

P007 Emerging roles of class II phosphoinositide 3-kinase in S6K activation

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Several lines of evidence suggest that generation of the lipid product phosphatidylinositol-3-phosphate (PtdIns-3-P) by the class III phosphoinositide 3-kinase (PI3K) hVps34 is involved in the amino acids- and glucose-dependent activation of S6K. We have recently demonstrated that besides the hVps34-dependent PtdIns-3-P pool localized in endosomal compartment, another pool of this phosphoinositide is specifically generated at the plasma membrane of muscle cells upon insulin stimulation. Moreover we have reported that the synthesis of the insulin-mediated PtdIns-3-P pool is mediated by a class II PI3K isoform, PI3K-C2alpha. Here we show that downregulation of PI3K-C2alpha, using specific shRNA, strongly impairs the insulin- and insulin-like growth factor-1 (IGF-1)-induced activation of S6K in muscle cells. In the same conditions, hVps34 inhibition only slightly reduces the insulin- and IGF-1-dependent S6K activation. Moreover such a slight effect is still detectable in the PI3K-C2alpha knocked down cells suggesting that a co-operative activation of distinct classes of PI3Ks from different nutritional inputs is probably needed to fully activate S6K. Due to the emerging role of S6K in nutrients overload-associated insulin resistance and in regulation of beta cell mass our data suggest that PI3K-C2alpha may have a critical role in both processes.