March 2020

Mixed-lineage kinase-3 (MLK3) plays a negative modulatory role in insulin secretion from the pancreatic β-cell

Tyler Russeth
Wayne State University School of Medicine, gm7353@wayne.edu

Vijayalakshmi Thamilselvan
Eugene Applebaum College of Pharmacy and Health Sciences, aj0833@wayne.edu

Anjaneyulu Kowluru
Wayne State University School of Medicine, Eugene Applebaum College of Pharmacy and Health Sciences, John D. Dingell VA Medical Center, akowluru@med.wayne.edu

Mixed-lineage kinase-3 (MLK3) plays a negative modulatory role in insulin secretion from the pancreatic β-cell

Tyler Russeth[1], Vijayalakshmi Thamilselvan[2], PhD, and Anjaneyulu Kowluru[1,2,3], PhD

[1]Wayne State University School of Medicine

[2]Eugene Applebaum College of Pharmacy and Health Sciences

[3]John D. Dingell VA Medical Center

Key words: Islet beta-cell, protein kinase, insulin secretion, mixed-lineage kinase 3

Abstract:

Glucose-stimulated insulin secretion (GSIS) from the pancreatic β-cell in response to elevated levels of glucose is controlled by a variety of signals including intracellular calcium and nucleotides such as cAMP, ATP and GTP. These cellular signals are responsible for activation of specific kinases that mediate phosphorylation of key exocytotic proteins that lead to GSIS. In the context of protein kinases, mixed-lineage kinases (MLKs) have been implicated in an assortment of cellular functions, including cell proliferation and apoptosis. However, very little is known on potential regulatory roles of MLKs in islet β-cell function, including GSIS. The goal of this study is to determine the roles of MLK3 in GSIS. Initial data indicated that MLK3 is expressed in clonal β-cells (INS-1 832/13) and human islets. INS-1 832/13 cell exposure to stimulatory glucose (20mM) resulted in a time-dependent increase in phosphorylation of MLK3 at T277 and S281 with peak phosphorylation within 20 minutes. URMC-099, a known inhibitor of MLK3, markedly suppressed glucose-induced MLK3 phosphorylation under stimulatory glucose conditions. Moreover, URMC-099 significantly increased insulin secretion under basal (2.5mM) and stimulatory glucose exposure conditions, suggesting a suppressive role for MLK3 in insulin secretion. Together, these studies provide evidence that MLK3 is in fact expressed in clonal and primary β-cells and inhibition of glucose-induced phosphorylation of MLK3 results in potentiation of GSIS. Studies are underway to further confirm our pharmacological findings using molecular biological (siRNA-MLK3) approaches.