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MECHANISMS OF DISEASE

Blame ROS

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URLs

Insulin resistance is a hallmark of type-2 diabetes and several other pathologies, including obesity, sepsis and metabolic syndrome. But, the signals that trigger insulin resistance in so many contexts remain unknown. Reporting in *Nature*, Houstis *et al.* now show that reactive oxygen species (ROS) have a causal role in inducing three forms of insulin resistance.

Both the inflammatory cytokine tumour necrosis factor-α (TNFα) and the glucocorticoid dexamethasone have been used previously to induce insulin resistance in tissue-culture adipocytes and they are physiologically relevant *in vivo* — elevated levels of TNFα and dexamethasone have been associated with several insulin-resistance pathologies. However, these ligands signal through distinct pathways and induce distinct cellular responses. TNFα is a pro-inflammatory cytokine, whereas dexamethasone has anti-inflammatory properties.

To understand the cellular basis of insulin resistance, Houstis *et al.* compared the effects of these two different treatments by analysing genome-wide gene expression in control untreated adipocytes and TNFα-treated or dexamethasone-treated adipocytes. Bioinformatic analysis showed that a substantial fraction (18%) of the 34 genes that were upregulated in response to both treatments were related to ROS. Measurements of the cellular redox state confirmed the above result. To test whether ROS might have a causal role in insulin resistance, the authors treated TNFα- or dexamethasone-pretreated adipocytes with antioxidant molecules or transfected them with transgenes that encoded scavenging enzymes. Antioxidant treatment improved glucose uptake in response to insulin.

Houstis *et al.* then tested whether antioxidant molecules could be used to improve glucose homeostasis in an *in vivo* model of insulin resistance, the leptin-deficient *ob/ob* mouse. Antioxidant treatment resulted in a dose-dependent improvement in glucose tolerance and insulin sensitivity, but it did not fully prevent the development of insulin resistance. This indicates that either the drug that was used was not sufficiently potent, or that ROS are not the only cause of insulin resistance.

These findings raise many questions. For example, what other mechanisms might be involved in inducing insulin resistance? What is the trigger for the generation of ROS, and what are the downstream pathways that link elevated ROS levels to insulin resistance?

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ORIGINAL RESEARCH PAPER Houstis, N. *et al.* Reactive oxygen species have a causal role in multiple forms of insulin resistance. *Nature* **440**, 944–948 (2006)