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A central role for GRB10 in regulation of islet function in man

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Variants in the growth factor receptor-bound protein 10 (GRB10) gene were in a GWAS meta-analysis associated with reduced glucose-stimulated insulin secretion and increased risk of type 2 diabetes (T2D) if inherited from the father, but inexplicably reduced fasting glucose when inherited from the mother. GRB10 is a negative regulator of insulin signaling and imprinted in a parent-of-origin fashion in different tissues. GRB10 knock-down in human pancreatic islets showed reduced insulin and glucagon secretion, which together with changes in insulin sensitivity may explain the paradoxical reduction of glucose despite a decrease in insulin secretion. Together, these findings suggest that tissue-specific methylation and possibly imprinting of GRB10 can influence glucose metabolism and contribute to T2D pathogenesis. The data also emphasize the need in genetic studies to consider whether risk alleles are inherited from the mother or the father.

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