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REVIEW

The complex role of Fcγ receptors in the pathology of arthritis

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Abstract Autoantibodies of the IgG class and the immune complexes they form are central players in the pathology of rheumatoid arthritis (RA). Receptors for the Fc part of IgG, FcγR constitute one of the main effector mechanisms through which IgG immune complexes exert their action. The different members of the FcγR family exhibit extensive structural homology leading to redundancy in ligand specificity and signal transduction. Moreover, the initiation of effector mechanisms by IgG immune complexes can also be mediated by the complement system. This strong redundancy and high degree of complexity hampers a direct in vivo analysis of antibody effector pathways. Over the last decade, mice deficient for different combinations of FcγR have been generated by gene targeting. These knockout mice provide excellent tools to define the specific contribution of the different FcγR to IgG effector pathways in well-established in vivo mouse models for arthritis. This review will discuss the results of the studies that analyze the role of the different members of the FcγR family in murine arthritis models and their implications for our understanding of the human disease.

Keywords Fcγ receptors · Rheumatoid arthritis · Animal models · Knockout mice · Immune complexes

Abbreviations

KO	knockout
RANKL	receptor activator of NFκB ligand
IL-1β	interleukin-1β
Mφ	macrophage
DC	dendritic cell
FDC	follicular dendritic cell
bCII	bovine type II collagen
ADCC	antibody-dependent cell-mediated cytotoxicity
Th	T helper cell

Introduction

Rheumatoid arthritis

Rheumatoid Arthritis (RA) is a chronic, debilitating disease of the joints, characterized by sequential steps of infiltration of leukocytes, proliferation of cells in the synovial membrane, angiogenesis, and pannus formation that eventually results in the irreversible destruction of cartilage and bone. Affecting 1% of the Western population, RA is the most frequent autoimmune disease [1].

Role of autoantibodies in arthritis

There is long-standing evidence for the existence of increased titers of various autoantibodies in RA patients and in animal models of RA. However, their direct involvement in disease initiation and progression has been a matter of debate. One of the earliest identified autoantibodies to be associated with RA is rheumatoid factor (RF), an antibody directed against the constant region of IgG. However, its association with RA is not very specific: only 60–70% of all RA patients are positive for RF, and RF is also found in other disorders [2]. The recently identified anticyclic citrullinated peptide (anti-CCP) antibodies have similar sensitivity, but a specificity up to 99% [3, 4]. Citrullination is a posttranslational modification of proteins,

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in which arginine is converted to citrulline by a specialized enzyme, the peptidyl arginine deiminase. Both RF and anti-CCP could be present for as long as 9 years before the disease onset, and levels of antibodies are associated with disease severity [5, 6]. In addition, therapeutic approaches targeting autoantibody producing B cells with anti-CD20 monoclonal antibody show promising results in arthritis [7, 8].

A number of observations in murine models indicate that B cells and humoral immunity are indispensable for arthritis development. Mice deficient for B lymphocytes are protected against arthritis induced by immunization [9]. Moreover in most [10, 11], but not all [12], animal models serum from animals suffering from arthritis or purified antibodies derived from these animals are directly pathogenic and capable of inducing arthritis in healthy mice of a variety of inbred strains. Taken together, these findings indicate a crucial role for B cells and antibodies in the pathology of arthritis.

Autoantibodies form immune complexes (IC) with their cognate antigen. ICs are potent activators of a variety of effector mechanisms including activation of effector cells via cross-linking different receptors for the Fc part of IgG, FcγR, expressed on the surface of these cells, and interactions with the complement system. It is believed that deposited ICs can initiate and perpetuate chronic inflammation, which results in the destruction of the tissue, when left uncontrolled. The prominent role of autoantibodies and immune complexes in the pathophysiology of RA has brought FcR and complement in the forefront of interest in arthritis research [13].

Fcγ receptors

FcγR, belonging to the Ig supergene family of leukocyte FcR, are transmembrane glycoproteins composed of a ligand binding α subunit with two or three extracellular Ig-like domains, a transmembrane and an intracellular region. The high affinity FcγRI (CD64) and the low affinity receptors for complexed IgG, FcγRIIB (CD32), FcγRIII (CD16), and FcγRIV, all belong to this group. The α subunits of the activating receptors FcγRI, FcγRIII, and FcγRIV form a multi-subunit complex with a common γ-chain [14, 15]. The γ-chain is not only required for signal transduction, but also for the cell surface expression of the receptor complex. Therefore, γ-chain knockout (KO) mice do not functionally express FcγRI, FcγRIII, and FcγRIV [14, 15]. The γ-chain shares the presence of a conserved signaling motif, the immunoreceptor tyrosine-based activation motif (ITAM), with signal transduction subunits of the T and B lymphocyte receptor complexes. Cross-linking of a γ subunit-containing FcR by IC initiates signal transduction via recruitment and subsequent activation of intracellular tyrosine kinases, switching on effector mechanisms. In contrast, the intracellular part of the single-chain receptor FcγRIIB contains an inhibitory motif named immunoreceptor tyrosine-based inhibition motif (ITIM). Co-ligation of an “ITIM receptor” with an “ITAM receptor” by an IC results in the recruitment of various classes of phosphatases, which initiates the downregulation of the “ITAM-triggered” activation signals [16]. Regulation of cellular activation by the ITAM–ITIM motif pair have been described for other receptors in the immune system. The involvement of FcγRIIB in the immune response is complex and takes place at different levels. Cross-linking of FcγRIIB with the B-cell receptor forms an important negative feedback mechanism to control antibody production. FcγRIIB KO mice develop higher antibody titers compared to wild-type mice after immunization [17]. Moreover, FcγRIIB deficiency renders C57Bl6, but not Balb/c, mice highly susceptible to autoimmune diseases like arthritis [18]. Whether this is dependent on the expression of FcγRIIB on B cells, macrophages (Mφs), FDCs, or DCs (or a combination of these) is still a matter of debate. The dependency of the autoimmune phenotype of the FcγRIIB KO on genetic background indicates that additional genetic factors substantially modulate the function of FcγRIIB.

Although unique, the α subunits of the FcγR are highly conserved in their ligand binding extracellular domain, displaying 70–98% homology. They exhibit distinct but overlapping ligand specificity and expression patterns (Table 1). IgG1 binds with low affinity preferentially to FcγRII and FcγRIII; IgG2a binds with high affinity to FcγRI and with low affinity to FcγRIII and FcγRIV; IgG2b interacts with low affinity to all FcγRs, but with the highest affinity for FcγRIV [15, 19–21]. The expression of FcγRI is restricted to mononuclear cells, while FcγRII and FcγRIII have a much broader expression pattern (Table 1). Under resting conditions, FcγRIII is the activating receptor with the highest expression, while the low basal expression

Table 1 Murine leukocyte Fcγ receptors, their expression pattern, and isotype specificity

FcγR	Expression pattern	Isotype preference
FcγR I	Monocytes, Mφ, DCs	IgG2a > IgG2b >> IgG1 >> IgG3
FcγR IIB	B cells, monocytes, Mφ, DCs, neutrophils, mast cells	IgG2b ≥ IgG1 >> IgG2a >>> IgG3
FcγR III	Monocytes, Mφ, DCs, neutrophils, mast cells, NK cells	IgG1 > IgG2a > IgG2b >>> IgG3
FcγR IV	Monocytes, Mφ, DCs, neutrophils	IgG2a = IgG2b

of FcγRI and FcγRIV is strongly increased in response to cytokines such as interferon gamma (IFNγ) [15, 19]. Many aspects of the immune response are affected by FcγR-mediated regulation ranging from antigen presentation, antibody production, IC clearance (phagocytosis, endocytosis), and antibody-dependent cell-mediated cytotoxicity to release of inflammatory mediators, implying possible roles in autoimmunity on multiple levels [22].

Arthritis is a complex polygenic disease. The role of FcγR in arthritis cannot be defined without recognizing the importance of other immune players. First of all, the effector pathways initiated by the interaction of IC with either FcR or complement are highly redundant. In most arthritis models, complement factor C5 and the C5a–C5aR interaction are indispensable [23–26]. Moreover, a direct cross talk between FcγR and the complement system can occur. Binding of complement fragment C5a to the C5a receptor skews the balance of activating vs inhibiting FcγR, thereby facilitating cell activation. FcγR triggering on the other hand results in enhanced secretion of complement components [27]. Dual involvement of the two-effector pathways has been observed in other models of autoimmunity [28] and hypersensitivity [29].

The strong association of arthritis with MHC class II haplotypes suggests a prominent role for autoreactive T helper cells (Th) in the initial phase of arthritis. Moreover, T cell help is required for class switching and the production of high amounts of Ig as seen in the mouse models of arthritis. T cells are also found in large quantities in the inflamed joints. However, their role in the downstream effector phase of arthritis is still unclear. Although there are indications that Th cells may contribute directly to joint pathology by regulating osteoclastogenesis through the receptor activator of NFκB ligand [30] and the release of cytokines [e.g., tumor necrosis factor alpha (TNF-α)], it is more likely that they act indirectly by modifying the function of effector cells (e.g., upregulation of the activating FcγR) through secretion of cytokines, such as IFNγ [31].

Animal models of rheumatoid arthritis

Over the years, a number of animal models that resemble important features of human RA have been established [32]. Most models are based on either a spontaneously developing or an actively induced autoimmune response. Arthritis can be induced actively by immunization with joint-specific antigens (e.g., collagen, proteoglycan) or the ubiquitous antigen glycose-6-phosphate isomerase (GPI). Spontaneous arthritis arises in mice, in which autoreactive T cells escape central tolerance, for example in the T-cell receptor (TCR) transgenic K/B×N model [33] or in mice with a point mutation in the crucial T cell-specific signal transduction molecule Zap-70 [34]. The complex initial phase can be bypassed by direct activation of downstream effector pathways. Passive immunization with anti-collagen type II antibodies or injection of serum from K/B×N mice induces arthritis by triggering antibody effector pathways. Transgenic mice overexpressing the further downstream effector TNFα [35] or deficient for the downstream negative regulator IL1ra [36] develop arthritis spontaneously. In a different approach, called antigen-induced arthritis (AIA), several aspects of arthritis can be mimicked by the immunization of mice against the foreign antigen, methylated bovine serum albumin (mBSA), that sticks to the cartilage surface, followed by a challenge injection of the antigen directly into the knee joint [37]. In the passive variant of AIA, called immune complex-induced arthritis (ICA), mice are injected with antigen-specific antibodies and challenged with the antigen (e.g., lysozyme) injected directly in the joint [38].

The study of mice deficient for different FcγR in a variety of these mouse models of arthritis has enabled us to begin to define the role of these FcγR in this complex chronic immunological disease.

FcγR knockout mice in arthritis models

Collagen-induced arthritis

Collagen-induced arthritis (CIA) is the most widely accepted animal model for human RA. In this model, susceptible rodent strains (e.g., DBA/1 mice) are immunized with bovine collagen type II (bCII) resulting in antibodies that cross-react with murine collagen type II, an abundant antigen in the joint [39]. Collagen-specific Th1-type T cells, anti-collagen antibodies, and inflammatory cytokines are typical for CIA. Progressive arthritis develops, showing pathology strongly resembling that of human RA, e.g., thickened synovium, pannus formation, and destruction of cartilage and bone. Collagen-specific T and B cells are both required for disease induction, and CIA can be transferred with serum from diseased animals into recipient strains [11].

When FcRγ-chain KO DBA/1 mice are immunized with bCII, almost complete protection against arthritis development is observed, despite similar cellular and humoral immunity against bCII as compared to wild-type controls [40]. In common with the FcRγ-chain KO, FcγRIII KO DBA/1 mice show an almost complete protection against CIA development, suggesting that FcγRIII is the dominant FcγR in this model [41]. Protection by deletion of activating FcγR most likely happens at the level of downstream antibody effector pathways, as shown by the unperturbed cellular and humoral immunity against bCII in both of these studies.

The nature and location of the effector cells involved is not yet clear. In vivo killing of phagocytic synovial lining cells, by local administration of chondronate containing liposomes, renders mice resistant to CIA suggesting an absolute requirement for joint resident Mφs in CIA [42]. The important role of Mφs is confirmed recently, showing that the adoptive transfer of FcγRIII$^+$ peritoneal Mφs renders FcγRIII KO mice susceptible to CIA [43]. An essential role for neutrophils is suggested by the findings that C5-dependent recruitment of neutrophils is an early event in CIA and that no signs of arthritis develop in the absence of C5 [25].

FcγRIIB KO DBA/1 mice develop CIA with an earlier onset and enhanced severity, and as expected, exhibit higher anti-bCII titers as compared to wild-type controls [40]. In the absence of FcγRIIB, up to 50% of normally CIA-resistant C57Bl6 mice can develop CIA [18]. These mice have unchanged T-cell proliferation to bCII, suggesting that FcγRIIB deficiency does not affect antigen presentation in this model. The elevated anti-bCII antibody titers are more pronounced in diseased animals [18]. Taking advantage of the susceptibility of C57Bl6 FcγRIIB KO mice for CIA, we analyzed the development of CIA in C57Bl6 FcγRIIB/ FcγRIII and FcγRIIB/FcγRI double KO and FcγRIIB/ FcγRI/FcγRIII triple KO mice. Preliminary data suggest that all activating FcγR can play a role in CIA (our unpublished observations).

Proteoglycan-induced arthritis

In Balb/c mice, proteoglycan-induced arthritis (PGIA) can be established by immunization with the heterologous joint component, human proteoglycan. After the systemic IgG response against human PG cross-reactive antibodies against murine PG emerge, which results in immune complex formation and inflammation in the joint.

FcγRIIB KO mice exhibit earlier onset and increased severity, as well as increased anti-PG titers in their circulation compared to wild-type controls. In contrast, development of PGIA is completely abolished in FcR γ-chain KO mice [44]. Resistance to PGIA of the FcR γ-chain KO is the result of impaired downstream effector mechanisms since FcR γ-chain KO mice exhibit similar anti-PG titers, and FcR γ-chain KO splenocytes from immunized mice induce similar arthritis as wild-type splenocytes upon adoptive transfer. FcγRIII is the major activating FcγR as development of PGIA was inhibited in FcγRIII KO mice, whereas FcγRI KO mice showed similar disease as wild-type animals [45]. Anti-PG titers were all similar in wild-type controls and FcγRI and FcγRIII KO mice, whereas reduced cytokine and chemokine levels were found in the hind paws of FcγRIII KO mice suffering from PGIA.

Taken together, FcγRIII is a crucial player in the downstream effector phase of PGIA by controlling the further downstream release of inflammatory cytokines and chemokines, while FcγRIIB plays an inhibitory role.

GPI-induced arthritis

The role of glucose-6-phosphate isomerase, a glycolytic enzyme expressed in every cell, as an arthritogenic antigen has emerged from the K/B×N mice that develop severe arthritis spontaneously. In this model, the transgenic KRN TCR recognizes GPI-derived peptides in the context of the H2-A^{g7} MHC of the NOD strain. With the help of antigen-specific T cells, GPI-specific B cells secrete high amounts of anti-GPI antibodies that are directly pathogenic [10]. The disease is transferable with sera from sick animals [33], providing an excellent passive model (as described in "K/B×N serum transfer model").

DBA/1 mice develop arthritis after immunization with human GPI and this disease cannot be transferred by serum or purified antibodies [12]. Nonetheless, FcγR are clearly involved, since FcR γ-chain KO mice are largely protected; FcγRIIB KO mice suffer from more severe arthritis compared to wild-type controls. In contrast to the spontaneous K/B×N TCR transgenic model, depletion of Th cells reverses established disease in this model [12].

Collagen type II antibody-induced arthritis

Injection of a cocktail of four anti-CII monoclonal antibodies (moAb) in combination with lipopolysaccharide (LPS) induces arthritis symptoms in wild-type Balb/c mice [46]. Disease induction is blocked in FcR γ-chain KO mice and is greatly attenuated in FcγRIII-deficient mice [47]. Young FcγRIIB KO mice do not show enhanced disease compared to wild-type controls, but aged FcγRIIB KO Balb/c mice develop arthritis even without LPS injection. Arthritis with an incidence up to 50% can be induced in wild-type DBA/1 mice by injection of large doses (9 mg) of single monoclonal anti-CII antibody [48]. FcR γ-chain KO DBA/1 mice are fully protected against anti-bCII moAb-induced arthritis. FcγRIII is indispensable on the DBA/1 background when the injected anti-CII moAb is of the IgG2b or IgG1 isotype. IgG2a anti-CII mediated arthritis appears unaffected in the FcγRIII KO [48], suggesting a role for FcγRI and/or FcγRIV under these conditions. FcγRIIB KO DBA/1 mice have higher incidence and severity compared to wild-type controls in anti-CII mediated arthritis [48]. These results largely confirm what was found earlier for CIA in the DBA/1 background [40]. In addition, the alternative complement pathway (factor B) is indispensable in the effector phase for anti-CII antibody-induced arthritis, whereas C4 deficiency has no effect on disease development [49], as was described earlier for K/B×N serum-induced arthritis [23].

In an extensive study comparing the two passive arthritis models of anti-CII induced arthritis and K/B×N serum-induced arthritis (as described in "K/B×N serum transfer model"), the biodistribution of anti-CII and anti-GPI of the K/B×N serum was analyzed using micro-positron emission tomography [50]. In contrast to anti-GPI antibodies, anti-CII antibodies fail to localize to distal joints within the first 45 min after administration. Injection of systemic preformed irrelevant small ICs substantially enhances joint localization of anti-CII, indicating that soluble ICs in the blood are required for arthritogenic Abs (e.g., anti-CII) to gain access to their target organs, the joints. By inducing vascular permeability, the irrelevant ICs facilitate the rapid influx of anti-CII to the joints. The front and rear limbs appear to be particularly sensitive to IC-induced vasodilatation. FcγRIII, neutrophils and mast cells are essential for the localization of the IC to the joint, whereas C5 acts at a later stage [50].

The C5aR KO on the Balb/c background is protected against anti-CII induced arthritis despite unchanged anti-CII deposition in the joints, while the C3aR KO is indistinguishable from wild-type Balb/c mice [51]. In vivo depletion of neutrophils using the neutrophil-specific antibody GR-1 completely inhibits anti-CII induced arthritis. Moreover, neutrophil depletion in mice that had already developed arthritis ameliorates the disease [52].

The results with the passive anti-CII moAb induced arthritis model confirm the essential role of the activating FcγRs (mainly FcγRIII) in the effector phase of the disease independent from the genetic background. Their role is two fold: firstly initiation of vasodilatation to facilitate entry of the autoantibodies specifically to the joint and secondly triggering of effector cells locally by newly formed IC to drive a severe inflammation. The inhibitory role of FcγRIIB seems to be age- and/or background-dependent.

K/B×N serum transfer model

Serum from K/B×N mice that have developed arthritis spontaneously (as described in "GPI-induced arthritis") is able to induce arthritis in diverse recipient strains. The arthritogenic properties of the serum were identified in the Ig fraction as anti-GPI antibodies of the IgG1 isotype [10]. Anti-GPI monoclonal antibodies are only pathogenic when a combination of antibodies recognizing different epitopes are administered, indicating the need for multiple antibodies per antigen molecule in the GPI/anti-GPI complexes in this model [53]. K/B×N serum-induced arthritis can be established in the absence of T and B cells, indicating that the end-stage effector phase is completely dependent on the innate immune system [10].

FcR γ-chain KO mice are completely protected against the development of arthritis after injection of K/B×N sera, while FcγRIII deficiency greatly attenuated disease development. FcγRI knockout mice display a similar disease course as wild-type littermates [23]. In a more detailed study, it was found that prolonged repeated injection of sera from arthritic K/B×N mice into healthy FcR γ-chain KO recipients induces subclinical joint damage that results in the erosion of cartilage and bone [54]. This study also confirmed that FcγRIII is a crucial, but not exclusive, mediator of joint inflammation, as protection from K/B×N arthritis by FcγRIII deficiency was not complete [54]. Our recent experiments in K/B×N serum-induced arthritis confirmed a prominent role for FcγRIII, while a comparison of FcγRII/III with FcγRI/II/III KO mice pointed to a role of FcγRI under these conditions. Furthermore, a comparison of FcγRI/III with FcR γ-chain KO mice suggested a role for FcγRIV (our unpublished observations).

FcγRIIB was first identified by genetic screening as a possible player in K/B×N arthritis; however, confirmation using gene-targeted mice failed to prove this [55]. In other studies, however, a clear inhibitory role for FcγRIIB in this model has been found [54] (our unpublished observation).

Mast cells [56] and neutrophils [57] are indispensable effector cell types in K/B×N serum-induced arthritis. In addition, C5 KO mice are resistant to arthritis induction in this model [23]. The early influx of neutrophils into the joint is abrogated in FcγRIII KO and C5 KO mice. Using different techniques, two independent studies have shown that localization of the arthritic antibodies to the joint in K/B×N serum-induced arthritis depends on local vasopermeability around the joints, which relies on the unique anatomical characteristics of the joint itself or the surrounding vasculature [50, 58]. Vasopermeability depends on FcγRIII, neutrophils, mast cells [50, 58], and unexpectedly FcR γ-chain expressing cells outside the joint [58], but not on complement [50, 58], TNF-α or IL-1β [58]. These results together suggest a disease scenario that is partly reminiscent of IgG-induced anaphylaxis [59].

The C5a-C5aR axis and the alternative complement pathway, IL-1β, and to a lesser extent TNF-α are required for K/B×N arthritis, whereas the classical complement pathway and IL-6 are dispensable [23, 60].

In summary, the K/B×N serum transfer model confirms the prominent role of FcγRIII in the downstream effector phase of arthritis, but also indicates a secondary role for FcγRI and FcγRIV. In this passive model FcγRIIB acts as a negative regulator of arthritis development.

Antigen-induced arthritis

Antigen-induced arthritis is initiated by immunization using the foreign antigen methylated BSA (mBSA) with complete

Freund's adjuvant, establishing strong antigen-specific cellular and humoral immunity, followed by intra-articular injection of the antigen (challenge) into the knee joints. AIA is dependent on antigen-specific T cells and immune complex formation.

In FcR γ-chain KO mice, the inflammatory response in AIA, as determined by measuring the swelling of the inflamed knee joint until day 7 after the challenge, is significantly decreased compared to the response in wild-type controls [37]. However, in FcγRI and FcγRIII KO mice, the inflammatory response is unchanged, indicating either that FcγRI and FcγRIII are redundant or that FcγRIV plays a substantial role [61]. At day 7 after challenge, influx of inflammatory cells and deposition of IC and complement components is comparable to controls in FcR γ-chain, FcγRI, and FcγRIII KO strains [37, 61]. FcγRIIB KO mice and FcγRI/ FcγRII/ FcγRIII triple KO mice have elevated numbers of inflammatory cells, however, without changing the polymorphonuclear leukocyte/macrophage ratio [61]. Early cartilage destruction in all FcγR KO strains, as reflected by PG depletion, is comparable to the early cartilage destruction in wild-type littermates [37, 61]. This reversible phase of cartilage destruction is most probably an IC-independent feature of joint inflammation, because it is also observed in the IC-independent zymosan-induced arthritis [62]. More interestingly, hallmarks of severe cartilage damage, as determined by the formation of the matrix metalloproteinase (MMP)-induced neoepitope VDIPEN, erosion of cartilage matrix or chondrocyte death are absent in γ-chain KO mice and FcγRI/ FcγRII/ FcγRIII triple KO mice, unchanged in FcγRIII KO mice, greatly decreased in FcγRI KO mice, and elevated in FcγRIIB KO mice compared to wild-type mice. These results suggest a dominant role for FcγRI and a minor role for FcγRIII in the chronic phase of cartilage destruction [37, 61]. In contrast, bone destruction is similar in FcR γ-chain KO and wild-type control mice, while in FcγRIIB KO and FcγRI/ FcγRII/ FcγRIII triple KO mice, bone erosion is increased [85].

Cellular immunity as determined by measuring proliferation of splenic lymphocytes against mBSA is unaltered in γ-chain, FcγRI, FcγRIII, and FcγRIIB KO mice [37, 61]. The levels of circulating antibodies against mBSA are similar in γ-chain, FcγRI and FcγRIII KO mice and in wild-type controls, but significantly increased in FcγRIIB KO and FcγRI/ FcγRII/ FcγRIII triple KO mice [37, 61, 85]. These observations indicate that activating FcγR are involved in the far downstream effector phase of AIA, most likely by activation of latent MMPs [37].

AIA develops similarly in mast cell-deficient (WBB6F1-W/Wv) mice and wild-type controls suggesting that mast cells do not play a role in this model [63]. In contrast, Mφs appear to be crucial, as selective removal of synovial macrophages before AIA induction inhibits arthritis [64].

From these complex data can be concluded that the FcR γ-chain is absolutely required for inflammation and cartilage destruction, but not for bone destruction in AIA. The individual activating FcγR are redundant in inflammation, and FcγRI plays a dominant role in cartilage destruction in this model. FcγRII is a strong inhibitor of inflammation and bone erosion.

Immune complex-mediated arthritis

In immune complex-mediated arthritis (ICA), mice are passively immunized against the foreign antigen lysozyme by transfer of rabbit-anti-lysozyme antiserum and subsequently challenged by direct injection of lysozyme in the knee joints.

FcR γ-chain and FcγRIII single KO mice, and FcγRI/III double KO mice are resistant to ICA, while FcγRI KO mice show similar disease as wild-type controls [65–67], indicating that FcγRIII is the dominant activating receptor in this passive model. However, both FcγRI and FcγRIII KO mice show reduced cartilage destruction [67]. In FcγRIIB knockout mice, both inflammation and cartilage destruction are increased compared to controls [38].

Compared to FcγRI/III KO mice, FcγRI/II/III triple KO mice have substantially increased inflammation, and tremendously increased deposition of IC in the knee joints. These observations indicate that, in addition to its important role in the downregulation of the B cell receptor and FcR signaling, FcγRIIB is also involved in the clearance of soluble IC, which is consistent with in vitro findings [65]. Moreover, under these extreme conditions, inflammation becomes independent from FcγRI and FcγRIII. However, despite the increased joint inflammation, the FcγRI/II/III triple KO mice show virtually no MMP-mediated cartilage destruction and chondrocyte death [65] leaving little room for a substantial role of the recently identified FcγRIV in the pathology of ICA.

ICA is thought to be mediated primarily by synovial macrophages [68]. FcγR expression on macrophages determines the severity and chronicity of inflammation and cartilage destruction in ICA [66]. It is hypothesized that in AIA, activated T cells present in the joints act as a source of cytokines such as IFNγ, which can increase FcγR expression on monocytes and Mφs, whereas in ICA these T cells are absent. This explains the difference in FcγR involvement between AIA and ICA in the following way. FcγRI expression during AIA is upregulated by T cell derived IFNγ, hence, late cartilage destruction becomes entirely FcγRI-dependent. Artificially induced local overexpression of IFNγ by adenovirus expression vectors in the knee during ICA results in elevated chondrocyte death in wild-type and FcγRIII KO mice, but not in FcγRI KO mice [69, 70]. However, MMP-induced proteoglycan damage is elevated in FcγRI KO mice as well, indicating that FcγRIII—when upregulated by IFNγ—is able to mediate this process [69]. In FcγRIII KO mice IFNγ—most likely through increasing FcγRI expression on resident macrophages in the joint—is able to bypass FcγRIII requirement for inflammation during ICA. This study also proves that both FcγRI and FcγRIII can contribute to MMP-mediated destruction of cartilage [70].

In conclusion, FcγRIII is the major mediator of joint inflammation in ICA, while FcγRI and FcγRIII are similarly important in mediating severe cartilage destruction. In the downstream effector phase, FcγRIIB is not only involved in arthritis development by negatively regulating the signaling of the activating FcγR, but also by mediating soluble IC clearance. There are little or no indications for a role of FcγRIV.

Role of antibody effector pathways in rheumatoid arthritis

A number of studies indicate that FcγR play an important role in the human chronic autoimmune disease rheumatoid arthritis. In humans, the FcγR gene family is more complex than in mice. In addition to the FcR γ-chain-associated activating FcγRI and FcγRIIIA and the inhibiting FcγRIIB, two other human FcγR exist: the activating single-chain ITAM-containing receptor FcγRIIA and FcγRIIIB with a phosphatidylinositol anchor. It is proposed that FcγRIIA and FcγRIIIA should be considered as the human counterparts of mouse FcγRIII and FcγRIV, respectively [16]. Moreover, the distinct biological functions of the four different subclasses of IgG (IgG1, IgG2a, IgG2b and IgG3 in mice and IgG1, IgG2, IgG3 and IgG4 in humans) do not fully overlap between mouse and man. All together, these species differences hamper a direct extrapolation of the results with mouse models to the human disease.

Polymorphisms in the gene of FcγRIIIA have been correlated to various aspects of RA [71–74]. FcγRIIA has also been implicated in RA [75], while human FcγRIIA transgenic mice become susceptible to CIA on non-permissive background [76]. Altered expression levels of FcγR in RA patients on circulating monocytes [77] or DCs [78] have also been reported.

The promising results with anti-CD20 therapy, targeting autoantibody-producing B cells in RA, not only indicate that, as in arthritis in mice, autoantibodies play an important role, but also that in humans therapeutic intervention upstream in antibody effector pathways might be a useful alternative for anti-TNF therapy.

Concluding remarks

From the studies on FcγR KO mice in a variety of arthritis models on different genetic backgrounds, a common picture emerges with respect to the contribution of the FcγR to the pathology of the disease. It can be concluded that activating FcγR are crucial players in the downstream effector phase of arthritis, but have little or no role in the afferent and central phase. Although FcγRIII plays the most prominent role, there are strong indications that also FcγRI, and to a lesser extent FcγRIV, are involved resulting in the following hierarchy: FcγRIII > FcγRI > FcγRIV. Results with the different FcγR KO mice in murine arthritis models are summerized in Table 2.

The dominant role of FcγRIII probably reflects its broad expression pattern (Table 1), high basal expression level, and different ligand specificity compared to the other activating receptors. In mice, FcγRIII is the only activating FcγR expressed on mast cells and NK cells. In contrast FcγRI is exclusively expressed on mononuclear cells (monocytes, Mφs and DCs) that also express FcγRIII at higher levels in resting conditions. FcγRIII is the only activating receptor that binds IgG1 IC, but it is also capable of binding IgG2a IC quite effectively (Table 1). The roles of FcγRI and FcγRIV seem to be more strictly regulated, suggesting that these receptors function mainly in fine tuning the downstream antibody effector pathways. The expression of FcγRI and FcγRIV, being low under resting conditions, increases more strongly in response to proinflammatory cytokines than the expression of FcγRIII. Moreover, newly formed IgG2a IC have to compete with monomeric IgG2a for binding to the high affinity receptor FcγRI. A scenario might be that in a very early phase of an IC-mediated inflammatory response, FcγRIII is the first receptor to become triggered, resulting in the release of proinflammatory mediators, e.g., cytokines, chemokines, vasoactive amines, etc., inducing upregulation of the expression of FcγRI and FcγRIV and attraction of other effector cells. In addition, the dominant IgG subclass within the antibody response, e.g., IgG1, IgG2a or IgG2b, will determine to what extent the different activating receptors will become triggered in the later phase. This scenario would be in agreement with the models proposed for the K/B×N serum-induced arthritis. Upon intravenous injection of serum small IgG-GPI IC are formed, that cross-link FcγR on effector cells that have access to circulating IC, most likely neutrophils, which express FcγRIII [50]. It is also proposed that FcR γ-chain, expressing cells other than neutrophils or mast cells in an organ distant from the joint

Table 2 Overview of arthritis in FcγR KO mice

Strain	Parameters	Active models			Passive models		Intra-articular induction	
		CIA (DBA/1)	PGIA	GPI induced	Anti-CII Ab	K/B×N serum	AIA	ICA
FcR γ-chain KO	Inflammation	↓	↓	↓	↓↓	↓↓	↓	↓
	Joint pathology	↓	↓	↓	↓↓	↓↓	↓↓	↓
FcγR III KO	Inflammation	↓	↓↓	ND	↓	↓	=	↓
	Joint pathology	↓	↓	ND	↓	↓	=	↓↓
FcγR I KO	Inflammation	ND	=	ND	ND	=	=	=
	Joint pathology	ND	=	ND	ND	=	↓	↓
FcγR IIB KO	Inflammation	↑	↑	↑	↑	↑	↑	↑
	Joint pathology	↑	↑	↑	↑	↑	↑	↑

An arrow down denotes a decrease in the parameter; two arrows down denote a marked decrease in the parameter. An arrow pointing up denotes an increase in the parameter. An equal sign represents an unchanged parameter. Inflammation indicates edema and/or cellular infiltration in the joints. Joint pathology stands for histological changes, e.g., destruction of the cartilage and/or the bone.

ND Not determined as compared to wild type controls

(probably the liver), are required [58]. The observation that FcγRIII KO mice can be rendered susceptible to CIA upon transfer of FcγRIII$^+$ peritoneal macrophages indicates that the candidate cell type could be the peritoneal macrophage [43]. This first interaction triggers the release of inflammatory mediators causing macromolecular vasopermeability in the vasculature of the joints, which appears to be particularly sensitive, allowing the IC to cross-link FcγRIII on mast cells found in close proximity to the microvasculature in the synovium. The activated mast cells release mediators such as vasoactive amines, which further enhances vasodilatation. This model also explains why mast cells are not required in AIA. In AIA the arthritis-inducing IC are formed in situ in the knee joint upon intra-articular injection of the antigen, bypassing the mast cell-dependent process of vasodilatation required in the anti-CII and K/B×N serum-induced arthritis models for the delivery of the arthritogenic antibodies into the joints.

Once inside the joint, the autoantibodies bind to the self-antigen at the surface of the articular cartilage forming new IC that trigger the alternative pathway of complement and might activate neutrophils, mast cells, Mφs, and NK cells via cross-linking of their FcγR resulting in the release of the anaphylatoxin C5a, proinflammatory cytokines, chemokines, and other inflammatory mediators. At this stage, complement (alternative pathway and C5 effector pathway) seems to be the dominant effector pathway driving inflammation and, especially, recruitment of inflammatory cells, e.g., neutrophils. In contrast to organs like the kidney and muscle, the cartilage surface of the joints is devoid of cell membrane-bound negative controlling factors (e.g., DAF/CD55 and MCP/CD46) of the alternative pathway of complement [79]. All together, these events result in a further increase of vasodilatation and influx of autoantibodies and leukocytes. In K/B×N serum-induced arthritis, the process is still reversible until this stage, as is shown by the injection of anti-C5 antibodies and the requirement for repeated injections of serum with (anti-GPI) autoantibodies to maintain the arthritis [23]. In a prolonged severe inflammation, the process enters a chronic phase, in which the role of macrophages, synoviocytes, chondrocytes, and osteoclasts, and the inflammatory cytokines IL-1β, TNFα and MMPs becomes prominent, resulting in sequential pathological changes, i.e., synovial hyperplasia, pannus formation, and finally irreversible cartilage and bone destruction. Independent from factors that play a role in the initial phase of arthritis, e.g., method of immunization (active vs passive), isotype of the arthritogenic antibody (IgG2a vs IgG1), autoantigen (CII vs GPI or proteoglycan), and genetic background (C57Bl6 vs Balb/c), the antibody effector pathways converge to a common downstream effector pathway causing tissue damage [55, 80]. Overexpression of TNF-α [35] or deficiency of the negative regulator IL1ra [36] is sufficient to develop arthritis spontaneously. All together, this strongly suggests that the role of IC and FcγR in cartilage and bone destruction is indirect by triggering the release of downstream effector cytokines (such as IL-1β and TNF-α) and MMPs. However, it is not yet clear which FcγR on what effector cells initiates the release of these factors. In AIA, FcγRI exclusively expressed on mononuclear cells is the dominant activating FcγR involved in cartilage destruction. Although in ICA, FcγRIII also plays a role in this pathogenic process, leaving open the opportunity that neutrophils are also involved, the disease can be blocked by depletion of macrophages only [68]. In RA patients, a correlation between macrophage number and erosion of cartilage matrix has been reported [81]. These data suggest a dominant role for Mφs in cartilage destruction. In conclusion, within the total downstream effector phase of arthritis, three sequential steps can be recognized. The first step is the FcγR (FcγRIII)-dependent entry of autoantibodies into the joint followed by a complement-dependent recruitment of effector cells (alternative pathway and C5 complement effector pathway). Finally, in the third step, which is also FcγR-dependent, release of proinflammatory cytokines and MMPs that cause the irreversible pathogenic changes in the tissue, is triggered.

The broad expression pattern of FcγRIIB, including not only the effector cells of the myeloid lineage, but also B lymphocytes and FDCs (Table 1) and its specific role in a negative feedback mechanism controlling antibody production, sets FcγRIIB somewhat apart from the activating receptors. FcγRIIB acts as a major regulator in murine arthritis by regulating antibody titers, activation of effector cells, and endocytosis of ICs. Its association with autoimmunity is strain-dependent, indicating that other genetic factors are strongly involved. Detailed analysis of the complex role of the activating FcγRIII and the inhibiting FcγRIIB with their broad expression patterns should strongly benefit from the availability of conditional KO models.

In the light of the strong indications from (KO) mouse models that FcγR are important players in arthritis, it is somewhat surprising that genetic screenings did not reveal very strong associations between polymorphisms in FcγR and predisposition to arthritis development [82]. Although genetic screenings identified similar susceptibility loci (C5 and FcγRIIB) in both CIA and the K/B×N serum transfer model, [55, 80], there is a discrepancy also in mice between the outcome of functional studies and genetic linkage studies. However, very recently, copy number polymorphisms of different genes with important functions in immunity, including FcγR, could be associated with autoimmune disease in rats, humans, and mice [83, 84]. Therefore, future extensive genetic screening for copy number polymorphisms in humans might provide evidence for a strong association between copy number polymorphisms of the different members of the FcγR gene family and RA. This would be in agreement with functional studies in mice that predict that overexpression, but not impairment of activating FcγR, might lower the threshold for the triggering of effector pathways by pathogenic IC.

The most effective RA therapy, based on the inhibition of TNF-α by treatment with anti-TNF-α antibodies, has several constraints. An alternative is intervention in antibody effector pathways more upstream. The growing detailed insight in how individual FcγR on different cell types contribute to arthritic pathology will aid the design of improved anti-rheumatoid drugs.

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