SCUBE2 regulates adherens junction dynamics and vascular barrier function during inflammation

Ruey-Bing Yang, PhD

Abstract

SCUBE2 (**S**ignal peptide-**CUB**-**e**pidermal growth factor-like domain-containing protein **2**) is a secreted or membrane-bound protein originally identified from endothelial cells (ECs). Our previous work showed that SCUBE2 forms a complex with E-cadherin and stabilizes epithelial adherens junctions (AJs) to promote epithelial phenotypes. However, it remains unclear whether SCUBE2 also interacts with vascular endothelial (VE)-cadherin and modulates EC barrier function. In this study, we investigated whether and how SCUBE2 in ECs regulates vascular barrier maintenance. We showed that SCUBE2 colocalized and interacted with VE-cadherin and VE-protein tyrosine phosphatase (VE-PTP) within EC AJs. Furthermore, SCUBE2 knockdown disrupted EC AJs and increased EC permeability. Expression of EC SCUBE2 was suppressed at both mRNA and protein levels via the nuclear factor-κB (NF-κB) signaling pathway in response to pro-inflammatory cytokines or permeability-inducing agents. In line with these findings, EC-specific deletion of *Scube2* (EC-KO) in mice impaired baseline barrier function and worsened vascular leakiness of peripheral capillaries after local injection of histamine or vascular endothelial growth factor. EC-KO mice were also sensitive to pulmonary vascular hyperpermeability and leukocyte infiltration in response to acute endotoxin- or influenza virus-induced systemic inflammation. Meanwhile, EC-specific SCUBE2-overexpressing mice were protected from these effects. Molecular studies suggested that SCUBE2 acts as a scaffold molecule enabling VE-PTP to dephosphorylate VE-cadherin, which prevents VE-

cadherin internalization and stabilizes EC AJs. As such, loss of SCUBE2 resulted in hyperphosphorylation of VE-cadherin at tyrosine 685, which led to its endocytosis, thus destabilizing EC AJs and reducing barrier function. All of these effects were exacerbated by inflammatory insults. We found that SCUBE2 contributes to vascular integrity by recruiting VE-PTP to dephosphorylate VE-cadherin and stabilize AJs, thereby promoting EC barrier function. Moreover, our data suggest that genetic overexpression or pharmacological upregulation of SCUBE2 may help to prevent vascular leakage and edema in inflammatory diseases.