J Musculoskel Neuron Interact 2002; 2(6):517-520

Perspective Article

Hylonome

Molecular regulation of the chondrocyte phenotype

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Keywords: Cartilage, Osteoarthritis, Collagen, Gene Regulation, Cytokines

The chondrocyte is a specialized mesenchymal cell that is responsible for synthesis of the matrix proteins that provide tensile strength and resistance to mechanical loading of the articular cartilage. The failure of chondrocytes within the joint to maintain the balance between synthesis and degradation of the cartilage extracellular matrix is a major component of the pathogenesis of osteoarthritis (OA). Repetitive mechanical injury, which may be exacerbated by genetic abnormalities that produce joint instability, is the primary causative factor in OA. Adult articular chondrocytes normally maintain a low turnover rate of replacement of cartilage matrix proteins, but have a limited capacity to repair major cartilage lesions. Early changes in OA include activation of chondrocyte proliferation and biosynthesis of inflammatory cytokines and matrix-degrading proteinase[1]. These early changes in synthetic activity also include the attempt by the resident chondrocytes to regenerate the matrix with cartilage-specific components such as collagens II, IX, and XI and aggrecan, although incorporation of these molecules into the normal cartilage architecture may be defective. There is also evidence of phenotypic modulation due to increased expression of collagen types I, IIA, III, IV, and X[2].

The central role of the proinflammatory, catabolic cytokines, particularly IL-1 and TNF-α, in promoting the destruction of articular cartilage in joint diseases such as rheumatoid arthritis and osteoarthritis is well established, based on *in vitro* and *in vivo* studies[1,3,4]. The earliest descriptions of IL-1 included "mononuclear cell factor", a product of rheumatoid synovium that stimulated the synthesis of collagenase and prostaglandin E2 (PGE_2), and "catabolin", a product of normal porcine synovium that stimulated cartilage breakdown. The chondrocyte is the cellular target of cytokine action in cartilage, and IL-1β and TNF-α colocalize with matrix metalloproteinase (MMP) production in superficial regions of OA cartilage[5]. IL-1β also contributes to cartilage depletion by suppressing the expression of cartilage-specific genes, including types II, IX, and XI collagens and aggrecan[6-9]. Furthermore, IL-1 contributes to the loss of cartilage-specific phenotype by stimulating type I collagen gene expression[8,10,11]. IL-1 also stimulates cyclooxygenase-2 (COX-2) gene expression resulting in increased secretion of PGE_2, which opposes the effects of IL-1 by inhibiting type I and stimulating type II collagen gene expression[8,10-12]. Interestingly, the IL-1-induced COX-2 response is dependent upon the differentiated phenotype of the chondrocytes[13]. The chondroprotective effects of exogenous COX-2 products or endogenously produced prostaglandins may be mediated by EP receptors or via activation of the transcription factor PPARγ, which has been shown to reverse the IL-1-mediated inhibition of proteoglycan synthesis in chondrocytes[14]. Furthermore, the acute increases in COX-2 products may explain the early increases in cartilage matrix proteins observed in OA.

IL-1 and TNF-α increase the transcription of MMP-13, COX-2, iNOS and other genes associated with inflammation and cartilage destruction via the stress-activated protein kinases (SAPKs), also termed c-Jun N-terminal kinases (JNKs), and p38 MAPK[15-18]. The SAPKs are a subfamily of the extracellular signal-regulated kinase (ERK) family of serine/threonine kinases, but unlike the mitogen-activated protein kinases (MAPKs), ERK-1 and ERK-2, they are weakly activated by growth factors. The SAPKs primarily mediate phosphorylation and activation of c-Jun and ATF-2, while the ERK1/2 kinases activate ELK-1, which together with the serum response factor (SRF) controls transcription via the serum response element that mediates the expression of many immediate-early genes such as c-Fos and Egr-1. Thus, the SAPK and MAPK cascades provide a convenient means of dissociating cytokine- from mitogen-activated signaling responses. We reported recently that the selective p38 MAPK inhibitor, SB203580, partially reverses the inhibitory effect of IL-1 on COL2A1 expression at concentrations that do not inhibit IL-1-induced JNK phosphorylation[19]. Since the JNK and p38 MAPK signaling pathways are known primarily to mediate induction by IL-1 of gene expression, our findings that p38 MAPK and JNK are critical signals in transcriptional sup-

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Accepted 1 August 2002

pression of COL2A1 expression are somewhat novel.

We showed previously that IL-1β decreases the levels of α1(II) procollagen mRNA by inhibiting COL2A1 gene transcription[12]. IL-1β treatment of quiescent human chondrocytes also induces the expression of immediate early gene mRNAs encoding the transcription factors, c-Fos, c-Jun, Jun B, and Egr-1, preceding downregulation of COL2A1 mRNA levels[20]. However, direct binding to COL2A1 regulatory sequences of IL-1β-induced nuclear protein complexes containing these factors has not been demonstrated. TNF-α and IFN-γ also inhibit type II collagen synthesis via transcriptional mechanisms that are both distinct from and overlapping with those transducing the effects of IL-1β[12,21-23].

IL-1β is known to induce or activate members of the NF-κB, Jun/Fos, C-EBP, and ETS families of transcription factors, which may then induce or modulate the expression of MMPs, COX-2, and other genes involved in inflammatory and destructive processes. Cytokine regulation of transcription is not fully understood in connective tissue cells, even with regard to genes that have been well studied, such as collagenase-1 (MMP-1). AP-1 (Jun/Fos) is necessary for expression of MMP-1, -3, and -13 genes, whereas the inductive response to IL-1 requires NF-κB and ETS factors. However, since the regulation of a significant number of cytokine-responsive genes cannot be attributed exclusively to direct interaction of NF-κB with DNA elements, alternative pathways may play critical roles in the transcriptional regulation of these genes. For example, C/EBPβ and γ, rather than NF-κB, are critical for induction of the COX-2 and PLA2 promoters by IL-1[24] and are involved in the inhibition of type I and type II collagen gene transcription by TNF[25,26].

Studies *in vivo* have shown that expression of the type II collagen gene is tightly regulated during development at different stages of chondrogenesis and endochondral bone formation and during growth plate formation. Structural and functional analyses of the promoter and first intron regions of type II collagen genes from different species have revealed multiple potential regulatory elements[27-29]. Functional binding motifs for Sp1 family members[27,30,31], E-box-binding, bHLH proteins[32], and the zinc finger protein[33], have been identified in the proximal promoter region. Sox9, the first transcription factor to specify the chondrogenic lineage, activates type II collagen gene transcription by binding to the first intron enhancer through its high mobility group DNA-binding domain and acts cooperatively with L-Sox5 and Sox6[34]. It has been proposed that downregulation of Sox9 expression by interleukin-1 (IL-1) or upregulation by fibroblast growth factors (FGFs) or bone morphogenetic proteins (BMPs) determines the regulation of type II collagen gene transcription by these cytokines[35,36]. The homeobox protein, Dlx-2, is also stimulated by BMP-2 and acts via the intronic enhancer to increase Col2a1 expression[37].

To provide reproducible models for studying cytokine regulation of chondrocyte gene expression, we developed immortalized human chondrocyte cell lines using plasmid and retroviral vectors expressing SV40-TAg[19,20]. Proteoglycans, IGF binding proteins, and integrins, and proliferative rates in these cell lines have been characterized[38-40]. T/C-28a2, C-28/I2, and C-20/A4, derived from juvenile costal cartilage, have been used in several laboratories to study a variety of general and specific chondrocyte functions[41-50]. All four of these cell lines maintain chondrocyte responses to IL-1 and express endogenous COL2A1 mRNA, as well as transiently transfected COL2A1 gene sequences[19,20]. They have been used by a number of collaborators to transiently or stably express reporter genes or recombinant wild-type and mutant proteins[13,48,51-53]. Thus, these cell lines have served as convenient models for testing approaches for gene therapy. For example, the tsT/AC62 cells have been used as a model to test the capacity of UV-activated gene transduction to enhance AAV-mediated gene therapy in articular cartilage[54]. Also, RNA interference (RNAi) and antisense DNA was used to target cathepsin B expression for gene silencing in the C-28/I2 and T/C-28a2 cells[55].

Studies in my laboratory have used the immortalized chondrocyte cell lines as reproducible models to delineate the IL-1β-induced signaling pathways and transcription factors involved in suppression of type II collagen gene transcription. Functional analysis of the human type II collagen gene (COL2A1) regulatory sequences indicate that there are enhancer and silencer elements in both the distal promoter and first intron regions. In transient transfections using the pGL2 reporter vector, the proximal promoter expresses strongly in the absence of the Sox9-binding intronic enhancer. Furthermore, the constitutive Sox9, L-Sox5 and Sox6 mRNA levels are not suppressed by IL-1β and the IL-1β response is retained in the COL2A1 promoter region spanning –577/+125 bp in the absence or presence of the 309 bp intronic enhancer. Thus, our studies suggest that the role of Sox9 and related HMG factors, which are architectural proteins that function to bend and unwind DNA, is to maintain an open chromatin network surrounding the constitutively active COL2A1 promoter.

Our results further show that at least one IL-1-induced transcription factor, Egr-1, interacts directly with the core COL2A1 promoter and reduces its strong constitutive activity by competing with Sp1 for binding. The rapid response observed is consistent with early cytokine-activated events that are usually associated with positive responses but produce a negative response in this promoter context. Overexpression of the co-activator CBP reverses the inhibitory effect of IL-1-activated Egr-1. Thus, Egr-1 may prevent interactions among CBP, Sp1 and TATA-binding proteins and thereby permit transcriptional repression by other IL-1β-induced factors that bind to upstream promoter sequences. Candidate factors are C/EBP and ETS family members that are known to be involved in cytokine regulation of other genes[25-27,57]. Our results support the notion that there are multiple pathways and transcription factors mediating the effects of IL-1β on COL2A1 gene expression. Overall our findings will lead to further understanding of the cellular and molecular mechanisms by which catabolic cytokines suppress the differentiated phenotype in chondrocytes and aid in the development of novel targeted therapies that will block the adverse effects of catabolic cytokines on the expression of cartilage matrix genes.

Acknowledgments

This work was supported in part by NIH grant AR45378 and a Biomedical Science Grant from the Arthritis Foundation.

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