



Extracellular Purines in Acute Lung Injury Preservation

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Abstract

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 involved in the preservation of barrier integrity are largely unknown. Recently, attention has been given to the therapeutic potential of purinergic agonists in the treatment of cardiovascular and pulmonary diseases. We have demonstrated that extracellular ATP (stable analog, ATP γ S) and its degradation product, adenosine can strengthen EC barrier via activation of P2Y and P1 type 2A receptors, respectively. We also demonstrated that, ATP γ S and adenosine induce activation of small GTPase, Rac 1 and this correlates with a significant attenuation of lipopolysaccharide (LPS)-induced EC permeability increase. Conversely, introduction of active Rac1 into EC strengthens EC barrier. In parallel, extracellular purines induce activation of Protein Kinase A (PKA)/Myosin Light Chain (MLC) Phosphatase (MLCP) cascade and this also correlates with attenuation of LPS-induced EC permeability. Therefore, the ability of ATP and adenosine to strengthen EC barrier appears to be dependent on Rac1 and MLCP activation. 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 Rac1 and PKA/MLCP cascade leading to EC cytoskeletal changes.

Biography

Alexander D Verin has completed his PhD from Moscow State University, Moscow, Russia and Post-doctoral studies from University of Indiana, USA. Currently, he is a Professor in Vascular Biology Center and Pulmonary Division at Augusta University, Augusta, GA. He has published more than 150 papers in reputed journals and serving as an Editor-in Chief of Vessels Plus, and as Editorial Board Member in several other journals in the field of cardiovascular research. In addition, he was a Reviewer for a number of highly regarded journals (ex. Circulation Research, Critical Care Medicine, Physiological Reviews, PNAS).