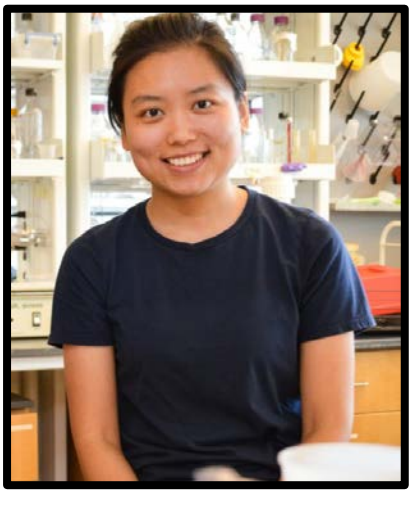
THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

Siqi Gao

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE
GRADUATE COLLEGE
Department of Cell Biology

October 21, 2020 | 2:00 pm
| Location: Zoom Meeting ID: 978 8010 4348 | Password: 204383 |
https://omrf.zoom.us/j/97880104348?pwd=QklJN0MzRWdJcERmQTYyMEI5dzJRUT09



Effects of Plasmin and RIPK3 on Murine Vascular Development and Integrity

COMMITTEE IN CHARGE: Courtney T. Griffin, PhD; Florea Lupu, PhD; Eric W. Howard, PhD; Lorin E. Olson, PhD; Lijun Xia, MD, PhD

ABSTRACT: Vascular development and integrity are essential for ensuring mammalian survival and proper function. Our work has revealed that two factors—the serine protease plasmin and receptor interacting serine/threonine-protein kinase 3 (RIPK3)—influence vascular development and integrity from different aspects. Plasmin has been considered to be largely beneficial to the vasculature because its fibrinolytic function helps to maintain vessel lumen patency and because its proteolytic function promotes extracellular matrix remodeling. However, we found that excessive plasmin-mediated extracellular matrix degradation compromises hepatic vascular integrity in a murine acetaminophen overdose model. Moreover, pharmacological inhibition or genetic reduction of plasmin activity prevents liver bleeding in this toxicity model. RIPK3 is well known for its roles in a form of programmed cell death called necroptosis and in inflammatory responses. We found that repression of *Ripk3* transcription is important for murine vascular integrity at midgestation. Next, by utilizing an unbiased CRISPR-based technique, we identified NFκB1 as a new transcriptional regulator of *Ripk3* in endothelial cells, particularly under inflammatory conditions. Finally, we revealed a novel role for RIPK3 in regulating growth factor receptor expression on endothelial cells to promote angiogenesis. These findings provide new insights into factors and mechanisms affecting murine vascular development and integrity, and they demonstrate the importance of tightly regulating plasmin activity and endothelial RIPK3 expression in order to develop and maintain healthy vascular networks.