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A new branch connecting thermogenesis and diabetes

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Abstract

Systemic accumulation of branched-chain amino acids (BCAAs) is a major metabolic hallmark and contributor to insulin resistance associated with obesity. A recent report identifies SLC25A44 as the BCAA transporter in mitochondrial membranes and shows that BCAA catabolism in brown adipose tissue significantly affects thermogenic activity, systemic BCAA clearance, energy expenditure and overall metabolic health.

The predominant paradigm for the pathogenesis of obesity and diabetes has long been that increased intake or dysregulated metabolism of fat and sugar drive disease. Therefore, much effort has been made to restore fatty acid and glucose homeostasis in overweight individuals and those with diabetes. However, 50 years ago, the Cahill laboratory made a puzzling clinical observation that the plasma levels of several amino acids, including all the BCAAs, are significantly elevated in obese individuals and positively correlated with the severity of insulin insensitivity[1]. This finding went largely unnoticed until about 10 years ago, when the Newgard laboratory published a landmark study using unbiased metabolomic profiling and found that the plasma levels of BCAAs were the most significant metabolic signature associated with the severity of insulin resistance among obese individuals[2]. Several follow-up studies based on human genetics, clinical analysis and animal models subsequently demonstrated that impaired BCAA catabolism is not only a metabolic hallmark associated with diabetes and obesity but also a significant contributor to the disease onset and progression[3–6]. These studies led to the emergence of a new paradigm implicating BCAA catabolic activity in the pathogenesis of obesity-associated diabetes. Indeed, pharmacological enhancement of BCAA catabolic activity has been shown to be highly efficacious in ameliorating insulin resistance and hyperglycaemia in experimental models of diabetes and obesity[3,7], thus suggesting that targeting BCAA catabolism has therapeutic potential[8,9].

However, the mechanisms underlying BCAA-mediated global metabolic regulation remain enigmatic. An earlier hypothesis from Cahill proposed that elevated BCAA levels might be a compensatory, and perhaps even beneficial, response necessary to promote insulin production and secretion from pancreatic β-cells[1]. However, this hypothesis does not explain how BCAA accumulation promotes insulin resistance. Recently, a downstream catabolic

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Competing interests

The authors declare no competing interests.

product of valine, 3-hydroxyisobutyrate, has been shown to promote lipid uptake in skeletal muscle, thus linking BCAA catabolism to lipotoxicity and insulin resistance in muscle tissue under chronic metabolic challenge[10]. More recently, Newgard and colleagues have uncovered that hepatic ATP-citrate lyase is another functional substrate of the branched-chain α-ketoacid dehydrogenase kinase[4], thus offering a potential molecular link between the BCAA catabolic machinery and fatty acid accumulation in the liver, another common pathological feature that can promote insulin resistance. However, the association between BCAAs and diabetes appears to be specific to obese rather than lean individuals[2,3], thus suggesting an indispensable involvement of adipose tissue in BCAA-induced insulin resistance. In addition, there are major gaps in the current knowledge of BCAA function in adipose tissue under physiological or pathological conditions. As reported in *Nature,* Yoneshiro et al. have now offered some interesting and potentially important new insights into BCAA function in the regulation of thermogenic activity and energy expenditure in brown adipose tissue (BAT)[11].

BAT is a major site of thermogenesis and energy expenditure, particularly under hypothermic challenge. Yoneshiro et al. first investigated the effects of cold exposure on metabolic profiles in humans and mice. Although fatty acids and glucose are the main fuels used in BAT for thermogenesis, the authors observed a significant decrease in plasma BCAA levels, which correlated with thermogenic activity in BAT. The connection between BAT activity and BCAA levels was corroborated by the observation that BAT had the highest BCAA catabolic activity among different adipose tissues, and this activity increased further after cold exposure. To further establish the direct causal relationships among BAT-specific BCAA uptake and utilization, global BCAA clearance and thermogenic activity, the investigators generated a mouse model in which BCAA catabolic activity was specifically inhibited in BAT. In this model, BAT-specific inhibition of BCAA catabolism led to systemic impairment of BCAA clearance. More importantly, inhibition of BCAA catabolism in BAT increased weight gain, glucose intolerance and insulin resistance when animals were fed a high-fat diet. Therefore, the study provides the first evidence that normal BCAA catabolic activity is essential for BAT thermogenesis and contributes to organismal energy expenditure. BAT-specific BCAA catabolic activity is not only relevant to systemic BCAA clearance but also an important contributor to overall metabolic health and the pathogenesis of obesity and insulin resistance.

Yoneshiro et al. also uncovered an important missing piece in the catabolic machinery for BCAA[11]. Because the biochemical machinery of BCAA catabolism is located primarily in the mitochondrial matrix, where BCAA degradation occurs, BCAAs must be transported from the cytosol across the mitochondrial membrane. The molecular identity of this transporter had previously been unknown. In this report, the authors identified SLC25A44, a member of the mitochondrial membrane transporter family with no known substrate, as the elusive mitochondrial transporter of BCAA and validated its specificity with extensive cellular and cell-free assays. Furthermore, genetic inactivation of the *Slc25a44* gene in BAT recapitulated the effects of BCAA catabolic inhibition on thermogenic effects, systemic BCAA clearance and cell-autonomous energy expenditure, thus validating the indispensable role of this transporter in BCAA catabolic flux (Fig. 1).

The emerging importance of BCAA in metabolic regulation and health clearly involves diverse mechanisms that probably operate in a cell-type specific manner. The report by Yoneshiro et al. has revealed substantial pieces to the overall puzzle by delineating the functional importance of BCAAs in BAT physiology and organismal energy expenditure as well as by establishing the molecular identity of the BCAA mitochondrial transporter. However, many questions remain to be answered. For example, although BCAAs drive de novo lipogenesis in adipose tissue[12], BCAA-derived branched-chain fatty acids constitute only a small fraction of the total fatty acid pool used by BAT during thermogenesis[11]. Therefore, BCAAs are likely to serve as signalling molecules in metabolic control, for example by inhibiting the activity of the key glycolytic enzyme pyruvate dehydrogenase[13]. Whether BCAA accumulation or BCAA catabolic-flux defects are the ultimate culprit in insulin resistance remains to be demonstrated. Given that BCAA function and catabolic activity vary among different tissues, BCAA catabolic defects in skeletal muscle, heart, liver and fat may have different effects on local and global metabolic activities[4,12,13]. How BCAAs cross-interact and contribute to systemic insulin resistance, for example via indirect influences on amino acid balance and appetite control[14], will also need to be fully elucidated. Finally, the identification of the mitochondrial BCAA transporter might provide an exciting new molecular target to manipulate BCAA catabolic activity to treat metabolic and other disorders.

Beyond metabolic disorders, BCAA catabolic activity has been implicated in many other human diseases, including genetic disorders such as maple syrup urine diseases, heart failure, cancer and neurological diseases[9]. The molecular and metabolic insights revealed in this study may also shed new light on the pathogenic processes of these human diseases.

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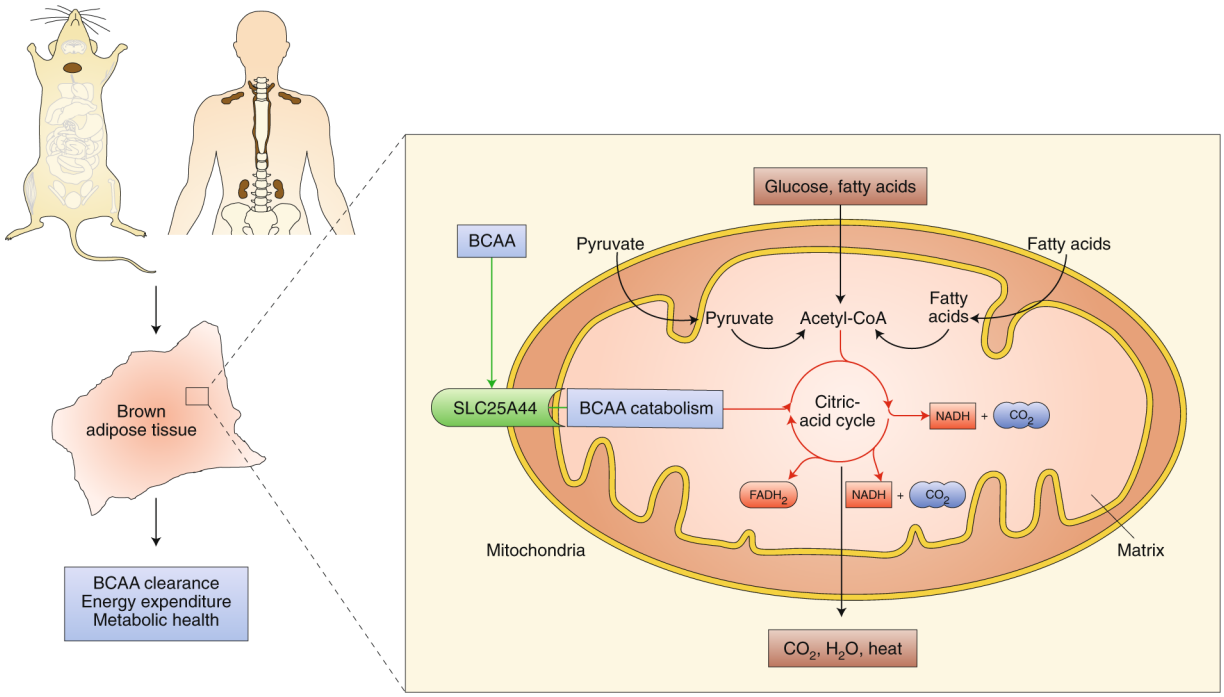

Fig. 1 |. Illustration of BCAA transportation across the mitochondrial membrane and intra-mitochondrial catabolism in BAT.

BCAA catabolism in BAT regulates thermogenesis and organismal energy expenditure, obesity and diabetes.