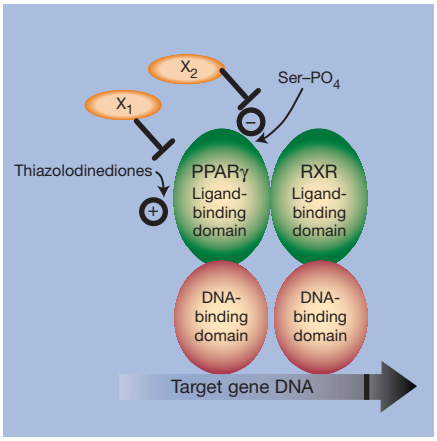

Figure 1 **Molecular complex formed by dimerization of PPARγ and the retinoid X receptor (RXR). Binding of ligand such as thiazolidinedione to either transcription factor can activate the complex, allowing the DNA-binding domain to bind the promoter region of target genes and activate transcription. 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 PPARγ inhibits its activity, and mutation of an adjacent amino acid (X_2) blocks this site. This increases PPARγ signalling, and is associated with obesity[6].**

Although disease-causing mutations of PPARγ are rare, might the insulin resistance associated with human obesity result from impaired PPARγ 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 PPARγ ligands[2], an alternative explanation presents itself. If obesity alters the availability of these fatty acids, it could reduce PPARγ signalling and produce insulin resistance. But there are other ways to regulate the function of PPARγ. For example, phosphorylation of PPARγ 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 PPARγ function.

The two PPARγ 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 PPARγ by thiazolidinediones. By contrast, the obesity-inducing PPARγ 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 PPARγ function. In each case, affected patients have one mutant and one normal allele, suggesting that the mutant PPARγ molecule dominates functionally over the normal protein. Indeed, Barroso and colleagues found that the function of normal PPARγ 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 PPARγ 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 PPARγ mutations, yet the interaction of these two parameters is critical for glucose homeostasis[10]. 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 PPARγ mutation[6]. 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 PPARγ causes obesity without the expected metabolic consequences, whereas too little PPARγ 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**

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