**Fcγ RECEPTORS DIRECTLY MEDIATE CARTILAGE BUT NOT BONE DESTRUCTION: UNCOUPLING FROM JOINT INFLAMMATION**

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ABSTRACT INTRODUCTION:

Murine antigen-induced arthritis (AIA) is characterized by immune complex dependent chronic joint inflammation and severe cartilage and bone destruction. Recently we demonstrated that activating FcγRI and III and inhibiting FcγRII are crucial in mediating cartilage destruction during AIA (1,2). Now we studied the relation between synovial inflammation and concomitant occurrence of cartilage and bone erosion at conditions of variable inflammation in FcγRI/-/- mice.

METHODS:

AIA was induced by injecting methylated BSA (mBSA:60 µg) into knee joints of various FcγRI/-/- mice (FcγRI/II/III-/- and wildtype (WT) controls previously immunized with mBSA/FCA. Histology of knee joints was taken at day 7 after AIA induction. Joint inflammation was scored in the knee joint cavity (exudate) and synovial layer (infiltrate). Cartilage destruction was measured as chondrocyte death in various cartilage layers of the knee joint (tibia, femur, patella). Chondrocyte death was expressed as % of area containing empty lacunae compared to the total cartilage area. Bone destruction was determined on 10 different well-defined spots of total knee joint sections using an arbitrary score from 0-3 per spot and expressed as the sum of these scores. Cathepsin K, receptor activator of NF-κB (RANKL) and osteoprotegerin (OPG) were detected using immunolocalisation and measured using image analysis.

RESULTS SECTION:

In the absence of the inhibiting FcγRII (FcγRII/-/-), joint inflammation at day 7 was significantly higher (infiltrate 93% and exudate 200% higher) when compared to WT controls. Both cartilage and bone destruction were significantly elevated (100% and 156% respectively), suggesting that activating FcγRI may be involved in both cartilage and bone destruction (FIG 1 B versus E).

However, when arthritis was induced in knee joints of mice lacking activating FcγRI and III (but not FcγRIIb), cartilage destruction was completely absent, whereas bone erosion was not significantly different from WT controls (FIG 1 A versus D). Joint inflammation was comparable between the two groups, indicating that activating FcγR are crucial in mediating cartilage, which occurred uncoupled from joint inflammation, whereas bone destruction followed the degree of inflammation. This tendency was again observed in mice lacking all three FcγR. Of great interest, joint inflammation was significantly elevated (infiltrate and exudate, 100% and 188% respectively) in FcγRII/III-/- knee joints, due to inefficient clearance of immune complexes (2). Although joint inflammation was much higher in the FcγRII/III-/- knee joints, cartilage destruction was lowered by 92% whereas in contrast bone erosion was raised by 200%, again implying that the amount of cellular influx is correlated to bone erosion (FIG 1 C versus F).

FIG 2

**A**: WT control  **B**: FcγRII/III-/-

RANKL, a crucial regulator of osteoclast differentiation was 40% lower in the inflammatory cell mass of FcγRII/III-/- mice whereas OPG, a decoy receptor for RANKL, competing against RANK was comparable to WT controls. The decreased RANKL/OPG ratio did however not prevent development of higher bone erosion in inflamed FcγRII/III-/- knee joints probably due to strongly increased inflammation. Cathepsin K, an important product of osteoclasts, involved in bone destruction, showed a strong correlation with joint inflammation. Significantly more cathepsin K was observed along the bone surface in day 7 FcγRII/III-/- arthritic knee joints when compared to their controls (FIG 2 B versus A; see arrow).

DISCUSSION:

In the present study we find that FcγR are crucial in mediating cartilage destruction independent of joint inflammation. In contrast, FcγRI are not directly involved in bone erosion. Indirectly however, the presence of immune complexes can drive joint inflammation and bone erosion. Immunomodulation leading to decrease of activating FcγR and increase of inhibiting FcγRII may directly ameliorate cartilage destruction and indirectly also bone erosion by downregulating joint inflammation.

References:


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