Sara Nichole Koenig
PhD Candidate

“Investigation of Notch1 Functions in Aortic Valve Disease and Ascending Aortic Aneurysms”

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Biomedical Research Tower 105
1pm
VITA

May 13th, 1987 . . . . . . . . . . . . . . . . . . . . . . . . Born – Mayfield, OH

2009 . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . B.A. Botany-
Microbiology, Ohio Wesleyan University,
Delaware, OH

2009-2012 . . . . . . . . . . . . . . . . . . . . . . . . . . . Research Associate,
Garg Laboratory,
Nationwide Children’s Hospital,
Columbus, OH

2012-present . . . . . . . . . . . . . . . . . . . . . . . . . Graduate Research
Associate, Biomedical
Sciences, The Ohio State University,
Columbus, OH

COMMITTEE MEMBERS

Vidu Garg, MD, Advisor

Brenda Lilly, PhD

Joy Lincoln, PhD

Ray Hershberger, MD
ABSTRACT

Congenital heart disease is the most common type of birth defect, affecting ~2% of the population. Malformations involving the cardiac outflow tract and semilunar valves account for >50% of these cases predominantly because of bicuspid aortic valve (BAV), which has an estimated prevalence of 1% in the population. Mutations in NOTCH1 have been previously reported to be a cause of BAV and BAV-associated aortopathy in non-syndromic autosomal-dominant human pedigrees. Ascending aortic aneurysms (AscAA) are associated with BAV and are a significant cause of morbidity and mortality in humans. While the exact etiology is unknown, hemodynamic and genetic factors play important roles. Here, we have sought to determine the roles for Notch1 in aortic valve disease and AscAA, and we have identified distinct cell lineages in which loss of Notch1 contributes to BAV and AscAA.

We previously described a highly penetrant mouse model of aortic valve disease in Notch1-haploinsufficient adult mice backcrossed into a Nos3-null background (Notch1+/−; Nos3−/− mice). Notch1+/−;Nos3−/− mice have BAV with thickened valve cusps and associated stenosis and regurgitation. In chapter 2, we describe the congenital cardiac abnormalities in Notch1+/−; Nos3−/− embryos that lead to ~65% lethality by postnatal day 10. Although expected Mendelian ratios of Notch1+/−;Nos3−/− embryos were found at embryonic day 18.5, histological examination revealed thickened, malformed semilunar valve leaflets accompanied by additional anomalies of the cardiac outflow tract. In addition, we generated mice with cell-specific Notch1 haploinsufficiency in endothelial and endothelial-derived cells in a Nos3-null background and found that Notch1fl/+;Tie2-Cre+/−; Nos3−/− mice recapitulate the congenital cardiac phenotype of Notch1+/−;Nos3−/− embryos, demonstrating a role for endothelial Notch1 in the proper development of the semilunar valves and cardiac outflow tract.
As AscAA is associated with BAV, and mutations in \textit{NOTCH1} have been identified in families with BAV-associated aortopathy, we sought to determine if the \textit{Notch1}^{+/-};\textit{Nos3}^{-/-} mice develop AscAA. Echocardiographic analysis of \textit{Notch1}^{+/-};\textit{Nos3}^{-/-} mice revealed mild aortopathy. Furthermore, examination of the proximal aorta of \textit{Notch1}^{+/-};\textit{Nos3}^{-/-} mice revealed elastic fiber degradation, increased matrix metalloproteinase 2 expression, and increased smooth muscle cell apoptosis – features characteristic of aneurysmal disease. These findings implicate a novel role for Notch1 in BAV-associated aortopathy of the proximal aorta.

Finally, we sought to determine if loss of Notch1 contributes to aortic dilation in the absence of valve disease. We found that \textit{Notch1} haploinsufficiency exacerbates the aortic root aneurysm seen in the Marfan syndrome mouse model and that heterozygous deletion of \textit{Notch1} in the second heart field (SHF) lineage recapitulates this exacerbated phenotype. Lineage tracing analysis suggests that loss of Notch1 in the SHF reduces the number of SHF-derived smooth muscle cells in the aortic root, and RNA-seq analysis demonstrates distinct in vivo expression patterns between lineage-specific regions of the ascending aorta. Finally, \textit{Notch1}^{+/-} mice in a predominantly 129S6 background develop AscAA localized to the aortic root, demonstrating that loss of Notch1 is sufficient to cause AscAA. These findings highlight a lineage-specific origin for AscAA and suggest that genes linked to the development of BAV may also contribute to AscAA.
RECENT ABSTRACTS AND PRESENTATION


ORAL PRESENTATIONS

Koenig, S.N. “Loss of Notch1 in the Secondary Heart Field Exacerbates Ascending Aortic Aneurysm and Causes Aortic Rupture in Marfan Syndrome Mice.” Edward F. Hayes Graduate Research Forum, The Ohio State University; Columbus, OH. February 2016.

RECENT PUBLICATIONS


AWARDS AND HONORS

Trainee Travel Award 2016
Nationwide Children’s Hospital

Outstanding Research by an Early Career Investigator 2015
Atherosclerosis, Thrombosis, and Vascular Biology Council
American Heart Association Scientific Sessions

Travel Award for Young Investigators 2015
Atherosclerosis, Thrombosis, and Vascular Biology Council
American Heart Association Scientific Sessions

Best of Basic Sciences Abstract 2015
American Heart Association Scientific Sessions

TL1 Pre-Doctoral Fellowship 2014-2016
Center for Clinical and Translational Science
The Ohio State University

FUTURE PLANS

After graduation, Sara will be working as a post-doctoral scientist in the lab of Dr. Peter Mohler at The Ohio State University where she will continue to investigate mechanisms of heart disease. These invaluable experiences will serve as a foundation for her future career in academic research.