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 Respiratory.

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