RMB CVRC Seminar

The Robert M. Berne Cardiovascular Research Center Presents

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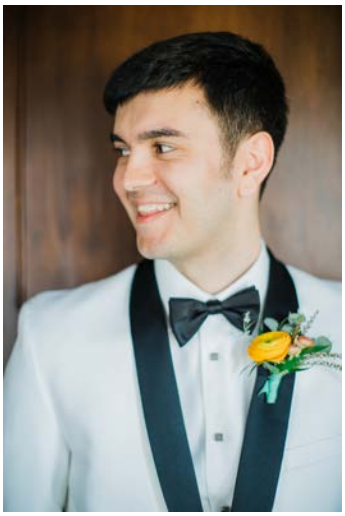

Rerouting Smooth Muscle Glycolysis Rescues Atherosclerosis-associated Mortality in Mice

Heart attacks or strokes stemming from rupture or erosion of unstable atherosclerotic plaques lead to over half a million deaths annually. Postmortem studies of human coronary arteries correlated stable atherosclerotic lesions with extracellular matrix (ECM)-rich regions known as fibrous caps. We have recently shown in murine and human lesions that fibrous caps are populated with ACTA2^{+} cells originating predominantly from smooth muscle cells (SMC), but also endothelial and myeloid cells. We believe these cells to be myofibroblast-like in nature, whose primary purpose is to produce and maintain the fibrous cap through ECM production. Using murine models of atherosclerosis, we and others have identified PDGF and TGFB as essential signaling factors for maintenance of fibrous cap stability. Based on these *in vivo* findings, we used recombinant PDGF and TGFB to phenotypically modulate SMC to an ECM-producing myofibroblast-like state. With this model system, we identified lactate-producing aerobic glycolysis as a critical requirement for SMC to phenotypically modulate to a myofibroblast-like state. Surprisingly, we found that pharmaceutical inhibition of pyruvate dehydrogenase augmented lactate production and expression of key ECM-associated genes *in vitro*. Taken together, we hypothesized that augmentation of SMC aerobic glycolysis would lead to enhanced plaque stability. To test this hypothesis *in vivo*, we generated a transgenic murine model of atherosclerosis (*Apoe*$^{-/-}$) with tamoxifen-inducible SMC lineage tracing (*Myh11*-Cre^{ERT2} <STOP>$^{FL/FL}$-eYFP) and an inducible SMC-specific deletion of pyruvate dehydrogenase (*Pdha1*^{FL}). We fed a tamoxifen-containing diet to *Pdha1*^{WT} and *Pdha1*^{FL} mice to generate *Pdha1*^{KO} mice and followed this with up to 18 weeks of Western diet (WD) feeding to induce formation of advanced atherosclerotic lesions. Surprisingly, *Pdha1*^{KO} mice showed significantly enhanced survival (95%) compared to the littermate control *Pdha1*^{WT} mice (74%) after 18 weeks of WD, revealing a possible therapeutic target to augment SMC-specific ECM production *in vivo*

Thursday January 25th, 2024
11:00 AM-12:00 PM
MR5 Room 3005

Refreshments served

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