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Abstract:

Type 2 diabetes involves defects in glucose-stimulated insulin secretion (GSIS) from the pancreatic beta cells in combination with defects in peripheral (muscle and adipose) tissue glucose uptake. Both GSIS and glucose uptake are regulated by Syntaxin 4 (Syn4)-Munc18c complexes. Importantly, reports link obesity and Type 2 diabetes in humans with changes in protein levels of Munc18c and Syn4; yet the molecular mechanisms underlying this requirement remain unclear. The central hypothesis proposed is that Syn4-Munc18c complexes are modulated by post-translational modifications and novel interactions. Toward this, we found that Syn4-Munc18c complexes are regulated by tyrosine phosphorylation of Munc18c at Y219 in beta cells. Munc18c tyrosine phosphorylation disrupts Syn4-Munc18c complexes, which leads to an increase in Munc18c associating with the double C2 domain protein Doc2β. Disruption of Syn4-Munc18c upon tyrosine phosphorylation results in an increase in Syn4-SNARE complex formation and GSIS from beta cells. Similarly, tyrosine phosphorylation of Munc18c at Y219 and also Y521, disrupts its association with Syn4 in insulin-stimulated 3T3L1

adipocytes and skeletal muscle. In vitro kinase assays further suggested that the insulin receptor tyrosine kinase targeted Y521 of Munc18c. Further investigations using 3T3L1 adipocytes and skeletal muscle extracts indicate that Munc18c interacts with the insulin receptor tyrosine kinase in an insulin-dependent manner, resulting in phosphorylation of Munc18c, coordinate with the timing of its dissociation from Syn4. Finally, we found that stimulus-induced changes occurred also with Syn4, most notably in the islet beta cells. Syn4-mediated insulin release requires F-actin remodeling to mobilize insulin granules to the plasma membrane. Our studies reveal that Syn4 directly associates with F-actin in MIN6 beta cells, and that the disruption of this complex correlates with increases in glucose-stimulated insulin secretion. Future studies will focus upon the potential link between Syn4, F-actin remodeling with Munc18c, to further gain understanding of the requirements for Syn4-Munc18c complexes in insulin secretion. In sum, given the parallels of Munc18c tyrosine phosphorylation in regulating Syn4-Munc18c interaction and exocytosis in beta cells and peripheral tissues, manipulations of this complex may have therapeutic potential as a strategy to treat Type 2 diabetes.

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