The Role of Amino Acids in Insulin Production and the Control of Glucose Homeostasis

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Amino acids (AA) are essential building blocks for cellular life. They are increasingly appreciated as potent chemical signals to modulate cellular functions. Previously, our lab has identified a small GTPase, Rab1A, as a key protein that delivers AA nutrient signals to activate mTOR, a master regulator of cellular metabolism. To understand the physiological significance of AA signalling, our lab generated a Rab1A knockout mouse model. Strikingly, the transgenic mice display phenotypes resembling type I diabetes mellitus, including hyperglycemia, insulin deficiency, and reduced body weight. Therefore, we hypothesize that this Rab1A-mTOR AA signalling pathway is critical for insulin expression in pancreatic beta-cells. The purpose of this study is to examine how AA regulates insulin transcription through the analysis of insulin promoter. A serial deletion of the insulin promoter was performed to identify the regulatory elements responsive to AA signals. To reflect the transcription activity in a real-time manner, we employed a quick-response luciferase reporter driven by the 500bp mouse insulin promoter. The bioluminescent activity of luciferase is correlated to insulin transcription rate. Results have shown that the A3 box, a core binding motif for the transcription factor Pdx1, is a key AA response element for insulin transcription. Additional studies revealed that AA controls insulin expression by modulating the activity of Pdx1. In the future, we hope to further investigate the Rab1A-mTORC1 AA signaling, which may provide insights on therapy development for diabetes.

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