Expression of TNF-α, VEGF, and MMP-3 mRNAs in synovial tissues and their roles in fibroblast-mediated osteogenesis in ankylosing spondylitis


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ABSTRACT. The aim of this study was to explore the mRNA levels of tumor necrosis factor-α (TNF-α), vessel endothelial growth factor (VEGF), and matrix metalloproteinase-3 (MMP-3) in synovial tissues in ankylosing spondylitis (AS), and to analyze the functions of these proteins in the differentiation of AS synovial tissue fibroblasts into osteoblasts (OB) and osteoclasts. Synovial tissue samples from 22 AS patients and 22 normal individuals were collected. In situ hybridization was utilized to detect TNF-α, VEGF, and MMP-3 transcripts. After counting numbers of positive cells, Spearman analysis was used to determine the correlation between transcriptional levels of the three mRNAs and the AS disease activity index (BASDAI) and the C-response protein (CRP) levels. With the addition of TNF-α, VEGF, or both factors into cultured normal synovial fibroblasts, osteocalcin (bone gla protein, BGP) secretion levels were compared. We found that expression of TNF-α, VEGF, and MMP-3 was identified exclusively in the disease group. mRNA levels were significantly positively...
correlated with BASDAI (r = 0.42, 0.38, and 0.47, respectively; P < 0.05) and CRP (r = 0.44, 0.34, and 0.47 respectively; P < 0.05) scores. The secretion level of BGP in normal synovial fibroblasts increased progressively with increasing concentrations of VEGF or TNF-α (P < 0.01 compared to levels before treatment). Furthermore, co-incubation using both VEGF and TNF-α significantly elevated BGP levels compared to the single addition of VEGF or TNF-α (P < 0.01). These results suggest TNF-α, VEGF, and MMP-3 might directly participate in the differentiation of fibroblasts into OBs.

**Key words:** Ankylosing spondylitis; Synovial tissues; Osteoclast; Tumor necrosis factor-α; Vessel endothelial growth factor; Matrix metalloproteinase-3