Active involvement of alarmins S100A8 and S100A9 in regulation of synovial activation and joint destruction during osteoarthritis

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Abstract introduction:

Breakdown of the cartilage matrix is one of the hall marks of osteoarthritis. Cartilage destruction is predominantly mediated by cytokines and enzymes. Selective elimination of synovial macrophages prior to induction of experimental osteoarthritis inhibited synovial activation and diminished cartilage destruction (1,2). The most prominent proteins released by activated macrophages are myeloid related proteins: MRPI8 (S100A8) and MRPI4(S100A9). These proteins have been shown to activate macrophages via TLR4 signalling (3) and stimulate chondrocytes to produce MMPs (4). Using S100A9 knockout mice which are also partly deficient for S100A8 we found that cartilage destruction was largely inhibited in a model of rheumatoid arthritis. This prompted us to investigate whether these proteins are also involved in synovial activation and cartilage destruction in osteoarthritis using two different experimental murine models.

Methods:

Experimental OA was either induced by injection of collagenase into murine knee joints, which causes local instability or by transection of the medial anterior meniscotibial ligament which leads to destabilisation of the medial meniscus (DMM). OA phenotypes were studied within 8 weeks after induction. Collagenase-induced-osteoarthritis involves chronic synovial activation in contrast to DMM. Synovial expression of S100A8 and S100A9 during the course of osteoarthritis was performed using immunolocalisation. Both models were induced in S100A9/- deficient mice (myeloid cells also lack S100A8 at the protein level). Synovial activation and cartilage destruction was measured by histology. Cartilage pathology was scored in a blinded way using an arbitrary score that considered both grade (0-6) and stage (0-5) of pathology. MMP-mediated cartilage destruction was measured with immunolocalisation using anti-VDIPEN antibodies.

Result section

Kinetic studies show that S100A8 and S100A9 expression were clearly detected in synovial macrophages during the course of collagenase-induced osteoarthritis at days 7,14 and 42. Expression of these proteins nicely correlated with thickening of the synovial lining layer comprising activated macrophages (figure 1). In contrast, in the mechanically induced DMM model, marginal expression of both proteins was seen, only evident at day 7 after induction and consistent with limited synovial thickening. Of interest, particularly the active form of S100A8 was expressed in chondrocytes of cartilage areas in which lesions preferentially developed at later time-points (data not shown).

In addition, cartilage destruction was measured in various cartilage surfaces (medial and lateral tibia and femur) of the knee joint. Cartilage destruction in S100A9/- mice was strongly and significantly lower in all surfaces and ranged from a 45% reduction in the lateral femur to 73% reduction in the medial femur (Figure 2). In line with this, MMP-mediated cartilage destruction (VDIPEN) was clearly present in cartilage of osteoarthritic controls but markedly decreased in medial cartilage layers of day 42 osteoarthritic S100A9/- mice, suggesting that S100A8/A9 are involved in activating MMPs. S100A8 and in lesser extent S100A9 stimulate chondrocytes to upregulate and activate MMPs (data not shown). In contrast, in the DMM model, where S100A8 and S100A9 was hardly expressed in the synovium, no differences in cartilage destruction were observed in S100A9/- and WT mice.

Discussion:

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

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References: