RESEARCH HIGHLIGHTS

Highlights the most important articles across the spectrum of topics relevant to the field of diabetes management

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Adiponectin regulates skeletal muscle functions through PGC-1 α

Evaluation of: Iwabu M, Yamauchi T, Okada-Iwabu M *et al.*: Adiponectin and AdipoR1 regulate PGC-1a and mitochondria by Ca2⁺ and AMPK/SIRT1. *Nature* 464(7293), 1313–1319 (2010).

Adiponectin is an important adipokine that regulates systemic insulin sensitivity and energy homeostasis. In mammals, there are two specific adiponectin receptors, termed AdipoR1 and AdipoR2, which mediate the physiological functions of adiponectin. AdipoR1 is highly expressed in skeletal muscle. In a recent issue of Nature, Iwabu et al. reported how AdipoR1 functions in this metabolically critical tissue. By using AdipoR1 muscle-specific knockout mice and C2C12 myocytes, they identified two regulatory pathways that confer adiponectin effects in the skeletal muscle via peroxisome proliferator-activated receptor y coactivator-1 α (PGC-1 α) [1]. The first pathway is mediated by Ca2+-CaMMKβ-CaMK, which induces expression of the PGC-1 α gene upon stimulation by adiponectin. The second pathway controlled is through deacetylation and activation of PGC-1a by SIRT1, a critical NAD+-dependent deacetylase, which can be activated by the key energy sensor AMPK. Since PGC-1a strongly promotes mitochondrial DNA synthesis and fatty acid oxidation, and suppresses oxidative stress, adiponectin enhances mitochondrial biogenesis and functions. Remarkably, muscle-specific knockout mice mice develop insulin resistance and glucose intolerance, and manifest reduced exercise endurance. However, these metabolic phenotypes can be effectively reversed by exercise, suggesting that AdipoR1-independent pathway(s) are also very important in skeletal muscle physiology. Further investigation of those exercise-activated pathways will offer additional important drug targets for diabetes therapeutics. The conclusion of this study is limited by a lack of animal models that have enhanced functions of adiponectin/AdipoR1 and their corresponding metabolic phenotype.



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Financial & competing interests disclosure

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Pancreatic α cells can be converted to β cells

Evaluation of: Thorel F, Népote V, Avril I et al.: Conversion of adult pancreatic α -cells to β -cells after extreme β -cell loss. *Nature* 464(7292), 1149–1154 (2010).

In Type 1 diabetes, pancreatic β cells are largely destroyed by autoimmunity. Thus, regeneration or replenishment of β cells is

the key to curing Type 1 diabetes. Under experimental, surgical or chemical injury conditions, the lost β cells can be replaced by replication of the remaining β cells. In addition, ectopic expression of three key proendocrine factors – Ngn3, Pdx1 and MafA – can convert acinar cells to insulinproducing β cells. Although embryonic



 α cells can be induced to become β -cells by ectopic expression of Pax4, until now it was not known that adult α cells can be converted to β cells under extreme loss of β cells (>99%). In the April 2010 issue of Nature, Thorel et al. reported this new mechanism of β -cell regeneration [1]. By using transgenic mice that carry an insulin promoter and the diphtheria toxin receptor coding sequence, pancreatic β cells can be specifically ablated after diphtheria toxin administration. A total of 15 days after β -cell ablation, mice developed severe diabetes with as little as 0.4% of β cells left in the pancreas. Remarkably, with insulin treatment for as long as 5 months, β -cell mass increases gradually to 1.2 and 17% of the normal amount after 1 and 10 months, respectively. Using an *in vivo* tracing approach, the authors found that the increase of β -cell mass was not due to replication of the spared β cells. Instead, by using lineage tracing, they demonstrated that β -cell regeneration is largely derived from α cells through a bihormonal stage (glucagon-/insulinpositive coexpressing cells). Overall, this study convincingly demonstrates that pancreatic β cells can be regenerated from adult α cells; however, this phenomenon only occurs under extreme B-cell loss. Therefore, whether such a conversion can be induced in Type 1 diabetics requires further studies.

The PI3K regulatory subunits $p85\alpha$ and $p85\beta$ modulate endoplasmic reticulum stress through XBP-1

Evaluation of: Park SW, Zhou Y, Lee J et al.: The regulatory subunits of PI3K, p85a and p85b, interact with XBP-1 and increase its nuclear translocation. *Nat. Med.* 16(4), 429–437 (2010). Winnay JN, Boucher J, Mori MA, Ueki K, Kahn CR: A regulatory subunit of phosphoinositide 3-kinase increases the nuclear accumulation of X-box-binding protein-1 to modulate the unfolded protein response. *Nat. Med.* 16(4), 438–445 (2010).

Endoplasmic reticulum (ER) plays critical roles in the synthesis and assembly of secretory and membrane proteins, metabolism of lipids and sterols, and storage of calcium. When demands for protein synthesis and assembly are over the ER capacity, unfolded protein response is triggered. If the unfolded protein response cannot be resolved in a timely manner, it leads to ER stress, which has been implicated in obesity and diabetes. X-box-binding protein-1 (XBP-1) is one of the key modulators in ER stress; however, it is largely unknown how XBP-1 activity is regulated. In the April 2010 issue of Nature Medicine, two groups reported that the p85 regulatory subunits of phosphoinositide 3-kinase (PI3K) play a crucial role in modulation of nuclear localization and function of XBP-1. By using a bacterial two-hybrid system, affinity purification-tandem mass spectrometry and coimmunoprecipitation, Park et al. and Winnay et al. have clearly demonstrated that $p85\alpha$ and $p85\beta$ physically interact with XBP-1. Such interactions promote XBP-1 nuclear translocation. Nuclear accumulation of XBP-1 consistently is decreased in p85 $\alpha^{-/-}$ fibroblasts, or p85 α and p85 β double knock-down mouse embryonic fibroblasts. As a result, decreased nuclear XBP-1 leads to impaired ER stress response to tunicamycin, an inducer of unfolded protein response. Interestingly, Park et al. also found that insulin dissociates p85 α and p85 β heterodimers and promotes p85\alpha- and p85\beta-mediated XBP-1 nuclear translocation. This delicate regulation is impaired by insulin resistance in obese ob/ob mice. Hepatic deficiency of $p85\alpha$ causes elevated inflammation in the mouse liver. By contrast, overexpression of p85 α or p85 β in the liver improves hyperglycemia and glucose intolerance in the ob/ob mice. These studies reveal a critical link between the insulin signaling pathway and ER stress and provide a potential target for prevention and treatment of obesity and diabetes. Nevertheless, there are still some unanswered questions in this area. For example, why does genetic deletion of *p85* in mice increase insulin sensitivity if p85 is needed for modulation of ER stress? Can simply increasing nuclear XBP-1 protect from developing obesity or diabetes?