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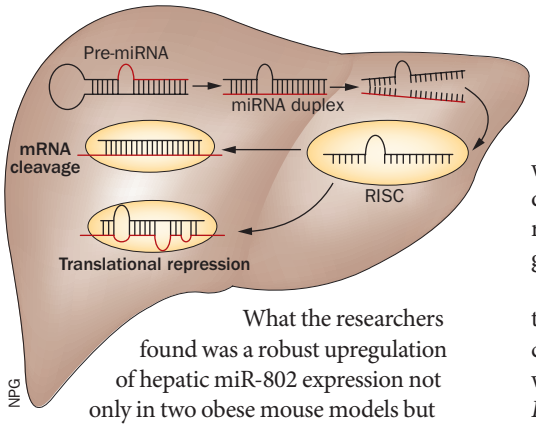
OBESITY

microRNA-dependent control of MODY gene expression contributes to obesity-associated insulin resistance

The transcription factor HNF-1β—a deficiency of which is known to cause a rare form of maturity-onset diabetes mellitus of the young (MODY)—has been implicated in the development of obesity-associated insulin resistance.

"Genetic variation and post-translational modification of components of the insulin signalling pathway cannot fully explain the clinical association of obesity and insulin resistance," explains senior investigator Jens C. Brüning (Max-Planck-Institute for Neurological Research, Cologne, Germany). Hence, his team investigated the contribution of post-transcriptional gene silencing via microRNAs (miRNAs) to the development of obesity-associated insulin resistance. "We aimed to achieve a high coverage in detecting miRNAs whose expression is altered in the liver of obese mouse models through microarray technology," says Brüning.



What the researchers found was a robust upregulation of hepatic miR-802 expression not only in two obese mouse models but also in patients with obesity. Furthermore, the investigators showed that miR-802 overexpression caused insulin resistance in lean mice and, conversely, that reducing miR-802 expression in obese mice improved glucose metabolism. Brüning and co-workers then identified the target of miR-802-dependent silencing: *HNF1B*. Mutations in this gene cause the rare genetic diabetes variant MODY 5, which is also known as RCAD (renal cysts and diabetes syndrome). "Knockdown of *HNF1B* expression in the mouse liver using small hairpin RNA caused insulin resistance, which, to our knowledge, is the first demonstration of a role for HNF-1β in the regulation of hepatic insulin sensitivity and glucose metabolism," comments Brüning.

In the future, the investigators hope to test the feasibility of miR-802 antagomirs—chemically engineered oligonucleotides that would prevent miR-802 from binding to the *HNF1B* mRNA molecule and thus preclude silencing—to treat obesity-associated insulin resistance and type 2 diabetes mellitus in nonhuman primate studies.

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Original article Kornfeld, J.-W. *et al.* Obesity-induced overexpression of miR-802 impairs glucose metabolism through silencing of *Hnf1b*. *Nature* **494**, 111–115 (2013)