Editorial

Activating and inhibitory Fcγ receptors in rheumatoid arthritis: from treatment to targeted therapies

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Abstract

Fcγ receptors (FcγRs) bind the constant Fc region of IgG molecules. IgG/antigen-containing immune complexes elicit a variety of effector functions in cells that express activating FcγRs. Because activating FcγRs are present on cells from the innate immune system, such as dendritic cells, monocytes/macrophages and granulocytes, these IgG receptors form a crucial link between the innate and the acquired immune systems. Recently, the ability to detect the inhibitory FcγRIIb on cells has indicated an imbalance between activating and inhibitory FcγRs in rheumatoid arthritis. This progress offers an opportunity to study modulation of FcγR balance and could stimulate development of FcγR-directed immunotherapy.

Activating Fcγ receptors (FcγRs; FcγRI, FcγRIIa, FcγRIIIa and FcγRIIIb) carry activation signalling motifs intracellularly, which upon binding of IgG/antigen-containing immune complexes can induce phagocytosis, antigen presentation, antibody-dependent cell mediated cytotoxicity, and complement-mediated lysis and cytokine secretion. Expression of FcγRIIb, which carries an inhibitory signalling motif, downregulates effector functions upon binding of IgG-containing immune complexes, thereby preventing proinflammatory responses mediated by activating FcγRs. Studies of surface expression of the inhibitory FcγRIIb in humans have for some time been hampered by the lack of availability of antibodies that can distinguish between FcγRIIb and FcγRIIa expression, because the extracellular part of these receptors is highly homologous.

In the previous issue of *Arthritis Research and Therapy*, Magnusson and coworkers [1] demonstrated increased expression of both the inhibitory FcγRIIb and activating FcγRs (FcγRI and FcγRIII) in synovial tissue of patients with rheumatoid arthritis (RA) compared with that from healthy control individuals. In addition, anti-inflammatory treatment with glucocorticoids was shown to reduce expression of activating FcγRs. Based on these data the authors conclude that because RA patients do not fail to upregulate inhibitory FcγRIIb receptors are upregulated in RA, targeting activating FcγRs may represent a valuable therapeutic strategy. Although FcγRIIb expression in RA synovial tissue is demonstrated in this study, the actual levels were not quantified and so it remains to be demonstrated whether the balance at the site of inflammation is skewed compared with the peripheral compartment. Recently, in the circulation of RA patients compared with healthy control individuals, a skewed balance toward activating receptors was demonstrated on monocytes [2]. Recent findings indicate that regulation of this FcγR balance markedly influences immunopathology in arthritic conditions.

The balance of activating and inhibitory receptors is of major importance to the elicited effector functions of cells upon engagement of IgG or IgG-containing immune complexes. *In vitro*, increased or sustained levels of activating over inhibitory FcγR expression on monocytes (for example, by interferon-γ) are associated with enhanced IgG-triggered proinflammatory cytokine production. In contrast, regulation of the FcγR balance in favour of inhibitory FcγRIIb expression (for instance, by IL-4 and IL-4 plus IL-10) is associated with prevention of IgG-triggered immune activation [2]. In accordance with this, in mice it has been shown that deficiency of activating FcγRs leads to inhibition of arthritis and immunopathology, whereas deficiency of the inhibitory FcγRIIb promotes arthritis and leads to increased immunopathology [3]. Supporting human *in vitro* findings, treatments that alter the balance between inhibitory and activating FcγRs influence experimental arthritis [4]. Although experimental data have shown the importance of shifting the FcγR balance toward the inhibitory FcγRIIb, the effects of

FcγR = Fcγ receptor; IL = interleukin; RA = rheumatoid arthritis.

antirheumatic therapies in RA patients on FcγR balance, either peripherally or locally, have not been studied. Thus far, studies have only shown therapies to modulate activating FcγRs; downregulation of activating FcγRs has been demonstrated for glucocorticosteroids (FcγRI), methotrexate (FcγRI and FcγRIIa) and anti-tumour necrosis factor-α (FcγRI), and upregulation for IL-10 (FcγRI and FcγRIIa). Future studies should document how the balance is altered by antirheumatic drugs and how a shift toward the inhibitory FcγRIIb can be optimized to improve treatment of arthritis. Considering the arthritis-inducing capacity of antibodies characteristic for RA [5], the new opportunity to study surface expression of inhibitory and activating FcγRs will lead to enhanced understanding of FcγR-mediated immunopathology in RA.

Apart from nonspecific modulation of the FcγR balance by existing or currently developed treatments, specific targeting of FcγRs offers a valuable therapeutic window of opportunity. Ways to silence gene expression of activating FcγRs or increase expression of FcγRIIb, for instance by using viral expression vectors, may represent approaches to regulate effector functions of FcγR-expressing cells. Illustrating the potential of specific FcγR targeting, it was recently shown that specific blockade of FcγRIIa inhibits IgG-triggered proinflammatory cytokine production by dendritic cells (tumour necrosis factor-α, IL-6 and IL-8) [6]. In contrast, specific blockade of FcγRIIb enhanced this IgG-triggered cytokine production.

FcγRs, by promoting delivery of antigen via IgG-containing immune complexes to antigen-presenting cells such as macrophages and dendritic cells, potently promote T-cell activation in RA [7]. This function could contribute to the co-localization of and strong correlation between numbers of activating FcγR-expressing cells and T cells in RA synovial tissue [1]. By enhancing the capacity of effector T cells to activate B cells as well as fibroblasts and osteoclasts (and macrophages and dendritic cells), FcγRs thus efficiently augment inflammation and joint destruction in arthritic conditions. In inflamed RA synovial tissue, macrophages and dendritic cells have now been shown to express FcγRIIb in addition to activating FcγRs [1,8]. Considering the pivotal role played by these macrophages and dendritic cells in RA, and the influence of FcγR balance on these cells in RA, it is evident that more specific FcγR-directed therapies are required to suppress RA optimally. Even blocking reagents such as soluble FcγRs may lack sufficient therapeutic efficacy because they will prevent IgG-containing immune complexes from binding to activating but also inhibitory FcγRs. Drugs that shift the FcγR balance toward the inhibitory FcγRIIb, such as Fc-sialylated IgGs, which are present in intravenous immune globulin preparations, are likely to have greater therapeutic potential [4]. Enrichment for Fc-sialylated IgGs in intravenous immune globulin preparations (from 1% to 2%, to 20%) resulted in a 10-fold increased capacity to suppress experimental arthritis. Based on these findings, receptors for sialic acid are postulated as candidate receptors that could be exploited to induce FcγRIIb upregulation and suppress inflammation. Finally, specific blockade of FcγRIIa or other activating FcγRs or reagents that induce FcγRIIb-mediated inhibition [9,10] could be used to optimize treatment of RA as well as other rheumatic diseases.

Competing interests

The author declares that they have no competing interests.

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