

## 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 FcγRIIIa 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 Fc $\gamma$ R balance, either peripherally or locally, have not been studied. Thus far, studies have only shown therapies to modulate activating Fc $\gamma$ Rs; downregulation of activating Fc $\gamma$ Rs has been demonstrated for glucocorticosteroids (Fc $\gamma$ RI), methotrexate (Fc $\gamma$ RI and Fc $\gamma$ RIIa) and anti-tumour necrosis factor- $\alpha$  (Fc $\gamma$ RI), and upregulation for IL-10 (Fc $\gamma$ RI and Fc $\gamma$ RIIa). Future studies should document how the balance is altered by antirheumatic drugs and how a shift toward the inhibitory Fc $\gamma$ RIIb 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 Fc $\gamma$ Rs will lead to enhanced understanding of Fc $\gamma$ R-mediated immunopathology in RA.

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

Fc $\gamma$ Rs, 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 colocalization of and strong correlation between numbers of activating Fc $\gamma$ R-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), Fc $\gamma$ Rs 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 Fc $\gamma$ RIIb in addition to activating Fc $\gamma$ Rs [1,8]. Considering the pivotal role played by these macrophages and dendritic cells in RA, and the influence of Fc $\gamma$ R balance on these cells in RA, it is evident that more specific Fc $\gamma$ R-directed therapies are required to suppress RA optimally. Even blocking reagents such as soluble Fc $\gamma$ Rs may lack sufficient therapeutic efficacy because they will prevent IgG-containing immune complexes from binding to activating but also inhibitory Fc $\gamma$ Rs. Drugs that shift the Fc $\gamma$ R balance toward the inhibitory Fc $\gamma$ RIIb, 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 Fc $\gamma$ RIIb upregulation and suppress inflammation. Finally, specific blockade of Fc $\gamma$ RIIa or other activating Fc $\gamma$ Rs or reagents that induce Fc $\gamma$ RIIb-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.

## References

1. Magnusson SE, Engstrom M, Jacob U, Ulfgren AK, Kleinau S: **High synovial expression of the inhibitory Fc $\gamma$ RIIb in rheumatoid arthritis.** *Arthritis Res Ther* 2007, **9**:R51.
2. Wijngaarden S, van de Winkel JG, Jacobs KM, Bijlsma JW, Lafeber FP, van Roon JA: **A shift in the balance of inhibitory and activating Fc $\gamma$  receptors on monocytes toward the inhibitory Fc $\gamma$  receptor IIb is associated with prevention of monocyte activation in rheumatoid arthritis.** *Arthritis Rheum* 2004, **50**:3878-3887.
3. Kagari T, Tanaka D, Doi H, Shimozato T: **Essential role of Fc $\gamma$  receptors in anti-type II collagen antibody-induced arthritis.** *J Immunol* 2003, **170**:4318-4324.
4. Kaneko Y, Nimmerjahn F, Ravetch JV: **Anti-inflammatory activity of immunoglobulin G resulting from Fc sialylation.** *Science* 2006, **313**:670-673.
5. Petkova SB, Konstantinov KN, Sproule TJ, Lyons BL, Awwami MA, Roopenian DC: **Human antibodies induce arthritis in mice deficient in the low-affinity inhibitory IgG receptor Fc $\gamma$  receptor IIb.** *J Exp Med* 2006, **203**:275-280.
6. Boruchov AM, Heller G, Veri MC, Bonvini E, Ravetch JV, Young JW: **Activating and inhibitory IgG Fc receptors on human DCs mediate opposing functions.** *J Clin Invest* 2005, **115**:2914-2923.
7. Sallusto F, Lanzavecchia A: **Efficient presentation of soluble antigen by cultured human dendritic cells is maintained by granulocyte/macrophage colony-stimulating factor plus interleukin 4 and downregulated by tumor necrosis factor alpha.** *J Exp Med* 1994, **179**:1109-1118.
8. Radstake TR, Franke B, Wenink MH, Nabbe KC, Coenen MJ, Welsing P, Bonvini E, Koenig S, van den Berg WB, Barrera P, et al.: **The functional variant of the inhibitory Fc $\gamma$  receptor IIb (CD32B) is associated with the rate of radiologic joint damage and dendritic cell function in rheumatoid arthritis.** *Arthritis Rheum* 2006, **54**:3828-3837.
9. van Royen-Kerkhof A, Sanders EA, Walraven V, Voorhorst-Ogink M, Saeland E, Teeling JL, Gerritsen A, van Dijk MA, Kuis W, Rijkers GT, et al.: **A novel human CD32 mAb blocks experimental immune haemolytic anaemia in Fc $\gamma$ RIIA transgenic mice.** *Br J Haematol* 2005, **130**:130-137.
10. Monari C, Koziel TR, Paganelli F, Pericolini E, Perito S, Bistoni F, Casadevall A, Vecchiarelli A: **Microbial immune suppression mediated by direct engagement of inhibitory Fc receptor.** *J Immunol* 2006, **177**:6842-6851.