

P023 Lack of TXNIP protects beta cells against glucotoxicity
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Glucotoxicity plays a major role in pancreatic beta cell apoptosis and diabetes progression, but the factors involved have remained largely unknown.

Our recent studies have identified thioredoxin-interacting protein (TXNIP) as a novel pro-apoptotic beta cell factor that is induced by glucose suggesting that TXNIP may play a role in beta cell glucotoxicity. Incubation of INS-1 beta cells and isolated primary mouse and human islets at high glucose led to a significant increase in TXNIP as well as in apoptosis. Very similar results were obtained *in vivo* in islets of diabetic mice. To determine whether TXNIP plays a causative role in glucotoxic beta cell death, we used TXNIP-deficient islets of HcB-19 mice harboring a natural nonsense mutation in the TXNIP gene. We incubated islets of HcB-19 and C3H control mice at low and high glucose and assessed them for TXNIP expression and apoptosis.

Interestingly, while in C3H islets high glucose led again to significantly elevated TXNIP and apoptosis levels as measured by TUNEL and cleaved caspase-3, no increase in apoptosis was observed in TXNIP-deficient HcB-19 islets indicating that TXNIP is required for beta cell death caused by glucotoxicity.

Thus, inhibition of TXNIP protects against glucotoxic beta cell apoptosis and therefore may represent a novel therapeutic approach to halt diabetes progression.