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Title: A critical role for p130^{Cas} 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). p130^{Cas} 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 p130^{Cas} 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 p130^{Cas} 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 p130^{Cas} 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 p130^{Cas} 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 p130^{cas} and ERK1/2 activation and regress established PH. Our findings demonstrate that p130^{Cas} signaling plays a critical role in iPAH by modulating pulmonary vascular cell migration, proliferation and by acting as an amplifier of RTKs downstream signals.