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Extracellular purines in lung endothelial barrier regulation

Endothelial cells (EC) form a semi-permeable barrier between the interior space of blood vessels and the underlying tissues. In acute lung injury (ALI) the EC barrier is weakened leading to increased permeability. The mechanisms that govern the highly clinically relevant process of increased EC permeability are under intense investigation. Little is known about the processes that determine barrier enhancement or preservation. Recently, attention has been given to the therapeutic potential of purinergic agonists in the treatment of cardiovascular and pulmonary diseases. Our data indicate that ATP and its degradation product adenosine are able to protect and restore EC barrier *in vitro* and *in vivo*.We and others show that adenosine induces rapid increases in cAMP level and activation of protein kinase A (PKA)/myosin light chain (MLC) phosphatase (MLCP) cascade and this correlates with a significant attenuation of lipopolysaccharide (LPS)-induced EC permeability. In contrast, ATP induced PKA/MLCP activation and EC barrier enhancement without increase in cAMP. We also have shown the involvement of P2Y receptors coupled to Gi2 or Gq (for ATP) and P1 A2A receptors coupled to Gs (for adenosine) in purine-induced EC barrier enhancement. In addition, we have shown that inhibition of MLCP leads to the phosphorylation of several cytoskeletal targets, which correlates with permeability increase suggesting that dephosphorylation of these proteins may be involved in the barrier-enhancing effect. Further, introduction of active MLCP subunits into the lung endothelium reduces LPS-induced lung inflammation strongly supporting the positive role of MLCP activity in EC barrier preservation against ALI in murine model. Collectively, our data strongly suggest that EC barrier preservation induced by extracellular purines is dependent upon activation of specific purinergic receptor/G-protein complexes. Further, purine-induced EC barrier preservation requires the coordinated activation of PKA signaling and MLCP activation leading to EC cytoskeletal changes.

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 Respirology. 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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