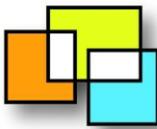


Donnelly Center

PDF and RA Seminar Series



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Role of MicroRNA-146a in Vascular Inflammation and Atherosclerosis

Inflammation plays a vital role in acute and chronic diseases of the vasculature, including sepsis and atherosclerosis, respectively. Molecular mechanisms such as microRNAs are key regulators of signaling pathways and are important in governing the balance between physiological and pathological inflammatory responses. While numerous studies have placed miR-146a amongst the echelon of anti-inflammatory microRNAs, the role of endogenous *miR-146a* in vascular inflammatory diseases, including atherosclerosis, remains unknown. Therapies that directly repress vascular inflammation are expected to impede the development of sepsis and atherosclerosis. Furthermore, elevation of miR-146a expression in atherosclerotic plaques in humans and polymorphisms in the miR-146a precursor that are associated with coronary artery disease, are suggestive of a role for this microRNA in atherogenesis. Therefore, this study aims to elucidate the regulation of endothelial activation by miR-146a and to determine the role of endogenous miR-146a in a mouse model of atherosclerosis. Surprisingly, despite the ability of this microRNA to restrain cytokine production in bone marrow-derived cells, loss of this microRNA resulted in reduced atherosclerosis. This was accompanied by hematopoietic stem cell exhaustion and a corresponding reduction in levels of circulating pro-atherogenic cells. Enhanced inflammatory signaling occurred even though circulating levels of VLDL cholesterol were diminished in these mice. Within the vasculature, miR-146a restrained endothelial activation through the regulation of transcriptional and post-transcriptional inflammatory pathways, and loss of *miR-146a* in the vasculature enhanced atherosclerosis. This study reveals a critical function for a single microRNA in the control of the intensity of inflammatory responses to inflammatory stimuli such as hypercholesterolemia, and highlights the detrimental effects of unrestrained inflammatory signaling in multiple organs: bone marrow (hematopoietic stem cell exhaustion), spleen (extramedullary hematopoiesis and splenomegaly), liver (cholesterol homeostasis defects) and the vasculature (enhanced endothelial cell activation and monocyte recruitment). Importantly, these findings provide a further impetus to therapeutically augment miR-146a expression/function in atherosclerosis.

DATE: Monday January 22nd, 2018

TIME: 12:00 – 1:00 pm

LOCATION: Red Room



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