The role of phospholipids in controlling GLUT4 exocytosis

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Class I phosphatidylinositol 3-kinases (PI3K) generating phosphatidylinositol(3,4,5)trisphosphate, PtdIns(3,4,5)P_3, have a well established role in cellular signalling. This is particularly true in the muscle cell insulin signalling cascade that regulates the uptake and metabolism of glucose to control blood glucose homeostasis. Insulin via the insulin receptor triggers a cascade of protein phosphorylation and translocation events leading to a localized accumulation of PtdIns(3,4,5)P_3 in the plasma membrane. This in turn allows a series of translocation and phosphorylation events that lead to the insertion of the GLUT4 glucose transporter into the plasma membrane.

We have recently established a role for an additional class of PI3K and 3-phosphorylated lipid in this process. Knockdown of the α isoform of class II PI3K (PI3KC2α) in myoblasts reduced insulin-stimulated glucose uptake due to reduced translocation of GLUT4 to the plasma membrane. PI3KC2α appears to represent a component of an novel and independent signalling cascade as the 'classical' class I PI3K cascade appeared unaffected in the knockdown cells. Analysis of PtdIns species identified a lack of insulin-stimulated accumulation of PtdIns3P in the PI3KC2α knockdown clones identifying the *in vivo* product of PI3KC2α, which was previously unclear, and that this lipid plays a role in GLUT4 translocation. Using a variety of state-of-the-art live cell imaging techniques we have endeavoured to identify the molecular step regulated by PI3KC2α generated PtdIns3P.