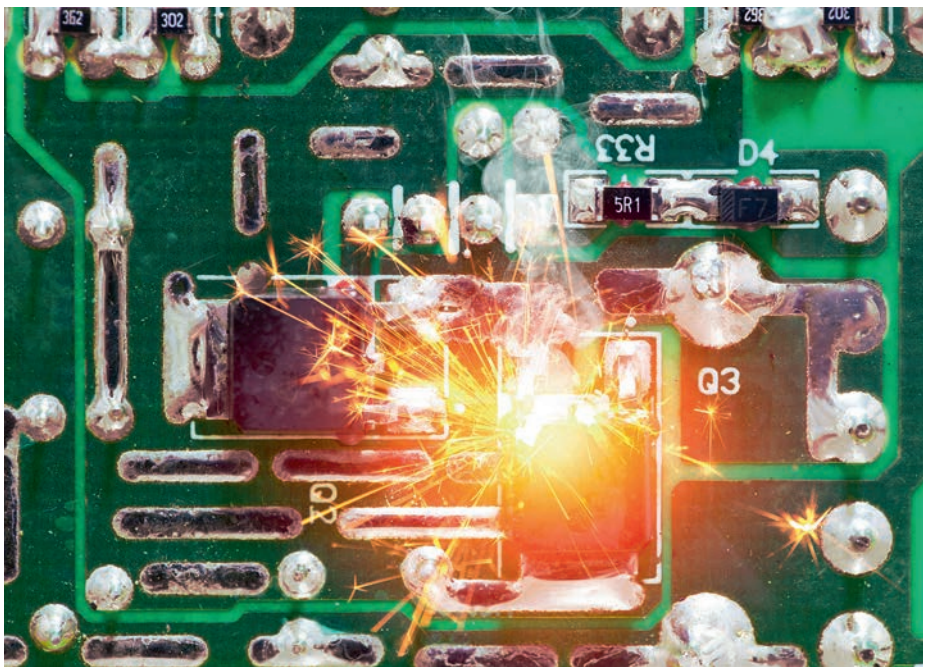
Milestone 12

TNF short-circuits the insulin receptor

By the 1990s, it was well established that the immune system's destruction of pancreatic β-cells that produce insulin results in type 1 diabetes (Milestones 7 and 8). However, the mechanisms responsible for the development of type 2 diabetes, which was linked to insulin resistance, were still unclear. What was known at the time was that insulin resistance was seen in numerous disease conditions, including chronic infections and cancer, and was ubiquitously linked with obesity.

A major breakthrough in understanding the mechanistic basis of insulin resistance — and why this is observed in such a diverse range of conditions — came with the publication of several key studies in the 1990s by Gökhan Hotamisligil and co-workers in the laboratory of Bruce Spiegelman. In two papers published in 1993 and 1995, these scientists found that the pro-inflammatory cytokine tumour necrosis factor (TNF) is upregulated in the adipose tissues of obese animals and humans with obesity and that blocking TNF improves insulin sensitivity in animal models of obesity. These observations were followed by a 1996 study that identified the molecular basis of TNF-driven insulin resistance. Productive signalling through the insulin receptor involves its autophosphorylation in response to insulin binding and the subsequent tyrosine phosphorylation of insulin receptor substrate 1 (IRS1). Hotamisligil et al. found that TNF disrupts this process by inducing serine phosphorylation of IRS1, which converts IRS1 into an inhibitor of the insulin receptor and prevents productive signalling following insulin binding. They further showed that this inhibitory form of IRS1 was present in the adipose tissue and muscle of obese animals and was responsible for insulin resistance in these tissues.

"type 2 diabetes and obesity itself are chronic inflammatory diseases in their own right, and not simply metabolic disorders"



These findings helped to explain why numerous chronic diseases were associated with insulin resistance. Moreover, the work of Hotamisligil, Spiegelman and others contributed to the eventual appreciation that type 2 diabetes and obesity itself are chronic inflammatory diseases in their own right, and not simply metabolic disorders. Subsequent research, including two key studies published in 2003 from the laboratories of Hong Chen and Anthony Ferrante, showed that obesity induces immune cell changes in adipose tissue that affect insulin sensitivity. These authors found that macrophages are increased in adipose tissue during obesity and produce TNF and other inflammatory mediators that promote insulin resistance. Shortly after this, it was shown that specifically disrupting NF-κB signalling in myeloid cells could alleviate obesity-induced insulin resistance. Many other immune cell types have since been studied in obesity and, in general, obesity is linked with activation of pro-inflammatory immune cell responses and the suppression of anti-inflammatory ones.

A key question that has still not been fully resolved is how obesity initiates inflammation in the first place. Current thinking in the field is that chronic nutrient overload can result in endoplasmic reticulum (ER) stress, which may fuel tissue inflammation by promoting cell death or the production of pro-inflammatory mediators that are linked with the ER stress response.

Yvonne Bordon Senior Editor,
Nature Reviews Immunology

Milestone studies

Hotamisligil, G. S., Shargill, N. S. & Spiegelman, B. M. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. *Science* **259**, 87–91 (1993) | Hotamisligil, G. S. et al. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. *J. Clin. Invest.* **95**, 2409–2415 (1995) | Hotamisligil, G. S. et al. IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF-α- and obesity-induced insulin resistance. *Science* **271**, 665–670 (1996)

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