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METABOLISM

Reducing oxygen consumption in fat

Low oxygen levels are a hallmark of expanding fat tissue in obesity, and can lead to type 2 diabetes. In addition to a lack of adequate blood supply, increased oxygen demand in fat cells now emerges as being key to this harmful state.

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A major cause of type 2 diabetes is obesity, in which fat cells expand rapidly, in both size and number, and their oxygen demand outstrips supply. This low-oxygen state, known as hypoxia, leads to upregulation of the anti-hypoxic protein HIF-1α, which in turn causes tissue inflammation and prevents fat cells (adipocytes) from responding normally to insulin[1,2]. Hypoxia in expanding fat is often thought of mainly as a problem of supply, caused by the inability of blood vessels that deliver oxygen to grow as fast as the surrounding tissue[3,4]. Writing in *Nature Metabolism*, Seo *et al.*[5] highlight a pathway by which excessive oxygen consumption in adipocytes can also contribute to hypoxia in expanding fat tissue. This pathway involves the enhanced activity of the enzyme adenine nucleotide translocase 2 (ANT2) in energy-generating organelles called mitochondria.

During normal mitochondrial respiration, electrons are transferred between a series of molecules, and this transfer is coupled to the removal of hydrogen ions (H^+, also known as protons) from the central matrix of the mitochondrion into the space between its outer and inner membranes. This process creates a proton gradient that drives the production of energy-carrying ATP molecules in mitochondria by the enzyme ATP synthase. But the process can become uncoupled if protons leak across the inner mitochondrial membrane. Uncoupled respiration results in inefficient ATP production, and thereby increases the intracellular demand for oxygen for further respiration.

High levels of uncoupled respiration can alter cellular physiology, and inhibiting uncoupled respiration with various compounds increases cellular oxygen levels, decreasing hypoxia and so reducing HIF-1α levels[6]. Any manipulation that leads to a decrease in cellular HIF-1α activity in fat is metabolically beneficial[1]. Thus, a better understanding of uncoupled respiration and how to manipulate it is desirable.

Previous work[7] by the group that carried out the current study has shown that the rate of oxygen consumption in the white adipocytes of mice increases if the animals eat a high-fat diet. The group proposed that increased levels of circulating free fatty acids in the blood of obese animals led to activation of ANT2. Excessive ANT2 activity results in an increased proton leak back into the mitochondrion[8], leading to elevated levels of uncoupled mitochondrial respiration.

Seo *et al.* have now developed a mouse model in which expression of the *Ant2* gene is lowered specifically in adipocytes, enabling them to provide proof of this mechanism in the current study. First, the authors showed that the mutant mice became as obese as wild-type mice when fed a high-fat diet, with no difference in total body weight or physical activity between the two groups. However, an increase in adipocyte size (hypertrophy) led to higher fat-tissue weight in *Ant2*-mutant mice than in controls. Despite the well-documented association between adipocyte hypertrophy and hypoxia, the authors found that intracellular oxygen tension — a measure of the concentration of oxygen in the cell, which is decreased in hypoxia — was higher in *Ant2*-mutant mice than in controls. The group showed that the maintenance of oxygen tension was attributable to a decrease in oxygen consumption, rather than to changes in oxygen supply or blood-vessel density, suggesting that ANT2 is a crucial determinant of the rate at which adipocytes consume oxygen in obese animals.

The improved adipocyte oxygen tension in the *Ant2*-mutant mice was independent of

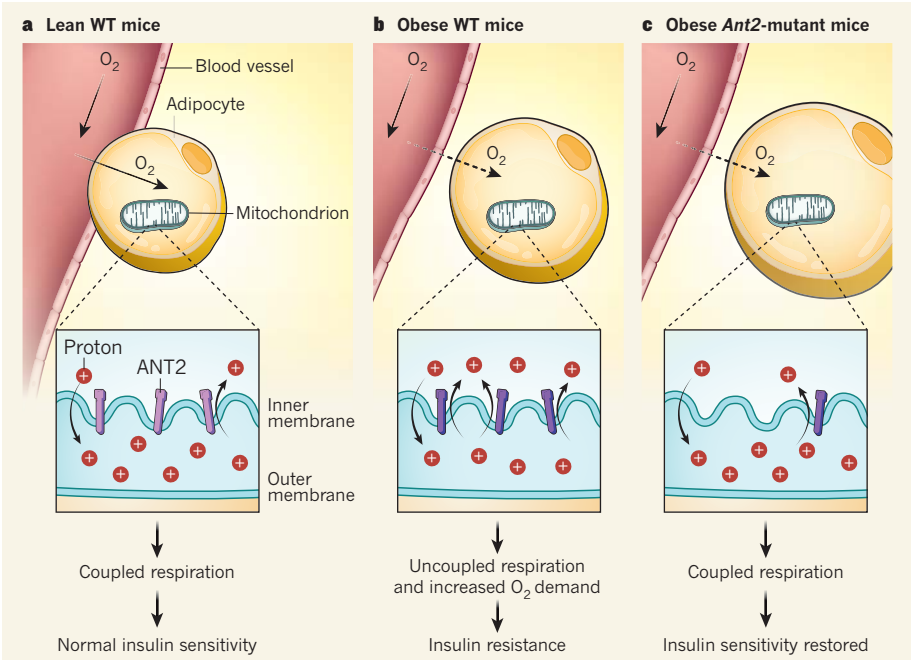

Figure 1 | The ANT2 enzyme in obesity. **a**, Fat cells (adipocytes) receive oxygen from surrounding blood vessels for coupled respiration, in which protons (positively charged hydrogen ions) are removed from the centre of organelles called mitochondria into the space between the inner and outer membranes, generating a membrane potential that drives energy production. The enzyme ANT2 causes proton leakage back into the organelle. This can lead to less-efficient, uncoupled respiration, but ANT2 activity is low in lean wild-type (WT) mice. Coupled respiration ensures normal insulin sensitivity in fat in these animals. **b**, In obese WT mice, adipocytes become larger and receive less oxygen (dashed arrow) owing to lack of an adequate blood supply. Seo *et al.*[5] report that, in addition, oxygen demand increases because ANT2 activity is increased in obese animals (indicated by darker colour), which lowers membrane potential and drives uncoupled respiration. This leads to insulin resistance (a hallmark of diabetes) in the surrounding tissue. **c**, Reducing adipocyte expression of the *Ant2* gene in obese mice decreases ANT2 levels, lowers the rate of uncoupled respiration and therefore decreases oxygen demand, and so restores insulin sensitivity. (Surprisingly, the adipocytes of these mutant animals are larger than those of obese WT mice, but display higher insulin sensitivity.)

ATP synthase, indicating that it did not relate to changes in coupled mitochondrial respiration. Instead, Seo and colleagues confirmed that the mutation led to a decrease in the leakage of protons across the inner mitochondrial membrane that increased the electrical potential across the membrane. This, in turn, enabled more-efficient energy production and less-uncoupled respiration (Fig. 1), and so improved adipocyte survival.

A range of immune cells are recruited to expanded fat tissue, triggering inflammatory responses and tissue scarring known as fibrosis. But Seo *et al.* showed that the functional improvement in mitochondria caused by adipocyte-specific *Ant2* depletion reduces this response — an improvement that is also seen if vascular density is increased in fat tissue through genetic engineering[4]. As expected, this decrease in inflammation and fibrosis led to improved glucose tolerance and enhanced insulin sensitivity in the livers of the *Ant2*-mutant mice. Moreover, the researchers showed that depletion of *Ant2* in the adipocytes of mice that have already developed glucose intolerance and insulin resistance can reverse these effects.

These findings are of interest for several reasons. First, many studies have emphasized the need for adequate vascularization in fat to prevent hypoxia[9]. But Seo and co-workers put the adipocyte centre stage as a driving force for hypoxia, highlighting how a defect in the fat cell that leads to intracellular oxygen depletion can drive much broader metabolic changes. Second, the authors' *Ant2*-deficient mice show an overall increase in adipocyte size. This finding is counter-intuitive, because adipocyte hypertrophy is generally associated with defective metabolism — this observation therefore needs further investigation. One possible explanation is that reduced HIF-1α levels in the hypertrophic cells promote their survival. Third, the researchers demonstrate that intracellular oxygen tension is higher in the fat of people who have metabolically normal obesity than in those with metabolically abnormal obesity. This is in line with the respective insulin sensitivities of these conditions, indicating that the authors' findings might have clinical relevance.

Seo and colleagues' work defines modulation of ANT2 as a potential strategy to improve systemic metabolic defects, including type 2 diabetes. Combined with the fact that ANT2 has been suggested to be an attractive anticancer target[10], this makes ANT2 modulators prime candidates for drug development. This is even more appealing in light of the fact that Seo *et al.* only partly inhibited *Ant2* expression in the current study, rather than completely deleting the gene. Thus, small-molecule drugs, which can only partially block the activity of their target enzyme, might provide the desired effects. Efforts to identify such inhibitors should prove rewarding in the future. ■

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