DOI 10.18699/SBB-2022-633

Current views on the mechanisms of aging

Panov A.V.[1]*, Semenova E.V.[2], Dikalov S.I.[3]

[1] *Federal Scientific Center for Family Health and Human Reproduction Problems, Irkutsk, Russia*

[2] *Ogarev Mordovia State University, Saransk, Russia*

[3] *Division of Clinical Pharmacology, Vanderbilt University Medical Center, Nashville, USA*

** Alexander.panov55@gmail.com*

Key words: aging, metabolic syndrome, mitochondria, oxidative stress

Motivation and Aim: We live at a time when many earlier paradigms are denied and replaced with new ones, which is particularly true for the studies of mitochondrial dysfunctions in the mechanisms of aging and associated diseases in humans. Recently it was discovered that the proteinaceous "shield" of nucleoids protects mtDNA from oxidative damages and that there is no actual proof for the free radical direct effects on mtDNA [reviewed in 1]. Moreover, researchers finally realized that practically all studied oxygen radicals, such as superoxide radical ($O_2^{\bullet}$), nitric oxide ($^{\bullet}NO$), peroxynitrite ($^{\bullet}ONO_2$), and even hydroxyl radical ($^{\bullet}OH$), are either chemically not active enough, or live too short, or formed only locally. Thus neither of them can be responsible for the slow and unavoidable process of gradual accumulation of damages and dysfunctions, which we name "aging." Studies of changes in genomics, proteomics, and other "omics" were of little help in understanding mechanisms of aging and pathogeneses of diseases mainly because these approaches have not been accompanied by the simultaneous research on changes in the related functions. Aging is, with few exceptions, a fundamental phenomenon for all living organisms on Earth. In 2013, Barja summarized the numerous studies on life longevities of various species: "Only two parameters currently correlate with species longevity in the right sense (reversely): the mitochondrial rate of reactive oxygen species (ROS) production and the degree of fatty acid unsaturation of tissue membranes" [2]. At first glance, a strange conclusion. Here, we will briefly outline the features of new paradigms related to oxidative stress, mechanisms of aging, and age-related diseases to confirm the correctness of Barja's conclusion.

Gender variations in the rates of aging. One of the critical features of aging among mammals is that females age slower and live longer [3]. Studies on human energy metabolism have shown significant gender differences, particularly in the consumption of fatty acids [reviewed in 1, 4]. Olivetty et al. (1995) found that men's hearts undergo a linear loss of approximately 64 million cells from the age of 17 to 95, whereas, in women, the structural properties of the heart remained unchanged [5]. In our experiments, we have shown that long-chain fatty acids oxidize at a high rate only in the presence of supporting substrates, which are amino acids and mitochondrial metabolites pyruvate and succinate [4, 6]. Studies on the gender differences in energy metabolism have shown that women consume more fatty acids (FAs) than men, whereas men, in addition to FAs, consume significant amounts of pyruvate and amino acids [7, 8]. We have suggested that before menopause, women oxidize FAs less efficiently and thus produce less ROS than men [1, 4]. However, after menopause, with the development of

the metabolic syndrome (MetS), women's energy metabolism becomes similar to men's, and the rate of aging accelerates [9].

Metabolic syndrome is the consequence of the transition to the porstreproductive stage of human ontogenesis. From this point of view [1, 4], most external and metabolic features of MetS reflect the fact that this stage of ontogenesis is governed by the genes of our distant ancestors, at least for the people living in the Northern Hemisphere. At MetS, fatty acids become the primary energy source for all functions, which dramatically increases the production of superoxide radicals and their protonated form perhydroxyl radical ($HO_2^{\bullet}$), which is the inducer of the isoprostane pathway of lipid peroxidation (IPLP) in mitochondria [4,10]. $HO_2^{\bullet}$ induces IPLP of polyunsaturated fatty acids with the formation of hundreds of products, some of which resemble prostaglandins; others are highly reactive and form stable adducts with cardiolipin, phosphatidylethanolamine, or proteins [Reviewed in 10]. As a result, the rate of aging during MetS becomes accelerated. Most complications observed in patients with MetS originate from the inconsistencies between the metabolic phenotype acquired after the transition to the postreproductive stage and excessive consumption of food rich in carbohydrates and a sedentary lifestyle [1, 4, 10].

References

1. Panov A., Darenskaya M.A., Dikalov S.I., Kolesnikov S.I. Chapter 3. Metabolic syndrome as the first stage of eldership; the beginning of real aging. In: Amornyotin S. (Ed.). Update in Geriatrics. InTech, 2021:1-31. doi: 10.5772/intechopen.95464.
2. Barja G. Updating the mitochondrial free radical theory of aging: an integrated view, key aspects, and confounding concepts. *Antioxid Redox Signal*. 2013;19(12):1420-1445. doi: 10.1089/ars.2012.5148.
3. Lemaitre J.F. et al. Sex differences in adult lifespan and aging rates of mortality across wild mammals. *PNAS USA*. 2020;117(15):8546-8553. doi: 10.1073/pnas.1911999117.
4. Panov A., Mayorov V.I., Dikalov S. Metabolic syndrome and beta-oxidation of long-chain fatty acids in the brain, heart, and kidney mitochondria. *Int J Mol Sci*. 2022;23(7):4047. doi: 10.3390/ijms23074047.
5. Olivetti G. et al. Gender differences and aging: effects on the human heart. *J Am Coll Cardiol*. 1995;26:1068-1079. doi: 10.1016/0735-1097(95)00282-288.
6. Panov A.V. Synergistic oxidation of fatty acids, glucose, and amino acids metabolites by isolated rat heart mitochondria. *EC Cardiology*. 2018:198-208.
7. Tarnopolsky M.A. Gender differences in substrate metabolism during endurance exercise. *Can J Appl Physiol*. 2000;25(4):312-327. doi: 10.1139/h00-024.
8. Lamont L.S., McCullough A.J., Kalhan S.C. Gender differences in the regulation of amino acid metabolism. *J Appl Physiol*. 2003;95:1259-1265. doi: 10.1152/japplphysiol.01028.2002.
9. Carr M.C. The emergence of the metabolic syndrome with menopause. *J Clin Endocrinol Metabol*. 2003;88(6):2404-2411. doi: 10.1210/jc.2003-030242.
10. Panov A. Perhydroxyl radical (HO_2•) as inducer of the isoprostane lipid peroxidation in mitochondria. *Mol Biol*. 2018;52:295-305. doi: 10.1134/S0026 893318020097.