Novel actin/tropomyosin filaments that regulate glucose uptake and insulin secretion

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Type II Diabetes is Australia's fastest growing chronic disease where its onset is linked to two exocytic processes, altered glucose uptake and insulin secretion. In the former process, the glucose transporter, GLUT4, is trafficked in specialised vesicles to the surface membranes, while insulin secretion occurs through fusion of insulin-containing granules with the pancreatic β-cell surface. The actin cytoskeleton in known to play critical roles in both of these processes. We have identified a novel non-sarcomeric actin filament system in skeletal muscle defined by the tropomyosin (Tm) isoform, Tm5NM1 (Kee *et al.*, 2004). Immunofluorescence microscopy studies on muscle sections and isolated fibres indicate that this filament structure is associated with the T-tubule membrane system, a major site of glucose uptake in muscle. Further immunolocalisation and immunoprecipitation studies indicates that Tm5NM1 interacts with Syntaxin-4, a protein necessary for GLUT4 insertion into the plasma membrane. This suggests a role for Tm5NM1 in GLUT4 trafficking and glucose uptake. To understand the function of this actin/Tm structure we have created tissue-wide Tm5NM1 transgenic (Tg) and knock-out (KO) mice. Insulin tolerance tests revealed that the Tg mice clear glucose from the blood more rapidly than wild-type (WT) mice suggesting that these mice display increased insulin sensitivity ($p < 0.001$, *t*-test). Insulin caused a similar increase in Akt phosphorylation, a major upstream regulator of GLUT4 translocation, in skeletal muscle and adipose tissue from both Tg and KO mice suggesting that Tm5NM1 is acting downstream of insulin signalling, consistent with a role in GLUT4 trafficking itself. Glucose tolerance tests revealed that in addition to enhanced insulin sensitivity these animals also displayed ($p < 0.001$, *t*-test at all time points), an increase in basal and glucose-stimulated insulin secretion suggesting that Tm5NM1 has a role in pancreatic insulin secretion. In conclusion, we have identified novel actin/Tm filaments that may regulate the exocytic processes of glucose uptake and insulin secretion. The results of these studies have implications for conditions of altered glucose uptake and insulin secretion, such as Type II diabetes and obesity.

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