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Aging as a Result of the Implementation of the Phenoptosis Program

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Abstract—There are two main points of view on the driving force of aging: destructive action of free radicals generated by mitochondria and implementation of the genetic program. The free-radical theory dominating now asserts that there are no specific genes of aging, as the evolutionary theory proves inability of natural selection to differentiate separate individuals by longevity. The concept of programmed aging, named phenoptosis, has no wide recognition, since it contradicts postulates of the evolutionary theory of aging and, moreover, has no mechanism for the implementation of the program. The present review shows the following: (1) contrary to the statement of the evolutionary theory of aging, the species-specific longevity is controlled by selection but the interpopulation one rather than individual; hence, there are specific genes of aging; (2) primarily programmed process causing aging is a decrease in the bioenergetics level; and (3) this causes age-related increase of the level of free radicals. Hence, the free-radical theory should be incorporated into the theory of programmed aging as one of the components. The key diagram of the mechanism of programmed aging is presented.

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Gerontology has entered the XXI century with a huge empirical baggage [1–3] but without a theory capable of generalizing data and discovering general regularities of the aging process. Instead, by the end of the XX century, more than 300 different theories were developed [4]. As noted on this subject by Vijg [5], the approach of researchers to the problem of aging is not very logical, since each deeply trusts in his own theory only. There is still no consistent opinion on what is the primiry driving force of aging.

The prevailing present view is that aging is a result exposure of an organism to free radicals generated by mitochondria. The free-radical theory is attractive in that it suggests a simple and convincing mechanism of the degradation of an organism with age and is supported by the modern evolutionary theory of aging, which denies existence of longevity genes [6, 7].

According to the opposite viewpoint, aging is a result of implementation of the genetic program of organism's self-destruction, called phenoptosis [8]. No mechanism of the implementation of this program has still been suggested, and this viewpoint contradicts postulates of the evolutionary theory of aging, and, therefore, has not received wide recognition. However, empiric facts which, as known, are the "supreme judge" of all theories, evidence in favor of a programmed aging. First, the species-specific lifespan, as an inheritated trait, can only be programmed; second, a great number genes affecting lifespan were discovered; and, third, the fact that longevity is programmed in nature is supported by the results of numerous demographic research.

The free-radical theory of aging is based on two undeniable facts: deleterious free radicals are generated by the mitochondrial bioenergetic machine, and their quantity increases with age. However, the predictions of this theory are largely not confirmed by experiment. But, what is the most important, the theory does not bring the expected practical result. Thus, having summarized long-standing applied research, Howes [9] stated that the free-radical theory had led gerontology to deadlock: Extensive half-century experiments with antioxidants gave results neither in extension of the maximum lifespan nor in suppression of age-related pandemics of cancer, diabetes, or cardiovascular diseases.

Obviously, a necessity has arisen to change theoretical benchmarks and properly substantiate the concept of programmed aging. The aim of the present review is to summarize evidence in favor of this concept and to give, on its basis, a general outline of the mechanism of implementation of the phenoptosis program.

Modern Views on the Reasons of Aging

The suggestion that lifespan is controlled by natural selection was first advanced by one of the founders of the evolutionary theory Wallace as early as the XIX century [10]. At the same time, the father of the modern genetics Weismann [11] stated that the longevity program is transferred from generation to generation in the germ plasm (genome). However, the level of scientific development at that time did not allow them and their followers to find a concrete mechanism of the natural selection of this specific trait. Moreover, in 1952 Medawar [12] showed that lifespan is not controlled by natural selection. He noted that animals almost never live to an old age under natural conitions and die of various external reasons in a fairly young age; as a result, natural selection cannot differentiate them in terms of longevity. Consequently, no specific genes programming aging can exist.

To explain the reasons for age-related body degradation, Harman in 1956 [13] developed a simple, down-to-earth descriptive, and logically perfect free-radical theory of aging, which suggests that an organism degrades under the action of various damaging factors. To explain the driving forces of the longevity evolution, Williams advanced a theory of antagonistic pleoitropy [14]. The theory suggests existence of genes coding traits which maintain vitality of an organism in the young age but suppress it in the post-reproductive period. As a result, such traits should be maintained by natural selection and accumulated. The disposable soma theory developed later incorporated both these concepts [15] and, in an improved version, is mentioned as the evolutionary theory of aging [6, 7].

The evolutionary theory of aging states [16–19] that there are no specific genes programming aging, and an organism degrades largely under the action of reactive oxygen species (ROS) generated by mitochondria. They damage cellular structures, including the structures of mitochondria themselves, which enhances production of ROS. This circulus vituosus leads to continuous self-destruction of the organism. Destructive processes are counteracted by reparation and antioxidant mechanisms which are programmed but not efficient enough to neutralize completely the damaging factors and repair damages. This insufficiency is explained by the fact that natural resources are always limited and distributed between expenses for reproduction and maintaining stability of an organism (soma). Priority is given to reproduction, and, therefore, soma is maintained far beyond need. As a result, the more abundant is the habitat, the more resources remain for maintaining soma and the longer is the species-specific lifespan, and vice versa [6, 7]. With reference to this theory, it was stated fairly recently that the nature of aging and longevity is no longer an unsolved problem of biology [18, 19].

However, no experimental evidence has still been obtained for this mechanism of aging. Numerous negative results were obtained in research on the molecular mechanism of age-related increase of the level of free radicals [20–26]. Moreover, this theory contradicts ecological observations [27] and results of widely known experiments on calorie restriction [28], which showed that the restriction of food resources prolongs life and decreases reproductive activity, contrary to what is expected by this theory.

The idea of programmed aging has been revived in our day by the Acad. V.P. Skulachev, but from quite different positions [29]. Having analyzed the accumulated experimental evidence on the programmed death of biological structures at the subcellular (mitoptosis), cellular (apoptosis), and supercellular (organoptosis) levels, he has formulated a general principle: “Any sufficiently complex biological system has a self-destruction program which is implemented if the given system is harmful or simply unnecessary for systems that occupy a higher step in the hierarchy of biological structures” [9]. From this principle it follows that an organism, being the next step in the hierarchy of biological structures, too, has its seld-destruction program, viz. phenoptosis [30, 31]. Aging is considered as the implementation of the phenoptosis program. Consequently, we have to suggest existence of genes programming both longevity and natural selection which would control the development of this trait in the evolution process. But, on the other hand, the Medawar’s argument is undeniable: Natural selection, indeed, cannot discriminate individual organisms in terms of lifespan. The way to overcome this collision is shown by the same Skulachev’s principle: The next (after the organismal) step in the

hierarchy of biological structures is population. Consequently, the solution should be searched for at the populational rather that organismal level.

Medawar drew his conclusion based on an individual natural selection, the only type of natural selection known at that time. At the second half of the XX century the evolution theory made progress in the understanding of natural laws. It was found out, in particular, that natural selection is a two-stage process. At the first stage, the classical (after Darwin) individual selection eliminates organisms the least adapted to the habitat, and genes belonging to the remaining species form the gene pool of a population. At the second stage the interpopulation (group) selection eliminates less viable populations of a biological species [32, 33].

Consideration of the evolutional aspects of longevity from these, new positions showed that the species-specific lifespan is controlled by natural selection, but this is an interpopulation rather than individual selection [34]. Consequently, aging-programming genes actually exist.

This statement is of critical importance, since it eliminates an insurmountable barrier in the way of the development of the mechanism of programmed aging. Below we provide (in a slightly shortened form) evidence for this statement.

Essence of Interpopulation Selection

As a unit of group selection we consider a population, namely a group of individual representatives of a species, which constantly inhabit at a certain territory, have a common unique gene pool and hindered gene exchange with neighboring groups, and react as a comprehensive whole to varied habitat conditions. Populations belonging to the same species are heterogeneous in their traits: There are no genetically identical populations [35].

The welfare criterion of any population on the modern evolution scale is its size. However, this parameter is extremely difficult to determine, since the wildlife experiences constant size [36]. These all-embracing "waves of life" described by Chetverikov as early as 1905 (cf. [27]) are intrinsic to all biological communities, from a population to landscape, and occur in wide, quantitative, and time ranges [37]. Because of that, an observable size of any population is, in essence, its value at an instantaneous time slice [38]. The size of a population can vary with time hundreds, thousands, and, in certain species, millions times [39]. More informative is the average size, i.e. a size averaged over a certain observation period. When theoretically averaged over a very long time period, this characteristic is considered as a dynamic equilibrium size N_{eq}, and all fluctuations occur around this point. The amplitude of size fluctuations depends on the force of extrinsic factors and on the sensitivity of the population to exposure to these factors [40]. No less important characteristics are the maximum N_{max} and minimum N_{min} population sizes, namely, the highest and lowest fluctuation points.

The essence of interpopulation selection consists in that the probability of population death depends on N_{min}. The case in point is that there is a genetically effective size of a population [41, 42], i.e. a minimum size which is still sufficient for the population to successfully reproduce in natural conditions [43, 44]. If in the clurse of fluctions the size of a population gets lower this level at least for some time, the population is doomed to extinction after several successive generations due to gene drift [45–47]. The more sensitive is the population to extrinsic factors, the large is the amplitude of fluctuations of its size, and, consequently, the probability that the size will fall below the point of no return. This sensitivity depends on the genetic constitution of a concrete population. Threats to populations come from unfavorable sets of environmental circumstances, which directly affects their size, as well as from favorable circumstances, since excessive birsts of size give way to deeper depressions [48].

Mechanism of Natural Selection of Species-selective Longevity

As follows from the aforesaid, to find out the regularities of the evolution of a concrete trait, one should explore the impact of this trait of N_{min}, i.e. correlate the minimum population size on the qualitative measure of this trait. Natural selection always works to increase N_{min}.

To solve this concrete problem, we made use of a regularity observed by ecologists [48], according to which the intrisic rate of population growth r_{in}, net rate of population reproduction R_0, and lifespan of one generation T are interrelated by the equation:

$$r_{in} = \ln R_0 / T.$$

To find out how the species-specific lifespan stabilized in the course of evolution and what predetrmines its value, we developed a mathematical

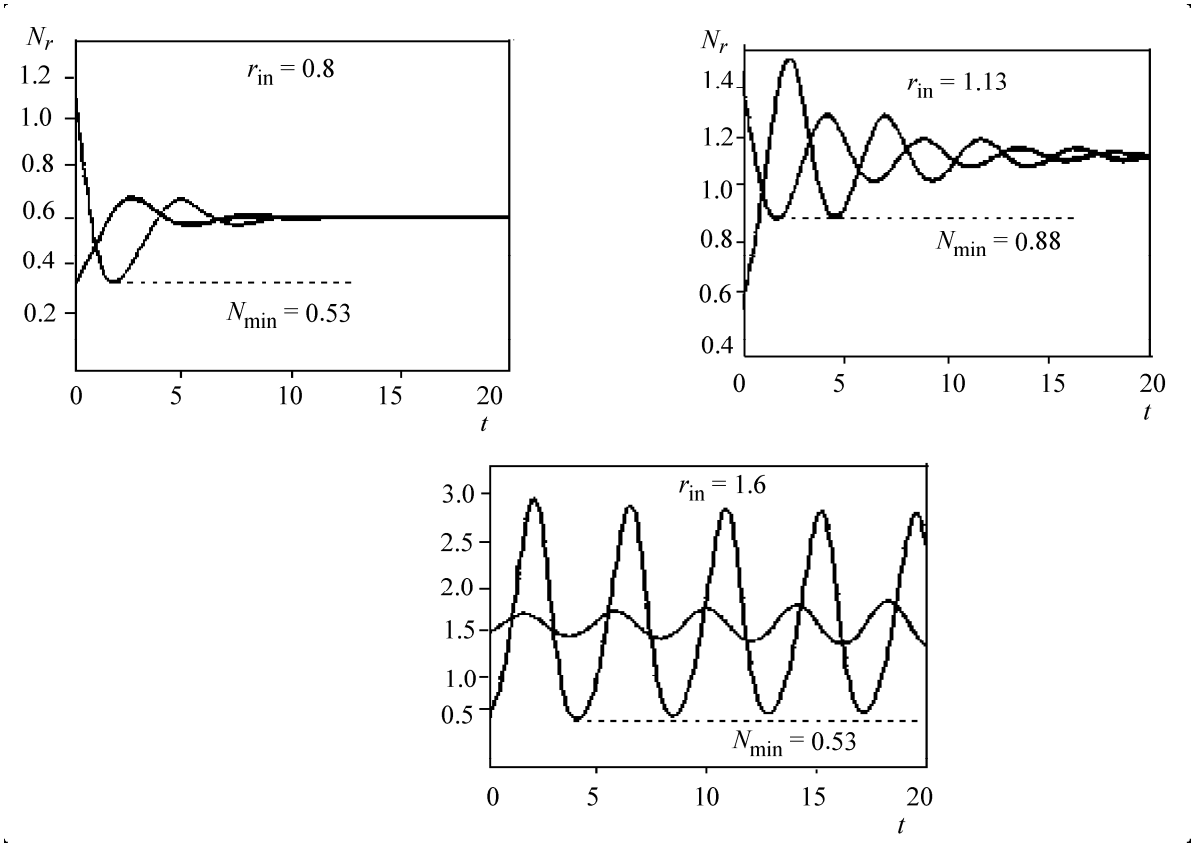

Fig. 1. Effect of the intrinsic rate of population growth r_{in} on fluctuation parameters of population size (calculated for the delay time $\tau = 1$ and environmental pressure $p = 1$). Axes: (x) time t and (y) relative population size N_r (current size N_t divided by the equilibrium size N_{eq} at t_0).

model (see Annex). The calculations showed that over the course of evolution the intrisic rate of population growth r_{in} stabilizes at a strictly defined levelwhich depends on the pressure of the environment in the ecological niche of the species. This occurs in the following way. Fluctuations in population sizes, as mentioned above, are inevitable in force of environmental fluctuations and are harmful as they increases the risk of population death. In periods when unfavorable circumstances decrease population size, this decrease will be smaller (consequently, the lower is the risk of death), if the intrisic rate of population growth is high, since it counteracts the decrease of size. But, being a favorable factor at the depression stage, a high r_{in} value will pose threat, when the population size will start to grow, since now it will favor a larger population size (after which a deeper depression will occur). The effect of too low r_{in} values is the same in strength but opposite in direction.

A natural population cannot have such extreme or arbitrary intrinsic growth rates. There is a certain optimum r_{in} value which provides a minimally possible amplitude of size fluctuations of the population, and, as a consequence, a minimum possible risk of its death (Fig. 1). The $N_{min}(r_{in})$ function calculated for a constant environmental pressure has a maximum at a definite r_{in} (Fig. 2). Since the risk of population death is inversely related to N_{min}, then selection exerts pressure on the population from the side of both high and low r_{in} values, stabilizing the intrisic rate of population growth at a certain level.

The calculations also showed that the r_{in} value maintained by natural selection, depends on the environmental pressure in the ecological niche of the species (availability of resources, number of predators, parasites, etc.): The higher r_{in}, the higher its value stabilized by selection (Fig. 3).

The mathematical model allowed us to understand the mechanism of functionining of a biological system, by putting r_{in} in one-to-one correspondence with environmental pressure. However, the calculations take no account the biological sence of r_{in}. The

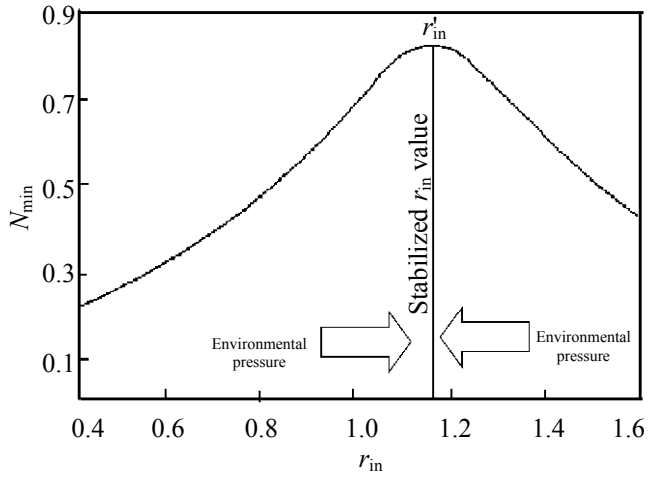

Fig. 2. Stabilization of the intrinsic rate of population growth by interpopulation natural selection.

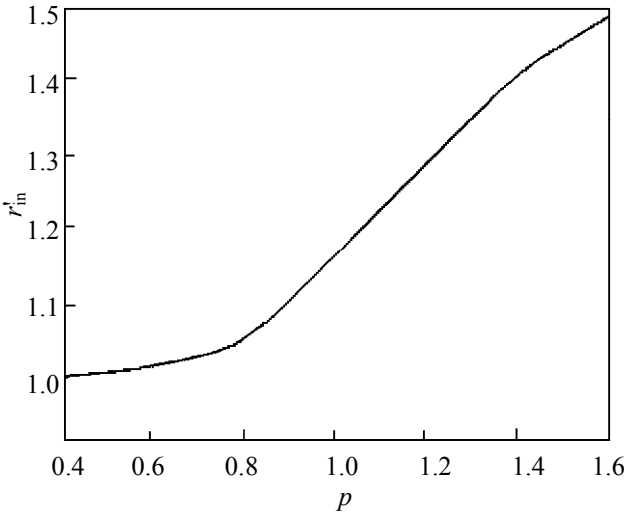

Fig. 3. Dependence of the selection-stabilized intrinsic rate of population growth r'_{in} on environmental pressure p.

intrinsic rate of population growth is a formal characteristic which cannot be programmed directly. According the regularity previously established by ecologists [48], the rate of population growth is predetermined by the net rate of population reproduction R_0 and lifespan of one generation T:

$$r_{in} = \ln R_0 / T.$$

Actually, really programmed traits are the lifespan and reporoduction rate of species comprising a population: The higher is the environmental pressure in the ecological niche of the species, the shorter is the lifespan and reproduction rate of the species. However, since r_{in} depends on two programmed traits, its changes in the evolution process can occur both due to a similtaneous change of reproduction rate and longevity and due to an independent change of each of these traits. Therefore, one should speak about correlations between lifespan and environmental pressure and between fecundity and environmental pressure, rather than about a strict dependence.

Theoretically (this does not follow from calculations), a third correlation can be suggested. The deficit of food resources is, while not the only, but a weighty component of environmental pressure for most species. Therefore, enhancing environmetal pressure showld entail a decrease in animal size, since as resourses are empoverished under the conditions of increasing fecundity, the resourse supply per one individual species decreases. The fact that each of these traits correlates with environmental pressure predetermines their mutual correlation. The information that these three mutual correlations are actually observed in the nature is contained in most textbooks on ecology and numerous papers. The correlation between environmental pressure and these traits has never been mentioned in the literature, but it is also clearly ob-served. Let us consider extreme examples. Elephants or whales which have little enemies and enough resources are huge in size and live, respectively, 100 and 200 years, and their females deliver one per 2–3 years. On the other hand, mouse-like rodents are the target of a multitude of predators and, what is more, have an unstable food base and are small in size, live 2–3 years and constantly reproduce under any conditions.

The aforesaid allows one principal conclusion: The species-specific lifespan is controlled by natural selection and presetermined by environmental pressure in the ecological niche of the species. Consequently, there are specific genes programming longevity.

Mechanism of Programmed Aging

To etablish the existence of genes responsible for programmin longevity is insufficient for understading the nature of aging. One should know the mechanism of implementation of this program. Note that life is a complex of interrelated physiological processes driven of the mitochondrial energy of the bioenegretic machine, while aging is “a retardation of all physological functions of an organism” [1]. Such retardation can theoretically be caused by either a

damage of the structures fulfilling these functions (this is the basic postulate of the free-radical theory) or a decrease of the level of the bioenergeic processes, which can inhibit all physiological functions to a level incompatible with life (only one of these opportunities can be programmed).

Age-related bioenergetics decay was discovered as early as the XIX century by the decreased level of basal metabolism and many times confirmed in further experiments. The explanation of the mitochondrial theory consists in that the action of ROS on mitochondria leads to irreversible damages of their structures. However, experiments revealed no accumulation of such damages: Being transferred to HeLa ρ^0 cells {HeLa cells without mitochondrial DNA (mtDNA), mitochondria of old donors exhibit a full-scale functional activity [22]. Transfer of HeLa cell nuclei to cells of old donors, too, restored the energetic functions of mitochondria [25, 26]. Accoring to the authors of the cited works, the latter result provides evidence to show that the decay of the bioenergetic function is programmed in the nuclear genome. No less convincing evidence was reported by Hamilton et al. [21]. They exposed hepatocytes of young and old rats to γ irradiation. The enhanced level of DNA (including mtDNA) damage, observed after irradiation, returned to the age-related level of damages in a short time. This result rules out an irreversible damage of cellular structures and existence of circulus vituosus, otherwise cells would be impossible to get out of the "mutational well" created in the experiemnts and return to the starting state. An analogous experiment was set up by the very life: Niether Hiroshima nor Chernobyl caused no acceleration of the normal physiological aging in their resident humans and other beings. It only remains to conclude that the bioenergetics decay is programmed by the nuclear genome.

However, this conclusion faces one more difficulty: It was shown that the rate of ROS generation increases progressively with the electrochemical proton gradient $\Delta\psi$ and NADH/NAD^+ ratio [49, 50], which measure the level of cellular bioenergetics. Consequently, the programmed age-related bioenergetic decay decreases the mitochondrial ROS level. However, numerous experiments revealed increased levels of ROS in all body tissues. By contrast, bats and birds that live an order of magnitude longer than terrestial animals feature a higher level of bioenergetics and, at the same time, lower level of ROS than in terrestial animals of the same size [51–53]. This fact can be explained by different experimental conditions in vitro and real conditions *in vivo* [54]. The mentioned *in vitro* studies of the dependence of ROS generation rate on $\Delta\psi$ and NADH/NAD^+ were performed on isolated mitochondria, and, therewith, the incubation medium was specially doped with reagents neutralizing the antioxidant protection. The ROS level measured in *in vivo* experiments is a dynamic value determined by the relative rates of their generation and detoxification of the antioxidant system [55]. Analysis of the mitochondrial ROS-scavenging mechanism with account for the thermodynamics of the processes that occur showed that the bioenergetics decay can increase the ROS level [56]. This takes place on aging and, according to experimental data, in flying vertebrates.

The conclusion that under physiological conditions the ROS level is inversely related to the bioenergetics level is the second most critically important (after evolutionary) moment for the understanding of the nature of aging: It explains the mechanism of programmed aging, which includes the mechanism postulated by the free-radical theory, as one of the functional components. Let us give a brief substantiation of this conclusion.

The mitochondrial ROS-scavenging mechanism is a chain of consecutive interrelated reactions: An increase of $\Delta\psi$ and NADH/NAD^+ enhances production of superoxide radical anions ($O_2^{\bullet-}$) in the electron transport chain, and these species are rapidly transformed into hydrogen peroxide with superoxide dismutase (Fig. 4). Hydrogen peroxide is then reduced along two pathways. The major pathway is the antioxidant mechanism which is activated by two similarly functioning enzymes: glutathione peroxidase (GSHPx) and thioredoxin peroxidase (for bravity, we dwell here on the GSHPx pathway only). When reduced by the GSHPx pathway, H_2O_2 takes up two electrons from reduced glutathione (2GSH) and two electrons from the medium, after which it decomposes to form two water molecules: $H_2O_2 + 2e^- + 2H^+ = 2H_2O$. The glutathione oxidized in this reaction (GSSG) is again reduced by NADH which, in its turn, is reduced by oxidizing NADH to NAD^+, and the latter is reduced in the Krebs cycle. This chain of consecutive redox reactions is a channel for transferring electrons generated in the Krebs cycle to glutathione peroxidase. The activity of glutathione peroxidase depends on the redox state of glutathione, i.e. the 2GSH/GSSG ratio which, in its turn, is determined by the NAD(P)H/$NAD(P)^+$ ratio which measures the lavel of cellular bioenegretics (its

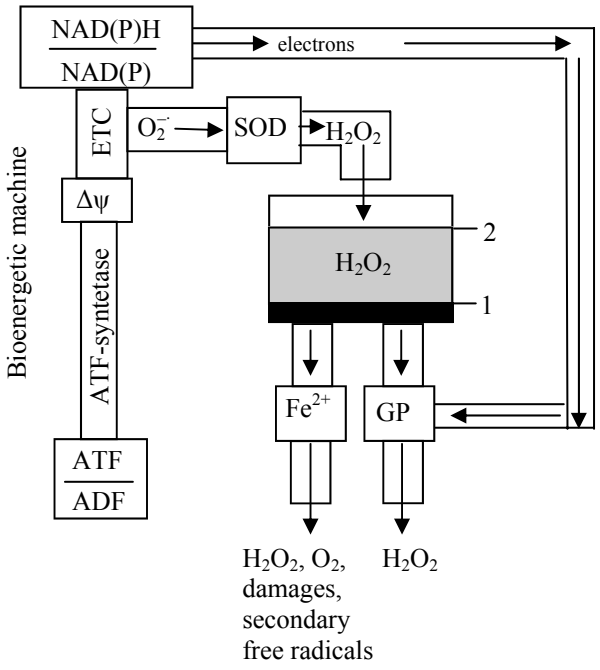

Fig. 4. Simplified scheme of ROS-scavenging mechanism. (ETC) Electron transport chain, (SOD) superoxide dismutase, and (GP) glutathione peroxidase. In young cells [a high $NAD(P)H/NAD(P)^+$ ratio], glutathione peroxidase is very active, and, therefore, the H_2O_2 content is low (level 1) and the flow through the Fenton's reaction system is weak. With age, the $NAD(P)H/NAD(P)^+$ ratio decreases. The activity of the enzyme decreases, and the H_2O_2 content increases (level 2). As a result, the flow through the Fenton's reaction system increases, thus increasing the content of ROS and their aggressiveness. For details, see *Usp. Gerontol.*, 2006, vol. 18, p. 23.

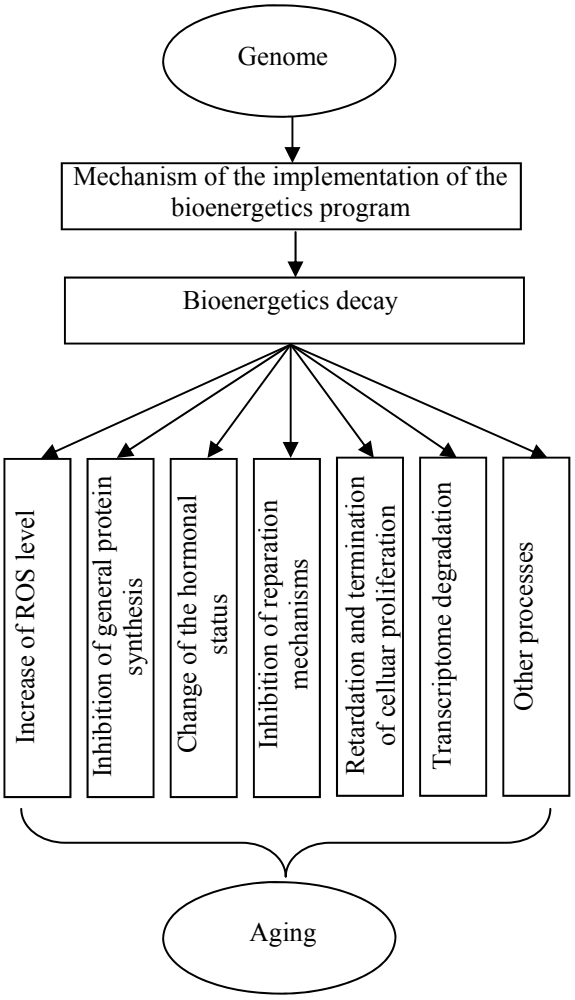

Fig. 5. Shcematic mechanism of programmed aging. The genome primarily programs bioenergetics decay, which gives rise to a series of destructive processes inhibiting all body functions.

primary driving force generated in the Krebs cycle). Thus, the higher the bioenergetics level, the more efficient is the antioxidant mechanism.

The second pathway is catalyzed by Fe^{2+} (Fenton's reaction) and here hyrogen peroxide, being a powerful oxidant (e^0 = 1.77 V), "fends" electrons for its reduction by oxidizing adjacent macromolecules. This reactions gives water, oxygen, damaged macromolecules, as well as secondary free radicals, including hydroxyl which is the most agressive radical on record. Thus, the hazard of ROS is associated with the Fenton's reaction.

According to chemical kinetics laws, the flows along these two channels are distributed proportionally to catalyst activity. The enzymes involved in the first pathway (glutathione peroxidase and thioredoxin peroxidase) are always much more active than Fe^{2+}, but they need energy makeup, whereas Fe^{2+} not. Therefore, as the glutathione peroxidase and thioredoxin peroxidase activity decreases as the programmed bioenergetics decay occurs. As a result, less H_2O_2 is removed by this major channel, and its content increases, which, according to the mass action law, enhances the flow through the Fenton's reaction with all its consequences. Consequently, the age-related bioenergetics decay increases the level of ROS and their aggressiveness, even though the electron transport chain produces less supeoxide.

The age-related increase of the level of free radicals looks now not as a trigger of aging but as one of the consequences of the programmed bioenergetics decay**.** Schematically, the mechanis of phenoptosis are presented in Fig. 5. The nuclear genome programs

bioenergetics decay which entails a number of secondary processes: increase of the ROS level, inhibition of general protein synthesis [57–59], change of the hormonal status [60], retardation and termination of cellular proliferation [61], transcriptome degradation [62], etc. Each of these processes can cause an avalanche of subsequent degenerative changes. For example, increased ROS level causes cataract, Alzheimer's disease, vascular diseases, etc. The inhibition of general protein synthesis is no less harmful: According to [57], it leads to a deficit of enzymes for maintaining reparation mechanisms and normal cellular metabolism and inefficient removal from cells of damaged and inactivated macromolecules, and adversely affects the efficiency of intra- and intercellular signaling pathways and production and secretion of hormones, antibodies, neuromediators, and components of the extracellular matrix. Equally harmful are other secondary consequences of the bioenergetics decay. Together they are responsible for the general age-related organism degradation called aging.

CONCLUSIONS

The presented information shows that the species-specific lifespan is controlled by natural selection and, consequently, programmed. The primary programmed process determining the rate of aging is a decay of the bioenergetics level, which triggers a series of secondary processes leading to a degradation of all body functions.

Manipulations with each of the secondary processes separately (for example, ROS scavenging with antioxidants) can only compensate for the damage caused by this specific process. To control lifespan, one should search for approaches to controlling cellular bioenergetics.

ANNEX

Mathematical Model of the Interpopulation Natural Selection of Species-Specific Lifespan

Populations of a certain abstract vertebrate species with overlapping generations in natural habitat conditions are considered.

The rate of population size change dN/dt is determined by the difference between the reproduction dNb/dt and mortality dNm/dt rates

$$dN/dt = dNb/dt - dNm/dt. \quad (1)$$

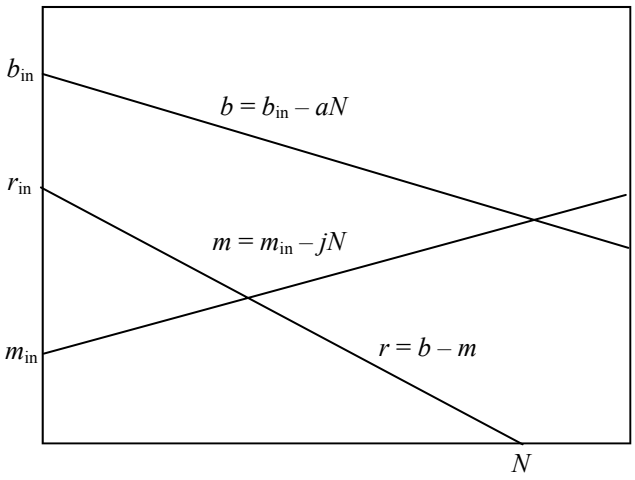

Fig. 6. Dependence of birth rate b, mortality m, and population growth rate r on population size N. Increase of the population size decreases reproduction and increases mortality with respect of the intrinsic values b_{in} and m_{in}. The rate of population growth decreases with increasing size and reaches zero at $b = m$.

The size of a population is an essential factor of its own habitat, and, therefore, these values (reproduction and mortality) are size-proportional:

$$dNb/dt = bN;\ dNm/dt = mN, \quad (2)$$

where b and m are the reproduction and mortality factors.

The effect of reproduction and mortality on population size is not direct but is mediated by a change of habitat conditions. When the population density increases, the food resources are depleted, the number of predators, parasites, and infections increases, and the living space per one population member decreases. This all enhances the environental pressure on the population, as a result of which the reproduction factor decreases, while the mortality factor increases (Fig. 6):

$$b = b_{in} - aN;\ m = m_{in} + jN, \quad (3)$$

where b_{in} and m_{in} are the intrinsic reproduction and mortality factors which are realized only at a small size (theoretically, at $N \to 0$); and a and j are factors characterizing the environmental pressure on reproduction and mortality, respectively.

Subsituting b and m from Eq. (3) to Eq. (1) and incluing Eq. (2), we obtain:

$$dN/dt = (b - m)N = (b_{in} - m_{in})N - (a + j)N^2. \quad (4)$$

Introducing the denotations $b_{in} - m_{in} = r_{in}$ and $a + j = p$, we write down (4) as

$$dN/dt = N(r_{in} - pN), \quad (5)$$

where r_{in} is the intrinsic rate of population growth ($time^{-1}$) and p, environmental pressure ($time^{-1}N^{-1}$).

In the ecological literature, the population dynamics is considered at the long-term scale or at the current moment. The average size of a population existing for a long time under invariable environmental conditions is constant. This is a measure of the environment capacity with respect to the given population and defined as the dynamic equilibrium size N_{eq}.

As mentioned in the paper's body, the intrisic rate of population growth r_{in} and lifespan of one generation T are interrelated by the equation: $r_{in} = \ln R_0/T$. Taking this into account, we write Eq. (5) for a dynamically equilibrium population at the long-term evolution scale in the following form:

$$dN/dt = N(\ln R_0/T - pN_{eq})$$

Analysis of this equation allows us to determine the trend in variation of the "lifespan" trait at varied environmental pressure in the ecological niche of the species. Since at the evolution time scale $dN/dt = 0$, then $\ln R_0/T = pN_{eq}$. From this it follows that if the environmental pressure will increase, the $\ln R_0/T$ value will also increase, i.e. the lifespan will decrease and the fecundity will increase, and vice versa. To understand the mechanism of the natural selection responsible for such changes, let us consider the dynamics of population size at the current moment.

At the short-term scale, the dynamics of any population are complicated by size–environmental pressure feedbacks. Changing population size changes food consumption and the level of parasites, predators, and infections and other factors in the environment. Therewith, the environmental situation changes with a certain delay. If, for example, as a response to a certain unfavorable factor, the population size had decreased and then started to increase to reach N_{eq} by by time t, then the environment will only respond by the corresponding increase of the pressure on the population in a certain time interval τ. This time is necessary to expend additional food resources and to reproduce parasites, predators, etc. Immediately after the population size has increased to N_{eq}, the environmental pressure is equal to that at time t, i.e. τ. As a result, the population will continue to grow after N_{eq} to reach $N_{max} > N_{eq}$. Since this state is non-equilibrium, then the population size will become to decrease, and, having passed the equilibrium point, will reach, be the same reason, $N_{min} < N_{eq}$, etc. This is the nature of autofluctuations of population size about the equlibrium point [63]. With account for the delay effect, Eq. (5) takes the form:

$$dN_t/dt = N_t[r_{in} - pN_{(t-\tau)}]. \quad (6)$$

Numerical solution of this equation with respect to N_t (it does not have an analytical solution) shows that the minimum population size depends on all the three parameters: τ, r_{in}, and p. The introduced value τ, like p, is a parameter of the environment, which relates to the rate of variation of the most essential factors in the ecological niche of the species [64]. In reality, τ is a distributed multifactor characteristic of the environment [65, 66], but to solve tasks analogous to the present one, it can be assumed discrete with no sacrifice in results [65].

Let us introduce the following denotations: N_t, relative population size (size at the current moment divided by N_{eq}) and N_0, relative initial population size. To find out what is the net effect of r_{in} on the minimum size N_{min}, we suggest that a randomly chosen N_0 value is a result of exposure to environmental factors, and the subsequent dynamics of size fluctuations are determined by population parameters. Therewith, it will be remembered that the fluctuations of environmental parameters are stochastic both in time and in value. Favorable environmental factors, naturally, increase the population with respect to the equilibrium value ($N_0 > 1$), whereas unfavorable factors decrease it ($N_0 < 1$). We call the first kind of fluctuations positive extrinsic perturbations and the second kind, negative. The responses of populations on positive and negative perturbations are different, and we consider them separately. For comparable calculation results, let us assume that $N_0 = 1.5$ correspond to positive extrinsic perturbations and $N_0 = 0.5$ to negative. For the overwhelming majority of species in the nature, the fluctuations of size, caused by extrinsic perturbations, are decaying ones. Therefore, here we take for N_{min} the minimum size reached in the first fluctuation period after extrinsic perturbation.

For calculations we have to determine the range of variation of τ. The calculations show that at constant r_{in} and p values ($r_{in} = 1$, $p = 1$) the species whose ecological niche has $\tau \leq 0.3$ are the least sensitive to extrinsic perturbations: Irrespective of the sign of the extrinsic perturbation, their size steadily returns to N_{eq}.

In the $0.3 < \tau < 1.6$ range, the size fluctuatively returns to equilibrium, and, therewith, as τ increases, the fluctuation amplitude continuously increases, decreasing N_{min}. Further increase of τ causes nondecaying auto-fluctuations with increasing amplitude. At $\tau > 2.5$, populations get unviable: A slightest extrinsic perturba-tion induces enhancing autofluctuations which decrease N_{min} to zero. Since vertebrate species with a nondecaying regime of size fluctuations is quite rarely observed in the nature (mostly in mouse-like rodents), then in the ecological niche of the overwhelming majority of species the τ value appears to vary in the range 0.4–1.5. Therefore, in the calculations we assume that this environmental paramets for populations of abstract species is equal to 1.

Numerical solution of Eq. (6) shows that the variation of r_{in} with varied environmental pressure affecting both N_{eq} and the amplitude of fluctuations, thereby affects N_{min}. The consequences of this phenomenon are described in the paper's body.

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