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'ALARMIN'S' S100A8 AND A9 ARE ACTIVELY INVOLVED IN REGULATION OF SYNOVIAL ACTIVATION AND JOINT DESTRUCTION DURING MOUSE AND HUMAN OSTEOARTHRITIS

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Background and objectives Prominent proteins released by activated macrophages are the 'alarmins' S100 A8 and A9. There is increasing belief that synovial tissue activation contributes to OA cartilage pathology. The aim was to explore active involvement of S100A8/A9 in cartilage destruction in experimental osteoarthritis models that differ in degree of synovial activation and to evaluate the presence of S100A8/S100A9 in sera and synovia of patients with early symptomatic OA

Material and methods Experimental OA was either induced by transection of the medial anterior meniscotibial ligament which leads to destabilisation of the medial meniscus (DMM) or by injection of collagenase into murine knee joints, which causes overall ligament damage and broad instability. Collagenase-induced-osteoarthritis involves chronic synovial activation in contrast to DMM. Synovial expression of S100A8 and S100A9 was measured using immunolocalisation. Both models were induced in S100A9^{-/-} deficient mice (myeloid cells also lack S100A8 at the protein level). Primary chondrocytes were stimulated with S100A8 and A9 and MMP levels were measured using RT-PCR Arthroscopic biopsies (30) and sera (200) were taken from patients with early symptomatic OA (CHECK cohort, The Netherlands). Protein levels of S100A8 and A9 was determined using immunolocalisation or ELISA

and related to joint destruction (Kellgren Lawrence score) at year two.

Results In collagenase-induced osteoarthritis, showing marked synovial activation S100A8 and S100A9 was strongly upregulated in synovium at day 7 and remained high at days 14, 28 and 42. In contrast IL-1 β was expressed in early stages only. Using S100A9^{-/-} mice, the authors found a major impact of s100A8 and A9 on synovial activation and OA cartilage destruction. Synovial activation was 62% lower at day 42. Cartilage destruction was significantly lower in all surfaces and ranged from a 45% reduction in the lateral tibia to 73% reduction in the medial femur. When primary mouse chondrocytes were stimulated with S100A8 or S100A9, a strong upregulation of particularly MMP-3 mRNA level was found indicating a direct role of S100A8/A9 in cartilage destruction. In contrast, in the DMM model in which synovial involvement is scant no role of S100A8/A9 was found for the focal OA cartilage destruction.

Arthroscopic synovial biopsies taken from patients in the early symptomatic OA CHECK cohort identified substantial S100A8 and A9 mRNA and protein expression and levels correlated with synovial lining thickness, cellularity in subintima and joint destruction. Serum S100A8/A9 protein levels were significantly enhanced at base line in patients showing pronounced progression of joint destruction in 2 years.

Conclusions Alarmins S100A8/S100A9 are crucial proteins involved in synovial activation and cartilage destruction during OA and high levels may predict joint destruction in human OA.