Thrombin Induces VEGF Production in Airway Smooth Muscle Via Prostanoid and PAR-1/4 Independent Mechanisms

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Thrombin plays an important role in inflammatory and proliferative processes, inducing cellular and molecular events relevant to tissue remodelling. In asthmatic patients' airways increased thrombin generation occurs. The proliferation of cultured human airway smooth muscle (HAS cells is promoted by thrombin and it may play a role in airway remodelling. Many actions of thrombin have been attributed to activation of protease-activated receptors (PARs). Thrombin is known to elicit cytokine production in other cell types, but these effects have not been well characterized in HASM. Thrombin is considered to be a potent stimulator of angiogenesis. Vascular endothelial growth factor's (VEGF) interaction with and regulation by thrombin has also been reported in other cell systems. Evidence suggests VEGF may be a major contributor to vascular remodelling and we have shown that HASM are a rich source of VEGF. Here we report that VEGF secretion by HASM cells was increased by thrombin. Experiments were performed in confluent primary cultures of HASM cells, growth arrested for 24 hours prior to experiments. VEGF protein was measured by ELISA, PGE_2 production by RIA, COX-2 production by western blotting and luciferase reporter gene assays performed using a 2.6kb fragment of the VEGF promoter. Thrombin increased VEGF production in a time and concentration dependent manner. Thrombin up-regulated VEGF promoter activity suggesting thrombin regulates VEGF expression transcriptionally in HASM cells. The COX inhibitors indomethacin and NS398 did not inhibit VEGF production by thrombin nor the thrombin induced luciferase activity suggesting that thrombin induced VEGF secretion was not prostanoid mediated. Experiments with PAR 1 and PAR 4-specific receptor activating peptides (SFLLRN and GYPGQV) suggest that VEGF levels were independent of PAR 1 and 4. In conclusion thrombin activates VEGF production transcriptionally via a non-COX, non-PAR 1, PAR 4 mechanism.

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