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Endoglin expression is regulated by transcriptional cooperation between the hypoxia and transforming growth factor-beta pathways.

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Abstract

Endoglin is a transforming growth factor-beta (TGF-beta) co-receptor expressed mainly on endothelial cells and involved in cardiovascular development, angiogenesis, and vascular remodeling. This is illustrated by the fact that mutations in the endoglin gene give rise to hereditary hemorrhagic telangiectasia type 1, a dominant vascular disease with clinical manifestations that originate by a mechanism of haploinsufficiency. Thus, studies on the regulated expression of endoglin are crucial to devising therapeutic strategies for hereditary hemorrhagic telangiectasia type 1. Endoglin is highly expressed in the neovasculature associated with hypoxia such as ischemic tissues and tumors, but the molecular mechanism of this up-regulation is unknown. Here, we have investigated the possible regulation of endoglin expression by hypoxia. Surface protein, transcript, and promoter activity levels of endoglin were found to be up-regulated by hypoxia, indicating that the regulation takes place at the transcriptional level. A hypoxia-responsive element downstream of the main transcription start site of the endoglin gene was functionally characterized. Whereas hypoxia alone moderately stimulated endoglin transcription, addition of TGF-beta under hypoxic conditions resulted in transcriptional cooperation between both signaling pathways, leading to marked stimulation of endoglin expression. Because basal endoglin transcription is sustained by Sp1, and TGF-beta and hypoxia signaling pathways are mediated by Smad proteins and hypoxia-inducible factor-1 (HIF-1), respectively, the involvement of these transcription factors was analyzed. Functional and co-immunoprecipitation experiments demonstrated the existence of a multiprotein complex (Sp1.Smad3.HIF-1) on the endoglin promoter, mediating the cooperation between the hypoxia and TGF-beta pathways. Within this multiprotein complex, Smad3 appears to function not only as a coactivator factor, but also as an adaptor between HIF-1 and Sp1. We propose that basal endoglin transcription (highly dependent on Sp1) may switch from a constitutive to an inducible state through Sp1 interaction with HIF-1 and Smad transcription factors, induced by hypoxia and TGF-beta, respectively.