Transcriptional regulation in the pathogenesis of osteoarthritis

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Many risk factors such as biomechanical stress on the articular cartilage imposed by joint overloading due to obesity, repetitive damage of the joint tissues by injury of the menisci and ligaments, abnormal joint alignment play crucial role in the pathogenesis of osteoarthritis (OA). Inflammation, a host response mechanism which is triggered to cope with the environmental stress, is an important contributor, at least, in the early stage of this disease process. Cytokines and growth factors produced during inflammation promote substantial changes of the cellular activities in the surrounding cells. It has been shown that synovial inflammation triggers a cascade of events which subsequently reach the chondrocyte cells of the articular cartilage activating inflammatory events in the chondrocytes leading to cartilage destruction. One major consequence of OA is the hypertrophy of the subchondral bone and new bone formation at the joint margins causing osteophyte formation. Apparently, distinct biological events such as cartilage degradation and abnormal mode of cartilage repair converge in OA. Thinning and erosion of the cartilage matrix are primarily mediated by chondrocyte- and synovial cell-derived matrix metalloproteinases (MMPs). Some of the molecular events associated with bone development such as the presence of osteocalcin, alkaline phosphatase, VEGF and the type X collagen are evident in the chondrocytes of OA cartilage suggesting that an abnormal reinitiation of some developmentally regulated extracellular matrix (ECM) synthesizing activities might be responsible for osteophyte formation. To address how these diverse groups of genes are activated in OA chondrocytes, we have studied the induction mechanism of some of these genes. Our studies have identified an inflammatory cytokine-responsive transcription factor, SAF-1, which is abundantly present in OA cartilage tissues. Further studies have identified SAF-1 as a major transcriptional regulator for increased synthesis of, at least, two matrix degrading metalloproteinases MMP -1 and -9 and an angiogenic protein, VEGF, under arthritic condition. Expression of RANKL, a regulator of bone growth, is negatively regulated by SAF-1 suggesting its possible role in promoting osteophyte formation in the joint margins. Together, our studies provide evidence implicating SAF-1 as an important factor in the pathogenesis of OA.