

## Setting sail for glucose homeostasis with the AKAP150-PP2B-anchor

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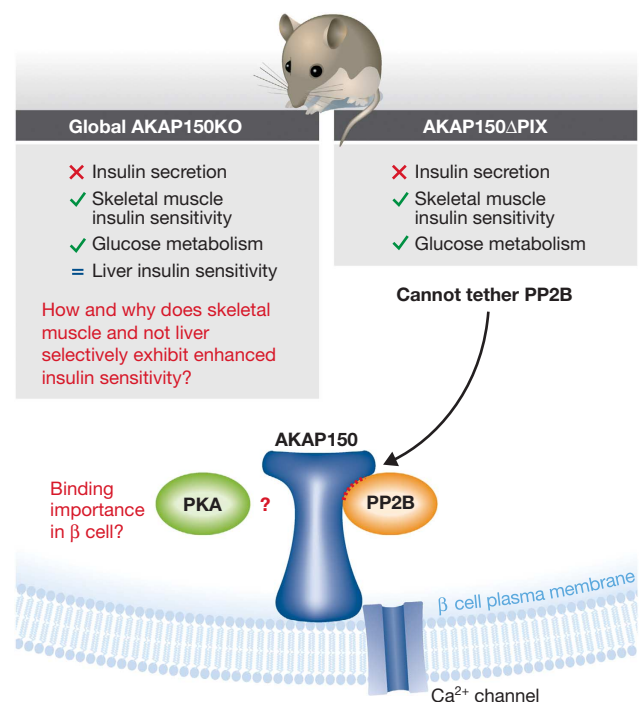
**Glucose-stimulated insulin secretion, controlled by multiple protein phosphorylation events, is critical for the regulation of glucose homeostasis. Protein kinase A (PKA) is known to play a role in  $\beta$  cell physiology, but the role of its anchoring protein is not fully understood. Hinke *et al* (2012) illustrate the significance of A-kinase anchoring protein 150 in tethering protein phosphatase 2B to mediate nutrient-stimulated insulin secretion and thus modulate glucose homeostasis.**

Insulin secretion is a key component in the regulation of glucose homeostasis. The initiation of glucose-stimulated insulin secretion (GSIS) is coordinated by numerous protein phosphorylation and dephosphorylation events in the  $\beta$  cell (Jones and Persaud, 1998). PKA and protein phosphatase 2B (PP2B or calcineurin—a  $\text{Ca}^{2+}$ /calmodulin-dependent enzyme) are examples of enzymes that can influence the release of insulin. The combined effects of these enzymes propagate GSIS, which is mediated intracellularly via an increase in ATP concentration,  $\text{Ca}^{2+}$  influx via the voltage-dependent  $\text{Ca}^{2+}$  channel (VDCC) and cyclic AMP (cAMP) signalling. At the same time, these enzymes can also regulate glucose usage (e.g., via glycogen synthase) in insulin-sensitive tissues such as the skeletal muscle.

cAMP signalling serves to potentiate GSIS via either (1) PKA-dependent or (2) PKA-independent mechanisms (involving cAMP-binding protein Epac2A (exchange protein directly activated by cAMP 2)). A-kinase anchoring protein (AKAP) belongs to a group of regulatory proteins that interacts with cAMP-dependent PKA (Pidoux and Tasken, 2010; Welch *et al*, 2010). It can regulate the differential usage of kinase versus phosphatase, thereby controlling metabolic outcomes in specific tissues. Although it is known that PKA phosphorylation regulates  $\beta$  cell physiology, the role of such anchoring proteins is less clear (Faruque *et al*, 2009; Lester *et al*, 2001). For example, while disruption of the AKAP–PKA interaction has been reported to decrease insulin secretion (Lester *et al*, 1997), the specific regulatory protein that anchors PKA has yet to be identified.

In this study, Hinke *et al* (2012) sought to identify the specific anchoring protein that tethers PKA, and to elucidate its function. Two AKAP proteins, namely, AKAP150 and AKAP220 were first shortlisted from an overlay assay used to detect RII (regulatory subunit of PKA) binding proteins.

Subsequently, only AKAP150 was found to be important for nutrient-stimulated insulin secretion. Mice with a global knockout of AKAP150 (AKAP150KO) exhibited insulin secretory defects. AKAP150 binds to and regulates the phosphorylation-dependent VDCC. Thus, these AKAP150KO mice exhibited decreased basal  $\text{Ca}^{2+}$  current and glucose-stimulated  $\text{Ca}^{2+}$  influx in isolated  $\beta$  cells. One reason for the decrease in  $\text{Ca}^{2+}$  current could be attributed to a mislocation of its binding partner PP2B (discussed below). Glucose-stimulated



**Figure 1** AKAP150 tethered to PP2B at a seven-residue PlixIT motif mediates nutrient-stimulated insulin secretion and glucose homeostasis. Both global AKAP150KO and AKAP150 $\Delta$ PIX (AKAP150-PP2B binding abolished) mice exhibit insulin secretory defects, enhanced insulin sensitivity in skeletal muscle and overall improved glucose tolerance. This infers the importance of AKAP150-PP2B tethering for glucose homeostasis. 'Tick' indicates an increase or improvement. 'Cross' indicates a defect or impairment. 'Equal sign' indicates no change or no effect. Questions emerging from this study are highlighted in red.

cAMP fluctuation which is necessary for insulin secretion (Dyachok *et al.*, 2008) was also abolished in AKAP150KO mice. Therefore, AKAP150KO mice exhibit an insulin secretory defect due to multiple impairments including (1) decreased Ca<sup>2+</sup> influx and (2) defective cAMP production.

Surprisingly, while the authors report that global AKAP150KO mice secrete less insulin, the skeletal muscle, an insulin-sensitive peripheral tissue, exhibited improved blood glucose clearance likely due to increased phosphorylation of IRS-1 and Akt/PKB, and activation of AMPK that resulted in improved insulin sensitivity. On the other hand,  $\beta$  cell-specific AKAP150KO mice secrete less insulin upon glucose stimulation despite increased insulin content in the  $\beta$  cell that occurs as an adaptation to the impaired glucose tolerance. These mice clearly exhibited an impaired glucose tolerance that is due to defective insulin secretion because they do not exhibit an increase in insulin sensitivity. Together, these data indicate that the skeletal muscle selectively adapts to the global absence of AKAP150 to compensate for the decrease in insulin in the body. Notably, AKAP150 is also expressed in the liver but does not exhibit compensatory effects while AKAP150 is not expressed in the adipose tissue.

AKAP150 can anchor numerous enzymes with different metabolic activities. For instance, it binds PKA and PP2B, two enzymes with opposing functions, to the cell surface membrane. Hinke *et al.* (2012) further investigated the impact of disrupting specific binding partners of AKAP150. Unexpectedly, AKAP150 $\Delta$ 36 mice that lack residues 705–724 and therefore cannot bind PKA exclusively are effectively metabolically normal. It is thus surprising that the anchoring of PKA to AKAP150 is not necessary for proper insulin release although this interaction is important in other cellular systems (Lu *et al.*, 2008, 2011). AKAP150 $\Delta$ PIX mice lacking residues 655–661 and thus unable to tether to PP2B at a seven-residue P1xIxIT motif demonstrate the same metabolic phenotype as global AKAP150KO mice. This suggests that AKAP150 is critical for tethering PP2B, and that PP2B is the key molecule necessary for insulin secretion in  $\beta$  cells. PP2B is also a determinant of the metabolic phenotypes such as improved insulin sensitivity and glucose handling upon loss of anchorage of PP2B.

Overall, Hinke *et al.* (2012) used complementary *in vivo* approaches including animal physiology, and *in vitro* islet culture and live-cell imaging to demonstrate the importance

of the kinase/phosphatase anchoring protein AKAP150 in regulating nutrient-stimulated insulin secretion and modulating glucose homeostasis in mice (Figure 1). However, it is likely that there are AKAP150-independent mechanisms regulating insulin secretion since islets from AKAP150KO mice continued to respond to glucose stimulation and secrete insulin in both static and dynamic conditions, albeit at lower levels compared to wild-type mice. Importantly, the authors also identified AKAP150 tethering to PP2B as a key molecular event that regulates insulin secretion and glucose homeostasis (Figure 1). Thus, targeting the AKAP150–PP2B interface and the P1xIxIT motif could be therapeutically useful for increasing insulin sensitivity in patients with diabetes and metabolic syndromes. This could involve designing molecules or chemical compounds to bind the motif and block interaction between AKAP150 and PP2B. In parallel, the safety of systemic blockade of this interaction needs to be ascertained. Alternatively, skeletal muscle-specific AKAP150 $\Delta$ PIX mice could be generated to determine if the metabolic phenotype is similar to global AKAP150 $\Delta$ PIX mice. Should this be the case, then localized pharmacological blockade of AKAP150–PP2B interaction could be considered.

Several issues worth pursuing include (1) determining the differential adaptive response of the skeletal muscle versus the liver to alterations in insulin sensitivity in global AKAP150KO mice, (2) further investigating the functional relevance of AKAP150 tethering to PKA (by generating  $\beta$  cell-specific AKAP150 $\Delta$ 36 mice) as there is probably a biological rationale for their interaction, (3) exploring whether AKAP150-related or other proteins are expressed and act in different adipose tissue depots, (4) determining whether AKAP150 acts in a similar manner in ‘human’ skeletal muscle and  $\beta$  cells, and (5) examining if polymorphisms in human genes that encode AKAP150 tethering proteins are linked to disorders of glucose metabolism.

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## Conflict of interest

The authors declare that they have no conflict of interest.

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