THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

Md. Riaj Mahamud

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE
GRADUATE COLLEGE

Department of Cell Biology
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Biomedical Research Center, Room 109

GATA2 CONTROLS LYMPHATIC ENDOTHELIAL CELL JUNCTIONAL INTEGRITY AND LYMPHOVENOUS VALVE MORPHOGENESIS THROUGH *MIR-126*

COMMITTEE IN CHARGE: Sathish Srinivasan, PhD; Eric W. Howard, PhD; Florea Lupu, PhD; Lorin E. Olson, PhD; Lijun Xia, PhD; Xin Zhang, PhD

ABSTRACT: Mutations in the transcription factor GATA2 cause lymphedema. GATA2 is necessary for the development of lymphatic valves (LVs) and lymphovenous valves (LVVs), and for the patterning of lymphatic vessels. The mechanism of GATA2 action during lymphatic vasculature development remain poorly understood. The goal of this work is to gain insights into the pathogenesis of lymphedema and the mechanisms of GATA2 during lymphatic vasculature development. Here, we report that GATA2 is not necessary for valvular endothelial cell (VEC) differentiation. Instead, GATA2 is required for VEC maintenance and morphogenesis. GATA2 is also necessary for the expression of cell junction molecules VE-Cadherin and Claudin5 in lymphatic vessels. We identified *miR-126* as a target of GATA2, and *miR-126*$^{-/-}$ embryos recapitulate the phenotypes of mice lacking GATA2. Primary human lymphatic endothelial cells (HLECs) lacking GATA2 (GATA2$^{\Delta HLEC}$) have altered expression of Claudin5 and VE-Cadherin, and blocking *miR-126* activity in HLECs phenocopies these changes in expression. Importantly, overexpression of *miR-126* in GATA2$^{\Delta HLEC}$ significantly rescues the cell junction defects. Thus, our work defines a new mechanism of GATA2 action during lymphatic vasculature development and uncovers *miR-126* as a novel regulator of mammalian lymphatic vascular development.