couplings to the Higgs boson, which are determined by the masses of the decay products. Because bottom quarks are among the heaviest fermions, the decay to these particles is the most common, occurring about 58% of the time. But even though this decay is dominant, in proton–proton collisions the signal is overwhelmed by the background of bottom quarks produced by the strong nuclear interaction. For this reason, the discovery of the Higgs boson in 2012 involved decays only to vector bosons: photons from the electromagnetic interaction and weak vector bosons from the weak interaction.

To observe the decay to bottom quarks, the two collaborations had to look for subdominant modes of Higgs-boson production, such as the production of the Higgs boson together with a weak vector boson (Fig. 1). A deep understanding of the responses of the particle detector, and sophisticated data-analysis methods that included machine learning, were needed to precisely reconstruct the energies and momenta of the weak vector bosons, tag the jets of particles arising from the bottom quarks, model all the backgrounds and separate these backgrounds from the signal.

The findings are not entirely surprising, for at least two reasons. First, there have been several pieces of evidence for the decay of the Higgs boson to bottom quarks in the past. In 2012, a signal at the level of 2.8 standard deviations was claimed by scientists at the Tevatron proton–antiproton collider, located near Chicago[11]. Between 2012 and 2018, the ATLAS and CMS collaborations regularly reported outcomes of their search for the decay. In their latest papers before the current work, they obtained evidence at the level of 3.6 and 3.8 standard deviations, respectively[12,13]. These different pieces of evidence could be considered as a combined observation of the decay.

Second, many other experimental results at the LHC are constraining what could actually be observed regarding this decay. For example, if the Higgs boson had behaved as in the standard model, but had had zero coupling to bottom quarks, the yields of all the other decay modes would be enhanced by a factor of about 2.4, which is contradicted by the data. Considering the overall picture, unless there exist unexpected cancelling effects, the allowed deviations from the standard model are at the level of a few per cent — below the current 20% sensitivity of experiments at the LHC.

Nevertheless, the current results are a great achievement and constitute a major milestone in particle physics. Together with observations earlier this year of the Higgs boson decaying to tau particles[14] and the production of the Higgs boson together with top quarks[15,16], the findings directly establish interactions between the Higgs boson and the third family of fermions, therefore pointing to the Higgs field as the origin of fermion masses.

The results are the starting point of an era of precision measurement for the couplings of the Higgs boson to fermions. With more data from the LHC — in particular, after upgrades to the beam intensity in a few years — an accuracy of a few per cent in the measurements should be obtained. This would open the possibility of finding deviations from the standard model and of, for example, uncovering currently unknown particles.

Another milestone would be observing the couplings of the Higgs boson to the second family of fermions. The decay of the Higgs boson to a pair of muons is within the reach of the future upgraded LHC. However, because of the extremely high background in proton–proton collisions, the decay to charm quarks could probably be demonstrated only by using a giant electron–positron collider, which is yet to be constructed. The Higgs boson is therefore far from having revealed all of its secrets. ■

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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 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 anti-cancer 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. ■

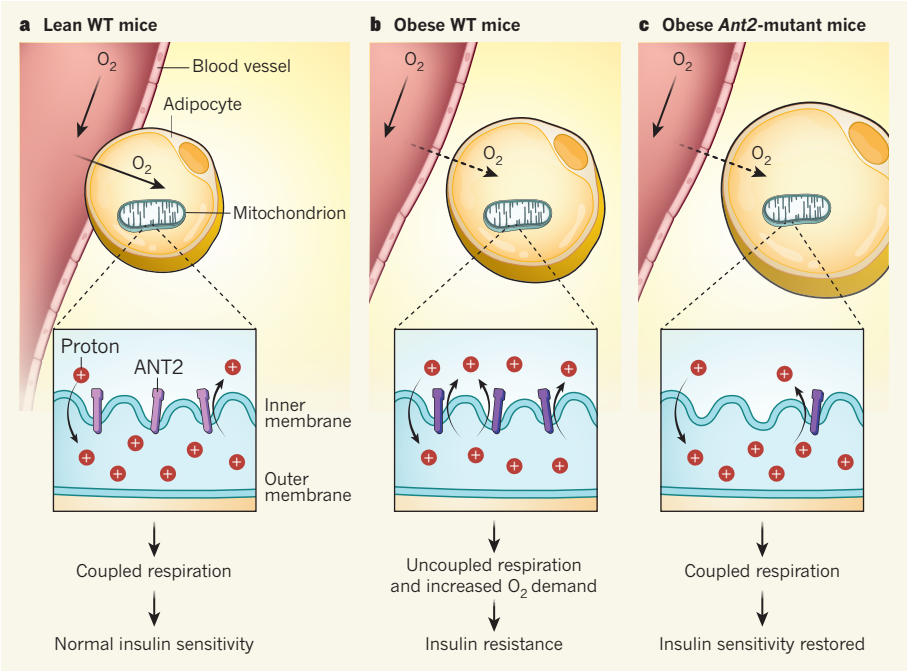

Figure 1 | The ANT2 enzyme in obesity. **a**, Fat cells (adipocytes) receive oxygen from surrounding blood vessels for coupled respiration, in which protons (positively charged hydrogen ions) are removed from the centre of organelles called mitochondria into the space between the inner and outer membranes, 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.)

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