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sGC activation promotes angiogenesis

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Endogenously produced nitric oxide (NO) has been shown to play a permissive role in angiogenesis. Although soluble guanylyl cyclase (sGC) and cGMP generation regulate many of the vascular actions of NO, the role of cGMP in new blood vessel formation has not been studied in detail. Using pharmacological inhibitors and gene-transfer approaches we have investigated the role of sGC in angiogenesis and angiogenesis-related properties of endothelial cells (EC). Initially, we used the chicken chorioallantoic membrane (CAM) as an *in vivo* model of angiogenesis. We found that sGC is present and enzymatically active in CAM during the days of maximal angiogenesis. Inhibition of endogenous sGC in the CAM by ODQ inhibited neovascularization, whereas exposure to the NO-independent/heme-dependent activator of sGC, BAY 41–2272 promoted neovessel formation. Similarly, PDE-5-mediated inhibition of cGMP breakdown by either sildenafil or zaprinast resulted in increased angiogenesis. Using zebrafish as a model of vascular development, we observed that sGC inhibition led to an abnormal angiogenic response in certain vascular beds. *In vitro*, increased levels of cGMP due to either (a) pharmacological activation of sGC, (b) adenovirus-mediated sGC gene transfer or (c) PDE-5 inhibition, increased EC proliferation, migration and assembly into tube-like structure formations. In addition, inhibition of sGC blocked capillary morphogenesis on matrigel. Moreover, we observed that sGC mediates the migratory action of vascular EC growth factor. In order to study the signaling pathways implicated in cGMP-stimulated angiogenesis, we determined the phosphorylation status of mitogen-activated protein kinase (MAPK) members after sGC activation/overexpression. Adenoviral-mediated over-expression of sGC in EC increased both extracellular signal-regulated kinase 1/2 (ERK1/2) and p38 MAPK in an ODQ-sensitive manner, suggesting that these mitogen-activated protein kinases are downstream effectors of sGC in EC. Moreover, inhibition of p38 attenuated the cGMP-stimulated EC mobilization, while inhibition of MEK1/2 blocked cGMP-induced cell growth. We conclude that increased levels of intracellular cGMP promote neovascularization, and that sGC activators and PDE-5 inhibitors are new classes of agents that could be used to modulate neovessel formation.