

HDAC9 and Brg1 are Implicated in Pathological Vascular Remodeling. AJ Jolly (MD/PhD, MSTP Program), A. Dubner, M. Mutryn, KA. Strand, K. Moulton, R. Nemenoff, S. Lu, and M. Weiser-Evans, Department of Medicine, University of Colorado Anschutz Medical Campus.

Vascular fibrosis is an irreversible consequence of pathological vascular remodeling that develops in response to many forms of cardiovascular disease including chronic hypertension and atherosclerosis. Given cardiovascular disease remains the #1 killer of Americans and people worldwide, pathological vascular remodeling emerges as an important topic of study as patients currently do not have reliable treatment options to improve quality of life. Our lab identified a unique population of multipotent smooth muscle-derived Sca1+ progenitor cells that reside in the adventitia of blood vessels (AdvSca1-SM cells). In setting of vascular disease, AdvSca1-SM cells greatly expand in the adventitial region and differentiate into myofibroblasts and contribute to the development of vascular remodeling and fibrosis. The epigenetic remodeling proteins HDAC9 and Brg1 are upregulated uniquely in the AdvSca1-SM population in the setting of vascular injury, but how HDAC9 and Brg1 affect AdvSca1-SM differentiation remains unknown. Using a combination of in vitro and in vivo approaches, we aim to define the role of HDAC9 and Brg1 in progenitor cell-induced vascular remodeling. We hypothesize that HDAC9 and Brg1 remodel chromatin and preferentially drive AdvSca1-SM cell differentiation towards pathologic myofibroblasts and inhibition of HDAC9 and Brg1 will disrupt AdvSca1-SM differentiation into myofibroblasts and attenuate pathological vascular remodeling. AdvSca1-SM cells are isolated and differentiated into myofibroblasts with TGF- $\beta$  and also treated with the Brg1 bromodomain inhibitor PFI-3 to study the function of Brg1 in TGF- $\beta$  stimulated AdvSca1-SM cells. Using a highly reliable cell fate-mapping Cre-lox system, AdvSca1-SM cells are tracked with high fidelity after acute vascular injury induced by carotid ligation. The small molecule TMP195 is administered to mice with vascular injury to define the role of HDAC9 in pathological vascular remodeling. Recent results suggest Brg1 is required for TGF- $\beta$  induced myofibroblast differentiation of AdvSca1-SM cells in vitro. Further, animal studies convey that pharmacological inhibition of HDAC9 attenuates pathological vascular remodeling as compared to control animals. Ultimately, these results support the conclusion that Brg1 and HDAC9 play an essential role in facilitating the differentiation of AdvSca1-SM cells into myofibroblasts and are heavily implicated in pathological vascular remodeling.