Commentary

BAT Expansion: A Panacea against Obesity? Lessons from LKB1

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Obesity is defined as a state where excess fat accumulation in the white adipose tissue (WAT) causes adverse health problems (Cui et al., 2017). The major concern of obesity is its association with insulin resistance, type 2 diabetes and fatty liver, as well cardiovascular disorders and several types of cancer (Renehan et al., 2015; Cui et al., 2017). Therefore, controlling obesity should have a beneficial knock-on effect on all these dreadful complications. For this reason, much effort is currently invested on identifying the basic molecular mechanisms controlling energy balance.

The brown adipose tissue (BAT) is a specialized tissue responsible for heat production through non-shivering thermogenesis (NST), which elevates energy expenditure and reduces adiposity and circulating lipids. This thermogenic property of BAT is mediated by uncoupled protein 1 (UCP1), a mitochondrial protein that uncouples electron transport from ATP production, leading to generation of heat (Nedergaard and Cannon, 2014). Thermogenic cells were also identified in WAT. The beige or brite (“brown in white”) adipocytes can be induced (a process called browning) by sympathetic innervation, cold exposure and chemical or hormonal stimulations (Nedergaard and Cannon, 2014). Notably, although BAT was traditionally considered important only in small or hibernating mammals and in newborn humans, brown and beige fat cell have recently been detected in adult people (Nedergaard et al., 2007; Nedergaard and Cannon, 2014). Nevertheless, BAT is known to improve metabolic health, the long-term consequences of such pharmacological activation (Broeders et al., 2015) and/or BAT expansion (Shan et al., 2016) have been proposed, the possible side effects of these strategies remain still obscure.

In this issue of EBioMedicine, Shihuan Kuang and colleagues move beyond the simple expansion of BAT to show that BAT expansion is associated to harmful side effects that may discard it as therapeutic option (Xiong et al., 2017). This is of relevance, because other approaches of BAT expansion may not render the same devastating effects and therefore be suitable clinical options. A direct effect of LKB1 in neuronal degenerative effects have been reported. The rat insulin 2 promoter-Cre (RIP2-Cre) model leads to deletion of LKB1 mainly in pancreatic beta-cells but also leads to ectopic deletion of LKB1 in the nervous system (spinal cord and some brain parts). These animals also develop hindlimb dysfunction and axon degeneration, reduced nerve conductance and hindlimb paralysis, intestinal inflammation and neuropathy characterized by abnormal axon morphology, axon degeneration, reduced nerve conductance and hindlimb paralysis, starting at the age of 8 months (See. Fig. 1) (Shan et al., 2016). Overall, these results suggest that inhibition of LKB1 in adipocytes could be an interesting strategy to increase energy expenditure in the context of obesity. However, a deeper analysis of this mouse model, as reported in this issue of EBioMedicine, reveals that knocking down LKB1 in adipocytes induces late-onset expression of inflammatory cytokines in interscapular BAT (but not WAT) and epineurial brown adipocytes, eliciting macrophage infiltration in sciatic nerves (Xiong et al., 2017). This process, that occurs through decreased AMPK phosphorylation and activation of mechanistic target of rapamycin (mTOR) pathway, leads to peripheral neuropathy characterized by abnormal axon morphology, axon degeneration, reduced nerve conductance and hindlimb paralysis, starting at the age of 8 months (See. Fig. 1). Notably, pharmacological or genetic inhibition of mTOR ameliorates inflammation and prevents paralysis (Xiong et al., 2017).

The implication of these data relates to several novel findings, with relevance in the clinical practice. Firstly, Kuang and colleagues describe a new mechanism linking BAT expansion with peripheral neuropathy. Therefore, although manipulation of BAT function and expansion is known to improve metabolic health, the long-term consequences of this manipulation are associated to harmful side effects that may discard it as therapeutic option. In this regard, a question that needs to be addressed is whether BAT inflammation and neuropathy are processes linked to BAT expansion per se or exclusively to LKB1 manipulation. This is of relevance, because other approaches of BAT expansion may not render the same devastating effects and therefore be suitable clinical options. A direct effect of LKB1 in neuronal degenerative effects have been reported. The rat insulin 2 promoter-Cre (RIP2-Cre) model leads to deletion of LKB1 mainly in pancreatic beta-cells but also leads to ectopic deletion of LKB1 in the nervous system (spinal cord and some brain parts).
Degeneration associated to demyelination and macrophage infiltration (Sun et al., 2011); whether this manipulation is associated to BAT hypertrophy is unknown. By contrast, in the adipocq-Cre model in Kuang study, the authors did not detect direct deletion of LKB1 in the nervous system. Other studies have also established the adipocyte specificity of the adipocq-Cre mouse (Lee et al., 2013). Therefore, the phenotype in adipocq-Cre model is unlikely due to a direct effect of LKB1 in neuronal cells. Secondly, these data suggest that inhibition of mTOR signaling is an efficient strategy for the clinical treatment of inflammation-induced peripheral neuropathy and subsequent paralysis. This is also supported by recent data about RAD001 (everolimus), an analog of rapamycin and the only mTOR inhibitor approved by the Food and Drug Administration (FDA) for the treatment of several types of cancer. Treatment with RAD001 protects rats from the symptoms of experimental autoimmune neuritis, as shown by decreased paralysis, diminished inflammatory cell infiltration, reduction in demyelination of peripheral nerves and improved nerve conduction, by a mechanism involving the downregulating of pro-inflammatory cytokines as well as upregulating the release of anti-inflammatory cytokines (Han et al., 2016). Therefore, alongside those data, the current evidence indicates that in addition to its role in cancer therapy, mTOR can be a promising clinical target for the treatment of inflammation-induced neuropathies.

In summary, the new study of Kuang and colleagues establishes the pathophysiological role of LKB1 ablation in brown fat, which, despite improving metabolic disturbances, is associated to middle age neuropathy and specific hindlimb paralysis. Of note, inhibition of the mTOR pathway counteracts these deleterious side effects. Overall, the relevance of these findings has a clear translational potential as it may provide new clinical strategies not only for the treatment of obesity but also to ameliorate some of the symptoms of damage or diseases affecting peripheral nerves.

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Competing interest

Author declares no competing (financial, personal or professional) of interest.
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