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Abstract:

Glucose homeostasis is maintained through the coordinated actions of insulin secretion from pancreatic beta cells and insulin action in peripheral tissues. Dysfunction of insulin action yields insulin resistance, and when coupled with altered insulin secretion, results in type 2 diabetes (T2D). Exocytosis of intracellular vesicles, such as insulin granules and glucose transporter (GLUT4) vesicles is carried out by similar SNARE (soluble NSF attachment receptor) protein isoforms and

Munc18 proteins. An additional regulatory protein, Doc2b, was implicated in the regulation of these particular exocytosis events in clonal cell lines, but relevance of Doc2b in the maintenance of whole body glucose homeostasis in vivo remained unknown. The objective of my doctoral work was to delineate the mechanisms underlying regulation of insulin secretion and glucose uptake by Doc2b in effort to identify new therapeutic targets within these processes for the prevention and/or treatment of T2D. Towards this, mice deficient in Doc2b (Doc2b-/- knockout mice) were assessed for in vivo alterations in glucose homeostasis. Doc2b knockout mice were highly susceptible to preclinical T2D, exhibiting significant whole-body glucose intolerance related to insulin secretion insufficiency as well as peripheral insulin resistance. These phenotypic defects were accounted for by defects in assembly of SNARE complexes. Having determined that Doc2b was required in the control over whole body glycemia in vivo, whether Doc2b is also limiting for these mechanisms in vivo was examined. To study this, novel Doc2b transgenic (Tg) mice were engineered to express ~3 fold more Doc2b exclusively in pancreas, skeletal muscle and fat tissues. Compared to normal littermate mice, Doc2b Tg mice had improved glucose tolerance, related to concurrent enhancements in insulin mumsecretion from beta cells and insulin-stimulated glucose uptake in the skeletal muscle. At the molecular level, Doc2b overexpression promoted SNARE complex assembly, increasing exocytotic capacities in both cellular processes. These results unveiled the concept that intentional elevation of Doc2b could provide a means of mitigating two primary aberrations underlying T2D development.

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