RCAN1 is critical for β-cell mitochondrial function and is overexpressed in human Type 2 diabetes

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Type 2 diabetes (T2D) is a complex metabolic disorder characterized by elevated blood glucose levels. Pancreatic β-cell dysfunction and reduced insulin output in the presence of insulin resistance is the primary defect resulting in T2D. It is unknown what triggers the switch from β-cell compensation to β-cell failure but studies from human T2D islets indicate reduced glucose-stimulated insulin secretion underlined by mitochondrial dysfunction and a diminished capacity to produce ATP. We have established that Regulator of calcineurin 1 (RCAN1) is a stress-induced protein expressed in β-cells that can regulate insulin secretion. We find that RCAN1 expression is increased in T2D islets in humans and mice. Patch clamp studies confirmed that β-cells overexpressing RCAN1 display significant reductions in glucose-induced membrane depolarization and in depolarization-induced exocytosis, with both of these defects being attributable to reduced ATP generation. Inclusion of equimolar ATP inside single β-cells rescued this exocytosis defect. Direct measurements of β-cell mitochondrial output demonstrate that increased RCAN1 perturbs mitochondrial function, and thus ATP production, and that this occurs due to altered functionality of the ADP/ATP translocator. Thus, we provide evidence that increased RCAN1 expression may drive some of the key metabolic changes that underlie the development of β-cell dysfunction in T2D.