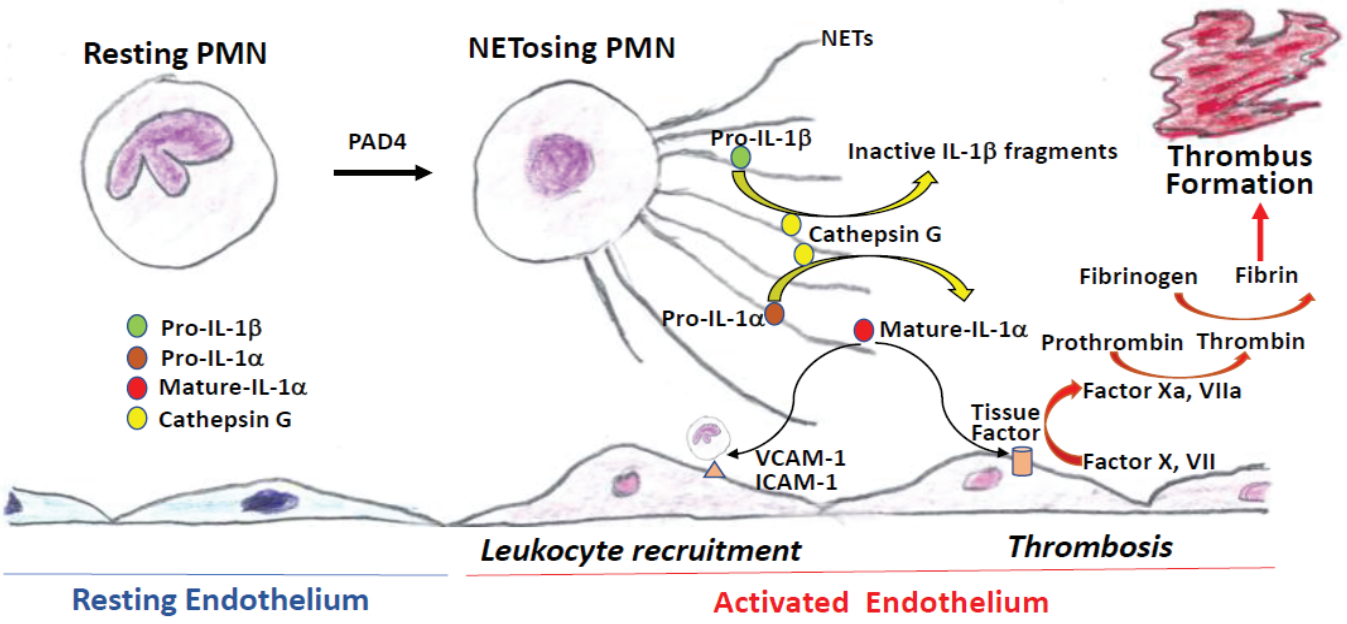

VCAM-1: Vascular cell adhesion molecule-1; ICAM-1: Intracellular adhesion molecule-1
IL-1: Interleukin-1; PMN: Polymorphonuclear leukocyte; NET: Neutrophil extracellular trap; PAD4: peptidylargininedeiminase 4

Interleukin-1α mediates endothelial cell activation by neutrophil extracellular traps. When neutrophils undergo NETosis, the extruded DNA strands associate with numerous proteins including the precursor forms of IL-1α and β and serine proteinases produced by the granulocytes. The results presented here show that the neutrophil – derived proteinase cathepsin G processes pro-IL-1α to the more active mature form by limited proteolysis, but degrades pro-IL-1β to inactive fragments. This pathway likely operates in vivo, as cathepsin G retains activity even in the presence of plasma proteinase inhibitors. NETs bearing mature IL-1α can activate endothelial cells to express adhesion molecules that can recruit further leukocytes, and elicit the local production of the potent procoagulant tissue factor. Thus, activation of endothelial cells by this NET-associated cytokine can amplify, sustain, and propagate local vascular inflammation and also promote thrombosis. These results have particular importance for postulated mechanisms of thrombosis due to superficial erosion. We have proposed a "multi-hit" pathway for the pathogenesis of this mode of arterial thrombosis: an initial endothelial desquamation with inadequate local repair, followed by an amplification phase. NET-associated IL-1α could participate in the amplification phase by aggravating the consequences of local endothelial erosion and promotion of the formation and persistence of arterial thrombi that lead to clinical events.