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METABOLISM

# Keeping insulin secretion in check

> COP1 promotes insulin secretion by counteracting the inhibitory effects of ETVs

Insulin secretion by pancreatic β-cells reduces blood glucose levels and must be regulated to prevent physiologically detrimental hyper- and hypoglycaemic states. Dixit and colleagues now report that the ubiquitin ligase COP1 (also known as RFWD2) promotes insulin secretion in mice by inducing the degradation of transcription factors ETV1, ETV4 and ETV5.

The authors found that *Cop1* is highly expressed in the pancreas in adult mice, and that mice became hyperglycaemic and glucose intolerant following *Cop1* inactivation in adult β-cells. Further analysis showed that the hyperglycaemia seen in these mutant mice (ΔCop1β mice) was due to a decrease in glucose-stimulated insulin secretion (GSIS). In ΔCop1β mice, β-cells appeared normal and accumulated insulin, suggesting a direct effect of *Cop1* deletion on insulin release from these cells. Indeed, the docking of insulin granules at the plasma membrane and exocytosis were impaired.

As ETVs have been previously shown to be ubiquitylated and targeted for degradation by COP1, the authors investigated whether ETVs are COP1 substrates in the pancreas. Indeed, ETV4 and ETV5 levels were higher in pancreatic islets of ΔCop1β mice than in control islets. Moreover, deletion of all three *Etv* genes (*Etv1*, *Etv4* and *Etv5*) rescued the hyperglycaemic and glucose intolerance phenotype, indicating that higher levels of these ETV proteins, resulting from COP1 deficiency, impair insulin secretion.

Next, the authors identified exocyst 6 (*Exoc6*) and synaptotagmin-like 3 (*Sytl3*) as direct targets of ETVs. EXOC6 is a component of the exocyst complex, and SYTL3 is a RAB GTPase-interacting protein; they are both involved in insulin granule docking and, importantly, their combined overexpression inhibited insulin secretion.

Thus, this work uncovers a mechanism through which COP1 promotes insulin secretion by counteracting the inhibitory effects of ETVs. The authors propose that ETV activity may be important when there is a risk of insulin exhaustion (such as during sustained glucose exposure), whereas COP1 may be activated in response to increased demand for glucose secretion. The physiological importance of such a mechanism remains to be clarified.

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**ORIGINAL ARTICLE** Suriben, R. *et al.* β-cell insulin secretion requires the ubiquitin ligase COP1. *Cell* **163**, 1457–1467 (2015)