Epigenetic control of pathological vascular remodeling: Role of smooth muscle-derived AdvSca1-SM progenitor cell induction of HDAC9-Brg1

Austin Jolly, Allison Dubiner, Marie Mutryn, Rebecca Tucker, Keith Strand, Karen Moulton, Raphael Nemenoff, Sizhao Lu, Mary Weiser-Evans

Division of Renal Diseases and Hypertension, Department of Medicine
Consortium for Fibrosis Research and Translation

Background
- Atherosclerosis and restenosis induce neointima formation and pathological vascular remodeling marker by inflammation and fibrosis. Classically overlooked, the adventitial layer of the blood vessel is the site of dynamic processes that influence vascular physiology.
- Using a vascular smooth muscle cell (SMC)-specific fate-mapping approach, the Weiser-Evans lab discovered a unique subpopulation of adventitial Sca1+ multipotential progenitor cells that originate from reprogrammed SMCs and are major contributors to vascular adventitia remodeling (termed AdvSca1-SM cells)1.
- Recently, the epigenetic regulators Brg1 and HDAC9 were shown to form a complex to repress SMC gene expression and the mature SMC phenotype2,3.
- Using RNA-Seq approaches, we found that AdvSca1-SM cells downregulate stemness-related genes (Figure 1A) and upregulate Brg1 and HDAC9 in response to vascular injury (Figure 1B).

HYPOTHESIS ONE: Based on these findings, we hypothesize that disease-induced upregulation of Brg1 and HDAC9 drives AdvSca1-SM cells toward an inflammatory, fibrotic phenotype and inhibition of Brg1 and HDAC9 would facilitate AdvSca1-SM cells toward a reparative mature SMC phenotype.

Results
- Using RNA-Seq approaches, compared to mature SMCs and other adventitial progenitor cell populations, genes associated with hedgehog/Wnt signaling were found overrepresented in AdvSca1-SM cells. As the hedgehog-induced transcriptional regulator, Gli1, was among those uniquely expressed by AdvSca1-SM cells, we took advantage of this to generate Gli1-promoter-YFP reporter mice to construct a novel AdvSca1-SM cell fate-mapping system to selectively track these cells in the context of vascular disease (Figure 2).

HYPOTHESIS TWO: As AdvSca1-SM cells are activated early in response to vascular injury1, we hypothesize that AdvSca1-SM cells adopt a myofibroblast and/or macrophage phenotype in response to injury to promote the pro-inflammatory, pro-fibrotic environment contributing to vascular remodeling. Gli1-YFP AdvSca1-SM reporter mice will be used to test this.

References
3. Majesky MW, et al. Injured adventitial and intramural arteries demonstrate a significant expression of Gli1 (YFP) in AdvSca1-SM cells that predominantly contribute to advential remodeling as well as mural remodeling. These data suggest the use of this reliable fate-mapping system for tracking AdvSca1-SM cells and illustrate the cell populations properly to respond to the setting of vascular disease. Cell Stem Cell, 407 (2013).

Acknowledgements: MSTP Program (Cara Wilson, Joseph Hruby, Patricia Ernst, Liz Bowen); the Weiser-Evans lab (Marie Mutryn, Sizhao Lu, Keith Strand, Allison Dubiner)

Funding: R01 HL3011834 (Weiser-Evans), R01 HL3009129 (Weiser-Evans), R01 HL3012525 (Majesky; Weiser-Evans subcontract), AHA Pre-doc 20PRE3200015 (Jolly)

References
3. Majesky MW, et al. Injured adventitial and intramural arteries demonstrate a significant expression of Gli1 (YFP) in AdvSca1-SM cells that predominantly contribute to advential remodeling as well as mural remodeling. These data suggest the use of this reliable fate-mapping system for tracking AdvSca1-SM cells and illustrate the cell populations properly to respond to the setting of vascular disease. Cell Stem Cell, 407 (2013).