Mitochondrial fission: firing up mitochondria in brown adipose tissue

Arwen W Gao & Riekelt H Houtkooper

Brown adipose tissue (BAT) is an important site for energy expenditure, for instance to generate heat in times of cold exposure. BAT expansion and activation can increase energy dissipation of an organism. This involves the coordinated activation of mitochondrial metabolism and heat generation through uncoupling of oxidative phosphorylation. In this issue of The EMBO Journal, the Shirihai group uncovers a novel potentiation pathway for BAT energy expenditure. Changes in mitochondrial dynamics, in particular mitochondrial fission, act in synergy with fatty acid-induced uncoupling to activate BAT metabolism in response to the hormone norepinephrine.

See also: J Wikstrom et al (March 2014)

Energy expenditure refers to the breakdown of nutrients in response to external cues and is used to generate usable energy. For instance, physical exercise increases nutrient oxidation and ATP synthesis in muscle tissue, while cold exposure increases energy expenditure in BAT for the generation of heat (Liesa & Shirihai, 2013). This involves the coordinated activation of mitochondrial function, such as enhanced fat breakdown and oxidative phosphorylation. While normally acting in healthy metabolism, changes in mitochondrial function are often observed in cells or tissues of patients with metabolic disorders, such as insulin resistance or type 2 diabetes. This suggests that mitochondrial dysfunction is key to these disorders. As a result, deficient mitochondrial oxidative capacity leads to accumulation and toxicity of lipids in adipose tissue, skeletal muscle and the liver of these patients (Schooneman et al, 2013).

With this in mind, therapies are being developed to improve mitochondrial metabolism and energy homeostasis in the context of metabolic disease (Andreux et al, 2013). These therapies are primarily aimed to induce mitochondrial biogenesis, and several promising compounds have emerged over the last decade. What has become apparent, however, is that merely increasing the number of mitochondria may not be sufficient to rescue its function. Therefore, efforts are centered around improving mitochondrial quality control, such as the unfolded protein response, antioxidants, and mitophagy (Andreux et al, 2013). Mitochondrial dynamics provide another layer of mitochondrial quality control and involves repetitive cycles of mitochondrial fusion and fission, which are followed by selective degradation of non-functional mitochondria (Youle & van der Bliek, 2012). Indeed, mitochondrial dynamics change with nutritional conditions and are important to maintain healthy mitochondrial function; mitochondria under caloric excess maintain a fragmented state, whereas mitochondria under caloric restriction stay primarily in a fused state (Liesa & Shirihai, 2013). But how is mitochondrial dynamics caused in normal physiology?

In this issue, Wikstrom and colleagues demonstrate how mitochondrial fission serves as a physiological regulator for energy expenditure in BAT (Wikstrom et al, 2013). BAT energy expenditure is induced upon cold exposure by adrenergic stimulation. While norepinephrine (NE) is known to stimulate the release of free fatty acid from adipose tissue and subsequent mitochondrial uncoupling (Fedorenko et al, 2012), this does not fully explain the activation of BAT thermogenesis. Therefore, Wikstrom et al set out to investigate amplifying mechanisms and focused on mitochondrial architecture. Indeed, both cold exposure and adrenergic stimulation induced rapid mitochondrial fragmentation that precedes the depolarization associated with heat production (Wikstrom et al, 2013). This involves PKA-dependent phosphorylation of the fusion protein DRP1 at the specific serine-600 residue (Han et al, 2008). Importantly, proper mitochondrial fission was essential to potentiate depolarization. Blocking fission using a dominant negative mutant of DRP1 blunted depolarization. On the other hand, forcing mitochondria into a fragmented state by inhibiting the fusion machinery enhanced the susceptibility to fatty acid-induced uncoupling. Taken together, mitochondrial reorganization and free fatty acid release synergize to facilitate uncoupling and thereby heat production (Wikstrom et al, 2013).

The bimodal activation of heat production in BAT, involving rapid reorganization of mitochondrial ultrastructure and lipid-induced uncoupling (Fig 1), may represent a fail-safe to prevent relentless nutrient breakdown. This suggests that only when adrenergic stimulation activates both branches of the pathway, energy expenditure reaches its full capacity. Despite the recent progress in our understanding of mitochondrial morphology and its impact on metabolic functionality, several questions remain. For instance, how does mitochondrial morphology and BAT thermogenesis respond to cold exposure/NE-stimulation under physiological conditions of lipid accumulation? How do these change during fasting or obese conditions? Do similar mechanisms exist in other tissues or cell types? Interestingly, it
was previously shown that starvation leads to remodeling of mitochondria in cultured cells into a more fused state, which is associated with maintained ATP levels and prevention of mitochondrial breakdown through autophagy (Gomes et al., 2011).

Conversely, and supporting the new findings of Wikstrom et al. (2014), mutant mice for the mitochondrial plasticity regulator Oma1 display mitochondrial hyperfusion, but are generally obese with impaired cold tolerance (Quiros et al., 2012). It will hence be imperative to understand the tissue-specific effects of mitochondrial fission on energy expenditure and dissociate how physiological cues impact these processes before therapies targeting mitochondrial dynamics can be widely applied.

Acknowledgements
RHH is financially supported by a ZonMw-VENI grant (number 91613050).

Conflict of interest
The authors declare that they have no conflict of interest.

References