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Class II PI3K-C2α is essential for vascular barrier integrity

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Abstract

Vascular barrier function, which is structurally supported mainly by the adherens junction (AJ) comprising VE-cadherin and its intracellular associated proteins, maintains low vascular permeability to prevent inflammation in healthy vasculatures. The assembly and disassembly of the AJ is tightly controlled by extracellular mediators through regulating intracellular signaling molecules including Rho GTPases. Phosphatidylinositol (PI) 3-kinase (PI3K) family regulates diverse cellular functions; while class I PI3Ks and class III Vps34 are well-characterized, the physiological roles of PI3K class II, which comprises C2α, C2β and C2γ and exclusively produces PI(3)P, remain largely unknown. We generated C2α knockout (KO) mice and analyzed the phenotypes of the mice. C2α-null mice were embryonic lethal due to severe defects in angiogenesis. C2α+/- mice and inducible endothelial cell (EC)-specific C2α-deleted mice exhibited vascular barrier dysfunction: C2α-KO mice were much more sensitive to challenge with an anaphylaxis mediator platelet-activating factor with increased lethality and chronic infusion of angiotensin II with the formation of dissecting aneurysms. In aorta of C2α-KO mice, matrix metalloproteinases (MMP)-2/9 activities and infiltrating macrophages were increased. In EC, siRNA-mediated PI3K-C2α knockdown induced decreased PI(3)P-enriched endosomes, impaired endosomal trafficking, and defective delivery of VE-cadherin to EC junctions and its assembly. PI3K-C2α knockdown also impeded cell signaling including vascular VEGF receptor-2 internalization and Rho activation on the endosomes. Thus, our data disclose the novel crucial functions of PI3K-C2α in barrier integrity and vascular formation and represents a new therapeutic target for vascular diseases.