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REVIEW

Transcription Factor Nrf2 and Mitochondria – Friends or Foes in the Regulation of Aging Rate

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Abstract—At the first sight, the transcription factor Nrf2 as a master regulator of cellular antioxidant systems, and mitochondria as the main source of reactive oxygen species (ROS), should play the opposite roles in determining the pace of aging. However, since the causes of aging cannot be confined to the oxidative stress, the role of Nrf2 role cannot be limited to the regulation of antioxidant systems, and moreover, the role of mitochondria is not confined to the ROS production. In this review, we discussed only one aspect of this problem, namely, the molecular mechanisms of interaction between Nrf2 and mitochondria that influence the rate of aging and the lifespan. Experimental data accumulated so far show that the Nrf2 activity positively affects both the mitochondrial dynamics and mitochondrial quality control. Nrf2 influences the mitochondrial function through various mechanisms, e.g., regulation of nuclear genome-encoded mitochondrial proteins and changes in the balance of ROS or other metabolites that affect the functioning of mitochondria. In turn, multiple regulatory proteins functionally associated with the mitochondria affect the Nrf2 activity and even form mutual regulatory loops with Nrf2. We believe that these loops enable the fine-tuning of the cellular redox balance and, possibly, of the cellular metabolism as a whole. It has been commonly accepted for a long time that all mitochondrial regulatory signals are mediated by the nuclear genome-encoded proteins, whereas the mitochondrial genome encodes only a few respiratory chain proteins and two ribosomal RNAs. Relatively recently, mtDNA-encoded signal peptides have been discovered. In this review, we discuss the data on their interactions with the nuclear regulatory systems, first of all, Nrf2, and their possible involvement in the regulation of the aging rate. The interactions between regulatory cascades that link the programs ensuring the maintenance of cellular homeostasis and cellular responses to the oxidative stress are a significant part of both aging and anti-aging programs. Therefore, understanding these interactions will be of great help in searching for the molecular targets to counteract aging-associated diseases and aging itself.

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Keywords: Nrf2, mitochondria, aging, lifespan, oxidative stress, aging diseases, antioxidants

INTRODUCTION

Internal factors that determine the rate of aging and the shape of the survival curves (*pace and shape of aging*) include both aging- and anti-aging programs, which, according to modern concepts, represent a set of signaling gene cascades [1]. The maintenance of homeostasis depends on many interdependent reactions, and its efficiency deteriorates with age [1-7]. It is assumed that the nuclear and mitochondrial genomes have evolved together and encode the factors that regulate each other and form a genetically determined system of bidirectional

Abbreviations: ARE, antioxidant response element; HO-1, heme oxygenase 1; GSK3, glycogen synthase kinase 3; GST, glutathione S-transferase; Keap1, Kelch-like ECH-associated protein 1; MOTS-c, mitochondrial open reading frame 12S rRNA type c; Nrf2, nuclear factor erythroid 2-related factor 2; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator) ROS, reactive oxygen species; SOD, superoxide dismutase.

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communications. Since the publication of D. Harman [8], mitochondria have been considered as a machine that causes cell death and, to a large extent, determines the lifespan and the rate of organismal aging [8-10]. Nrf2 (nuclear factor erythroid 2-related factor 2) is a key transcription factor in the maintenance of cell redox balance that plays a central role in reducing intracellular oxidative stress, slowing down the aging, and preventing age-related diseases [1, 2, 11]. Nrf2 is one of the main regulators of cellular homeostasis. In humans, it controls expression of more than 200 genes associated with the biotransformation reactions, redox homeostasis, energy metabolism, DNA repair, and proteostasis, which together form a powerful cell defense system [1, 2].

To combat the generated reactive oxygen species (ROS), cells have an efficient antioxidant system consisting of enzymatic and non-enzymatic antioxidants. Enzymatic antioxidants include catalase (CAT) (found primarily in peroxisomes and, to a lesser extent, in the mitochondria), glutathione peroxidase (GPX) (cytoplasm and mitochondria), glutathione reductase (GR) (cytoplasm and mitochondria), glutathione S-transferase (GST) (cytosol), NAD(P)H oxidase (membrane and cytosol), peroxiredoxins (various intracellular compartments), and superoxide dismutase (SOD). The latter is represented by three isoforms: SOD1 (Cu-Zn-superoxide dismutase) located in the mitochondria/intermembrane space and cytosol, SOD2 (Mn-SOD) located in the mitochondrial matrix, and SOD3 (Cu-ZnSOD) located in the extracellular space [12]. Nrf2 targets genes with *cis* antioxidant response elements (AREs) that encode mitochondria-related proteins, such as thioredoxin, glucose 6-phosphate dehydrogenase, GST, NAD(P)H:quinone oxidoreductase 1 (Nqo1), and heme oxygenase 1 (HO-1) [13]. These proteins are involved in the antioxidant defense, NADH regeneration, and iron metabolism. Therefore, there is a close relationship between Nrf2 and mtROS homeostasis [14].

Aging is a complex process; its rate depends on many factors. Mitochondria and the Nrf2-mediated antioxidant defense system are important players in the regulation of aging. This review discusses the mechanisms of their mutual influence in the redox-mediated regulation of aging rate.

REGULATORY CROSS-INFLUENCES BETWEEN Nrf2 AND MITOCHONDRIA

Regulatory cross-influences between Nrf2 and mitochondria play an important role in cellular bioenergetics, biosynthesis, and apoptosis. To ensure the homeostasis maintenance and the quality control, the morphology of mitochondria can rapidly change via fusion or fission (the so-called mitochondrial dynamics) in response to the external factors and alterations in the metabolic status. The damaged mitochondria are removed by mitophagy. Although mitochondria are one of the sources of ROS, they themselves are vulnerable to the oxidative stress. Endogenous antioxidant defense systems play an important role in the cell survival under physiological and pathological conditions. Thus, in contrast to the Nrf2 inhibition by synoviolin during endoplasmic reticulum (ER) stress [15], PERK-mediated Nrf2 activation during ER stress protects mitochondria by stabilizing the mitochondrial dynamics, metabolism, and quality control [16].

The balance between the mitochondrial fission/fusion, mitochondrial turnover (biogenesis/mitophagy), as well as calcium and ROS homeostasis are important for maintaining the normal functioning of mitochondria [17]. When these processes are disrupted, dysfunctional mitochondria produce large amounts of ROS, leading to the oxidative stress and development of various pathologies [17, 18]. ROS are generated in several cellular compartments, such as the cell membrane, cytoplasm, ER, peroxisomes, and Golgi apparatus, but their main source is mitochondria [19, 20]. Depending on the level of ROS production, mitochondria naturally affect the Nrf2 activity. In turn, Nrf2 together with the transcription factor NRF1 (nuclear respiratory factor 1) and transcription coactivators PGC-1α (peroxisome proliferator-activated receptor-γ coactivator) and PGC-1β, are the key regulators of mitochondrial biogenesis. They are involved in the transcription of nuclear genes encoding mitochondrial proteins and TFAM (mitochondrial transcription factor A), which controls transcription of the respiratory chain genes encoded in the mtDNA [21].

Nrf2 is a nuclear factor sensitive to ROS; its activity varies depending on the ROS level. The adaptation of cells to these variations affects multiple cellular functions, including glucose and lipid homeostasis [18]. Thus, the knockout of the Nrf2-encoding gene (*Nfe2l2*) causes a decrease in the mitochondrial membrane potential and the level of ATP production [22]. The gene for the UCP3 uncoupling protein contains an ARE and is a target of Nrf2, which binds to the *UCP3* promoter after exposure to H_2O_2. Hence, the UCP3-mediated proton leakage in response to H_2O_2 might affect the cell survival [23]. The *NRF1* gene also contains an ARE and is regulated by Nrf2. The hyperactivation of HO-1 in cardiomyocytes results in the Nrf2-dependent stimulation of the *NRF1* expression and mitochondrial biogenesis [24].

Many processes of mitochondrial physiology and homeostasis depend on the Nrf2 activity [25-27], such as mitochondrial bioenergetics [28], mitochondrial biogenesis [29], fatty acid oxidation [30], respiration [22], ATP production [31], membrane potential [32], redox homeostasis [33], structural integrity and protection from oxidative stress [34], and mitochondrial mobility and dynamics [35]. Under stress conditions, Nrf2 maintains the quality and integrity of mitochondria by stimulating the p62-dependent mitophagy. The p62-encoding gene (*SQSTM1*),

is a direct target of Nrf2, and the p62 protein competes with Nrf2 for binding to the inhibitor protein Keap1 (Kelch-like ECH-associated protein 1) [26]. Nrf2 can also indirectly affect the mitochondrial activity by changing the levels of metabolites and antioxidants essential for the functioning of the mitochondria [36-38]. The genes coding for the essential factors of mitochondrial biogenesis NRF1 and TFAM are direct targets of Nrf2 [38]. The activity of the key mitochondrial biogenesis protein PGC-1α is also stimulated by Nrf2; in turn, PGC-1α inactivates GSK3β, which induces proteasomal degradation of Nrf2. Therefore, Nrf2 and PGC-1α form a positive regulatory loop that plays an important role in the redox homeostasis and maintenance of the number of mitochondria in the cell. Mutual regulatory associations with Nrf2 have been described for other mitochondrial proteins, such as DJ-1, PGAM5, and frataxin [38].

Beside mitochondrial biogenesis and homeostasis, Nrf2 is known to be involved in the maintenance of cellular redox homeostasis. It controls the production of ROS by regulating the biosynthesis, utilization, and regeneration of glutathione (GSH), thioredoxin, and NADPH [39]. The activation of Nrf2 induces expression of mitochondrial antioxidant proteins GR, GPX, thioredoxin reductase 2, peroxiredoxin 3, peroxiredoxin 5, and SOD2, thus counteracting the upregulation of ROS generation in the oxidative stress [25].

Nrf2 is also involved in the regulation of redox activity of metal ions, in particular, in the iron homeostasis [40, 41]. Iron oxidation is closely related to the oxygen transport and consumption, as well as ROS production [42]. The gene for ferrochelatase, an enzyme that catalyzes the last step in the heme biosynthesis by incorporating ferrous iron into protoporphyrin, is a direct target of Nrf2 [43]. The expression of genes encoding both ferritin chains and ferroportin is also regulated by Nrf2 [42].

Mitochondrial peptides can play a special role in coordinating cell responses of the nucleus and mitochondria to the oxidative and other stresses Human mtDNA contains only 13 genes encoding respiratory chain proteins, for which no signaling functions have been described so far. It has long been believed that the active pathways of communication between the nucleus and mitochondria are mediated exclusively by the factors encoded in the nuclear genome. The vast majority of mitochondrial proteins are encoded by the nuclear genes, allowing the nucleus to almost completely control the mitochondrial biogenesis, dynamics, and functioning [44, 45]. However, in the last few years, the regulatory role of bioactive mitochondria-derived peptides (MDPs) encoded by the short open reading frames (sORFs) in the mitochondrial genome, has been actively studied [44]. Eight MDPs have been described so far: humanin, MOTS-c (mitochondrial open reading frame of the 12S rRNA type-c), and six small humanin-like peptides (SHLP1-6). As the name implies, MOTS-c is encoded by the 12S rRNA. Humanin and SHLP1-6 are encoded by the mitochondrial 16S rRNA. Humanin specifically binds the insulin-like growth factor binding protein 3 (IGFBP-3) [46] and the anti-apoptotic factor Bcl-2 [47]. It has been identified in the brain fractions of Alzheimer's disease patients as a protective factor against toxins (e.g., β-amyloid characteristic of this pathology [48]) and as an important factor for normal cardiac function [49]. The beneficial effects of the systematic use of MDPs have been demonstrated in various rodent models of metabolic stress [50].

There is fairly convincing evidence of the positive effect of MDPs on the age-related metabolic disorders and other impairments associated with old age. The levels of humanin, SHLP2, and MOTS-c decrease with age; the activity of these MDPs positively correlates with longevity [51-57]. The content of humanin in mice and humans is negatively regulated by the growth hormone (GH)/insulin-like growth factor-1 (IGF-1) signaling axis [58]. The level of humanin is increased in the blood of long-lived GH-deficient Ames mice and, on the contrary, is diminished in the short-lived GH-transgenic mice [58].

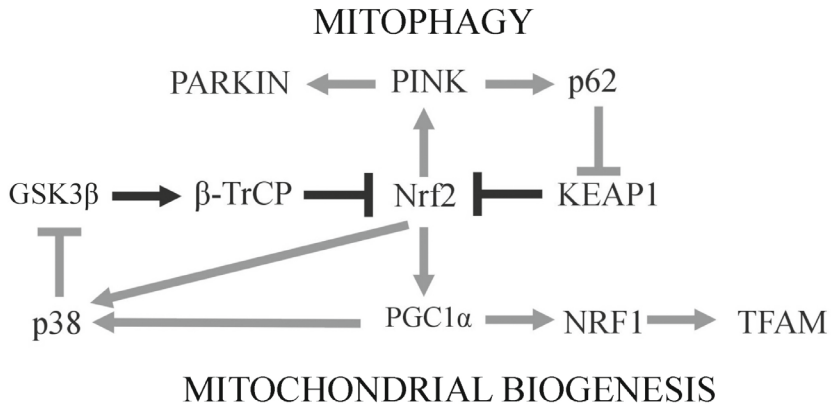
MOTS-c acts as a regulator of metabolic homeostasis and can prevent the development of the diet-induced insulin resistance and obesity, as well as the age-related insulin resistance in mice [53, 59, 60]. HEK293 cells overexpressing MOTS-c are resistant to the metabolic stress caused by glucose and serum deprivation [44]. It has been shown that only a small fraction of MOTS-c localizes to the nucleus in the cells under physiological conditions, while various stress factors induce its rapid translocation to the nucleus, accompanied by changes in the gene expression [44, 61]. Interestingly, the level of MOTS-c in the mitochondria and cytoplasm decreases in this case. It appears that this MDP plays a role of the stress-induced signal between the cellular compartments. MOTS-c is present in the blood plasma, where it acts as a "mitokine", i.e., a carrier of mitochondrial signals that affect the cells of various organs in a hormone-like manner [61]. It prevents the diet-induced obesity and insulin resistance, restores muscle sensitivity to insulin in aged mice, activates AMPK in skeletal muscles, and improves physical endurance (running) regardless of the body weight by affecting the energy metabolism and increasing the adaptive response to cold shock and exercise-induced stress [61]. It has been shown that MOTS-c has the anti-inflammatory and vasoprotective properties and reduces expression of various inflammatory factors (TNF-α, IL-6, IL-1β) [62, 63]. All these effects of MOTS-c partially depend on SIRT1 and AMPK [44, 53], two important interrelated proteins that regulate the lifespan of model organisms [64, 65]. It is noteworthy that by translocating to the nucleus in the case of cellular stress, MOTS-c regulates the expression of adaptive genes by interacting with the stress-dependent transcription factors, in particular, Nrf2 [44, 45, 61, 66].

The mechanisms by which MOTS-c targets the genes are poorly understood. Based on the available data, both translocation to the nucleus and binding to the gene promoters depend on the MOTS-c interaction with the nuclear proteins [44]. For example, co-immunoprecipitation experiments revealed that MOTS-c binds to Nrf2. However, under the action of stress factors, Nrf2 and MOTS-c are translocated to the nucleus independently of each other [44]. Moreover, electrophoretic mobility shift assays revealed direct binding of MOTS-c to the ARE-containing promoter regions of the Nrf2 target genes, such as *Hmox1* (coding for HO-1), *Nqo1*, *Ugt1A1*, *Ugt1A6*, *Txn*, *Ftl*, and *Gpx2*. This binding of Nrf2 with the ARE-containing promoter regions was significantly stimulated in the presence of MOTS-c. However, sulforaphane (10 μM, 16 h) stimulated the Nrf2-dependent expression of *Hmox1* even in the case of actinonin-induced depletion of MOTS-c. Apparently, MOTS-c is not the only Nrf2 cofactor [67]. It can be assumed that by disrupting the functioning of the respiratory chain, actinonin leads to the increased generation of ROS and, as a result, Nrf2 translocation to the nucleus and upregulation of the *Hmox1* expression [68]. Culturing HEK293 cells transfected with a MOTS-c overexpressing vector under glucose deficit conditions altered the expression of 802 genes (412 were downregulated and 390 were upregulated) [44]. Some of the MOTS-c activated genes were the targets of Nrf2. The promoters of genes regulated by MOTS-c contains the sequences interacting with the activating transcription factors 1 and 7 (ATF1 and ATF7) and JUND, which are related to Nrf2 and cross-regulate the ARE-containing genes [69, 70]. In this case, the genes targeted by ATF1 and JUND also partially coincided with the genes regulated by MOTS-c. Interestingly, the overlap between the genes targeted by Nrf2, ATF1, and JUND was incomplete, although expression of all these genes is regulated through AREs, thus pointing to a complex mechanism of the target genes selection in such regulation.

MITOCHONDRIAL BIOGENESIS

Mitochondrial biogenesis is a complex, strictly regulated process that requires close coordination between mitochondrial and nuclear transcription factors [71]. The markers of mitochondrial biogenesis include the mtDNA/nDNA ratio and expression levels of genes encoding mitochondrial regulatory proteins, such as PGC-1α, TFAM, NRF1, and mitochondrial transcription factor B1 (TFB1M). Apart from the expression of mitochondrial genes, mitochondrial biogenesis also requires the synthesis of nucleotides and phospholipids. By activating the PI3K/Akt signaling, Nrf2 promotes the expression of genes involved in the pentose phosphate pathway, *de novo* nucleotide synthesis, NADPH production, purine biosynthesis, and glutamine metabolism [72].

PGC-1α is a coactivator of the PPAR-γ nuclear receptor, which controls the development and metabolism of adipose tissue and muscles [73]. Together with Nrf2, PGC-1α coactivates NRF1 and then, upon Akt phosphorylation and GSK3β inactivation, activates TFAM, which is required to maintain normal mtDNA levels [74] (figure). The protein encoded by the Nrf2 target gene *Hmox1* was found to stimulate the mitochondrial biogenesis by activating the Akt/Nrf2/NRF1 signaling cascade in the mouse heart [24]. Later, the same laboratory showed that the mitochondrial biogenesis is associated with an increase in the expression of two anti-inflammatory genes, *IL10* and *IL1Ra*, through the redox regulation of HO-1/ CO and Nrf2 in the mitochondria of human hepatoma HepG2 cells and liver cells *in vivo* [75]. In addition to acting as the main regulator of mitochondrial biogenesis, PGC1-α participates in the antioxidant defense by modulating the transcription of the *SOD2* gene and the level of SOD2 [74]. Overexpression of *PGC1-α* in HK-2 cells protected the cells from the hydrogen peroxide-induced oxidative stress [76]. The knockout the



Nrf2 plays an important role in the mitochondrial and cellular homeostasis. Simplified scheme of mitophagy and mitochondrial biogenesis pathways mediated by p62 and PGC1-α, respectively, upon Nrf2 activation that indicates an existence of the mitophagy-associated regulatory loop (including p62, Keap1 and Nrf2) and another regulatory loop (including PGC1-α, p38, GSK3β, and Nrf2) associated with the mitochondrial biogenesis. Lines with arrows, stimulation (including catalysis); lines with blunt ends, inhibition

Nrf2-encoding gene (*Nfe2l2*) demonstrated that this cytoprotective effect was mediated by Nrf2. Its suppression by a p38 inhibitor suggested that this effect is based on the Nrf2 activation via inhibition of its negative regulator GSK3β by p38 (figure). On the other hand, lowering the Nrf2 production with a siRNA reduced the content of PGC1-α [77]. Elevated ROS levels, for example, in cancer, can lead to the retrograde signaling through the JNK/PGC1-α pathway with the increased complex II phosphorylation and increased mitochondrial biogenesis [78, 79]. The knockdown of Nrf2 in a human colon cancer cell line blocked the hypoxia-induced activation of HIF-1α [80].

AMP-activated protein kinase (AMPK). AMPK is the main energy sensor in eukaryotic cells, also known as a guardian of metabolism and mitochondrial homeostasis [81]. It is involved in several important mitochondrial processes, such as mitophagy, mitochondrial dynamics and transcription, and mitochondria biogenesis. It also influences circadian rhythms via phosphorylation and destabilization of the CRY and PER proteins. Thus, AMPK phosphorylates the circadian rhythm protein CRY1, which promotes its degradation [82]. On the other hand, the subunit composition of AMPK, its subcellular localization, and substrate phosphorylation depend on the time of day [83]. It has been shown that AMPK activates Nrf2 by inhibiting GSK3β [84]. The convergence between the AMPK and Nrf2 pathways is important, for example, for the anti-inflammatory effects of berberine on the lipopolysaccharide-stimulated macrophages and endotoxin shock-exposed mice [85].

Activation of AMPK leads to the metabolism reprogramming with the activation of catabolism and suppression of anabolism via phosphorylation of key factors in multiple biosynthetic pathways, including those mediated by the mammalian target of rapamycin (mTOR) [81]. Nrf2 can also directly regulate expression of the *mTOR* gene by binding to its promoter [86]. One of the AMPK activators is serine/threonine kinase LKB1, a known tumor suppressor [87]. Experiments on the tissue-specific knockouts of the *LKB1* gene in mice showed that in most tissues, LKB1 is the main mediator of adaptive AMPK activation during the energy stress. Therefore, there is a link between the regulation of energy metabolism and tumor suppression.

One of the mechanisms by which mitochondria regulate expression of the antioxidant genes is associated with the PGAM5 protein. PGAM5 can bind both Nrf2 and Keap1. It forms the tertiary complexes with these proteins and transports them to the outer mitochondrial membrane due to the mitochondrial localization signal present in its molecule [88]. The knockdown of *Keap1* and/or *PGAM5* increases the Nrf2 activity. The PGAM5 inhibitor LFHP-1c enhances Nrf2 activation in the ischemic stroke caused by the disruption of the blood–brain barrier integrity [89].

CONCLUSION

Aging is associated with the increase in ROS production and oxidative stress accompanied by the reduction in the activity of main antioxidant defense systems, which contributes to the development of a wide range of diseases [90]. Age-related changes can lead to the downregulation of expression of the Nrf2 target genes (*Nqo1*, *Hmox1*, *GCL*) due to the decrease in the content of Nrf2 mRNA and protein, reduced Nrf2 levels in the nucleus, impaired Nrf2 binding to AREs, and Nrf2-mediated suppression of gene expression (see reviews [91-93]). Thus, the age-related decrease in the synthesis of glutathione, the main antioxidant in the cell, can be caused by the dysregulation of the ARE-mediated gene expression. The chemoprotective agents targeting Keap1, such as lipoic acid, sulforaphane, and other Nrf2 activators, can only partially (and increasingly less efficiently with age) compensate for this loss [94-99] by suppressing the Keap1 pathway of the Nrf2 degradation, but not preventing it. The functional connection between Nrf2 and mitochondrial network can be realized through the interaction of this transcription factor with the mitochondrial proteins or through the fine-tuning of the ROS balance. The mechanisms of retrograde signaling from the mitochondria to the nucleus in response to the cellular stress are well known and include mitochondrial unfolded protein response (UPRmt) [100-102] and damage-associated molecular patterns (DAMPs) [103]). The 16-amino acid MOTS-c peptide encoded in the mitochondrial genome, actively translocates to the nucleus in response to the metabolic stress in coordination with the nuclear proteins AMPK and SIRT1 and directly regulates expression of the ARE-containing target genes in the nuclear genome, in particularly, by interacting with Nrf2. Interaction with MOTS-c promotes Nrf2 binding to the target genes. Overexpression of MOTS-c protects the cells from the stress caused by glucose or serum deprivation. These results demonstrate an important role of this mitochondrial peptide after its translocation to the nucleus in the response of nuclear genes to the metabolic stress [44]. This mechanism and similar functional relationships can potentially become the cornerstone for new therapeutic approaches to combat a wide range of human age-related pathologies, including oncological diseases [104]. MDPs are functionally similar to the peptides of endosymbiotic proto-mitochondrial bacteria that had been used by the bacteria to communicate with eukaryotic ancestral cells [105]. It is likely that the two genomes have co-evolved to cross-regulate each other in order to coordinate diverse cellular functions. Future research on the Nrf2 signaling and ability of various substances that activate the Nrf2 pathway to prevent age-associated chronic diseases will provide further insight into the role of Nrf2 activation as a possible longevity-promoting intervention.

Contributions. G. A. Shilovsky developed the study concept and wrote the article; G. A. Shilovsky and V. V. Ashapkin wrote and edited the article and prepared the figure.

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