Suppression of typel collagen gene expression by prostaglandins in fibroblasts is mediated at the transcriptional level.

賴文福
Riquet FB;Lai WFT;Birkhead JR;SuenLF;Karsenty G;Goldring MB

摘要

Abstract

BACKGROUND: Tissues undergoing a chronic inflammatory process, such as the synovium in rheumatoid arthritis, are characterized by the infiltration of lymphocytes of different subsets and activation of monocyte/macrophages. Interleukin-1 (IL-1), a monocyte/ macrophage product that stimulates synovial fibroblasts to produce matrix metalloproteinases (MMPs), prostaglandins, and other cytokines, also has profound effects on the synthesis of extracellular matrix components such as type I collagen. In previous studies, we have shown that synovial fibroblasts and chondrocytes isolated from human joint tissues are particularly sensitive to prostaglandins, which modulate the effects of IL-1 on collagen gene expression in an autocrine manner. MATERIALS AND METHODS: BALBc/3T3 fibroblasts were treated with IL-1 and prostaglandins in the absence and presence of indomethacin to inhibit endogenous prostaglandin biosynthesis. Collagen synthesis was analyzed by SDS-PAGE as [3H]proline-labeled, secreted proteins, and prostaglandin production and cyclic adenosine 3',5'-cyclic monophosphate (camp) content were assayed. The expression of type I collagen gene (Col1a1) promoter-reporter gene constructs was examined in transient transfection experiments, and the binding of nuclear factors to the Col1a1 promoter region spanning -222 bp/+ 116 bp was analyzed by DNase I footprinting and electrophoretic mobility shift (EMSA) assays. RESULTS: IL-1 increased the synthesis of type I and type III collagens in BALBc/3T3 fibroblasts; greater increases were observed when IL-1-stimulated synthesis of PGE2 was blocked by indomethacin. Transient transfection experiments demonstrated dose-dependent inhibition of the-222 bp Col1a1 promoter by exogenously added prostaglandins with the order of potency of PGF2alpha > PGE2 > PGE1 DNase I footprinting showed increased protection, which extended from the region immediately upstream of the TATA box, owing to the binding of nuclear factors from PGE2- or PGE1-treated BALBc/3T3 cells. EMSA analysis showed zinc-dependent differences in the binding of nuclear factors from untreated and prostaglandin-treated cells to the -84 bp/-29 bp region of the Col1a1 promoter. CONCLUSIONS: These results show that the inhibition of Col1a1 expression by IL-1 in fibroblasts is mediated by prostaglandins at the transcriptional

level and suggest that PGE-responsive factors may interact directly or indirectly with basal regulatory elements in the proximal promoter region of the Col1a1 gene.