

De novo carnitine biosynthesis contributes to environmental adaptation

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Auger *et al.* report in *Science* that the orphan transporter SLC25A45 enables N6, N6, N6-trimethyllysine to enter the mitochondrion, where it is converted to carnitine. Mice lacking *Slc25a45* have reduced capacity to switch fuels from carbohydrate to lipid.

Certain environmental conditions, such as fasting or cold exposure, require animals to switch from carbohydrates to lipids as their major energy source. Carnitine is a critical metabolite for fatty acid oxidation, as it is required for the transport of long-chain fatty acids into mitochondria^{1,2}. In carnivores and omnivores, most carnitine comes from red meat, dairy, or fish in the diet. In vegetarians, vegans, or herbivores, however, carnitine must be synthesized *de novo*. This occurs within mitochondria, using the methylated amino acid N6, N6, N6-trimethyllysine (TML) as a precursor³. The mechanism by which TML enters the mitochondria, however, has been elusive. Three groups now independently show that the orphan solute carrier SLC25A45 is the major mitochondrial transporter for TML⁴⁻⁶. All three groups used publicly available datasets of metabolites, gene expression, or phylogenetic analysis to infer such a role for SLC25A45.

The three groups all showed that carnitine synthesis in cultured cells requires SLC25A45 to transport TML into the mitochondria. The study by Auger *et al.*⁶ goes further, demonstrating that mice globally lacking *Slc25a45* have carnitine deficiency and impairment of the fatty acid oxidation systemically, and shift to a carbohydrate-based energy economy. The shift to obligate consumption of glucose over fatty acids in these mice is profound enough to cause mild hypoglycemia. Interestingly, loss of SLC25A45 specifically in either the liver or the kidney does not affect the abundance of carnitine in those organs. This is consistent with the idea that carnitine can be produced and exported into the blood by many different cell types, which can then compensate for deficient local carnitine synthesis in tissue-specific knock-out animals.

To determine the physiological importance of SLC25A45-mediated carnitine synthesis *in vivo*, Auger and colleagues then subjected *Slc25a45* null mice to a condition that requires fatty acid oxidation, namely cold exposure. Normally, when a mouse is housed in cold conditions, it activates thermogenic adipose tissue to create heat. This process requires the oxidation of fatty acids derived either from the diet or from adipose lipolysis. Consistent with a requirement for carnitine synthesis for fatty acid oxidation, mice lacking *Slc25a45* were unable to tolerate cold temperatures. This could be mitigated by treating mice with a carnitine-rich diet.

Another scenario requiring fatty acid oxidation involves the

therapeutic response to GLP-1 receptor agonists (GLP-1RAs), such as semaglutide, which are widely used to treat obesity and type 2 diabetes. Semaglutide treatment decreases food intake, which leads to fuel switching from carbohydrates to lipids. Auger *et al.* demonstrated that obese mice lacking *Slc25a45* showed a reduced response to semaglutide, the full activity of which was restored by systemic supplementation of L-carnitine.

The authors also predicted the structure of SLC25A45 and identified a potential mechanism for the TML-SLC25A45 interaction, and used molecular dynamics simulations to demonstrate a stable TML-SLC25A45 complex in the inner mitochondrial membrane. Site-directed mutagenesis confirmed the importance of at least one amino acid residue predicted to be critical in TML binding and transport. These results beg the question of whether drugs could be designed that increase TML import into the mitochondrion, thus enhancing fatty acid oxidation and possibly “boosting” the effect of GLP-1RAs. Alternatively, or in addition, carnitine supplementation could be used to circumvent the need for TML importation.

It is worthwhile to point out that the depletion of SLC25A45 does not fully block the *de novo* biosynthesis of carnitine, as minor but detectable production of carnitine still occurs in hepatocytes that lack *Slc25a45*. These data, combined with the fact that expression of *Slc25a45* is virtually undetectable in some organs (e.g., pancreas), suggest that alternative pathways for TML transportation or carnitine *de novo* biosynthesis may exist, at least in some cell types.

These studies were, of course, performed in laboratory mice, which are maintained on diets that are very low in carnitine. Most humans who are not vegetarians or vegans, however, get the bulk of their carnitine from the diet, and not from *de novo* synthesis⁷. One wonders whether alterations in carnitine synthesis pathways, such as those described in these studies, may have enabled the transition from meat-eating hunter-gatherer societies to more agrarian-based societies^{8,9}.

These papers highlight several key points. First, this is yet another example of the rapid and ongoing “de-orphanization” of SLC transporters¹⁰. Many research groups around the world are working tirelessly to identify the substrates and physiological importance of the many SLC family members for which we do not yet have a clear picture of their function. Second, these studies highlight how mitochondrial metabolism is central to fuel homeostasis and the adaptive response to metabolic challenges. Finally, and no less important, we see how the thoughtful analysis and integration of publicly available data can lead to biological insights. Given

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the current pace of “omics” research, we should expect that additional biological insights will emerge rapidly.

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COMPETING INTERESTS

J.L. is the inventor of China patent ZL 202211126387.6. The other authors declare no competing interests.

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ADDITIONAL INFORMATION

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