METABOLISM

A is for adipokine

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Adipokines are hormones that signal changes in fatty-tissue mass and energy status so as to control fuel usage. A fat-derived adipokine that binds to vitamin A provides a new link between obesity and insulin resistance.

The worldwide epidemic of obesity has been accompanied by a surge in the incidence of diabetes[1]. Normally, control of blood glucose levels depends on the efficient action of insulin, which stimulates uptake of glucose from the blood and slows its output from the liver. In both obesity and diabetes, target tissues such as muscle and liver fail to adjust glucose metabolism appropriately in response to insulin. The onset of this 'insulin-resistant' condition is intimately associated with weight gain[1], suggesting that increased fatty adipose tissue generates a signal (or signals) that interferes with the action of insulin. Consistent with this notion, in this issue Yang *et al.* (page 356)[2] report that a factor derived from fat cells, called retinol binding protein-4 (RBP4), can impair insulin sensitivity throughout the body. RBP4 joins a growing list of fat-derived peptides that modulate glucose homeostasis.

The significance of adipose tissue as an endocrine organ first surfaced in 1995 with the ground-breaking discovery of leptin[3]. This fat-derived hormone controls body weight by regulating both feeding behaviour and energy expenditure. Ensuing research uncovered a whole family of adipose-derived 'adipokines' (for example, adiponectin, TNF-α, resistin) that signal changes in the mass of adipose tissue and energy status to other organs that control fuel usage[4]. From a clinical viewpoint, each of these secreted peptides represents a possible drug target with the potential to uncouple insulin resistance from obesity.

Yang and colleagues' findings[2] may provide the solution to a long-standing paradox in diabetes research. The expression of GLUT4, an insulin-regulated glucose transporter, is greatly reduced in the fat cells (adipocytes) but not in the muscle cells of rodents and humans that are obese and have insulin resistance[5]. This is surprising given the predominant role of muscle in the disposal of glucose. The first clues to solving this puzzle emerged from studies in which the expression of GLUT4 was either ablated or increased specifically in adipose tissue[6,7]. Mice lacking GLUT4 in their adipose tissue are prone to diabetes[8], whereas those with overexpression of GLUT4 exhibit increased efficiency of glucose clearance[6]. These changes in whole-body insulin action occur through alterations in the sensitivity of muscle and liver cells to insulin, thereby implicating an 'adipocrine' substance that allows fat to communicate with peripheral tissues. However, a survey of the known adipose-derived factors, including leptin, free fatty acids and TNF-α, failed to reveal a candidate that responded to the GLUT4 manipulations in a convincing manner.

Now Yang *et al.* have used DNA microarrays to search for other adipokines. They identified RBP4 as a secreted protein that is regulated

PARASITOLOGY

Triple genome triumph

There is welcome news for scientists working on sleeping sickness, Chagas' disease and visceral leishmaniasis: the genomes of the three trypanosome parasites responsible for these devastating illnesses have now been cracked. The sequences from *Trypanosoma brucei*, *Trypanosoma cruzi* and *Leishmania major* were published in last week's *Science* by an array of international research teams (*Science* **309,** 416–422, 409–415, 436–442; 2005).

In the terminology of global public health, these diseases don't even fall into the category of 'neglected diseases' such as malaria and tuberculosis. Rather, they are classed as 'most neglected diseases' — which nonetheless kill millions. But those affected have little means of paying for treatment, making drug development unprofitable. Consequently, there are no vaccines, and medicines are few, expensive and usually toxic.

Treatment of sleeping sickness, for example, still relies on melarsoprol, a 50-year-old drug that is ineffective in a third of patients and kills 5% of those who take it. The high rate of fatal reactions is accepted because the disease is otherwise lethal. New therapies are clearly needed, and the availability of the parasite genomes is a step towards finding drug targets and vaccine candidates.

The three parasites share around 6,200 'core' genes, so the proteins these encode might provide targets for drugs that are effective against all three. The parasites make a large and diverse set of kinase and phosphatase enzymes. This means that there could well be regulatory and other processes used by the organisms that could be vulnerable to disruption by drugs.

Many species-specific genes were also identified in the genome sequences, providing potential species- and stage-specific targets. Although the three parasites share many subcellular structures, such as kinetoplasts and glycosomes, the organisms are very different. They are spread by different insects, attack different tissues and cause different pathologies. The specimens of *L. major* pictured are in the form that is transmitted to humans by sand flies.

PHOTOTAKE INC./ALAMY

Each parasite also has its own mechanism for evading the human immune system: *T. brucei* does not enter its victim's cells, and evades the immune system by constantly changing its main surface proteins; *T. cruzi* holes up inside cells, but uses a similar strategy to hide from the immune system; and *L. major* infects certain immune cells and interferes with their function.

Producing effective treatments against these parasites will be a lengthy process, but initial research is already under way by not-for-profit drugs groups such as the Institute for OneWorld Health (www.oneworldhealth.org) and the Drugs for Neglected Diseases Initiative (www.dndi.org). The genome sequences will provide such initiatives with a wealth of data and leads.

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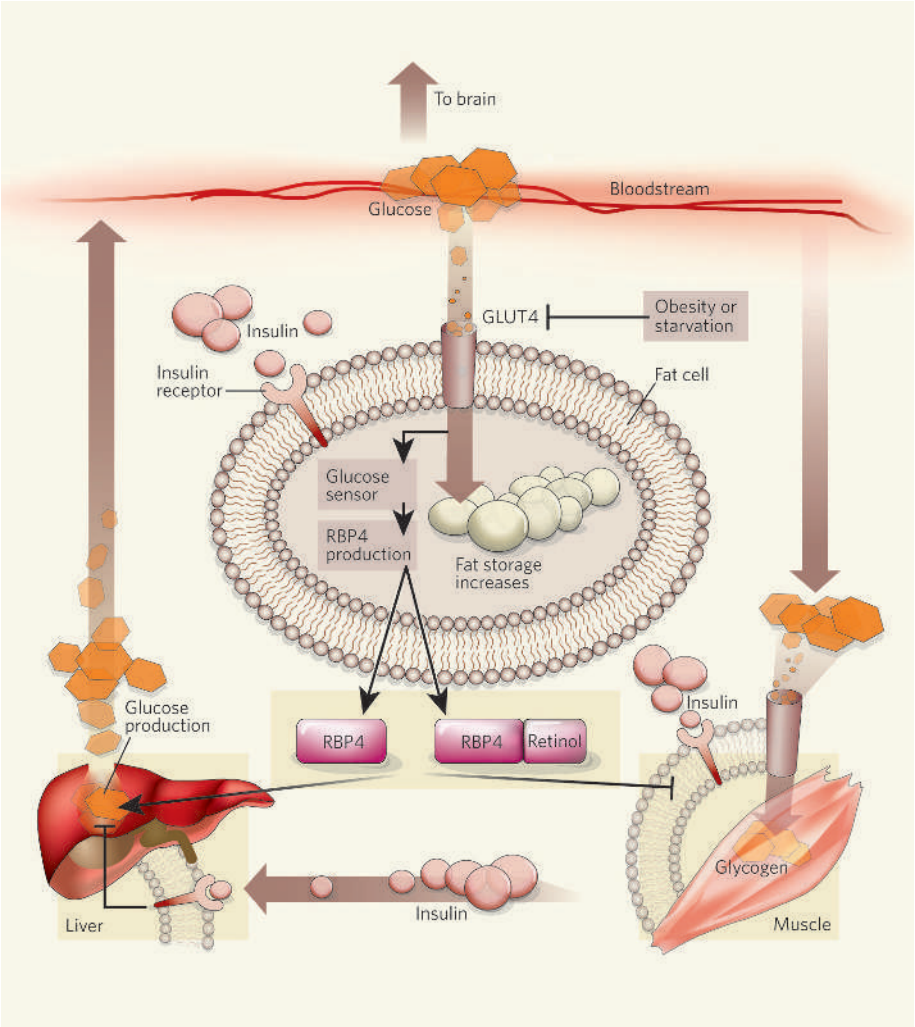

Figure 1 | Retinol binding protein-4 (RBP4) in glucose metabolism. In normal individuals, binding of insulin to its receptor on the cell membrane stimulates glucose uptake into muscle and fat cells through the GLUT4 transporter. It also inhibits glucose production in liver, thereby maintaining normal glucose levels in the blood. In adipose tissue, glucose provides fuel for the synthesis of fat stores, which serve as the body's main energy reservoir. Yang *et al.*[2] found that the decrease in GLUT4 expression that occurs in the fatty tissue of obese animals is accompanied by increased expression and secretion of the fat-derived factor RBP4. This factor, possibly working in concert with retinol (vitamin A), impairs insulin signalling in muscle, inhibiting glucose uptake, and interferes with insulin-mediated suppression of glucose production in the liver, causing blood glucose levels to rise.

reciprocally in adipose tissue of mice overexpressing GLUT4 and those lacking GLUT4. The authors provide comprehensive support for RBP4 as the elusive link between GLUT4 suppression in adipose tissue and insulin resistance, and as a central mediator of insulin action generally (Fig. 1). Circulating RBP4 levels are raised in five independent mouse models of obesity and insulin resistance, as well as in obese humans. In mice lacking GLUT4, a drug used to treat diabetes, rosiglitazone, lowers circulating RBP4 levels and normalizes insulin sensitivity. Increasing the circulating levels of RBP4 results in glucose intolerance, and conversely, deleting the RBP4 gene in mice increases insulin sensitivity. Finally, Yang *et al.* show that treatment of mice with the synthetic retinoid fenretinide, which increases the excretion of RBP4, lowering its levels in the blood, ameliorates insulin resistance caused by high-fat feeding.

The mechanisms by which RBP4 affect insulin action are partially elucidated. In muscle, RBP4 decreases the activity of the enzyme PI-3 kinase and the phosphorylation of insulin receptor substrate-1, both effects being clear markers of impaired insulin action. Increasing RBP4 does not alter PI-3 kinase activity in liver, yet glucose production in the liver is clearly increased, in concert with increased expression of a key enzyme in the glucose production pathway, phosphoenolpyruvate carboxykinase (PEPCK).

As its name suggests, RBP4 was previously known as a transporter for retinol (vitamin A)[9]. It is unclear whether the link between RBP4 and insulin action involves changes in retinol metabolism or delivery. Of interest in this context is the fact that PEPCK expression is stimulated by retinoids, an effect that could be mediated by enhanced delivery of the retinol ligand by RBP4. However, Yang *et al.*[2] also show that RBP4 stimulates PEPCK expression and glucose production in cultured rat cells, which could imply that the peptide has a direct effect, although no high-affinity receptor for RBP4 has been identified. In addition, retinol serves as a precursor for the synthesis of ligands of the RAR and RXR nuclear hormone receptors[10]. RXR is a partner for a family of receptors (peroxisome-proliferator-activated receptors) that regulate transcription of genes involved in fatty-acid metabolism[11]. RBP4 might therefore be related to diabetes through dysregulation of intramuscular and/or hepatic fatty-acid metabolism, a well-recognized component of insulin resistance[12].

Finally, did the adipocyte GLUT4–RBP4 system evolve as a response to obesity and overeating, or for other purposes? Interestingly, food deprivation (for example, overnight fasting) promotes insulin resistance, and dramatically reduces GLUT4 expression in adipose tissue[13]. Whether RPB4 levels rise in response to this mode of GLUT4 regulation is not known. But if they do, this might indicate that the GLUT4–RBP4 system evolved as a mechanism for restricting glucose uptake by peripheral tissues under famine conditions, thereby sparing glucose for the brain, which depends on the sugar as its primary energy source. An early consequence of obesity, in contrast, may be development of insulin resistance in the adipocyte. This would result in the same fall in GLUT4 expression that occurs during fasting, causing the adipocytes in essence to mistake obesity for starvation. Clearly, the study by Yang *et al.*[2] moves the adipocyte and its secreted factors closer to the epicentre of the diabetes and obesity epidemic. ■

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