Abstract:
Vascular fibrosis is a major complication of hypertension and atherosclerosis, yet it is largely untreatable. Natriuretic peptides (NPs) repress fibrogenic activation of vascular smooth muscle cells (VSMCs), but the intracellular mechanism mediating this effect remains undetermined. Here we show that inhibition of RhoA through phosphorylation at Ser188, the site targeted by the NP effector cyclic GMP (cGMP)-dependent protein kinase I (cGK I), is critical to fully exert antifibrotic potential. cGK I (+/-) mouse blood vessels exhibited an attenuated P-RhoA level and concurrently increased RhoA/ROCK signaling. Importantly, cGK I insufficiency caused dynamic recruitment of ROCK into the fibrogenic programs, thereby eliciting exaggerated vascular hypertrophy and fibrosis. Transgenic expression of cGK I-unphosphorylatable RhoA(A188) in VSMCs augmented ROCK activity, vascular hypertrophy, and fibrosis more prominently than did that of wild-type RhoA, consistent with the notion that RhoA(A188) escapes the intrinsic inhibition by cGK I. Additionally, VSMCs expressing RhoA(A188) became refractory to the antifibrotic effects of NPs. Our results identify cGK I-mediated Ser188 phosphorylation of RhoA as a converging node for pro- and antifibrotic signals and may explain how diminished cGMP signaling, commonly associated with vascular
malfuunction, predisposes individuals to vascular fibrosis.