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Mitofusins: Mighty Regulators of Metabolism

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Mitochondria are central regulators of cellular metabolism but how their function in a subset of cells affects whole-body energy balance is less understood. Two studies in this issue of *Cell* identify how diet-dependent modulation of mitochondrial fusion in specific neuronal circuits impact the metabolic status of an animal.

The involvement of mitochondria in eukaryotic cellular functions has been known for over 100 years (Ernster and Schatz, 1981). Mitochondria play fundamental roles in providing the energetic needs for cellular function (Ernster and Schatz, 1981), cellular death (apoptosis via caspases (Green, 1998), and damage (e.g., via generation of reactive oxygen species). Structure-function studies starting from the classic pioneering electron microscopy (EM) work of Palade (Palade, 1953) also revealed that mitochondria are dynamically changing organelles interacting with many intracellular organelles, including the endoplasmic reticulum (ER). It is less clear, however, how these intracellular events govern systemic functions and, whether mitochondrial dynamics in specific subpopulations of cells impact the integrative physiology of the organism. Two related papers in this issue of *Cell* address these issues by providing new clues into how neuronal mitochondria contribute to the regulation of whole body energy metabolism.

In the first paper, EM studies by Dietrich et al. (2013) report that mitochondria in hypothalamic neurons that produce the orexigenic peptide, agouti-related peptide (Agrp), demonstrate distinctions in terms of number, shape, and size depending on the metabolic state of the animal. They also find that these changes are under the control of mitofusins 1 and 2, which are nuclear encoded proteins involved in mitochondrial fusion in response to feeding and overfeeding. Mitofusin 2, in particular also has a role in anchoring mitochondria to the ER (Ishihara et al., 2004; Santel et al., 2003; Eura et al., 2003). Specifically, they demonstrate that mitochondrial fusion in Agrp neurons is a critical response to a high fat diet to mediate weight gain by increased fat mass. If fusion of the mitochondria is disrupted by deletion of either mitofusin, Agrp neurons were electrically impaired and weight gain and fat stores are diminished. To nail down the underlying intracellular events mediating this regulation, Dietrich et al. manipulate intracellular ATP levels with an approach akin to the meticulous efforts of Swiss watchmakers: they performed patch-clamp experiments in individual Agrp neurons without breaking the perikaryal membrane to record membrane potential to find that if ATP levels were equal in Agrp neurons of mitofusin knockout and control mice, the altered electric activity of Agrp neurons disappeared. Thus, Dietrich et al. establish that mitochondrial dynamics controlled by mitofusin 1 and 2 are fundamental contributors to the ability of Agrp neurons to energetically adapt to the changing metabolic environment and increase firing to assure proper storage of excess energy in the form of fat. From an evolutionary perspective, this is a critical trait as food has often been scarce for most species, including humans. While the disruption of mitochondrial fusion blocked weight gain of mice of both genders, remarkably, they detected altered feeding behavior only in female mice lacking mitofusin 2. Whether this is is due to developmental compensatory mechanisms, or because only a subpopulation of Agrp neurons is affected by mitofusins remains to be addressed. Nevertheless, it is intriguing to point out that Dietrich and colleagues now provide a counterpoint to their earlier discovery of plasticity of Agrp neuronal afferents (Pinto et al., 2004; Horvath et al., 2010) in a form of internal mitochondrial plasticity of the same cells.

In contrast, the companion paper by Schneeberger et al. (2013) tells a very different story regarding the role of mitofusin 2 in hypothalamic anorexigenic, pro-opiomelanocortin- (POMC) producing neurons. The authors observe in alterations mitochondrial networks in POMC neurons using confocal microscopy, and by using EM, they find that high fat diet feeding dramatically reduces mitochondria-ER connectivity. This prompted the authors to ask whether molecules responsible tethering the mitochondria to ER could be altered in the hypothalamus of HFD-fed mice. They indeed find that mitofusin 2, levels are suppressed in the hypothalamus of HFD exposed mice. Further, mitochondria in POMC neurons with mitofusin 2 KO have altered shape and decreased contacts with ER. Proper projections of POMC cells were not observable in hypothalamic target cites of these animals and POMC-specific mitofusin 2 KO mice became morbidly obese. What eventually explains these changes in POMC cellular malfunction is the demonstration that absence of mitofusin 2 in POMC neurons leads to a marked induction of ER stress. This leads to ER stress-induced leptin resistance, hyperphagia, reduced energy expenditure and obesity, thereby arguing for a fundamentally important role for mitochondria-ER connectivity for proper ER function. Schneeberger et al. further find that

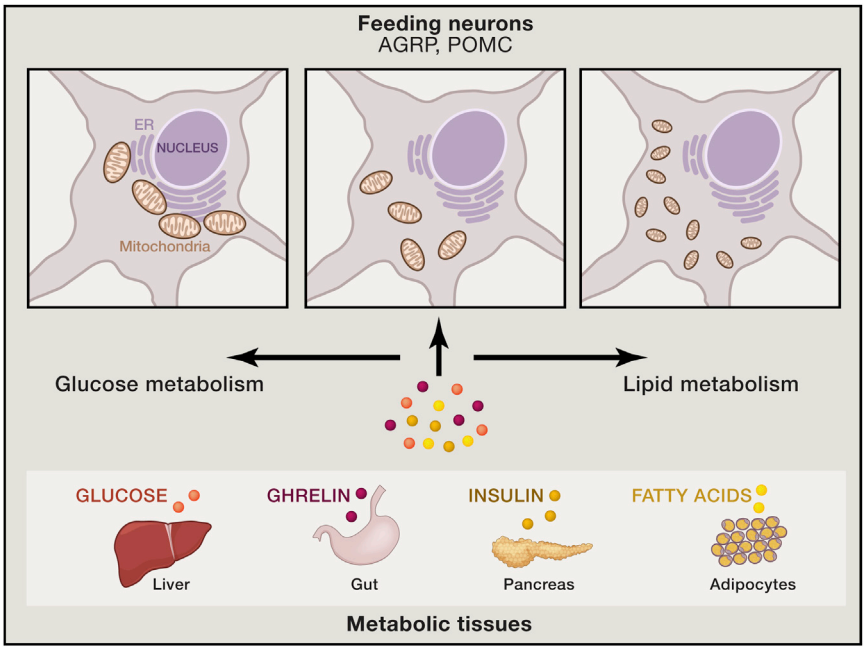

Figure 1. In response to different feeding states, the mitochondria of AGRP and POMC neurons undergo dynamic changes in size and proximity to the ER

These localized changes drive systemic changes in whole-body energy balance and fat mass, likely through modulation of function of distal metabolic tissues and integration of hormonal cues from these tissues back to the hypothalamus.

administration of chemical shaperones are able to blunt the ER stress response in the hypothalamus leading to re-establishment of proper POMC projections and a dramatic reversal of the metabolic phenotype of mice. From this, it is reasonable to assume that the actual projections of POMC cells were likely in place all the time in the mutant mice, but it was the transport of neuropeptides that was blocked due to ER stress. Interestingly, interfering with mitofusin 1 in POMC neurons did not result in phenotypic changes of mice. Note, however, that Agrp -specific mitofusin 1 KO mice also showed no major phenotype on standard chow diet, but when placed on HFD, significant alterations occurred (Dietrich et al.). Whether that may be the case with the POMC-specific mitofusin 1 KO animals, will need further investigations. Additionally, in contrast to Dietrich et al., Schneeberger and colleagues did not assess electric activity of POMC neurons in wild-type and mutant mice. While it is anticipated that altered electric activity of POMC neurons would be present in mitofusin 2 KO mice, this will also need to be tested.

In conclusion, the two papers synergize to provide independent insights to the two subpopulations of hypothalamic neurons revolving around the same proteins involved in mitochondrial fusion. The papers bring new neurobiological insights by unmasking circuit-specific mitochondrial dynamics and highlight the critical importance of cellular biological processes in specific hypothalamic neuronal populations in integrative physiology of whole body energy and glucose metabolism (Figure 1). How the changes in mitochondrial dynamics in these neurons directly affect distal metabolic organs such as the liver, gut and pancreas, as well how hormones or metabolites produced by these organs feed back into the hypothalamus will provide the next avenue of investigation.

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