Background and Objective Alarmins S100A8 and S100A9 are members of the S100 family of Ca2+-binding proteins that are involved in the pathology of rheumatoid arthritis (RA). These molecules are released in large amounts by activated macrophages or monocytes either as monomers or as a heterodimeric complex. From arthritis studies in S100A9 knock-out mice, it appears that S100A8 and S100A9 play an essential role in cartilage degradation. We investigated whether S100A8, S100A9 and/or S100A8/S100A9 complex could skew human chondrocytes towards a catabolic phenotype advantageous of cartilage breakdown, with upregulation and activation of MMPs, upregulation of pro-inflammatory cytokines and downregulation of cartilage matrix proteins. S100A8 and/or S100A9 may prove crucial markers for measuring cartilage destruction.

Methods S100A8 and S100A9 protein detection was performed in human cartilage from RA and osteoarthritis (OA) patients using immunohistochemistry. Human chondrocytes were isolated from patients undergoing joint replacement and stimulated with recombinant S100A8, S100A9, S100A8/S9 heterodimer and interleukin 1b (IL-1b). mRNA levels of matrix metalloproteinases (MMPs), cytokines and cartilage matrix molecules were determined with qPCR and protein levels using Luminex.

Results S100A8 and S100A9 protein were abundantly present in and around chondrocytes of cartilage derived from RA and OA patients as shown by immunolocalisation. In addition, S100A8 and S100A9, but not the S100A8/S9 heterodimer, upregulated mRNA expression of MMPs in human chondrocytes (MMP1&3 fourfold and MMP9&13 threefold). Furthermore S100A8 and S100A9 upregulated IL-6 mRNA expression (11-fold) and protein production and downregulated RNA expression of matrix molecules aggrecan and collagen type II and X (twofold to threefold), again with no effect of the heterodimer. The catabolic effect of S100A8 and S100A9 was comparable to IL-1b effects, but there was no additive effect of S100 with IL-1b, suggesting independent mechanisms.

Conclusions S100A8 and S100A9 are found in and around human chondrocytes suggesting that these small sized monomeric molecules (10 kD) are able to penetrate the cartilage matrix. S100A8 and S100A9, but not the heteromeric S100A8/S100A9 complex can skew human chondrocytes towards a catabolic phenotype advantageous of cartilage breakdown, with upregulation and activation of MMPs, upregulation of pro-inflammatory cytokines and downregulation of cartilage matrix proteins. S100A8 and/or S100A9 may prove crucial markers for measuring cartilage destruction.

Reference