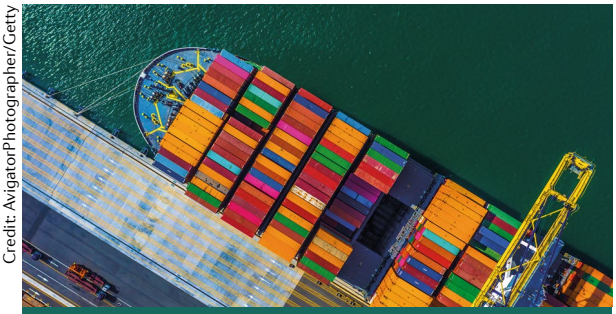

Credit: AvigatorPhotographer/Getty

METABOLISM

Newly characterized mitochondrial BCAA transporter

Emerging evidence suggests that brown adipose tissue (BAT) has roles outside of thermogenesis, including acting as a metabolic sink for glucose and fatty acids. Now, Shingo Kajimura and colleagues report that the catabolism of branched-chain amino acids (BCAAs) in BAT is reliant on a newly characterized mitochondrial BCAA transporter, SLC25A44.

"The existence of a mitochondrial BCAA transporter has been suggested for over 20 years," explains Kajimura. "Many cells contain the mitochondria-localized branched-chain aminotransferase, BAT2, which suggests that BCAAs could be transported into the mitochondrial matrix, but whether this is the case or not has been a long-standing mystery." As BAT exclusively utilizes BCAAs in the mitochondria, the authors felt that BAT would be an ideal discovery tool in the search for a mitochondrial BCAA transporter.

To investigate the role of BAT in BCAA uptake, Kajimura and colleagues used genetic mouse models, including BAT-deletion mice (UCP1-Cre x PPARγ) and mice that had the key enzyme for BCAA catabolism, BCKDH, deleted specifically from BAT. "We unexpectedly found that BAT actively uptakes BCAAs and promotes BCAA clearance from the circulation," explains Kajimura. "In addition, the disruption of BCKDH in BAT impaired BCAA clearance and induced obesity and diabetes mellitus in mice."

Next, Kajimura and colleagues used biochemical techniques and conducted metabolomics in mice and humans to further investigate the role of BAT as a metabolic sink. The team found that in response to cold stimuli, mitochondria within BAT potently uptake BCAAs, which in turn promotes the clearance of BCAAs from the circulation. The uptake of BCAAs into mitochondria was reliant on the mitochondrial BCAA transporter SLC25A44, which is part of the SLC25A family of solute carrier transporter proteins.

The authors now want to investigate whether it is possible to enhance the mitochondrial BCAA transport activity. "BCAA oxidation in mitochondria is impaired in individuals with obesity and patients with diabetes mellitus," concludes Kajimura "The enhancement of mitochondrial BCAA transport activity could be a new therapeutic opportunity for these diseases."

Alan Morris

ORIGINAL ARTICLE Yoneshiro, T. et al. BCAA catabolism in brown fat controls energy homeostasis through SLC25A44. *Nature* **572**, 614–619 (2019)

IMMUNOMETABOLISM

New roles for inflammation-associated hormone

The function of growth and differentiation factor 15 (GDF15), which is an inflammation-associated hormone, is not well defined. A study published in *Cell* now identifies new roles for GDF15 in mediating tissue tolerance through metabolic adaptation during acute inflammation.

Sepsis is a condition of maladaptive inflammation and tissue damage in response to a systemic infection. The researchers examined serum samples of patients with sepsis induced by bacteria, viruses or both agents, and found that GDF15 levels were elevated in all cases. Moreover, plasma levels of GDF15 were increased in mouse models of bacterial and viral inflammation. Interestingly, GDF15 was necessary for survival in these mouse models, as antibody blockade of GDF15 led to significantly more mortality.

In both mouse models of bacterial and viral inflammation, GDF15 was found to be cardioprotective, as antibody blockade of plasma GDF15 was associated with cardiac tissue damage and altered cardiac function. GDF15 blockade was also associated with decreased body temperature in the mouse model of bacterial inflammation.

An assessment of multiple metabolic parameters in the mouse model of bacterial inflammation found that GDF15 blockade was associated with significantly decreased serum levels of all triglycerides. Further analysis revealed that this decrease was owing to reduced hepatic triglyceride production and export caused by impaired hepatic β-adrenergic signalling.

Finally, intraperitoneal administration of a triglyceride formula commonly given to

NEUROENDOCRINOLOGY

GIP's role in energy balance and leptin resistance

The actions of leptin, a key hormone in the control of energy balance, are disrupted in obesity. However, the drivers underlying leptin resistance in neurons during obesity have been unclear; new research aims to address this gap in our knowledge.

"We have screened for circulating factors that potentially cause leptin resistance using cultured brain slices," explains author Makoto Fukuda. "The gut-derived hormone GIP came up as a potent hit as a cause of leptin resistance, which turned our attention to a potential link between GIP, the brain and metabolism." The researchers used a range of approaches to investigate the actions of GIP, including Gipg03 — a neutralizing monoclonal antibody for the GIP receptor.

Central administration of Gipg03 reduced the body weight, food intake and fat mass of high-fat diet-fed obese mice, and serum levels of leptin were also decreased in these mice. Furthermore, brain infusion of Gipg013 resulted in decreased expression of SOC3, which is a protein that inhibits leptin signalling.

Next, the researchers injected GIP into the lateral ventricles of lean C57BL/6J mice and assessed leptin sensitivity. They found that the injection of GIP resulted in the anorectic response to exogenous leptin becoming blunted. These effects were not seen when mice lacking *Gipr* were injected, which shows that GIP acts through its receptor to blunt leptin-dependent effects.

Previous work has shown that neural RAP1 drives leptin resistance, so the researchers also centrally injected GIP into mice with *Rap1* deficiency. These mice were protected from GIP-mediated leptin resistance, unlike their littermate controls, which suggests that activation of RAP1 is also necessary