Fc Gamma Receptors as Regulators of Bone Destruction in Inflammatory Arthritis

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Bone erosion is one of the primary features of inflammatory arthritis and is caused by excessive differentiation and activation of osteoclasts. Fc gamma receptors (FcγRs) have been implicated in osteoclastogenesis. Our recent studies demonstrate that joint-deposited lupus IgG inhibited RANKL-induced osteoclastogenesis. FcγRI is required for RANKL-induced osteoclastogenesis and lupus IgG-induced signaling transduction. We reviewed the results of studies that analyzed the association between FcγRs and bone erosion in inflammatory arthritis. The analysis revealed the dual roles of FcγRs in bone destruction in inflammatory arthritis. Thus, IgG/FcγR signaling molecules may serve as potential therapeutic targets against bone erosion.

Keywords: FcγRs, autoantibodies, osteoclasts, bone erosion, inflammatory arthritis

INTRODUCTION

Inflammatory arthritis is a group of diseases characterized by joint inflammation and bone damage. About 0.1% of adults develop inflammatory arthritis annually (1). Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by progressive synovitis and bone destruction, causing irreversible joint damage and disability (1–4). Bone erosion is the central hallmark of RA in ultrasonography identification (5, 6). Anti-citrullinated protein antibodies (ACPAs) are considered to be among the leading risk factors for bone destruction in RA (7). Ankylosing spondylitis (AS) and psoriatic arthritis (PsA) are other common inflammatory arthritis diseases with bone destruction (8, 9).

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by multi-organ tissue damage and high levels of autoantibodies in the serum (10). Arthritis is a common clinical manifestation with a prevalence of 69 to 95% in patients with SLE (11). However, only 4 to 6% of patients with SLE arthritis display bone erosion on plain radiographs (12–14). As to ACPA positive SLE patients, which are also called rhupus patients, they often overlapped clinical features and fulfilled American College of Rheumatology (ACR) criteria for RA classification (15, 16). It is still unclear why lupus arthritis without ACPA lacks bone destruction. Recently, FcγRs have been reported to exert a regulatory effect on osteoclastogenesis (17–25). Our recent study demonstrated that joint-deposited lupus IgG triggered arthritis without bone erosion in mice and lupus IgG inhibited osteoclastogenesis induced by receptor activator of nuclear factor kappa-B ligand (RANKL). FcγRI exerted an inhibitory effect of lupus IgG on RANKL-induced osteoclastogenesis (26). Our study suggests that FcγR could function as critical regulators of inflammatory arthritis.
Here, we review the published studies and demonstrate the association between the FcγR and bone erosion in inflammatory arthritis.

**Fcγ RECEPTOR FAMILY**

FcγRs are receptors for the constant (Fc) region of IgG; these are expressed widely on the surface of immune cells, including monocytes, macrophages, neutrophils, dendritic cells (DCs), B cells, natural killer cells, and mast cells. Four different classes of FcγRs have been identified in mice, namely FcγRI, FcγRIIIB, FcγRIII, and FcγRIV (27–29). The human and primate FcγR classifications are more complex. Humans possess six classic FcγRs with different IgG binding capacity and downstream signaling pathways: FcγRI (CD64), FcγRIIA (CD32A), FcγRIIB (CD32B), FcγRIIC (CD32C), FcγRIIIA (CD16A), and FcγRIIIB (CD16B), which are encoded by genes FCGR1A, FCGR2A, FCGR2B, FCGR2C, FCGR3A, and FCGR3B, respectively (Figure 1).

The affinity of FcγRs for IgG depends on the type of FcγR and IgG isotypes (30–36). FcγRI is the only known high-affinity FcγR ($10^8$–$10^9$ M$^{-1}$) with a restricted isotype specificity. In contrast, FcγRII and FcγRIII have a low affinity for IgG (about $10^6$ M$^{-1}$) with a broader isotype binding pattern (31, 32). FcγRIV is a novel receptor conserved across all mammalian species with an intermediate affinity ($10^7$ M$^{-1}$) and restricted subclass specificity (29, 37). FcγRIIIA is engaged by IgG1 and IgG2, whereas FcγRI and FcγRIV are engaged by IgG2 only (35). The affinity of mouse FcγRs is significantly higher compared with their corresponding human FcγRs (36).

FcγRs are divided into activating and inhibitory receptors and coexpressed on the same cell (38). Activating FcγRs, including FcγRI and FcγRIII, contain an immunoreceptor tyrosine-based activation (ITAM) in intracellular structure and transmit their signals via the ITAM, which recruits spleen tyrosine kinase (Syk) (39). FcγRIIB is the only known inhibitory FcγR with an immunoreceptor tyrosine-based inhibitory motif (ITIM) in its intracytoplasmic domain (40). The phosphorylation of ITIM counteracts the signals mediated by activating FcγRs (41–43). FcγRIIB is expressed widely on B cells, macrophages, and mast cells and downregulates several cellular functions, such as B-cell activation and mast cell degranulation (44). The activating-to-inhibitory (A/I) ratio on the same cell acts as the specific checkpoint for the arrest or progression of an immune response. Surprisingly, when monomeric or low-affinity immune complexes bind to activating FcγRs, the normally activating ITAM domain cannot induce co-aggregation of activating receptors, thereby partially phosphorylating the ITAM domain. Thus, partial tyrosine phosphorylation of ITAM by Src family kinases may result in the recruitment of inhibitory SHIP. This is called inhibitory ITAM (ITAMi) signal and is important in maintaining immune homeostasis (45–47).

Unlike other activating FcγRs, FcγRII proteins do not require the common FcγR-γ-chain for stable expression or function. They all have signaling motifs in their intracellular cytoplasmic domains (48). All the above FcγRs are transmembrane receptors.

![FIGURE 1](https://www.frontiersin.org) | The family of classical Fc receptors for IgG. Schematic representations of FcγRs with respect to the cell membrane (brown bar), in complex with their respective signaling subunits. Mouse and humans have one high-affinity receptor, FcγRI; all other FcγRs have a low-to-medium affinity for the antibody Fc fragment.
glycoproteins, except for human FcγRIIB, which is expressed on neutrophils and is a glycoporphatidylinositol (GPI)-anchored protein (49, 50). The mechanisms by which FcγRIIB transduces signals are still unknown (51).

**FcγRs AND ARTHRITIS**

During autoimmune diseases, such as RA and SLE, the autoantibodies and immune complexes cause inflammation via FcR aggregation (52). The altered expression of FcγRs on immune cells in the circulation and synovium of RA patients is the first indication of their involvement in inflammation (53–60). The absence of all FcγRs does not affect the number of osteoclast precursors or their osteoclastogenic potential. However, it reduces joint inflammation and bone erosion during inflammatory arthritis (61). FcγRIIB is particularly critical for maintaining the balance of an efficient inflammatory response or countering unwanted autoimmunity attacks. Multiple clinical studies have shown that FcγRIIB is a reliable biomarker for SLE susceptibility in different ethnic groups. FcγRIIB and its signaling pathways represent a vital checkpoint in peripheral and central tolerance and in controlling the development of autoreactive antibodies (62).

In addition to the altered expression of FcγRs, genetic variants associated with related single-nucleotide polymorphisms (SNPs) in populations with RA and lupus arthritis have been reported. Several genes encoding FcγRs that alter the affinity of FcγRs for IgGs have been described in several RA populations. In particular, some of these, such as the hFcγRIIa-R131 variant, which is related to an increased risk of developing RA, even influence the susceptibility to RA development and the response to treatment (63–70). In addition, an association between lupus arthritis and the FCG2RA as well as FCG2RA low copy number genotypes has been observed in Taiwan patients with SLE. The FCG2RA low copy number genotype was significantly enriched in patients with SLE having arthritis (71–73). Moreover, the meta-analysis revealed the association of the FcγRIIa-R131 allele with SLE, especially in African Americans, whereas the FcγRIIa-F176 allele was associated with SLE in Caucasians and other groups (74). Furthermore, Tsang et al. demonstrated the association between low-affinity FcγR polymorphisms and susceptibility to SLE (75).

Studies using FcγR gene-deficient mice have greatly enhanced our understanding of the role of FcγRs in inflammatory arthritis (76, 77). The lack of activating FcγRs alleviates the disease severity in arthritis models (78–81). In different disease phases of inflammatory arthritis, the individual activating FcγRs have different significance (36, 61, 82–86). In the absence of FcγRI, FcγRIIB, and FcγRIIa, FcγRIIV is sufficient to induce arthritis alone (35). In contrast with activating FcγRs, the inhibitory FcγRIIB suppresses inflammation by inhibiting the activating signaling, as well as providing negative feedback on the production of autoantibodies by B cells (87–92).

Autoantibodies and their immune complexes play a central role in shaping a pro-inflammatory environment. Indeed, complexes of ACPA and rheumatoid factor (RF) induce the production of potent inflammatory cytokines (93–96). This effect is predominantly mediated by FcγR signaling on macrophages (51, 97). Tumor necrosis factor (TNF)-α, in combination with cytokines interleukin (IL)-4 and IL-13, downregulates FcγR-mediated function by decreasing the expression of activating FcγRs, suggesting that downregulated activating FcγRs might have an anti-inflammatory effect (98).

The Fc receptors on white blood cells are essential for effective phagocytosis of immune complexes and bacteria. Moreover, FcγRI is upregulated during infection. FcγRI (CD64) has previously been reported to distinguish systemic infections from inflammatory autoimmune diseases and viral infections. Patients without inflammatory and infectious conditions, such as osteoarthritis, have a lower level of neutrophil FcγRI than those with infections (99–104). Oppegaard et al. investigated the use of FcγRI in discerning septic arthritis from inflammatory joint disease and found that FcγRI is highly specific for infectious diseases, including septic arthritis. However, its sensitivity is poor in local infections (104). Although distinct meta-analyses have confirmed this, more large prospective studies need to be conducted to verify several cut-off values reported in the neutrophil FcγRI test in the clinical setting (105, 106).

Human and murine activating FcγRs are not functionally equivalent. A few studies performed in transgenic mice expressing human FcγRs examined their involvement in inflammatory arthritis (107). The results confirmed that the expression of the human FcγRIIA is associated with spontaneous autoimmune inflammation, with a crucial role in autoimmune diseases (92).

**FcγR ROLE IN BONE EROSION**

**Osteoclast Activation and Differentiation**

Bone balance depends on a dynamic regulation of bone formation and resorption, which are predominantly mediated by osteoblasts and osteoclasts, respectively (108, 109). Enhanced osteoclast activity could result in severe bone destruction as exemplified in autoimmune inflammatory diseases such as RA, whereas defective osteoblast differentiation causes diseases with a high bone mass, including osteopetrosis. Osteoclasts are the only bone-resorbing cells and play a central role in bone erosion. Osteoclasts are derived from multinucleated progenitors of the monocyte/macrophage family and are the link between immune and bone systems. RANK and RANKL are critical factors that together regulate osteoclast functions. In addition, macrophage colony-stimulating factor (M-CSF) is an essential cytokine in osteoclastogenesis (109–111). RANKL is majorly secreted by osteoblasts, osteocytes, T cells, and endothelial cells. And osteocytes express a much higher amount of RANKL required for osteoclastogenesis than osteoblasts (112, 113). The most important negative regulator of RANKL is the decay receptor osteoprotegerin (OPG), which inhibits osteoclastogenesis by preventing RANKL–RANK interaction. The RANKL–RANK–OPG system modulates bone homeostasis by regulating
osteoclasts (114). Osteoblasts and osteocytes also produce OPG to suppress osteoclastogenesis by masking RANKL signaling (115, 116). RANKL initiates osteoclastogenesis by inducing nuclear factor of activated T-cells, cytoplasmic 1 (NFATc1), via TNF receptor-associated factor 6 (TRAF6) and c-Fos pathways (117) (Figure 2). NFATc1 is the master transcription factor for pro-osteoclastogenic genes. In addition, several pro-inflammatory cytokines produced by innate immune cells and T cells, such as TNFα, IL-17, IL-1, and IL-6, stimulate osteoclastogenesis directly or indirectly (118).

**FcγRs and Osteoclastogenesis**

Apart from the M-CSF and RANKL signaling, an ITAM costimulatory signal provided by the accessory protein for RANKL-RANK is required for osteoclastogenesis (119). Takayanagi et al. first reported that the activation of NFATc1 was insufficient for terminal differentiation of monocytes/macrophages into osteoclasts; calcium signals and calcineurin activation are essential for this process (117, 120). Calcium signals in myeloid cells are provided by the ITAM-bearing proteins, Fc receptor γ subunit, and its functional analog DNAX activation protein of 12 kDa (DAP12). Both the accessory proteins are intracellular adaptor molecules and play a crucial function in transducing the costimulatory signals for RANKL (121). Mice lacking the accessory proteins display a severe osteopetrotic phenotype with deficient osteoclast function (122).

FcγRy-chain is associated with immunoglobulin (Ig)-like receptors, such as osteoclast-associated receptor (OSCAR) and paired Ig-like receptor-A (PIR-A) (Figure 2). DAP12 is associated with its signaling counterpart, triggering receptor expressed on myeloid cell-2 (TREM-2), and signal-regulatory protein β1 (SIRPβ1), which are expressed on the cell membrane of osteoclast precursors and are essential for the communication between osteoclast precursors (33, 123). Activation of RANKL-RANK rapidly phosphorylates the ITAM motifs and recruits the protein kinase Syk, subsequently activating multiple downstream signaling cascades, such as phospholipase Cγ (PLCγ) and Bruton’s tyrosine kinase (BTK) as well as Tec kinases. They all enhance the effects of RANKL-signaling by augmenting the calcium influx required for the activation of NFATc1. NFATc1 subsequently migrates to the nucleus, where it binds to its gene promoter and triggers an auto-amplifying feedback loop (124, 125).

Osteoclasts and their precursors express FcγR (126), whereas FcγRI, FcγRIIB, and FcγRIIIA are significantly upregulated during human ex vivo osteoclastogenesis (127). Blocking of the FcR and deleting the FcγR gene reduce osteoclastogenesis.
stimulated by IgG complexes on osteoclast precursor cells (25). Although FcγRs are required for osteoclastogenesis and bone resorption in inflammatory disorders, their specific role in bone homeostasis is not completely understood.

FcγRs and Bone Erosion

Costimulatory signals mediated by the ITAM motif cooperate with RANKL for bone homeostasis, suggesting the link between ITAM-harboring adaptors FcγRs and bone erosion (117). As an important link binding the bone system and immune system, FcγRs are not only receptors for the Fc portion of IgG but are also costimulatory molecules for RANKL-induced osteoclastogenesis (119, 121). Bone damage has been reported in seropositive RA patients before clinical disease onset, highlighting that osteoclastogenesis is independent of joint inflammation (128). This finding challenged the concept that inflammation is the primary trigger for bone erosion in inflammatory arthritis and indicated that bone loss might precede inflammation (129).

The expression of Fcγ receptors on osteoclast precursor cells and mature osteoclasts has been measured. FcγRI and FcγRIII are primarily expressed on human osteoclasts, whereas the inhibitory FcγRIIB is majorly expressed on mature osteoclasts (127). Under physiological conditions, activating FcγRI and FcγRIV in mice does not have a major role in bone characteristics and osteoclast development (22). Bone homeostasis is not significantly different in mice with FcγRI or IV deficiency compared with wild mice (17). In addition, the deficiency of FcγRIIB does not affect osteoclastogenesis (23). Activating FcγRs transmit the positive signal. In contrast, FcγRIII functions as an inhibitory receptor in the differentiation of osteoclast precursor cells under physiological conditions. FcγRIII deprives the FcγRsubunit’s availability for other Ig-like receptors activating receptors, such as PIR-A and OSCAR, thus transmitting an ITAM-mediated inhibitory signal for osteoclastogenesis (130). Naïve FcγRII^{−/−} mice have increased osteoclast numbers and an osteoporotic phenotype (22).

The relative importance of various FcγRs in osteoclastogenesis changes in the inflammatory arthritis microenvironment. Studies demonstrated that the stimulation of FcγRI and FcγRIV increases both osteoclast differentiation and function both in vitro and in vivo (22, 30). FcγRIII levels are increased, and FcγRIIB levels are decreased on bone marrow cells from mice with collagen-induced arthritis (CIA), indicating that FcγRIII induces osteoclastogenesis under inflammatory conditions (22). Furthermore, human RA patients with the FcγRIIIa-158V allele endure severe bone erosion compared with patients with the FcγRIIIa-158F allele (131, 132). Similarly, artificial crosslinking of FcγRI and FcγRIV leads to increased osteoclast differentiation without affecting their resorbing function in vitro (17). Osteoclast numbers and bone erosion were decreased in FcγRIV^{−/−} mice compared with wild mice in a serum transfer model (17). FcγRIIB^{−/−} mice spontaneously developed osteoporosis, which was reversed by an additional knockout of activating FcγRs (22).

De-sialylated IgGs binding to FcγRs with strong affinity have substantially high stimulatory effects on both murine and human osteoclasts (127, 133). In addition, IgGs were less sialylated during inflammation (22). Harre et al. confirmed that the interactions between immune complexes and osteoclasts were related to the degree of IgG sialylation, and only non-sialylated or low-sialylated immune complexes drive osteoclastogenesis. RA patients with low Fc sialylation levels of IgGs have significantly higher bone loss. The pro-osteoclastogenic effect of non-sialylated immune complexes is a common feature of all IgG antibodies (127). A recent study showed that in induced pluripotent stem cell derived mesenchymal stem cell (iMSCs), the sialylation degree of IgG determines the antibodies directed osteogenic potential by regulating immune responses and osteoclastogenesis (24), but desialylated IgG complexes do not affect arthritis-mediated bone loss (134).

Although the signaling of activating FcγRs mediated by immune complex increases osteoclast differentiation, different results exist for immune complex/FcγR on osteoclastogenesis and osteoclast function (Table 1). Previous studies demonstrated the immune complex-induced inhibition of osteoclastogenesis, which possibly acts via activating FcγRs (23, 139). This suggests that FcγRs may have dual roles in bone destruction in inflammatory arthritis. High levels of autoantibodies are a characteristic feature of SLE compared with other inflammatory arthritis (140, 141). The deposition of autoantibodies or immune complexes causes lupus nephritis (142), skin damage (143), splenomegaly (144), and damage to other organs. Lupus IgG can promote the differentiation of monocytes into DCs (145). These indicate that lupus autoantibodies may also play a protective role in bone destruction in inflammatory arthritis. Recently, our research results (26) demonstrated that joint-deposited lupus IgG induced arthritis without bone erosion by intraarticular injection of lupus IgG in mice. Monocytes/macrophages and their product TNFα are required for the development of lupus IgG-induced arthritis. To understand the mechanism of lupus IgG-induced arthritis with deficiency of bone erosion, we determined whether lupus IgG inhibited RANKL-induced osteoclastogenesis. We found that lupus IgG directly suppressed RANKL-induced osteoclastogenesis in a dose-dependent manner in vitro. The inhibitory effect of lupus IgG on osteoclastogenesis is related to timepoint in lupus IgG and RANKL treated macrophages. Deficiency of FcγRII and FcγRIII did not affect the inhibitory effect of lupus IgG on osteoclastogenesis, indicating that the inhibitory effect of lupus IgG on osteoclastogenesis is dependent on FcγRI. Lupus IgG and RANKL can downregulate the surface expression of FcγRI on bone marrow macrophages (20). Research results suggest that lupus IgG inhibits osteoclastogenesis by competitively occupying FcγRI on monocytes/macrophages and reducing RANKL signaling. The effect of activation or repression of RANKL-induced osteoclastogenesis depends on the extent of FcγRI occupancy by IgG. This protective mechanism explains non-destructive arthritis in SLE. In addition, it implies that FcγRI could be a therapeutic target for bone erosion in inflammatory arthritis.

The deposition of ACPA is important for osteoclastogenesis in RA (146). Different studies have identified that ACPA prevalence is significantly increased in SLE patients with erosive arthritis (16). Recent studies have explored the direct effect of ACPA-mediated bone erosion. ACPA IgG together with their citrullinated antigens forms immune complexes that
stimulate immune cells via their interaction with FcRs (93, 147). By using polyclonal ACPAs purified from ACPA-containing serum of RA patients, Harre et al. provided the first validation that ACPAs can directly promote osteoclast differentiation and activation (7). ACPA IgG might affect osteoclastogenesis by the activation of Fc receptors on osteoclasts directly. IgG Fc sialylation is crucial for immune complex–osteoclast interactions (127). Besides, ACPA IgG is shown less sialylated than random IgG (148). There are other published papers regarding the detailed mechanisms of ACPA’s direct regulation, but the exact mechanism of ACPA’s direct effect on erosion remains unclear (149–152).

**FcγR IMMUNOTHERAPY**

The crucial role of FcγRs in both inflammatory arthritis and bone erosion may offer a promising therapeutic target for bone destruction in inflammatory arthritis. One indirect mechanism involves the neutralization of autoimmune IgG Fc by soluble FcγRs. These drugs include the recombinant soluble FcγRIIB receptor SM101 (NCT03851341) and monoclonal antibody targeted the receptors. For example, antagonistic monoclonal antibody against the hFcγRIIA has been shown to be effective in a patient with immune thrombocytopenia (ITP) refractory to all conventional therapies (153). And human recombinant soluble FcγRIIB treatment could ameliorate collagen-induced arthritis by reducing immune complexes-stimulated inflammation and joint swelling (154). Besides, recombinant human soluble FcγRII was evaluated as an effective therapeutic strategy in inhibiting chronic murine lupus pathology (155).

Another mechanism involves the direct blocking of the IgG-binding site on FcγRs. Recombinant multimeric Fc fragments with a high affinity for FcγRs have been shown to be efficacious in animal models of RA, ITP, and graft-versus-host disease (GVHD) (156). These include PF-06755347 (NCT03275740), CSL730 (NCT04446000) and CSL777 (Preclinical) (157). However, nonspecific crosslinking of activating FcγRs could lead to undesired clinical adverse events, and monovalent antibody derivatives, such as Fab, may reduce severe clinical adverse events (158). Up to now, results of above molecules from clinical trials have been promising in autoimmune diseases, but further long-term data are needed (159, 160).

Intravenous immunoglobulin (IVIG) treatment is efficient in several different immune disorders (161, 162). IVIG consists predominantly of IgG and a small fraction of immune complexes. It exerts anti-inflammatory effects in both humans and animal models by its Fc but not Fab fragments (163). Besides, previous studies confirmed that IVIG could directly inhibits human osteoclastogenesis by suppressing the RANK signaling, the suppressive effect is partly mediated by IgG immune complexes contained within IVIG preparations (138). Our study showed that lupus IgG induced synovial inflammation but inhibited RANKL-induced osteoclastogenesis. The suppressive effect is mediated by the competitive occupation of FcγRI on monocytes/macrophages (26).

**CONCLUSIONS AND FUTURE PERSPECTIVES**

Bone erosions are remarkable features in inflammatory arthritis, such as RA, but not in lupus arthritis. Osteoclasts are major cells for bone erosions. Activating FcγR containing ITAM motifs is required for RANKL-induced osteoclastogenesis. FcγR can effectively regulate inflammatory arthritis and bone erosions. Based on published studies, we conclude that FcγR may have dual roles in osteoclastogenesis. The effect of activating and inhibiting...
osteooclasis depends on the extent of FcγRI occupancy by IgG and RANKL, respectively. Specific IgG molecules or Fc fragments with a high affinity for FcγRI designed to occupy FcγRI may exert the inhibitory effect on bone erosion. The sialylation level of IgG Fc binding to FcγRs needs to be taken into account as well. A deeper understanding of FcγRs involved in physiological and pathological osteoclasis will be valuable in identifying new targets and developing potential therapeutic strategies for inflammatory arthritis.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

REFERENCES

1. Ledingham J, Snowden N, Ide Z. Diagnosis and Early Management of Inflammatory Arthritis. BMJ (2017) 358:j3248. doi: 10.1136/bmj.j3248
2. Firestein GS. Evolving Concepts of Rheumatoid Arthritis. Nature (2003) 423:356–61. doi: 10.1038/nature01661
3. Symmons D, Turner G, Webb R, Asten P, Barrett E, Lunt M, et al. The Prevalence of Rheumatoid Arthritis in the United Kingdom: New Estimates for a New Century. Rheumatol (Oxford) (2002) 41:793–800. doi: 10.1093/rheumatology/7.7.793
4. Lee DM, Weinblatt ME. Rheumatoid Arthritis. Lancet (2001) 358:903–11. doi: 10.1016/S0140-6736(01)06075-5
5. Di Ceglie I, Kruisbergen NNL, van den Bosch MHJ, van Lent P. Fc-gamma Receptors and S100A8/A9 Cause Bone Erosion During Rheumatoid Arthritis. Do They Act as Partners in Crime? Rheumatol (Oxford) (2019) 58:1331–43. doi: 10.1093/rheumatology/kez218
6. Cipolletta E, Smerilli G, Di Matteo A, Di Battista J, Di Carlo M, Grassi W, et al. The Sonographic Identification of Cortical Bone Interruptions in Rheumatoid Arthritis: A Morphological Approach. Ther Adv Musculoskelet Dis (2021) 13:1759720x211004326. doi: 10.1177/1759720x211004326
7. Harre U, Georgess D, Bang H, Bozee A, Axmann R, Ossipova E, et al. Induction of Osteoclastogenesis and Bone Loss by Human Autoantibodies Against Citrullinated Vimentin. J Clin Invest (2012) 122:1791–802. doi: 10.1172/JCI69975
8. Beringer A, Miossec P. Systemic Effects of IL-17 in Inflammatory Arthritis. Nat Rev Rheumatol (2019) 15:491–501. doi: 10.1038/s41584-019-0243-5
9. Crowson CS, Mattessal E, Myasoedova E, Michel CJ, Ernste FC, Warrington KJ, et al. The Lifetime Risk of Adult-Onset Rheumatoid Arthritis and Other Inflammatory Autoimmune Rheumatic Diseases. Arthritis Rheum J Clin Invest (2011) 63:633–9. doi: 10.1002/art.30155
10. Kaul A, Gordon C, Crow MK, Touma Z, Urowitz MB, van Vollenhoven R, et al. Systemic Lupus Erythematosus. Nat Rev DisPrimers (2016) 2:16039. doi: 10.1038/nrdp.2016.39
11. Grossman JM. Lupus Arthritis. Best Pract Res Clin Rheumatol (2009) 23:495–506. doi: 10.1016/j.berch.2009.04.003
12. Mahmoud K, Zayat A, Vital EM. Musculoskeletal Manifestations of Systemic Lupus Erythematosus. Curr Opin Rheumatol (2017) 29:486–92. doi: 10.1097/BOR.0000000000000421
13. Esdale JM, Danoff D, Rosenthal L, Gutkowski A. Deforming Arthritis in Systemic Lupus Erythematosus. Ann Rheum Dis (1981) 40:124–6. doi: 10.1136/ard.40.2.124
14. Grigor R, Edmonds J, Lewkonia R, Resniahn B, Hughes GR. Systemic Lupus Erythematosus: A Prospective Analysis. Ann Rheum Dis (1978) 37:121–8. doi: 10.1136/ard.37.2.121
15. Bouchoukouy D, Djemouh K, Rachidi N, Babasaci R, Ould Ali L, Salah K, et al. Association of Markers of Rheumatoid Arthritis in Lupus. Is it a Rhusus? Annales biologie clinique (2020) 78:201–5. doi: 10.1684/abc.2020.1518
16. Budhram A, Chu R, Rusta-Sallehy S, Ioannidis G, Denburg JA, Adachi JD, et al. Anti-Cyclic Citrullinated Peptide Antibody as a Marker of Erosive Arthritis in Patients With Systemic Lupus Erythematosus: A Systematic Review and Meta-Analysis. Lupus (2014) 23:1156–63. doi: 10.1177/0961203314540967
17. Seelig M, Hillenhoff U, David JP, Schett G, Tuckermann J, Lux A, et al. Inflammatory Monocytes and Fcgamma Receptor IV on Osteoclasts Are Critical for Bone Destruction During Inflammatory Arthritis in Mice. Proc Natl Acad Sci USA (2013) 110:10729–34. doi: 10.1073/pnas.1301001110
18. Boross P, van Lent PL, Martin-Ramirez J, van der Kaa J, Mulder MH, Claassens JW, et al. Destructive Arthritis in the Absence of Both FcgammaRI and Fcgammadii. J Immunol (2008) 180:5083–91. doi: 10.4049/jimmunol.180.7.5083
19. Ji H, Ohmura K, Mahmood U, Lee DM, Hofhuis FM, Boackle SA, et al. Arthritis Critically Dependent on Innate Immune System Players. Immunity (2002) 16:157–68. doi: 10.1016/S0140-6736(02)00275-3
20. Kleinau S, Martinsson P, Heyman B. Induction and Suppression of Collagen-Induced Arthritis Is Dependent on Distinct Fcgamma Receptors. J Exp Med (2000) 191:1611–6. doi: 10.1084/jem.191.9.1611
21. van Lent PL, Grevers L, Lubberts E, de Vries TJ, Nabbe KC, Verbeek S, et al. Fcgamma Receptors Directly Mediate Cartilage, But Not Bone, Destruction in Murine Antigen-Induced Arthritis: Uncoupling of Cartilage Damage From Bone Erosion and Joint Inflammation. Arthritis Rheum (2006) 54:3868–77. doi: 10.1002/art.22253
22. Negishi-Koga T, Gober HJ, Sumiya E, Komatsu N, Okamoto K, Sawa S, et al. Immune Complexes Regulate Bone Metabolism Through Fcgamma Signalling. Nat Commun (2015) 6:6637. doi: 10.1038/ncomms7637
23. Grevers LC, de Vries TJ, Everts V, Verbeek JS, van den Berg WB, Van Lent PL. Immune Complex-Induced Inhibition of Osteoclastogenesis is Mediated Via Activating But Not Inhibitory Fcgamma Receptors on Myeloid Precursor Cells. Ann Rheum Dis (2013) 72:278–85. doi: 10.1136/annrheumdis-2012-201568
24. Wu Q, Yang Y, Xie D, Li S, Liu Y, Shu L, et al. The Sialylation Profile of IgG Determines the Efficiency of Antibody Directed Osteogenic Differentiation of iMSCs by Modulating Local Immune Responses and Osteoclastogenesis. Acta biomaterialia (2020) 114:221–32. doi: 10.1016/j.actbio.2020.07.055
25. Kamohara A, Hirata H, Xu X, Shiraki M, Yamada S, Zhang JQ, et al. IgG Immune Complexes With Staphylococcus Aureus Protein A Enhance Osteoclast Differentiation and Bone Resorption by Stimulating Fc Receptors and TLR2. Int Immunol (2020) 32:89–104. doi: 10.1093/intimm/dxz063
26. Qiao W, Ding H, Zuo Y, Jiang L, Zhou J, Han X, et al. Lupus IgG Deposition Causes Arthritis But Inhibits Bone Destruction Through Competitive Occupation of FcgammaRI and Reduced RANKL Signalling. Clin Transl Immunology (2019) 9:e1174. doi: 10.1002/ctii.2019
27. Nimmerjahn F, Ravetch JV. Fcgamma Receptors as Regulators of Immune Responses. Nat Rev Immunol (2003) 3:109–19. doi: 10.1038/nri90110

AUTHOR CONTRIBUTIONS

YZ and G-MD designed the manuscript and figures. YZ and G-MD drafted the manuscript and approved the final version of the manuscript. G-MD revised the final version of the manuscript critically. All authors contributed to the article and approved the submitted version.

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36. Nimmerjahn F, Lux A, Albert H, Woigk M, Lehmann C, Dudziak D, et al.

29. Nimmerjahn F, Bruhns P, Horiuchi K, Ravetch JV. FcγRIγ: A Novel FcR With Distinct IgG Subclass Specificity. Immunity (2005) 23:41–51. doi: 10.1016/j.immuni.2005.05.010

30. Nimmerjahn F, Ravetch JV. Divergent Immunoglobulin G Subclass Activity Through Selective Fc Receptor Binding. Science (2005) 310:1510–2. doi: 10.1126/science.1119498

31. Bruhns P. Properties of Mouse and Human IgG Receptors and Their Contribution to Disease Models. Blood (2012) 119:5640–9. doi: 10.1182/blood-2012-01-380121

32. Hulett MD, Hogarth PM. Molecular Basis of Fc Receptor Function. J Exp Immunol (1994) 110:171–7. doi: 10.1016/0022-1759(94)90202-2

33. Kim N, Takami M, Rho J, Josien R, Choi Y. A Novel Member of the Leukocyte Receptor Complex Regulates Osteoclast Differentiation. J Exp Med (2002) 195:201–9. doi: 10.1084/jem.20011681

34. Bruhns P. Properties of Mouse and Human IgG Receptors and Their Contribution to Disease Models. Blood (2012) 119:5640–9. doi: 10.1182/blood-2012-01-380121

35. Mancardi DA, Jonsson F, Iannacosi B, Khan H, Van Rooijen N, Huerre M, et al. Cutting Edge: The Murine High-Affinity IgG Receptor FcγRIIAV Is Sufficient for Autoantibody-Induced Arthritis. J Immunol (2011) 186:1899–903. doi: 10.4049/jimmunol.1003642

36. Nimmerjahn F, Lux A, Albert H, Woigk M, Lehmann C, Dudziak D, et al. FcγRIIAV Deletion Reveals Its Central Role for IgG2a and IgG2b Activity In Vivo. Proc Natl Acad Sci USA (2010) 107:19396–401. doi: 10.1073/pnas.1014515107

37. Mechetina LV, Najshaskim AM, Volkova OY, Guselnikov SV, Fazulzin RZ, Alabey BY, et al. FCRL, A Novel Member of the Leukocyte Fc Receptor Family Possesses Unique Structural Features. Eur J Immunol (2002) 32:887–96. doi: 10.1002/eji.2001312128-1717

38. Ravetch JV, Lanier LL. Immune Inhibitory Receptors. Annu Rev Immunol (2002) 20:195–201. doi: 10.1146/annurev.immunol.20.1.203

39. Daeron M, Jaeger S, Du Pasquier L, Vivier E. Immunoreceptor Tyrosine-Immunoglobulin IgG Receptor FcγRIIAV Is Essential for the Effects on Clinical Outcome in Cancer Immunotherapy and Other Immune-Related Effects. J Clin Invest (2019) 139:712–22. doi: 10.1172/JCI125097

40. Ono M, Bolland S, Tempst P, Ravetch JV. Role of the Inositol Phosphatase SHIP in Negative Regulation of the Immune System by the Receptor Fc( Gamma)RIBB. Nature (1996) 383:263–6. doi: 10.1038/383263a0

41. Smith KG, Claxworthy MR. FcγRIIB in Autoimmunity and Infection: Evolutionary and Therapeutic Implications. Nat Rev Immunol (2010) 10:328–43. doi: 10.1038/nri2766

42. Takai T. Roles of Fc Receptors in Autoimmunity. Nat Rev Immunol (2002) 2:580–92. doi: 10.1038/nri858

43. Blank U, Launay P, Benhamou M, Monteiro RC. Inhibitory Itams as Novel Genes and Proteins Regulate the Functions of FcγReceptors. Cytoskeleton (2013) 70:352–62. doi: 10.1080/00907318.2013.763329

44. Takai T. Roles of Fc Receptors in Autoimmunity. Nat Rev Immunol (2002) 2:580–92. doi: 10.1038/nri858

45. Blank U, Launay P, Benhamou M, Monteiro RC. Inhibitory Itams as Novel Genes and Proteins Regulate the Functions of FcγReceptors. Cytoskeleton (2013) 70:352–62. doi: 10.1080/00907318.2013.763329

46. Pasquier B, Launay P, Kanamaru Y, Moora IC, Pirsch S, Ruffin C, et al. Identification of FcαRIα as an Inhibitory Receptor That Controls Inflammation: Dual Role of FcγIgαIγ. Immunity (2005) 22:21–42. doi: 10.1016/j.immuni.2004.11.017

47. Hamerman JA, Tchao NK, Lowell CA, Lanier LL. Enhanced Toll-Like Receptor Responses in the Absence of Signaling Adaptor DAP12. Nat Immunol (2005) 6:579–96. doi: 10.1038/ni204

48. Li X, Ptaszek TS, Brown EE, Edberg JC. FcγR Receptors: Structure, Function and Role as Genetic Risk Factors in SLE. Genes Immun (2009) 10:380–9. doi: 10.1038/sj.gene.6510973

49. Selvaraj P, Carpen O, Hibbs ML, Springer TA. Natural Killer Cell and Granulocyte Fc Gamma Receptor III (CD16) Differ in Membrane Anchor and Signal Transduction. J Immunol (1989) 143:283–8.

50. Selvaraj P, Rosse WF, Silber R, Springer TA. The Major Fc Receptor in Blood has a Phosphatidylinositol Anchor and Is Deficient in Paroxysmal Nocturnal Haemoglobinuria. Nature (1988) 333:565–7. doi: 10.1038/333565a0

51. Steffen U, Schett G, Boeze A. How Autoantibodies Regulate Osteoclast Induced Bone Loss in Rheumatoid Arthritis. Front Immunol 4.71 (2019). doi: 10.3389/fimmu.2019.01483.
68. Lee YH, Bae SC, Song GQ. FcGR2A, Fcgr3a, Fcgr3b Polymorphisms and Susceptibility to Rheumatoid Arthritis: A Meta-Analysis. Clin Exp Rheumatol (2015) 33:464-54.

69. Avila-Pedretti G, Tornero J, Fernandez-Nebro A, Blanco F, Gonzalez-Alvaro I, Canet ID, et al. Variation at FcGR2A and Functionally Related Genes Is Associated With the Response to anti-TNF Therapy in Rheumatoid Arthritis. Plod One (2015) 10:e0122088. doi: 10.1371/journal.pone.0122088

70. Ben Mkaddem S, Hayem G, Jonsson F, Rossato E, Boedec E, Boussetta T, et al. Shifting FcγRIIA-ITAM From Activation to Inhibitory Configuration Ameliorates Arthritis. J Clin Invest (2014) 124:3945–59. doi: 10.1172/jci74572

71. Chen JY, Wang CM, Ma CC, Luo SF, Edberg JC, Kimberly RP, et al. Association of a Transmembrane Polymorphism of Fcgamma Receptor IIb (FCGR2B) With Systemic Lupus Erythematosus in Taiwanese Patients. Arthritis Rheum (2006) 54:3908–17. doi: 10.1002/art.22220

72. Chen JY, Wang CM, Chang SW, Cheng CH, Wu VJ, Lin JC, et al. Association of FcgammaRIIIA and FcGR3B Copy Number Variations With Systemic Lupus Erythematosus and Rheumatoid Arthritis in Taiwanese Patients. Arthritis Rheumatol (2014) 66:3113–21. doi: 10.1002/art.38813

73. Ceccarelli F, Perricone C, Borgiani P, Ciccacci C, Rufini S, Cipriano E, et al. Genetic Factors in Systemic Lupus Erythematosus: Contribution to Disease Phenotype. J Immunol Res (2015) 2015:754647. doi: 10.1155/2015/754647

74. Lehrnbecher T, Foster CB, Zhu S, Leitman SF, Goldin LR, Huppi K, et al. Variant Genotypes of the Low-Affinity Fcγ Receptors in Two Control Populations and a Review of Low-Affinity Fcgamma Receptor Polymorphisms in Control and Disease Populations. Blood (1999) 94:4220–32. doi: 10.1182/blood.V94.12.4220

75. Kagari T, Tanaka D, Doi H, Shimozato T. Essential Role of Fc Gamma Receptor IIb in the Determination of Joint Inflammation and Cartilage Destruction During Immune Complex-Mediated Arthritis. Arthritis Rheum (2003) 48:255–65. doi: 10.1002/art.11721

76. van Lent PL, Nabbe K, Blom AB, Holthuysen AE, Slootjes A, van de Putte LB, et al. Role of Activatory Fc Gamma RI and Fc Gamma RII and Inhibitory Fc Gamma RII in Inflammation and Cartilage Destruction During Experimental Antigen-Induced Arthritis. Am J Pathol (2001) 159:2309–20. doi: 10.1016/s0002-9440(10)63081-7

77. Radstake TR, Franke B, Wenink MH, Nabbe KC, Coenen MJ, Welsing P, et al. The Functional Variant of the Inhibitory Fcgamma Receptor IIb (CD32B) Is Associated With the Rate of Radiologic Joint Damage and Dendritic Cell Function in Rheumatoid Arthritis. Arthritis Rheum (2006) 54:3828–37. doi: 10.1002/art.22275

78. Kagari T, Tanaka D, Doi H, Shimozato T. Essential Role of Fc Gamma Receptor IIb in the Determination of Joint Inflammation and Cartilage Destruction During Immune Complex-Mediated Arthritis. Arthritis Rheum (2003) 48:255–65. doi: 10.1002/art.11721

79. Yusa T, Kubo S, Yoshino T, Uijke A, Matsumura K, Ono M, et al. Deletion of Fcgamma Receptor IIb Renders H-2(b) Mice Susceptible to Collagen-Induced Arthritis. J Exp Med (1999) 189:187–94. doi: 10.1046/jem.189.1.187

80. Yilmaz-Elis AS, Ramirez JM, Asmawidjaja P, van der Kaa J, Mus AM, Brem MD, et al. FcgammaRIIB on Myeloid Cells Rather Than on B Cells Protects Fcgamma-Ridden Arthritic Mice. J Immunol (2014) 192:5540–7. doi: 10.4049/jimmunol.1303272

81. Brownlie RJ, Lawlor KE, Niederer HA, Cutler AI, Xiang Z, Clatworthy MR, et al. Distinct Cell-Specific Control of Autoimmunity and Infection by FcgammaRIIB. J Exp Med (2008) 205:883–95. doi: 10.1084/jem.20072565

82. Tan Sardjono C, Mottram PL, van de Velde NC, Powell MS, Power D, Slocombe RF, et al. Development of Spontaneous Multisystem Autoimmune Disease and Hypersensitivity to Antibody-Induced Inflammation in Fcgamma Receptor IIA-Transgenic Mice. Arthritis Rheum (2005) 52:3220–9. doi: 10.1002/art.21344

83. Anquetil F, Clavel C, Offer G, Serre G, Sebbag M. IgM and IgA Rheumatoid Factors Purified From Rheumatoid Arthritis Sera Boost the Fc Receptor- and Complement-Dependent Effector Functions of the Disease-Specific Anti-Citrullinated Protein Autoantibodies. J Immunol (2015) 194:3664–74. doi: 10.4049/jimmunol.1402334

84. Clavel C, Ceccato L, Anquetil F, Serre G, Sebbag M. Among Human Macrophages Polarised to Different Phenotypes, the M-CSF-oriented Cells Present the Highest Pro-Inflammatory Response to the Rheumatoid Arthritis-Specific Immune Complexes Containing ACPA. Ann Rheum Dis (2016) 75:2184–91. doi: 10.1136/annrheumdis-2015-208887

85. Laurent L, Clavel C, Lemaire O, Anquetil F, Cornillet M, Zabraniecki L, et al. Fcgamma Receptor Profile of Monocytes and Macrophages From Rheumatoid Arthritis Patients and Their Response to Immune Complexes Formed With Autoantibodies to Citrullinated Proteins. Ann Rheum Dis (2011) 70:1052–9. doi: 10.1136/ard.2010.142091

86. Machold KP, Stamm TA, Nell VP, Pfliogbel S, Aletaha D, Steiner G, et al. Very Recent Onset Rheumatoid Arthritis: Clinical and Serological Patient Characteristics Associated With Radiographic Progression Over the First Years of Disease. Rheumatol (Oxford) (2007) 46:342–9. doi: 10.1093/rheumatology/kei237

87. Clavel C, Nogueira L, Laurent L, Iobagiu C, Vincent C, Sebbag M, et al. Induction of Macrophage Secretion of Tumor Necrosis Factor Alpha Through Fcgamma Receptor Ila Engagement by Rheumatoid Arthritis-Specific Autoantibodies to Citrullinated Proteins Complexed With Fibrinogen. Arthritis Rheum (2008) 58:678–88. doi: 10.1002/art.23284

88. Liu Y, Masuda E, Blank MC, Kirou KA, Gao X, Park MS, et al. Cytokine-Related Fcgamma Receptor Proinflammatory Activity in Fibroblasts. J Leuko Biol (2005) 77:767–76. doi:10.1189/jlb.0904532

89. Allen E, Bakke AC, Purtier MZ, Deodhar A. Neutrophil CD64 Expression: Distinguishing Acute Inflammatory Autoimmune Disease From Systemic Inflammatory Disease. Ann Rheum Dis (2002) 61:522–5. doi:10.1136/ard.61.6.522

90. Hussein OA, El-Toukdhy MA, El-Rahman HS. Neutrophil CD64 Expression in Inflammatory Autoimmune Diseases: Its Value in Distinguishing Infection From Disease Flare. Immunol Invest (2010) 39:699–712. doi:10.3109/08820139.2010.491520
Fjaertoft G, Hakansson LD, Pauskens K, Sisask G, Venge P. Neutrophil CD64 (FcgammaRI) Expression Is a Specific Marker of Bacterial Infection: A Study on the Kinetics and the Impact of Major Surgery. *Scand J Infect Dis* (2007) 39:25–35. doi: 10.1080/03655400601133693

Fjaertoft G, Paulsen K, Hakansson L, Xu S, Venge P. Cell Surface Expression of FcgammaRI (CD64) on Neutrophils and Monocytes in Patients With Influenza A, With and Without Complications. *Scand J Infect Dis* (2005) 37:882–9. doi: 10.1080/03655400500348929

Bourantas S, Wang TT, Dahan R, Maamary J, Ravetch JV. Signaling by Antibodies: Recent Progress. *Annu Rev Immunol* (2017) 35:285–311. doi: 10.1146/annurev-immunol-051116-052433

Oppegaard O, Skodvin B, Halse AK, Langeland N. CD64 as a Potential Biomarker in Septic Arthritis. *BMC Infect Dis* (2013) 13:278. doi: 10.1186/1471-2334-13-278

Li S, Huang X, Chen Z, Zhong H, Peng Q, Deng Y, et al. Neutrophil CD64 Expression as a Biomarker in the Early Diagnosis of Bacterial Infection: A Meta-Analysis. *Int J Infect Dis* (2013) 17:e12–23. doi: 10.1016/j.ijid.2012.07.017

Cid J, Aguinaco R, Garcia-Pardo G, Llorente A. Neutrophil CD64 Expression as Marker of Bacterial Infection: A Systematic Review and Meta-Analysis. *J Infect* (2010) 60:313–9. doi: 10.1016/j.jinf.2010.02.013

Tsiboi N, Ernandez T, Li X, Nishi H, Cullere X, Mekala D, et al. Regulation of Human Neutrophil Fcgamma Receptor IIa by C5a Receptor Promotes Inflammatory Arthritis in Mice. *Arthritis Rheum* (2011) 63:467–78. doi: 10.1002/art.30141

Karsenty G, Wagner EF. Reaching a Genetic and Molecular Understanding of Skeletal Development. *Dev Cell* (2002) 2:239–406. doi: 10.1016/s1534-5807(02)00157-0

Teitelbaum SL, Ross FP. Genetic Regulation of Osteoclast Development and Function. *Nat Rev Genet* (2003) 4:293–304. doi: 10.1016/s1534-5807(02)00369-6

Boyle WJ, Simonet WS, Lacey DL. Osteoclast Differentiation and Activation. *Nat Rev Rheumatol* (2012) 8:280–4. doi: 10.1038/nrrheum.2012-020958

Kleyer A, Schett G. Arthritis and Bone Loss: A Hen and Egg Story. *Curr Opin Rheumatol* (2014) 26:167–72. doi: 10.1097/RHU.00000000000000907

Onuora S. Osteoimmunology: IgG Immune Complexes Directly Regulate Bone Homeostasis. *Nat Rev Rheumatol* (2015) 11:257. doi: 10.1038/nrrheum.2015.51

Karsten CM, Kohl J. A Bone to Pick with Fc Gamma Receptors. *Ann Transl Med* (2015) 3:218. doi: 10.3978/j.issn.2305-5839.2015.07.11

Kastbom A, Ahmadi A, Soderkvist P, Skogh T. The 158V Polymorphism of Fc Gamma Receptor Type IIIA in Early Rheumatoid Arthritis: Increased Susceptibility and Severity in Male Patients (the Swedish TIRA Project). *Rheumatol (Oxford)* (2005) 44:1294–8. doi: 10.1093/rheumatology/kei010

Pagan JD, Kataoka M, Anthony RM. Engineered Sialylation of Pathogenic Antibodies In Vivo Attenuates Autoimmune Disease. *Cell* (2018) 172:564– 577 e513. doi: 10.1016/j.cell.2017.11.041

Sahic E, Westerlund A, Lagerquist MK, Lerner UH, Carlsten H, Henning P, et al. Immunoglobulin G Complexes Without Sialic Acids Enhance Osteoclastogenesis But do not Affect Arthritis-Mediated Bone Loss. *Scand J Immunol* (2019) 93:e13009. doi: 10.1111/sj.13009

Zeng KQ, Gong FY, Pan XH, Miao J, Gong Z, Wang J, et al. IgG Immunocomplexes Drive the Differentiation of a Novel Subset of Osteoclasts Independent of RANKL and Inflammatory Cytokines. *J Bone Miner Res* (2021). doi: 10.1002/jbmr.4281

van Lent P, Nabbe KC, Boross P, Blom AB, Roth J, Holhuyzen A, et al. The Inhibitory Receptor FcgammaRIIIB Reduces Joint Inflammation and Destruction in Experimental Immune Complex-Mediated Arthritis Not Only by Inhibition of FcgammaRIIIB/III But Also by Efficient Clearance and Endocytosis of Immune Complexes. *Am J Pathol* (2003) 163:1839–48. doi: 10.1016/s0002-7863(10)63543-2

Visitchanakun P, Sawiorn W, Jongsawattanapisan P, Leelacharnvichkul A, Psitkul P, Lotinun S. Lupus-Like Disease in Fc gamma RIIB(-/-) Mice Induces Osteopenia. *J Cell Physiol* (2019) 234:2548–59. doi: 10.1002/jcp.29509

MacLellan LM, Montgomery J, Sugiyama F, Kitson SM, Thummler K, Silverman GJ, et al. Co-Opting Endogenous Immunoglobulin for the Regulation of Inflammation and Osteoclastogenesis in Humans and Mice. *Arthritis Rheum* (2011) 63:3987–907. doi: 10.1002/art.30629

Tsokos GC. Systemic Lupus Erythematosus. A Disease With a Complex Pathogenesis. *Lancet* (2001) 358:SupplS565. doi: 10.1016/s0140-6736(01)07077-5

Salmon JF, Pricop L. Human Receptors for Immunoglobulin G: Key Elements in the Pathogenesis of Rheumatic Disease. *Arthritis Rheum* (2001) 44:739–50. doi: 10.1002/1529-0131(200104)44:4<739::AID-ANR129.3.CO;2-O
142. Zuniga R, Markowitz GS, Arkachaisri T, Imperatore EA, D’Agati VD, Salmon JE. Identification of IgG Subclasses and C-reactive Protein in Lupus Nephritis: The Relationship Between the Composition of Immune Deposits and FcGamma Receptor Type IIA Alleles. *Arthritis Rheum* (2003) 48:460–70. doi: 10.1002/art.10930

143. Deng GM, Tsokos GC. Pathogenesis and Targeted Treatment of Skin Injury in SLE. *Nat Rev Rheumatol* (2015) 11:663–9. doi: 10.1038/nrrheum.2015.106

144. Zhang Q, Xiang L, Zaman MH, Dong W, He G, Deng GM. Predominant Role of Immunoglobulin G in the Pathogenesis of Splenomegaly in Murine Lupus. *Front Immunol* (2019) 10:3020. doi: 10.3389/fimmu.2019.03020

145. Deng GM, Liu L, Kyttarinen VC, Tsokos GC. Lupus Serum IgG Induces Skin Inflammation Through the TNFRI Signaling Pathway. *J Immunol* (2010) 184:7154–61. doi: 10.4049/jimmunol.0902514

146. Malmstrom V, Catriola AL, Klæreskog L. The Immunopathogenesis of Seropositive Rheumatoid Arthritis: From Triggering to Targeting. *Nat Rev Immunol* (2017) 17:60–75. doi: 10.1038/nri.2016.124

147. Aurell M, Machuca-Gayet I, Coury F. Rheumatoid Arthritis in the View of Osteoimmunology. *Biomolecules* (2020) 11:48. doi: 10.3390/biom11010048

148. Scherer HU, van der Woude D, Ioan-Facsinay A, Bülow A, Trouw LA, Wang J, et al. Glycan Profiling of Anti-Citrullinated Protein Antibodies Isolated From Human Serum and Synovial Fluid. *Arthritis Rheum* (2010) 62:1620–9. doi: 10.1002/art.27414

149. Correction: Autoantibodies to Citrullinated Proteins Induce Joint Pain Independent of Inflammation Via a Chemokine-Dependent Mechanism. *Ann Rheum Dis* (2019) 78:865. doi: 10.1136/annrheumdis-2015-208094corr1

150. Wigerblad G, Bas DB, Fernandes-Cerqueira C, Krishnamurthy A, Nandakumar KS, Rogoz K, et al. Autoantibodies to Citrullinated Proteins Induce Joint Pain Independent of Inflammation Via a Chemokine-Dependent Mechanism. *Ann Rheum Dis* (2016) 75:730–8. doi: 10.1136/annrheumdis-208094

151. Correction: Identification of a Novel Chemokine-Dependent Molecular Mechanism Underlying Rheumatoid Arthritis-Associated Autoantibody-Mediated Bone Loss. *Ann Rheum Dis* (2019) 78:866. doi: 10.1136/annrheumdis-2015-208093corr1

152. Krishnamurthy A, Joshua V, Hai Hensvold A, Jin T, Sun M, Vivar N, et al. Identification of a Novel Chemokine-Dependent Molecular Mechanism Underlying Rheumatoid Arthritis-Associated Autoantibody-Mediated Bone Loss. *Ann Rheum Dis* (2016) 75:721–9. doi: 10.1136/annrheumdis-2015-208093

153. Clarkson SB, Bussel JB, Kimberly RP, Valinsky JE, Nachman RL, Unkeless JC. Treatment of Refractory Immune Thrombocytopenic Purpura With an anti-Fc Gamma-Receptor Antibody. *N Engl J Med* (1986) 314:1236–9. doi: 10.1056/nejm198605083141907

154. Magnusson SE, Andrén M, Nilsson KE, Søndermann P, Jacob U, Kleinau S. Acceleration of Collagen-Induced Arthritis by Human Recombinant Soluble FcgammaRIIa. *Clin Immunol* (2008) 127:225–33. doi: 10.1016/j.clim.2008.02.002

155. Werwitzke S, Trick D, Søndermann P, Kamino K, Schlegelberger B, Kniesch K, et al. Treatment of Lupus-Prone NZB/NZW F1 Mice With Recombinant Soluble Fc Gamma Receptor II (CD32). *Ann Rheum Dis* (2008) 67:154–61. doi: 10.1136/ard.2006.068981

156. Jain A, Olsen HS, Vyasatrya R, Burch E, Sakoda Y, Mérigeon EY, et al. Fully Recombinant IgG2a Fc Multimers (Stradomers) Effectively Treat Collagen-Induced Arthritis and Prevent Idiopathic Thrombocytopenic Purpura in Mice. *Arthritis Res Ther* (2012) 14:R192. doi: 10.1186/ar4024

157. Zuercher AW, Spirig R, Baz Morelli A, Rowe T, Käsermann F. Next-generations Fc Receptor-Targeting Biologics for Autoimmune Diseases. *Autoimmun Rev* (2019) 18:102366. doi: 10.1016/j.autrev.2019.102366

158. Yu X, Lazarus AH. Targeting FcγRs to Treat Antibody-Dependent Autoimmunity. *Autoimmun Rev* (2016) 15:510–2. doi: 10.1016/j.autrev.2016.02.006

159. Konstaninova TS, Leonidovna IV, Hellmann A, Kyrucz-Krzemien S, Tillmanns S, Søndermann P, et al. Interim Results From a Phase Ib/ia Clinical Trial With the Soluble Fc-Gamma IIb Receptor SM101 for the Treatment of Primary Immune Thrombocytopenia. *Blood* (2012) 120:3388. doi: 10.1182/blood.V120.21.3388.3388

160. Tillmanns S, Kolligs C, D’Cruz DP, Doria A, Hachulla E, Voll RE, et al. SM101, a Novel Recombinant, Soluble, Human Fc Gamma IIb Receptor, in the Treatment of Systemic Lupus Erythematosus: Results of a Double-Blind, Placebo-Controlled Multicenter Study. *Arthritis Rheumatol* (2014) 66: S1238–8. doi: 10.1002/art.38914

161. Clynns R. Protective Mechanisms of IVIG. *Curr Opin Immunol* (2007) 19:646–51. doi: 10.1016/j.coi.2007.09.004

162. Nimmerjahn F, Ravetch JV. Anti-Inflammatory Actions of Intravenous Immunoglobulin. *Annu Rev Immunol* (2008) 26:513–33. doi: 10.1146/annurev.immunol.26.021607.090232

163. Schwab I, Nimmerjahn F. Intravenous Immunoglobulin Therapy: How Does IgG Modulate the Immune System? *Nat Rev Immunol* (2013) 13:176–89. doi: 10.1038/nri3401

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer PZ declared a shared affiliation with the authors to the handling editor at the time of review.

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