25 ACTIVATING FCγ RECEPTORS MEDIATE IMMUNE COMPLEX-INDUCED INHIBITION OF OSTEOCLASTOGENESIS

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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 Fcγ receptors (FcγR) 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 FcγRs in osteoclastogenesis and osteoclast function.

Materials and methods Bone destruction was analysed in arthritic knee joints of FcγRIIB-deficient, FcRγ-chain$^{-/-}$ (lacking expression of activating FcγRs), 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 TNFα or LPS. Additionally, mature osteoclasts were stimulated with ICs. Experiments were analysed for osteoclast formation, bone resorption, and the expression of FcγRs and osteoclast markers.

Results Bone erosions and cathepsin K-positive osteoclast numbers were significantly increased during antigen-induced arthritis in the knee joints of FcγRIIB-deficient mice. All FcγR classes were highly expressed on bone marrow-derived osteoclast progenitors. On mature osteoclasts, as compared to macrophages, expression of the inhibitory FcγRIIB was similar, whereas expression of activating FcγRs 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 FcγRIIB$^{-/-}$ precursors and bone resorption remained inhibited. In contrast, ICs could not inhibit osteoclast formation or bone resorption of FcRγ-chain$^{-/-}$ precursors. When IC-inhibited osteoclastogenesis was followed by stimulation with TNFα or LPS, the inhibitory effects of ICs were overruled.

Conclusions Activating FcγRs, but not the inhibitory FcγRIIB, mediate IC-induced inhibition of osteoclastogenesis. In the presence of pro-inflammatory mediators like TNFα and LPS the inhibitory effect might be overruled. This suggests that the balance of FcγR-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.