FCR GAMMA CHAIN DETERMINES SEVERE CARTILAGE DESTRUCTION DURING EXPERIMENTAL ANTIGEN-INDUCED ARTHRITIS.

**VAN LENT, P.** **VAN VULLEN, H.** **BLOM, A.** **HOLTHUYSEN, A.** **VAN DE PUTTE, L.** **VAN DE WINKEL, J.** **VAN DEN BERG, W.**

**Department of Rheumatology, University Hospital Nijmegen, Geert Grootplein Zuid 8, Nijmegen, The Netherlands.** Dep of Rheumatology, University Hospital Nijmegen, Geert Grootplein Zuid 8, 6525 AS, Nijmegen, The Netherlands., 024-3616568, Fax: 024-3540403, P. vanlent@reuma.azn.nl

INTRODUCTION: IgG containing immune complexes are abundantly found in joint structures of patients with chronic arthritis. The role which these immune complexes play in joint pathology is still a matter of debate. Earlier studies done by our lab revealed that comparing different murine experimental models for arthritis, severe cartilage destruction was only found in those models in which immune complexes were found (1). IgG immune complexes communicate with hematopoietic cells via Fcγ receptors and three classes of these receptors (FcγRI, II and III) have been described. Cross-linking of FcγRI and III results in activation of intracellular signaling pathways. The γ chain is an essential component of FcγRII and FcγRIII but also of FcγRI present on mast cells and the T cell receptor CD3 complex on γδ T cells. In the present study we used Fcγ chain deficient mice (Fcγ γ−/−) to examine the role of Fcγ γ chain in severe cartilage destruction in knee joints with chronic experimental antigen-induced arthritis (AIA).

METHODS: Fcγ γ−/− (obtained from Dr T. Saito, Chiba, Japan) and control C57BL/6 mice were immunized with methylated BSA in complete Freunds adjuvant followed by injection of arthritis by local injection of mBSA into the right knee joint. Total knee joint sections were made to study cartilage destruction. Breakdown of proteoglycans from the cartilage matrix was determined by loss of red staining in safranin-O stained sections. Chondrocyte death was measured by determining empty lacunae and with the TUNEL assay in cryostate sections. Erosion was detected as ruffling of the cartilage surface. Aggrecan breakdown in cartilage caused by metalloproteinasases (MMP) was studied by immunolocalisation using specific antibodies against the aminoacids VDIPEN of the C-termius.

RESULTS: Three weeks after immunisation both cellular (T cell responses) as measured by lymphocyte stimulation and humoral (total IgG, IgG1, IgG2a and IgG2b levels as measured by ELISA) immunity raised against mBSA was comparable in both strains. Histology showed that at day 7 after AIA induction sustained inflammation proved significantly lower in the joint cavity but not in the synovium of Fcγ γ−/− mice. In various cartilage layers (femur,tibia,patella) of control arthritic knee joints, marked depletion of proteoglycans (40-70%) was found which was comparable to Fcγ γ−/−. Strikingly, chondrocyte death which varied from 22-50% in cartilage layers of control arthritic joints was completely absent in Fcγ γ−/−. In the control arthritic group mild erosion of the cartilage surfaces was found in 5 out of 8 animals. In the arthritic knee joints of Fcγ γ−/−, cartilage surfaces appeared normal and erosion was found in only one out of eight animals. Furthermore MMP-induced aggrecan neoepitopes which were abundantly found in controls (FIG 1A) were also completely absent in Fcγ chain γ−/−(FIG 1B). Nevertheless, latent MMPs were present in the cartilage matrix as seen in p-aminophenyl mercuric acetate (APMA) activated patellae.

FIG 1

A

B

DISCUSSION: In this study we show that the Fcγ γ chain is involved in cartilage erosion during antigen-induced arthritis. We believe that the activating FcγRI and RIII present on hematopoietic cells like macrophages and polymorphs are important in the observed cartilage destruction. Mast cells expressing the γ chain containing FcγRI were not important in cartilage destruction within this model (2) whereas the present study shows that also T cell responses (γδ T cells) against the methylated BSA were also comparable between the two strains. The absence of MMP-induced neoepitopes in the Fcγ γ−/− mice was not the result of the somewhat milder inflammation observed within knee joints of this strain. Eliciting a much milder arthritis in knee joints of control animals still showed considerable MMP-induced neoepitopes. Severe cartilage destruction is probably mediated by activation of latent metalloproteinase (like stromelysin-1 and collagenases) which appeared to be present in the cartilage matrix. The interaction between IgG –immune complexes and FcγRII and III on hematopoietic cells may release mediators (oxygen radicals,enzymes like elastase) which are of crucial importance in activating latent cartilage degrading MMPs. FcγRI and III may form new targets for therapeutic intervention of the destructive phase of chronic arthritis.


**Department of Immunology, University Hospital Utrecht, Lundlaan 6, Utrecht, The Netherlands.