Robert M. Berne CVRC Seminar

The Robert M. Berne Cardiovascular Research Center Presents

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Epigenetic Control of Smooth Muscle Differentiation: Insights from Smooth Muscle Dysfunction Syndrome

Heterozygous *ACTA2* p.R179 pathogenic variants cause Smooth Muscle Dysfunction Syndrome. *ACTA2* encodes smooth muscle α-actin (SMA), and the p.R179 variant disrupts nuclear localization of SMA, leading to incomplete differentiation of smooth muscle cells (SMCs). SMCs from a conditional knock-in mouse model (*Acta2*R179C/+) are incompletely differentiated, leading to enhanced SMC migration and proliferation that may drive the occlusive lesions. Furthermore, *Acta2*R179C/+ SMCs have increased glycolysis and reduced oxidative respiration on Seahorse analyses. Nicotinamide riboside (NR) treatment restores oxidative respiration through increased complex I activity in *Acta2*R179C/+ SMCs, and surprisingly also increases SMC differentiation and decreases migration. *Acta2*R179C/+ mice and littermate controls were subjected to carotid artery ligation (CAL), and 25% of *Acta2*R179C/+ mice died due to strokes while all control mice survived ($p<0.01$). Surviving *Acta2*R179C/+ mice have signs of hypoxic brain injury and neuron death at three days post-CAL and persistent occlusive carotid artery lesions at 21 days post-CAL. Treatment of female *Acta2*R179C/+ mice with NR reduces death (Kaplan-Meier $p=0.02$) and resolves persistent lesions ($p=0.05$) in *Acta2*R179C/+ mice after CAL. The mechanism by which NR treatment increases SMC differentiation is not intuitive. Our data suggests that high glycolytic flux in *Acta2*R179C/+SMCs leads to increased accumulation of 2-hydroxygluterate (2-HG), which has been previously shown to inhibit TET2, a master regulator of SMC differentiation. NR reduces glycolysis and 2-HG, increasing TET2 activity and driving increased SMC identity.

Thursday September 18, 2025
11:00 AM-12:00 PM
MR5 Room 3005

Refreshments served
Hosted by: Laura Shankman, PhD

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