Title:
Regulation of α2δ-1 by TCF7L2 and the roles of mechanotransduction on calcium signaling and glucose stimulated insulin secretion

Background:
Glucose-stimulated insulin secretion occurs by Ca\(^{2+}\)-dependent exocytosis and in this respect, Ca\(^{2+}\) entering via voltage-gated calcium channels (VGCC) play an important role. The auxiliary subunits of VGCC, α2δ and β subunits have been suggested to control VGCC trafficking to the plasma membrane, but also to influence certain of the channels’ biophysical properties. Transcription factor 7-like 2 (TCF7L2), is the most significantly common genetic variation associated with human type 2-diabetes. It has been shown to regulate the Cacna2d1 gene, however, the functional consequences in terms of protein levels and beta cell function are still missing.

The consensus model of glucose-stimulated insulin secretion is incomplete, ion channels other than the K\(_{ATP}\) channel are needed for generating the glucose-dependent depolarization. Piezo1 and 2 are identified as mechanosensitive channels non-selectively allowing passage of Na\(^{+}\), K\(^{+}\) and Ca\(^{2+}\), which can generate an overall depolarizing effect missing in the beta cell consensus model.

Aim:
1. To determine whether TCF7L2 indirectly controls beta-cell Ca\(^{2+}\) signaling and insulin secretion via regulation of α2δ-1.
2. To establish whether mechanosensitive channels are involved in glucose-stimulated insulin secretion and T2D development.

Method:
Real-time qPCR; Western blot; Immunostaining; Ca\(^{2+}\) imaging; Patch clamp; Insulin secretion

Preliminary results:
TCF7L2 regulates mRNA and protein levels of α2δ-1. Suppression of α2δ-1 decreased voltage-gated Ca\(^{2+}\) currents and high glucose/depolarization-evoked Ca\(^{2+}\) signaling, resulting from impaired trafficking of Cav1.2 to the plasma membrane and accumulation in the recycling endosomes. Finally, this impaired the capacity for glucose-induced insulin secretion in Cacna2d1-silenced cells.

We identified the heterologous distribution of Piezo1 in low/ high glucose treated pancreatic β cells. Piezo1 mediated Ca\(^{2+}\) signaling in response to high glucose but not upon high K\(^{+}\) stimulation. The inhibitors of mechanosensitive channels, GsMTx4 and ruthenium red, as well as silencing of Piezo1 reduced glucose stimulated insulin secretion. The activator Yoda1 in contrast pronouncedly increase it.

Significance:
The data suggests an important role for Tcf7L2, α2δ-1 and mechanosensitive channel Piezo1 in insulin secretion, offers strong support for determining the risk for T2D.