

Endoglin increases eNOS expression by modulating Smad2 protein levels and Smad2-dependent TGF- β signaling

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The endothelial nitric oxide synthase (eNOS) is a critical regulator of cardiovascular homeostasis, whose dysregulation leads to different vascular pathologies. Endoglin is a component of the transforming growth factor beta (TGF- β) receptor complex present in endothelial cells that is involved in angiogenesis, cardiovascular development, and vascular homeostasis. Haploinsufficient expression of endoglin has been shown to downregulate endothelium-derived nitric oxide in endoglin $^{+/-}$ (Eng $^{+/-}$) mice and cultured endothelial cells. Here, we find that TGF- β 1 leads to an increased vasodilatation in Eng $^{+/+}$ mice that is severely impaired in Eng $^{+/-}$ mice, suggesting the involvement of endoglin in the TGF- β regulated vascular homeostasis. The endoglin-dependent induction of eNOS occurs at the transcriptional level and is mediated by the type I TGF- β receptor ALK5 and its downstream substrate Smad2. In addition, Smad2-specific signaling is upregulated in endoglin-induced endothelial cells, whereas i