

Wednesday, November 6, 2019

LSC 3 | 1:00 - 2:00PM



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## “Defensins: Link between innate immunity, atherosclerosis and thrombosis”

Neutrophil defensins (human neutrophil peptides, HNPs) are cationic and hydrophobic anti-microbial peptides that insert into the membranes of enveloped microbes leading to lysis and death. HNPs are the predominant protein by mass secreted by activated human neutrophils. We have been studying the potential adverse effects of released HNPs into host tissue. We found an abundance of HNPs in lung tissue after acute injury and in human atherosclerotic vessels, even in the absence of intact neutrophils. In vitro studies revealed prothrombotic (inhibition of fibrinolysis and ADAMTS13) and proatherogenic (inhibition of Lp(a) and LDL metabolism) effects of HNPs on cultured human vascular cells and inhibition of vascular contractility and angiogenesis in ex vivo models. To investigate whether similar effects were seen in vivo, we studied a transgenic mouse expressing HNP-1, the predominant species, because mouse neutrophils do not express this family of antimicrobial peptides. We observed that release of HNP1 into the lung augments lung injury and hemorrhage by disrupting endothelial-epithelial cell barrier function. Expression of HNP1 also enhances deposition of lipids and ingress of macrophages in the aorta due to formation and retention of LDL-HNP-1 complexes. HNP1 expressing mice also develop markedly larger thrombi than wild type mice and they develop resistance to heparin. Ingestion of colchicine to prevent release of HNP1 from neutrophils reverses formation of LDL/HNP-1 complexes and attenuates formation of atherogenic lesions and prevents and reverses the prothrombotic/heparin resistant phenotype. These results suggest that HNPs may provide an enduring footprint of neutrophil activation and that exuberant and persistent release and retention of these peptides may contribute to the development of diverse acute and chronic vascular disorders.

Please note that due to some technical difficulties we  
are unable to webcast this seminar.