MACROPHAGES MEDIATE EARLY CARTILAGE DAMAGE IN EXPERIMENTAL OSTEOARTHRITIS THROUGH PRODUCTION OF MATRIX METALLOPROTEINASES IN THE SYNOVIIUM

+*Blom, A B; *van Lent, P L; *van der Kraan, P M; **van Rooijen, N; ***Roth, J; *van den Berg, W B
*Experimental Rheumatology, Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands
a.blom@reuma.umcn.nl

ABSTRACT

INTRODUCTION:
Osteoarthritis (OA) is a disease that affects millions of people worldwide and causes joint pain and loss of movement, which may ultimately result in necessity for joint replacement. Not much is known about the etiology of the disease. Synovial macrophages have been shown to be very important in mediating inflammation and cartilage damage during murine experimental models for rheumatoid arthritis. However, also in OA recent studies suggest that synovial cells recent suggest that synovial cells may be involved in the occurring pathology. Recently we have shown involvement of synovial macrophages in OA-like pathology during experimental OA [1].

The purpose of this study was to further elucidate the mechanism via which synovial macrophages are involved in the generation of MMP-mediated OA-like pathology.

METHODS:
OA was induced in knee joints from which macrophages had previously been depleted using liposomies containing clodronate. Induction of OA was performed by 2 intra-articular injections of collagenase on alternate days into the murine knee joints. The intra-articular collagenase damages ligaments and tendons, which results in loss of stability of the murine knee joint. At day 3 and 7 after induction of OA, synovial tissue and cartilage was isolated and processed for RT-PCR. mRNA for MMP-2, MMP-3, MMP-9, MMP-12 and TIMP-1, -2 and -3. At day 7 and 14, whole knee joints were isolated and processed for histology. Immunohistochemistry for F4/80 and SaO staining was performed and scored. Statistical analysis was done using the Students t-test or the Mann Whitney U-test, and changes were considered significant when p<0.05. All animal experiments were performed after approval by the local ethics committee.

RESULTS SECTION:
At t=7 and t=14 a significantly lower amount of macrophages was present in the synovial lining of osteoarthritic knee joints that had previously been injected with clodronate-liposomies. However, no significant effect of clodronate treatment was observed on macrophages in deeper layers of the synovium. The decreased presence of macrophages correlated well with the earlier described amelioration of MMP-mediated cartilage damage. At day 3 after induction of OA, no significant differences were found comparing MMP/TIMP expression in control OA synovium and macrophage depleted synovial tissue (figure 1a and 1b). However, at day 7 after induction, a strong upregulation of MMP-2 (30-fold) and MMP-3 (60-fold) was found in OA tissue of control joints, whereas expression in synovium of macrophage-depleted joints was not significantly different from naive controls (figure 1c and 1d). Also MMP-9 was upregulated in control OA synovium (4-fold), MMP-12 was not regulated. In macrophage-depleted synovium,

REFERENCES

AFFILIATED INSTITUTIONS FOR CO-AUTHORS:
** Vrije Universiteit Medical Center, Amsterdam, The Netherlands
*** Institute of Experimental Dermatology, University of Munster, Munster, Germany.

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