THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

Megan L. Brophy

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE
GRADUATE COLLEGE
DEPARTMENT OF BIOCHEMISTRY AND MOLECULAR BIOLOGY

Thursday, February 8, 2018, 11:00 a.m.
Room 276, Basic Sciences Education Building, OUHSC

Myeloid-specific deletion of epsins 1 and 2 ameliorates atherosclerosis by preventing LRP-1 downregulation and inflammatory macrophage phenotype

COMMITTEE IN CHARGE: Hong Chen, PhD, Co-Chair, Ann Louise Olson, PhD, Co-Chair, Guangpu Li, PhD, Hiroyuki Matsumoto, PhD, Karla Rodgers, PhD, Xin Zhang, PhD

ABSTRACT: Atherosclerosis is caused by the immune and inflammatory cell infiltration of the vascular wall, leading to enhanced inflammation and lipid accumulation. Understanding the molecular mechanisms underlying this disease is critical for the development of new therapies. Our recently studies demonstrate that endothelial epsins, a family of ubiquitin-binding endocytic adaptors are critical regulators of atherosclerosis. However, whether epsins in macrophages play a role in regulating vascular inflammation is unknown. We hypothesize that epsins in macrophages promote inflammation to facilitate atherogenesis. We engineered myeloid cell- specific epsins double knockout mice (LysM-DKO) on an ApoE$^{-/-}$ background fed Western diet. These mice exhibited very little atherosclerotic lesion formation, diminished immune and inflammatory cell content in aortas, and reduced necrotic core content but increased smooth muscle cell content in aortic root sections. Epsin deficiency hindered foam cell formation and suppressed the pro-inflammatory macrophage phenotype but increased efferocytosis and the anti-inflammatory macrophage phenotype in primary macrophages. Mechanistically, we show that epsin loss specifically increases total and surface levels of LRP-1, a protein with anti- atherosclerotic properties. We further show that epsin and LRP-1 interact via epsin's Ubiquitin Interacting Motif (UIM) domain. Oxidized LDL treatment increased LRP-1 ubiquitination and subsequent binding to epsin while mutation of cytoplasmic lysine residues attenuated LRP-1 ubiquitination, suggesting that epsin promotes the ubiquitin-dependent internalization and degradation of LRP-1. Importantly, ApoE$^{-/-}$/LysM-DKO mice on LRP-1 heterozygous background restored atherosclerosis, suggesting that epsin-mediated LRP-1 downregulation in macrophages plays a pivotal role in propelling atherogenesis. Macrophage epsins promote atherogenesis, in part, by facilitating pro-inflammatory macrophage recruitment and potentiating foam cell formation by downregulating LRP-1, implicating that targeting epsins in macrophages may serve as a novel therapeutic strategy to treat atheroma.