IN BRIEF

DIABETES

The CREB coactivator TORC2 is a key regulator of fasting glucose metabolism.

Seung-Hoi, K. *et al*. *Nature* 7 Sep 2005 (doi:10.1038/nature03967)

Glucose homeostasis is regulated both systemically by hormones and at the cellular level by ATP status, but the exact way in which these pathways converge is unknown. Seung-Hoi *et al.* show that the coactivator transducer of regulated CREB activity-2 (TORC2) inhibits gluconeogenesis, and suggest that blocking the phosphorylation and nuclear translocation of TORC2 might be a potential therapeutic strategy against diabetes.

AGEING

Suppression of aging in mice by the hormone Klotho.

Kurosu, H. *et al. Science* **309**, 1829–1833 (2005)

A defect in the *Klotho* gene was recently shown to accelerate ageing in mice, but the underlying mechanism remained unknown. Kurosu *et al.* show that Klotho is a circulating peptide hormone and that its overexpression blocks insulin action possibly by suppressing phosphorylation of insulin and insulin-like growth factor-1 (IGF1) receptors. As inhibition of insulin signalling is known to be associated with life-span extension, it seems that Klotho could function as an anti-ageing hormone in mammals.

BIOTECHNOLOGY

Combinatorial polyketide biosynthesis by *de novo* design and rearrangement of modular polyketide synthase genes.

Menzella, H. G. *et al. Nature Biotechnol.* **23**, 1171–1176 (2005)

The synthesis of 'unnatural' natural products by altering or replacing individual polyketide synthase (PKS) gene modules is laborious and time-consuming. Menzella *et al.* present a combinatorial method for producing polyketides in which the facile synthesis and interchange of PKS modules is facilitated by use of a repeated set of flanking restriction sites. They used the method to synthesize 14 modules from eight PKS gene clusters and associated them in 154 bimodular combinations. Almost half of the combinations successfully mediated biosynthesis of a polyketide in *Escherichia coli*.

GENE THERAPY

Tumour-targeted, systemic delivery of therapeutic viral vectors using hitchhiking on antigen-specific T cells.

Cole, C. J. *et al*. *Nature Med.* 18 Sep 2005 (doi:10.1038/nm1297)

Systemic delivery of genes to tumours in immunocompetent individuals is hindered by non-specificity, vector neutralization and an inability to target the virus directly to tumours. The authors of this paper exploited the fact that T cells circulate freely and accumulate at sites where specific antigens are expressed. Adoptive transfer of T cells loaded with virus was shown to cure established metastatic disease in mice, whereas T cells alone had no effect. Adsorption to cell carriers might therefore enable systemic delivery of viral vectors for a variety of indications that would benefit from gene therapy.

INFECTIOUS DISEASE

Emptying reservoirs of latent HIV-1

Highly active antiretroviral therapy (HAART) has considerably reduced the morbidity and mortality associated with human immunodeficiency virus type-1 (HIV-1) infection, but fails to eradicate the virus. By targeting an enzyme that is important for the persistent infection of HIV-1, Lehrman and colleagues have identified a new strategy that provides encouragement that a cure for this infection might be found, which they report in the *Lancet*.

HAART regimes — which are based on combinations of drugs that target different steps in the viral life cycle — can potently suppress viral replication. However, the persistence of replication-competent provirus in resting CD4$^+$ T cells provides a source for renewed viral replication following cessation of therapy. Attempts have been made to eliminate this reservoir of 'latently infected' cells by activating them with interleukin-2 (IL-2) in patients receiving HAART, but although reductions in the number of latently infected cells were achieved, the reservoirs were refilled after treatment was stopped. Furthermore, the widespread T-cell activation caused by IL-2 could increase the risk of negative treatment outcomes.

To circumvent this issue, Lehrman and colleagues investigated an alternative strategy based on evidence that agents that selectively induce the expression of latent proviral genes might allow clearance of HIV-1 from resting cells, without the nonspecific activation of T cells. One such agent, the well-known anticonvulsant valproic acid (VA), inhibits histone deacetylase-1 (HDAC1), an enzyme involved in chromatin remodelling that is important for the maintenance of the latency of integrated HIV-1, and has been shown to induce HIV expression in resting CD4$^+$ T cells *ex vivo*.

To assess the efficacy of VA to deplete HIV-1 infection of resting CD4$^+$ T cells *in vivo*, the authors conducted a study involving four adult volunteers infected with HIV-1 who were being treated with HAART and had undetectable levels of virus in their blood (viraemia) for more than two years. To prevent the spread of infection during treatment with VA, the HAART regimes of the patients were intensified with the fusion-entry inhibitor enfuvirtide for 4–6 weeks before VA was added to the intensified HAART regime.

After 16–18 weeks of treatment with VA and the intensified HAART regime there was a significant (average ~75%) drop in the infected resting CD4$^+$ cell count in three patients, indicating that targeting drugs at molecules required for maintaining the latency of HIV-1 might be a viable strategy for eliminating HIV-1 infection from this persistent reservoir. Nevertheless, as the authors point out, their pilot study is limited and leaves many questions unanswered, such as the individual therapeutic effects of VA and enfuvirtide, which is the focus of an ongoing study. In addition, despite the administration of enfuvirtide, two patients maintained persistent, low-level viraemia, and it is unclear whether this viraemia originated from resting cells or whether this shows that the therapy is not reaching all replicating compartments. Further investigations to clarify these issues will be needed to strengthen the hope that HIV-1 could one day be eradicated.

Samantha Barton

References and links

ORIGINAL RESEARCH PAPER Lehrman, G. *et al.* Depletion of latent HIV-1 infection *in vivo*: a proof-of-concept study. *Lancet* **366**, 549–555 (2005)