THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

Sarah Ann Colijn

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE

GRADUATE COLLEGE
Department of Cell Biology

Monday, August 19, 2019 | 2:00 pm
Biomedical Research Center, Room 109

Cell-Specific Regulation and Function of RIPK3 in the Embryonic and Postnatal Vasculature

COMMITTEE IN CHARGE: Courtney T. Griffin, PhD; Lawrence I. Rothblum, PhD; Lorin E. Olson, PhD; Florea Lupu, PhD; Rodger P. McEver, MD

ABSTRACT: Receptor-interacting serine/threonine-protein kinase 3 (RIPK3) is well known for its role in the programmed cell death pathway called necroptosis. However, emerging data suggest that necroptosis accounts for only a part of RIPK3 function. Our lab has found that RIPK3 is a particular protein of interest in the embryonic and postnatal vasculature through non-necroptotic mechanisms. We first revealed that suppression of *Ripk3* transcription in endothelial cells is critical in order to maintain vascular integrity at midgestation, though RIPK3-mediated vascular rupture does not depend on endothelial cell necroptosis. We also showed that the chromatin-remodeling enzyme CHD4 supports midgestation vascular integrity by preventing transcriptional activation of endothelial *Ripk3* in response to gestational hypoxia. Next, we discovered a novel—and unexpected—role for RIPK3 in the postnatal vascular disease atherosclerosis. Surprisingly, atherosclerotic lesions are more severe when RIPK3 is deleted in either endothelial cells or macrophages in a mouse model of atherosclerosis, indicating that RIPK3 is athero-protective in these cell types. Moreover, we found little evidence to indicate that necroptosis plays a role in atherosclerosis pathology. These findings conflict with previous theories about how RIPK3 functions in atherosclerosis. Based on our embryonic and postnatal data, we argue that there are cell-specific regulations and novel functions of RIPK3 in the vasculature. Thus, understanding how RIPK3 is regulated and how it functions in various diseases and tissues is essential in order to assess the benefits and disadvantages of targeting RIPK3 in a clinical disease context.