Rac regulates thrombin-induced tissue factor expression in pulmonary artery smooth muscle cells involving the nuclear factor-kappaB pathway.

Abstract:
Pulmonary hypertension is associated with enhanced thrombogenicity of the vessel wall contributing to vascular remodeling. However, the signaling mechanisms promoting this prothrombotic state are not resolved. Here we investigated the role of the GTPase Rac in the regulation of tissue factor (TF) expression and activity in response to thrombin in pulmonary artery smooth muscle cells (PASMC). TF mRNA and protein expression and surface procoagulant activity were increased by thrombin in PASMC. These responses were enhanced in the presence of the constitutively active Rac mutant RacG12V, but were abrogated in cells expressing dominant-negative RacT17N. Thrombin and RacG12V also increased human TF promoter activity primarily involving a sequence between -636 and -111 bp containing a distal, nuclear factor-kappaB (NFkappaB)-dependent enhancer element. Indeed, thrombin and RacG12V stimulated NFkappaB-dependent transcriptional activity, and overexpression of p50/p65 significantly increased human TF promoter activity. Moreover, in RacG12V-overexpressing cells, TF promoter activity was significantly decreased by coexpression of dominant-negative mutants of IkappaBalpha and IkappaBKalpha, which prevent NFkappaB activation. As enhanced NFkappaB activity has been observed in patients with pulmonary hypertension,
Rac-dependent activation of the NFκB pathway may be a critical element promoting thrombin-induced TF expression and activity, and thus a prothrombotic state in pulmonary hypertension.