Abstract

Background: Alarmins S100A8 and S100A9 are found in high amounts in the synovial fluid of osteoarthritis (OA) patients. Recently, we found that S100A8 and S100A9 are associated with cartilage degradation in murine collagenase-induced OA. In the current study, we investigated whether S100A8 and/or S100A9 can have a catabolic effect on chondrocytes from OA patients.

Methods: In cartilage from end stage OA, we stained for S100A8 and S100A9 protein, MMP-1 and -3 and a cartilage breakdown epitope specific for MMPs (VDIPEN) using immunohistochemistry. mRNA levels of MMPs, cytokines and cartilage matrix molecules were determined with RT-qPCR, protein levels of MMPs and cytokines with Luminex. For receptor blocking studies, specific inhibitors for Toll-like receptor 4 (TLR4) (intracellular TAK242) were used.

Results: In cartilage of OA patients, localisation of S100A8 and S100A9 protein was found close to chondrocytes and was associated with proteoglycan (PG) depletion, MMP1 and -3 and VDIPEN expression. Stimulation of OA chondrocytes for 24 hours with recombinant human S100A8 and S100A9 caused a significant upregulation of the catabolic genes MMP1, -3, -9 and -13, IL-6, IL-8 and MCP-1 at the mRNA and protein level. Moreover, the expression of anabolic markers aggrecan and collagen type II was significantly reduced at the mRNA level. Blocking TLR4 almost completely inhibited the upregulation of MMP-3, IL-6, IL-8, MCP-1 and down-regulation of collagen type II by S100A9 in OA chondrocytes. Finally, the catabolic effect of S100A8 and S100A9 was significantly more pronounced in chondrocytes from OA patients when compared to non-OA. TLR4 mRNA expression was enhanced in OA chondrocytes, which might explain the increased sensitivity.

Conclusion: S100A8 and S100A9 have a catabolic effect on human chondrocytes that is dependent on TLR4. OA chondrocytes are more sensitive for S100-stimulation than normal chondrocytes. This study underlines the potential of S100A8 and S100A9 as mediators of cartilage damage during OA.