**JNK1 plays a causal role in palmitate-induced β-cell dysfunction in vivo**

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Obesity has recently been described as an epidemic due to an increase in incidence, and is described as a long term imbalance between energy generation and energy expenditure due to changes in lifestyle. In obesity, chronically elevated circulating free fatty acids (FFA) potentially cause β-cell dysfunction which leads to type 2 diabetes (T2D). In vitro data have identified various cellular mechanisms leading to FFA-induced β-cell dysfunction such as oxidative stress and endoplasmic reticulum (ER) stress.

One other potential mechanism includes the FFA-induced activation of inflammatory kinase c-Jun N-terminal kinase (JNK). As an effector protein part of the mitogen-activated protein kinases (MAPK) pathway, JNK is able to respond to various stress signals in the cell. Sustained activation of JNK by prolonged stress, such as by elevated FFA, can reduce insulin signaling and β-cell insulin secretion. JNK can increase serine phosphorylation of IRS proteins, thus decreasing their tyrosine phosphorylation and activation. This will hinder insulin action, which in the β-cell is important for insulin gene transcription and translation. More precisely, inactivation of IRS1/2 will impede downstream activation of PI3K/Akt pathway. Reduced Akt activation will decrease the degradation of transcription factor FoxO1, allowing for nuclear translocation of FoxO1. Nuclear localization of FoxO1 will prevent Pdx1, the transcription factor required for insulin gene transcription, from entering the nucleus. In addition, JNK can also directly increase nuclear translocation of FoxO1 by phosphorylation. Thus, activation of JNK within β-cells can reduce the amount of insulin produced. This perturbation of the insulin signaling pathway inside β-cells is known as β-cell insulin resistance.

Previous in vitro studies from our group have demonstrated that islets of JNK1-null mice are protected from the effect of palmitate but not oleate on inducing β-cell dysfunction, suggesting that activation of JNK1 is specific to saturated FFA. Thus, we hypothesized that saturated FFA-induced β-cell dysfunction is mediated in part by JNK.

Due to its detergent effects, palmitate cannot be infused directly into circulation. Thus, ethylpalmitate was used, as the ethyl group reduces the toxic effect. Mice can hydrolyze the ethyl group in circulation, producing palmitate and ethanol. JNK1-null (KO) mice and their littermate controls (WT) were infused with ethylpalmitate or ethanol vehicle for 48 hours, after which their pancreatic islets were isolated for ex vivo determination of insulin secretion.

We confirmed that ethylpalmitate infusion does significantly increase plasma FFA as compared to vehicle infusion. We found that WT mice infused with ethylpalmitate demonstrated significantly decreased insulin secretion as compared with WT mice infused with vehicle, whereas JNK1-null mice infused with ethylpalmitate had similar insulin secretion as controls. These data suggest that JNK1 plays a causal role in saturated FFA-induced β-cell dysfunction in vivo. This data emphasizes the importance of JNK1, and identifies JNK1 as a potential target for manipulation in preserving β-cell function. Future studies will involve the use of β-cell specific JNK1-null mice, as the β-cell response of a whole-body JNK1-null mice to elevated FFA will be influenced tremendously peripheral JNK1 deficiency.