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Abstract

Bone metabolism is strictly regulated by two types of functional cells, osteoblasts and osteoclasts, which are responsible for bone formation and bone resorption, respectively. In addition, the microvasculature, provided by capillary endothelial cells, is essential for bone metabolism. Vascular endothelial growth factor (VEGF) is a potent mitogen for vascular endothelial cells and acts as an angiogenic factor to induce the proliferation of endothelial cells. It has also been shown that VEGF is synthesized by osteoblasts in response to various physiological agents, including transforming growth factor-β (TGF-β). We previously showed that TGF-β stimulates VEGF synthesis via p44/p42 mitogen-activated protein (MAP) kinase, p38 MAP kinase and stress-activated protein kinase/c-*Jun* N-terminal kinase (SAPK/JNK) in osteoblast-like MC3T3-E1 cells. In the present study, we investigated the involvement of Rac, which is a member of the Rho family of small GTPases, in the TGF-β-stimulated VEGF synthesis in MC3T3-E1 cells. TGF-β markedly increased the levels of GTP-bound Rac. NSC23766, a selective inhibitor of Rac-guanine nucleotide exchange factor interaction, significantly increased both the release of VEGF and the mRNA expression levels induced by TGF-β. In addition, the release of VEGF stimulated by TGF-β was amplified in Rac-knock down cells. Meanwhile, SIS3, a specific inhibitor of TGF-β-dependent Smad3 phosphorylation, significantly reduced the TGF-β-stimulated VEGF release. However, the phosphorylation of Smad2 or Smad3 induced by TGF-β was hardly affected by NSC23766. On the other hand, NSC23766 enhanced the TGF-β-induced phosphorylation of p38 MAP kinase without affecting the phosphorylation of p44/p42 MAP kinase or SAPK/JNK. Furthermore, the phosphorylation of p38 MAP kinase induced by TGF-β was markedly upregulated in the Rac-knock down cells. These results strongly suggest that Rac negatively regulates the TGF-β-stimulated VEGF synthesis via the inhibition of p38 MAP kinase in osteoblasts.