LKB1 regulates glucagon secretion and cell proliferation in pancreatic alpha cells

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Introduction: LKB1 inhibits insulin secretion and cell growth in pancreatic islet β cells via mTOR signalling pathways. However, the role of LKB1 in controlling secretion of glucagon, a counter regulatory hormone of insulin also released from pancreatic islets, is not known. Methods: Silencing of LKB1 in clonal αTC1-9 cells was achieved using Dharmacon smartpool RNA oligonucleotides targeting coding regions of LKB1. Glucagon secretion was assessed during incubation of αTC1-9 cells in modified Kreb’s-Ringer solution supplemented with 0.1 or 17 mM glucose for 1h. Secreted and total glucagon was measured using radiomunoassay. Results: LKB1 siRNA reduced both LKB1 mRNA and protein levels in αTC1-9 cells by ~50%. Silencing of LKB1 led to increased glucagon secretion from cells incubated with 17 mM glucose by ~30%. Whilst the degree of phosphorylation of AMP-activated protein kinase (AMPK) α- (catalytic) subunits on T172, and its downstream target, acetyl-CoA carboxylase (ACC), on S72 were reduced, P70S6K, one of the main downstream targets of mTOR signalling pathways displayed enhanced phosphorylation at T389. Immunoreactivity of the proliferation marker Ki67, and the number of cells undergoing mitosis, were increased by LKB1 silencing. Conclusion: LKB1 might serve as an inhibitory regulator of glucagon secretion and cell growth in pancreatic islet alpha cells. *In vivo* studies on mice in which LKB1 is inactivated by CreLoxP-mediated deletion selectively in the alpha cell will allow this hypothesis to be tested directly.