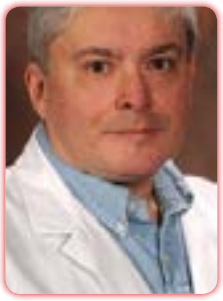
Alexander D Verin, J Pulm Respir Med 2016, 6:4(Suppl)
http://dx.doi.org/10.4172/2161-105X.C1.012

4th International Conference and Exhibition on

Lung & Respiratory Care

August 01-02, 2016 Manchester, UK



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MAP kinases in endothelial permeability

It is established that edemagenic agonists (thrombin, LPS)-induced endothelial cell (EC) barrier dysfunction is tightly linked to myosin light chain (MLC)-dependent EC contraction and cytoskeletal reorganization. In this study, we examined the role of MAP kinases (p38 and p42/44) as potentially important enzymes in MLC-independent, agonist-mediated EC contractile responses and permeability. We demonstrated that thrombin significantly increased MAPK activities. Specific inhibition of p38 and p42/44 MAPK significantly attenuated thrombin-induced increases in F-actin stress fibers and permeability reflecting the involvement of MAPK in thrombin-mediated EC barrier compromise. Next, we examined potential cytoskeletal targets of thrombin-induced MAPK activation. MAPK inhibition did not alter basal and thrombin-induced EC MLC phosphorylation but significantly increased phosphorylation of caldesmon (Cad), an action- and myosin-binding regulatory protein. Similar to smooth muscle, phosphorylation of Cad can potentially facilitate agonist-induced contraction and lead to EC barrier dysfunction. Under basal conditions Cad co-immunoprecipitated with actin and myosin suggesting a functional complex. Thrombin decreased the amount of myosin, but not actin in non-denaturing Cad immunoprecipitates suggesting decreased Cad/myosin interaction. Immunoblotting with anti-phospho Cad antibody to MAPK phosphorylation sites on Cad demonstrated that thrombin-mediated EC activation leads to direct phosphorylation of Cad by MAPK. Inhibition of MAPK significantly attenuated thrombin-induced Cad phosphorylation. These data strongly suggest the direct link between edemagenic agonists-mediated EC contractile response and permeability, activation of MAPK cascades and Cad phosphorylation.

Biography

Alexander D Verin has completed his PhD from Moscow State University, Moscow Russia and Post-doctoral studies from University of Indiana. Currently he is a Professor at Vascular Biology Center and Pulmonary Division at Augusta University, Augusta, GA. He has published more than 135 papers in reputed journals and serving as an Academic Editor of *British Journal of Medicine and Medical Research* and *Cardiology and Angiology*, and an Editorial Board Member in several other journals in the field of pulmonary/cardiovascular research such as *Cardiovascular Pharmacology, Journal of Multidisciplinary Pathology, Tissue Barriers* and *World Journal of Respirology*.

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