A proatherogenic role for cGMP-dependent protein kinase in vascular smooth muscle cells.

Abstract:
Nitric oxide (NO) exerts both antiatherogenic and proatherogenic effects, but the cellular and molecular mechanisms that contribute to modulation of atherosclerosis by NO are not understood completely. The cGMP-dependent protein kinase I (cGKI) is a potential mediator of NO signaling in vascular smooth muscle cells (SMCs). Postnatal ablation of cGKI selectively in the SMCs of mice reduced atherosclerotic lesion area, demonstrating that smooth muscle cGKI promotes atherogenesis. Cell-fate mapping indicated that cGKI is involved in the development of SMC-derived plaque cells. Activation of endogenous cGKI in primary aortic SMCs resulted in cells with increased levels of proliferation; increased levels of vascular cell adhesion molecule-1, peroxisome proliferator-activated receptor gamma, and phosphatidylinositol 3-kinase/Akt signaling; and decreased plasminogen activator inhibitor 1 mRNA, which all are potentially proatherogenic properties. Taken together, these results highlight the pathophysiologic significance of vascular SMCs in atherogenesis and identify a key role for cGKI in the development of atherogenic SMCs in vitro and in vivo. We suggest that activation of smooth muscle cGKI contributes to the proatherogenic effect of NO and that inhibition of cGKI might be a therapeutic option for treating atherosclerosis in humans.

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