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Microtubule-mediated signaling in lung endothelial barrier regulation

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The vascular endothelium (EC) acts as a semi-selective barrier between the interior space of blood vessels and underlying tissues. Disruption of the EC barrier is a prominent feature of acute lung injury (ALI). EC permeability is regulated by a balance between contractile and tethering forces and is dependent on the functional coordination of interrelated elements of the cytoskeleton, namely microfilaments (MF) and microtubules (MT). Edemagenic agents such as the serine protease thrombin induce EC barrier dysfunction primarily via MF-driven contraction. In contrast, information about the role of the MT network in EC barrier regulation is limited. Our data indicate that MT remodeling is directly involved in thrombin-induced EC barrier compromise. MT disruption by microtubule inhibitors or thrombin significantly increases EC permeability. Conversely, stabilization of MTs by taxol attenuates thrombin-induced EC permeability increase indicating the importance of MTs in maintaining the EC barrier. Thrombin-induced EC barrier compromise involves activation of heterotrimeric G-proteins, G12 and G13, followed by activation of Rho and p38 MAPK signaling. Inhibition of this cascade attenuates the effect of thrombin on MT structure suggesting the involvement of these pathways in MT remodeling. Thrombin induces phosphorylation of several MT- and MF-associated regulatory proteins, including caldesmon, HSP-27 and tau, which are potentially responsible for thrombin-induced changes in MF and MF structure. We hypothesize that thrombin-induced activation of G12 and G13 leads to activation of Rho and p38 MAPK signaling, phosphorylation of cytoskeletal regulatory proteins, coordinated MT and MF remodeling and finally to barrier compromise.

Biography

Alexander D Verin has completed his PhD from Moscow State University, Moscow Russia and Postdoctoral studies from University of Indiana, School of Medicine. Currently he is a Professor of Vascular Biology and Medicine at Vascular Biology Center and Pulmonary Division at Georgia Regents University, Augusta, GA. He has published more than 135 papers in reputed journals and serving as an Academic Editor of Cardiology and Angiology and an Editorial Board Member in several other journals in the field of pulmonary and cardiovascular research such as *Cardiovascular Pharmacology*, *Journal of Multidisciplinary Pathology*, *Journal of Vascular Diagnostics*, *The Journal of Biopharmaceutics Sciences*, *Tissue Barriers*, *World Journal of Respiratory*. In addition, he served as Editorial Board Member in *American Journal of Physiology (Lung)* from 2006 to 2011 and was a reviewer for a number of highly reputed journals (ex. *Circulation Research*, *Critical Care Medicine*, *Physiological Reviews*, *PNAS*).

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