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A mechanism for anti-chondrogenic effects of IL1

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Keywords

Chondrocyte, collagen, NFkappaB, sox9, transcription

Context

The transcription factor Sox9 has been characterised as a master regulator of chondrocyte differentiation. In the absence of Sox9 activity, mesenchymal cells are unable to differentiate into chondrocytes, or to express chondrocyte-specific markers such as aggrecan and collagen (col) 2a1, 9a2 and 11a2. The pro-inflammatory cytokines interleukin-1? (IL-1?) and tumor necrosis factor alpha (TNF-a) are inhibitors of the chondrocyte phenotype, and downregulate the expression of chondrocyte markers. To investigate mechanisms of negative regulation of cartilage function by IL-1? and TNF-a.

Significant findings

IL-1&#946 dose-dependently downregulated the expression of Sox9 (rapidly) and col2a1 (more slowly) at the mRNA level in primary mouse chondrocytes. In the mouse chondrocyte cell line MC615 a similar downregulation of mRNAs was shown not to involve changes in mRNA stability. In transiently transfected chondrocytes Sox9-dependent reporter constructs were constitutively active (due to endogenous Sox9), but could be inactivated by IL-1&#946. In the presence of co-expressed Sox9, the activity of such reporters was increased, and they were insensitive to IL-1&#946. The negative effects of IL-1&#946 upon Sox9 reporter constructs could be blocked by overexpression of the NF-? inhibitor I?B, and reproduced by overexpression of NF-?B subunits p50 and p65. PDTC (pyrrolidine dicarbamate), an inhibitor of I?B degradation, interfered with the negative effects of IL-1? upon Sox9 protein expression. Additional experiments showed TNF-a downregulated Sox9 protein, and inhibited a Sox9-dependent reporter construct. The inhibitory effect of TNF-a appeared to be NF-?B-dependent, suggesting that TNF-a and IL-1? employ similar mechanisms to inhibit cartilage-specific gene expression.

Comments

The latest paper from this excellent laboratory suggests a mechanism for negative regulation of cartilage function by pro-inflammatory cytokines. The gene expression studies by transient transfection of primary chondrocytes are impressive. It is disappointing that the studies of mRNA stability are performed in a chondrocyte cell line rather than in primary cells; however, this is a very minor criticism.

Methods

Gene expression at the mRNA and protein levels was quantitated by northern and western blotting. Stabilities of mRNAs were assessed by 'chase' experiments using the transcriptional inhibitor DRB. Sox9 activity was assessed by transient transfections of primary mouse chondrocytes using a proprietary transfection reagent. Luciferase reporter constructs contained multiple copies of a Sox9 binding site derived from a col2a1 enhancer.

References

1. Murakami S, Lefebvre V, de Crombrugghe B: Potent inhibition of the master chondrogenic factor sox9 gene by interleukin-1 and tumor necrosis factor-alpha. J Biol Chem. 2000, 275: 3687-3692.