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The role of mitochondrial derived peptides (MDPs) in metabolism

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The term "mitokines" refers to signals derived from mitochondria that have an impact on other cells or tissues (Durieux et al., 2011). Rather than being simply a set of DNA composed by 37 genes, the mitochondrial DNA (mtDNA) is quite complex and includes small RNAs (Mercer et al., 2011). Mitochondrial-derived peptides (MDPs) are encoded by functional short open reading frames (sORFs) in the mtDNA. Until very recently, humanin, a 24-amino-acid peptide encoded in the 16S rRNA region with strong cytoprotective effects against various stresses and diseases (Hashimoto et al., 2001), was the only recognized MDP. Lee et al have recently reported another MDP, named *mitochondrial open reading frame of the 12S rRNA-c* (MOTS-c), which regulates insulin sensitivity and metabolic homeostasis (Lee et al., 2015).

The peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) is a master modulator of metabolism, with a key function in mitochondrial biogenesis (Sanchis-Gomar et al., 2014). A PGC-1α-related activator that is currently regarded as a putative molecular target to mitigate excess adiposity and insulin resistance is the 5' AMP-activated protein kinase (AMPK) (Price et al., 2012). CNX-012-570, a compound with a highly potent AMPK-activating effect, improves insulin sensitivity and reduces body weight gain (Anil et al., 2014). MOTS-c targets the folate cycle thereby reducing *de novo* purine biosynthesis, which results in accumulation of 5-amino-1-β-D-ribofuranosyl-imidazole-4-carboxamide (AICAR) and subsequent AMPK activation (Lee et al., 2015). Therefore, a positive feed-forward loop could be hypothesized, involving MOTS-c production in mitochondria, cellular AICAR accumulation and AMPK activation, followed by PGC-1α phosphorylation and subsequent enhanced mitochondrial biogenesis, which in turn would increase MOTS-c production.

The effect of MOTS-c on the AMPK axis can affect glucose homeostasis, e.g., MOTS-c infused mice show protection against insulin resistance and obesity induced by a high-

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fat diet (Lee et al., 2015). Although strategies targeting the AICAR-AMPK axis are not new, MOTS-c could be a more suitable pharmacological target since Lee et al showed that a highly metabolic tissue, such as the skeletal muscle, is the key target site for the activity of this mytokine (Lee et al., 2015). Therefore, MOTS-c acts directly on the muscle tissue, where therapies for insulin resistance are likely to exert the strongest possible effect. In addition, liver toxicities induced by drugs like metformin, AICAR or methotrexate could be avoided, emphasizing the great potential of MOTS-c as a target for novel therapies.

The findings presented by Lee et al show that MDPs play a role in whole-body metabolic balance in mice, which highlights the importance of mitochondria not just as end-point fat burners but also as key players in endocrine regulation. Interestingly, the protection conferred by MOTS-c against the deleterious effects of a high-fat diet shares many similarities with that provided by regular exercise (Tofolo et al., 2014). The stimuli elicited by exercise induce phenotype modifications at the skeletal muscle level that increase oxidative capacity and fat utilization while reducing lipid-mediated insulin resistance (Samuel and Shulman, 2012). One of the key factors in the skeletal muscle reprogramming induced by regular exercise is activation of the PGC-1α axis, leading to increased mitochondrial biogenesis, and hence, higher mitochondrial content. In fact, a broad range of PGC-1α-related target activators represent a promising opportunity for treatment of ectopic lipid accumulation (‘lipotoxicity’) and insulin resistance, which are also under current investigation (Srivastava et al., 2012). It is also possible that aging might reduce mitochondrial activity and MDPs expression while regular exercise would have the opposite, ‘anti-aging’ effect (**Figure 1**). According to this point of view, exercise could enhance the endocrine and paracrine action of skeletal muscle-derived MDPs such as MOTS-c.

Lee et al have identified a mitokine that is potentially associated with metabolic diseases such as diabetes and obesity. This newly discovered mitokine could also play an important role in the pathophysiology of aging-related diseases, since, along with mitochondrial dysfunction, reduced expression of MDPs could be responsible, at least partly, for the metabolic imbalance driven by aging (Lee et al., 2015). Interestingly, the potential role of MOTS-c in regulating other biological functions, including perhaps metabolism in cancer cells (by virtue of its inhibiting effect on *de novo* purine synthesis), remains to be studied.

MOTS-c activity and its role in regulating metabolism should be confirmed and better understood (particularly, the putative upstream factors regulating MOTS-c expression) to develop safe and useful drugs to counter obesity and related diseases. A key challenge is to determine whether MOTS-c could be similarly modulated in humans as well as to establish its therapeutic potential. Once these knowledge gaps are filled, the use of mitokines for therapeutic purposes could become a realistic option.

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Conflict of interests

The authors declare no conflict of interests.

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Figure legend

Figure 1. Schematic representation of the role of MOTS-c in metabolism and possible effects of exercise (blue) and aging (red) on the MOTS-c – AMPK axis. Abbreviations:

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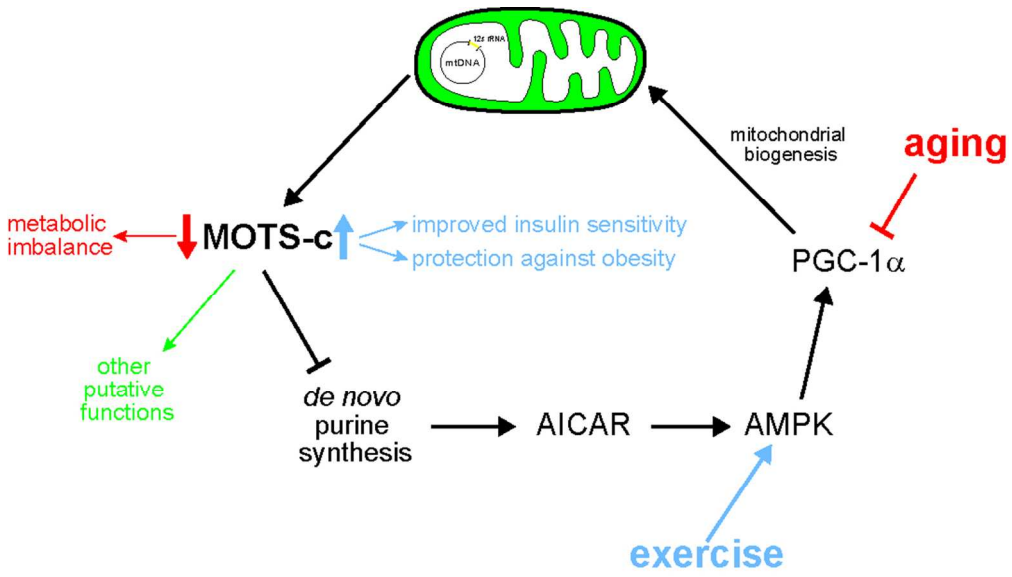
AICAR, 5-amino-1-β-D-ribofuranosyl-imidazole-4-carboxamide; AMPK, 5' AMP-activated protein kinase; MOTS-c, mitochondrial open reading frame of the 12S rRNA-c; mtDNA, mitochondrial DNA; PGC-1α, peroxisome proliferator-activated receptor γ coactivator-1α.



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