

# Role of IQGAP1-Estrogen Receptor $\alpha$ -AMPK Axis in the Sex Differences of Type 2 Diabetes

Rawan Moussa<sup>1\*</sup>, Alice Lu<sup>1</sup>, Mahasin A. Osman, PhD<sup>2</sup>

<sup>1</sup>College of Medicine and Life Sciences, The University of Toledo, Toledo, OH

43614

<sup>2</sup>Division of Hematology and Oncology, Department of Medicine, The University of

Toledo, Toledo, OH 43614

\*Corresponding author: [alice.lu@utoledo.edu](mailto:alice.lu@utoledo.edu)

**Keywords:** Sex differences in Type 2 Diabetes, IQGAP1, Estrogen receptor alpha, AMPK

Published: 14 December 2023

Type 2 diabetes (T2D) is a 2-hit chronic metabolic disorder arising from defects in insulin secretion from pancreatic  $\beta$ -cells and insulin sensitivity in peripheral tissues. Population studies indicated that T2D affects more men than women. The mammalian target of rapamycin (mTOR) and its downstream key energy sensor AMPK $\alpha$  have been largely implicated in T2D. Strong evidence suggests that the estrogen receptor  $\alpha$  (ER $\alpha$ ) influences AMPK activity and T2D sex disparity, but the molecular mechanisms remain unclear. The scaffold signaling protein IQGAP1 binds AMPK $\alpha$  and ER $\alpha$  and regulates insulin secretion in pancreatic  $\beta$ -cells. Here, we aim to test the novel hypothesis that an IQGAP1-ER $\alpha$ -AMPKs signaling axis plays a role in the disparity of T2D and exerts its effects in the pancreas. Preliminary results revealed significant metabolic differences in male and female mice lacking IQGAP1 (KO) and fed a high-fat diet (HFD) compared to control groups. While all KO mice exhibited significant decreases in body weight, the female mice were much leaner and ate less food. Furthermore, metabolic analyses indicated a significant reduction in insulin levels in KO male mice on HFD while the female mice displayed improved glucose homeostasis likely due to enhanced insulin secretion. Insulin, gene expression levels and co-localization of the pathway components in the pancreas are being investigated in treated and control mice groups. Overall, the study likely will provide important new insights into the determinants of sex-differences of T2D and reveal potential diagnostic biomarkers for future therapies.