ROLE OF FCGAMMARII AND FCGAMMARIII IN CARTILAGE DAMAGE DURING MURINE EXPERIMENTAL ANTIGEN-INDUCED ARTHRITIS

INTRODUCTION:

IgG-containing immune complexes, which are found in most arthritic joints, communicate with hematopoietic cells using three classes of Fc receptors (FcRI, FcRII, FcRIII). Cross-linking of FcRI and FcRII results in activation whereas cross-linking of FcRIII leads to inhibition of intra-cellular signaling pathways in vitro. In a previous study we found that if antigen-induced arthritis (AIA) was elicited in knee joints of FcR-/- and FcRII-/- mice which lack functional FcRI and III, joint inflammation was somewhat lower and severe cartilage destruction was completely absent (1). We now examined the relative role of FcRI and III in cartilage damage in vivo and further defined the potential protective role of FcRII using arthritis models in FcRIII and FcRII deficient mice.

METHODS:

FcRII and FcRIII-/- mice and their controls were immunized with methylated mBSA in complete Freund's adjuvant followed by induction of arthritis by local injection of 60 Tg of mBSA into the right knee joint. The course of inflammation was studied by 99mTc uptake. Chronic inflammation and cartilage damage (depletion of proteoglycans and matrix erosion) was studied histologically with hematoxylin or safranin-O. Depletion of proteoglycans was measured as loss of red staining using automated image analysis. Erosion was detected as ruffling of the cartilage surface. Aggrecan breakdown in cartilage caused by metalloproteinases (MMPs) was studied by immunolocalisation using specific antibodies against the aminocids VDIPEN of the C-terminus. VDIPEN expression is a marker for severe cartilage destruction.

RESULTS:

Three weeks after immunization both cellular (T cell responses as measured by lymphocyte stimulation) and humoral (total IgG, IgG1, IgG2b levels) immunity raised against mBSA was comparable in all groups examined. IgG2a levels were comparable in FcRIII-/- but higher in FcRII-/- if compared to controls.

In knee joints of arthritic FcRIII-/-, swelling at day 1, 3 and 7 was comparable to controls. Histologically at day 7 after AIA, exudate and infiltrate was similar. Cartilage damage like proteoglycan depletion, MMP-mediated neoeptopes (VDIPEN) and matrix erosion was also not different from controls.

In contrast, arthritic FcRII-/- showed a significantly higher joint swelling (53% at day 1 and 92% at day 7 after AIA) if compared to controls. Histologically, at day 7 after AIA induction, exudate and infiltrate in the knee joint was also significantly higher (respectively 100% and 388%). In the chronic phase of AIA, cartilage destruction was significantly elevated in FcRII-/-.

MMP-induced neoeptopes determined in various cartilage layers (tibia and femur) were higher in the tibia (155-360%) and in the femur (67-75%) if compared to controls (FIG 1). Depletion of proteoglycans from the cartilage was similar (40-70%) between the two groups. Furthermore elevated chondrocyte death (from 25-50% in controls to 40-70% in FcRII-/-) and more pronounced cartilage matrix erosion (from 1.2 in controls to 2.5 in FcRII-/-) on an arbitrary scale from 0-3) was found in FcRII-/-.

DISCUSSION:

In this study we show that FcRIII deficiency does not result in reduced MMP-mediated cartilage destruction and cartilage matrix erosion during antigen-induced arthritis. In a previous study we showed that antigen-induced arthritis elicited in FcR K-chain -/- mice which lack functional FcRI and III failed to develop severe MMP-mediated cartilage destruction. This may indicate that FcRI is the most important activating FcR or even more plausible, that FcRI and FcRII are redundant.

Probably FcRI and III present on polymorphs and macrophages are important in the observed cartilage destruction. Mast cells which also express FcR appeared to be not important within this model whereas the present study also shows that mBSA specific T cell responses are not different between the two strains.

In contrast, absence of the inhibiting FcRII leads to both significantly more inflammation and severe cartilage destruction. Co-aggregation of FcRII with activating FcRII/FcRIII followed by cross-linking with IgG immune complexes, inhibits intra-cellular signalling and production of pro-inflammatory mediators. A crucial step in severe cartilage destruction is activation of latent metalloproteinases (like stromelysin-1 and collagenases) which are released in the articular cartilage matrix after cytokine (IL-1, IL-17) exposure. The interaction between IgG-immune complexes and FcR on hematopoetic cells may release mediators (oxygen radicals, enzymes like elastase) which are pivotal in activating latent cartilage degrading MMPs (2). The balance of the activating FcRI and III and the control by the inhibiting FcRII may determine the release of MMP-activating mediators. Inhibition of FcRI and III using overexpression of FcRII is at present under investigation and may form a new therapeutic intervention of the destructive phase of chronic arthritis.


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