Commentary

MOLECULAR METABOLISM

Do mitochondria care about insulin resistance?

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In this issue of Molecular Metabolism, Martin et al. addressed the intensively debated term "mitochondrial dysfunction" in the context of insulin resistance using a comprehensive cell-autonomous approach, which allowed constant substrate delivery to distinct insulin-sensitive cell types circumventing confounding effects of in vivo inter-tissue crosstalk [1]. The authors provoked and titrated the reduction of oxidative phosphorylation (OXPHOS) by inhibiting respiratory complexes I and V in 3T3L1 adipocyte and FAO hepatoma cell cultures, and assessed the effects on insulin sensitivity. Inhibition of OXPHOS reduced the insulin action in adipocytes but had insulin-sensitizing effects in hepatocytes. Interestingly, these effects occurred independently of the production of reactive oxygen species (ROS).

Although using the misleading term "mitochondrial dysfunction", which should be avoided as it implies one unifying abnormality of mitochondria, the authors took effort to assess several interdependent aspects of mitochondrial function such as respiration, membrane potential, and ROS production. An even more comprehensive assessment of mitochondrial function could have been obtained by integrating additional features into this multi-component analysis, such as β-oxidation, tricarboxylic acid (TCA) cycle activity, and mitochondrial content or density. Of note, it is of interest to examine whether their findings would also hold true for other cell types, such as the β-cell or the skeletal muscle cell, which is mainly responsible for insulin-mediated whole-body glucose disposal and oxidative adaptation to physical training as well as a key player in the pathogenesis of insulin resistance and type 2 diabetes mellitus (T2DM).

The finding of tissue-specific functional characteristics of mitochondria is not unexpected, as mitochondrial metabolism is tailored to meet the metabolic and bioenergetic demands of divergent tissues such as brain, heart, liver, adipose tissue, or skeletal muscle by means of their broad range of OXPHOS capacity. This diversity results from different combinations of mitochondrial content, amount of electron transport chain complexes, and their intrinsic activities, which can be viewed as an adaptation to the variable substrate fluxes and may further account for tissue-specific interference of mitochondrial function with insulin sensitivity.

The relationship between mitochondrial function and insulin sensitivity is influenced by various factors: (i) the tissue or cell type, as pointed by the study by Martin et al. [1], (ii) the mitochondrial features examined, (iii) the mode of insulin resistance, and (iv) time-dependent interaction.

First, the postulate that reduced mitochondrial function uniformly associates with insulin resistance is based on studies in human skeletal muscle in vivo and in vitro [2]. Nevertheless, upregulated OXPHOS gene expression has been already found in liver of T2DM patients [3].

Second, inhibition of individual mitochondrial features such as β-oxidation vs. OXPHOS might cause opposing effects on insulin sensitivity. For example, mice exhibiting genetic defects related to impaired β-oxidation exhibit reduced hepatic insulin sensitivity [4], whereas mice with inherited OXPHOS defects can present with improved insulin sensitivity [5]. It is also important to differentiate between the distinct components of one mitochondrial feature such as the respiratory complexes I–V. Martin et al. contribute to unraveling this diversity, by showing differential effects on insulin sensitivity in hepatocytes and adipocytes depending on selective inhibition of complex I or V [1]. These findings might pave the way to novel individualized therapeutic approaches for improving insulin sensitivity, by targeting not only specific tissues and mitochondrial features, but also distinct mitochondrial proteins and their bioactive subunits.

Third, the choice of model of insulin resistance likely affects the results of studies on a relationship between mitochondrial features and insulin sensitivity. In highly insulin resistant first-degree relatives of T2DM patients, reduction of muscle mitochondrial density and function tightly associates with insulin resistance [6], while muscle mitochondrial function is not necessarily impaired in all T2DM patients [7]. Similarly, hepatic mitochondrial function could be enhanced in obese humans with fatty liver, but impaired in patients with T2DM and non-alcoholic steatohepatitis [8]. In this context, the cellular models of insulin resistance such as used in the present study, i.e. tumor necrosis factor-α or chronic insulin exposure, might further influence the results due to their different mechanisms of action.

Finally, opposing alterations of mitochondrial features may occur during the time course of the development of insulin resistance under in vivo conditions. At the onset of diabetes, NOD mice become insulin resistant at the level of both muscle and liver, while oxidative capacity decreases in muscle and transiently rises in the liver [9]. This might result from sequential activation of tissue-specific pathways linked to glucolipotoxicity.

Although the underlying mechanisms remain still unresolved, it has been postulated that the insulin-dependent vs. -independent glucose carriers in myocytes and hepatocytes might render these cells differentially

This commentary refers to "Mitochondrial dysfunction has divergent, cell type-dependent effects on insulin action by Sheree D. Martin et al.", 10.1016/j.molmet.2014.02.001.

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Received March 28, 2014 • Accepted April 1, 2014 • Available online 18 April 2014

http://dx.doi.org/10.1016/j.molmet.2014.04.004

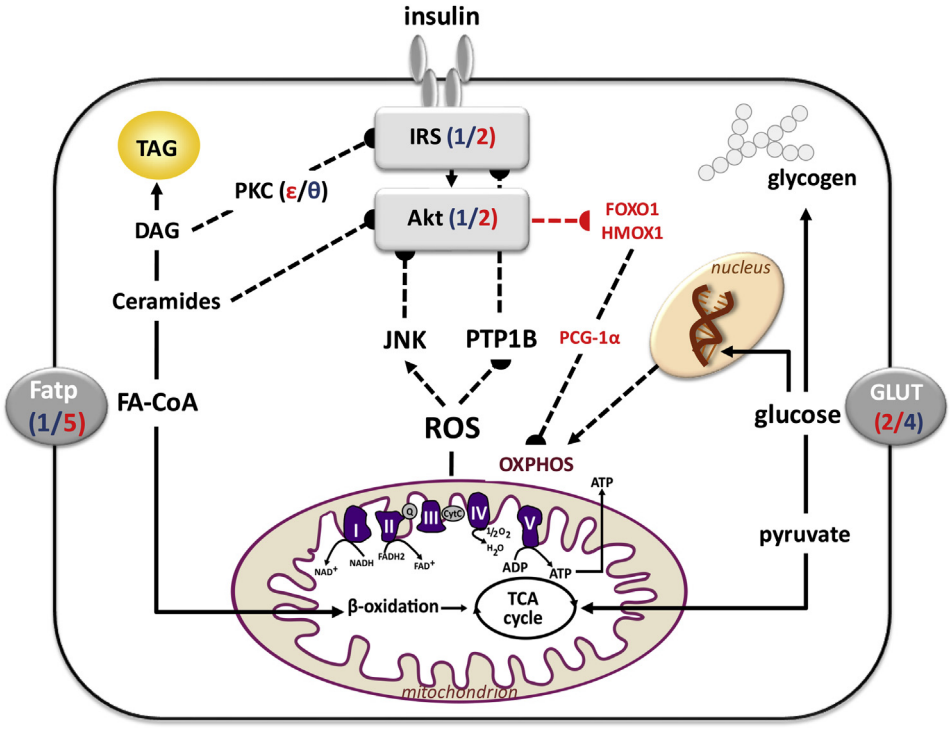

Figure 1: This figure illustrates the major interactions between features of mitochondrial function and insulin action in an unspecified insulin-sensitive cell (hepatocyte or myocyte). Red color denotes liver- and blue color muscle-specific pathways and mediators. In liver tissue, insulin resistance may induce impairment of mitochondrial OXPHOS capacity by failing to suppress FOXO1 and its downstream target HMOX1, leading to a declined NAD^+/NADH ratio, reduced sirtuin action and impaired mitochondrial biogenesis via decreased PGC-1a activity. In both liver and muscle tissue, alterations of distinct mitochondrial features might impact upon insulin sensitivity by altered ROS production and/or incomplete fatty acid oxidation and intracellular accumulation of toxic lipid intermediates such as diacylglycerols and ceramides, which promote ectopic steatosis and disrupt insulin signal transduction. Mitochondrial ROS may either promote insulin resistance by activating stress-induced serine—threonine kinases such as JNK, or enhance insulin sensitivity by oxidatively inhibiting PTP1B, which is a negative regulator of insulin receptor. Based on this dual impact of ROS on insulin sensitivity depending on the tissue involved and the severity of oxidative stress, the role of ROS as possible mediator of the relationship between mitochondrial function and insulin sensitivity needs to be thoroughly assessed, and novel unrecognized mediators need to be identified. Abbreviations: ADP, adenosine diphosphate; ATP, adenosine triphosphate; cytc, cytochrome c; DAG, diacylglycerols; FA-CoA, fatty acid coenzyme A; FADH2, flavine adenine dinucleotide; Fatp, fatty acid transporter protein; FOXO1, forkhead box O1; GLUT, glucose transporter; HMOX1, heme-oxygenase 1; IRS, insulin receptor substrate; I-V, electron transport chain complexes I-V; JNK, c-Jun N-terminal kinase; NADH, nicotinamide adenine dinucleotide; OXPHOS, oxidative phosphorylation; PGC-1a, PPAR γ co-activator 1a; PKC, protein kinase C; PTP1B, protein tyrosine phosphatase 1B; Q, coenzyme Q; ROS, reactive oxygen species; TAG, triacylglycerols; TCA, tricarboxylic acid cycle.

susceptible to the regulatory effects of fasting glycemia on mitochondrial function [3] (Figure 1). Furthermore, the unique mitochondrial characteristics such as the semi-autonomous hepatic TCA cycle, which is not tightly coupled to β-oxidation, need to be considered. On the other hand, greater lipid availability can induce insulin resistance via toxic lipid intermediates such as the diacylglycerol-protein kinase C or the ceramide-toll-like receptor-4 pathway, but maybe also via incomplete fat oxidation (Figure 1). Conversely, lipid exposure can decrease ATP production at least in human skeletal muscle [7].

Another interesting finding of Martin et al. is the uniform absence of any effect of ROS on the relationship between impairment of mitochondrial OXPHOS and insulin sensitivity. This seems counterintuitive, as ROS has been proposed to mediate insulin resistance in the face of lower mitochondrial function. However, at least certain forms of oxidative stress, i.e. exercise training, ameliorate insulin resistance, and induce adaptive responses promoting endogenous antioxidant defense capacity, in line with the concept of mitohormesis [10]. Nevertheless, further research is warranted to re-examine the role of oxidant and anti-oxidant pathways with regard to mitochondrial function and insulin sensitivity.

Taken together, the study by Martin et al. highlights that the interaction between mitochondria and insulin sensitivity is not only tissue-specific, but also site-specific. Although supporting the contention of mitochondrial diversity, many questions remain unanswered: (i) is the relationship between mitochondrial function and insulin resistance bidirectional, or in other words what are causes and consequences in different tissues, (ii) what are the precise mechanisms accounting for the peculiar relationship of hepatic mitochondria with insulin sensitivity, when compared to other tissues, and (iii) which other — if not ROS — are the downstream effectors mediating the interference between mitochondrial function and insulin sensitivity? To elucidate these issues, further cell or organelle-based studies such as the one by Martin et al. will remain important, but clinical studies are also needed to assess simultaneously multiple mitochondrial features in different tissues of well-phenotyped insulin resistant humans.

ACKNOWLEDGMENTS

CK received support from the National Foundation of State Scholarships of Greece and the EFSD Albert Renold Research Fellowship grant. The work of MR is supported by the Ministry of Science and Research of the State of North Rhine-Westphalia (MIWF NRW) and the Federal Ministry of Health, Germany (BMG). This study was supported in part by a grant of the Federal Ministry for Research (BMBF) to the Centers for Diabetes Research (DZD e.V.) and by a grant of the Helmholtz Alliance Imaging and Curing Environmental Metabolic Diseases (ICEMED). No potential conflicts of interest relevant to this article were reported.

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