Nature Reviews Endocrinology | Published online 26 Aug 2016; doi:10.1038/nrendo.2016.149

METABOLISM

Defects in BCAA oxidation impair lipid metabolism

Branched-chain amino acids (BCAAs) have been implicated in the increased risk of developing insulin resistance and type 2 diabetes mellitus (T2DM) but the underlying mechanism has been unclear. However, in a new study published in *Molecular Metabolism*, investigators have used a combination of transcriptomics and metabolomics to show that defective BCAA catabolism impairs lipid metabolism, which might contribute to insulin resistance and the development of T2DM.

The team recruited 11 patients with T2DM and 40 normoglycaemic individuals. The latter population were then divided into two groups; those who were insulin resistant and those who were insulin sensitive based on the median insulin sensitivity value of the group. A skeletal muscle biopsy sample was taken from all individuals; gene expression analyses and metabolomics were used to identify genes associated with insulin sensitivity.

Of the transcripts identified, genes involved in BCAA catabolism were highly correlated with insulin sensitivity and were also downregulated in individuals with insulin resistance or T2DM. Expression of *Mut*, one the genes that had the highest correlation, was also found to be reduced in mice fed a high-fat diet. *Mut,* and other genes involved in BCAA metabolism, were also downregulated in C2C12 myotubes that were exposed to palmitate and oleate, which indicates that BCAA metabolism is disrupted during lipid excess.

Using a metabolomic approach, the team then found that levels of branched-chain ketoacids were all decreased in muscle from insulin-resistant individuals, as were citric acid cycle intermediates. Medium-chain acylcarnitines were also elevated, which taken together suggests that fatty acid metabolism is impaired in these muscle samples. Furthermore, these effects seemed to be dependent on changes in the flux of metabolites via the BCAA oxidation pathway.

Finally, to assess the *in vivo* effects of defective BCAA metabolism, the team used a *Mut* mutant mouse line. Homozygous mutations in *Mut* were lethal; however, $Mut^{+/-}$ mice were viable, gained more weight than wild-type litter mates and had a 43% increase in fasting levels of insulin and glucose. The muscle triglyceride content in $Mut^{+/-}$ mice was also higher than wild-type mice, highlighting that lipid metabolism is altered in these mice.

"We identified alterations in multiple genes of the BCAA metabolic pathway as well as in BCAA-related metabolites in muscle from humans with insulin resistance," explain Mary-Elizabeth Patti and Carles Lerin, who led the study. "Our study indicates that perturbations in muscle BCAA metabolism may contribute to metabolic phenotypes associated with insulin resistance and T2DM risk."

The authors hope that their findings might be translated into diagnostic testing for T2DM, even before evidence of prediabetes, and that targeting the oxidative flux of BCAAs might be a therapeutic strategy for T2DM. "By combining cell culture, mouse models, computer modelling and human cohorts, our aim is to ultimately design novel and more efficient prevention strategies for T2DM," conclude Patti and Lerin.

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ORIGINAL ARTICLE Lerin, C. *et al.* Defects in muscle branched-chain amino acid oxidation contribute to impaired lipid metabolism. *Mol. Metab.* http://dx.doi.org/10.1016/j.molmet.2016.08.001 (2016)