

demonstrate¹ some of the generality of this principle in other games such as tic-tac-toe (noughts and crosses) and those involving a mix of collaborative strategies between the players (the so-called Prisoner's Dilemma). All of this shows that organisms in nature achieve what is called intelligence through a fascinating mix of evolution, adaptation and learning — with the possibility of inspiring those interested in computation not only to build smarter machines but also to get a

better understanding of the nature of intelligence itself. ■

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Diabetes

Insulin resistance and obesity

Michael W. Schwartz and Steven E. Kahn

Type 2 diabetes mellitus is a serious health problem in the Western world. It arises when resistance to the glucose-lowering effects of insulin combines with impaired insulin secretion to raise the levels of glucose in the blood beyond the normal range. Studies into the molecular basis of insulin resistance have focused on the peroxisome proliferator-activated receptor gamma (PPAR γ). This molecule, a member of the nuclear-hormone-receptor family, is the cellular target of thiazolidinedione drugs, which are used to treat diabetes by increasing sensitivity to insulin.

What are the endogenous ligands for PPAR γ ? How does it promote the insulin-stimulated uptake of glucose? And is this effect essential for the normal action of insulin? The answer to the last of these questions may be nearer thanks to a study by Barroso *et al.*¹ on page 880 of this issue. They

report the identification of two loss-of-function mutations of PPAR γ that are associated with severe insulin resistance and type 2 diabetes mellitus in humans. Although such mutations are rare — detected in just three of 85 insulin-resistant people, and none of 314 controls — the implication that PPAR γ is required for normal insulin sensitivity in humans is an important advance.

Found in the nucleus of many cells, particularly fat cells, PPAR γ is both a receptor and a transcription factor. When PPAR γ is bound by ligand, such as a thiazolidinedione, it becomes activated and binds to specific DNA sequences in gene promoters. Then, in complex with another transcription factor known as the retinoid X receptor (RXR), it activates the transcription of specific genes² (Fig. 1, overleaf). One of the best-studied effects of activated PPAR γ is its ability to induce differentiation of fibroblasts or other undifferenti-

ated cells into mature fat cells². Signalling by the PPAR γ -RXR complex is also implicated in the synthesis of biologically active compounds by vascular endothelial cells³ and circulating immune cells⁴. Mutations in PPAR γ may contribute to cancer⁵, and increased PPAR γ signalling (owing to a mutation that increases its intrinsic activity) is also associated with human obesity⁶.

Barroso *et al.*¹ now show that the people affected by loss-of-function PPAR γ mutations (one affects a mother and her son; the other affects an unrelated woman) share common elements of the 'insulin resistance syndrome'. Symptoms include insulin resistance, diabetes, high blood pressure, dyslipidaemia (an abnormal plasma-lipid profile) and a skin-pigmentation disorder known as acanthosis nigricans. But a cardinal feature of the insulin-resistance syndrome that these people do not show is obesity. Reduced PPAR γ signalling therefore seems to cause insulin resistance in the absence of obesity.

This observation contrasts sharply with the symptoms of gain-of-function mutation of PPAR γ , reported last year by Ristow *et al.*⁶. In their study, obesity was associated with relatively low levels of insulin, suggesting an increased sensitivity to insulin. However, neither report^{1,6} includes a measurement of insulin sensitivity. Moreover, a third mutation in PPAR γ has variable effects on body weight and insulin sensitivity^{7,8}. Nevertheless, all of these findings indicate that by increasing PPAR γ function it may be possible to prevent insulin resistance from occurring when normally it would (for example, in the obese state). Conversely, mutations in PPAR γ that cause reduced function could lead to insulin resistance in lean people, in whom it would not normally occur.

Antarctica

Vast snow dunes frozen in time

Release of data gathered during the Cold War continues to deliver scientific surprises. The latest example emerged at last week's American Geophysical Union meeting in San Francisco, where glaciologists reported new findings about Antarctica based on satellite data. The revelation came from comparisons of modern satellite images of snow dunes (such as the one shown here) with recently declassified pictures originally taken by intelligence satellites in 1963.

The first complete map of Antarctica, produced in 1997 with data from the Canadian satellite Radarsat, revealed many unexpected features, including vast tracts of snow dunes. These

megadunes are up to 100 kilometres long, lie 1 or 2 kilometres apart but are only a few metres high. In East Antarctica fields of the dunes cover an area larger than the state of California.

At the meeting Mark Fahnestock (University of Maryland) described how he and Ted Scambos (University of Colorado) compared data from satellites of the US National Oceanic and Atmospheric Administration and from the 1960s military images. It might be thought that the snow dunes would move, even if only slowly, because of the fierce, constant winds that blow across the East Antarctic plateau. It turns out, however, that they have not — at least over the past 30 years. Little is



known about how the megadunes formed, but it is unlikely that they grew from drifting snow in the way that sand dunes are built from sand.

Across the other side of the continent, on the West Antarctic ice sheet, vast streams of ice flow into the sea. The source of the ice streams has so far eluded explorers and satellites alike. At another talk at the meeting, Robert Bindshadler

(NASA Goddard Space Flight Center) described high-resolution data from Radarsat that reveals several small and slow-flowing tributaries that are feeding the large frozen rivers with snow from the interior. One of the biggest uncertainties in predicting sea-level rises in response to climate change is the uncertain behaviour of the Antarctic ice sheets. So new data (however old) is always welcome. **Sarah Tomlin**

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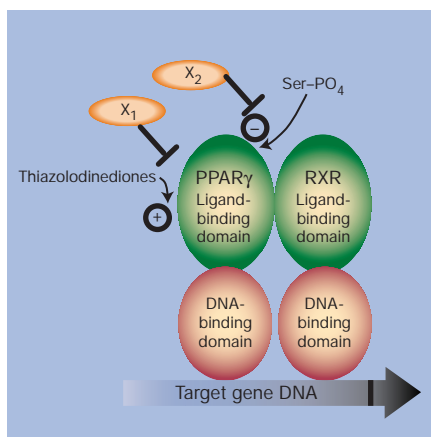


Figure 1 Molecular complex formed by dimerization of PPAR γ and the retinoid X receptor (RXR). Binding of ligand such as thiazolidinedione to either transcription factor can activate the complex, allowing the DNA-binding domain to bind the promoter region of target genes and activate transcription. Barroso *et al.*¹ have shown that mutations that impair ligand binding (X_1) disrupt this process and are associated with insulin resistance and normal body weight in humans. Serine phosphorylation (Ser-PO $_4$) of PPAR γ inhibits its activity, and mutation of an adjacent amino acid (X_2) blocks this site. This increases PPAR γ signalling, and is associated with obesity⁶.

Although disease-causing mutations of PPAR γ are rare, might the insulin resistance associated with human obesity result from impaired PPAR γ signalling in the absence of a mutation? Insulin resistance is especially likely to occur when excess fat is deposited within the abdominal cavity. This reduces the insulin sensitivity of fat cells and also of other tissues including skeletal muscle and liver. But how might expanding adipose stores causes insulin resistance? One explanation is that increased release of free fatty acids from triglyceride-laden fat cells provides an alternative metabolic substrate, which decreases the need for glucose as a fuel. As a result, insulin-stimulated glucose clearance from the blood is reduced, an effect that is manifest as insulin resistance.

However, because some free fatty acids may be PPAR γ ligands², an alternative explanation presents itself. If obesity alters the availability of these fatty acids, it could reduce PPAR γ signalling and produce insulin resistance. But there are other ways to regulate the function of PPAR γ . For example, phosphorylation of PPAR γ on serine residues reduces its function, even in the presence of thiazolidinediones^{2,9}. This is another potential mechanism whereby expanding fat stores might impair PPAR γ function.

The two PPAR γ mutations reported by Barroso *et al.*¹ lead to amino-acid substitutions in regions of the molecule involved in ligand binding. As a result, these changes

impair the activation of PPAR γ by thiazolidinediones. By contrast, the obesity-inducing PPAR γ mutation reported by Ristow *et al.*⁶ results in an amino-acid substitution adjacent to the serine phosphorylation site. This mutation impairs phosphorylation, thereby increasing PPAR γ function. In each case, affected patients have one mutant and one normal allele, suggesting that the mutant PPAR γ molecule dominates functionally over the normal protein. Indeed, Barroso and colleagues found that the function of normal PPAR γ was impaired when they co-expressed it in tissue culture with either of the mutant proteins. Such 'dominant-negative' mutations are well documented in other nuclear-receptor systems, and they help to explain how a single mutant allele can cause disease.

The study of PPAR γ mutations is expanding what we know about the involvement of this molecule in human health and disease. However, the demonstration of clinical abnormalities in a small number of patients who have a mutation is not proof that the mutation caused the symptoms. Determining how these patients respond to treatment with thiazolidinediones would provide important additional information. Moreover, neither insulin sensitivity nor insulin secretion were quantified in people with PPAR γ mutations, yet the interaction of these two parameters is critical for glucose homeostasis¹⁰. The importance of taking these measurements is highlighted by the presence of type 2 diabetes in three of four obese people with the gain-of-function PPAR γ mutation⁶. Perhaps the low insulin levels in these people reflect impaired insulin secretion rather than increased insulin sensitivity.

We need more information before we can conclude that too much PPAR γ causes obesity without the expected metabolic consequences, whereas too little PPAR γ elicits the metabolic consequences without obesity. But continued study of this important molecule could yield new approaches to the treatment of diseases such as obesity and diabetes, which take an enormous toll on human health. ■

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Daedalus

The art of slow change

Art, says Daedalus, seems to divide into two main camps. Some arts are quite static (pictures, statues and so on). Others (music, cinema, ballet) supply rapid change for a short time. But our aesthetic sense evolved in a world of constant slight change. Much of the charm of the natural world, such as the sea, the sky, the landscape, and indeed the appreciation of human fellowship, depends on slow change within certain expected limits. Daedalus is now exploring this neglected aesthetic.

The only current art form of slow change, gardening, gives constant pleasure from the steady subtle development of the plants. It is remarkably popular. But no engineering structures are designed to grow like plants. Instead, our buildings and monuments, though static, usually aim to be 'new and exciting'. This is self-defeating; shock and excitement are the most fleeting, least sensible goals for an architect or mason. Yet a building which changed slowly all the time would pose daunting technical challenges. So as a pilot project, Daedalus is devising a slowly-changing statue. Its pose and demeanour will drift subtly all the time. Instead of rapidly fading into the unnoticed urban background, it will retain interest and value to the frequent viewer.

Similarly, modern display technology should make possible a slowly-changing picture, perhaps like the ageing portrait of Dorian Gray in Oscar Wilde's story. It would drift slowly and subtly on a timescale of hours, days or months. It might play out a slow story, drift seemingly at random, or follow some environmental lead; but every time one glanced at it, it would be subtly different.

The most pleasing forms of change will take a long time to recognize and optimize — existing art forms have taken centuries to reach their current state of impasse. But in utilitarian mood, Daedalus likes the idea of driving his pictures or statues from the weather forecast, or the stock-market index. The viewer might come to think — or at least to intuit — 'The mayor looks happy today, it's going to be sunny' or 'Keynes has had an angry slouch all week, maybe it's time to shift a little into gilts'. Municipal patrons of the arts will support DREADCO's project more open-handedly if it serves a practical and civic-minded purpose.

David Jones

The further Inventions of Daedalus (Oxford University Press), 148 past Daedalus columns expanded and illustrated, is now on sale. Special *Nature* offer: m.curtis@nature.com