IN BRIEF

AGEING

Reversing inflammaging

Aberrant activation of the NLRP3 inflammasome can result in pathological inflammation and has been associated with ageing-associated diseases. Here, He et al. report that NLRP3 is modified by acetylation in macrophages that facilitates the assembly and activation of the NLRP3 inflammasome. Sirtuin 2, an NAD^+-dependent deacetylase and metabolic sensor, was found to mediate NLRP3 deacetylation and repress NLRP3 inflammasome activity. In a novel cell-based system and mouse models, SIRT2 overexpression or NLRP3 deacetylation reversed ageing-associated inflammation and insulin resistance.

ORIGINAL ARTICLE He, M. et al. An acetylation switch of the NLRP3 inflammasome regulates aging-associated chronic inflammation and insulin resistance. *Cell Metab.* **31**, 1–12 (2020)

CANCER

Epigenetic therapy prevents AML

Eliminating preleukaemic cells with targeted therapy is an attractive approach for disease prevention. To investigate this concept, Uckelmann et al. studied *Npm1c/Dnmt3a* mutant mice and cell lines, which are predisposed to develop acute myeloid leukaemia (AML). Mutant *NPM1c* induced self-renewal properties in myeloid progenitor cells, which act as leukaemia-initiating cells. In mice, oral administration of the small molecule VTP-50469, which targets the interaction between the histone methyltransferase MLL1 and adaptor protein Menin, eradicated preleukaemic *Npm1c*-mutant myeloid progenitor cells, prevented AML development and extended survival.

ORIGINAL ARTICLE Uckelmann, H. J. et al. Therapeutic targeting of preleukemia cells in a mouse model of *NPM1* mutant acute myeloid leukemia. *Science* **367**, 586–590 (2020)

METABOLIC DISEASE

GPCR agonist targets obesity and diabetes

Postmenopausal women are particularly susceptible to weight gain and associated metabolic dysfunction due to the loss of ovarian oestrodiol (E2). The metabolic effects of E2 have been largely attributed to the nuclear oestrogen receptor (ER) α and ERβ, and the role of the G-protein coupled ER (GPER) remains unclear. Now, Sharma et al. report that the small molecule GPER agonist G-1 decreases body weight, fat mass and inflammation, while increasing energy expenditure and improving glucose homeostasis in ovariectomized female mice. In addition, G-1 prevented further weight gain in diet-induced obese male mice and improved glucose tolerance.

ORIGINAL ARTICLE Sharma, G. et al. Preclinical efficacy of the GPER-selective agonist G-1 in mouse models of obesity and diabetes. *Sci. Transl Med.* **12**, eaau5956 (2020)

PARKINSON DISEASE

Reducing α–synuclein accumulation

Most cases of young-onset Parkinson disease (YOPD) are not associated with known genetic mutations. To investigate YOPD pathogenesis, Laperle et al. generated iPSC lines from control individuals and patients with YOPD with no known mutations and differentiated them to midbrain dopaminergic (mDA) neural cultures. Increased accumulation of soluble α-synuclein protein, elevated phosphorylated PKCα and dysregulated lysosomal biogenesis and function were observed in YOPD mDA cultures. Striatal injection of mice with the phorbol ester PEP005 (FDA-approved for actinic keratosis) decreased α-synuclein accumulation and p-PKCα levels, while enhancing levels of tyrosine hydroxylase, a dopaminergic neuron marker.

ORIGINAL ARTICLE Laperle, A. H. et al. iPSC modeling of young-onset Parkinson's disease reveals a molecular signature of disease and novel therapeutic candidates. *Nat. Med.* https://doi.org/10.1038/s41591-019-0739-1 (2020)

CARDIOVASCULAR DISEASE

Dual-acting peptide tackles triglycerides

Hypertriglyceridaemia (HTG) is a causal risk factor for cardiovascular disease, and in patients with familial hyperchylomicronaemia (FC), HTG often leads to acute pancreatitis. Writing in *Science Translational Medicine*, Wolska, Remaley, Devalaraja and colleagues report the development of a dual apolipoprotein C-II mimetic–apolipoprotein C-III antagonist peptide, which rapidly lowers plasma triglyceride (TG) levels in mouse models.

TGs are transported by lipoproteins and hydrolysed by the enzyme lipoprotein lipase (LPL), to produce free fatty acids for energy or storage. Apolipoproteins C-II and C-III regulate lipoprotein metabolism, respectively activating and inhibiting LPL. ApoC-III also exhibits LPL-independent effects, blocking hepatic uptake of TG-rich lipoproteins.

Previously, the authors developed an apoC-II mimetic peptide that activates LPL to decrease serum TG levels. This mimetic peptide contained the C-terminal helix of native apoC-II (responsible for LPL activation), but the N-terminal helix (which mediates binding to lipoproteins) was replaced by a synthetic helical peptide, 18A, designed to bind lipoproteins more tightly. However, as this 18A helix has no homology to any known human protein, this raised the risk of immunogenicity.

Building on this, the authors have now used all-atom molecular dynamics simulations, structural prediction programmes and biophysical techniques to develop a new TG-lowering peptide, D6PV, in which the 18A helix is replaced with a modified central region of apoC-II, while the C-terminal LPL activation domain is retained.

Ex vivo, in apoC-II-deficient human plasma, D6PV was more potent than full-length apoC-II in activating LPL. Furthermore, D6PV increased LPL-dependent lipolysis in pooled plasma from patients with moderate HTG.

In an apoC-II-deficient mouse model of HTG, intraperitoneal injection of D6PV rapidly decreased plasma TG levels, by about 70% after 1 hour and 85% after 3 hours. D6PV also reduced TG levels after a bolus injection of Intralipid (an artificial TG emulsion), in both apoC-II-deficient and wild-type mice.

Credit: Chris Ryan/Stone/Getty Images Plus

Next, the authors investigated whether the effects of D6PV might also be mediated by apoC-III antagonism. D6PV completely prevented apoC-III-mediated inhibition of TG lipolysis ex vivo in human HTG plasma. Furthermore, treatment of human *APOC3*-transgenic (Tg) mice with D6PV decreased total plasma apoC-III by 85%, and reduced plasma TG levels by 80% within just 3 hours.

Consistent with the known LPL-independent effects of apoC-III, D6PV also lowered TG levels by 50% in Lpl knockout mice.

Notably, D6PV exhibited favourable subcutaneous bioavailability and a long terminal half-life in nonhuman primates.

The authors hope to develop this dual-acting apoC-II mimetic and apoC-III antagonist initially for in-hospital care of FC-associated acute pancreatitis and subsequently for HTG and cardiovascular disease. Based on the half-life they have observed so far, they believe this could be developed as a once-a-week therapy.

Sarah Crunkhorn

ORIGINAL ARTICLE Wolska, A. et al. A dual apolipoprotein C-II mimetic–apolipoprotein C-III antagonist peptide lowers plasma triglycerides. *Sci. Transl Med.* **12**, eaaw7905 (2020)