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IN BRIEF

METABOLISM

AMPKα2 mediates nicotine-induced insulin resistance

Cigarette smoking is known to be associated with insulin resistance and hyperinsulinaemia; however, the mechanisms underlying this link have been unclear. Now, a study published in *Nature Medicine* has established that AMP-activated protein kinase α2 (AMPKα2) is an essential mediator of the insulin resistance induced by cigarette smoking. Experiments in mice revealed that the nicotine in cigarette smoke activates AMPKα2 in adipocytes, which reduces levels of MAP kinase phosphatase-1 (MKP1). As a result, p38 mitogen-activated protein kinase and c-Jun N-terminal kinase are activated, which leads to the phosphorylation and subsequent degradation of insulin receptor substrate and consequently lipolysis is no longer inhibited by insulin. This mechanism leads to insulin resistance in spite of reduced adiposity in cigarette smokers.

Original article Wu, Y. *et al.* Activation of AMPKα2 in adipocytes is essential for nicotine-induced insulin resistance *in vivo*. *Nat. Med.* doi:10.1038/nm.3826

STEM CELLS

Treatment based on stem cells could be effective in T2DM

Type 2 diabetes mellitus (T2DM) can be ameliorated with a regimen based on stem cells, according to new findings in mice. The researchers began by feeding SCID-beige mice a high-fat diet to generate an immunodeficient model of T2DM. The mice received a transplant of macroencapsulated pancreatic progenitor cells, which matured into glucose-responsive insulin-secreting cells. After 24 weeks (during which the mice were on a high-fat diet), glucose tolerance was improved. However, the mice still had evidence of hyperglycaemia and obesity. Therefore, a second cohort was treated with an antidiabetic drug in addition to receiving the transplant. This combination therapy resulted in rapid improvements in body weight. Furthermore, mice that received sitagliptin or metformin following the transplant had improved hyperglycaemia after just 12 weeks.

Original article Briun, J. E. *et al.* Treating diet-induced diabetes and obesity with human embryonic stem cell-derived pancreatic progenitor cells and antidiabetic drugs. *Cell Rep.* doi:10.1016/j.stemcr.2015.02.011

PANCREATIC CANCER

Genetic changes underlying insulinomas revealed

Using exome and targeted sequencing, researchers have identified identical somatic mutations in the DNA-binding zinc finger of the transcription factor Yin Yang 1 (YY1) in 14 of 43 insulinomas. The 372T>R substitution resulted in mutated YY1 binding a different DNA motif to wild-type YY1, which considerably alters gene expression. In tumours that contained this mutated form of YY1, expression of *ADCY1* and *CACNA2D2* was increased. The products of these genes are involved in key pathways (cAMP and Ca^{2+} signalling pathways) that regulate insulin secretion. Increased expression of *ADCY1* and *CACNA2D2* leads to increased insulin secretion via activation of these signalling pathways. The 372T>R mutation was not found in pancreatic tumours that do not secrete insulin, suggesting that the mutation is specific to insulinomas.

Original article Cromer, M. K. *et al.* Neomorphic effects of recurrent somatic mutations in *Yin Yang 1* in insulin-producing adenomas. *Proc. Natl Acad. Sci. USA* doi:10.1073/pnas.1503696112