

P016 cAMP-dependent phosphorylation of rpS6 by glucagon like peptide-1 in pancreatic β -cells and the identification of a third *in vivo* rpS6 kinase

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S6K1/2 and the phosphorylation of ribosomal protein S6 (rpS6) play a positive role in controlling pancreatic β -cell size and function. We demonstrate that agents which stimulate increases in cAMP in pancreatic β -cells, such as the incretin hormone glucagon like peptide-1 (GLP1) or forskolin, stimulate the activation of S6K1/2 and the phosphorylation of rpS6 at Ser(240/244) through a pathway that is dependent upon the activation of PI3 kinase and mTOR but independent of PKB. In contrast, the phosphorylation of rpS6 at Ser(235/236) occurs independently of mTOR activation and the activation of the currently known *in vivo* rpS6 kinases via a pathway that is sensitive to inhibitors of PKA. This cAMP-dependent rpS6 kinase activity is also sensitive to PKI *in vitro* and recombinant cAMP-dependent kinase catalytic subunit (PKAc) exclusively phosphorylates recombinant rpS6 on Ser(235/236) *in vitro*. Interestingly, even though GLP1 stimulated phosphorylation of rpS6 on Ser(235/236) in β -cells does not require increased mTOR activity, it is sensitive to rapamycin through the activation of protein phosphatase 2A, which we show dephosphorylates rpS6 exclusively at Ser(235/236) without affecting the phosphorylation of Ser(240/244). In conclusion, these results provide evidence that agents which elevate cAMP in pancreatic β -cells stimulate the phosphorylation of rpS6 on Ser(235/236) and Ser(240/244) via two distinct signalling pathways dependent on mTOR: where Ser(235/236) is exclusively phosphorylated by a novel *in vivo* rpS6 kinase PKA and Ser(240/244) is phosphorylated by S6K.