22-VIRC-455-AHA-VD

The Histone Methyl Transferase (SUV39H1) Promotes Smooth Muscle Cell Dedifferentiation

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Objectives: The phenotypic plasticity of vascular smooth muscle cells (VSMCs) is central to growth and remodeling processes, but also contributes to the pathology of atherosclerosis, restenosis, and other cardiovascular diseases. This ability of VSMCs to reversibly differentiate and dedifferentiate is incompletely understood. SUV39H1, a histone methyltransferase, specifically trimethylates Lys-9 of histone H3 (H3K9me3), resulting in epigenetic transcriptional repression. We hypothesized that SUV39H1 plays a role in VSMC phenotypic switching.

Methods: Using knockdown, quantitative polymerase chain reaction, Western blot, chromatin immunoprecipitation, RNA sequencing, and murine vascular injury to determine the role of SUV39H1 in VSMC plasticity.

Results: A quantitative polymerase chain reaction array screen of epigenetic regulators revealed that SUV39H1 is upregulated with platelet-derived growth factor -induced dedifferentiation, but downregulated with rapamycin-induced differentiation in human coronary artery smooth muscle cells. SUV39H1 knockdown promoted differentiation measured by increased contractile gene, protein expression, enhanced contractility, decreased migration, proliferation, and dedifferentiation-associated gene expression. RNA sequencing transcriptomics confirmed changes in multiple pathways consistent with a role for SUV39H1 in promoting human coronary artery smooth muscle cell dedifferentiation. Mechanistically, SUV39H1 knockdown suppressed expression of KLF4, the master transcriptional regulator of VSMC dedifferentiation, decreasing KLF4 messenger RNA stability and upregulating miRNA143, a known repressor of KLF4. siSUV39H1 also increased expression of KDM4a, a JMJD family lysine demethylase that targets H3K9me3. Chromatin immunoprecipitation assays at contractile gene promoters showed significant decrease in the H3K9me3 mark and increase in H3K27Ac after SUV39H1 knockdown. In vivo, we noted a significant increase in SUV39H1 and H3K9me3 expression in murine carotid artery ligation induced intimal hyperplasia.

Conclusions: We identify SUV39H1 as an epigenetic regulator of VSMC phenotype whose expression and activity increase with dedifferentiation in vitro and in vivo. Platelet-derived growth factor promotes H3K9me3 repressive marks at contractile genes by promoting expression of SUV39H1, which also inhibits the KDM4a. Understanding the role of SUV39H1 in VSMC plasticity may reveal new therapeutic strategies for treating vascular diseases.

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Single Cell Gene Expression Of Brachial Artery In Response To Increased Shear Stress

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Objective: Blood flow dynamics modulate vascular development, homeostasis, and contribute to vascular pathobiology. However, it is unknown how shear stress influences cellular transcriptomics of the arterial wall. Two-stage hemodialysis access surgeries provide an opportunity to compare native vessels with vessels after exposure to significantly altered hemodynamics.

Methods: Single-cell sequencing was performed on brachial artery samples obtained from three patients at the time of first and second stage surgeries. Arterial cellular composition and temporal changes in gene expression were quantified after sequencing and functional analyses were performed on differentially expressed genes.

Results: Compositional changes and gene expression dynamics were highest in the smooth muscle cell (SMC) populations followed by fibroblasts. SMCs were clustered into contractile (classical) and modified populations, with the latter having lower expression of contractile markers. Downregulation of the transcription factor ARNTL was the most significant controller in contractile SMCs and fibroblasts, and second behind heat-inducible factor 1α in modified SMCs. Macrophages had a significant increase in composition, but few dynamic genes suggest a return to quiescence. Endothelial cells showed minimal changes with dynamic genes responding to mechanical stimulus. An ingenuity pathway analysis revealed activation of EIF2 signaling in both SMC and fibroblast clusters, promoting translation. The top divergent pathway among SMC clusters is PI3/AKT signaling, with increased vascular remodeling, proliferation, and cell death in the contractile group.

Conclusions: Cellular processes are overall downregulated in modified SMCs, which represent the majority of SMCs after vascular adaption. This study is the first single-cell characterization of normal human artery and its cellular response to increased hemodynamic forces, specifically detailing cellular compositional changes and their associated dynamic genes.

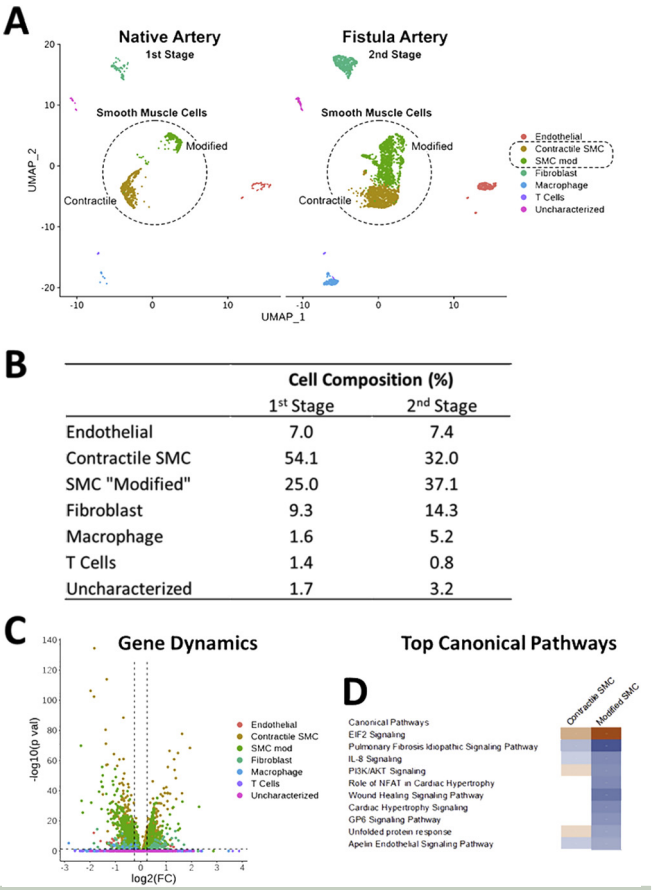

Fig.

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The Epigenetic Enzyme KMT2A/MLL1 Is a Driver of Coronavirus-associated Coagulopathy

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