# The role of Fc$\gamma$ receptors in murine autoimmune thrombocytopenia

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BASIC SCIENCE

# The role of Fcγ receptors in murine autoimmune thrombocytopenia

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**Abstract** Immune thrombocytopenia (ITP) can become a life-threatening condition that requires immediate medical attention. The loss in platelet numbers during ITP can be induced by a variety of triggers. Anti-platelet antibodies of several isotypes and subclasses are a major cause for ITP and are a hallmark of many complex autoimmune diseases such as systemic lupus erythematosus. Mouse models have been important to understand the effector pathways involved in antibody-mediated platelet depletion. Therapeutic interventions based on these results have been proven successful in treating human ITP, thus validating the use of these model systems. One major problem that remains to be answered is which cell populations are crucial for platelet removal. Targeting these cells directly might be a novel therapeutic strategy and will also be important to understand the underlying biological mechanisms.

**Keywords** Autoimmunity · ITP · Immunoglobulin G · Inflammation · Fc receptors

## Introduction

Per year, roughly 0.05% to 0.1% of the population are estimated to develop immune thrombocytopenia (ITP) in the USA and Europe [1, 2]. Half of these cases occur in children, where in the majority of cases, ITP is transient and resolves spontaneously after several months. Therefore, there is no urgent need for treatment, and observing platelet counts on a regular basis is usually sufficient. In adults, however, ITP often becomes chronic and requires medical intervention [2, 3]. Depending on the magnitude of platelet reduction, several mild to life-threatening symptoms, including bleeding at cutaneous, gingival, intracranial, and internal sites, can occur. It is accepted that platelet-specific antibodies of the immunoglobulin (IgG) isotype are a major cause for immune-mediated platelet depletion. Platelet-associated IgG can be detected in approximately 50–70% of the patients with ITP, and more than 50% of newborn children of mothers with ITP will have a transient thrombocytopenia due to the transfer of IgG through the placenta [1, 4, 5]. Similarly, infusion of serum from thrombocytopenic patients induced rapid platelet depletion in healthy volunteers [6]. Moreover, strategies aiming at depletion of autoantibody-producing B cells such as depletion with monoclonal antibodies (e.g., rituximab) or splenectomy are means to interfere with platelet depletion [3, 7]. It is still unclear what triggers the generation of platelet-specific IgG. As ITP can coincide with certain infections, one possibility might be the generation of cross-reactive antibodies during a pathogen-specific immune response recognizing platelet antigens [8]. The dominant target structures detected by murine and human platelet-specific IgG are glycoproteins (GP) such as GPIb, GPIIb, GPIIIa, or complexes thereof [3, 9–12]. Very similar targets are recognized by murine platelet-specific autoantibodies arising in a variety of autoimmune-prone mouse strains such as BXSB mice or BXSB/NZW F1 offspring [13]. Electron microscopy studies in human ITP patients have demonstrated that platelets can be taken up by monocytes, and injection of radio-labeled platelets showed that the major sites where platelets redistribute to after autoantibody injection are the spleen, the liver, and the lung [3, 14–17]. These results led to the conclusion that the reticulo-

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endothelial system is the major site for autoantibody-mediated platelet removal. The cells of this system are of hematopoietic and non-hematopoietic origins and express receptors specific for the immunoglobulin G (IgG) Fc fragment. Cross-linking of Fcγ receptors (FcγR) by IgG-coated platelets results in the phagocytosis of these immune complexes and their removal from the circulation [18]. Other mechanisms that are discussed in the literature are complement-mediated lysis of platelets and the involvement of cytotoxic T cells [1, 19]. While all these observations imply some role for these different effector pathways and organs, they cannot distinguish between the importance of the individual pathways for the observed platelet depletion in patients. Thus, further studies in animal models are of major importance to decipher the role of the different effector mechanisms and to develop novel therapeutic concepts. This review will discuss some of the recent insights that have been gained with respect to effector mechanisms leading to platelet depletion in mice and how this knowledge might translate to novel strategies for therapy.

## Immunoglobulin G-mediated effector pathways

As has been discussed for humans, mainly two effector pathways were suspected to be important for IgG-mediated platelet removal in mice. Both of these pathways are dependent on the antibody constant domain, which in the case of IgG can bind to cell surface receptors on innate immune effector cells (FcγR) or activate the complement pathway [18, 20, 21]. FcγRs are widely expressed on cells of the innate (e.g., monocytes, mast cells, neutrophils, NK cells) and adaptive (B cells) immune system. In addition, FcγR expression has been demonstrated on dendritic cells and non-hematopoietic tissues such as endothelial and neuronal cells. Depending on the cell type, cross-linking of these receptors results in a variety of effector functions including antibody-dependent cell-mediated cytotoxicity, phagocytosis, release of pro-inflammatory mediators, or IgG-mediated feedback inhibition of B cells [18, 22]. The family of murine and human FcγRs consists of several members that can be distinguished by two different means. First, by the affinity of the individual receptors for the different IgG subclasses (IgG1, IgG2a, IgG2b, and IgG3 in mice) (Fig. 1). FcγRI (CD64) is the only receptor which can bind to monomeric IgG, whereas all the other receptors can bind IgG only in the form of immune complexes (IC). In general, the higher the affinity of the individual receptor, the narrower its specificity. Thus, FcγRI selectively binds to IgG2a with high affinity, FcγRIV binds IgG2a and IgG2b with intermediate affinity and FcγRIIB and FcγRIII bind IgG1, IgG2a, and IgG2b with low affinity [23]. This in vitro binding pattern reflects the importance of the individual FcγRs for the activity of the individual IgG subclasses in different in vivo model systems. Thus, IgG1 is essentially dependent on FcγRIII, whereas IgG2a and IgG2b are additionally dependent on FcγRI and FcγRIV [24–31]. The second distinguishing feature within the family of FcγRs is whether they transduce activating or inhibitory signals. There is one inhibitory FcγR, FcγRIIB that shows a broad expression pattern on hematopoietic and non-hematopoetic tissues [32, 33]. In contrast, FcγRI, FcγRIII, and FcγRIV are activating receptors which have a more restricted cell type expression pattern. None of the activating receptors can signal autonomously but has to associate with signaling adaptor molecules such as the FcR common γ chain (γ chain). On cell types such as monocytes, macrophages, and neutrophils, activating FcγRs are coexpressed with the inhibitory FcγRIIB [34]. Thus, FcγRs set a threshold for cell activation as ICs will trigger both activating and inhibitory signaling pathways. The affinity of the individual IgG subclasses to the respective activating and the inhibitory FcγRIIB will determine antibody activity. Pro-inflammatory mediators, such as TNF-α, IFN-γ, or C5a, modulate IgG subclass activity by changing the ratio of activating to inhibitory FcγR expression [23, 35]. In addition to the differential binding of the individual IgG subclasses to FcγRs, there is a differential capacity to activate the complement pathway. Whereas IgG1 is very inefficient in triggering the classical pathway of complement activation by binding to C1q, the other three IgG subclasses can do so efficiently. Therefore, it was suggested that the activity of IgG2a and IgG2b might be dependent on both, cellular FcγRs and the complement pathway.

## Effector pathways involved in murine ITP

Several platelet-specific monoclonal antibodies or polyclonal sera specific for mouse platelets can be used to induce ITP [29, 36–41]. One common antibody is the CD41-specific rat IgG1 clone MWReg30. As rat IgG1 is very similar to mouse IgG1, it is not efficient in activating mouse complement and can only bind to mouse FcγRIIB and FcγRIII. Consistent with these features, using either a blocking antibody for mouse FcγRIII or the FcγRIII knockout mouse completely prevented MWReg-induced platelet depletion [37, 40]. Similarly, a mouse IgG1 subclass switch variant derived from the platelet-specific mouse antibody clone 6A6 generated from (NZW×BSXB) F1 animals was completely dependent on FcγRIII [29]. More importantly, 6A6–IgG2a and IgG2b subclass variants were also fully dependent on cellular FcγRs for their activity despite their capacity to activate the complement pathway. Consistent with this observation, an IgG3 subclass variant, which does not bind to any of the known FcγRs with significant affinity but activates the complement pathway, did not lead to significant platelet depletion [29].

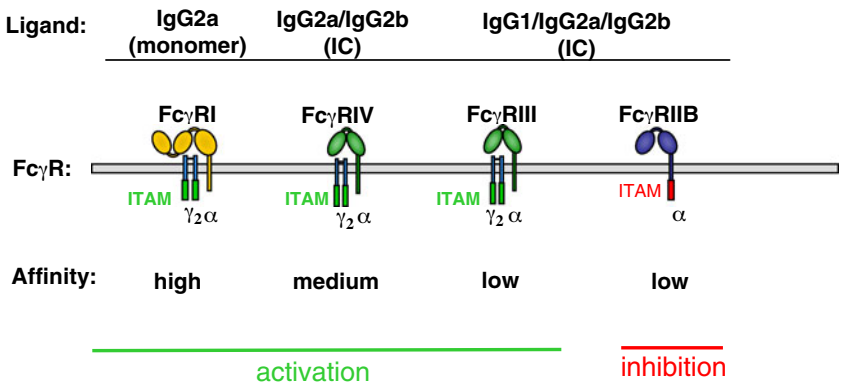


**Fig. 1** Antibody Fcγ receptor interactions. Shown is the family of FcγRs in mice and their interactions with immunoglobulin G subclasses. The principal distinguishing feature between the family members is the differential affinity for IgG subclasses, the specificity for a certain subclass, and the signal that they transduce. *ITIM* immunoreceptor tyrosine-based inhibitory motiv, *ITAM* immunoreceptor tyrosine-based activation motif, *IC* immune complex

These results led to the conclusion that the complement system did not seem to be a major player for IgG-mediated platelet depletion in mice. Interestingly, a novel pathway resulting in a complement component C3-independent generation of C5a has been shown to be important for murine autoimmune hemolytic anemia induced by injection of red blood cell-specific IgGs [19, 35]. Although the details of this novel pathway are not entirely clear, it was suggested that C5a could be generated in an FcγR-dependent fashion and act as a pro-inflammatory mediator changing the ratio of activating to inhibitory FcγR expression towards a higher level of activating FcγRs. Using either C5a receptor-deficient mice or biological inhibitors of C5a should answer whether this pathway is involved in murine ITP as well and whether this might be a promising novel therapeutic approach for human ITP. Another interesting observation was made with respect to the level of involvement of individual activating FcγRs for IgG2a and IgG2b-mediated platelet clearance. In contrast to the capacity of IgG2a to bind to the high affinity FcγRI, mice with a deletion of this receptor did not have altered rates of IgG2a mediated platelet clearance [29]. In contrast, blocking antibodies for the medium affinity receptor FcγRIV resulted in an impaired platelet clearance. Similar results were obtained in human ITP patients where blocking antibodies to FcγRIIIA, which is the human ortholog of murine FcγRIV [23, 42], but not to human FcγRI were very efficient in blocking platelet depletion [43–46]. Thus, FcγRs are instrumental for IgG-mediated platelet depletion for murine and human ITP and are an attractive target for therapeutic intervention. Indeed, the injection of anti-D antibodies directed against red blood cells is an efficient means to block ITP by generating immune complexes that will compete for binding to activating FcγRs on innate immune effector cells. A problem arising with the use of FcγRIIIA-blocking antibodies in human therapy is the induction of severe neutropenia due to cross-reactivity of the therapeutic antibody with human FcγRIIIB expressed on neutrophils, thereby targeting them for attack via antibody-dependent cellular cytotoxicity. The use of antibody variants with a mutated Fc fragment or F(ab)2 fragments might reduce this unwanted side effect. Recent evidence suggests that a long known therapy for ITP, the intravenous infusion of high doses of immunoglobulin G molecules pooled from thousands of donors (IVIg therapy), might mediate its anti-inflammatory activity by upregulating the inhibitory FcγRIIB in mice and humans, thereby changing the threshold for innate immune effector cell activation [47, 48].

## Effector cells and organs involved in murine (and human) ITP

As we now have a fairly complete picture of the molecular mechanisms responsible for IgG subclass-dependent platelet depletion, the crucial next question is which cell types express these receptors and where they are located (Fig. 2). Although this sounds trivial at first glance, we are only at the beginning to define the great variety of cell subpopulations in the myeloid lineage for example [49]. In humans, removal of the spleen is one option to stabilize platelet counts. In general, however, only 60–70% of the patients respond to this therapy, and in many cases, this does not lead to a full recovery of platelet numbers but rather stabilizes them on an acceptable level [2, 3]. Similar results have been obtained with autoimmune-prone mouse strains that develop anti-platelet antibodies spontaneously [50]. Of note, removal of the spleen also depletes a considerable number of autoantibody-producing plasma cells and plasma blasts. It is hard to evaluate therefore to what extent removal of splenic phagocytic cells contributes to the overall therapeutic effect. Thus, it is a safe assumption that

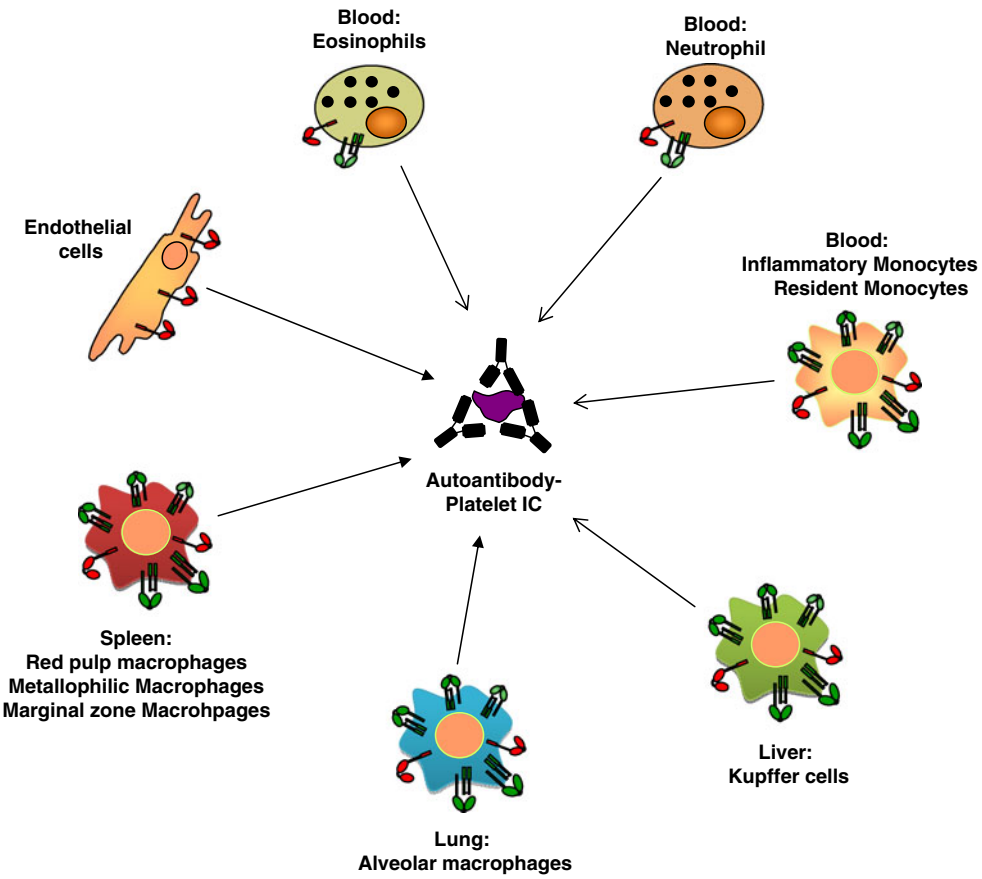


**Fig. 2** The hunters and the prey. Shown are the effector cells and organs, which could be involved in autoantibody-mediated platelet depletion in ITP. In the blood, several cell types such as eosinophils, neutrophils, and monocyte subpopulations might be involved in platelet phagocytosis. In organs such as the lungs, the spleen, and the liver, tissue-resident macrophages are prime candidates as responsible effector cells. Besides cells of the hematopoietic system, non-hematopoietic cells such as endothelial cells express FcγRs and might phagocytose platelet-containing immune complexes

other organs or cell populations outside the spleen are involved in platelet removal. Interestingly, there seems to be an age-dependent involvement of different organs. During early age, splenectomy leads to better clinical responses than later in life [3]. Besides the spleen, the liver was suggested to be involved in removal of antibody-bound platelets. Using radioactively labeled platelets, it has been shown that a proportion of the injected radioactivity ends up in the liver after 24 h [16, 17]. While this is interesting, it does not exclude that cells after having taken up antibody-coated platelets migrate to the liver subsequently. In fact, injection of anti-platelet antibodies leads to a maximum of platelet depletion within 1 to 4 h in mice and humans [6, 29]. As further studies cannot be done in humans, murine model systems are required. The problem here is that a lot of crucial information regarding the mechanism and players involved in IgG-mediated effects have only been identified recently and are still under investigation. For example, the mouse ortholog to human FcγRIIIA has only been identified 4 years ago and is still not fully characterized [42, 51]. More importantly, monoclonal antibodies specific for all mouse-activating FcγRs have become available only recently. Therefore, there are still many open questions with respect to the exact FcγR expression pattern on individual cell types. In the blood, FcγRIII (important for IgG1-mediated platelet depletion) and FcγRIV (important for IgG2a/IgG2b-mediated platelet depletion) are largely expressed on monocytes and neutrophils [18, 42]. NK cells, mast cells, eosinophils, and dendritic cells on the other hand largely lack expression of FcγRIV but do express FcγRIII. Besides the blood, most other organs such as the spleen, the liver, the lung, and the kidney contain cell types expressing different FcγRs. One of the dominant sources of FcγR expression in these organs are tissue-specific resident macrophages and endothelial cells. In the liver for example, Kupffer cells seem to express activating FcγRs in the spleen, red pulp macrophages are highly positive for FcγRs and thus could be involved in antibody-mediated platelet depletion [30]. In addition, strong FcγR expression can be detected on endothelial cells, although here, the dominant receptor seems to be the inhibitory FcγRIIB and probably FcγRIII to some degree. Therefore, either tissue-resident macrophages or blood monocytes and neutrophils could be involved in IgG2a/IgG2b-mediated platelet depletion, whereas IgG1-mediated platelet depletion could be triggered by other cell types as well. One of the cell types that can be excluded are NK cells as they do neither express FcγRIV nor co-express the inhibitory FcγRIIB, which regulates the activity of all IgG subclasses in mice [18]. Ideally mice with cell type-specific deletions of individual activating FcγRs would be required to come to definitive conclusions. Until these animals

become available, surrogate systems need to be used. Liposomes containing cytotoxic substances result in the specific depletion of monocytes and macrophages in the blood and in tissues such as the lung, the liver, and the spleen [52]. Indeed, liposome-treated mice showed an impaired platelet clearance mediated by a polyclonal rabbit anti-mouse platelet serum suggesting that monocytes and macrophages are involved in this process. As there are many different subpopulations of monocytes and macrophages, it is unclear which of these are important [49]. In addition, tissue macrophages are sometimes involved in maintenance of tissue organization, and depletion of spleen macrophages often leads to secondary rearrangements in structure, which might be important for antibody-mediated platelet depletion. One step closer to the human system, mice transgenic for human FcγRs have been developed and will be useful to study the impact of human FcγRs in a mouse model in vivo [53].

## Conclusion and outlook

Taken together, recent studies have shed some light on the molecular pathways involved in immunoglobulin G-mediated platelet depletion. Despite the efficient activation of the complement pathway by the most active IgG subclasses, it seems clear that this does not directly contribute to platelet removal but may serve as an enhancing mechanism to modulate activating and inhibitory FcγR expression. In contrast, studies in humans and mice clearly indicate the importance of cellular FcγRs for platelet removal. As there are many different cell types that express the relevant FcγRs, it is unclear which of these contribute to platelet depletion. In addition, many of these cell populations are located in a variety of tissues and organs and thus are difficult to analyze. Although splenic cell populations seem to be involved in antibody-mediated platelet removal, it seems clear that alternative pathways independent of the spleen must exist and need to be characterized in detail to gain a deeper insight into the biology and pathomechanism of ITP.

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