Mitochondria and Aging

Insights from the GSA Publication, What's Hot: Cellular Nutrition and Its Influence on Age-Associated Cellular Decline

GSA Momentum Discussion, a podcast from The Gerontological Society of America

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Welcome to the Gerontological Society of America Momentum Discussion podcast series, where researchers, educators, and practitioners stimulate dialogue on trends with great momentum to advance gerontology. The content of the podcast today was developed by GSA, and this program has received a grant from Nestle Health Sciences.

Dr. Fielding:

Welcome to the podcast. I'm Roger Fielding, and I'm the Associate Director of the Jean Mayer, USDA Human Nutrition Research Center on Aging. And I'm also the Lead Scientist of the Nutrition, Exercise physiology, and Sarcopenia Team here at the Human Nutrition Research Center on Aging. I'm excited to be your host for a series of podcasts that are based on the GSA What's Hot publication, Cellular Nutrition and Its Influence on Age-Associated Cellular Decline.

Researchers have identified several molecular pathways at a cellular level, including within the mitochondria, which appear to influence both aging and age-related chronic disease. These cellular changes associated with aging are cumulatively referred to as age-associated cellular decline, or AACD. Identifying AACD risk factors and intervening with cellular nutrients earlier in the aging process, before major mobility disabilities and disease driven limitations emerge, could help improve overall healthy aging.

Today we will focus specifically on what researchers are learning about the importance of mitochondrial function. To discuss this with me, I'm pleased to introduce Dr. Anthony Molina, who is Vice Chief of Research in the Division of Geriatrics, Gerontology, and Palliative Care at the University of California San Diego School of Medicine. Dr. Molina is an expert in the study of age-related mitochondrial function. Welcome Anthony.

Dr. Molina:

Good morning, Roger. I'm delighted to be here and I'm looking forward to our discussion.

Dr. Fielding:

Let’s start with a question about the key components of age-associated cellular decline are or AACD—what are those?

Dr. Molina:

Sure, great place to start. Age-associated cellular decline refers to the accumulation of various molecular changes that occur over time, such as over the course of a human life, and are thought to underlie key features of aging, including overall physiological decline. Some of these cellular molecular hallmarks include senescence, epigenetic changes, genome instability, and loss of proteostasis.

However, despite tremendous interest in the biology of aging, there's still a number of key questions about age-associated cellular decline, including the interrelationship of these molecular changes with one another. These changes appear to work as a coordinated network and there's many questions about causality that are still remaining. For example, age-related, mitochondrial bioenergetic decline is one of the most widely recognized cellular hallmarks of aging. And it's directly involved in other aspects of AACD, including stem cell function, autophagy, inflammation, and even senescence.

Dr. Fielding:

That is a perfect segue to our next question. How do you think about the relationship of mitochondria or mitochondrial function and chronologic aging?

Dr. Molina:

Sure. Well, speaking for my lab, we think about mitochondrial dysfunction as a convergence point for numerous age-related conditions. By definition, we all know that life requires energy and mitochondria are responsible for about 90% of the energy that our cells use to power their normal everyday function. But interestingly, while age related bioenergetic decline is systemic, there are some systems that are more susceptible to the effects of bioenergetic decline than others. A good example of this is our brains. Brains account for about 2% of our total body mass but they're responsible for about 20% of our total energy demand. Therefore, it probably comes as no surprise that age-related neurological diseases such as Alzheimer's, which we study in my lab, have been linked to systemic bioenergetic decline that is measurable in both the brain as well as in peripheral cells.

Now, on the other hand, pound for pound, skeletal muscle has a much lower metabolic demand—about 18-fold lower than the brain. However, because of its sheer size, the overall energy demand is very high. Therefore, links between mitochondrial function and physical ability are also widely recognized. That said looking beyond brain and muscle, there are numerous age-related diseases and disorders that have been linked to mitochondrial dysfunction, including cardiovascular disease, cancer, and metabolic syndrome.

Dr. Fielding:

That's really interesting. I wonder when you talk about these different rates of mitochondrial aging, if you will, in different tissues, are there also thought to be some systemic regulators of mitochondrial function in general that that affect all different cells? Have you looked at that?

Dr. Molina:

That's certainly a topic that we're very interested in at the moment and we've been developing approaches to address that specific question, Roger, and something that we're focusing on in the years to come.

Dr. Fielding:

Excellent. What are some of the promising targets for intervention when talking about mitochondria? How can we fix them if they're broken?

Dr. Molina:

Sure. Not surprisingly, the development of mitochondrial therapeutics has been focused on primary mitochondrial diseases—either genetic diseases that affect mitochondrial DNA or nuclear DNA that encode for mitochondrial proteins. However, as we're now continuing to learn more about the role of mitochondria in health and disease, particularly in diseases aging, mitochondria are emerging as potential therapeutic targets for more common pathologies and diseases.

Importantly, what we're seeing is that there are similar patterns of mitochondrial impairments shared among diseases of different origins and with different pathological processes. For example, changes in reactive oxygen species, energy production, calcium handling, and homeostasis, mitochondrial quality control, and NAD signaling, have been reported in the pathogenesis of diseases affecting different organ systems. So, for this reason, we think that targeting mitochondria may be an efficient way of addressing multiple diseases at the same time. And really when you think about it, this is in line with the basic principles of geroscience, which has gotten garnered a lot of attention in recent years. Geroscience

proposes that targeting the underlying biological hallmarks of aging, such as the ones we discussed earlier as the potential to treat multiple age-related diseases and conditions, at the same time.

Dr. Fielding:

Just a quick question. For patients with primary mitochondrial diseases, did those patients exhibit sort of hallmarks of accelerated aging?

Dr. Molina:

I think so. I mean, these are pediatric conditions. If you look at the symptoms associated with primary mitochondrial disease, it does certainly look like accelerated aging, so features of frailty and cognitive impairments.

Dr. Fielding:

It's really interesting that one of the hallmarks of this area of geroscience focuses on mitochondria. Do you think it's going to be enough to just target one of those areas, such as just targeting mitochondria function? Is that going to get people over the hump of sort of preventing disability or maintaining healthy brain function, or something like that?

Dr. Molina:

I think that's the million-dollar question. Like I said, there there's many different biological hallmarks of aging. And again, until we know how these are interconnected with one another, where the nodes are, what the causalities are, we really don't know the answer to that question. But I think what we're finding is at least with mitochondria, this seems to drive many of the other cellular changes that occur with aging.

Dr. Fielding:

And what are some of the ways that we know or might be able to target age-related, mitochondrial bioenergetic decline now? Are there things that we could use now that can help with this?

Dr. Molina:

I don't know about things we can immediately use now. I think some of those trials remain to be done, but Mike Murphy and Richard Hartley published a great Nature Reviews article a few years ago that summarized some of the ways that small molecules can target mitochondria. In our GSA, What's Hot newsletter, we identified three broad strategies for discussion. The three categories we highlighted in the newsletter are mitochondrial repair and preservation, mitochondrial quality control, and mitochondrial signaling.

Targeting repair and preservation refers to strategies for managing ROS and protecting mitochondrial DNA from damage. Mitochondrial quality control includes strategies that target mitochondrial biogenesis, mitochondrial fusion and fission, and mitochondrial autophagy, all of which have been linked to various diseases. And finally, mitochondrial signaling includes calcium signaling the ratio of ATP to ADP and the activity of molecules such as NAD (nicotinamide adenine dinucleotide), which has signaling roles that affect numerous cellular functions, including functions related to senescence in immune cell function, which we have associated with aging.

Now, I know that some of the nutritional and behavioral and lifestyle interventions that can target mitochondria metabolism are also discussed in this podcast series by our colleagues. But importantly, I should say that while we're becoming familiar with the consequences of age-related bioenergetic decline, there's still a lot more work to be done to fully understand its causes. So, again, this is something that the field has been increasingly focused on, and these efforts for multiple research groups are going to reveal other strategies for targeting age related mitochondrial decline.

Dr. Fielding:

Just to follow up on some of your comments about the many ways that mitochondria can be affected by aging, when you talk about repair mechanisms, you were talking about ROS and what does ROS exactly refer to?

Dr. Molina:

ROS refers to reactive oxygen species. One of the original theories about mitochondrial aging is the mitochondria free-radical theory of aging. Now, as we revisit some of these early theories about mitochondrial aging, we're finding that some of the things that we thought early on aren't quite true. So, while ROS is damaging, and damaging to mitochondrial DNA, we are still learning how these mitochondrial DNA mutations and deletions may propagate further damage.

Dr. Fielding:

Great. Thank you, Anthony. And how else can we utilize mitochondria to promote healthy aging? Is this some sort of magic bullet that we can stimulate to preserve our cognitive and physical functioning as we get older? I mean, we're all sort of looking for that. You know, I'm 60 now, so I'm, I'm really, you know, looking. So, is there anything we can do?

Dr. Molina:

Well, I think we know there are really benefits of behavioral interventions, diet, and exercise, that sort of thing. But I do think there's other as aspects of mitochondria and mitochondria bioenergetics that we can utilize to help promote healthy aging. So, for example, there's a number of groups around the country, including my own that are trying to advance the approaches we have at our disposal for measuring mitochondria function in humans. These human mitochondrial bioenergetic profiling approaches can serve as important outcomes for clinical trials, such as the ones you mentioned.

Looking at evaluating interventions designed to promote mitochondrial function is going to require these sorts of reliable outcomes. However, I and many others believe that some of these approaches for human mitochondrial bioenergetic profiling can also have important diagnostic and prognostic applications. So, when I think about the basic premise for mitochondrial profiling and aging, in addition to differences in our intrinsic bioenergetic capacities, the rate at which mitochondrial bioenergetic function changes over time can differ between individuals and it is influenced by many factors, including behavior, environment, nutrition, and lifestyle. Now, because some of these effects are cumulative, we are now exploring whether an individual's unique bioenergetic capacity is reflective of their biological age and can be used to determine that individual's risk for developing age-related diseases or disorders. Now, importantly, as we've been discussing this morning, mitochondrial bioenergetics is highly modifiable. So, knowing one’s bioenergetic status may inform on more personalized strategies for promoting healthy aging.

Dr. Fielding:

That’s great, I think your approaches and the work that you and your group have been doing in terms of developing either non or minimally invasive ways to assess these markers or measures of mitochondrial function are really important and could serve as very valuable biomarkers for diagnostics and for the aging field going forward. So, we're really pleased to hear some of the exciting work that you and your team are doing. Thank you, Anthony, for a terrific discussion today.

This podcast is one of three on the topic of cellular nutrition and its influence on age-associated cellular decline. The other two podcasts focus on nutrition and cellular aging with Dr. Sai Das, and cellular aging in everyday practice with Dr. Nathan LeBrasseur. For more in-depth information on this topic, please refer to the GSA What's Hot publication, Cellular Nutrition and Its Influence on Age-Associated Cellular Decline. Thank you and have a great day.