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Title: A critical role for p130Cas in the progression of pulmonary hypertension in humans and rodents

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Body: Pulmonary arterial hypertension (PAH) is a progressive and fatal disease characterized by pulmonary arterial muscularization due to excessive pulmonary vascular cell proliferation and migration, a phenotype dependent upon growth factors and activation of receptor tyrosine kinases (RTKs). p130Cas is an adaptor protein involved in several cellular signaling pathways that control cell migration, proliferation and survival. We hypothesized that in experimental and idiopathic PAH p130Cas signaling is over-activated, thereby facilitating the intracellular transmission of signal induced by fibroblast growth factor (FGF)2, epidermal growth factor (EGF), and platelet derived growth factor (PDGF). In iPAH patients, levels of p130Cas protein are higher in the serum, in walls of distal pulmonary arteries, in cultured smooth muscle (PA-SMCs) and pulmonary endothelial cells (P-ECs) than controls. These abnormalities in the p130Cas signaling were also found to be in the chronically hypoxic mice and monocrotaline-injected rats. We next obtained evidence for convergence and amplification of the growth-stimulating effect of EGF, FGF2 and PDGF signaling pathways via p130Cas signaling pathway. Finally, we found that daily treatment with each of the EGF-R inhibitor gefitinib, the FGF-R inhibitor dovitinib and the PDGF-R inhibitor imatinib started 2 weeks after a subcutaneous monocrotaline injection substantially attenuate the abnormal increase in p130Cas and ERK1/2 activation and regress established PH. Our findings demonstrate that p130Cas signaling plays a critical role in iPAH by modulating pulmonary vascular cell migration, proliferation and by acting as an amplifier of RTKs downstream signals.