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Bioenergetics Theory of Aging

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1. Introduction

The average lifespan of people in developed countries has tripled since ancient times while its maximum longevity (about 120 years) has remained invariable. The strategic goal of gerontology is to exceed this limit, i.e. to develop remedies which would allow the living of an indefinitely long life. However there have not been any significant advances in solving this problem so far. There is still no answer to even the fundamental question: what is the primary cause of degradation for all of an organism's functions (otherwise known as aging)? Actually, there are too many answers to this question: over 300 aging theories have been developed, and each of them provides a different response (Medvedev, 1990), although the majority of these theories now have only historical importance. Theories of aging are traditionally divided into two alternative groups. First, stochastic theories claim that there are no specific aging genes and that an organism's deterioration is the result of damaging factors. Second, and by way of contrast, programmed-aging theories assert that longevity is predetermined by a genetic program. Stochastic theories have dominated the discussion since gerontology became a branch of science, and the idea that aging is programmed has not yet received wide recognition, even though there is a lot of empirical evidence supporting it. There are several factors which impede the wide recognition of this idea. First, there is no evidence that longevity is under the control of natural selection; and second, there is no convincing mechanism the programmed of aging. Adherents of this view currently search for longevity genes in a practically blind or ad hoc fashion (Holzenberger et al., 2003; Kenyon, 2010). Many such genes have been found for various organisms, ranging from unicellular creatures to mammals, but it is still unclear what processes they control (Anisimov, 2003).

There are several different theories which are currently under consideration and which are based on reliable, proven evidence: i) the free radical theory which claims that aging is caused by an increased damage rate in cell structures due to an increased generation-rate of reactive oxygen species (ROS) by their own mitochondria; ii) the protein error theory which states that the primary cause is the age-dependent retardation of the protein synthesis rate; iii) the replicative senescence theory which argues that an age-dependent organism's senility is caused by the limitation of cell proliferation. There is also reliable evidence in support of other theories which are not as popular, for instance the immunological theory and several versions of neuroendocrinal theories.

The goal of this report is: (1) to show that despite the beliefs of the supporters of the stochastic theories, longevity is controlled by natural selection, i.e. specific aging genes exist; (2) such genes program a lowering of the bioenergetics level (degradation of Gibbs energy, ΔG). In turn, such degradation results in an age-dependent increase in the ROS generation rate, a decrease in the protein synthesis rate, and a limitation of cell division. These three phenomena form the basis for a large number of secondary destructive processes which result in the degradation of all physiological organisms' functions, i.e. the causes of aging. The very idea that bioenergetics exerts an impact upon aging is not a novelty. Hasty and Vijg (2002) have recently stated in theory that proper energy-saving could support a living system indefinitely. B.N. Ames (2004) has remarked that mitochondrial bioenergetics supports the metabolism's cell processes and that its attenuation can result in the age-dependent degradation of all of an organism's physiological functions. And indeed, life as a phenomenon is characterised by a number of physical and chemical processes driven by the power of the bioenergetics machine. A gradual decrease in bioenergetics level can cause the degradation of all vital processes. However they also believe that the cause of age-dependent bioenergetics attenuation is to be identified with the mechanism postulated by the free-radical theory. The following fact seems to reject the assumption of the direct programming of bioenergetics attenuation: one of main bioenergetics parameters is the mitochondrial membrane potential Δψ. In vitro tests have shown that the superoxide ($O_2^{\bullet-}$) generation rate in the electron transport chain decreases as Δψ decreases. Consequently, in the process of bioenergetics attenuation the ROS level should decrease, but the tests show its increase in all tissues. And only that version of the vicious cycle brought forward by the free-radical theory can explain this paradox. Another mechanism which we have already suggested explains the increase in the number of reactive oxygen species during programmed bioenergetics attenuation (Trubitsyn, 2006). The bioenergetics mechanism of aging under consideration represents the integration of several of the author's articles published earlier (Trubitsyn, 2006, 2006a, 2009, 2010, 2011).

2. The increase in the level of reactive oxygen species is predetermined by programmed bioenergetics decay

2.1 Introduction

The free-radical theory of aging (the theory of oxidative stress, the oxidative damage theory and the mitochondrial theory of aging) was proposed by D. Harman (1956) in the middle of the 20th century and its improved version continues to dominate discussion. Its supporters claim that there are no specific aging genes because longevity cannot be controlled by natural selection (Kirkwood, 2002, 2008; Medawar, 1952). According to their view, age-dependent organism degradation results from the damage to cell structures by the ROS that are generated by mitochondria (Trifunovic & Larsson, 2008). This theory fascinates researchers by virtue of its simplicity and clarity. Indeed, it has been established that as an organism gets older, the ROS generation by the mitochondrial respiratory chain (electron transport chain) increases and the amount of damage to cell structures increases as well. The conclusion is obvious and the method for preventing aging is equally so: the neutralisation ROS by antioxidants. The age-dependent increase in the ROS generation rate is assumed to be just that: the ROS generated by mitochondria produce injury to its own mitochondrial DNA (mtDNA), which results in a defect in the respiratory chain. This, in turn, increases the rate of ROS production and as a result a vicious cycle arises.

When the free radical theory of aging appeared, it stirred up a brisk discussion which continues to this day. Empirical data has shown that there is no appreciable loss in the respiratory chain's functions during aging (Barrientos et al., 1996; Rasmussen et al., 2003). This is also supported by experiments indirectly related to the electron transport chain. For example, research into intra-cellular organelle transfers has shown that the mitochondria of old donors recover their functional activity completely when transferred to ρ0 HeLa cells (HeLa cells free of mtDNA) (Hayashi et al., 1994; Isobe et al., 1998). Mitochondrial dysfunctions are also eliminated when HeLa cell nuclei are transferred into the cells of old donors (Isobe et al., 1997). The authors concluded that nuclear factors are responsible for age-related mitochondrial deficiency. In addition, the conclusion that the age-dependent accumulation of mtDNA mutations is modulated by the nuclear genome was also made by Yao et al. (2007). The discussion has become especially vigorous over the last decade. On the one hand, based on this theory, it was claimed that "aging is no longer an unsolved problem in biology" (Hayflick, 2007; Holliday, 2006). On the other hand, R.M. Howes (2006) has declared that the "overly exuberant and exaggerated past expectations and claims of the free-radical theory have been quieted by extensive randomised, double-blind, controlled human studies. A half century of data demonstrates its lack of predictability and it has not been validated by the scientific method. Widespread use of antioxidants has failed to quell the current pandemic of cancer, diabetes, and cardiovascular disease or [even] to stop or reverse the aging process." His position is also supported by G. Bjelakovic et al. (2008) who have collected a great deal of data to show that antioxidants neither result in the beneficial effects expected nor do they increase life expectancy (in the best-case scenario). Gems & Doonan (2009) asked a question in a recent review: "Is the theory really dead, or does it just need to be modified?" Actually, there is more than ample evidence against the aging mechanism postulated by this theory than there is evidence in support of it.

2.2 Schema of the mitochondrial bioenergetics machine

Mitochondria generate about 90 percent of the energy in any eukaryotic cell. Therefore, only the mitochondrial bioenergetics machine will be considered here. Any energy system can be quantitatively described by its propellant power (F) and by its effect (A): F = kA: this is the force and the work in mechanical engineering (k is the friction) and the electromotive force and current in electrical engineering (k is the resistance). It is the free-energy change (Gibbs energy, ΔG) and current in chemical thermodynamics (in bioenergetics in particular). Such terms as the bioenergetics level and the level of energy production are used in bioenergetics to express the propellant power. To make it clear, let us recall that the ΔG of macroergic (high-energy) coenzymes that function in the bioenergetics machine (ATP, NAD, NADP, GSH, etc.) is determined by the value of their concentrations ratio of the reduced form to the oxidised one and by the temperature. For ATP, for instance, $\Delta G = \Delta G^0 - RT \ln[ATP]/[ADP][P_i]$, where ΔG^0 is the standard Gibbs energy that is measured with everything at 1 molar concentration: $[ATP] = [ADP] = [P_i] = 1M$; R is the gas constant; T is the absolute temperature. The more negative Gibbs energy there is, the higher the energy potential the bioenergetics machine generates. As follows from the above expression for ΔG, the concentrations ratio of the reduced to oxidised forms of macroergic coenzymes ($[ATP]/[ADP]$, $[NADH]/[NAD^+]$, etc.) is the only variable which determines the energy potential for warm-blooded animals.
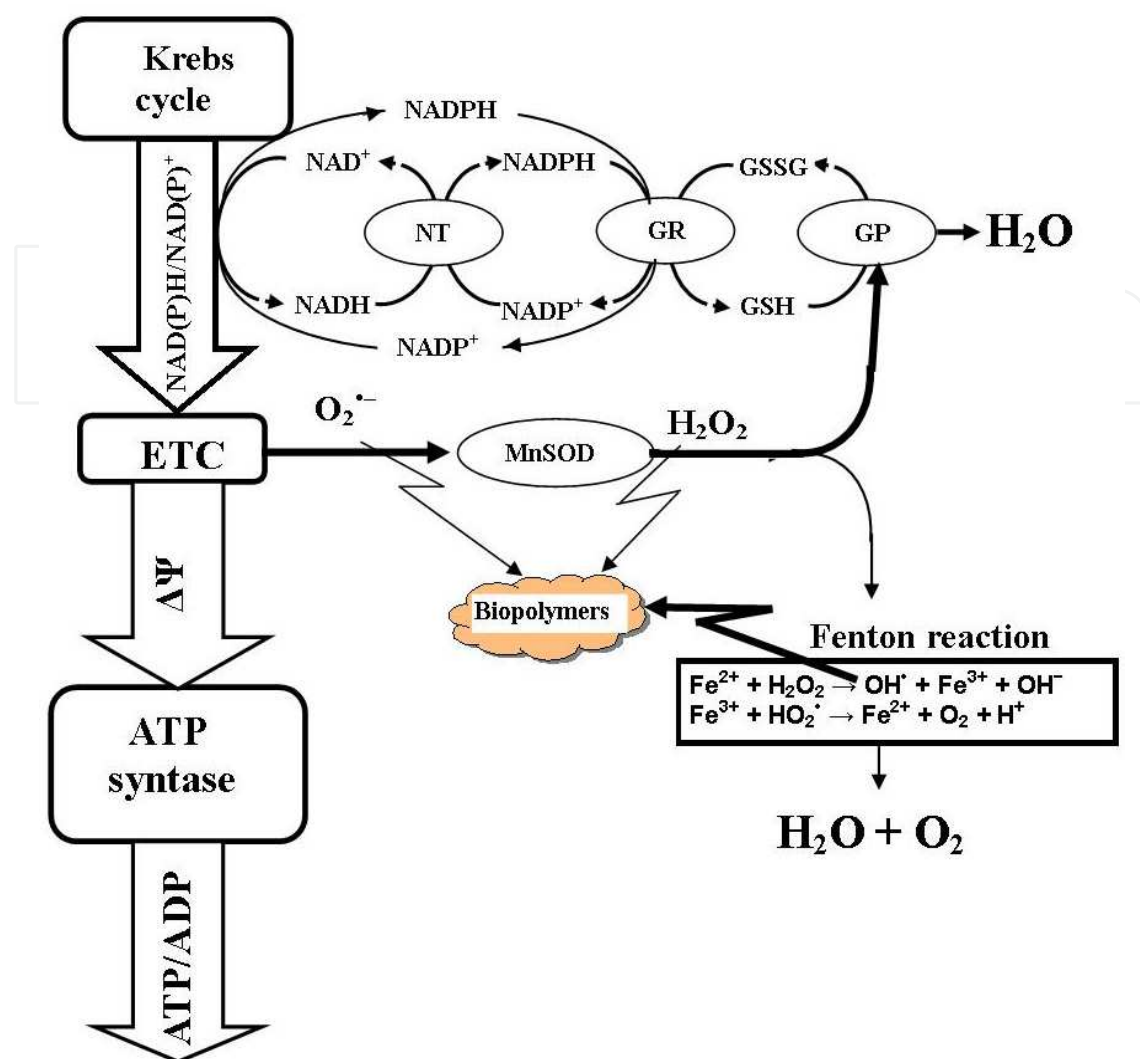
Bioenergetics machine. The primary motive power, NADH/NAD⁺, is created in the Krebs cycle. The mitochondrial membrane potential, Δψ, is created by the electron flow from NADH to oxygen through the electron transport chain (ETC). ATP-synthase phosphorylates ADP into ATP at the expense of Δψ. *Scavenging mechanism.* The superoxide radical ($O_2^{\bullet-}$) produced by ETC is transformed into hydrogen peroxide, H_2O_2, by manganese superoxide dismutase (MnSOD). H_2O_2 is then decomposed into H_2O and O_2 mainly through the reaction that is catalyzed by glutathione peroxidase (GP) and partially through the Fenton reaction; the last produces an extremely aggressive hydroxyl radical. The glutathione peroxidase activity mainly predetermines the rate of the scavenging process. This activity is sustained by the energy provided by glutathione (GSH) oxidation. The thus GSSG formed is reduced again into GSH at the expense of the oxidation of NADPH in a reaction that is catalysed by glutathione reductase (GR). The NADP⁺ formed is reduced in turn at the expense of the oxidation of NADH in the reaction catalysed by nicotinamide nucleotide transhydrogenase (NT). The NAD⁺ formed is reduced by the reactions of the Krebs cycle. The NADP⁺ can also be directly reduced in the isocitrate dehydrogenase reaction of the Krebs cycle. The chain of these redox reactions is the electrons' pipeline from the Krebs cycle to glutathione peroxidase. *The mechanism of ROS increase.* The programmed bioenergetics decline leads to a proportional decrease in GP activity, which increases the H_2O_2 level. As hydrogen peroxide is a substrate for the Fenton reaction, this augments the H_2O_2 flow through the Fenton reaction, which elevates the content of free radicals. Thus, a decline in the bioenergetics level is followed by an increase in the total amount of reactive oxygen species and its aggressiveness.

Fig. 1. Scheme explaining the mechanism of the ROS increase under the bioenergetics decline.

Researchers divide energy-metabolism reactions into a different number of functional blocks depending upon their purpose. For example, Ainscow and Brand (1998) have divided it into nine blocks connected to each other by five intermediates. To solve the problem under consideration, the bioenergetics machine may be divided into three blocks (the Krebs cycle, the electron transport chain and ATP-synthase) connected by two intermediates ([NADH]/[NAD$^+$] and $\Delta\psi$ (Fig.1)). According to this scheme, the output potential ([ATP]/[ADP]) is generated in three stages. At the first stage, the primary electromotive force, [NADH]/[NAD$^+$], is created by reducing NAD$^+$ to NADH. This serves as the propellant power for stage two where electrons are transferred from NADH to oxygen via the electron transport chain, generating the mitochondrial membrane potential $\Delta\psi$. At the third stage, $\Delta\psi$ is the electromotive force for ATP-synthase which generates the output potential. If there are no excessive loads (in stage four or close to it) then the [NADH]/[NAD$^+$] change results in a proportional change in $\Delta\psi$ and in [ATP]/[ADP].
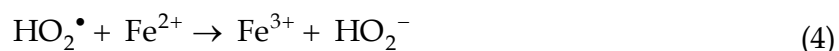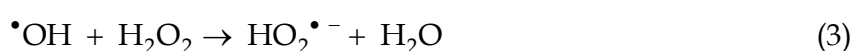
2.3 ROS-scavenging mechanisms

During the aerobic metabolism, a small number of the electrons that flow from NADH via the respiratory chain react with oxygen directly reducing oxygen to superoxide anion ($O_2^{\bullet-}$ or $HO_2^{\bullet}$) (Demin et al., 1998; Scandalios, 2002a) which can damage cell biopolymers. Cells have a protective system that can be conditionally divided into three functional lines of defence: preventative mechanisms, ROS-scavenging mechanisms, and emergency-response mechanisms. The preventative mechanisms either prevent $O_2^{\bullet-}$ generation or oxidise superoxide back into O_2 at its location of generation (Brand, 2000; Skulachev, 2001). The emergency-response mechanisms are actuated when the ROS amount exceeds a critical level and when the cumulative effect of other mechanisms cannot improve the situation. However ROS not only damage biopolymers but it also plays an important role in the regulation of transcription factors, growth factors and other intracellular signal systems (Brigelius-Flohe et al., 2003; Cerimele et al, 2005; Rhee, 1999; Scandalios, 2002). The cell needs ROS, but their concentration should be maintained at a safe level. Therefore, there is a dedicated ROS-scavenging mechanism to maintain the ROS homeostasis. This mechanism performs the $O_2^{\bullet-}$ detoxification through a two-stage process (Fig. 1). At first, the manganese-containing mitochondrial superoxide dismutase (MnSOD) transforms superoxide into hydrogen peroxide (H_2O_2) (Jonas et al., 1989; Scandalios, 2002a) which is then decomposed by catalase and peroxidases. Most H_2O_2 is decomposed in cytosol by catalase and in the mitochondrial matrix by the glutathione and thioredoxin systems (catalase is absent in the mitochondrial matrix) (Wei et al., 2001). The glutathione system consists of glutathione peroxidase (GP) and glutathione reductase (GR). The GP potency is maintained due to the oxidation of glutathione (GSH) which is converted into its disulphide form (GSSG). Next, the GR catalyses the reduction of the oxidised glutathione at the expense of NADPH oxidation (Arai et al., 1999; Jo et al., 2001; Iantomasi et al., 1993). The NADP$^+$ thus formed is reduced again to NADPH in the isocitrate dehydrogenase reaction of the Krebs cycle (Jo et al., 2001). There is an analogous system – the thioredoxin system – which functions in parallel with the glutathione system and which also consists of thioredoxin peroxidase (TP) and thioredoxin reductase (TR) (Jo et al, 2001; Nordberg & Arner, 2001). Similarly, the TP potency is maintained by the oxidation of thioredoxin which is then reduced by TR, also at the expense of NADPH oxidation (Lewin et l., 2001). For the sake of simplicity, this parallel system is not shown in Fig. 1. The reaction that is catalysed by these peroxidases is

simple: H_2O_2 takes two electrons from the glutathione (thioredoxin) and two protons from the environment and then decays into two water molecules: $H_2O_2 + 2e^- + 2H^+ = 2H_2O$. Only GP and TP catalyse this reaction directly; the other reactions are a pipeline by which energy is transferred from the Krebs cycle to glutathione peroxidase with thioredoxin peroxidase providing their activity (Iantomasi et al., 1993). The activity of any energy-dependent chemical reaction depends upon the energy supply (Westerhoff & van Dam, 1987). Therefore, the more the $NADPH/NADP^+$ ratio is generated in the Krebs cycle, the higher the GP and TP activity, and vice versa. It was shown experimentally that bioenergetics attenuation results in decrease of the scavenging mechanism's activity (Jo et al., 2001). It should be also noted that the ROS-scavenging mechanism can to some extent adapt to changes in the ROS level: the cell responds to a higher ROS concentration by a higher synthesis rate for MnSOD and glutathione-system enzymes (Meewes et al., 2001). An increase in the gene expression of those enzymes is mediated by the transcription nuclear factor-κB that is activated under excessive amounts of ROS (Scandalios, 2002a; Schreck et al., 1991).

2.4 Fenton reaction

There is additional the ferrous-ion catalysed means of hydrogen peroxide decomposition, which is called the Fenton reaction. In its simplest form, the Fenton chemistry is a chain mechanism of certain reactions in which H_2O_2 breaks up into water and oxygen and where Fe^{2+} is regenerated (Dunford, 2002):

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {}^{\bullet}OH + HO^- \tag{1}$$

$$Fe^{2+} + {}^{\bullet}OH \rightarrow Fe^{3+} + HO^- \tag{2}$$

$${}^{\bullet}OH + H_2O_2 \rightarrow HO_2^{\bullet -} + H_2O \tag{3}$$

$$HO_2^{\bullet} + Fe^{2+} \rightarrow Fe^{3+} + HO_2^- \tag{4}$$

$$HO_2^{\bullet} + Fe^{3+} \rightarrow Fe^{2+} + O_2 + H^+ \tag{5}$$

As distinct from the glutathione system, the iron decomposes H_2O_2 due to its ability to undergo cyclic oxidation and reduction. However, such redox activity of iron can generate free radicals capable of causing a wide range of biological injuries (Liu et al. 2003). The hydroxyl radicals (${}^{\bullet}OH$) formed during the Fenton reaction are true chemical predators: indeed, the reactivity of ${}^{\bullet}OH$ is so great that, if they are formed in living systems, they will react immediately with whatever biological molecule is in their vicinity, producing secondary radicals of variable reactivity (Halliwell & Gutteridge 1984; Yu & Anderson 1997). Among $O_2^{\bullet-}$, H_2O_2 and ${}^{\bullet}OH$, only the hydroxyl radical can directly cause double-stranded DNA breaks (Aruoma 1994).

2.5 The mechanism of age-dependent increase in ROS level

The Fenton reaction actually shunts the ROS-scavenging mechanism. As a result, H_2O_2 molecules are decomposed both by the glutathione system and the Fenton reaction. As the two ways of hydrogen peroxide decomposition compete for the substratum, the fraction of

H_2O_2 which can produce $^{\bullet}OH$ (Q_r) is predetermined by both the activity of the Fenton reaction (A_f) and that of glutathione peroxidase (A_g): $Q_r = A_f /(A_f + A_g)$. Thus, the lower the level of the activity of glutathione peroxidase and thioredoxin peroxidase, the higher the level of ROS production.

As has been mentioned, a decrease in the energy metabolism rate should, in theory, result in a lowering of the $O_2^{\bullet-}$ generation rate. Indeed, this is just what happens. However the concentration of the other ROS does not only depend upon the $O_2^{\bullet-}$ generation rate: the programmed age-dependent delay in the bioenergetics level results in a decrease in GP and TP activity. This raises the concentration of their substrate, H_2O_2. Since hydrogen peroxide is a substrate for the Fenton reaction as well, it augments the current through this reaction. As a result, the total amount of ROS and their aggressiveness increases despite a decrease in the $O_2^{\bullet-}$ generation rate.

2.6 Conclusion

Accordingly, the leading cause of the age-dependent increase in the amount of ROS and its aggressiveness is a programmed attenuation of cellular bioenergetics rather than a progressive accumulation of mutations in mtDNA due to the creation of a vicious cycle.

3. The age-dependent attenuation of bioenergetics underlies a decrease in the general level of protein synthesis

3.1 Introduction

A different popular aging theory, the protein-error theory, is based on the indisputable fact that the bulk protein synthesis slows down during aging (Rattan, 1996, 2009; Ryazanov & Nefsky, 2002). According to the theory, such retardation results in a decreasing protein turnover rate which causes the accumulation of defective macromolecules. S.I.S. Ratton (1996), who has investigated this process in detail, reports that "the implications and consequences of slower rates of protein synthesis are manifold, including a decrease in the availability of enzymes for the maintenance, repair and normal metabolic functioning of the cell, an inefficient removal of inactive, abnormal and damaged macromolecules in the cell, the inefficiency of the intracellular and intercellular signalling pathways, and a decrease in the production and secretion of hormones, antibodies, neurotransmitters and the components of the extra cellular matrix." The reason behind a slower protein synthesis rate is seen in the stochastic accumulation of molecular damage and the progressive failure of maintenance and repair (Rattan, 2009). It entails damage to fragments of the translation mechanism: "a decline in the efficiency and accuracy of ribosomes, an increase in the levels of rRNA and tRNA, and a decrease in the amounts and activities of elongation factors" (Rattan, 2006). At the same time, there is empirical evidence which allows for the explanation of the slowing down of overall protein synthesis by the attenuation of cellular bioenergetics.

3.2 The mechanism for the decrease in the level of cell protein synthesis

It was D.A. Young (1969) who discovered a relationship between the protein synthesis rate and the bioenergetics level for the first time. When conducting experiments on glucocorticoid hormones, he noticed that the rate of amino acids inclusion into a growing polypeptide chain depends upon the entry of carbohydrates (glucose, pyruvate, and lactate) into cells. An assumption was made that this effect is connected with the ATP generation rate. It was shown thereafter that the protein synthesis rate depends upon the ADP/ATP and GDP/GTP ratios

rather than on the absolute ATP value (Hucull et al., 1985; Mendelsohn et al., 1977; Young, 1970). In these tests, minor changes in the nucleotide diphosphate /nucleotide triphosphate ratio resulted in a significant effect on the range corresponding to a physiological energy level. The authors came to the conclusion that the ADP/ATP and/or GDP/GTP ratios are a physiological regulator of the protein synthesis rate.
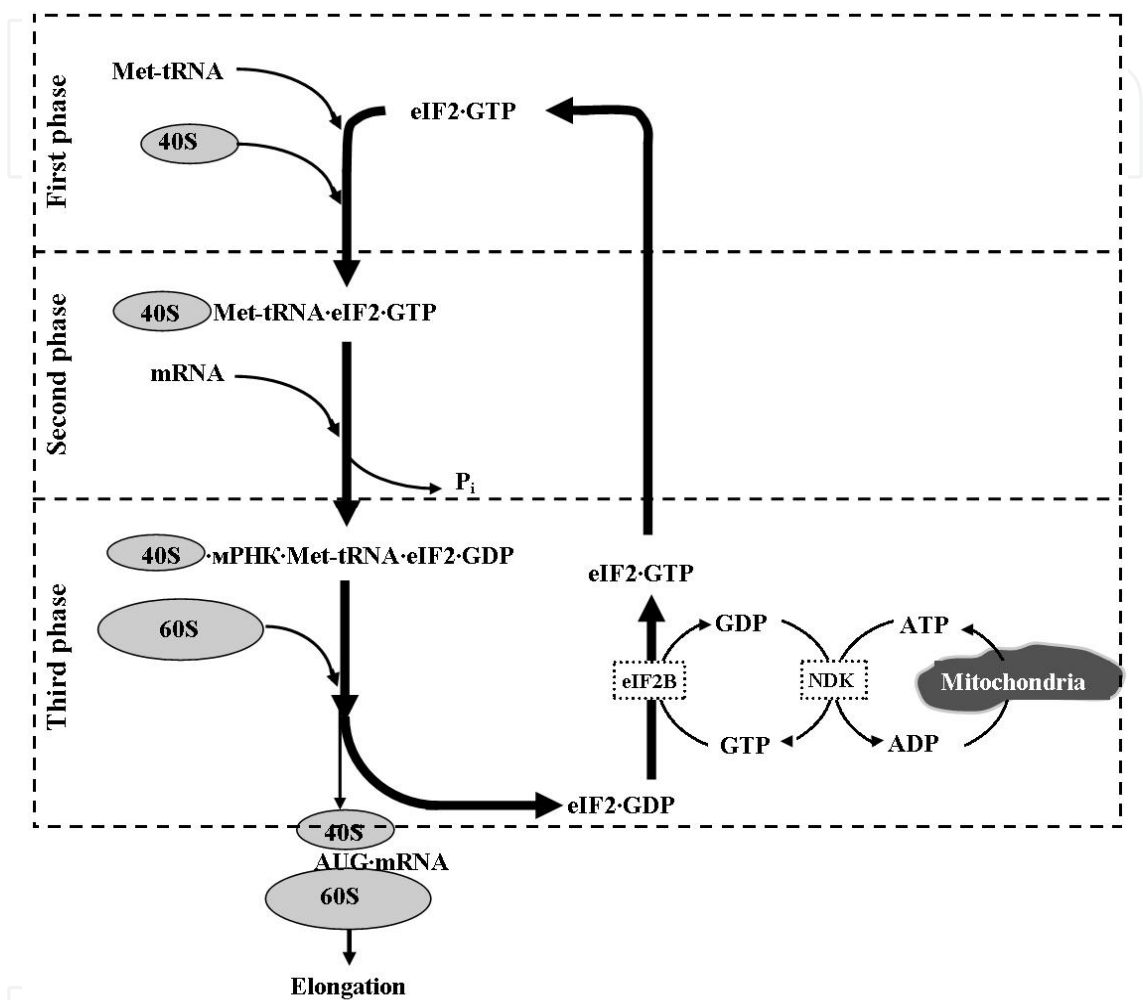
The initiation of translation can be divided into three phases. Phase one: the initiator methionine transport RNA (Met-tRNA) binds with the pre-existing binary complex eIF2·GTP and the 40S ribosomal subunit to provide the pre-initiation complex 40S·Met-tRNA·eIF2·GTP. Phase two: the pre-initiation complex binds to messenger RNA (mRNA). When the pre-initiation complex stops at the initiation codon of the mRNA, the GTP molecule is hydrolysed to GDP, inorganic phosphorus (P_i) is liberated and the energy of oxidation is spent on bond formation. This powers the ejection of the factors bound to the 40S ribosomal subunit in the third phase. The continuity of the initiation of these events requires the recycling of initiation factor molecules. eIF2 is released as an inactive binary complex with GDP and requires a guanine nucleotide exchange factor, eIF2·B, to catalyse regeneration of the eIF2·GTP. Energy support of regeneration is carried out at the expense of GTP oxidation. The GDP formed is then reduced at the expense of ATP oxidation in a reaction catalysed by nucleoside diphosphate kinase (NDK). The ADP formed is in turn reduced to ATP in the mitochondrial bioenergetics machine. The programmed bioenergetics decline decreases the eIF2 recirculation rate and thus reduces the general level of protein synthesis.

Fig. 2. The simplified scheme for the initiation of translation and its connection with bioenergetics.

The molecular mechanism of protein synthesis is currently well-understood and has been detailed in a number of reviews (Pain, 1996; Rattan, 2009). It was shown that the protein synthesis rate for eukaryotes is controlled at the translation level (Hucul, et al., 1985; Kimball et al., 1998). Among three translation stages (initiation, elongation and termination), the regulatory stage is the initiation (Hucul, et al., 1985; Kimball et al., 1998). The goal of this stage is the sequential binding of first the 40s and then the 60s ribosomal subunit to a messenger RNA molecule. At least 12 recirculation eukaryotic initiation factors (eIF) are involved in this stage. The initiation process can be divided into three phases (Fig. 2): (1) the association of the Met-tRNA initiator and several initiation factors with the 40s ribosomal subunit so as to form the pre-initiation complex; (2) the binding of this complex to a messenger RNA (mRNA) molecule, and (3) the addition of the 60s ribosomal subunit to assemble an 80s ribosome at the initiation codon.

The first initiation phase starts with the binding of the Met-tRNA initiator to a pre-existing double complex eIF2·GTP. When this preinitiation complex binds to mRNA at the second phase, GTP is oxidised to form GDP, and the oxidation energy is used to create bonds, with inorganic phosphorus being released. At the third stage, when the goal has been reached, the preinitiation complex disintegrates into separate initiation factors; these factors are then recycled to catalyse further initiation events. eIF2 is released as a binary complex with GDP, which is stable but not functionally active, i.e. it is unable to bind to a new Met-tRNA. A guanine nucleotide exchange factor, eIF2B, is required to catalyse the regeneration of the eIF2·GTP. Energy for such regeneration is provided by ATP oxidation to form ADP and the ADP is then reduced in the bioenergetics machine. Thus, the total protein synthesis level is originally regulated by the eIF2 recirculation rate which, in turn, depends upon the cellular bioenergetics value.

If the GDP-to-eIF2·GDP reduction is interrupted, the protein synthesis in the cell is blocked (Clemens, 1994). The natural mechanism protecting an organism in various stressful situations is based on this phenomenon: the phosphorylating of α-subunit eIF2 by different specific protein kinases blocks the reaction of the GDP-to-GTP exchange, which results in a complete protein synthesis termination in the cell followed by apoptosis (Clemens, 1994; Clemens et al., 2000). Such specific protein kinases are expressed in the cell when emergencies occur, such as an occurrence of the double-stranded replicative form of viral RNA (Jeffrey et al. 2002; Pain, 1996; Robert et al., 2006), irreparable damage of the genetic apparatus (Zykova et al., 2007; Jeffrey et al, 2002), acute shortage in amino acids (Clemens et al., 2001; Harmon et al., 1984), and malignant cell transformation (Clemens, 1994, Mendelsohn et al., 1977). Under normal physiological conditions when there are no specific protein kinases, the GDP-to-GTP exchange rate in the eIF2·GDP complex (and, consequently, the total protein synthesis rate) is regulated by the cellular bioenergetics (Hucull et al., 1985).

3.3 Conclusion

Programmed bioenergetics decline is the original cause of overall protein synthesis decrease rather than the stochastic accumulation of molecular damage.

4. The Hayflick limit is caused by the age-related decrease in the bioenergetics level

4.1 Introduction

Tissue senility is the most visible phenomenon and one of the most harmful phenomena of organism aging. Its cause was determined half a century ago (Hayflick & Moorhead, 1961):

higher eukaryotic cells do not divide infinitely, and, after a certain number of doublings, they enter a nondividing but viable state. Human fibroblasts, for example, are able to divide 53 ± 6 times over 302 ± 27 days and be in a stationary state for 305 ± 41 more days (Bayreuther et al., 1988). This limitation of division, the Hayflick limit, underlies the replicative aging theory, which is recognized to be one of the most striking modern aging theories (Anisimov, 2003). The main postulate of this theory is that, due to accumulation of old nondividing cells, tissue renewing homeostasis is violated, which causes their degradation (Hornsby, 2002; Itahana et al., 2004; Yegorov & Zelenin, 2003).

4.2 Modern views on the cause of cell proliferation limitation

A convincing mechanism of termination of old cells division was predicted theoretically by A.M. Olovnikov in 1971 and then confirmed experimentally (Greider & Blackburn, 1985). Vertebrates' chromosome ends from the DNA 3'-end have repeating nucleotide sequences—telomeres. They prevent fusion of chromosome ends, protect DNA from nuclease digestion, and participate in doubled chromosome disjunction in mitosis. In embryonic cells telomeres are synthesized by a special enzyme telomerase, which most somatic cells do not have. Because of the necessity of RNA-primer during DNA reduplication initiation, the telomere ends of somatic cells chromosomes are shortened with every cycle. As a result, after a certain number of doublings, the telomere end is depleted and divisions are terminated due to chromosome erosion (Itahana et al., 2004). This mechanism was confirmed by numerous empirical facts: 90–95% of potentially immortal cancer cells possess telomerase activity and the telomere end of their chromosomes is not shortened; suppression of telomerase activity in these cells causes shortening of the telomere end and division termination, i.e., aging; and restoration of telomerase activity makes them potentially immortal again. Therewith, facts contradictory to this conception were accumulated. The most convincing of them were obtained by a research group led by Blasco (Blasco et al., 1997). They obtained mice zygotes lacking a telomerase gene but with full-sized initial chromosome telomere ends. Mice developed from these zygotes were not only viable, but also fertile. This initial telomere length was sufficient to maintain normal viability of six mouse generations. In the first generation, for example, mice passed through youth and maturity successfully and died in old age having 80% of telomeres in reserve. Only in the fifth and sixth generations did anomalies caused by chromosome telomere end depletion appear. These data were confirmed by another group of authors led by Herrera (Herrera et al., 1999). They obtained an analogous mouse line, but with a shortened initial telomere end, and repeated the experiments of Blasco et al. These mice were viable for only four generations, and anomalies in late generations were related with depletion of telomeres in cells of tissues with the most intensive proliferation (Lee et al., 1998). By the present time, researchers of the telomere mechanism incline to the conclusion that loss of the telomere end indeed leads to chromosome erosion and cell death, but cell proliferation termination during normal physiological cell aging happens earlier than this critical moment and a cell that has expended all its proliferative potential still contains a significant telomere reserve. The telomere mechanism serves as an additional barrier on the road to reproduction of malignant cells (Itahana et al., 2004). The conclusion that there is nonparticipation of the telomere apparatus in the mechanism of termination of old cells' division could have been drawn from the very beginning. It followed from the results of the initial Hayflick experiments that, after a certain number of doublings, a cell enters a nondividing, but viable, state, and there is no sense in discussing viability if division termination due to chromosome

erosion is accepted. Therefore, the question of the Hayflick limit's nature is without answer. Apparently, an alternative reason for this phenomenon should be looked for in the mechanism of cell division.

4.3 The reason for termination of proliferation of old cells

The cell division cycle (proliferative cycle) is divided into four phases (Sherr, 1994): G1, S, G2, and M (Fig.1).
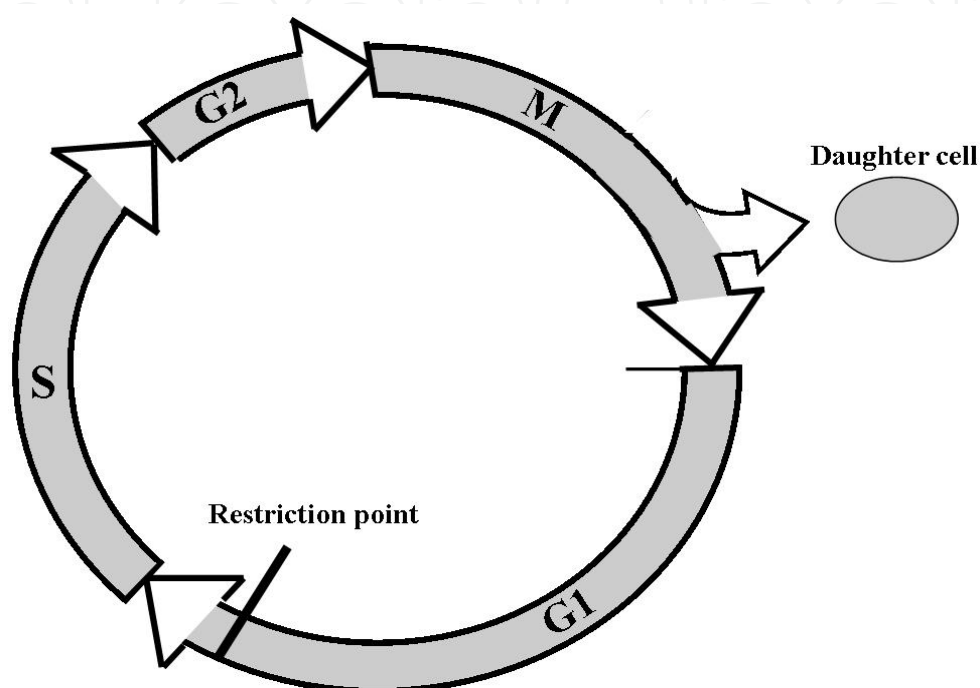
Cycle of cell reduplication is divided into 4 phases: G1 (gap 1), S (synthesis), G2 (gap 2), and M (mitosis).

Fig. 3. Phases of proliferative cell cycle.

In the G1-phase, precursor molecules necessary for DNA reduplication and doubling of all cell structures in the following division are synthesized. In the following S-phase, DNA is reduplicated, and after a short G2-phase, a cell enters M. Numerous studies have showed that all non dividing cells stay in the G1-phase. If a cell has passed through this phase, then it will pass through other phases automatically with almost equal speed. As far as entry of old cells into irreversible proliferative quiescence is concerned, we will be interested only in events occurring in the G1-phase. Control of the cell division rate is performed by endogenous and exogenous (for a cell) regulatory factors that are stimulators and inhibitors of proliferation. As an example of such regulation, the data of one of the first works in this field (Leof, et al., 1982) accurately reflecting the essence of the phenomenon are shown. The effect of different growth factors on mouse fibroblasts was studied. It was shown that, right after mitosis completion, a cell enters a proliferative quiescence state between the M and G1-phases (the G0-phase). To be removed from this state, a cell needed an external proliferative signal from platelet derived growth factor (PDGF). No structural or biochemical changes in a quiescent cell happened without the signal, and it remained insensitive to other proliferative stimuli. This primary stimulus is a competence factor. After a cell has received

this signal, the biochemical reactions for new division cycle preparation begin, stopping a period of time. For further development of biochemical events, epidermal growth factor (EGF), not PDGF, was necessary. The addition of EGF caused continuation of biochemical and structural changes, but after some time a new halt at the G1/S-transition occurred, which was called the restriction point R. The passage of the last several hours of the G1-phase happened only under somatomedin C stimulation (Sm-C). The last two factors were called the first and the second progression factors. All tissue cells are stimulated by its growth factors. In addition to growth factors, passing through a cell cycle is regulated by a large group of inhibitors (Sherr & Roberts, 1999; Sherr, 2000). Cells can leave a cycle and move to a quiescent state. There are three types of quiescence. (1) Irreversible quiescence, or the terminal differentiation state, in which cells lose growth factors' receptors and become incapable of returning to a proliferative cycle (for example, neural, secretory, and muscular). (2) Temporal quiescence necessary for a cell to function within one or another tissue. This occurs if a cell does not receive the necessary proliferative stimulus from growth factors or there are exogenous inhibitors in the environment that void their proliferative signal. Such cells retain the integrity of their receptor apparatus, and, in appropriate conditions, they are able to come back to a cycle (for example, hepatocytes, fibroblasts, and others). (3) Proliferative quiescence of old cells that spend all their proliferative potential is similar to temporal quiescence. Cells retain their receptor apparatus and the integrity of all structures necessary for proliferation, although division does not occur.

The first experiments to determine the reasons for termination of proliferation of old cells were performed by Rittling et al. (1986). They studied 11 biochemical reactions happening sequentially in the G1-phase in young and old cells. It was shown that, in old cells, all reactions occur in the same way as in young cells, but old cells stop at the restriction point and deepen in quiescence, not reflecting the proliferative stimulus by the second progression factor. If after some period of time these cells are stimulated by proliferative factors again, they will pass through all the stages of preparation to transfer to the S-phase and will come back to a proliferative quiescence. The authors concluded that, in old cells that have expended all their proliferative potential, the restriction point becomes impassable.

Events happening in the restriction point are studied intensely, mainly by researchers of carcinogenesis. Their interest is due to the fact that malignant cells pass this point without stopping, while a delay of the cycle of dividing normal postembryonic cells here is obligatory and, for old cells, as has already been mentioned, this point becomes an insuperable barrier. To date significant success in studying biochemical events in this point has been achieved.

The main regulators of reactions occurring in the division cycle are cyclin-dependent kinases (Cdks). They are the controllers of all events: the determine the order of reactions, their duration, and their intensity (Sherr, 1996). The function of cyclin-dependent kinases is simple: de novo synthesized gene-regulating proteins of a division cycle E2F leaves a translational conveyor, figuratively speaking, in a package. This package is retinoblastoma protein (Rb). Until these proteins are bound with Rb, they are inactive. Cyclin-dependent kinases phosphorylate Rb protein, and, after that, regulatory proteins are released and activate genes necessary for the division cycle (Sherr, 2000; Frolov & Dyson, 2004). Cdks themselves can be in an active or inactive state. Regulation of cyclin-dependent kinases'

activity is quite complex (Morgan,1995) but it is enough to know two principal moments to uncover the discussed topic: (1) Cdk is activated when it is conjugated with a specific cyclin (which is evident from its name) and (2) an active Cdk-cyclin complex can be deactivated again if it is conjugated with a specific inhibitor of cyclin-dependent kinases. To date eight types of cyclin-dependent kinases marked with the numbers Cdk1, Cdk2, etc.; ten types of cyclins marked with the Latin letters cyclin A, cyclin B, etc.; and a large group of Cdk inhibitors that have individual number labels and represent several families have been found in mammals. Three Cdks (2, 4, and 6); the cyclins D, E, and A; and the inhibitors of INK4 (p15^{ink4b}, p16^{ink4a}, p18^{ink4c}, and p19^{ink4d}) and CIP/KIP families (p21^{cip1}, p27^{kip1}, and p57^{kip2}) regulate passage through G1 (Sherr & Roberts 1999; Sherr, 2000). INK4 inhibitors specifically interact with Cdk4 and 6 and function in the G1-phase until the restriction point, and CIP/KIP interact with all Cdks. Research on G1-phase events has increased greatly in the past decade. New biochemical participants and ways in which they interact have been found. Information about them can be found in several reviews and original papers (Bockstaele et al., 2009; Larrea et al., 2008; Rahimi & Leoff, 2007; Sherr, 2000). Here only the main events minimally sufficient for understanding of termination of old cells division will be discussed. Leaving out the details, the G1-phase passing scheme discussed in (Sherr, 1996; Sherr & Roberts, 1999) can be shown in the following way (Fig. 4). The level of inhibitor p27 in quiescent cells is high, which prevents the reaction for division preparation. In response to mitogen stimulation, cyclin D is expressed and the active complex cyclin D-Cdk4 is formed, as are phosphorylates Rb. As a result gene-regulating E2F proteins are released and phosphorylated Rb is degraded. Then E2F proteins activate enzyme genes necessary for DNA reduplication in the S-phase and cyclin E, Cdk2, and E2F genes. Released cyclin E and Cdk2 form an active E-Cdk2 complex, which began interacting with p27, phosphorylating Rb, and activating regulatory protein genes. It is important that the cyclin E-Cdk2 complex activates the genes of their components, i.e., it reproduces itself. As a result a positive feedback loop is formed and promotes rapid p27 removal and E2F proteins and S-phase proteins' avalanche-like increase, which allows a cell to pass through a restriction point. With this E2F increased expression induces synthesis of inhibitor p53, which terminates the E2F expression unnecessary in the S-phase. However, this and the following cycle reactions are outside the discussed topic. Two research groups simultaneously and independently drew a considerable specification of the character of interaction of p27 with active cyclin E-Cdk complex (Vlach et al, 1997; Sheaf et al., 1997). Until their works it was considered that p27 and active cyclin E-Cdk2 complex interaction had a single consequence—complex inactivation. They performed a study of the kinetics of the molecular interactions of these compounds and showed that not only does the inhibitor inactivate the complex, but the complex can also attack an inhibitor phosphorylating it on threonine 187.

Figuratively speaking, there is a competition for survival between inhibitor p27 and the cyclin E-Cdk2 complex. Its outcome is determined by the reaction energy supply: with a high ATP level, the cyclin E-Cdk2 complex has an advantage. It phosphorylates p27; after that, this inhibitor becomes a target for ubiquitin-dependent proteolytic machinery and is destroyed. If the bioenergetics level becomes lower than a certain value, then even p27 inactivates cyclin E-Cdk2. As a result a positive feedback loop of E2F synthesis and S-phase transition are blocked. An ability to inactivate its inhibitor belongs only to cyclin E-Cdk2 complex and was not found in other analogous complexes.
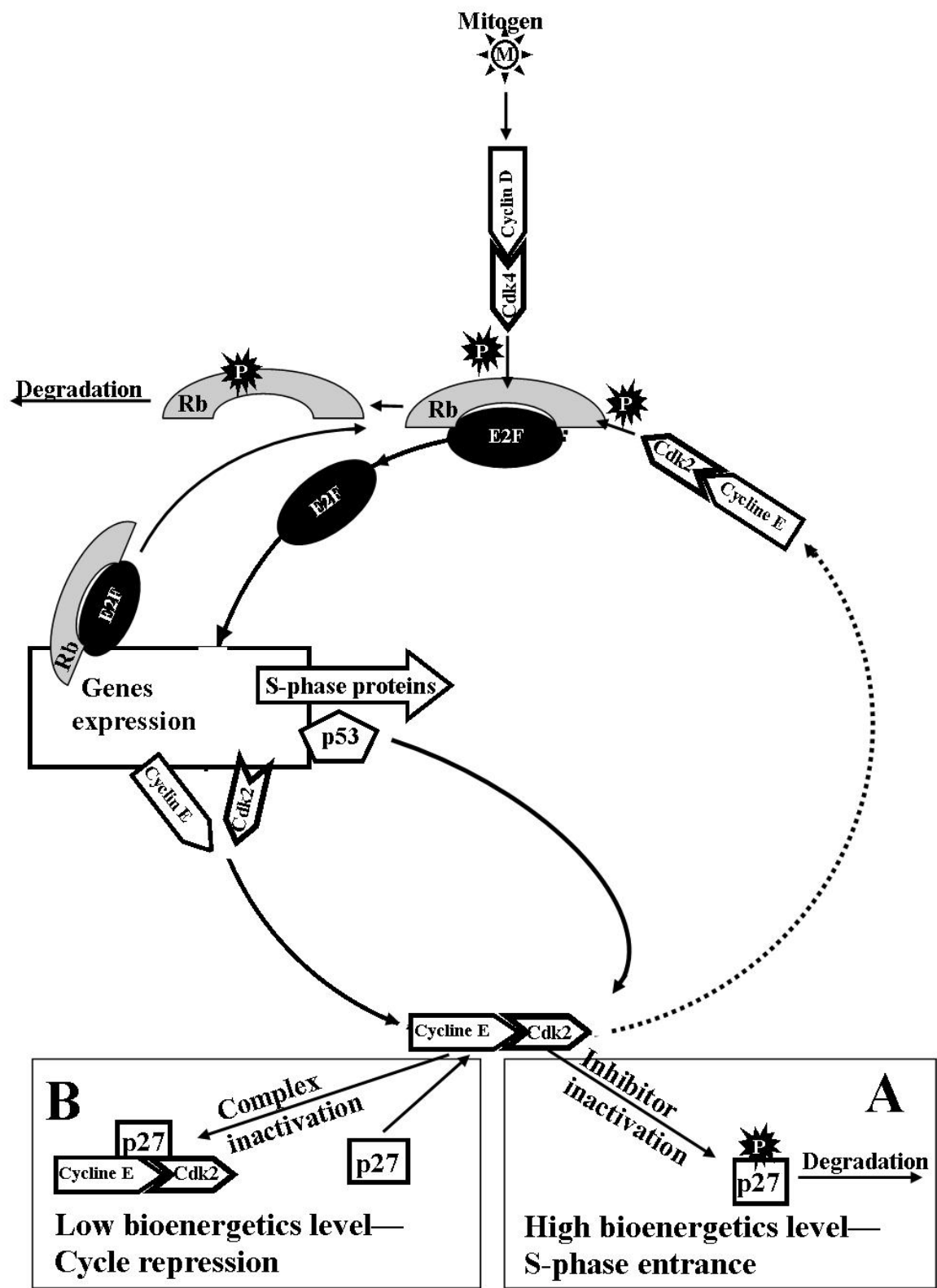
Fig. 4. Simplified scheme of control of passing through a restriction point.

In response to mitogen stimulation, an active cyclin D-Cdk4 complex is synthesized, which phosphorylates Rb protein. As a result gene-regulating E2F proteins are released and phosphorylated Rb degrades. E2F proteins activate genes of proteins essential for DNA

reduplication in the S-phase, cyclin E and cyclin-dependent kinase 2 (Cdk2) genes, as well as E2F itself. Combined cyclin E and Cdk2 form an active complex which interacts with inhibitor of cyclin-dependent kinases p27. Two consequences are possible. A. If the bioenergetics level is within the physiological norm, then Cdk2 activated by cyclin E phosphorylates p27. Then the inhibitor becomes a target for degradation. After that cyclin E-Cdk2 phosphorylates Rb and additional gene-regulating proteins are released. As E2F activates cyclin E, Cdk2, and E2F genes, then there is a positive feedback loop promoting rapid p27 removal and an avalanche-like increase of S-phase proteins, which allows a cell to pass through a restriction point. At the same time, increased expression of E2F induces inhibitor p53 synthesis, which inactivates cyclin the E-Cdk2 complex and terminates unnecessary S-phase E2F expression. B. If the bioenergetics level is below a certain critical level, then p27 forms a tight bond with the cyclin E-Cdk2 complex and inactivates it. As a result an increased expression of S-phase proteins does not occur, the p27 level remains high, and entry into the S-phase becomes impossible.

These data can explain the results of the abovementioned research by Rittling et al. The central event of the G1-phase restriction point of the cell cycle is triggering of a self-accelerating cascade of reactions controlled by the cyclin E-Cdk2 complex. This is an essential condition of inhibitor p27 removal and accumulation of all precursors for DNA reduplication and cell division. It is satisfied only with a normal physiological level of bioenergetics. When bioenergetics in old cells decreases until some threshold level, cyclin E-Cdk2 loses its ability to inactivate p27 and itself becomes a target. As a result inhibitor removal stops and S-phase transition becomes impossible. All this information can be summarized in the following way: cyclin-dependent kinase inhibitor p27 prevents passage through the restriction point. There is a special pump for its removal in a cell. Its work efficiency depends on the energy supply. During the programmed decrease of cell bioenergetics, below a certain threshold level, it stops inhibitor removal and cell division becomes impossible.

It should be mentioned that a critical level is achieved after a certain number of divisions. Thus, bioenergetics decrease and the lifespan depend not on the calendar time of an organism's existence, but from the number of past divisions in its critical tissues, i.e., the amount of the past divisions is a biological clock. An organism counts time on proliferative clock.

5. Longevity is under control of natural selection

5.1 Introduction

Several lines of evidence show that genes exert strong controls on longevity and patterns of aging (Carey, 2003; Holzenberger et al., 2003; Kenyon, 2010; Vaupel, 2003). Therefore, the specific genes that program longevity and the selective pressure that would lead the genes to the development during evolution are to exist (Bredesen, 2004; Mitteldorf, 2004; Skulachev, 2001). The most of evolutionists, nevertheless, deny the possibility that longevity is under the control of natural selection (Medawar, 1952; Kirkwood, 2002). In 1952 P.B.Medawar has shown that life expectancy is not under control of individual (Darwinian) natural selection. He has noticed that animals in habitat never live till an old age and perish from the various external reasons at youngish age; therefore the natural selection cannot differentiate them by the longevity sign. Hence the specific genes programming aging cannot exist. This conception dominates till now.

The aim of this section was to show the mechanism by which natural selection controls species-specific longevity. The ecological approach was used to solve the problem. As known from ecological laws, the intrinsic population growth rate (r_{in}), the length of the generation (T), and the net reproductive rate (R_0) are interconnected by dependence, according to the following formula: $r_{in}= lnR_0/T$ (MacArthur & Connell, 1966). It is shown here that during evolution the r_{in} value is stabilized by interpopulation (group) natural selection (not individual selection) at the level which corresponds to environmental pressure in the ecological niche of the species. This leads to the conclusion that species-specific longevity and fertility are under the control of natural selection and depend inversely on each other.

5.2 Population size oscillations and extinction risk

The state of a population's size over the long-term is a measure of population welfare. Stability or an increase in size testifies to the well-being of the community, but a decrease indicates that the population is under risk of extinction. A practical determination of this criterion represents a difficult problem because biological systems are dynamic. Successive changes in biological systems are termed "disturbance" (White & Pickett, 1985). Disturbances are inherent in all biological communities and occur on a wide range of quantitative, spatial, and temporal scales (Pickett & White, 1985). The size of any population determined by observation is in fact its value at an instantaneous time cut-off (Southwood, 1981). Population number can change in time by hundreds, thousands, and in some species, even by millions (Nicholson, 1954). Population size oscillations are forced by varying environmental factors, such as the infections, the availability of food, the number of predators and parasites, etc. The mean population size, population number averaged over some period of observation, is a much more informative characteristic. Based on theoretical averaging over a prolonged time interval, this parameter is considered to be the dynamically equilibrium size (N_{eq}). However, the fate of a population depends on its minimal size (N_{min}), i.e., the lowest value which a population reaches in the process of oscillations. N_{min} depends on both N_{eq} and swings in the population size. The minimal population size is a genetic bottleneck that is an evolutionary event in which the population is often reduced by several orders of magnitude (Leberg, 1992; Richards & Leberg, 1996). Populations are potentially immortal, but each of them is always subject to the risk of extinction due to minimum viable population size (Green, 2003; Tracy & George, 1992). The last is the smallest population size that will persist over some specified length of time with a specified probability (Hedrick & Gilpin, 1996). If a population size is reduced below this value, even if for a moment in time, then the population becomes doomed to extinction during future generations due to genetic drift (Cherry & Wakeley, 2003; Gilpin & Soule, 1986). Therefore, the extinction risk is maximal in the N_{min} state because a significant part of a population is prevented from reproducing. This increases genetic drift, as the rate of the drift is inversely proportional to the population size (Frankham, 1996; Lande, 1993; Shaffer, 1981).

5.3 The interpopulation natural selection

The mechanism of interpopulation natural selection is simple: "Small populations can fluctuate out of existence quite rapidly" (Leigh, 1975). In other words, preferred extinction

of populations having less N_{min} is the essence of interpopulation natural selection. Natural selection, as a whole, consists of two stages. During the first stage, the classical Darwin-Wallace individual selection rejects organisms which are less adapted to the given environment. As the members of the population serve as an environmental factor for each individual, attributes can arise that are useful only to their carriers but neutral or harmful for the other individuals. Such attributes become harmful for the community, but they are supported by individual natural selection. Longevity and a number of psychological attributes, for example, are a concern to them (Gadgil, 1975). The interpopulation selection takes such attributes under control as the populations are units of natural selection in the second stage (Levins, 1962; Wilson, 1973). If any attribute decreases N_{eq}, or increases the amplitude of oscillations and spreads in the population, then the population perishes as a whole. In contrast, the attributes that increase N_{min} promote population survival, which is an evolutionary mechanism for developing characteristics that are useless or even harmful for individuals, but beneficial for the community (e.g., altruism, care of posterity, and bravery). To determine the direction of evolution for a specific attribute of a species' populations, it is necessary to assess the dependence of N_{min} from a quantitative expression of this attribute. The pressure of group selection is always directed to an increase in N_{min}.

5.4 Evolution mechanism of longevity and fertility

To solve the problem under consideration, we need to consider the dynamics of populations of an abstract species of vertebrates with overlapping generations. In so doing, we shall determine the dependence on N_{min} from the intrinsic population growth rate (r_{in}) at a various value of environment pressure in the species' ecological niche, remembering thus that

$$r_{in} = lnR_0 / T \tag{1}$$

A change in size of population, dN/dt, depends on the difference between birth and death rates:

$$dN / dt = dN_b / dt - dN_m / dt. \tag{2}$$

Accordingly, population size influences birth and death rates:

$$dN_b / dt = bN \text{ and } dN_m / dt = mN \tag{3}$$

where b and m are density-dependent are birth and death rates, respectively.
Population size does not influence the birth and death rates directly, but through changes in environmental parameters. When the population size increases, food resources are exhausted, the number of predators and parasites grow, infections are increased, and living space per capita declines. All this raises the level of environmental pressure upon a population. As a result, the birth rate decreases but the death rate increases (Fig. 5):

$$b = b_{in} - aN; \ m = m_{in} + jN \tag{4}$$

where b_{in} and m_{in} are intrinsic are birth and death rates that are realized, provided that N is negligible; a and j are environmental pressures on the birth and death rates respectively.
Substituting b and m from equation (4) in equation (2), and taking into account equation (3), it follows that:

$$dN \, / \, dt \; = \; (b \, - \, m)N \; = \; (b_{in} - m_{in})N \; - \; (a \, + \, j)N^2 \qquad (5)$$

Having designated b_{in} - m_{in} = r_{in} and $a + j = p$, equation (5) can be rewritten as

$$dN \, / \, dt \; = \; N(r_{in} \, - \, pN) \qquad (6)$$

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

The dynamics of any population is complicated by feedback among population size and the environmental pressure. The environmental conditions vary after changes in population size with some time delay. Let, for example, population size grow from N_{min} at time t_0 to N_{eq} at time t. At once, as the population size reaches N_{eq}, the environmental pressure remains at the level that existed at the moment, t-τ. The time delay, τ, is the time necessary for the breeding of parasites and predators and a reduction of food resources and vital space per capita. As a result, the population size proceeds to increase to the equilibrium point N_{eq}, and reaches the point, N_{max}> N_{eq}. As this state is unstable, the population size is reduced and, for the same reason, passes the N_{eq} point and falls to N_{min}< N_{eq}; this is the nature of auto-oscillations about N_{eq} (Macfadien, 1963; May, 1973). Being forced out of the equilibrium condition, a population enters an auto-oscillation regimen and the amplitude of the oscillations can serve as a criterion of population responsiveness to environmental variability.
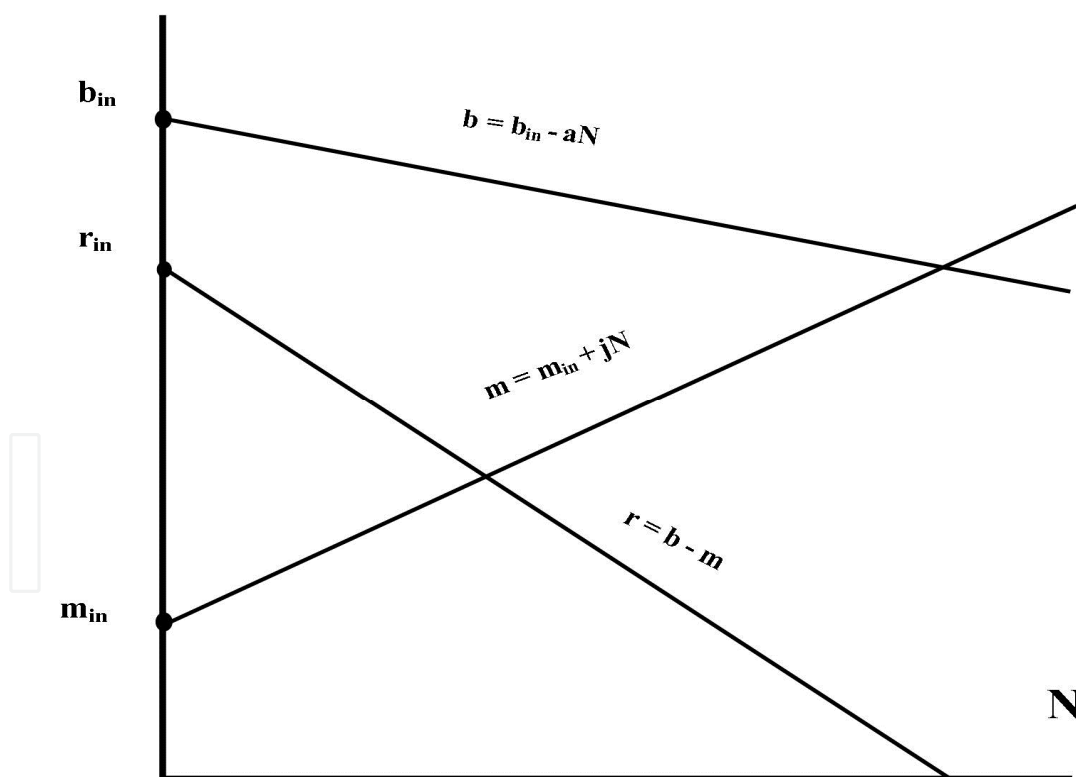

The increase in the population number leads to a decrease in b and an increase in both m and r relative to their intrinsic values, b_in, m_in, and r_in. The slopes of the line depend on the environmental pressure on the birthrate (a) and mortality (j).

Fig. 5. Dependence of birth (b) and death (m) rates and the population growth rate (r) from the population number (N).

With the delay effect, equation (6) becomes:

$$dN_t \, / \, dt \; = \; N_t(r_{in} - pN_{(t-\tau)}) \tag{7}$$
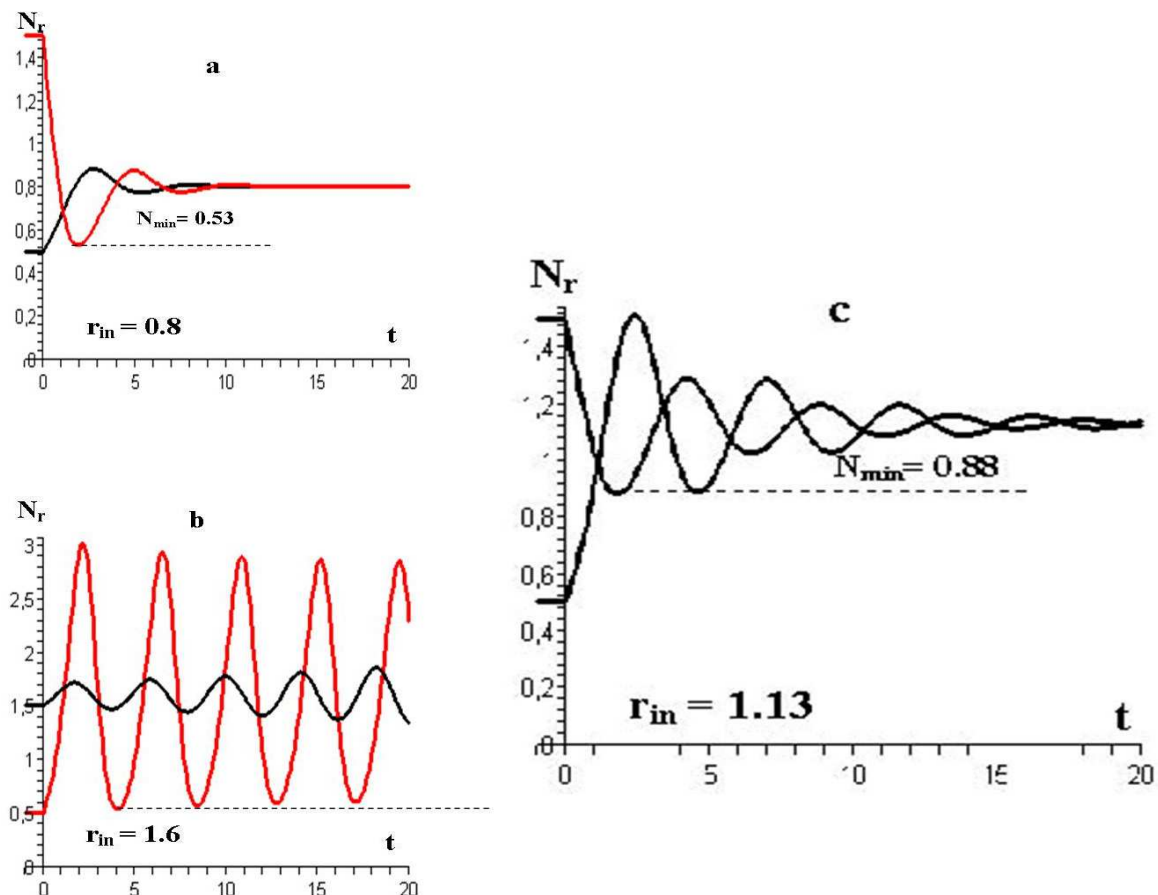
Exes: abscissa is time and the ordinate is the currant population number divided by the equilibrium at time t_0 ($N_r = N_t/N_{eq}$). The consequences of two situations in the environment are modulated (two curves): (1) a favorable coincidence that raises the outbreak of the population number ($N_0 > N_{eq} = 1.5$) and (2) coincidence of severe conditions that causes population depression ($N_0 < N_{eq} = 0.5$). (a) Populations having small values of r_{in} are reduced to the minimal value after outbreaks of numbers (red curve): coincidences of favorable circumstances in the environment threaten the existence of such populations to a greater extent. (b) Populations having large values of r_{in} reach the lowest number after a state of decay (red curve): coincidences of unfavorable circumstances threaten the existence of such populations to a greater extent. (c) There is an optimal r_{in} value under the present environmental pressure when favorable and unfavorable environment cataclysms are followed by an equal aftereffect. The value of N_{min} is maximal under this r_{in}; this r_{in} value is maintained by interpopulation selection.

Fig. 6. The influence of the intrinsic population growth rate on parameters of population size oscillations.

It can be seen that the dynamics of the population are determined by three parameters: τ and p, are factors of the habitat, but r_{in} is an intrinsic characteristic of the population. Each of the factors influences oscillation characteristics. Parameter τ is the regeneration time of density-dependent environmental factors. As the environmental pressure is a complex value, then τ is also a multifactorial distributed characteristic of the environment (Schley &

Gourley, 2000). However, it can be accepted as a discrete characteristic at solving many tasks analogous to our problem (May, 1981; Schley & Gourley, 2000). The numerical solution of equation (7) shows that τ influences the amplitude of the population size oscillations: the greater the τ, the greater the amplitude of oscillations. Species that are under $\tau < 0.3$ have the least variability; perturbed size of its populations monotonously return to the equilibrium state. In the range $0.3 < \tau < 1.6$, an oscillatory return to an equilibrium number occurs. The further τ increases cause continuous oscillations. If $\tau > 2.2$, then populations become non-viable; the smallest external disturbance provokes increasing oscillations that decrease N_{min} to nil. It is apparent that within an ecological niche, in the overwhelming majority of vertebrate species the τ value is limited by 0.4-1.5. Therefore, we shall accept in further calculations that this parameter of the ecological niche of the abstract species under consideration is equal to 1.

The numerical solution of equation (7) shows that the variation of r_{in} influences both the N_{eq} value and the amplitude of oscillations that predetermines changes in N_{min} (Fig. 6). The dependence of N_{min} from r_{in}, calculated with other parameters unchanged ($p = 1$; $\tau = 1$), is shown in Fig. 7. The curve of dependence $N_{min}(r_{in})$ has a maximum under certain $\acute{r}_{in}$. As mentioned above, the selective pressure is always directed to an increase in N_{min}. In the case in point, the directions of selective pressure are opposite from larger and smaller r_{in} values. Hence, it appears that the intrinsic rate of population growth is stabilized by group selection on the level which corresponds to the maximal N_{min} value:
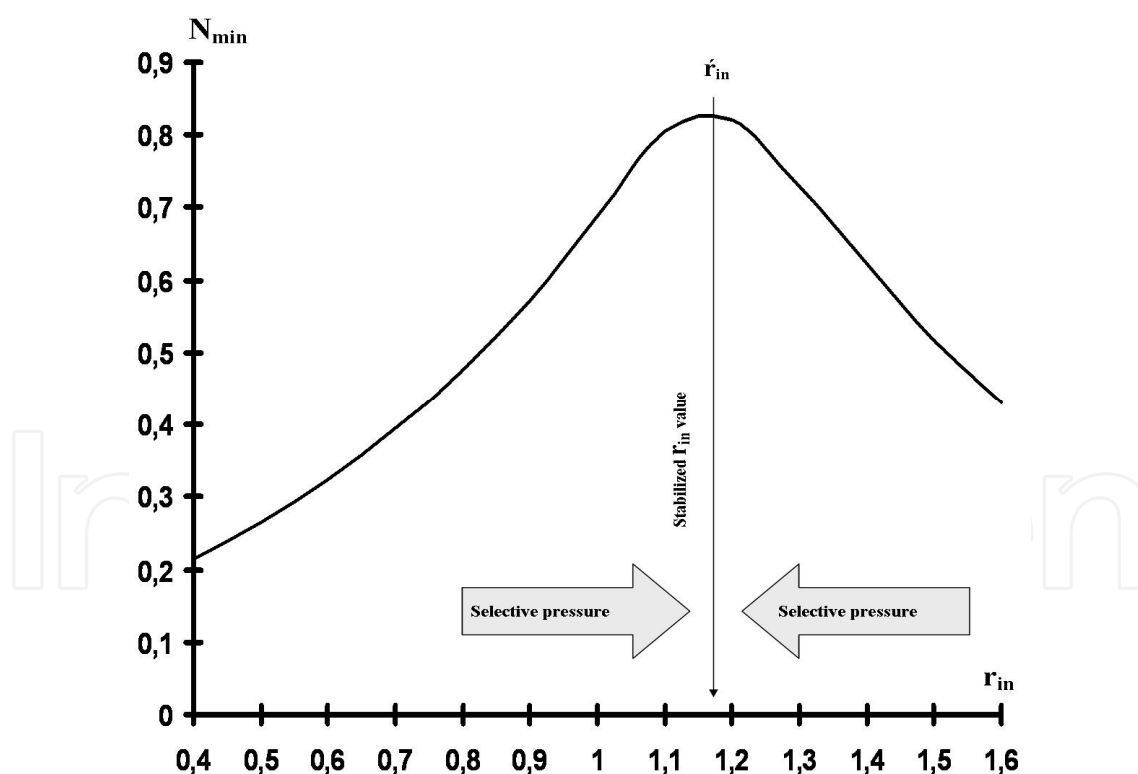

Under constant environmental parameters ($p = 1$; $\tau = 1$) the curve of dependence $N_{min}(r_{in})$ has a maximum under a certain $\acute{r}_{in}$. As the extinction risk is inversely proportional to N_{min}, then selective pressure pushes r_{in} of populations of species to this value.

Fig. 7. Scheme of stabilization of the intrinsic population growth rate by interpopulation selection.

if the environmental pressure is constant, then any population of a species deviating from this value will have a greater extinction risk. As $r_{in} = lnR_0/T$, then the length of the generation and the net reproduction rate are stabilized by interpopulation natural selection. On a long-term temporal scale, the environmental pressure becomes constant.

However, in the course of evolution, it can gradually vary during a change of parameters of an ecological niche under influence, for example, changes of climate. The calculated dependence of the stabilized $\acute{r}_{in}$ value from p shows that variation in environmental pressure causes a change of the stabilized intrinsic population growth rate: the greater the p value, the greater the $\acute{r}_{in}$.
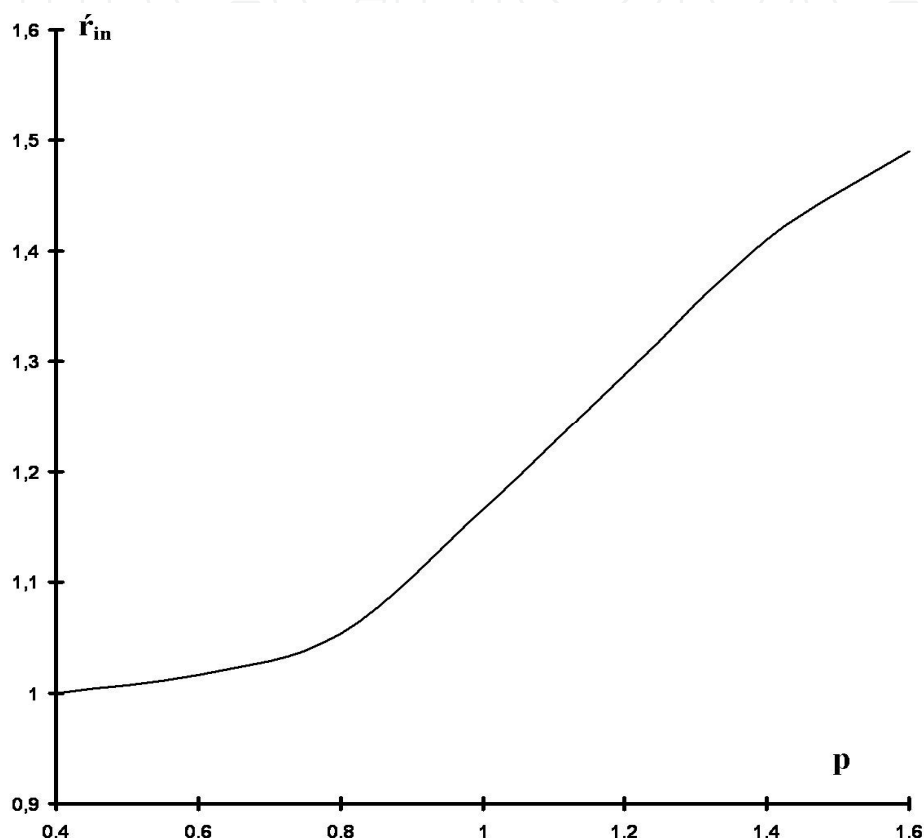
An increase in environmental press in the ecological niche of a species in the course of evolution causes growth of the intrinsic population growth rate and vice versa.

Fig. 8. The dependence of a stabilized intrinsic population growth rate ($\acute{r}_{in}$) from environmental pressure (p).

Thus, the value of the intrinsic rate of population growth is under natural selection control and it is predetermined by environmental pressure within the ecological niche of the species.

The conclusion that the intrinsic rate of population growth is stabilized by interpopulation natural selection can be made logically without resorting to mathematical calculations. Population size oscillations are inevitable because of stochastic variations in the environment and are harmful as they increase the extinction risk. The intrinsic rate of the population growth influences population responsiveness to environmental fluctuations. When a population is in a state of size reduction, the maximal r_{in} is preferably for oscillation damping. Under these conditions, a decrease in population size in any given half cycle of the oscillation will be minimal as the high rate of breeding serves as a brake for the decrease.

But, such r_{in} values will become threatening when the opposite phase begins as it intensifies the increase in population size. According to the theory of risk spread, the greater the extension of a population on top, the deeper it falls in foot. The same intensification of amplitudes is provoked by an inverse extreme value of the intrinsic population growth rate. A natural population cannot have such an extreme or any arbitrary of r_{in} value. There is an optimal value of the intrinsic rate of population growth which ensures minimal possible population oscillation (Fig. 6). That value is sustained by interpopulation natural selection because deflection of the r_{in} to any side from the value increases the population extinction risk; the above-stated mathematical calculations alone have demonstrated this.

Let's look now what in fact is hidden behind the intrinsic population growth rate. According to equation (1), these are two population characteristics: 1) the net reproduction rate and 2) the length of the generation, neither of which can be programmed by the genome directly. In a general sense, the length of the generation is the time from which the individuals are born to the time most offspring, on average, are produced for a population. The concept of "post-reproductive age" is applicable to the full only to post-industrial man and his/her pets. Animals of post-reproductive age are rare in natural habitats (Medawar, 1952). Analyses of cohort life tables of natural populations show that the length of the generation is actually equal to the mean survival of the population age-groups. Thus the average longevity in the habitat is under natural selection control.
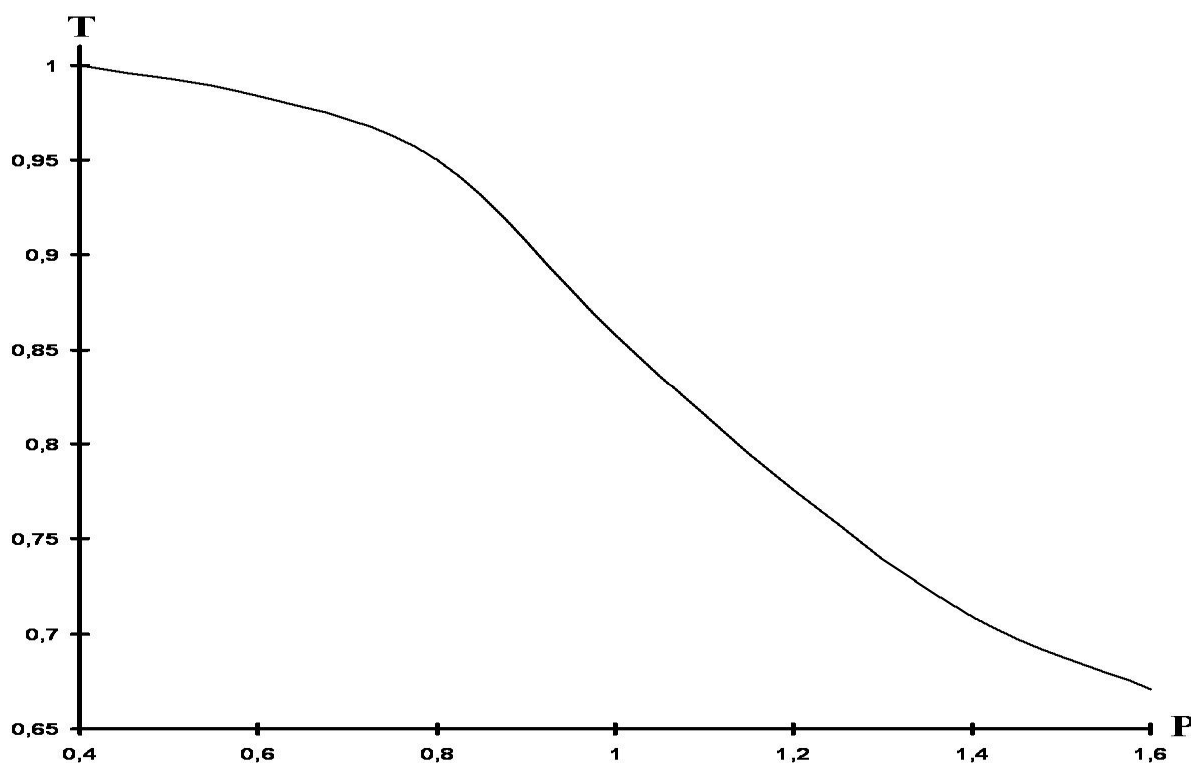
The increase in environmental pressure in a species ecological niche results in a longevity decrease.

Fig. 9. Dependence of longevity (T) on environmental pressure in the ecological niche of a species.

The variation in the net reproduction rate corresponds to the variation in fertility of the population members. To understand it, we should recollect that $R_0 = N_T/N_0$, where N_0 is the

initial population size and N_T is the population size one generation later. It is apparent that if R_0 is increasing in evolution, the fertility is growing, and vice versa.

Thus, longevity and fertility are actually under the control of interpopulation natural selection. The selective pressure acts on both components of r_{in} simultaneously, but the distribution of forces are unequal for different species because of environmental factor specificity. As a result, only a correlation between longevity and fertility exist in nature. This evolution mechanism of longevity is apparently applicable only for vertebrata. Invertebrates, by virtue of their huge variety, can have others, and various, evolution mechanisms determine species specific longevity.

6. The mechanism of aging

According to the above considerations, the mechanism of programmed aging is represented as follows (Fig. 10): the genetic program controls the only function – bioenergetics decline. The latter causes the increase in the ROS level, a lowering of the protein synthesis rate, the cessation of cells dividing and some other processes; every one of them in turn spawns a number of secondary harmful processes. As the number of cells dividing (proliferative time) increases, these destructive phenomena in an organism's tissues augment progressively, which gradually leads to the organism's destruction.
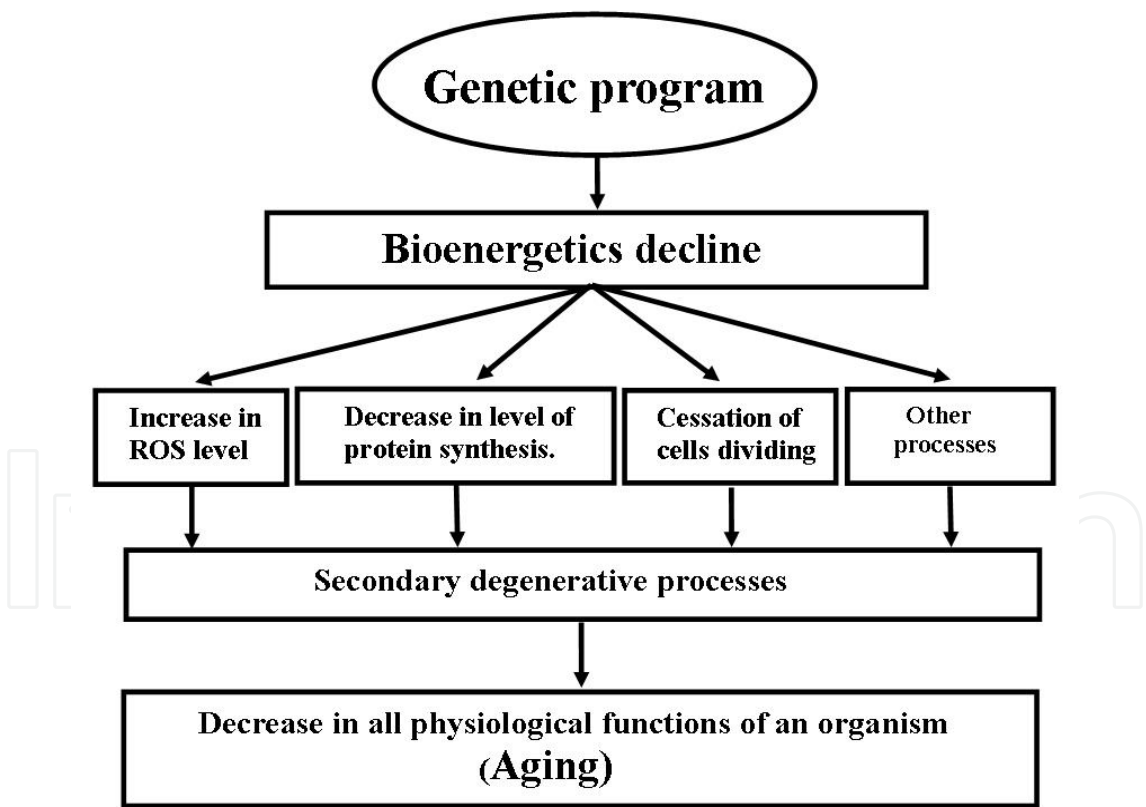
The genetic program decreases the bioenergetics level as the number of cell divisions augments. This results in the increase in the ROS level, the lowering of the protein synthesis rate, the cessation of cells dividing and some other injurious processes. In turn, each one of them spawns a number of secondary harmful processes which leads to a decrease in all of the physiological functions of an organism, i.e. aging.

Fig. 10. Scheme of the bioenergetics mechanism of aging.

7. Conclussion

Gerontology has entered the 21 Century with significant empirical baggage but without a theory capable of generalising the data and discovering the general regularities of the aging process. Instead, as mentioned, more than 300 different theories have been developed. There is still no consistent opinion as to what the primary driving force of aging actually is. The majority of researchers are convinced that there are no genes for aging and that stochastic factors underlie the aging. Those who trust in the programmed theory assume that almost every process influencing aging is governed by its own genes, i.e. aging is multifactorial. According to this, genes of aging exist and they control the sole driving force of aging – proliferative-dependent bioenergetics decline. It can be shown that this programmed process underlies, whether expressly or by implication, any theory of aging based on real phenomenon. This can provide the basis for the creation of a united theory of aging.

The present situation in modern gerontology does not suggest any hope of the achievement of the abovementioned strategic aim: numerous efforts to elaborate a remedy for senescence based on stochastic theories have yielded no result. The strict restriction of food (calorie restriction) is the only trick that has been developed which authentically increases species' maximal lifespan. The mechanism for this phenomenon is not yet understood, but it is easily explained by the bioenergetics theory: the lack of food detains cell division which in turn leads to a lag of the proliferative clock relative to calendar time. The programmed theories do not much promise success because of the large number of genes that operate in the ageing process. A decrease in the level of bioenergetics is apparently programmed by only a few genes. The analysis of the evolutionary plasticity of fruit fly populations has shown that longevity is programmed by no more than by three genes (Mylnikov, 1997).

One relevant inference to be made of the theory stated above is that the manipulation of any secondary phenomenon generated by the decline in bioenergetics cannot give effect to an increase in the maximal lifespan. A means to operate bioenergetics has to be found - it is the only way towards healthy and unlimited longevity. This is complicated problem but it can be solved in the near future: the bioenergetics machine is already studied well enough, the regulator of energetical homeostasis is visible, and the potent arsenal of experimental techniques is created. The period depends mainly on facilities for research.

8. References

Ainscow, E.K. & Brand, M.D. (1998). Control analysis of systems with reaction blocks that 'cross-talk'. *Biochemica et Biophysica Acta*, Vol. 1366, pp. 284-290, ISSN 0006-3002.

Anisimov, V.N. (2001). Life span extension and cancer risk: myths and reality *Experimental Gerontology*, Vol. 36, Issue 7, pp. 1101-1136, ISSN 0531-5565

Anisimov, V.N. (2003). Priorities in Fundamental Research in Gerontology: Russian Contribution. *Advances in Gerontology*, Vol. 12, pp. 9–27, ISSN 1561-9125.

Arai, M., Imai, H., Koumura, T., Yoshida, M., Emoto, K., Umeda, M., Chiba, N. & Nakagawa, Y. (1999). Mitochondrial phospholipid hydroperoxide glutathione

peroxidase plays a major role in preventing oxidative injury to cell. *Journal of Biological chemistry*, Vol. 274, Issue 8, pp. 4924-4933, ISSN 0021-9258.

Barrientos, A., Casademont, J., Rotig, A., Miro, O., Urbano-Marquez, A., Rustin, P. & Gardellach, F. (1996). Absence of relationship between the level of electron transport chain activities and aging in human skeletal muscle. *Biochemical and Biophysical Research Communication,* Vol. 229, Issue 2, pp. 536-539, ISSN 0006-291X.

Bayreuther, K., Rodemann, P., Hommel, R., Dittmann, K., Albiez, M. & Francz, P.I. (1988). Human Skin Fibroblasts in Vitro Differentiate Along a Terminal Cell Lineage. *Proceedings National Academy of Sciences USA*, Vol.85, No.14, pp. 5112-5116. ISSN 0027-8424.

Bjelakovic, G., Nikolova, D., Gluud, L.L., Simonetti, R.G. & Gluud, C. (2008). Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. *Cochrane Database of Systematic Reviews*, Issue 2, Art. No. CD 007176, ISSN 1469-493X .

Blasco, M.A., Lee, H.W., Hande, M.P., Samper, E., Lansdorp, P.M., DePinho, R.A. & Greider, C.W. (1997). Telomere Shortening and Tumor Formation by Mouse Cells Lacking Telomerase RNA. *Cell,* Vol. 91, No. 1, pp. 25–34, ISSN 0092-8674.

Bockstaele, L., Bisteau, X., Paternot, S., Roger, P.P. (2009). Different Regulation of Cycline-dependent Kinase 4 (CDK4) and CDK6, Evidence That CDK4 Might Not Be Activated by CDK7, and Design of CDK6 Activating Mutation. *Molecular and Cell Biology*, Vol. 29, No. 15, pp. 4188–4200, ISSN 0270-7306.

Brand, M.D. (2000). Uncoupling to survive? The role of mitochondrial inefficiency in aging. *Experimental Gerontology*, Vol. 35, pp. 811-820, ISSN 0531-5565.

Bratic, I. & Trifunovic, A. Mitochondrial energy metabolism and ageing. (2010). *Biochimica et Biophysica Acta*, Vol. 1797, pp. 961–967, ISSN 0006-3002.

Bredesen, D.E. (2004). Non-existent aging program: haw dos it work? *Aging Cell,* Vol.3, No.5, pp. 255-259, ISSN: 1474-9718

Brigelius-Flohe, R., Banning, A. & Schnurr, K. (2003). Selenium-dependent enzymes in endothelial cell function. *Antioxidants and Redox Signaling*, Vol. 5, No. 2, pp. 205-215, ISSN 1523-0864.

Carey, J.R. (2003). Life span: a conceptual overview. In *Life span: evolutionary, ecological, and demographic perspectives.* Carey, J.R. & Tuljapurkar, S., eds., pp. 1-18, Population council, ISBN: 0878341110, New York.

Cerimele, F., Battle, T., Lynch, R., Frank, D.A., Murad, E., Cohen, C., Macaron, N., Sixbey, J., Smith, K., Watnick, R.S., Eliopoulos A., Shehata, B. & Arbiser, J.L. (2005). Reactive oxygen species signaling and MAPK activation distinguish Epstein-Barr Virus (EBV)-positive versus EBV-negative Burkitt's Lymphoma. *Proceedings National Academy of Sciences USA*, Vol. 102, No.1, pp. 175-179, ISSN 0027-8424.

Cherry, J.L. & Wakeley, J. (2003). A diffusion approximation for selection and drift in a subdivided populations. *Genetics,* Vol. 163, No. 1, pp. 421-428, ISSN 0016-6731.

Clemens, M.J. (1994). Regulation of eukaryotic protein synthesis by protein kinases that phosphorylate initiation factor eIF-2. *Molecular Biology Reports,* Vol. 19, pp. 201-10, ISSN 0301-4851

Clemens, M.J., Bushell, M., Jeffrey, I.W., Pain, V.M. & Morley, S.J. (2000). Translation initiation factor modifications and the regulation of protein synthesis in apoptotic cells. *Cell Death & Differentiation.* Vol. 7, No. 7, pp. 603-615, ISSN 1350-9047.

Clemens, M.J., Pain, V.M., Wong, S-T. & Henshaw, E.C. (1982). Phosphorylation inhibits guanine nucleotide exchange on eukaryotic initiation factor 2. *Nature,* Vol. 296. pp. 93-95, ISSN 0028-0836.

Demin, O.V., Kholodenko, B.N. & Skulachev, V.P. (1998). A model of O_2^- generation in the complex III of the electron transport chain. *Molecular and cell biology,* Vol. 184, No 1-2, pp. 21-33, ISSN 0270-7306.

Dunford, H.B. (2002). Oxidations of iron(II)/(III) by hydrogen peroxide: from aquo to Enzyme. *Coordination Chemistry Reviews*, Vol. 233-234, pp. 311-318, ISSN 0010-8545

Frankham, R. (1996). Relationship of genetic variation to population size in wildlife. *Conservation Biology*, Vol. 10, No. 6, pp. 1500-1508, ISSN 0888-8892.

Frolov, M.V. & Dyson, N.J. (2004). Molecular Mechanism of E2F-dependent Activation and pRB-mediated Repression. *Journal of Cell Sciences*, Vol. 117, No. 1, pp. 2173-2181, ISSN 0021-9533.

Gadgil, M. (1975). Evolution of social behavior through interpopulation selection. *Proceedings of National Academy of Science USA*, Vol. 72, No. 3, pp. 1199–1201, ISSN 0027-8424.

Gems, D. & Doonan, R. (2009). Antioxidant defense and aging in C. elegans. Is the oxidative damage theory of aging wrong? *Cell Cycle*, Vol. 8, No. 11, pp. 1681-1687, ISSN 1538-4101.

Gilpin, M.E. & Soulé, M. E. (1986). Minimum viable populations: processes of species extinction. In *The science of scarcity and diversity*. Soule, M.E., ed., pp.19-34. Conservation biology: Sinauer Associates, ISBN: 0878937951, Sunderland.

Green, D.M. (2003). The ecology of extinction: population fluctuation and decline in amphibians. *Biological conservation*, Vol. 111, Issue 3, pp. 331-343, ISSN 0006-3207.

Greider, C. W. & Blackburn, E. H. (1985). Identification of a Specific Telomere Terminal Transferase Activity in Tetrahymena Extracts. *Cell*, Vol. 43, No. 1, pp. 405–413, ISSN 0092-8674.

Halliwell, B. & Gutteridge, J.M.C. (1984). Oxygen toxicity, oxygen radicals, transition metals and disease. Biochemical Journal, Vol. 219, No.1, pp. 1-14, ISSN 0006-2936.

Harman, D. (1956) Aging: a theory based on free radical and radiation therapy. *Journal of Gerontology*, Vol. 11, pp. 298-300.

Harmon, C.S., Proud, C.G. & Pain, V.M. (1984). Effect of starvation, diabetes and acute insulin treatment on a regulation of polypeptide-chain initiation in rat skeletal muscle. *Biochemical Journal*, Vol. 223, pp. 687-696, ISSN 0006-2936.

Hasty, P. & Vijg J. (2002). Genomic priorities in aging. *Science*, Vol. 296, No. 5571, pp.1250-1251, ISSN 0036-8075.

Hayashi, J-I., Ohta, S., Kagawa, Y., Kondo, H., Kaneda, H., Yonekawa, H., Takai, D. & Miyabayashi , S. (1994). Nuclear but not mitochondrial genome involvement in human age-related mitochondrial dysfunction. Functional integrity of mitochondrial DNA from aged subjects. *Journal of Biological Chemistry*, Vol. 269, Issue 9, pp. 6878-6883, ISSN 0021-9258.

Hayflick, L. & Moorhead, P. S. (1961). The Serial Cultivation of Human Diploid Cell Strains. *Experimental Cell Research*, Vol.25, No.15, pp. 585–621, ISSN 0014-48-24.

Hayflick, L. (2007). Biological aging is no longer an unsolved problem. *Annals of the New York Academy of Sciences*, Vol. 1100, pp. 1-13, ISSN 1749-6632.

Hedrick, P.W. & Gilpin, M.E. (1996). Genetic effective size of a metapopulation. In *Metapopulation biology: ecology, genetics and evolution,* Hanski, I. & Gilpin, M.E., eds, pp. 165-191, Academic Press, ISBN 0123234468, New York.

Herrera, E., Samper, E., Martin-Caballero, J., Flores, J.M., Lee, H-W. & Blasco, M.A. (1999). Disease States Associated With Telomerase Deficiency Appear Earlier in Mice With Short Telomeres. *EMBO Journal*, Vol.18, pp. 1950–2960, ISSN 0261-4189.

Holliday, R. (2006). Aging is no longer an unsolved problem in biology. *Annals of the New York Academy of Sciences*, Vol. 1067, pp. 1-9, ISSN 1749-6632

Halliwell, B. & Gutteridge, J.M.C. (1984). Oxygen toxicity, oxygen radicals, transition metals and disease. *Biochemical Journal*, Vol. 219, No.1, pp. 1-14, ISSN 0006-2936.

Holzenberger, M., Dupont, J., Ducos, B., Leneuve P., Geloen, A., Even, P.C., Cervera, P. & Le Bouc, Y. (2003). IGF-1 receptor regulates lifespan and resistance to oxidative stress in mice. *Nature* 421, 182-187, ISSN 0047-6374.

Hornsby, P.J. (2002). Cellular Senescence and Tissue Aging in Vivo. *Journal of Gerontology series A: Biological and Medical Sciences*, Vol. 57, No. 7, pp. B251–B256, ISSN 1079-5006.

Howes, R.M. (2006). The free radical fantasy. A panoply of paradoxes. *Annals of the New York Academy of Sciences*, Vol. 1067, pp. 22-26, ISSN 1749-6632

Hucull, J.H., Henshaw, E.S. & Young, D.A. (1985). Nucleotide diphosphate regulation of overall rates of protein biosynthesis acting at the level of initiation. *The Journal of Biological chemistry*, Vol. 260, No. 29, pp. 15585-15591, ISSN 0021-9258.

Jeffrey, I.W., Bushell, M., Tilleray, V.J., Morley, S. & Clemens, M.J. (2002). Inhibition of protein synthesis in apoptosis: Differential requirements by the tumor necrosis factor α family and a DNA-damaging agent for caspases and the Double-stranded RNA-dependent Protein Kinase. *Cancer Research*, Vol. 62, No. 8, pp. 2272 – 2280, ISSN 0008-5472.

Jo, S.H., Son, M.K., Koh, H.J., Lee, S.M., Song, I.H., Kim, Y.O., Lee, Y.S., Jeong, K.S., Kim, W.B., Park, J.W., Song, B.J. & Huh, T.L. (2001). Control of mitochondrial redox balance and cellular defense against oxidative damage by mitochondrial NADP+-dependent isocitrate dehydrogenase. *Journal of Biological chemistry*, Vol. 276, No. 19, pp. 16168-16176, ISSN 0021-9258.

Jonas, S.K., Riley, P.A. & Willson, R.L. (1989). Hydrogen peroxide cytotoxicity. Low-temperature enhancement by ascorbate or reduced lipoate. *Biochemical Journal,* Vol. 264, No.3, pp. 651-655, ISSN 0006-2936.

Iantomasi, T., Favilli, F., Marraccini, P., Stio, M., Treves, C., Quattrone, A., Capaccioli, S., Vincenzini, M.T. & Quatrone, A. (1993). Age and GSH metabolism in rat cerebral-cortex, as related to oxidative and energy parameters. *Mechanism of Ageing and Development,* Vol. 70, No. 1-2, pp. 65-82, ISSN 0047-6374.

Isobe, K., Kishino, S., Inoue, K., Takai, D., Hirawake, H., Kita, K., Miyabayashi, S. & Hayashi, J-I. (1997). Identification of inheritance modes of mitochondrial diseases by introduction of pure nuclei from mtDNA-less HeLa cells to patient-derived fibroblasts. *The Journal of Biological chemistry*, Vol. 272, No. 19, pp. 12606-12610. ISSN 0021-9258.

Isobe, K., Ito, S., Hosaka, H., Iwamura, Y., Kondo, H., Kagawa, Y. & Hayashi, J-I. (1998). Nuclear-recessive mutations of factors involved in mitochondrial translation are

responsible for age-related respiration deficiency in human skin fibroblasts. *The Journal of Biological chemistry*, Vol. 273, No. 8, pp. 4601-4606. ISSN 0021-9258.

Itahana, K., Campisi, J., Goberdhan, P. & Dimri, G.P. (2004). Mechanisms of Cellular Senescence in Human and Mouse Cells. *Biogerontology,* Vol.5, No.1, pp. 1–10. ISSN 1389-5729

Kenyon, C.J. (2010). The genetics of ageing. *Nature*, Vol.464, pp.504-512, ISSN 0028-0836.

Kimball, S.R., Fabian, J.R., Pavitt, G.D., Hinnebusch, A.G. & Jefferson, L.S. (1998). Regulation of guanine nucleotide exchange through phosphorylation of eukaryotic initiation factor eIF2. Role of the a- and δ-subunits of eIF2B. *The Journal of Biological chemistry*, Vol. 273, No. 21, pp. 12841–12845, ISSN 0021-9258.

Kirkwood, T. B. L. (2002). Evolution of ageing. *Mechanism of Ageing and Development*, Vol. 123, Issue 7, pp. 737-745, ISSN 0047-6374.

Kirkwood, T. B. L. (2008). Understanding ageing from an evolutionary perspective. *Journal of Internal Medicine*, Vol. 263, pp. 117–127, ISSN 0954-6820.

Korshunov, S.S., Skulachov, V.P. & Starkov, A.A. (1997). High protonic potential actuates mechanism of production of reactive oxygen species in mitochondria. *FEBS Letters*, Vol. 416, Issue 1, pp. 15-18, ISSN 0014-5793.

Lande, R. (1993). Risk of population extinction from demographic and environmental stochasticity and random catastrophes. *American Naturalist*, Vol. 142, No. 6, pp. 911-927, ISSN 0003-0147.

Larrea, M. D., Liang, J., Da Silva, T., Hong, F., Shao, S.H., Han, K., Dumond, D. & Slingerland, J.M. (2008). Phosphorilation of p27kip1 Regulates Assembly and Activation of Cycline D1-Cdk4. *Molecular and Cellular Biology.* Vol.28, No.20, pp. 4662–4672. ISSN 0270-7306.

Leberg, P.L. (1992). Effects of population bottlenecks on genetic diversity as measured by allozyme electrophoresis. *Evolution,* Vol. 46, No.2, pp. 477-494, ISSN 0014-3820.

Lee, H.-W., Blasco, M. A., Gotlieb, G. J., Horner, I.I., Grieder, C.W. & DePinho, R.A. (1998). Essential Role of Mouse Telomerase in Highly Proliferative Organs. *Nature,* Vol.392, pp. 569–574. ISSN 0028-0836.

Leigh, E.G. (1975). Population fluctuations, community stability, and environmental variability. In *Ecology and Evolution of Communities*, Cody, M.L. & Diamond, J.M., eds, pp. 51-73, Harvard University Press, ISBN 0674224442, Harvard.

Leof, E. B., Wharton, W., Van Wyk, J. J., & Pledger,W. (1982). Epidermal Growth Factor (EGF) and Somatomedin C Regulate G1 Progression in Competent BALB/c 3T3 Cells. *Experimental Cell Research*, Vol. 141, Issue 1, pp. 107–115. ISSN 0014-4824.

Levins, R. (1962). Theory of fitness in a heterogeneous environment. 1. The fitness set and adaptive function. *American Naturalist*, Vol. 96, No. 891, pp. 361-373, ISSN 0003-0147.

Lewin, M.H., Hume, R., Howie, A.F., Richard, K., Arthur, J. R., Nicol, F., Walker, S. W. & Beckett, G. J. (2001). Thioredoxin reductase and cytoplasmic glutathione peroxidase activity in human foetal and neonatal liver. *Biochemica et Biophysica Acta*, Vol.1526. Issue 3, pp. 237-241, ISSN 0006-3002.

Lihtgow, G.J. & Andersen, J.K. (2000). The real Dorian Gray mouse. *BioEssays*, Vol. 22, No. 5, pp. 410-413, ISSN 0265-9247.

Liu, R., Liu, W., Doctrow, S.R. & Baudry, M. (2003). Iron toxicity in organotypic cultures of hippocampal slices: role of reactive oxygen species. *Journal of Neurochemistry*, Vol. 85, No. 2, pp. 492-502, ISSN 0169-5088.

Lloyd, R.V., Hanna P.M. & Mason, R.P. (1996). The origin of the hydroxyl radical oxygen in the Fenton reaction. *Free Radical Biology and Medicine,* Vol.22, No. 5, pp. 885-888, ISSN 0891-5849.

MacArthur, R.H. & Connell, J.H. (1966). *The theory of populations.* New York: Willey.

Macfadyen, A. (1966). *Animal ecology, aims and methods.* London: Isaac Pitman & Sons.

May, R.M. (1973). Time-delay versus in population model with two and three trophic levels. *Ecology*, Vol. 54, No. 2, pp. 315-325. ISSN 0012-9658.

May, R.M. (1981). Models for single population. In *Theoretical ecology. Principles and applications. Second edition,* May, R.M., ed., pp. 5-29, Blackwell, ISBN 0632007680, London.

Medawar, P.B. (1952). *An unsolved problem of biology.* Levis, London.

Medvedev, Z.A. (1990). An Attempt at a Rational Classification of Theories of Aging, *Biological Reviews*, Vol. 65, Issue 3, pp. 375–398, ISSN 1464-7931.

Meewes, C., Brenneisen, P., Wenk, J., Kuhr, L, Ma, W., Alikoski, J., Poswig, A., Krieg, T. & Scharffetter, K. (2001). Adaptive antioxidant response protects dermal fibroblast from UVA-induced phototoxicity. *Free Radical Biology and Medicine*, Vol. 30, Issue 3, pp. 686-698, ISSN 0891-5849.

Mendelsohn, S.L., Nordeen, S.K. & Young, D.A. (1977). Rapid changes in initiation-limited rates of protein synthesis in rat thymic lymphocytes correlate with energy charge. *Biochememical and Biophysical Research Communication*, Vol. 79, No. 1, pp. 53-60, ISSN 0006-291X.

Mitteldorf, J. (2004). Ageing selected for its own sake. *Evolutionary Ecology Research,* Vol. 6, pp.1–17, ISSN 1522-0613.

Montero, H., Rojas, M., Arias, C.F. & López, S. (2008). Rotavirus Infection Induces the Phosphorylation of eIF2α but Prevents the Formation of Stress Granules. *Journal of Viroljgy,* Vol. 82, No. 3, pp. 1496-1504, ISSN 0022-538X

Morgan, D. O. (1995). Principles of Cdk Regulation, *Nature*, Vol. 374, pp. 131–134, ISSN 0028- 0836.

Mylnikov, S.V. (1997). Genetic determination of rate of aging in some lines Drosopltila melanogaster. *Advanses in Gerontology*, Vol. 1, pp. 50-56, ISSN 1561-9125 (in Russian).

Nicholson, A.J. (1954). An outline of the dynamics of animal populations. *Australian Journal of Zoology*, Vol. 2, No. 1, pp. 9-65, ISSN 0004-959X.

Nordberg, J. & Arner E.S.J. (2001). Reactive oxygen species, antioxidants and the mammalian thioredoxin system. *Free Radical Biology and Medicine*, Vol. 31, No. 11, pp. 1287-1312, ISSN 0891-5849.

Pain, V.M. (1996). Initiation of protein synthesis in eukaryotic cells. *European Journal of Biochemistry* Vol. 236, No. 3, pp. 747-771, ISSN 0014-2956

Pickett, S.T.A. & White P.S. (1985). Patch dynamics: A synthesis. In *The ecology of natural disturbance and patch dynamics,* Pickett, S.T.A. & White, P.S., eds, pp. 371-384, Academic Press, ISBN 0125545215, London.

Rahimi, R. A. & Leoff, E. B. (2007). TGF-beta Signaling: a Tail of Two Responses. *Journal of Cellular Biochemistry*, Vol. 102, No.3, pp. 593–608, ISSN 0730-2312.

Rasmussen, U.F., Krustrup, P., Kjaer, M. & Rasmussen, H.N. (2003). Experimental evidence against the mitochondrial theory of aging. A study of isolated human skeletal muscle mitochondria. *Experimental Gerontology*, Vol.38, No. 8, pp. 877-886, ISSN 0531-5565.

Rattan, S. I. S. (1996). Synthesis, Modifications, and Turnover of Proteins During Aging, *Experimental Gerontjlogy*, Vol.31, No.1-2, pp. 33–47. ISSN 0531-5565

Rattan, S.I.S. (2006). Theories of biological aging: genes, proteins, and free radicals. *Free Radical Research*, Vol. 40, No. 12, pp. 1230-1238, ISSN 1071-5762.

Rattan, S. I. S. (2009). Synthesis, Modifications, and Turnover of Proteins During Aging. In *Protein Metabolism and Homeostasis in Aging*, Tavernarakis N. ed., Landes Bioscience and Springer Science+Business Media. ISBN 1441970010

Rittling, S.R., Brooks, K.M., Cristofalo, V.J. & Baserga, R. (1986). Expression of Cell Cycle Dependent Genes in Young and Senescent W1-38 Fibroblasts. *Procidings of National Academy of Sciences USA*, Vol. 83, pp. 3316–3320, ISSN 0027-8424.

Rhee, S.G. (1999). Redox signaling: hydrogen peroxide as intracellular messenger. *Experimental and Molecular Medicine*, Vol. 31, No. 2, pp. 53-59, ISSN 1226-3613.

Richards, C. & Leberg, P.L. (1996). Temporal changes in allele frequencies and a population's history of severe bottlenecks. *Conservation Biology*, Vol. 10, No. 3, pp. 832-839, ISSN 0888-8892.

Robert, F., Kapp, L.D., Khan, S.N., Acker, M.G., Kolitz, S., Kazemi, S., Kaufman, R.J., Merrick, W.C., Koromilas, A.E., Lorsch, J.R. & Pelletier, J. (2006). Initiation of protein synthesis by hepatitis C virus is refractory to reduced eIF2·GTP·met-RNA$_i^{met}$ ternary complex availability. *Molecular Biology of the Cell*, Vol. 17, pp. 4632-4644, ISSN 1059-1524.

Ryazanov, A.G. & Nefsky, B.S. (2002). Protein turnover plays a key role in aging. *Mechanism of Ageing and Development*, Vol. 123, No. 2-3, pp. 207-213, ISSN 0047-6374.

Scandalios, J.G. (2002). Oxidative stress responses–what have genome-scale studies taught us? *Genome Biology*, Vol. 3. No. 7, pp. 1019-1021, ISSN 1465-6906

Scandalios, J.G. (2002). The rise of ROS. *Trends in Biochemical Sciences*, Vol. 27. P. 483-486. ISSN. 0968-0004.

Schreck, R., Rieber, P. & Baeuerle. P.A. (1991). Reactive oxygen intermediates as apparently widely used messengers in the activation of the NF-kappa B transcription factor and HIV-1. *EMBO Journal*, Vol. 10, No. 8, pp. 2247-2258, USSN 0261-4189.

Shaffer, M.L. (1981). Minimum population sizes for species conservation. *BioScience*, Vol. 31, No. 2, pp. 131-134, ISSN: 0265-9247.

Sheaf, R.J., Groudine, M., Gordon, M., Roberts, J.M., & Clurman, B.E. (1997). Cycline E-CDK2 Is Regulator of p27kip1. *Genes and Development*, Vol.11, No.11, pp. 1464–1478. ISSN 0890-9369.

Sherr, C. J. (1994). G1 Phase Progression: Cycling on Cue. *Cell,* Vol. 79, No.4, pp. 551–555. ISSN 0092-8674.

Sherr, C. J. (1996). Cancer Cell Cycles. *Science,* Vol. 274, pp.1672–1677, ISSN 0036-8075.

Sherr, C.J. & Roberts, J.M. (1999). Cdk Inhibitors: Positive and Negative Regulators of G1 Phase Progression, *Genes and Development*, Vol. 13, No. 12, pp. 1501–1512, ISSN 0890- 9369.

Sherr, C.J. (2000). The Pezcoller Lecture: Cancer Cell Cycles Revisited. *Cancer Research*, Vol. 60, pp. 3689–3695, ISSN 0008-5472.

Schley, D. & Gourley, S.A. (2000). Linear stability criteria for population models with periodically perturbed delays. *Journal of Mathematical Biology,* Vol. 40, No. 6, pp. 500- 524, ISSN 0303-6812.

Skulachev, V.P. (2001). NAD(P)$^+$ decomposition and antioxidant defense of the cell. *FEBS Letters*, Vol. 492. Issue 1, pp. 1-3 ISSN 0014-5793.

Skulachev, V.P. (2001). The programmed death phenomena, aging, and the samurai low of biology. *Experimental Gerontoljgy*, Vol. 36, No. 7, pp. 995-1024, ISSN 0531-5565.

Southwood, T.R.E. (1981). Bionomic strategies and population parameters. In *Theoretical Ecology. Principles and applications.* Second Edition, May, R.M., ed., pp. 30-52, Blackwell, ISBN 0632007680, London.

Tracy, C.R. & George, T.L. (1992). On the determinants of extinction. *American Naturalist*, Vol. 139, No. 1, pp. 102-122, ISSN 0003-0147.

Trifunovic, A. & Larsson, N-G. (2008). Mitochondrial dysfunction as a cause of ageing. *Journal of Internal Medicine*, Vol. 263, No. 2, pp. 167–178, ISSN 0954-6820.

Trubitsyn, A.G., (2006). The Modified Variant of Mitochondrial Theory of Aging, *Advanses in Gerontology*, Vol. 18, pp. 21-28, ISSN 1561-9125, (In Russion).

Trubitsyn, A.G., (2006a). Evolution Mechanism of Species-Specific Lifespan, *Advanses in Gerontology*,Vol. 19, pp. 13-24, ISSN 1561-9125, (In Russion).

Trubitsyn, A.G., (2009). The Mechanism of Phenoptosis: 1. Age-Dependent Decrease of the Overall Rate of Protein Synthesis is Caused by the Programmed Attenuation of Bioenergetics, *Advanses in Gerontology*, VoL. 22, No. 2, pp. 223-227, ISSN 1561-9125, (In Russion).

Trubitsyn, A.G., (2010). Aging as a result of the implementation of the phenoptosis program. *Russian Journal of general chemistry*, Vol. 80, No. 7, 1490-1500, ISSN 1070-3632.

Trubitsyn, A.G. (2011). The Mechanism of Phenoptosis: 2. The Hayflick Limit Is Caused by Programmed Decrease of the Bioenergetics Level. *Advances in Gerontology*, Vol. 1, No. 2, pp. 147–152, ISSN 2079-0570.

Vaupel, J.W. (2003). Post-Darwinian longevity. In *Life span: evolutionary, ecological, and demographic perspectives,* Carey & Tuljapurkar, eds, pp. 258-269, Population Council,. ISBN, New York.

Vlach, J., Hennecke, S., & Amati, B. (1997) Phosphorylation-Depenedent Degradation of the Cyclin- Dependent Kinase Inhibitor p27[Kip1]. *The EMBO Journal*, Vol.16, pp. 5334–5344. ISSN 0261-4189

Wei, Y-H., Lu, C-Y., Wei C-Y., Ma, Y-S., & Lee, H-C. (2001). Oxidative stress in human aging and mitochondrial disease–consequences of defective mitochondrial respiration and impair antioxidant enzymes. *Chinese Journal of Physiology,* Vol.44. No. 1, pp. 1-11, ISSN: 0304- 4920

White, P.S., Pickett, S.T.A. (1985). Natural disturbance and patch dynamics: an introduction. In *The ecology of natural disturbance and patch dynamics*, Pickett, S.T.A. & White, P.S., eds., pp. 3-13, Academic Press, ISBN 0125545215, London.

Westerhoff, H.V., Van Dam, K. (1987). Thermodynamics and Control of Biological Free-Energy Transduction. Elsevier Science Publisher B.V. (Biomedical division), ISBN 0444807837 Amsterdam.

Wilson, E.O. (1973). Group selection and its significance for ecology. *BioScience*, Vol. 23, No. 11, pp. 631-638, ISSN 0265-9247.

Yegorov, E. E. & Zelenin, A. V. (2003). Duration of Senescent Cell Survival in Vitro As a Characteristic of Organism Longevity, an Additional to Proliferative Potential of Fibroblast, *FEBS Letters*. Vol. 541, Issue 1, pp. 6–10. ISSN 0014-5793.

Young, D.A. (1969). Glucocorticoid Action on Rat Thymus Cells. Interrelationships between carbohydrate, protein, and adenine nucleotide metabolism and cortisol effects on these functions *in vitro. Journal of Biological chemistry*, Vol. 244, No. 8, pp. 2210-2217, ISSN 0021-9258.

Young, D.A. (1970). Glucocorticoid Action on Rat Thymus Cells. II. Interrelationships between ribonucleic acid and protein metabolism and between cortisol and substrate effects on these metabolic parameters in vitro. *Journal of Biological chemistry*, Vol. 245, pp. 2747-2752. ISSN 0021-9258.

Yao, Y-G., Ellison, F. M., McCoy, J. P., Chen, J. and Young, N. S. (2007). Age-dependent accumulation of mtDNA mutations in murine hematopoietic stem cells is modulated by the nuclear genetic background. *Human Molecular Genetics*, Vol. 16, No. 3, pp. 286–294, ISSN 0964-6906.

Yu, T.W. & Anderson, D. (1997). Reactive oxygen species-induced DNA damage and its modification: A chemical investigation. *Mutation Research*, Vol. 379, Issue 2, pp. 201-210. ISSN 0027-5107

Zykova, T.A., Zhu, F, Zhang, M. Bode, Y, A. & Dong, Z. (2007). Involvement of ERKs, RSK2 and PKR in UVA-induced signal transduction toward phosphorylation of eIF2 (Ser[51]). *Carcinogenesis,* Vol. 28, No. 7, pp.1543-1551, ISSN 0143-3334
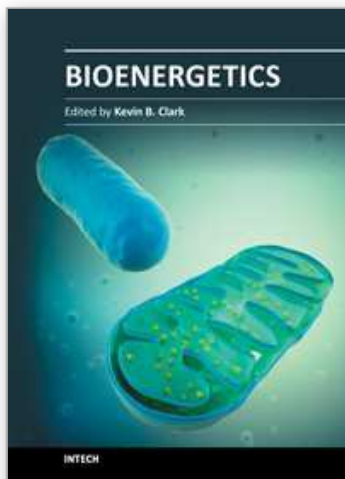
Bioenergetics

Edited by Dr Kevin Clark

Cellular life depends upon energy storage, transformation, utilization, and exchange in order to optimally function and to stay-off death. The over 200-year-old study of how cells transform biological fuels into usable energy, a process broadly known as bioenergetics, has produced celebrated traditions in explaining origins of life, metabolism, ecological adaptation, homeostasis, biosynthesis, aging, disease, and numerous other life processes. InTech's edited volume, Bioenergetics, brings together some of these traditions for readers through a collection of chapters written by international authorities. Novice and expert will find this book bridges scientific revolutions in organismic biology, membrane physiology, and molecular biology to advance the discipline of bioenergetics toward solving contemporary and future problems in metabolic diseases, life transitions and longevity, and performance optimization.

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