Insulin's reach

After a meal, pancreatic secretion of insulin tells peripheral tissues—mainly skeletal muscle and fat—to take up glucose. In type 2 diabetes, this signal is impaired by 'resistance' of peripheral tissues to insulin. Clinical data have shown that insulin resistance precedes the rise in blood sugar that defines diabetes, and have suggested that the disease may be averted by interventions at this early, insulin-resistant stage.

Two reports in the mid-1990s focused on the events that transduce the insulin signal, and offered key insights into the molecular basis of insulin resistance. These studies built on previous work identifying the insulin receptor, a transmembrane tyrosine kinase that phosphorylates insulin receptor substrate-1 (IRS-1), a cytoplasmic protein. IRS-1 in turn binds to and activates phosphatidylinositol-3′-OH kinase, setting in motion a cascade of events that ultimately results in targeting of glucose transporters to the cell surface.

Although this pathway was elucidated in cell culture experiments, its significance in intact animals was not clear. To ascertain the role of IRS-1 *in vivo*, Araki *et al.* (*Nature* **372**, 186; 1994) knocked out the mouse *Irs1* gene. The knockout mice were small at birth, and had impaired insulin response and abnormal glucose tolerance. What's more, these mice were shown to use an alternative, previously unidentified, insulin receptor substrate, IRS-2.

In a second study, Brüning *et al.* (*Cell* **88**, 561–572; 1997) showed that, although the loss of one copy of either the insulin receptor or IRS-1 had no metabolic defect, mice missing a single copy of each became diabetic with age, a pattern quite similar to human type 2 diabetes. This work not only provided a new mouse model of diabetes, but also demonstrated, in agreement with clinical observations, that diabetes can result from the combined effects of various metabolic 'insults'. Together, these two studies provide a molecular basis for developing therapies to combat insulin resistance. For example, later work has shown that IRS-1 activity is regulated by inflammation signals, suggesting that anti-inflammatory therapeutics could improve insulin signaling.—*CW*

Fat: boring no more

Igor Shpilenok

In 1995, Scherer *et al.* quietly introduced researchers to a molecule, now known as adiponectin, that would later emerge as a promising link between obesity and insulin resistance. After the discovery a year earlier of the identity of the *ob* 'fat gene', which encodes leptin, Scherer *et al.* searched for genes preferentially expressed during adipocyte differentiation. They emerged with a molecule they described as "structurally similar to a hibernation-specific protein isolated from Siberian chipmunks" (*J. Biol. Chem.* **270**, 26746–26749; 1995). The protein, like leptin, was secreted from adipocytes—previously thought to be inert storage units for fat, without endocrine activity. Scherer *et al.* also found that insulin boosted adiponectin secretion, providing evidence for an insulin-regulated secretory pathway in fat tissue. The connection of adiponectin with insulin grew tighter with later studies, including two in 2001 (Yamauchi *et al.*, *Nat. Med.* **7**, 941–946; 2001, and Berg *et al.*, *Nat. Med.* **7**, 947–953; 2001).These later studies established that adiponectin controls insulin sensitivity and glucose homeostasis. What's more, administration of the molecule reversed insulin resistance and partially restored normal glucose levels in mouse models of diabetes. These results jibe with other work, such as clinical studies showing decreases in adiponectin levels in obese humans. The receptor for the molecule and its associated signaling pathways—as well as the function of the chipmunk protein—remain opportunities for further investigation.—*SG*

Switch hitter

Puigserver *et al.* changed the way people think about metabolic regulation when they discovered the transcriptional coactivator PGC-1α in 1998 (*Cell* **92**, 829–839; 1998). The researchers, however, started out with a more modest objective: to uncover how cold-activated mitochondrial genes are controlled in brown fat, the mammalian heat-generating organ. They emerged with PGC-1α (PPAR-γ coactivator-1α), the expression of which spiked upon cold exposure. PGC-1α, they found, boosted the transcriptional activity of nuclear receptors such as PPAR-γ, and upregulated the heat-generating protein UCP-1 (uncoupling protein-1).

PGC-1α has since been to shown couple with a number of other transcription factors to coordinate gene expression not only in brown fat, but also in other arenas: the switch to lipid fuels during hibernation, synthesis of glucose by the liver during fasting, and fiber-type switching in muscle. This multitasking molecule provides a direct link between environmental stresses, such as cold or starvation, and the genetic regulation underlying the physiological response to those stresses.

The discovery of PGC-1α also had broader implications for the control of gene transcription Puigserver *et al.* showec that a coactivator that never directly contacts DNA can have a central role in altering an animal's physiology at the level of gene expression.—*PL*

Run on islets

When James Shapiro and colleagues successfully treated seven patients with type 1 diabetes by transplanting them with human pancreatic islet cells (*N. Engl. J. Med.* 343, 230–238; 2000), it came as a surprise to some in the diabetes research community. Previous attempts in humans had met with only spotty success, despite promising results in rodents as early as the 1970s. The Edmonton protocol, as it came to be known, triggered renewed excitement in the feasibility of transplant therapies to treat diabetes.

The new formula involved transplanting high-quality islets quickly, then treating patients with the right mix of immunosuppressive drugs. The mixture, for instance, did not include glucocorticoids, drugs used in previous attempts that can erode islet cell function. The seven patients in the trial were able to discontinue insulin therapy, and maintained normal blood glucose levels after the one-year benchmark. But further progress has been slow, tempering optimism. Patients require islets from at least two donors, and isolation is tricky; damaged islets produce less insulin, affecting the success rate of the procedure. The long-term outcome of islet transplantation and the daily immunosuppression regimen have yet to be determined.

As of last year, half of the patients treated as part of an ongoing multicenter trial of the Edmonton protocol were insulin independent. This outcome beats past success rates, and keeps alive interest in alternate immunomodulating regimens and new sources of cells, such as stem cells.—*AF*

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