RUTGERS
School of Graduate Studies

Office of Student Affairs and Admissions
SGS at New Jersey Medical School
Rutgers, The State University of New Jersey
185 South Orange Avenue, MSB C-696
Newark, NJ 07103

http://njms.rutgers.edu/gsbs/
p. 973-972-4511
f. 973-972-7148

YOU ARE INVITED TO ATTEND THE DEFENSE OF THE DOCTORAL DISSERTATION

"SMAD4: A Critical Regulator of Cardiac Neural Crest Cell Fate and Vascular Smooth Muscle Differentiation"

By

Brianna Alexander

Cell Biology, Neuroscience, and Physiology PhD Program

B.Sc. 2016, The Pennsylvania State University, Pennsylvania

Thesis Advisor:
Sophie Astrof, Ph.D.
Department of Cell Biology and Molecular Medicine, Rutgers NJMS

Tuesday, March 28th, 2023
2:30 P.M.
G-Level Conference room, G609B (Medical Science Building)

ABSTRACT

Congenital heart disease (CHD) is one of the most frequent human birth defects, occurring when there are defects in the formation or function of the heart/associated vasculature in newborn babies. Defects in the aortic arch arteries, the vessels connected to the heart which send oxygenated blood throughout the body, comprise some of the most severe CHD phenotypes.

The pharyngeal arch arteries are the precursor vessels which remodel into the aortic arch arteries during embryonic cardiovascular development. For proper arch artery remodeling, cardiac neural crest cells (NCs) must populate the pharyngeal arches and differentiate into vascular smooth muscle cells (vSMCs). vSMCs are critical to regulating vessel dynamics under blood flow, with defective smooth muscle coverage resulting in arch artery regression and potentially lethal CHD phenotypes. Given the critical role of vSMC differentiation in arch artery development, we sought to further elucidate mechanisms governing this process. SMAD4, the central mediator of canonical TGFβ signaling pathway, has been implicated in NC-to-vSMC differentiation; however, its distinct roles in vSMC differentiation and NC survival are unclear. Moreover, previous studies investigating SMAD4 in the NC relied on the Wnt1-Cre1 transgenic mouse model, which may have confounded the role of SMAD4 due to the problematic features of the transgene.

Here, we investigated the role of SMAD4 in cardiac NC differentiation to vSMCs using lineage-specific inducible mouse strains in an attempt to avoid early embryonic lethality and NC cell death. We found that with global loss of SMAD4, its role in vSMC differentiation could be uncoupled from its role in survival of the cardiac the NC in vivo. Moreover, we found that SMAD4 may have a role in the induction of fibronectin, a known mediator of NC-to-VSMC differentiation. When examining the cell type in which SMAD4 functions to mediate cardiac NC differentiation, we found that while SMAD4 expression in the endothelium was not required for NC differentiation, that NC cells have a cell-autonomous requirement for SMAD4 to ensure their proper vSMC differentiation as well as their contribution to and persistence in the pharyngeal arch mesenchyme, a requirement not observed in NCs contributing to other NC-derived structures, including the dorsal root ganglia. Overall, this study highlights the critical role of SMAD4 in the survival of the cardiac NC, their differentiation to vSMCs and their proper contribution to the developing pharyngeal arches. Importantly, it underscores the functional role of SMAD4 in the etiology of CHD phenotypes.