METABOLISM

Targeting a fat-accumulation gene

An enzyme that links two metabolic hubs has been found to be upregulated in the fat cells of overweight mice. Inhibition of the gene encoding this enzyme protects mice from diet-induced obesity. SEE LETTER P.258

CHARLES BRENNER

In recent decades, increased food availability has dramatically altered many people's diets. Each year, billions of tonnes of grain are fed to livestock or converted to ingredients for food. Consumption of the resulting meat, fat and processed carbohydrate by humans, accompanied by a decline in their energy expenditure, has created a nutritional overload that has resulted in increased adiposity and incidence of the resulting diseases worldwide. On page 258 of this issue, Kraus *et al.*[1] identify *Nnmt*, which encodes the enzyme nicotinamide *N*-methyltransferase (NNMT), as a gene whose activity is ramped up by nutritional overload, and they find that *Nnmt* is required for the accumulation of fat.

Fat storage is essential for animal development and survival, particularly in times of macronutrient (protein, fat and carbohydrate) limitation, which almost certainly drove 500 million years of animal evolution[2]. The insulin system allows animals to convert excess carbohydrate to fat — the most energy-rich component of an animal's body mass — in part by instructing adipose tissue to take up glucose from the bloodstream.

The ability to increase body mass on a high-fat diet is a trait that has increased animal survival throughout evolution. Only in circumstances of chronic over-nutrition does our ability to convert sugar to fat and to store excess fat predispose us to disease rather than to resistance to famine.

When the gene encoding the insulin-sensitive glucose-transporter protein GLUT4 is deleted from a mouse's fat cells, the animal develops insulin resistance in several tissues and cannot effectively clear blood glucose[3]. Because insulin stimulates GLUT4 activity and because GLUT4 is also required for insulin sensitivity, alteration of the GLUT4–insulin circuit has powerful effects on metabolism and can lead to diabetes. Components of this circuit could therefore emerge as drug targets to mitigate the effects of over-nutrition on human health.

Mice that lack or overexpress GLUT4 in fat are used as models for people sensitized to or resistant to diabetes, respectively[4]. To identify molecules involved in the development of diabetes, Kraus and colleagues used these animals to find genes that are highly expressed when GLUT4 is deleted and that are repressed when GLUT4 is overexpressed. *Nnmt* was the most inversely correlated gene. Indeed, overexpression of *Nnmt* has been shown[5] to correlate with body mass index in a human group susceptible to diabetes.

Although it would be unsurprising if *Nnmt* expression were a consequence of chronic over-nutrition, rather than a cause of weight gain, Kraus *et al.* found that *Nnmt* expression in adipose tissue is correlated not only with the percentage of fat in 20 mouse strains, but also with sensitivity to diet-induced obesity in 25 strains. This qualified *Nnmt* as a candidate mediator of weight gain.

Kraus and colleagues developed a drug to inhibit the expression of *Nnmt* in a mouse strain prone to weight gain on a high-fat diet. This drug reduced *Nnmt* expression in fat and liver, but not elsewhere. Remarkably, the authors found that treated mice became resistant to diet-induced obesity. It is important to note, however, that mice have a much more rapid metabolism than humans, and that the trial was preventive in nature: the treatment enabled lean mice to resist weight gain and maintain insulin sensitivity on a high-fat diet, but obese mice were not examined for loss of fat with treatment.

What does NNMT do, and how does its inhibition reduce the incorporation of dietary fat into adipose tissue? Kraus and co-workers observed that drug-treated mice on a high-fat diet did not eat less, move more, produce more heat or excrete more fat than control animals. Instead, the animals' oxygen consumption was increased, suggestive of increased levels of fat oxidation (the process by which fat is converted to energy), and they exhibited increased activity of pathways that impair the ability of fat cells to store fat.

NNMT is involved in regulation of the cofactor nicotinamide adenine dinucleotide (NAD), a molecule needed in reactions that convert macronutrients into energy and that also acts as a consumed substrate of enzymes that perform many regulatory roles[6]. NAD consumption produces nicotinamide, a precursor of NAD; this creates a demand for nicotinamide to be resynthesized to NAD — a process termed salvage. NNMT attaches a methyl group to nicotinamide, preventing salvage[7]. The methyl group comes from a second cofactor, *S*-adenosine methionine (SAM), which also participates in diverse gene-regulatory and metabolic processes[8]. The researchers found that expression of *Nnmt* tended to lower NAD and SAM levels in fat, suggesting

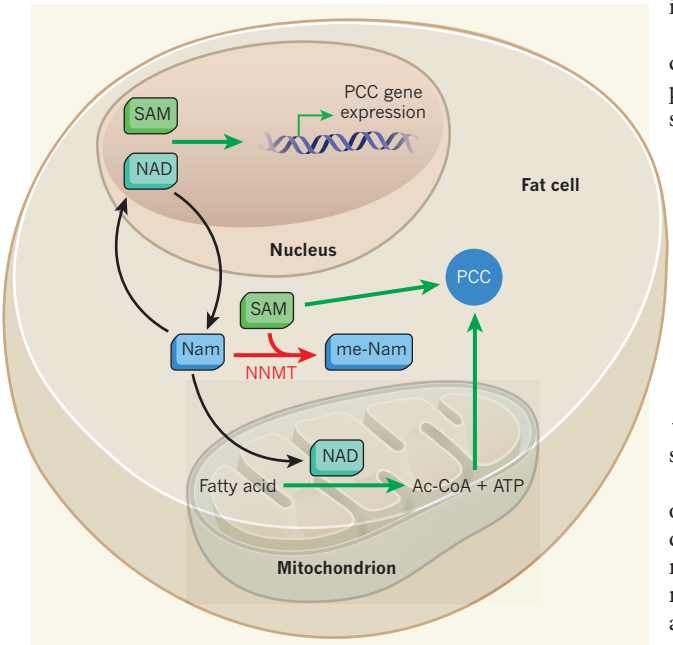

Figure 1 | Accelerating fat-cell metabolism. Kraus *et al.*[1] report that the enzyme nicotinamide *N*-methyltransferase (NNMT) is upregulated when fat levels increase, and that its inhibition prevents diet-induced obesity in mice. These effects are mediated by two cofactor molecules: nicotinamide adenine dinucleotide (NAD) and *S*-adenosine methionine (SAM). NAD consumption by enzymes produces nicotinamide (Nam), which can be resynthesized to NAD (salvage). However, NNMT adds a methyl group from SAM to nicotinamide (forming me-Nam), which prevents NAD salvage. NNMT inhibition therefore elevates levels of NAD and SAM, resulting in increased nuclear gene expression and cytoplasmic activity of the SAM-dependent polyamine catabolic cycle (PCC). PCC activation requires NAD-dependent fatty-acid oxidation and subsequent production of the molecules acetyl-CoA (Ac-CoA) and ATP in the mitochondrial cellular compartment. Pathways turned on by fat accumulation are shown in red. Those activated by NNMT inhibition are shown in green.

that either or both cofactor-dependent hubs are functionally modulated by NNMT in fat cells (Fig. 1).

Although methylated nicotinamide is abundant in obesity and correlates with *Nnmt* expression, it does not seem to promote weight gain per se. In fact, Kraus and colleagues found that, at high doses, methylated nicotinamide inhibits NNMT, with activities similar to those of their *Nnmt*-targeting drug. The researchers showed that changes in metabolism in the drug-treated mice arose from NNMT inhibition through enhanced NAD- and SAM-dependent gene expression and enzyme activities. This is because, by inhibiting NNMT, there is more nicotinamide salvage to NAD, and SAM levels are preserved. Both cofactors regulate the state of histones, proteins in the nucleus that are responsible for chromosome packaging and tuning gene expression, and this may account for the gene-expression changes that the authors observed in drug-treated mice.

In the NNMT-inhibited mouse, more fat is oxidized and less is stored. NAD has two potential roles in this process. First, fatty-acid oxidation (which occurs in an energy-generating organelle, the mitochondrion) requires NAD. In adipose tissue, poor NAD salvage might directly retard this process, making more fat available for storage. Second, fatty-acid oxidation proceeds through an intermediate molecule, acetyl-CoA, and conditions of nutritional overload lead to build-up of this intermediate. This results in inhibition of mitochondrial enzymes, owing to transfer of acetyl groups from acetyl-CoA to the enzymes[2]. Although these modifications make mitochondria sluggish, it has been argued[2] that the ability to maximize weight gain in episodes of over-nutrition has been selected for throughout animal evolution. Because removal of mitochondrial acetyl groups depends on NAD, NNMT inhibition might reactivate mitochondrial-enzyme activities by increasing deacetylation, thereby improving oxygen consumption.

Although the NAD-dependent effects of NNMT inhibition in mitochondria remain largely unknown, Kraus *et al.* showed that, in the cytoplasm, the polyamine catabolic cycle, which is SAM-dependent, is accelerated by NNMT inhibition. This cycle drives oxygen consumption, because it uses up acetyl-CoA and the nucleotide ATP, thereby demanding that mitchondria oxidize fuels to produce more of these molecules[9,10]. A candidate activator of the cycle was unlikely to be identified by conventional means. Inhibition of NNMT seems to have done the trick.

The contributions of NAD- and SAM-dependent processes to adipocyte metabolism require further quantitative investigation. But there is little doubt that NNMT, an enzyme that is not only upregulated in obesity, but is also required for weight gain, will be tested as a target for weight loss. ■

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QUANTUM PHYSICS

A strong hybrid couple

A single atom in an optical cavity is shown to interact strongly with an incoming photon and to switch the photon's state. This finding opens up a path towards optical quantum computation and quantum networks. SEE LETTERS P.237 & P.241

LUMING DUAN

When two torch beams cross, they go through each other without affecting one another. This means that the fundamental particles of light, photons, do not typically interact with each other, or with matter, unless designed to do so. Photons and matter interact when strong light beams propagate through a dense atomic medium, but this interaction is negligible for weak light pulses in a system of only a few atoms. In a future Internet based on the principles of quantum mechanics[1], which promises enhanced security and computational power, information will be carried by single photons, and the quantum state of those photons will need to be manipulated through their interaction with atoms. In this issue, Reiserer *et al.*[2] (page 237) and Tiecke *et al.*[3] (page 241) report independent experiments that bring this goal a step closer. The researchers have designed systems in which a single atom switches the state of a single photon contained in a faint light pulse.

The experiments represent the culmination of decades of research into atom–photon coupling in an optical cavity[1]. The Fabry–Perót version of an optical cavity consists of two highly reflective mirrors between which a photon bounces many times. This arrangement allows an atom trapped inside the cavity to be strongly coupled with the photon. Reiserer *et al.* used a Fabry–Perót cavity in which one of the mirrors has a significantly higher reflectivity, and thus lower transmissivity, than the other, so that a photon enters and leaves the cavity mainly through the lower-reflectivity mirror. Tiecke *et al.* designed a special type of cavity known as a photonic crystal cavity, which has the same function as Reiserer and colleagues' Fabry–Perót cavity but has a tiny

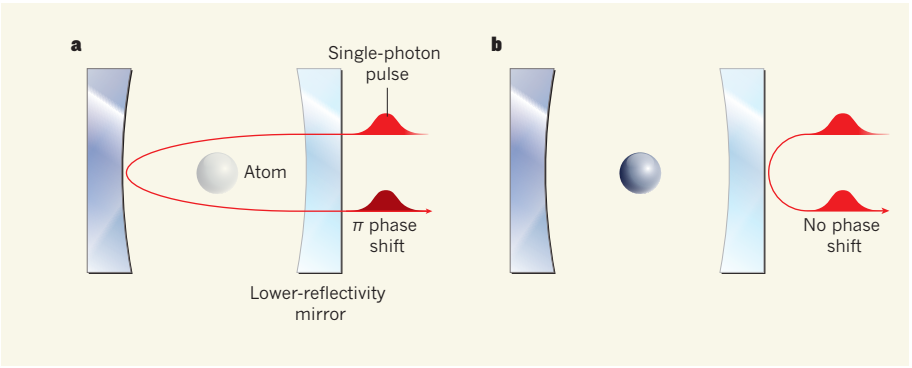

Figure 1 | An optical switch. Reiserer *et al.*[2] and Tiecke *et al.*[3] have designed systems in which a single atom trapped in an optical cavity, here formed by an arrangement of two mirrors of different reflectivity, switches the state of a photon in an incoming light pulse. **a**, If the atom is in a quantum state that does not couple with the cavity, equivalent to there being no atom in the device, a single-photon pulse resonant with one of the cavity's optical modes of oscillation will enter the cavity through the lower-reflectivity mirror and leave it with a phase shift of π radians, illustrated by a darker red than that of the original pulse. **b**, If the atom is in a state that couples with the cavity, it will shift the frequency of the cavity's mode and the pulse will now be off-resonant with it. Therefore, the pulse will not enter the cavity and will bounce back with no phase shift.