Nature Reviews Endocrinology **11**, 256 (2015); published online 10 March 2015;
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IN BRIEF

DIABETES

Proof of concept for a new type 2 diabetes mellitus therapy

Previous work in preclinical models has shown that the mitochondrial protonophore 2,4 dinitrophenol (DNP) is an effective treatment for nonalcoholic fatty liver disease, insulin resistance and obesity; however, the compound is too toxic for use in humans. Researchers have now developed a controlled-release oral formulation of DNP (CRMP) that produces mild mitochondrial uncoupling in the liver. Rats treated with CRMP had reduced incidences of hypertriglyceridaemia, insulin resistance, hepatic steatosis and diabetes mellitus, with no symptoms of systemic toxicity.

Original article Perry, R. J. *et al.* Controlled-release mitochondrial protonophore reverses diabetes and steatohepatitis in rats. *Science* doi:10.1126/science.aaa0672

BASIC RESEARCH

New insights into pancreatic β cell autophagy

Macroautophagy is suppressed in starved pancreatic β cells, in contrast to the majority of mammalian cells, according to new research. Upon starvation, nascent secretory insulin granules were degraded by lysosomes, a process that was controlled by protein kinase D. Furthermore, this degradation triggered recruitment of lysosomes and activation of the mammalian target of rapamycin (mTOR), which suppressed macroautophagy. The authors suggest that switching from macroautophagy to insulin granule degradation enables β cells to maintain low levels of insulin secretion during fasting.

Original article Goginashvili, A. *et al.* Insulin secretory granules control autophagy in pancreatic β cells. *Science* **347**, 878–882 (2015)

BONE

Mechanisms in osteoclast differentiation revealed

A new study published in *Nature Medicine* has shown that DNA methyltransferase 3a (Dnmt3a) links a shift towards oxidative metabolic processes with osteoclast differentiation. RANKL was found to be essential for osteoclastogenesis and induced the metabolic shift towards utilizing oxidative pathways (which is associated with increased production of S-adenosylmethionine [SAM]). SAM-mediated DNA methylation by Dnmt3a regulated osteoclastogenesis via epigenetic repression of anti-osteoclastogenic genes.

Original article Nishikawa, K. *et al.* DNA methyltransferase 3a regulates osteoclast differentiation by coupling to an S-adenosylmethionine-producing metabolic pathway. *Nat. Med.* doi:10.1038/nm.3774

LIPIDS

Effects of IL-1 inhibition on cardiometabolic risk

A new study has revealed that long-term inhibition of IL-1 α and IL-1 β increases the risk of developing cardiometabolic diseases, which could be the result of increased levels of proatherogenic lipids. The researchers created a genetic risk score that combined the effects of alleles of two common variants located upstream of the gene that encodes the IL-1 receptor antagonist (IL-1RA) and then tested its relationship with rheumatoid arthritis and four cardiometabolic diseases. Participants with the highest number of alleles that increased levels of IL-1RA had the greatest risk of cardiometabolic disease.

Original article The Interleukin 1 Genetics Consortium. Cardiometabolic effects of genetic upregulation of the interleukin 1 receptor antagonist: a Mendelian randomisation analysis. *Lancet Diabetes Endocrinol.* doi:10.1016/S2213-8587(15)00034-0