Nature Reviews Drug Discovery | AOP, published online 15 March 2013; doi:10.1038/nrd3988

METABOLIC DISORDERS

Breaking the links between inflammation and diabetes

Obesity is associated with chronic low-grade inflammation in adipose and liver tissues, which has been implicated in the development of insulin resistance and type 2 diabetes. Although the precise molecular links between inflammation and disrupted glucose homeostasis are not completely understood, the pro-inflammatory nuclear factor-κB (NF-κB) transcriptional programme is thought to be involved. Now, two papers identify approaches to inhibit the activity of the NF-κB pathway, which improved obesity-associated metabolic dysfunctions in mouse models.

NF-κB activation is triggered by the phosphorylation of the regulatory protein IκB by IκB kinases (IKKs). Previously, it was reported in mice that the expression of one of these kinases — IKKε — is increased during a high-fat diet (HFD) in adipose tissue and the liver, and deletion of IKKε renders these mice partially resistant to the deleterious metabolic effects of a HFD. With this in mind, Reilly and colleagues set out to identify a small-molecule inhibitor of IKKε as a potential therapeutic option to treat metabolic disorders.


Alamy/Garry Gay

By screening a library of 150,000 chemical compounds, they identified amlexanox as a high-affinity inhibitor of IKKε. Although amlexanox is currently used to treat asthma, allergic rhinitis and aphthous ulcers, its mechanism of action is unknown. Further *in vitro* studies revealed that the drug similarly inhibited another IKK: TANK-binding kinase 1 (TBK1).

Investigation of the therapeutic potential of amlexanox revealed that daily oral administration prevented HFD-induced weight gain in mice over a 12-week period and produced significant weight loss in two different mouse models of obesity (HFD-induced and leptin-resistant *ob/ob* mice), which exhibit insulin resistance and hyperglycaemia, after just 4 weeks. Furthermore, when HFD-induced obese mice were treated for 8 weeks, amlexanox improved insulin sensitivity, attenuated hepatic steatosis, reduced adipose tissue inflammation and promoted energy expenditure in adipose tissue through increased thermogenesis.

Meanwhile, Kiechl, Schett and colleagues focused on receptor activator of NF-κB ligand (RANKL), a potent activator of NF-κB that is involved in bone homeostasis. They showed that binding of RANKL to its receptor RANK in the liver activates NF-κB and promotes pro-inflammatory cytokine expression in the liver and insulin resistance.

First, they studied the 844 individuals who had participated in the Bruneck Study — a population-based survey on atherosclerosis and related traits carried out in Bruneck, Italy — and found that serum concentrations of soluble RANKL were positively correlated with the risk of developing type 2 diabetes.

Next, they used mouse models to investigate the mechanistic link between RANKL and type 2 diabetes. In contrast to control mice, hepatocyte-specific *Rank*-knockout ($Rank^{LKO}$) mice subjected to a HFD did not develop insulin resistance after 4 weeks. In addition, mice obtained by crossbreeding *ob/ob* mice with $Rank^{LKO}$ mice exhibited significantly lower fasting glucose concentrations and greater insulin sensitivity than *ob/ob* mice. Similar beneficial metabolic effects were observed when liver expression of *Rank* was downregulated by hydrodynamic injection of *Rank* short hairpin RNA lentiviral vectors (RANKi) in both HFD-treated and *ob/ob* mice. Importantly, blockade of *Rank* using RANKi inhibited activation of NF-κB and downstream pro-inflammatory signalling in the liver of mice exposed to a HFD.

Together, these studies demonstrate that NF-κB pathway inhibition is a promising approach for the treatment of obesity-related metabolic disorders. Importantly, like amlexanox, RANKL antagonists such as denosumab have been proven to be safe in patients and are currently used to treat osteoporosis.

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ORIGINAL RESEARCH PAPERS Reilly, S. M. *et al.* An inhibitor of the protein kinases TBK1 and IKK-ε improves obesity-related metabolic dysfunctions in mice. *Nature Med.* **19**, 313–321 (2013) | Kiechl, S. *et al.* Blockade of receptor activator of nuclear factor-κB (RANKL) signaling improves hepatic insulin resistance and prevents development of diabetes mellitus. *Nature Med.* **19**, 358–363 (2013)