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Abstract

Bone metabolism is tightly coordinated by two types of functional cells, osteoblasts and osteoclasts. In the adult skeletal system, bone tissue is continuously regenerated by the sequential process of resorption of old bone and formation of new bone, and bone mass is moderately maintained, so called bone remodeling. Multiple humoral factors including cytokines, hormones and growth factors take a part, and play a crucial role in bone remodeling process. In addition, the microvasculature is essential for bone metabolism. Vascular endothelial growth factor (VEGF), which is produced and secreted by various cells including osteoblasts, is a potent mitogen for vascular endothelial cells and acts as an angiogenic factor. We previously demonstrated that transforming growth factor-β (TGF-β) stimulates the synthesis of VEGF through the activation of p38 mitogen-activated protein (MAP) kinase in osteoblast-like MC3T3-E1 cells. Heat shock protein70 (HSP70) is a ubiquitously expressed molecular chaperone. In the present study, we investigated the involvement of HSP70 in the TGF-β-stimulated VEGF synthesis and the underlying mechanism in these cells. VER-155008 and YM-08, both of HSP70 inhibitors, significantly amplified the TGF-β-stimulated VEGF release. In addition, the expression level of VEGF mRNA induced by TGF-β was enhanced by VER-155008. These inhibitors markedly strengthened the TGF-β-induced phosphorylation of p38 MAP kinase. The TGF-β-induced phosphorylation of p38 MAP kinase was amplified in HSP70-knockdown cells. SB203580, an inhibitor of p38 MAP kinase, significantly suppressed the amplification by these inhibitors of the TGF-β-induced VEGF release. These results strongly suggest that HSP70 acts as a negative regulator in the TGF-β-stimulated VEGF synthesis in osteoblasts, and that the inhibitory effect of HSP70 is exerted at a point upstream of p38 MAP kinase.