

P026 TCF7L2 controls insulin gene expression and insulin secretion

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Background. Genetic studies have associated single nucleotide polymorphisms (SNPs) in of the gene encoding the *Wnt* signaling-associated transcription factor, TCF7L2, with type 2 diabetes and impaired insulin secretion. Recent evidence has suggested that inheritance of the at-risk T allele at SNP rs7903146 may increase the expression of this factor in human islets. However, the cellular mechanisms by which changes in TCF7L2 level may affect insulin secretion are unclear. Here, we use RNA silencing to investigate the role of TCF7L2 in rodent islets and beta clonal cells. Results. TCF7L2 silencing in INS-1(832/13) cells: increased the proportion of cells displaying a glucose- (20 vs 3 mmol/l) stimulated increase in $[Ca^{2+}]_i$ from $46\% \pm 10$ to $71\% \pm 3$ without affecting the magnitude of the Ca^{2+} response; enhanced secretion of co-transfected human growth hormone ($2.5\% \pm 0.2$ vs $5.26\% \pm 1.1$); abolished GLP-1-stimulated insulin secretion. Knockdown of TCF7L2 in CD1 mouse islets reduced glucose-stimulated insulin secretion ($98.6 \pm 0.36\%$ at 11 mmol/l glucose) and sharply reduced levels of preproinsulin ($-36.5 \pm 10.2\%$), and prohormone convertase-1/2 mRNA. Concurrent silencing of FoxO1 with TCF7L2 reversed the inhibitory effects of TCF7L2 depletion. Conclusions. Decreases in *TCF7L2* expression in primary beta cells impairs preproinsulin gene expression and insulin secretion, possibly by altering the balance between FoxO1 and TCF7L2-mediated transcriptional programmes.