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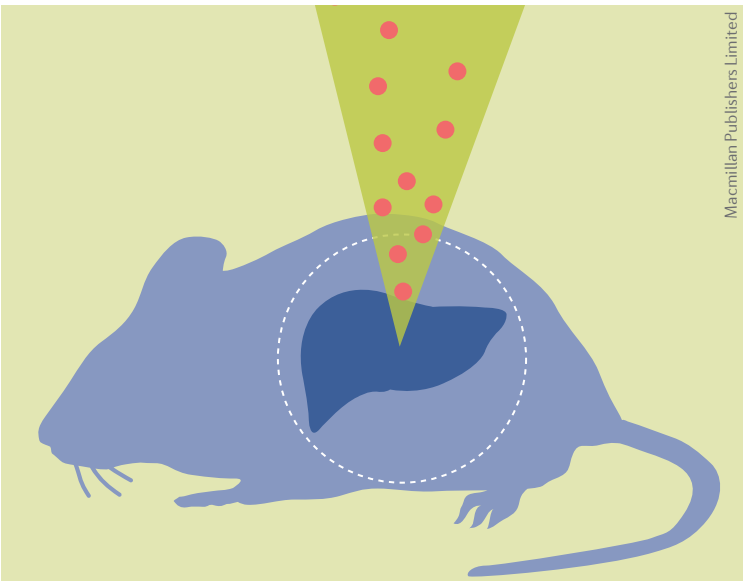

DIABETES

A new hope for insulin-sensitizing drugs

Although insulin-sensitizing therapeutics can prevent and treat diabetes mellitus, they are associated with a number of adverse effects, such as weight gain resulting from triglyceride accumulation, bone fractures and haemodynamic changes. Now, Domenico Accili and colleagues have discovered a series of small molecule inhibitors of forkhead box protein O (FOXO) that do not cause these adverse effects and therefore could lead to the next generation of insulin sensitizers in the treatment of diabetes mellitus.

In the liver, insulin inhibits the function of FOXO by inducing its translocation from the nucleus to the cytoplasm. When active, hepatic FOXO inhibits the expression of glucokinase, thus preventing the phosphorylation of glucose to glucose-6-phosphate. In parallel, hepatic FOXO stimulates glucose-6-phosphatase, an enzyme that promotes the hydrolysis of glucose-6-phosphate to glucose. Therefore, when FOXO is inhibited by insulin, the levels of glucokinase go up and the levels of glucose-6-phosphatase go down, resulting in a decrease in the production of glucose — an effect that could benefit patients with diabetes mellitus.

Glucokinase, however, also promotes lipogenesis, so when FOXO is inhibited by insulin, hepatic lipid synthesis increases, predisposing the liver to steatosis. These complex actions of FOXO in the liver underscore the difficulty in the design of insulin-sensitizing therapeutics, despite its strong biological validation.

"This study arose from the observation that FOXO has a dual function in the liver: it activates some genes, and inhibits others. The rationale was that if we understood how FOXO turns genes on and off, we could design a screen to distinguish between the two functions, and thus identify chemical modulators of selected functions," explains Accili. "We know why glucose-6-phosphatase goes up in the absence of insulin (when FOXO is active), but we were unsure of how FOXO inhibits glucokinase."

In the present study, Accili and colleagues found that in the absence of insulin a FOXO–SIN3A complex is bound to its promoter, which inhibits glucokinase. Insulin, however, inhibits the binding of this complex to its promoter, which results in glucokinase becoming active. Previously it was believed that insulin activates glucokinase through the binding of a transcriptional activator, but in this study Accili and his team show that insulin in fact inhibits a transcriptional repressor (FOXO–SIN3A). The authors also report the discovery of a series of small molecule inhibitors of FOXO, some of which have a generalized effect on all FOXO targets, and some that have a specific effect only on genes that FOXO activates.

"The design of insulin sensitizers that have a safe therapeutic profile has long bedevilled the field of diabetes mellitus drug development, as when the body is sensitized to insulin there are undesired effects, such as an increase in hepatic lipid synthesis," concludes Accili. "Our selective inhibitors have the ability to reduce glucose production, which is inappropriately high in diabetes mellitus, without increasing hepatic lipid synthesis. We plan to improve the chemistry of these compounds and obtain variants that can be used in clinical trials as insulin sensitizers in the treatment of diabetes mellitus."

Alan Morris

ORIGINAL ARTICLE Langlet, F. *et al.* Selective inhibition of FOXO1 activator/repressor balance modulates hepatic glucose handling. *Cell* http://dx.doi.org/10.1016/j.cell.2017.09.045 (2017)

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