4. Myeloid cells and innate immune receptors

A83 'ALARMINS' S100A8 AND A9 DETERMINE SYNOVIAL ACTIVATION AND JOINT DESTRUCTION DURING EXPERIMENTAL OSTEOARTHRITIS

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Objective Prominent proteins released by activated macrophages are the 'alarmins' S100A8 and S100A9 which can further reactivate macrophages via toll-like receptor 4 forming an autocrine positive feedback loop. There is increasing belief that synovial tissue activation contributes to osteoarthritis (OA) cartilage pathology The aim is to evaluate active involvement

of S100A8/A9 in cartilage destruction in experimental OA models that differ in degree of synovial activation.

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-OA 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 S100A9 and matrix metalloproteinase (MMP) levels were measured using RT-PCR.

Results The function of S100A8 and S100A9 was further studied in experimental OA models. Kinetic studies show that in surgically induced DMM model, S100A8 and S100A9 was marginally expressed within the synovium, only evident at day 7 after induction and consistent with limited synovial thickening. The degree of OA cartilage pathology was similar in S100A9$^{-/-}$ and wild-type (WT) mice at day 42 after induction of DMM. In contrast, during the course of collagenase-induced OA, S100A8 and S100A9 was strongly upregulated in synovium at day 7 and remained high at days 14, 28 and 42. Expression of these proteins nicely correlated with thickening of the synovial lining layer comprising macrophages with an activated phenotype. When collagenase-induced-OA was elicited in S100A9$^{-/-}$ mice, significantly lower synovial activation was observed when compared to WT mice. 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 MMP3 mRNA level was found indicating a direct role of S100A8/A9 in cartilage destruction.

Conclusions Alarmins S100A8/A9 play a crucial role in synovial activation and cartilage destruction in an OA model that shows clear synovial involvement. S100A8/A9 expression in the synovium causes pathology probably by stimulating MMP-mediated damage in the cartilage matrix.

Topic Myeloid cells and innate immune receptors.