



Name: Carly Kibbe

Email: kibbe@wisc.edu

Major Professor: Anath Shalev

Degree Objective: Ph.D. Endocrinology and Reproductive Physiology

Background: BS Biology, Univ Wisconsin - LaCrosse

Current Research Project:

My research projects focuses on the regulation of thioredoxin-interacting protein by forkhead boxO1 transcription factor in pancreatic beta cells. Thioredoxin-interacting protein (TXNIP) binds and inhibits thioredoxin, a redox regulator, resulting in increased cell apoptosis. Using mouse models, our lab has previously shown that TXNIP deficiency inhibits beta cell apoptosis and protects against type 1 and type 2 diabetes. These results suggest that TXNIP may be a possible target for therapies aimed to stop beta cell apoptosis in diabetic patients, however more must be known about the mechanisms regulating TXNIP. The forkhead box O1 transcription factor (FOXO1) has been shown to bind the TXNIP promoter and regulate the expression of TXNIP in liver and endothelial cells, but no data is available for pancreatic beta cells. Therefore, we first demonstrated that FOXO1 binds the TXNIP promoter in human islet cells, as assessed by Chromatin Immunoprecipitation (ChIP) assays. Using transient transfections of a FOXO1 expression plasmid we further showed that overexpression of FOXO1 in rat insulinoma (INS-1) cells significantly decreases endogenous TXNIP mRNA levels. Using luciferase reporter assays we also demonstrated that FOXO1 overexpression reduces TXNIP promoter activity in INS-1 cells. However, a promoter deletion analysis revealed that rather than the known consensus FOXO1 binding site, a downstream E-box-like motif was necessary for FOXO1 regulation of TXNIP. Using luciferase assays with a heterologous SV40 promoter containing two upstream E-box-like motif repeats we were also able to demonstrate that the E-box-like motif is sufficient for FOXO1 mediated repression. Our lab has previously shown that glucose-induced TXNIP expression is mediated through carbohydrate response element-binding protein (ChREBP) binding to this E-box-like motif in the TXNIP promoter. In fact, using another set of luciferase reporter assays we demonstrated that FOXO1 overexpression blocks glucose-induced TXNIP expression. Furthermore, using ChIP assays we showed that FOXO1 overexpression leads to decreased ChREBP binding to the TXNIP promoter. Together, these results demonstrate for the first time that FOXO1 downregulates TXNIP expression in pancreatic beta cells, and suggest that FOXO1 may act through ChREBP.

Honors:

Grants Received:

Publications:

National Presentations:



Other Presentations:

Oral Presentation, ERP Seminar 1/2010

Carly Kibbe, Ashley Schmitting, Hyunjoo Cha Molstad and Anath Shalev. FOXO1 Inhibits TXNIP Transcription in Pancreatic Beta Cells. ERP Annual Symposium 2010.

ERP Service:

ERP Symposium Committee 2009-2010

ERP Focus Group 2008-2010

ERP Social Committee 2010-2011