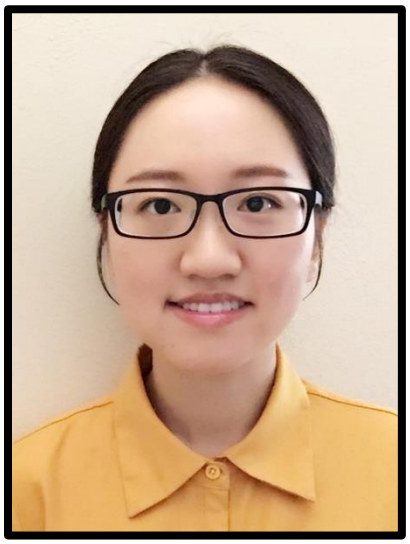
THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

Yue Li

FOR THE DEFENSE OF DOCTOR OF PHILOSOPHY DEGREE
GRADUATE COLLEGE
DEPARTMENT OF PHYSIOLOGY



Thursday, July 25, 2019 | 1:00pm
Biomedical Sciences Building, Room 631

THE REGULATION AND FUNCTION OF DTMEM214 IN THE CONTROL OF GLUCOSE HOMEOSTASIS IN DROSOPHILA

COMMITTEE IN CHARGE
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ABSTRACT: A better understanding of the molecular mechanisms that regulate glucose uptake and metabolism is required for treating metabolic disorders such as Type 2 diabetes (T2D) and obesity. The major goal of our study is to elucidate the molecular basis of glucose uptake and metabolism, using the efficient *Drosophila* model. In a systemic screen conducted in *Drosophila*, we identified that *Drosophila* transmembrane protein 214 (dTMEM214), when haploinsufficient, alters whole-body glucose level under normal diet (ND) and high sugar diet (HSD) conditions. dTMEM214 shares over 30% amino acid sequence homology with human TMEM214 (hTMEM214), and both dTMEM214 and

hTMEM214 are not known to be involved in energy metabolism. Our study shows that dTMEM214 regulates glucose homeostasis by controlling glucose absorption in the fly enterocyte. We further show that dTMEM214 is a very dynamic protein whose cellular distribution is directed by Rab4, a Ras-related GTP-binding protein associated with membrane recycling. Our results found that Rab4 colocalizes with dTMEM214 in the early endosomes and controls the distribution of dTMEM214 between the surface membrane and cytosol. To further identify the target of dTMEM214 in the enterocyte, we utilized a candidate-based approach and identified a novel role of *Drosophila* sodium/solute cotransporter 5A5 (dSLC5A5) in glucose absorption in the intestine. To our knowledge, dSLC5A5 is the first glucose transporter being reported in the *Drosophila* intestine. Our further studies showed that dSLC5A5 co-localizes with dTMEM214 in the enterocyte and its plasma membrane-to-cytosol distribution is regulated by dTMEM214 level. Last but not least, our loss- or gain-of-function experiments on dTMEM214, Rab4, and dSLC5A5 reveal their roles in the regulation of systemic glucose levels and glucose uptake into the enterocyte. Based on our findings, we propose that a previously-unrecognized Rab4-dTMEM214-dSLC5A5 pathway acts in the intestinal cell to critically direct glucose homeostasis under ND and HSD conditions. Our work may serve as the first step in a continuum of research that will provide important insights into the regulation of carbohydrate metabolism and diabetes pathogenesis in humans, and help guide the development of new and improved therapeutics for diabetes and other metabolic disorders.