Rasipa Regulates Vascular Tubulogenesis

Ke Xu, Ph.D.
The University of Texas Southwestern Medical Center at Dallas, 2011
Graduate School of Biomedical Sciences
Supervising Professor: Ondine Cleaver, Ph.D.

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Cardiovascular function depends on patent blood vessel formation by endothelial cells (ECs). However very little is known about the mechanisms underlying vascular 'tubulogenesis'. This study identifies Rasip1 as a unique, endothelial-specific regulator of Rho GTPase signaling, which is essential for endothelial lumen morphogenesis. We found that Rasip1 is strongly expressed in vascular endothelial cells throughout development across species. Similar to the well-characterized vascular markers VEGFR2 and PECAM, Rasip1 is specifically expressed in angioblasts prior to vessel formation, in the initial embryonic vascular plexus, in the growing blood vessels during angiogenesis and in the endothelium of mature blood vessels into the postnatal period. Rasip1 expression is undetectable in VEGFR2 null embryos, which lack endothelial cells, suggesting that Rasip1 is endothelial-specific. Ablation of Rasip1 both in vitro and in vivo strongly affects vascular integrity. Specifically, siRNA-mediated reduction of Rasip1 severely impairs angiogenesis in endothelial cell cultures, and morpholino knockdown experiments demonstrate that Rasip1 is required for embryonic vessel formation in frog embryos. Mice lacking Rasip1 fail to form patent lumens in all blood vessels, including the early endocardial tube. Rasipl null angioblasts fail to properly localize the polarity determinant Par3 and display defective cell polarity, resulting in mislocalized junctional complexes and loss of adhesion to extracellular matrix (ECM). Depletion of either Rasip1 or its binding partner RhoGAP Arhgap29 in cultured ECs blocks in vitro lumen formation, fundamentally alters the cytoskeleton and reduces integrin-dependent adhesion to ECM. These defects result from increased RhoA/ROCK/myosin II activity and blockade of Cdc42 and Rac1 signaling. Together, our work identify Rasip1 as a novel endothelial factor that plays an essential role in vascular tubulogenesis.