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DIABETES

Important role for MPC complex in hepatic gluconeogenesis

Gluconeogenesis is an important component of maintaining energy homeostasis; however, excessive gluconeogenesis is implicated in the development of type 2 diabetes mellitus (T2DM). Two recent papers demonstrate that mitochondrial pyruvate carrier (MPC) 1 and MPC2 (which make up the MPC protein complex) are required for efficient production of glucose in the liver, which could have implications for treating patients with T2DM.

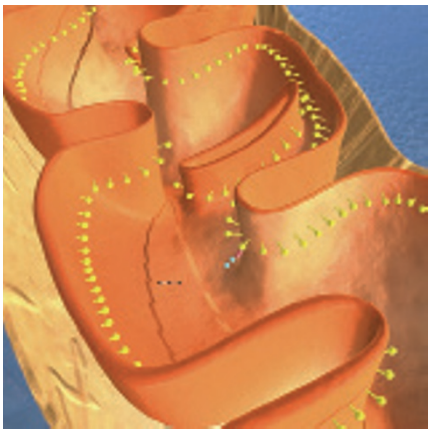
The biological functions of many highly conserved mitochondrial proteins, including the MPC protein complex, are not known. Previous studies have indicated that this protein complex might be involved in gluconeogenesis. Furthermore, pyruvate is one of the main substrates for hepatic gluconeogenesis, so it is likely that transport of pyruvate across the inner mitochondrial membrane is an important step. However, little is known about the precise involvement of the MPC protein complex in hepatic gluconeogenesis, which led two research groups to investigate this process.

In the first study, Eric Taylor and colleagues generated a mouse model with liver-specific *Mpc1* knock out (global knock out was embryonic lethal). The knockout mice exhibited changes in their metabolism, such as a decreased respiratory exchange rate. Importantly, although the fasting blood levels of glucose in these mice were decreased, levels were still within the normal range. Thus, gluconeogenesis is still occurring, albeit less efficiently than in wild-type mice, in the absence of pyruvate. "In mouse models, this loss of efficiency manifests as decreased hyperglycaemia in T2DM, increased fatty acid oxidation and decreased cholesterol levels, which are therapeutically desirable outcomes in patients with T2DM," explains Taylor.

The researchers postulated that the liver was adapting to the lack of pyruvate and utilizing alternative substrates for gluconeogenesis. A metabolomics analysis revealed that alanine (produced by transamination of pyruvate) and glutamine were being transported into the mitochondria, where they were used in gluconeogenesis. Taylor and his co-workers are now investigating whether this adaptive response also occurs in human primary hepatocytes. They are also researching the long-term effects of deleting the MPC protein complex.

In the second study, Brian Finck and co-workers generated a mouse model in which *Mpc2* was knocked out in the liver (as for *Mpc1*, global knock out of *Mpc2* was embryonic lethal). Using a pyruvate transport assay, the researchers demonstrated that mitochondria from the livers of *Mpc2*$^{-/-}$ mice accumulated less ^{14}C-pyruvic acid than mitochondria from wild-type mice. This finding indicates that without the MPC protein complex, mitochondrial pyruvate transport and metabolism are decreased. As in the study by Taylor and colleagues, Finck and co-workers found that although pyruvate was no longer being used to produce glucose in the liver, hepatic gluconeogenesis was still happening, probably through the use of amino acids as substrates instead of pyruvate.

Finck and colleagues then used a single dose of streptozotocin to leave knockout mice and wild-type mice insulin-deficient. The treated *Mpc2*$^{-/-}$ mice had lower blood glucose levels than the treated wild-type mice, which suggests that pyruvate transport in hepatic mitochondria is involved in glycaemic control in diabetes mellitus. "Mice lacking MPC in the liver are protected from developing diabetes mellitus, which suggests that targeting this complex with drugs to inhibit its formation might be beneficial in treating diabetes mellitus," says Finck. "This would seem to be quite feasible, as a number of small molecule inhibitors of the MPC protein complex have already been identified."



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However, Taylor cautions that the knockout mice also have increased urea cycle activity and exactly what effect this increased activity has in humans is unclear. Taylor also notes that targeted delivery would be important, as affecting the function of the MPC protein complex in organs other than the liver would have severe consequences.

Richard Kibbey, who was not involved in either study, feels that the findings of the two studies are important, but highlights the problematic lack of *in vivo* data to support the roles of the pyruvate–alanine cycle and increased ureagensis in hepatic gluconeogenesis. "If amino acid oxidation were to compensate fully for the loss of lactate-supported gluconeogenesis, then a similarly sized increase in urea turnover might be expected, accompanied by a significant increase in urea concentrations," states Kibbey. "A urea-cycle-dependent pathway appears less likely to provide significant compensation in the light of normal fasting and fed plasma urea concentrations." Taylor and Finck note that their data indicate increased ureagenesis is a component of a larger adaptive metabolism, which could also include increased renal clearance of serum urea.

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Original articles Gray, L. R. *et al.* Hepatic mitochondrial pyruvate carrier 1 is required for efficient regulation of gluconeogenesis and whole-body glucose homeostasis. *Cell Metab.* doi:10.1016/j.cmet.2015.07.027 | McCommis, K. S. *et al.* Loss of mitochondrial pyruvate carrier 2 in the liver leads to defects in gluconeogenesis and compensation via pyruvate-alanine cycling. *Cell Metab.* doi:10.1016/j.cmet.2015.07.028