25 ACTIVATING Fc γ RECEPTORS MEDIATE IMMUNE COMPLEX-INDUCED INHIBITION OF OSTEOCLASTOGENESIS

LC Grevers,¹ PLEM van Lent,¹ T J de Vries,² V Everts,² W B van den Berg¹ ¹*Department of Rheumatology Research and Advanced Therapeutics, Radboud University Nijmegen, Medical Centre, Nijmegen, The Netherlands;* ²*Department of Oral Cell Biology, Academic Centre for Dentistry Amsterdam, UVA and VU University Amsterdam, Amsterdam, The Netherlands*

10.1136/annrheumdis-2011-201237.25

Background Rheumatoid arthritis is characterised by osteoclast-mediated bone loss. Co-stimulatory signalling via ITAM- and ITIM-coupled receptors is essential for osteoclast formation and function. The ITAM- and ITIM-coupled Fc γ receptors (Fc γ R) play a crucial role in mediating inflammation and cartilage destruction in experimental arthritis, but their role in osteoclast-mediated bone loss is unknown.

Objectives To investigate the role of Fc γ Rs in osteoclastogenesis and osteoclast function.

Materials and methods Bone destruction was analysed in arthritic knee joints of Fc γ RIIB-deficient, Fc γ -chain^{-/-} (lacking expression of activating Fc γ Rs), and wild type mice. Bone marrow-derived osteoclast precursors were differentiated in vitro towards osteoclasts in the absence or presence of immune complexes (ICs) and stimulated thereafter for 24 h with or without TNF α or LPS. Additionally, mature osteoclasts were stimulated with ICs. Experiments were analysed for osteoclast formation, bone resorption, and the expression of Fc γ Rs and osteoclast markers.

Results Bone erosions and cathepsin K-positive osteoclast numbers were significantly increased during antigen-induced arthritis in the knee joints of Fc γ RIIB-deficient mice. All Fc γ R classes were highly expressed on bone marrow-derived osteoclast progenitors. On mature osteoclasts, as compared to macrophages, expression of the inhibitory Fc γ RIIB was similar, whereas expression of activating Fc γ Rs was significantly lower. IC stimulation of mature osteoclasts neither affected their number nor their bone resorptive capacity. Differentiation of bone marrow-derived precursors in the presence of ICs significantly inhibited osteoclast formation, bone resorption, and expression of the osteoclast markers cathepsin K, CTR, DC-STAMP and NFATc1. In the presence of ICs, osteoclastogenesis of Fc γ RIIB^{-/-} precursors and bone resorption remained inhibited. In contrast, ICs could not inhibit osteoclast formation or bone resorption of Fc γ -chain^{-/-} precursors. When IC-inhibited osteoclastogenesis was followed by stimulation with TNF α or LPS, the inhibitory effects of ICs were overruled.

Conclusions Activating Fc γ Rs, but not the inhibitory Fc γ RIIB, mediate IC-induced inhibition of osteoclastogenesis. In the presence of pro-inflammatory mediators like TNF α and LPS the inhibitory effect might be overruled. This suggests that the balance of Fc γ R-mediated induction of inflammation, through pro-inflammatory cytokine production, as well as the direct inhibitory effect of ICs on osteoclastogenesis determines the net effect on bone loss.