Mitochondrial fission: firing up mitochondria in brown adipose tissue

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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 Shirihi 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 & Shirihi, 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 Blik, 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 & Shirihi, 2013). But how is mitochondrial dynamics causally involved 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 fission 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

Figure 1. Role of mitochondrial dynamics in brown adipose tissue energy expenditure.

Upon cold exposure, mitochondrial oxidative phosphorylation needs to become uncoupled to generate heat. Wikstrom and colleagues show how mitochondrial fission potentiates free fatty acid-induced uncoupling. The cold-induced hormone norepinephrine (NE) induces a biphasic response. First, PKA-dependent phosphorylation at serine-600 of dynamin-related protein 1 (DRP1) leads to its accumulation on mitochondria, promoting fission and sensitizing the mitochondria to free fatty acids. In parallel, NE induces free fatty acid release from lipid droplets. The concerted actions following adrenergic stimulation lead to uncoupling in brown adipocytes and increase energy expenditure through heat production.

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.* (Wikstrom *et al.*, 2013), 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.

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Conflict of interest

The authors declare that they have no conflict of interest.

References

- Andreux PA, Houtkooper RH, Auwerx J (2013) Pharmacological approaches to restore mitochondrial function. *Nat Rev Drug Discov* 12: 465–483
- Fedorenko A, Lishko PV, Kirichok Y (2012) Mechanism of fatty-acid-dependent UCP1 uncoupling in brown fat mitochondria. *Cell* 151: 400–413
- Gomes LC, Di Benedetto G, Scorrano L (2011) During autophagy mitochondria elongate, are spared from degradation and sustain cell viability. *Nat Cell Biol* 13: 589–598
- Han XJ, Lu YF, Li SA, Kaitsuka T, Sato Y, Tomizawa K, Nairn AC, Takei K, Matsui H, Matsushita M (2008) CaM kinase I alpha-induced phosphorylation of Drp1 regulates mitochondrial morphology. *J Cell Biol* 182: 573–585
- Liesa M, Shirihai OS (2013) Mitochondrial dynamics in the regulation of nutrient utilization and energy expenditure. *Cell Metab* 17: 491–506
- Quiros PM, Ramsay AJ, Sala D, Fernandez-Vizarra E, Rodriguez F, Peinado JR, Fernandez-Garcia MS, Vega JA, Enriquez JA, Zorzano A, Lopez-Otin C (2012) Loss of mitochondrial protease OMA1 alters processing of the GTPase OPA1 and causes obesity and defective thermogenesis in mice. *EMBO J* 31: 2117–2133
- Schooneman MG, Vaz FM, Houten SM, Soeters MR (2013) Acylcarnitines: reflecting or inflicting insulin resistance? *Diabetes* 62: 1–8
- Wikstrom JD, Mahdavian K, Liesa M, Sereda SB, Si Y, Las G, Twig G, Petrovic N, Zingaretti C, Graham A, Cinti S, Corkey BE, Cannon B, Nedergaard J, Shirihai OS (2014) Hormone-induced mitochondrial fission is utilized by brown adipocytes as an amplification pathway for energy expenditure. *EMBO J* 33: 418–436
- Youle RJ, van der Bliek AM (2012) Mitochondrial fission, fusion, and stress. *Science* 337: 1062–1065