RESEARCH HIGHLIGHT

Carnitine biosynthesis governs fuel switching

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Cell Research (2026) 0:1–2; https://doi.org/10.1038/s41422-026-01229-5

In a recent *Science* study, Auger and colleagues identified SLC25A45 as a previously unrecognized mitochondrial trimethyllysine (TML) transporter that enables L-carnitine biosynthesis. By regulating mitochondrial TML availability, SLC25A45 links environmental stressors such as cold exposure and fasting to adaptive fuel switching toward fatty acid oxidation, thereby optimizing mitochondrial energetics and metabolic resilience.

Dynamic fuel switching in response to environmental stress is a fundamental adaptive strategy that allows organisms to efficiently match energy production to demand.[1] Environmental or metabolic stressors, including nutritional state, physical activity, hormonal regulation, and pathological conditions such as heart failure, cancer cachexia, and chronic liver disease, require appropriate fuel selection to maintain metabolic homeostasis.[2] Among these, cold exposure and fasting are well-studied paradigms that necessitate metabolic flexibility, prioritizing fatty acid oxidation over glucose catabolism to sustain systemic energy balance while sparing glucose for obligate tissues such as the brain.

Carnitine is an essential metabolite for fatty acid oxidation, as it facilitates the transport of long-chain fatty acids into mitochondria through the carnitine shuttle system, which involves carnitine palmitoyltransferase 1 (CPT1), carnitine-acylcarnitine translocase (CACT), and CPT2.[3] Endogenous de novo biosynthesis supplies a critical, regulated source that supports tissue-specific carnitine availability and metabolic adaptation. Carnitine biosynthesis begins with the transport of trimethyllysine (TML) into mitochondria and proceeds through sequential intermediates, including hydroxytrimethyllysine (HTML) and γ-butyrobetaine (γ-BB), ultimately yielding L-carnitine.[3] Disruption of carnitine availability leads not only to impaired fatty acid metabolism, but also to clinical manifestations.[4] Despite its central role in mitochondrial fatty acid oxidation and metabolic homeostasis, the molecular regulation and physiological significance of endogenous carnitine biosynthesis, as well as the identity of the initial transporter that introduces the precursor TML into this pathway, remain incompletely understood.

In a recent issue of *Science*, Auger et al. identified the previously unrecognized SLC25A45 as a mediator of TML transport into mitochondria, thereby enabling de novo L-carnitine biosynthesis.[5] A newly generated whole-body *Slc25a45* knockout (KO) mouse (*Slc25a45*$^{flox/flox}$; *CMV*-Cre), together with mitochondrial metabolomics and whole-cell tracing in the presence of D_9-TML, revealed that SLC25A45 depletion led to markedly reduced mitochondrial uptake of D_9-labeled TML. This defect was accompanied by decreased production of D_9-HTML, γ-BB, and L-carnitine. Reintroduction of SLC25A45 in KO HEK293 cells increased production of D_9-HTML and γ-BB, supporting an essential role for SLC25A45 in TML uptake and carnitine biosynthesis (Fig. 1, top). Building on the essential role of SLC25A45 in TML transport, the authors explored the structural basis for its mechanistic function. AlphaFold-based structural modeling revealed that SLC25A45 shares canonical features of solute carrier proteins, including a central channel-like cavity formed by six transmembrane α-helices that allows substrate access. Consensus docking and induced-fit docking further identified a thermodynamically favorable and stable TML–SLC25A45 complex, with TML adopting a conformation well accommodated within the channel cavity.

The authors investigated the biological significance of SLC25A45 in vivo. Given the central role of carnitine in fatty acid oxidation,[3] they examined whether SLC25A45 deficiency alters systemic fuel selection under basal conditions. Indirect calorimetry showed that KO mice displayed a higher respiratory exchange ratio (RER), indicative of a shift toward carbohydrate utilization. Consistent with this, KEGG pathway analysis revealed downregulation of β-oxidation in KO mice, accompanied by upregulation of glycolysis and mitochondrial oxidative phosphorylation, reflecting a systemic shift in fuel preference toward carbohydrates driven by carnitine depletion and impaired fatty acid oxidation.

SLC25A45 supports metabolic adaptation to environmental stress, including cold exposure and fasting-like states that require a shift toward fatty acid oxidation. Upon acute cold challenge, *Slc25a45*-deficient mice rapidly developed hypothermia, a phenotype fully rescued by carnitine supplementation. During chronic cold acclimation, KO mice maintained a higher RER than controls, indicating persistent reliance on carbohydrates. This defect was linked to impaired brown adipose tissue thermogenesis,[6] as reflected by reduced mitochondrial respiration and decreased circulating long-chain acylcarnitines (Fig. 1, middle). To model food restriction, the authors used semaglutide, a glucagon-like peptide-1 receptor (GLP1R) agonist that induces fasting-like metabolic responses.[7] Semaglutide-treated KO mice similarly failed to suppress RER or elevate circulating long-chain acylcarnitines and were resistant to GLP1R agonist-induced body weight and adipose mass loss (Fig. 1, bottom). Notably, carnitine supplementation restored adipose tissue loss, underscoring the requirement for SLC25A45-dependent carnitine biosynthesis in fuel switching and metabolic adaptation.

Collectively, Auger et al. identify SLC25A45 as a key metabolic switch and bottleneck that couples mitochondrial TML import to regulated carnitine biosynthesis during environmental adaptation. While the study establishes a compelling systemic role for SLC25A45 in fuel switching, important questions remain regarding the tissue-specific contributions of this pathway and how carnitine biosynthesis and utilization are differentially regulated across dietary, disease, and sexually dimorphic contexts. Although the authors generated multiple tissue-specific *Slc25a45* KO models and concluded that systemic carnitine availability reflects coordinated contributions from multiple

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Published online: 06 March 2026

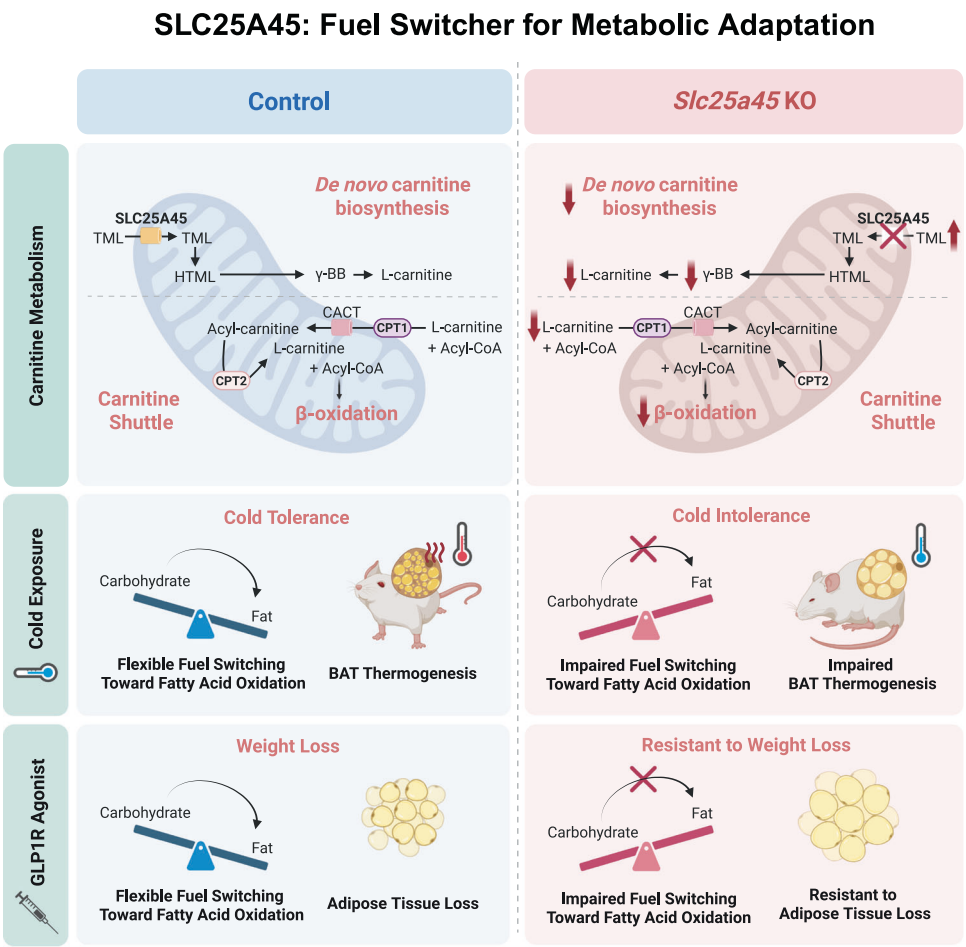

Fig. 1 SLC25A45 couples carnitine biosynthesis to adaptive fuel switching during metabolic stress. A graphical summary illustrates metabolite flux in carnitine metabolism (top), physiological responses to cold exposure (middle), and responses to food restriction, pharmacologically induced by GLP1R agonist treatment (bottom), comparing control and *Slc25a45* KO conditions. In control mice (left), SLC25A45 mediates mitochondrial uptake of TML, enabling de novo carnitine biosynthesis and efficient operation of the carnitine shuttle, thereby promoting fatty acid β-oxidation. Under environmental stressors such as cold exposure and food restriction, these mechanisms support brown adipose tissue (BAT) thermogenesis and adipose tissue loss, respectively, through flexible fuel switching toward fatty acid oxidation. In contrast, *Slc25a45* KO mice (right) exhibit impaired mitochondrial TML uptake and reduced L-carnitine production, resulting in suppressed β-oxidation. Consequently, SLC25A45 deficiency leads to cold intolerance and resistance to GLP1R agonist-induced body weight loss due to impaired fuel switching toward fatty acid oxidation.

organs, fuel reliance is likely to vary with dietary regimen, metabolic state, and pathology.[4] Moreover, females exhibit a biologically distinct metabolic context from males, shaped by sex-specific physiological programs, including pregnancy and lactation, which involve profound shifts in lipid metabolism and carnitine demand,[8] which remain largely unexplored. Addressing these dimensions will be essential for further understanding whether SLC25A45-dependent carnitine metabolism represents a universal adaptive mechanism or one selectively engaged under specific physiological or pathological conditions. Beyond defining a mitochondrial mechanism for fuel switching, this work provides a conceptual landscape for future investigation of metabolic adaptation across diverse physiological contexts, including exercise, distinct fasting paradigms, and hormone-driven metabolic regulation, and offers new insight into the determinants of responsiveness to GLP1R agonist-based anti-obesity therapies.

REFERENCES

1. Goodpaster, B. H. & Sparks, L. M. *Cell Metab.* **25**, 1027–1036 (2017).
2. Ang, J. C. et al. *Cell Rep. Med.* **6**, 102354 (2025).
3. Longo, N., Frigeni, M. & Pasquali, M. *Biochim. Biophys. Acta.* **1863**, 2422–2435 (2016).
4. Xiang, F. et al. *J. Transl. Med.* **23**, 324 (2025).
5. Auger, C. et al. *Science* **391**, eady5532 (2026).
6. Simcox, J. et al. *Cell Metab.* **26**, 509–522.e6 (2017).
7. Drucker, D. J. & Nauck, M. A. *Lancet* **368**, 1696–1705 (2006).
8. Manta-Vogli, P. D., Schulpis, K. H., Dotsikas, Y. & Loukas, Y. L. *Clin. Nutr.* **39**, 2337–2346 (2020).

ACKNOWLEDGEMENTS

The authors are supported by US NIH grants R01-DK55758, R01-DK099110, R01-DK127274, R01-DK143576 and R01-DK131537 and P01-AG051459 to P.E.S. and a post-doctoral fellowship from the American Diabetes Association 1-26-PDF-0669 to K.M.

ADDITIONAL INFORMATION

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