Webinar Q&A Report

Mitochondrial Membrane Lipids and Respiratory Efficiency

Questions in this Q&A Report were submitted during the live webinar, Mitochondrial Membrane Lipids and Respiratory Efficiency.

Answers have been provided by **Katsu Funai,** PhD, Associate Professor of Molecular Medicine at University of Utah.

1. **You talked about how mitochondrial inefficiency might have detrimental effects to health, but it seems that increased inefficiency would increase energy expenditure, which could help prevent obesity. Could you clarify your thoughts on that?**

K. Funai: It's highly context-dependent. It depends on which cell-type/tissue it is, and on which OXPHOS steps the inefficiency may be occurring. Decrease in the efficiency of ATP synthesis can increase energy expenditure to prevent obesity, but such inefficiency in heart could reduce contractility and promote malignant hyperthermia. Decrease in the efficiency of ATP synthesis would also adversely affect cellular function that depends highly on detecting ADP/ATP disturbance, such as in pancreatic beta cells. Decrease in the electron transfer promotes oxidative stress. Some level of oxidative stress is essential for normal cellular signaling, while excess oxidative stress may promote cellular dysfunction.

2. **You discussed how weight loss might increase the efficiency for ATP synthesis. How does exercise alter efficiency and how does that relate to exercise and its relationship to gaining weight?**

K. Funai: Exercise is known to improve energy efficiency for muscle contraction, including the efficiency of ATP synthesis. Doing so can maximize energy output for muscle contraction. In contrast, lack of exercise may reduce the efficiency of ATP synthesis. This would be predicted to increase energy expended per unit of force being generated, but by definition total work performed is reduced during physical inactivity and thus total energy expended is down. Regardless, I think it's important to understand how exercise or inactivity alters the efficiency of ATP synthesis because such mechanism may be harnessed to elevate energy expenditure.

3. Is the observed increase in TLCL after weight loss a long-lived phenomenon (i.e. does it revert back to lower levels after months/years?).

K. Funai: We don't know, but this is an excellent question. We know very little about phospholipid turnover in vivo. With respect to timing for weight loss, we know the duration of weight loss can affect the propensity for weight regain. So it would be useful to better understand how these changes occur in a time-dependent manner.

4. Is muscle atrophy with PSD knockout just a loss of ATP bioenergetics, or does it cause mitochondria signaling for apoptosis or autophagy/mitophagy?

K. Funai: I do not think that muscle atrophy with PSD knockout can be explained by reduced capacity for ATP synthesis. Skeletal muscle basal metabolic rate sits far below its maximal capacity, and the extent by which PSD knockout reduced this capacity, on its own, would not be predicted to result in severe defects we observed with PSD knockout. We have not completely ruled out apoptosis, but our experiments with mitochondrial-targeted catalase suggest that apoptosis induced by mitochondrial oxidative stress does not explain atrophy. We are actively investigating the role that autophagy may play in PSD knockout.

5. Have you investigated the role of mitochondrial lipids in mitochondrial aging?

K. Funai: We have not, but we are interested. One of the things to remember about mitochondrial lipidomic analysis is to consider how we should normalize lipid contents to. Some of the interventions we tested alter the protein-to-lipid content of mitochondria, so showing lipid content by nmol/mg of mitochondrial protein can be misleading. I suspect this is something that we would need to be paid attention to for aging studies.

6. Do you think that UCP1 function is dependent on cardiolipin?

K. Funai: Zach Gerhart-Hines group at Copenhagen published data suggesting that cardiolipin plays an important role in regulating UCP1 function. We are collaborating with his lab to actively pursue the role of cardiolipin in UCP1-dependent bioenergetics.

7. Would the processes of increased energy after weight loss also occur in both obese and non-obese models? What other tissues do you think could be affected by this weight loss (liver, heart, etc.?

K. Funai: We have only begun to study weight loss, so we have not tested weight loss in non-obese models. I think biology of many tissues would be affected by weight loss, but I am guessing that the question is on the efficiency of ATP synthesis. We have some preliminary data that suggest that the change in P/O is tissue-dependent with some tissues not showing changes in P/O. We are not 100% clear about our data because our P/O measurements for different tissues are still not completely optimized. We hope to be able to answer that question soon.

8. Do you think macronutrient composition (in an equal caloric prescription) could influence mitochondrial adaptations?

K. Funai: I think it can, but changes in macronutrient composition would also affect many different aspects of cellular biology so it would be tricky to make sure that changes in any mitochondrial adaptations is not secondarily to some other adaptations. Certainly, dietary intake of nutrient precursors for phospho-headgroups (choline, serine, ethanolamine, etc.) would be predicted to alter mitochondrial membrane lipids but this would also be highly tissue-dependent.

9. How fast do you think changes in CL or PE occur once regularly exercising?

K. Funai: We have some preliminary evidence on the time-course. However, because our exercise training protocol was graded exercise training (increasing dose), the comparison includes information for both time and dose. There are data that suggest that exercise dose is an important component to altering OXPHOS efficiency in muscle, so my guess is that CL and/or PE are also dose-dependent.

10. Do you think that dietary intake of specific fatty acids (such as linoleic acid) can impact inner mitochondrial membrane lipids?

K. Funai: Absolutely. Markus Keller's group at Innsbruck recently published a paper (Oemer, Cell Reports, 2020) that suggest that acyl-chain compositions of phospholipids are largely dependent on acyl-chain availability. It is difficult to know whether dietary fatty-acid composition can be altered to control mitochondrial efficiency because dietary fat goes everywhere.

Contact Information

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