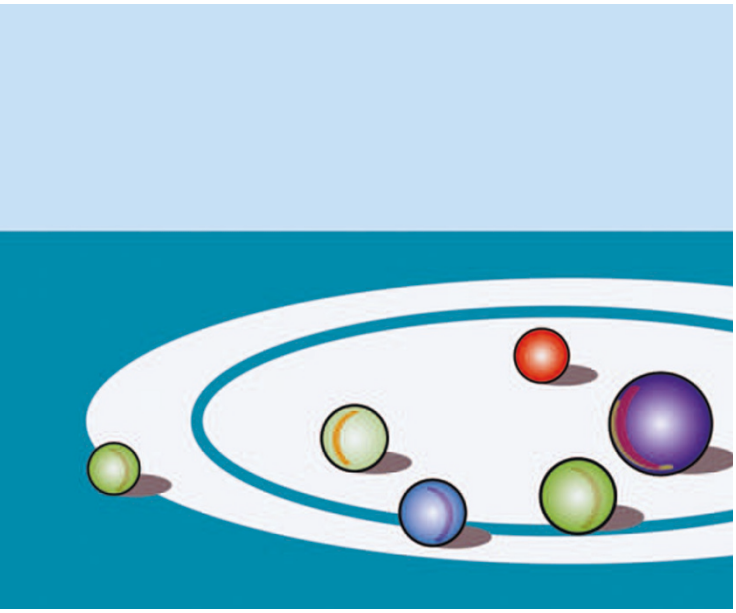
ANTIVIRAL DRUGS

Strategic targeting of the host



Current drugs against HIV type-1 (HIV-1) target a variety of viral proteins. Unfortunately, the genes encoding these proteins mutate rapidly, leading to drug-resistant viral variants arising during therapy and limiting the usefulness of a particular drug. An alternative approach is to inhibit non-essential host-cell proteins that are required for viral replication. In the May issue of *Nature Cell Biology*, Mark O'Connor and colleagues have identified a host protein, the ataxia-telangiectasia-mutated (ATM) kinase, as a new target for the development of antiretroviral therapies to treat HIV-1. This new research could allow the development of a new therapy that is effective against all HIV strains, substantially reducing the likelihood of drug resistance.

Mammalian cells respond to DNA damage by activating a number of response pathways to maintain genomic integrity. Integration into the host DNA is an essential step in the retroviral life cycle. A viral integrase is necessary for integration of viral product into the host genome, which cleaves the host DNA and then utilizes the host repair response in order to complete the integration process. Retroviral infections, such as those caused by HIV-1, activate a poorly understood repair pathway.

Evidence exists that the Ku-dependent non-homologous end-joining (NHEJ) pathway is required to support efficient retroviral infection. There is also some evidence of involvement of ATM kinase and a related protein, ataxia Rad-related (ATR), in this pathway. Both ATM and ATR are phosphatidyl-3-OH-kinase-like serine/threonine kinases that regulate cellular responses to DNA damage by controlling cell-cycle arrest and DNA-repair pathways. ATM is mutated in a rare genetic disease, A-T, that can lead to cancer, particularly leukaemia and lymphoma, and premature ageing.

The authors used genetic and pharmacological approaches to show that ATM has an important role in retroviral replication. They showed that the activity of HIV-1 integrase stimulates an ATM-dependent

DIABETES AND OBESITY

Battling the bulge with AGF

Creating a conventional knockout mouse can be a bit of a gamble — will there be a useful phenotype, or will it be embryonically lethal? Oike *et al.* have hit the jackpot in this respect by knocking out the gene encoding angiopoietin-related growth factor (AGF), which helped them establish that AGF, a circulating angiogenic orphan peptide secreted by the liver, counteracts obesity and related insulin resistance.

Although the AGF knockout proved to be 80% embryonically lethal due to cardiovascular defects, the surviving pups grew — too well. In fact, by 24 weeks of age, AGF-knockout mice (*Angptl6*$^{-/-}$) weighed approximately twice as much as wild-type mice. This increase was due to grossly enlarged adipocytes in their white adipose tissue and large amounts of lipid deposition in liver, skeletal muscle and brown adipose tissue. Conversely, mice transgenic for AGF were smaller than their wild-type counterparts, and managed to keep their shape even on a high-fat diet. Last but not least, wild-type mice with increased weight due to a high-fat diet lost significant amounts of weight when treated with an adenovirus encoding mouse AGF.

None of these effects could be attributed to differences in food intake. However, metabolic analysis of *Angptl6*$^{-/-}$ mice revealed a decrease in body temperature and whole-body oxygen consumption rates, indicating that lower energy expenditure due to reduced adaptive thermogenesis (heat production in response to diet or environment temperature) was the underlying cause for weight gain.

It was previously known that the brown adipose tissue and skeletal muscle regulate adaptive thermogenesis, mediated by peroxisome proliferator-activated receptor-α (PPARα), PPARδ, PPARγ and the PPARγ co-activator 1β (PGC-1β) and PGC-1α, in response to energy overload. All these factors were affected in the knockout mice. Furthermore, it was known that p38 mitogen-activated protein kinase (MAPK) enhances the stabilization and activation of the PGC-1 protein, and the present study established that AGF can activate p38 in muscle. The authors therefore propose that AGF stimulates fat burning in peripheral tissues through the p38 MAPK pathway and induces downstream effects on respiration and gene expression linked to mitochondrial uncoupling and energy expenditure. Furthermore, the angiogenic effects of AGF might antagonize obesity by facilitating energy expenditure through an increased number of microvessels, as observed in AGF transgenic mice.

Finally, the knockout mice were not only overweight, but were also affected by obesity-related severe hyperinsulinaemia, indicating insulin resistance. This condition, inducible by a high-fat diet in wild-type mice, could be reversed by adenoviral expression of AGF.

These studies clearly establish AGF as a potential target for developing pharmacological interventions to counteract obesity and related insulin resistance — the race will be on to identify the receptor for AGF and agonists that can mimic its effects.

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References and links

ORIGINAL RESEARCH PAPER Oike, Y. *et al.* Angiopoeitin-related growth factor antagonizes obesity and insulin resistance. *Nature Med.* **11**, 400–408 (2005)