Kidney cancer

Targeting glutamine use in RCC

Glutamine metabolism is dysregulated in renal cell carcinoma (RCC) and is being exploited as a therapeutic target. DeBerardinis and colleagues suggest that multiple strategies might be required to disrupt glutamine catabolism in RCC.

The researchers established patient-derived RCC tumour graft lines with similar genomic and metabolic alterations to those observed in human clear cell RCC. In mice bearing these *VHL*-mutant tumour grafts, an infusion of [U-^{13}C]glutamine led to enrichment of ^{13}C in glutamate and TCA cycle intermediates in the tumour grafts compared with normal kidney tissue. [^{11}C]glutamine PET/CT also suggested that glutamine is a key carbon source in these tumours in vivo.

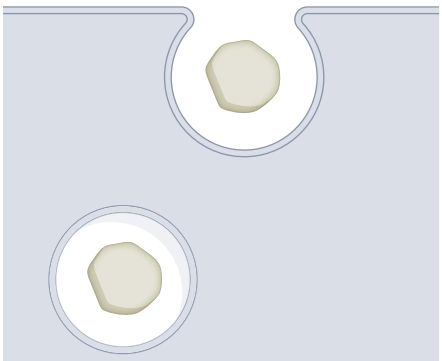
The glutaminase inhibitor CB-839, which has had a positive therapeutic effect in some patients with RCC, successfully reduced ^{13}C enrichment in glutamate, α-ketoglutarate and malate in a xenograft model compared with vehicle controls, but tumour volume was unaffected; residual glutamate labelling could still be observed in treated animals. Infusion of glutamine labelled on the amide nitrogen, which is acquired by orotate, confirmed that CB-839 could not fully disrupt glutamine metabolism, as labelled orotate was enriched in tumours compared with blood. In a xenograft model, the experimental amidotransferase inhibitor JHU-083 could not suppress the labelling of TCA cycle intermediates but reduced tumour growth compared with vehicle, suggesting that combination therapies might be required.

Monica Wang

Original article: Kaushik, A. K. et al. In vivo characterization of glutamine metabolism identifies therapeutic targets in clear cell renal cell carcinoma. *Sci. Adv.* eabp8293 (2022)

Physiology

VPS34 functions in the proximal tubule



VPS34 is a PI3K that is involved in endo-lysosomal and cellular processes, such as vesicle trafficking and metabolism. New findings now demonstrate that VPS34 also influences important endocytic, transport and metabolic processes in the kidney proximal tubule — a region that is important for transport and metabolic functions.

To better understand the role of VPS34 in the proximal tubule, Markus Rinschen and colleagues generated mice with inducible, tubule-specific deletion of VPS34. The mice were viable but demonstrated indices of kidney dysfunction, associated with some structural anomalies and alterations in the localization of proximal-tubule endocytic receptors. Proteomic analyses revealed a decrease in the abundance of nutrient transporters and in proteins of the retromer complex — a key component of the endosomal protein-sorting machinery. These changes were associated with a reduction in gluconeogenesis and a corresponding increase in β-oxidation and glutamine metabolism.

The researchers also noted a decrease in the abundance of apically located virus receptors, such as ACE2, in the knockout mice. Moreover, inhibition of VPS34 suppressed the ability of SARS-CoV-2 to infect human kidney organoids and cultured proximal-tubule cells. The authors say their work highlights functions of VS34 that may be important in the context of viral and metabolic disease.

Susan J. Allison

Original article: Rinschen, M. M. et al. VPS34-dependent control of apical membrane function of proximal tubule cells and nutrient recovery by the kidney. *Sci. Signal.* **15**, eabo7940 (2022)

Metabolism

Fasting induces structural and functional changes in the peritoneal membrane

A new study reports that fasting induces changes in aquaporin expression, water transport and adipocyte metabolism in the peritoneal membrane. These findings might have clinical relevance for patients on peritoneal dialysis.

The researchers focused on the most abundantly expressed aquaporins in the peritoneal membrane: AQP1, which facilitates water transport during peritoneal dialysis, and AQP7, which regulates glycerol efflux from adipocytes during fasting. They show that in human and mouse visceral adipose tissue, AQP1 is expressed in the microvascular endothelium, whereas AQP7 is mainly expressed in adipocytes.

In mice, fasting resulted in decreases in plasma glucose, body weight, body fat and adipocyte size; increases in plasma glycerol and corticosterone levels; changes in the levels of lipogenic and lipolytic factors; and upregulation of AQP1 and AQP7 in the peritoneum. Fasting also induced a significant increase in net ultrafiltration with no change in the transport of small solutes in a mouse model of peritoneal dialysis. Further studies using mice with knockout of *Aqp1* or *Aqp7* and a glucocorticoid antagonist demonstrated that AQP7 regulates the size of adipocytes in the peritoneal membrane, whereas the effect of fasting on ultrafiltration is mediated by glucocorticoid-induced upregulation of AQP1.

The researchers conclude that fasting induces a coordinated regulation of lipolytic and lipogenic factors in the visceral peritoneum with upregulation of AQP1 and AQP7, resulting in structural and functional changes in the peritoneal membrane. They speculate that a reduction in food intake might improve fluid removal during peritoneal dialysis and that factors that modulate AQP7 expression could potentially be beneficial for patients who experience an increase in visceral abdominal fat while receiving this treatment.

Ellen F. Carney

Original article: Costa, I. P. D. et al. Fasting influences aquaporin expression, water transport and adipocyte metabolism in the peritoneal membrane. *Nephrol. Dial. Transport.* https://doi.org/10.1093/ndt/gfac318 (2022)

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