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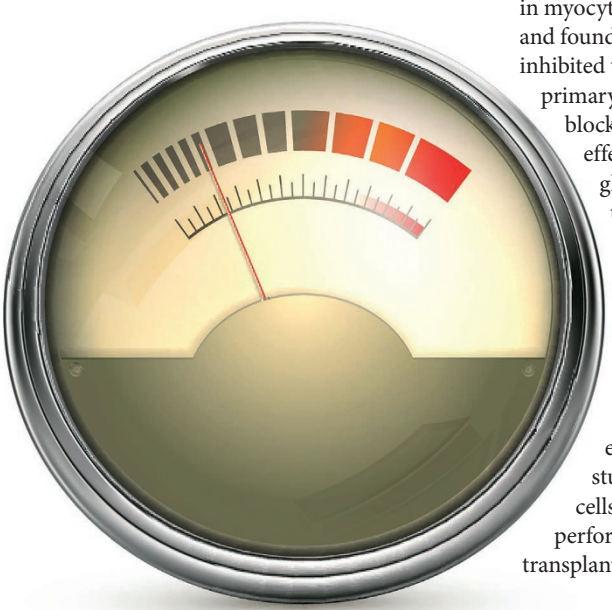
DIABETES

Turning down galectin 3 to combat insulin resistance

Insulin resistance is a hallmark of type 2 diabetes and is associated with inflammation of insulin target tissues such as adipose tissue, muscle and liver. A recent study by Olefsky and colleagues has shown that galectin 3 (GAL3) provides a crucial mechanistic link between inflammation and insulin resistance, and that pharmacological inhibition of GAL3 can increase insulin sensitivity in mice.

Previous work by the group had found that switching mice from a high-fat diet (HFD) to normal chow was accompanied by reduced expression of GAL3 by macrophages in adipose tissue as well as reductions in tissue inflammation and insulin resistance. In the current study, the authors sought to characterize the role of GAL3 in these processes.



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They found that *Gal3*-knockout mice gained the same amount of weight in response to a HFD as did wild-type mice but remained more glucose tolerant. *Gal3*-heterozygous mice, which retained a single copy of the *Gal3* allele, showed similar benefits to full knockout mice, which suggests that a partial blockade of GAL3 signalling might be sufficient to achieve metabolic improvements.

In HFD-fed obese mice, circulating GAL3 levels were considerably higher than in chow-fed lean mice. Importantly, these findings were mirrored in plasma samples from 52 obese and lean humans, and GAL3 levels were positively correlated with a measure of insulin resistance.

Next, the researchers measured insulin-stimulated glucose transport in myocyte and adipocyte cell lines and found that addition of GAL3 inhibited this process. Moreover, in primary mouse hepatocytes, GAL3 blocked the normal dampening effect of insulin on hepatic glucose output in response to glucagon. Together, these findings showed that GAL3 can directly induce insulin resistance in three important insulin target tissues.

Which cells might be the source of GAL3? With evidence from previous studies to implicate immune cells, Olefsky and co-workers performed bone marrow transplantation, in which wild-type mice received bone marrow from *Gal3*-knockout mice. The procedure cut circulating GAL3 levels by 90%, which demonstrated a haematopoietic cell source for GAL3.

Further experiments indicated that GAL3 exerts its insulin-desensitizing effects by directly binding to the insulin receptor at a site that is distinct from the insulin-binding domain, which leads to abrogation of insulin receptor signalling and glucose transporter 4 (GLUT4) translocation. In addition, GAL3 caused macrophage chemotaxis *in vitro* and in mice, and *Gal3*-knockout mice showed decreased expression of pro-inflammatory genes in adipose tissue compared with wild-type mice. Thus, GAL3 seems to exert dual effects — on the insulin receptor directly and on tissue inflammation — that cause insulin resistance.

Last, the authors showed that acute or chronic administration of a pharmacological inhibitor of GAL3, termed compound 47, improved oral glucose tolerance in HFD-fed obese mice.

Together, these studies suggest that GAL3 could be a fruitful target to tackle insulin resistance and associated tissue inflammation. A GAL3 inhibitor, GR-MD-02, is currently in phase II testing for non-alcoholic steatohepatitis.

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ORIGINAL ARTICLE Li, P. *et al.* Hematopoietic-derived galectin-3 causes cellular and systemic insulin resistance. *Cell* **167**, 973–984.e12 (2016)