Kathryn E. Husarek  
PhD Candidate  

“The Roles of the Angiotensin Type 1 Receptor and Vascular Smooth Muscle Cell Phenotype in Vascular Bed-Specific Remodeling in Type 2 Diabetes”  

Thursday, July 2, 2015  
130 Biomedical Research Tower  
10:00-11:00 am
VITA

December 16, 1986 . . . . . . . . . . . . . . . . . . . . Born – Houston, TX

May 2009 . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . B.S., Molecular and Cell Biology
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ABSTRACT

Type 2 diabetes mellitus (T2DM) constitutes 90% of diabetic cases. According to the CDC, cardiovascular complications are the leading cause of death in T2DM diabetics. Many cardiovascular complications are attributed to macrovascular diseases (stroke and coronary artery disease); however, T2DM patients can also have microvascular dysfunction including diabetic retinopathy and neuropathy. While most studies focus on macrovascular remodeling associated with these diseases, the impact of microvascular dysfunction and cardiovascular complications in T2DM patients is poorly understood, especially with regard to microvascular structural remodeling. Therefore, the goal of these studies was to better understand the mechanisms that dictate coronary microvascular remodeling in T2DM.

In part one of this dissertation, we investigated the role of the renin-angiotensin-aldosterone system (RAAS) in coronary microvascular remodeling in a mouse model of T2DM. The goal of this study was to determine whether the blockade of AT$_1$R signaling dictates vascular smooth muscle growth that partially underlies coronary arteriole remodeling in T2DM. Control and diabetic mice were given AT$_1$R blocker losartan via drinking water for 4 weeks. Using pressure myography, we found that coronary arterioles from 16-week diabetic mice undergo inward hypertrophic remodeling due to increased wall thickness and wall-to-lumen ratio with a decreased lumen diameter. This remodeling was accompanied by decreased elastic modulus. Losartan treatment decreased wall thickness, wall-to-lumen ratio, and coronary arteriole cell number in diabetic mice. Losartan treatment did not affect incremental elastic modulus. However, losartan improved coronary flow reserve. Our data suggest that Ang II-AT$_1$R signaling mediates, at least in part, coronary arteriole inward hypertrophic remodeling in T2DM without affecting vascular mechanics.
In part two of the dissertation, we investigated the role of vascular smooth muscle cell (VSMC) phenotype on coronary microvascular remodeling in a mouse model of T2DM. Under normal conditions, VSMCs exhibit a differentiated/contractile phenotype characterized by contractile function with little proliferation and ECM production. In response to injury, chronic hyperglycemia or growth factor activation, VSMCs lose their contractile phenotype and switch to a proliferative and/or synthetic phenotype characterized by increased proliferation/migration or ECM production, respectively. The goal of this study was to determine if VSMCs from macrovasculature and microvasculature exhibit distinct phenotypes that contribute to the vascular-bed specific remodeling seen in diabetic mice. We isolated and cultured VSMCs from coronary arterioles and the thoracic aorta from control and diabetic mice. We observed increased expression of proliferative proteins in diabetic coronary VSMCs compared to control coronary VSMCs, indicating a more proliferative phenotype. Due to the changes in decreased incremental elastic modulus in diabetic coronary arterioles, we investigated the VSMCs role in ECM synthesis. We observed differential expression of various ECM markers between vascular beds, revealing a possible change in VSMC phenotype and mechanism by which vascular-bed stiffness is altered in diabetes. In addition, coronary VSMCs have decreased mRNA and protein expression of contractile markers when compared to aortic VSMCs, indicating a less differentiated phenotype. We also observed differences between coronary VSMCs and aortic VSMCs in expression levels of VSMC transcriptional regulators, revealing a possible mechanism through which VSMC vascular bed-specific remodeling is regulated.
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