

## DIABETES

## New mechanism for insulin resistance

A metabolite of valine, a branched-chain amino acid, causes insulin resistance by promoting lipid accumulation in muscle, according to new findings.

Accumulation of fats in the liver and muscles is thought to contribute to insulin resistance in patients with type 2 diabetes mellitus. However, how fats get into the muscle has been unclear. A team of researchers, led by Zoltan Arany, set out to investigate this process. “We looked for, identified and purified a substance that is secreted by muscle cells and which causes cells of the blood vessel wall to increase transport of fats,” explains Arany.

The investigators used an assay in which conditioned medium from a mouse myoblast cell line was

added to human umbilical vein endothelial cells (HUVECs). Medium derived from muscle cells that overexpressed PGC-1 $\alpha$  caused increased uptake of fatty acids by HUVECs, compared with control medium. This result suggests that a paracrine factor regulated by PGC-1 $\alpha$  induces endothelial uptake of fatty acids. A series of experiments revealed that 3-hydroxyisobutyrate was the paracrine factor of interest.

As 3-hydroxyisobutyrate is a metabolite of valine, this finding explains the observation that many patients with type 2 diabetes mellitus have increased levels of valine. “Excess valine will get broken down, leading to high levels of 3-hydroxyisobutyrate, in turn leading to high fatty acid transport

into muscle, fat accumulation and insulin resistance,” comments Arany. These findings also highlight the importance of the vasculature in the development of insulin resistance, which opens up new therapeutic opportunities. “If we can block entry of toxic fats into muscle, we could target insulin resistance at the root of the problem,” says Arany. The team are now looking for methods to target this system with small molecules.

Claire Greenhill

**ORIGINAL ARTICLE** Jang, C. *et al.* A branched-chain amino acid metabolite drives vascular fatty acid transport and causes insulin resistance. *Nat. Med.* <http://dx.doi.org/10.1038/nm.4057> (2016)  
**FURTHER READING** Lynch, C. J. *et al.* Branched-chain amino acids in metabolic signalling and insulin resistance. *Nat. Rev. Endocrinol.* **10**, 723–736 (2014)