ mice show increased susceptibility to CIA and anti-collagen II mAb-induced arthritis | (155) |
| | | FcγR$^{-/-}$ | hFcγRIIA mediates experimental immune hemolytic anemia | (265) |
| | | C57BL/J6 ± hPF4$^{low}$hPF4$^{high}$ | Surface expression of PF4, but not heparin is required to induce hFcγRIIA$^{tg}$–dependent HIT | (178) |
| | | C57BL/6 × SJL $F_1$ | hFcγRIIA-dependent platelet activation by Bevacizumab IC | (179) |
| | | C57BL/6 × SJL $F_1$ | Small chemical entities inhibit CIA | (174) |
| | | C57BL/6 × SJL $F_1$ | hFcγRIIA-dependent platelet activation by CD40L IC | (180) |
| | | B6.SJL | hFcγRIIA$^{tg}$ mice are more sensitive to autoimmune arthritis | (266) |
| | | C57BL/6 | CalDAG-GEFI: a therapeutic target to inhibit thrombosis and thrombocytopenia acting on hFcγRIIA signaling pathway | (267) |
| | | FcγR$^{-/-}$, 3KO, 5KO | hFcγRIIA is sufficient for anaphylaxis, airway inflammation and PCA | (113) |
| | | C57BL/6J | hFcγRIIA cooperates with integrin signaling in platelets | (185) |
| | | FcγR$^{-/-}$ Nude | hFcγRIIA contributes to mAb-induced tumor reduction | (158) |
| | | FcRγ$^{-/-}$, C57BL/6J | hFcγRIIA ITAMi signaling to ameliorate arthritis | (125) |
| | | C57BL/6J | Platelet activation by influenza virus containing IC via hFcγRIIA | (181) |
| | | C57BL/6J | Platelet activation by bacteria through hFcγRIIA | (182) |

**Table 3.** (continued)

| Promoter | Expression | Strain | *In vivo* findings | Ref. |
|---|---|---|---|---|
| hMRP8 | Neutrophils, some monocytes | FcγR$^{-/-}$ | hFcγRIIA is sufficient for NTS nephritis and cutaneous RPA reaction, promotes neutrophil recruitment and tissue injury | (127) |
| | | FcγR$^{-/-}$ | hFcγRIIA on neutrophils is sufficient for K/BxN arthritis, cooperation with C5aR | (183) |
| | | FcγR$^{-/-}$ | hFcγRIIA mediates internalization of soluble IC and NETosis in RPA reaction | (184) |
| **CD32B (hFcγRIIB)** | | | | |
| hCD32B | B cells, splenic CD11c DCs, monocytes, neutrophils, eosinophils | C57Bl/6 | Ab-mediated coengagement of hFcγRIIB and CD19 suppresses humoral immunity in systemic lupus erythematosus | (160) |
| | | FcγR$^{-/-}$ or FcγRIIB$^{-/-}$ mice | Immunostimulatory and antitumor activity of chimeric mouse–human agonistic anti-CD40 Abs can be enhanced by hFcγRIIB | (151) |
| | | FcRα null | Confirmed hFcγRIIB-dependent vaccination in FcγR humanized mice | (63) |
| | | CD40$^{-/-}$ | Antitumor activity of agonistic anti-TNFR Abs requires differential hFcγRIIB coengagement | (186) |
| **CD16A (hFcγRIIIA)** | | | | |
| hCD16A | NK cells, macrophages | (C57B1/6 × CBA/CA) Fl | Promoter/Expression analysis | (152) |
| Unknown | NK cells and Unknown | SCID | Glycoengineering of a humanized anti-EGFR Ab leads to enhanced ADCC through hFcγRIIIA | (159) |
| **CD16B (hFcγRIIIB)** | | | | |
| hCD16B | Neutrophils | (C57B1/6 × CBA/CA) Fl | Promoter/Expression analysis | (152) |
| hMRP8 | Neutrophils, some monocytes | FcγR$^{-/-}$ | hFcγRIIIB is sufficient for NTS nephritis, cutaneous RPA reaction and promotes neutrophil recruitment | (127) |
| | | FcγR$^{-/-}$ | hFcγRIIIB mediates neutrophil tethering to intravascular IC and their uptake | (184) |
| **CD32A (hFcγRIIA) + CD16B (hFcγRIIIB)** | | | | |
| hMRP8 | Neutrophils, some monocytes | FcγR$^{-/-}$ | hFcγRIIA and hFcγRIIIB cooperate to induce NTS nephritis, cutaneous RPA reaction | (127) |
| **Multiple hFcγR-humanized mice** | | | | |
| Respective human promoters | Refer to single transgenes | FcRα null | Normal development of immune system, FcγR-mediated cytotoxic functions, ADCC, IC-mediated anaphylaxis | (63) |
| | | | Human IgG Fc–FcγR interactions contribute to antitoxin neutralizing antibody activity | (190) |
| | | | Ab Fc-engineering augments protection from lethal influenza in FcγR-humanized mice | (191) |
| | | | The *in vivo* protective activity of anti-HIV-1 bNAbs is dependent upon hFcγR engagement | (192) |
| | | | Antitumor human (h)IgG1 must engage hFcγRIIIA on macrophages to mediate ADCC, but also engage hFcγRIIA, on dendritic cells (DCs) to generate a potent vaccinal effect | (189) |
| **hFcRn** | | | | |
| hFcRn | Intestine + Unknown | mFcRn$^{-/-}$ | hFcRn expression restores serum half-life of hIgG in mFcRn$^{-/-}$ mice | (157) |
| | | mFcRn$^{-/-}$; mFcRn$^{-/-}$FcγRIIB$^{-/-}$ | hIgG with engineered high hFcRn binding affinity has enhanced half-life *in vivo*; inhibition of the binding of pathogenic Abs to hFcRn ameliorates arthritis | (162) |
| | | mFcRn$^{-/-}$ mβ2 m$^{-/-}$ hFcRn$^{tg}$ hβ2m$^{tg}$ | Blocking hFcRn using a peptide antagonist increases hIgG catabolism | (268) |
| | | 6KO | hFcRn restores arthritis susceptibility in 6KO mice | (34) |

showed that gluten may exacerbate IgA nephropathy by inducing a mucosal immune response leading to the presence of circulation complexes formed of human IgA, soluble hFcαRI, IgG, and gluten component gliadin (168).

*hFcεRI$^{tg}$ mice* on a mFcεRI$^{-/-}$ background have been used to demonstrate that hFcεRI is sufficient to trigger IgE-dependent passive systemic anaphylaxis (147). These mice also allowed to show that hFcεRI on conventional dendritic cells

and monocytes plays an important role in IgE serum clearance by capturing circulating IgE and trafficking it to the lysosomal compartment (169). Nigro et al. (170) also described an antitumor IgE-adjuvant model that was mediated by the hFcεRI transgene following injection of human IgE (similar data were obtained with mFcεRI following mouse IgE injection) (170).

*hFcγRI mice*: hFcγRI expressed on murine macrophages retains its properties to bind monomeric human IgG (being a high-affinity IgG receptor) and is capable of mediating phagocytosis and internalization of IgG-immune complexes *in vitro* (27). *In vivo* targeting of antigen to hFcγRI by vaccination of transgenic mice induced a strong antibody response (27), and hFcγRI on dendritic cells was found to enhance antigen cross-presentation and T-cell activation (110). hFcγRI was also found capable of mediating ADCC *in vivo* (141, 171), of contributing to IgG-dependent protection against malaria infection (172), and of contributing to clearance of antibody-opsonized red blood cells (173) or platelets (141). Furthermore, using these transgenic mice, we documented that hFcγRI could trigger diverse models of allergic and autoimmune diseases such as anaphylaxis, rheumatoid arthritis, or airway inflammation (141).

*hFcγRIIA*$^{tg}$ FcR$\gamma^{-/-}$ mice have revealed that the expression of hFcγRIIA was sufficient to restore IgG-dependent experimental autoimmune thrombocytopenia (150), rheumatoid arthritis (174), airway inflammation, and allergic reactions (113) in resistant mice. These data confirmed, indeed, the previous reports in wt mice expressing the hFcγRIIA transgene in models of thrombocytopenia, and rheumatoid arthritis (150, 155). A large body of work has been performed in order to understand the role of hFcγRIIA on platelets. Indeed, hFcγRIIA is the only activating FcγR expressed on human platelets, and mouse platelets do not express any FcR (reviewed in 156). hFcγRIIA$^{tg}$ mice are therefore an invaluable tool to assess the function of this receptor on platelets. hFcγRIIA on platelets allows the binding and endocytosis of immune complexes, suggesting an important role for human platelets in the clearance of soluble immune complexes (175). Antibodies binding to platelet antigens were described to either induce platelet immune clearance by hFcγRIIA-bearing phagocytic cells, or to trigger thrombocytopenia together with platelet activation and consequently thrombotic events when the opsonizing IgG Fc portion engages hFcγRIIA directly on the platelets themselves (150, 176–180). Along the same line it has been recently reported that influenza virus and bacteria may activate platelets via hFcγRIIA possibly accounting for clinical complications in severe cases (181, 182).

But not only platelet-expressed hFcγRIIA contributes to IgG-dependent responses *in vivo*: the Mayadas group further showed that MRP8-driven hFcγRIIA$^{tg}$ expression or hFcγRIIA$^{tg}$ expression on transferred human neutrophils was sufficient to restore autoantibody-induced arthritis, glomerulonephritis, and reverse passive Arthus reaction in resistant mice (127, 183), suggesting that hFcγR expression on neutrophils is critical for the induction of these autoimmune diseases. Correspondingly, hFcγRIIA was found to be capable of mediating IC internalization, to promote neutrophil and mast cell activation *in vitro* (113, 127) and the formation of neutrophil extracellular traps *in vivo* (184). Interestingly, work from the Monteiro group provided evidence supporting an ITAMi signaling (refer to section 'Mouse FcRs') *via* hFcγRIIA in a model of rheumatoid arthritis and suggested it as a therapeutic approach to ameliorate antibody-dependent autoimmune disease progression (125). Finally, we could recently demonstrate that human hFcγRIIA contributes to mAb-induced tumor immunotherapy (158).

This transgenic approach to mouse models of disease also led to greater appreciation of the interplay between different receptors and their signaling pathways. Cooperation between the platelet adhesion receptor αIIbβ3 and hFcγRIIA expressed on murine platelets was found to promote thrombus formation in both *in vitro* and *in vivo* models of vascular injury, demonstrating that hFcγRIIA is an important adapter molecule for integrin signaling (185). Similarly, cross-talk between hFcγRIIA and complement receptor C5aR was found to regulate neutrophil recruitment and joint injury in K/BxN serum-induced arthritis, as C5aR antagonists attenuated inflammation only in hFcγRIIA-expressing mice and not in FcR$\gamma^{-/-}$ or wt mice (183).

*hFcγRIIB*$^{tg}$ *mice*: Engagement of the inhibitory receptor hFcγRIIB provides attractive possibilities to reduce inflammatory and autoimmune conditions using immunotherapies. Indeed, an anti-human CD19 IgG1 antibody, engineered to interact with a higher affinity with hFcγRIIB ($S_{267}E/L_{328}F$ mutation in the IgG1 Fc domain; refer to section 'IgG mutations that affect IgG-FcγR interactions') suppressed cytokine-induced B-cell proliferation and humoral immunity in engrafted mice, reduced serum antibody levels, and promoted survival in mice engrafted with SLE patient-derived cells (160). Although this IgG1 mutant not only affects binding by hFcγRIIB but also by other hFcγRs (*Table* 5), it was nevertheless tested in a mouse model expressing only hFcγRIIB. That this mutation results in a predominant

engagement of hFcγRIIB has been reported by the Ravetch group in mice expressing activating and inhibitory hFcγRs (63). Finally, the hFcγRIIB transgenic mouse was used to demonstrate that immunostimulatory and antitumor activities of engineered agonistic αCD40 or anti-TNFR antibodies can be mediated by hFcγRIIB in an antibody-dependent manner (151, 186).

*hFcγRIIIA$^{tg}$ mice*: Although two different hFcγIIIA$^{tg}$ mouse lines have been generated (152, 159), most studies have examined how human FcγRIIIA may mediate the antitumor efficacy of therapeutic antibodies *in vitro* or in xenograft models; these findings have been reviewed elsewhere and will not be discussed further here (187, 188). The only functional study using hFcγIIIA$^{tg}$ mice demonstrated that a glyco-engineered anti-EGFR antibody with a higher affinity for CD16/hFcγRIII triggered more efficiently ADCC and had a superior efficacy against different tumors *in vivo* than the original antibody (159).

*hFcγRIIIB$^{tg}$ mice*: hFcγRIIIB expressed under the control of the MRP8 promoter on neutrophils and monocytes is sufficient to restore multiple Ig-dependent cellular functions and susceptibility to multiple models of antibody-mediated inflammation in FcRγ$^{-/-}$ mice. In a model of progressive nephrotoxic serum nephritis, hFcγRIIIB$^{tg}$ mice displayed glomerular neutrophil accumulation, however, in the absence of secondary macrophage recruitment or renal injury. Similarly, reverse passive Arthus reaction resulted in neutrophil accumulation in the skin albeit without a significant edema formation. Expression of hFcγRIIIB in addition to hFcγRIIA further exacerbated disease symptoms observed hFcγRIIA$^{tg}$/FcRγ$^{-/-}$ mice (127). Contrary to hFcγRIIA, hFcγRIIIB did not support neutrophil recruitment in response to soluble immune complexes as slow rolling and adhesion was not observed in hFcγRIIIB$^{tg}$/FcRγ$^{-/-}$ mice. When immune complexes were, however, deposited within the vasculature, hFcγRIIIB was found to promote neutrophil slow rolling and adhesion to the vessel wall in a Mac-1-dependent process and to mediate immune complexes internalization (184).

*Multiple hFcR$^{tg}$ mice*: Last but not least, a novel mouse model has been generated by intercrossing various transgenic mice (namely hFcγRI$^{tg}$/IIA$^{tg}$/IIB$^{tg}$/IIIA$^{tg}$/IIIB$^{tg}$) to mice that lack all classical endogenous IgG receptors (mFcγR$^{null}$) with the aim to recapitulate the complexity of the hFcγRs system and make it accessible for *in vivo* analysis. In these mice, activating hFcγRs mediate cytotoxic effector functions as anticipated and could be used to assess the effect of engineered mAbs in cell depletion assays and mAb-dependent cancer immunotherapy (63, 189). In the same mice, intravenous administration of heat-aggregated IgG triggered anaphylaxis, and coengagement of hFcγRIIB was shown to augment immunization/vaccination efficacy (63). Furthermore, these mice were used to underline the possibility to enhance antibody–hFcγR interactions to augment antibody-mediated toxin neutralization (190), protection during lethal influenza challenge (191) or in an HIV-1 mouse model (192), and tumor immunotherapy (189).

## The (mis)concepts on high-affinity IgG receptors: FcγRI and FcγRIV

*Take-home message*: High-affinity IgG receptors hFcγRI, mFcγRI, and mFcγRIV do participate to antibody-mediated biological reactions *in vivo* that are constrained rather by the expression pattern of these receptors than their high-affinity interaction with circulating IgG.

### High-affinity FcR–monomeric Ig interactions

Historically, FcRs had been discriminated among 'low-affinity' receptors that can only bind Ig when present in an immune complex, aggregated, or opsonized, and 'high-affinity' receptors that can also bind free or monomeric Ig. In humans and mice, the definition of high-affinity IgE receptor applies to hFcεRI and mFcεRI, and of high-affinity IgG receptor to hFcγRI, mFcγRI, and mFcγRIV, and—at acidic pH—to hFcRn and mFcRn. The receptors for divalent or polymeric Ig, i.e. PolyIgR, FcμR, and Fcα/μR, are by definition excluded from this terminology. It is important to understand, when considering FcRs, that the classical definition of high-affinity FcR applies to any receptor able to bind monomeric Ig in assays based on flow cytometry or ELISA that involve washing steps; a surface plasmon resonance experiment will not enable to conclude on this ability. The main issue for the field is that no distinction is made between a high-affinity receptor binding and retaining a ligand for a few minutes compared to a high-affinity receptor binding and retaining a ligand for days/weeks; the potential of contribution by those two types of receptors to antibody-mediated biological reactions is consequently extremely different. The comparison of high-affinity FcR for IgE and IgG is a textbook example of this issue. The human high-affinity IgE receptor hFcεRI binds monomeric human IgE with an affinity of $K_A \approx 9 \times 10^9\ M^{-1}$ corresponding to an association constant of $\approx 9 \times 10^4\ M^{-1}$ and a dissociation constant of $k_{off} \approx 1 \times 10^{-5}\ s^{-1}$, leading to a half-life of the interaction of $t_{1/2} > 19$ h (96). The human high-

affinity IgG receptor hFcγRI binds monomeric human IgG1 with an affinity of $K_A \approx 2.5 \times 10^7\ M^{-1}$ corresponding to an association constant of $k_{on} \approx 3.5 \times 10^4\ M^{-1}$ and a dissociation constant of $k_{off} \approx 1 \times 10^{-3}\ s^{-1}$ ($t_{1/2} \approx 3.6$ min) (141). Similarly, the mouse high-affinity IgG2a receptor mFcγRI binds monomeric mouse IgG2a with an affinity of $K_A \approx 2 \times 10^7\ M^{-1}$ (193) and a half-life of $t_{1/2} \approx 2.6$ min. Finally, the mouse high-affinity IgG2a/2b receptor mFcγRIV binds monomeric mouse IgG2a and IgG2b with an affinity of $K_A = 2.9 \times 10^7\ M^{-1}$ and $1.7 \times 10^7\ M^{-1}$, respectively (40) and half-lives of $3 < t_{1/2} < 10$ min (3). In summary, high-affinity IgE receptors bind IgE with approximately 400 times higher affinity and longer half-life than high-affinity IgG receptors bind IgG. Both receptor types are nevertheless included in the same category, i.e. high-affinity FcRs.

### High-affinity FcRs: *in vivo* occupancy/saturation?

It follows that biologically, a high-affinity IgE receptor is to be considered occupied/saturated *in vivo* for a period of approximately one day, whereas IgG receptor are only occupied/saturated for a period of 2–3 min only. This concept fits well with experimental practices for the induction of passive systemic anaphylaxis that occurs within minutes of allergen injection. Indeed, allergen-specific IgE is injected 24 h before allergen challenge in wt mice to enable sensitization of mFcεRI-expressing mast cells and basophils; the closer the time of injection to the time of challenge, the weaker the reaction. This delay is not necessary for IgG-induced passive systemic anaphylaxis in which preformed immune complexes can be injected to trigger mFcγRIV within minutes (60). Of note, our recent studies indicate that two/threefold higher concentrations of IgG2a/b antibodies (1–2 mg/mouse) are required for a significant contribution of the high-affinity IgG2a/b receptor mFcγRIV to be detected during passive systemic anaphylaxis compared to the concentrations required for that of the low-affinity IgG2a/b receptor mFcγRIII to be detected (300–500 μg/mouse) (H. Beutier, C. Gillis, B. Iannascoli, O. Godon, N. Van Rooijen, D.A. Mancardi, P. Bruhns, F. Jönsson, under review). Thus, a rapid *in vivo* triggering of mFcγRIV is possible but appears nevertheless restricted to conditions in which free IgG2a/b antibodies are present in amounts that enable favorable competition with prebound or free endogenous IgG2a/b immunoglobulins. These conditions appear critical in the circulation rather than in tissues, in which the local IgG concentration is lower. It follows that mFcγRIII is predominantly contributing to IgG-induced immediate hypersensitivity reactions, but it nevertheless allows mFcγRIV to contribute significantly to other *in vivo* reactions, e.g. IgG2b-induced autoimmune thrombocytopenia (40), or with mFcγRIII to autoimmune hemolytic anemia (194) and autoimmune arthritis (34, 51). Interestingly, most antibody-mediated disease models to which mFcγRIV has been reported to contribute significantly rely rather on tissue macrophages than on circulating cells (neutrophils or monocytes), reinforcing the notion that competition by endogenous IgG restricts but does not prevent its ability to be triggered *in vivo*.

When considering the affinity of mFcγRI for mouse IgG2a and the seric concentration of this immunoglobulin, Unkeless & Eisen (193) proposed in 1975 already that mFcγRI are 'probably saturated *in vivo*', which is a notion that is repeatedly found in most reviews and articles on FcγRs since. However, the same authors concluded in the same study that 'While the IgG2a/Fc complex is relatively stable, the half time for dissociation is still fairly rapid (2.6 min at 37°C). This suggests that under physiological conditions the macrophage surface is in a dynamic steady state, binding and releasing IgG2a molecules rapidly enough to allow the cell's antigen-binding capabilities to mirror the specificities of free IgG2a molecules in the cell's immediate microenvironment.' We fully agree with this statement and consider all IgG receptors, whether of low or high affinity, from humans or mice, able to interact within minutes with IgG-immune complexes (or opsonized cells) *in vivo*. A bias in the interpretation of the relatively poor role of mFcγRI in disease models in mice finds, in our view, its roots in the restricted pattern of expression of this receptor, i.e. some tissue resident macrophages and monocytes-derived dendritic cells, but not on inflammation-related effector population (e.g. neutrophils and monocytes). This restricted expression patterns does not enable mFcγRI to induce by itself autoimmune arthritis (K/BxN model) or passive or active systemic anaphylaxis as we demonstrated using $mFc\gamma RI^{only}$ mice (C. Gillis, personal communication). It nevertheless enables mFcγRI to contribute to tissue-based reactions, particularly involving Kupffer cells in the liver: reversed passive Arthus reaction (37), rheumatoid arthritis (38), autoimmune thrombocytopenia (C. Gillis, personal communication), and antibody-mediated antitumor therapy in liver and lung (66, 195). The notion that the contribution of a high-affinity IgG receptor is restricted rather by its expression pattern than its occupancy by monomeric IgG *in vivo* is supported by the broader abilities found for hFcγRI, whose expression extends to circulating monocytes and

primed/activated/inflammatory neutrophils, to induce by itself models of systemic anaphylaxis, autoimmune arthritis, autoimmune thrombocytopenia, lung inflammation, and tumor immunotherapy (141). Finally, cytokine-induced regulation of the binding of mFcγRI to IgG has been reported: mFcγRI, saturated with prebound IgG, was indeed found capable of effective immune complex binding upon cytokine stimulation (43). This cytokine-induced enhancing effect rather applies to IgG-containing immune complex binding but not to monomeric IgG, as discussed in (196). The relative contribution of cytokine-induced effects and duration of IgG–FcR interactions has not yet been addressed, but provide together ample support for claiming effector functions for high-affinity IgG receptors *in vivo*. Thus, similar to mFcγRIV, mFcγRI and hFcγRI can participate to biological reactions *in vivo* that are, in our view, constrained rather by their expression pattern than their high-affinity interaction with IgG. One may even propose that the half-life of the Ig–FcR interaction represents a measure of the delay between the *in vivo* binding to a given FcR or its triggering following injection of exogenous ligands (*Table* 4).

### Unhelpful terminology?

In conclusion, the 'high-affinity' and 'low-affinity' terminology appears unhelpful on one hand as it influences non-experts to believe that immediate reactions cannot occur through high-affinity FcRs, but helpful on the other hand as it allows to integrate the notion of competition with endogenous monomeric Ig when inducing disease or therapy by exogenous addition of antibodies. The notion of 'moderate-affinity' receptors introduced in the report describing mFcγRIV (40) (not as high affinity as the IgE–FcεRI interaction, but not as low as IgG–low-affinity FcγR) may appear tempting but is incompatible with the criterion defining high- and low-affinity FcRs, i.e. binding monomeric Ig or not. Furthermore, occupancy/saturation of a receptor *in vivo* is not only based on the affinity of the interaction but also on the concentration of ligand in the microenvironment, the density of receptor expression on a given cell type and on the internalization/recycling parameters of each receptor, that are rarely (if ever) taken into account. Adding to this complexity, (i) FcR polymorphisms in mice and humans have been described (1), and those affecting hFcγRIIA and hFcγRIIIA modulate their affinity for some human IgG subclasses (135); (ii) differential glycosylation of the same receptor when expressed on different cell types (e.g. hFcγRIIIA on monocytes or NK cells) leads to affinity variation; (iii) subunit binding to ligand-binding chains affect their affinity (e.g. FcRγ chain binding to hFcγRI; (iv) cytokine-induced inside-out signaling modifies the ability of mFcγRI to bind immune complexes *in vivo* (43) (reviewed in 44). All these parameters contribute to our understanding of how high-affinity FcRs can participate in the biological reactions despite their 'theoretical' saturation by monomeric IgG, which can, *in fine*, only be validated *in vivo*, but not extrapolated from affinity values or *in vitro* assays.

***Table* 4. Half-life ($t_{1/2}$) of FcR–monomeric Ig interactions**

| | IgE | IgG |
|---|---|---|
| Mouse | | |
| FcεRI | 19 h | – |
| FcεRII | – | – |
| FcγRI | – | 3–4 min |
| FcγRIIB | – | – |
| FcγRIII | – | – |
| FcγRIV | – | 3–10 min |
| Human | | |
| FcεRI | 19 h | – |
| FcεRII | – | – |
| FcγRI | – | 3 min |
| FcγRIIA | – | – |
| FcγRIIB | – | – |
| FcγRIIC | – | – |
| FcγRIIIA | – | – |
| FcγRIIIB | – | – |

–, low-affinity interactions.

## IgG Fc mutations that affect IgG–FcγR interactions

Many efforts have been made over the years to identify mutations that affect the affinity and specificity of IgG–FcγR interactions (131, 143, 197). The intent is to reduce or to increase the effector function of FcγR-expressing cells, or to target more specifically a given FcγR by using a mutated IgG antibody, e.g. inhibitory hFcγRIIB to favor cell inhibition, hFcγRIIIA to favor ADCC or hFcRn to favor IgG half-life or transcytosis to tissues. For antibodies that target soluble molecules like cytokines or chemokines, or cell surface molecules, especially those on immune cells, abrogating effector functions is a necessity to prevent adverse reactions (e.g. cytokine storm, anaphylaxis, cell depletion). Conversely, for antibodies intended for oncology use, increasing effector functions, i.e. ADCC, complement-dependent cytotoxicity (CDC), antibody-dependent phagocytosis (ADP), is desirable to increase their therapeutic activity. Human IgG subclasses possess already inherently different abilities to bind complement C1q, hFcγRs, hFcRn, hTRIM21, hFcRL5 (and hFcRL4?) (*Fig.* 2), and several interesting mutations

have been described that affect these interactions (*Table* 5). For example, rare antibodies possess unusual variable $V_H$ or $V_L$ regions, containing glycosylations that may influence the binding of their Fc domain to these receptors; these alterations are, however, often related to an increase in self-aggregation properties of these antibodies, leading to bivalent or multivalent interactions with a high avidity.

### hFcγR, hFcRn, and C1q binding sites on hIgG1

The same molecule, IgG, can thus be bound by various hFcγRs with different affinities, by C1q and FcRn, but also as reported recently by TRIM21 and FcRL5 (*Figs 1 and* 2). Abundant data are available on the binding site of hFcγRs, C1q, and FcRn on IgG, but that of TRIM21 and FcRL5 remain undefined. Notably, whereas hFcγRs, C1q, and hFcRn bind the Fc portion of IgG, their respective binding sites are different: hFcγRs bind IgG mainly at the CH2 domain, involving mainly residues Leu234, Leu235, Asp265, Ser298 (131); C1q binds IgG at the hinge region and at the CH2 domain, involving residues Asp270, Lys322, Pro329, and Pro331 (198); FcRn binds IgG at the CH2–CH3 domain interface, involving residues Ile253, His310, and His435 (131). The IgG–FcRn interaction is also highly pH dependent, with tight binding at pH 6.0, which becomes progressively weaker as near-neutral pH is approached (4, 199). Thus, even if the binding regions on the IgG Fc domain are somewhat overlapping between hFcγRs, C1q, and hFcRn, multiple studies have enabled to identify specific mutations that alter one or several interactions that are summarized non-exhaustively in *Table* 5.

### Outstanding IgG1 variants

Few mutations, or groups of mutation, in human IgG1 have been characterized thoroughly for their effect on binding to the family of hFcγRs (including polymorphic variants), hFcRn and C1q, and for their effect on the *in vivo* effector functions mediated by these receptors, e.g. ADCC, ADP, CDC, and protection from catabolism (estimated through the serum half-life of IgG). Most mutations have indeed only been characterized for their interaction either with 'classical' FcγRs but among them rarely hFcγRIIIB, with hFcRn or with C1q (*Table* 5). Different groups have nevertheless examined the same mutations, which allowed enriching the panorama of alterations in receptor binding capabilities and effector function for a handful of mutations. It is the case of the $N_{297}A$(NA), the $L_{234}A/L_{235}A$ (LALA), the $S_{239}D/H_{268}F/S_{324}T/I_{332}E$ and the $D_{270}A$ mutation (63, 131, 200, 201). The NA and the LALA mutations abrogate binding to all hFcγRs, strongly reduce/abrogate the binding to hC1q, but do not affect binding to hFcRn. It follows that ADCC, ADP, and CDC effector functions of IgG1 LALA or IgG1 $N_{297}A$ antibodies are abrogated, whereas their half-life *in vivo* are not affected (131, 202). These IgG1 variants thus represents prototypic mutations when searching for antibodies without any effector function *in vivo* as may be desired for anti-cytokine or chemokine antibodies or antibodies targeting particular surface molecules, e.g. the absence of hFcγR or hC1q binding preventing immune complexes to induce cytokine storms or unwanted cell depletion following antibody opsonization. The $S_{239}D/H_{268}F/S_{324}T/I_{332}E$ set of mutation increases binding to all hFcγRs tested and to C1q; it follows that ADCC, ADP, and CDC are significantly increased (200). The binding to hFcRn and the half-life of this IgG1 variant remains, however, unknown. The $D_{270}A$ mutation strongly reduces binding to a subset of hFcγRs (hFcγRIIA $R_{131}$, hFcγRIIB, hFcγRIIIA $F_{158}$) and hC1q, but does not affect binding to hFcγRI, hFcγRIIA $H_{131}$, nor hFcRn. The *in vivo* effector functions of IgG1 $D_{270}A$ antibodies have, however, not been addressed so far. Notably, such studies could enable to reveal the function of hFcγRI in mice expressing multiple hFcγR (hFcγRI, hFcγRIIA $R_{131}$, hFcγRIIB, hFcγRIIIA $F_{158}$, hFcγRIIIB) (63) without the necessity to use blocking antibodies against other hFcγRs than hFcγRI. Finally some sets of mutations in the Fc portion of IgG1 lead to important increases in affinity by hFcγRs (GASDIE mutation), hFcRn (YTE mutation), and more modestly by hC1q ($K_{326}W$) (*Table* 5). The subsequent effector functions have been reported to be increased: ADCC and ADP, half-life or CDC, respectively, but data are unfortunately missing on the effects of these IgG1 mutations on binding by other receptors or on the other IgG1-mediated effector functions.

## Conclusions

The family of mouse and human FcRs has recently extended quite remarkably with the cloning of novel receptors or the characterization of already identified molecules as immunoglobulin receptors, in particular TRIM21, FcRL5, and FcRL4. These novel FcRs do not only add up to the previously described FcRs, they change our view on the biological roles of this receptor family *in vivo* by extending the portfolio of effector functions that they can trigger. The regulation of cell activation (positively or negatively), endocytosis, and phagocytosis have been attributed to FcRs since decades, whereas recently described functions such as intra-

*Table* 5. **hIgG1 mutations affecting FcR- or C1q-binding, and effector functions**

| IgG1 variant (EU numbering) | hFcγR polymorphic variant | | | | | | | | | Function | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | I | IIA | | IIB | IIIA | | IIIB | hFcRn | hC1q | ADCC | ADP | CDC | $t_{1/2}$* | Refs |
| | | $R_{131}$ | $H_{131}$ | | $V_{158}$ | $F_{158}$ | | | | | | | | |
| - | 6x10$^7$ | 5x10$^6$ | 3x10$^6$ | 1x10$^5$ | 2x10$^5$ | 1x10$^5$ | 2x10$^5$ | 8x10$^6$ | 1x10$^8$ | + | + | + | 21 | (135) |
| fuc(-) | ≈ | ≈ | ≈ | ≈ | ↗↗ | ↗↗ | ? | ? | ? | ↑ | ↑ | ↓ | ↓ | (269) |
| $L_{234}A/L_{235}A$ **(LALA)** | - | - | - | - | - | - | - | ≈ | ↘ | - | - | ↓ | ≈ | (131, 202) |
| $G_{236}A$ | ↘ | ↗ | ↗ | ≈ | ≈ | ≈ | ? | ? | ? | ↓ | ↑ | ? | ? | (269, 270) |
| $S_{239}A$ | ≈ | ? | ≈ | ≈ | ? | ↘ | ? | ≈ | ? | ? | ? | ? | ? | (131) |
| $I_{253}A$ | ≈ | ? | ≈ | ≈ | ? | ≈ | ? | - | ? | ? | ? | ? | ↓ | (131, 162) |
| $S_{254}A$ | ≈ | ? | ≈ | ≈ | ? | ≈ | ? | - | ? | ? | ? | ? | ? | (131) |
| $D_{265}A$ | ↘ | ? | ↘↘ | ↘ | ? | ↘↘ | ? | ≈ | ? | ↓ | ? | ? | ? | (131) |
| $S_{267}E$ | ≈ | ↗↗ | ≈ | ↗↗ | ↘ | - | ? | ? | ↗ | ↓ | ↓ | ↑ | ? | (63, 200) |
| $D_{270}A$ | ≈ | ↘↘ | ≈ | ↘↘ | ? | ↘ or - | ? | ≈ | ↘ | ↓ | ? | ↓ | ? | (131, 201) |
| $R_{292}A$ | ≈ | ? | ↘ | ↘ | ? | ≈ | ? | ≈ | ? | ? | = | ? | ? | (131, 270) |
| $N_{297}A$ **(NA)** | ↘ | ? | ↘↘ | ↘↘ | ? | ↘↘ | - | ≈ | - | - | - | - | = | (63, 131, 271) |
| $S_{298}N$ | ? | ? | ↘↘ | ↘↘ | ? | ↘↘ | ? | | ? | ? | ? | ? | ? | (131) |
| $K_{322}A$ | ? | ? | ? | ? | ? | ? | ? | ? | ↘ | ? | ? | ↓ | ? | (201) |
| $K_{326}W$ | ? | ? | ? | ? | ? | ? | ? | ? | ↗ | ? | ? | ↑ | ? | (272) |
| $A_{327}Q$ | ≈ | ? | ↘ | ↘ | ? | ↘↘ | ? | ≈ | ? | ? | ? | ? | ? | (131) |
| $P_{329}A$ | ≈ | ? | ↘↘ | ↘ | ? | ↘ | ? | ≈ | ↘ | ? | ? | ↓ | ? | (131, 201) |
| $I_{332}E$ | ≈ | ≈ | ≈ | ≈ | ? | ↗ | ? | ? | ? | ↑ | ↑ | ? | ? | (269, 270) |
| $E_{333}A$ | ? | ? | ? | ? | ↗ | ? | ? | ? | ? | ↑ | ? | ↑ | ? | (201, 272) |
| $K_{338}A$ | ≈ | ? | ≈ | ≈ | ? | ↘ | ? | ≈ | ? | ? | ? | ? | ? | (131) |
| $N_{434}A$ | ? | ? | ? | ? | ? | ? | ? | ? | ? | ? | ? | ? | ↑ | (273) |
| $E_{233}P/L_{234}V/L_{235}A$ | - | ? | ? | ? | ? | ? | ? | ? | ? | ↓ | ? | ↓ | ? | (131, 274) |
| $E_{233}P/L_{234}V/L_{235}A/\Delta G_{236}$ + $A_{327}G/A_{330}S/P_{331}S$ | ↘ | ? | ? | ? | ? | ? | ? | ? | ? | ↓ | ? | ↓ | ? | (131, 274) |
| $L_{234}A/L_{235}A/K_{322}A$ | - | - | - | - | - | - | - | ≈ | - | - | - | - | ? | (202) |
| $L_{234}F/L_{235}E/P_{331}S$ | - | - | - | - | - | ? | - | ≈ | - | - | - | - | ? | (275) |
| $G_{236}A/I_{332}E$ | ≈ | ↗ | ↗ | ≈ | ≈ | ↗ | ? | ? | ? | ? | ? | ? | ? | (269) |
| $G_{236}A/S_{239}D/I_{332}E$ **(GASDIE)** | ≈ | ↗↗↗ | ↗↗↗ | ↗↗ | ↗↗ | ↗↗↗ | ? | ? | ? | ↑ | ↑ | ? | ? | (269, 270) |
| $G_{236}A/S_{239}D/A_{330}L/I_{332}E$ **(GASDALIE)** | ≈ | ↗↗ | ↗↗ | ≈ | ≈ | ↗↗↗ | ? | ? | ? | ↑ | ↑ | ? | ? | (63, 269) |
| $S_{239}D/I_{332}E$ | ↗ | ≈ | ↗ | ↗↗ | ↗↗ | ↗↗↗ | ? | ? | ? | ↑ | ↑ | ? | ? | (63, 269) |
| $S_{239}D/A_{330}L/I_{332}E$ **(SDALIE)** | ≈ | ? | ≈ | ? | ↗ | ? | ? | ? | - | ↑ | ↑ | ? | ? | (276) |
| $S_{239}D/H_{268}F/S_{324}T/I_{332}E$ | ↗ | ↗ | ↗ | ↗ | ↗↗↗ | ↗↗↗ | ? | ? | ↗ | ↑ | ↑ | ↑ | ? | (200) |
| $F_{243}L/R_{292}P/Y_{300}L/V_{305}I/P_{396}L$ | ? | ? | ? | ≈ | ↗ | ↗ | ? | ? | ? | ↑ | ? | ? | ? | (277) |
| $M_{252}Y/S_{254}T/T_{256}E$ **(YTE)** | ? | ? | ? | ? | ? | ? | ? | ↗↗ | ? | ↓ | ? | ? | ↑ | (132) |
| $M_{252}Y/S_{254}T/T_{256}E$ + $S_{239}D/A_{330}L/I_{332}E$ **(YTE-SDALIE)** | ? | ? | ? | ? | ? | ? | ? | ↗↗ | ? | = | ? | ? | ↑ | (132) |
| $P_{257}I/Q_{311}I$ | ? | ? | ? | ? | ? | ? | ? | ↗↗ | ? | ? | ? | ? | = | (278) |
| $S_{267}E/L_{328}F$ | ≈ | ↗↗ | ≈ | ↗↗ | ↘/- | ↘↘/- | ? | ? | ? | ↓ | # | ? | ? | (63, 279) |
| $T_{307}A/E_{380}A/N_{434}A$ | ? | ? | ≈ | ≈ | ? | ≈ | ? | ↗↗ | ? | ? | ? | ? | ↑ | (131, 160) |
| $K_{326}W/E_{333}S$ | ? | ? | ? | ? | ? | ? | ? | ? | ↗ | ? | ? | ↑ | ? | (272) |
| $E_{380}A/N_{434}A$ | ? | ? | ≈ | ≈ | ? | ≈ | ? | ↗ | ? | ? | ? | ? | ? | (131) |

**Column color**: green (activating hFcγR & effector function), red (inhibitory hFcγR), blue (transport/recycling FcR & serum half-life), brown (complement component or activity). **Affinity**: values of $K_A$ in $M^{-1}$. **Change in affinity**: -, abolished; ≈, change < 5-fold; ↘, 5-fold < decrease < 10-fold; ↘↘, 10-fold < decrease < 20-fold; ↗, 5-fold < increase < 10-fold; ↗↗, 10-fold < increase < 20-fold; ↗↗↗, increase > 20-fold. **Change in effector function**: =, unchanged; –, abolished; ↑, increased; ↓, decreased. *, half-life ($t_{1/2}$, days) measurements were performed in non-human primates. #, variable depending on the cell type, as exemplified for T cells and platelets in (63). ?, not determined.

cellular routing and proteasome addressing now implicate FcRs in intracellular processes also. An emerging notion is the possibility of a relay between FcRs expressed at the cell membrane and cytosolic FcRs; the former allowing internalization of immunoglobulin complexes that may be 'taken up' by the latter for a particular intracellular routing pathway toward degradation/proteasome or antigen presentation. The function of FcRL5 has yet to be described thoroughly, but its potential ability to mediate both activating (ITAM-based) and inhibitory (ITIM-based) signals is reminiscent of the dual activating (ITAM-based) and inhibitory (ITAMi-based) signaling that has been generalized to several FcRs already, including IgA and IgG receptors in humans and mice (refer to section 'Mouse FcR functions').

In our view, these last years have enabled in particular to re-define the properties and effector functions of several FcRs that had been overlooked or discarded from analyses in many earlier reports. Knockout mouse lines for every single mouse FcR enabled to define the loss-of-function caused by a given deficiency, but the generation of multiple FcR-deficiencies in the same animal model ('$FcR^{only}$' mice) enabled to define the ability of a given FcR in the absence of FcRs with redundant functions. This has been particularly beneficial for re-addressing the *in vivo* contributions of mouse and human high-affinity IgG receptor FcγRI (66, 141, 172, 195) and to define the intrinsic abilities of mouse FcγRIV (34, 60). A major limitation in the understanding of the role of human FcRs *in vivo* relies on the concept found in many reports and reviews that mouse and human FcR orthologs would possess similar effector functions *in vivo*. This is systematically proven wrong when comparing results obtained in mouse models expressing hFcR transgenes, mainly because of their strikingly different expression patterns (*Figs 1 and 2*) and of the misleading FcR nomenclature. The functional ortholog of hFcγRIIA is indeed mFcγRIII, whereas that of hFcγRIIIA is mFcγRIV (1). The identification of FcR polymorphisms in both species makes extrapolating human FcR effector function from results obtained studying mouse FcRs even less acceptable.

The subdivision of interests in the field between mouse FcRs versus human FcRs, activating (FcγRs) versus non-activating FcRs (e.g. FcRn), 'classical' versus 'non-classical' FcRs (TRIM21, FcRLs) appears to progressively disappear as evidence is provided that biological functions can be shared between species, that a given biological mechanism relies on both classical and non-classical FcRs (e.g. FcγRs and FcRn cooperation in antigen presentation following phagocytosis), and that FcRs may bind more than one class of immunoglobulin, even from more than one species. The effector functions of FcRs, formerly apprehended as being 'restricted' to activation, inhibition or recycling, have been broadened to intracellular trafficking and routing to degradation/proteasome or antigen processing/presentation pathways, to viral neutralization and to the control of cell differentiation. The generation of antibody mutants that loose or enhance their ability to induce effector functions in all or subsets of FcRs enables the generation of novel drug formats for safer or enhanced therapeutic antibodies. Converging efforts allow a comprehensive understanding of these mutations on FcR effector functions, which should largely profit from the current generation of fully FcR-humanized animal models. FcRs now represent targets for therapies, tools for enhanced vaccination or drug delivery, and biomarkers for antibody-related diseases (refer to other reviews in this volume). Happy times for FcR aficionados!

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