Role of protease-activated receptors (PARs) and G-proteins in thrombin induced monocyte/macrophage migration

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The recruitment of monocytes/macrophages to the sites of dysfunctional endothelium and transformation of these cells into foam cells by the uptake of oxidized lipoproteins in the sub endothelium are the major pathophysiological features of atherosclerosis. Since thrombin is produced at the sites of vascular injury and in order to understand its involvement in atherosclerosis, we tested its role in the modulation of THP-1 cell migration. Thrombin induced THP-1 cell migration in a dose dependent manner. Thrombin induced sequentially the tyrosine phosphorylation of Pyk2, Gab1 and p115 RhoGEF leading to Rac1 and RhoA-dependent Pak2 activation. Downstream to Pyk2, Gab1 formed a complex with p115 RhoGEF involving their PH domains. Furthermore, depletion of Pyk2, Gab1, p115 RhoGEF, Rac1, RhoA or Pak2 levels using their respective antisense oligos substantially attenuated thrombin-induced THP-1 cell cytoskeleton formation and migration. In addition, SCH79797, a selective PAR1 antagonist, inhibited thrombin-induced Pyk2, Gab1 and p115 RhoGEF tyrosine phosphorylation and Rac1-RhoA-dependent Pak2 activation resulting in diminished THP-1 cell cytoskeleton formation and migration. Together, these observations reveal that thrombin induces THP-1 cell migration via PAR1-dependent Pyk2-mediated Gab1 and p115 RhoGEF interactions leading to Rac1-RhoA-Pak2 activation. Based on these findings, we envision a role for thrombin and its receptor PAR1 in atherosclerosis.

Biography
Ravisekhar Gadepalli after completing his Postdoctoral studies (2009-2013) from St. Jude Children Research Hospital, Memphis, USA, has joined as a Faculty at AIIMS Jodhpur in 2013. He is an active Member of American Society for Microbiology and American Heart Association. He has several notable achievements and awards to his credit. His work in the field of Clinical Microbiology, Immunology and Vascular Biology has culminated in the publication of 18 research papers in peer reviewed journals (Proceedings of National Academy of Sciences USA, Journal of Biological Chemistry, Arteriosclerosis, Thrombosis and Vascular Biology, etc) of national and international repute with cumulative impact factor: 78.046 (Citation Index: 410). gade palli r@ aiims jodhpur. edu. in

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