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REVIEW

Modern Concepts on Mechanisms of Aging

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Abstract—A review of modern literature, concerning the basic concepts of the aging mechanisms, is presented. Widely accepted theories of aging such as the theory of mutation accumulation, the free radical theory, the theory of antagonistic pleiotropy, and the theory of organized soma, are examined. Methods of estimating the rate of aging are discussed. The most interesting publications on the above matters, issued in 1991-1994, are included in the review. The literature was selected with the help of Science Citation Index.

INTRODUCTION

The radical increase in life span and the related changes in the sex and age structure of the population represent some of the most significant global events that have changed our planet in the XX century. These changes cause substantial restructuring of the socioeconomic sphere of life and lead to a transformation of the human population as a recipient of global environmental and climatic changes. Therefore, it is of great importance to be able to evaluate and predict possible changes in life span, and the factors determining those changes.

An analysis of the dynamics and causes for life span nearly doubling in the XX century shows that this has occurred due to an increase of the median life span, while the maximum life span has remained the same [1]. Only the environmental component of mortality, caused in general by external factors' transformations including medical progress, changes in the way of life, etc., changed. So, the biological component of mortality based on mechanisms of an organism's vital functions formed through evolution remained unchanged [2]. It is evident that by the end of the century curves of relationship between life expectancy and the calendar year will approach a constant [3], indicating that possibilities for use of traditional health-care methods of life span increase will have been exhausted. Most experts believe that the crisis of medicine and public health exists throughout the world [4]. This outlines the need for new means and approaches to health improvement and for increasing life span. According to the literature, biology of life longevity as a study of fundamental processes and mechanisms of aging and, in particular, of the natural maximum human life span represents the most promising area of research.

Hypotheses aimed at aging mechanisms are extremely varied. Some consider the ecological aspects of population density [5], life history's influence on life span [6], the significance of certain species, attributes, such as mobility, in closely related species [7]. Several hypotheses suggest the role of some biochemical mechanisms in aging, such as the development of autoimmune processes [8] and the accumulation of several chemical substances, in particular, the age pigment lipofuscin [9]. There are attempts to develop models of aging on the basis of the thermodynamics of unequilibrium processes [10, 11].

For this review, we selected the most recognized theories having, from our point of view, a strong experimental basis.

PROGRAM OR DEPRECIATION?

Empirically, the aging process can be characterized as regular changes in biochemical, cytological, histological, and physiological levels taking place during the postnatal life of an organism. Apparently, this process proceeds permanently from birth and, probably, from the moment of conception. However, in practice, aging is considered as a combination of changes emerging at a later stage of ontogenesis when an organism's functions decrease substantially, it reaches a limitation of its adaptation capacities, develops etiologically different pathological reactions, resulting in a greater probability of death.

Although usual signs of aging are well studied in virtually all physiological systems, organs, and tissues, the primary reasons are still not clear which has lead to an emerging number of somewhat contradictory theories on aging.

The central question, which invariably arises when formulating a concept of the aging mechanism is whether aging is genetically programmed and caused by human evolution as a species or is analogous to a mechanical depreciation of a technical device gradually ensuring small breakages, eventually leading to a major breakdown of the device.

Hypotheses based on the programmed of life longevity have a long history and originate from the endocrine concept of aging, common at the beginning of the XX century. According to it, every period of an organisms life is dominated by a certain endocrine gland.

Youth is dominated by the thymus, puberty by the epiphysis, maturity by the gonads, and old age by the adrenal gland cortex. Hence, aging is the result of change in activity of different glands and their specific relationship. This theory did not explain reasons for that relationship and the mechanisms of aging in organisms having no endocrine system.

THEORY OF ANTAGONISTIC PLEIOTROPY

Currently, the theory of antagonistic pleiotropy is the most recognized among those on programmed development. It suggests that some genes, playing a positive role at early stages of an organism's development, can be harmful at later stages. This theory is based, in particular, on the negative correlation between reproduction and life span [12]. Some authors attempt to explain the positive impact of low-calorie diet on life span from this standpoint [13], although such influence can be explained to the same extent by a theory of organized soma, described below. As for the negative correlation, it is revealed mostly in the evolutional aspect than within a population [14], and is vaguely connected with the physiological and biochemical processes in an individual organism. Currently, most researchers are more critical of the theory of antagonistic pleiotropy. First of all, no genes corresponding to the theory were found yet [15]. Secondly, there is no positive correlation between development during the early stages of life and rate of aging [16]. Rather, such a correlation is found between vital capacity in youth and old age, and this contradicts the pleiotropic theory [17, 18]. As a consequence, this theory is not widely accepted today.

THEORY OF MUTATION ACCUMULATION

The theory of mutation accumulation represents the basis for another point of view. According to this theory, somatic mutations accumulate in an organism and deteriorate the cell functioning. Primarily, an accumulation of mutations influences cell repair after damage [17-19]. Needless to say, that recognition of the theory of somatic mutation accumulation can imply the denial of evolutionary determination of the life span [20]. However, this accumulation can be programmed in terms of the regular and progressive decrease in DNA repair activity with age.

In the context of the mutation accumulation theory, it was shown that an increase in the frequency of chromosome aberrations in somatic cells caused by an incorporation of thymidine analogue, led not only to the suppression of gonadotropic function of hypophysis and a greater probability of tumor growth, but also to a general decline in life span [21]. Obviously, this parallel decline in life span and gonadotropic function clearly contradicts the theory of antagonistic pleiotropy.

One aspect of the mutation accumulation theory is that extranuclear mutations, i.e., mutations not localized in the nuclear DNA but in the mitochondrial genes, are of most importance since mitochondrial DNA cannot resist damage due to the absence of histone-protectors and excision reparation [24].

This corresponds to the data indicating that, with mitochondrial aging, cells undergo notable morphological changes: the number of big mitochondria increases along with a decline in their specific surface, and the total number of mitochondria decreases. The constantly increasing formation of lipid peroxides on the internal mitochondrial membrane [25] can be considered as one reason of such mitochondrial mutations. In turn, due to these mutations, oxidation impairment in the respiratory chain occurs and causes subsequent mutations in nuclear DNA [26], although some authors point out that mutations of mitochondrial DNA do not influence protein synthesis in the respiratory chain [22],

FREE RADICAL THEORY

The role of free radicals in the general aging mechanisms, and in the origin of somatic mutations, in particular, is still a matter for discussion. Possible mechanisms of such mutations are still not clear, and several researchers have tried to reveal the entire combination of events leading to those mutations [27]. Generally, a substantial number of mutations constantly appear at any age, but they are just as constantly eliminated by repair mechanisms. Thus, the increase in somatic mutations with aging can primarily be connected with the functional damage of DNA repair, the activity of which can be assessed experimentally [28]. Free radicals, then, are considered to be a major factor of chromosomal or point mutations. This problem is discussed in detail in [29], and the authors conclude that a drop in the content or activity of the enzymes repairing oxidative damage can account for the age disturbances. Thus with age, the ability of cells to resist effects which activate oxidation decreases [30]. These results are supported by the fact that an increased resistance to the effects of oxidative stress positively correlates with life span [31]. It is important that this hypothesis can be experimentally examined due to an elaborated method which allows a simulation of oxidative stress in tissue cultures [32].

Even though the free radical theory is supported by many scientists [31, 33-35], it is the subject of much controversy. For example, the evidence shows that anti-oxidants have only a slight impact on the life span, at least, in small mammals [36]. There are also reports suggesting that, in many cases, no age deterioration of the membrane lipoprotein structure, as predicted by this theory, is found and that the number of oxidative radicals even decreases with age [37]. In addition, there is the opinion [38], that two types of free radicals exist, "good" and "bad". The former are nitrogen radicals. There are objections related to the accumulation of lipid peroxides with aging as well [39, 40]. There is also the belief [41], that condition of antioxidative system is a modulating rather than determining factor in aging.

The mutation accumulation theory and the closely related free radical theory of aging suggest that the rate of aging must depend on the nature and intensity of effects experienced by an organism during its life. Although the ratio between the rate of free radical formation and the development of defence mechanisms can be, to some extent, determined by genetic factors [42], life history must substantially influence the intensity of mutations in somatic cells, including mutations caused by free radicals. It is common to recommend the use of antioxidants to lower the number of free radicals in an organism [33], and a balanced, low-calorie diet with a reduced fat content.

THEORY OF ORGANIZED SOMA

The theory of organized soma suggests that energetic metabolism plays the central role in determining life span [42]. On the one hand, energy is necessary for life and, in particular, for repairing damage in cells. On the other hand, the main part of energy is stored as a result of oxidative phosphorylation which leads to the formation of free oxygen radicals affecting the cell structures, in particular, mitochondria. Therefore, to slow down the aging process means to obtain more energy without lipid oxidation and with as little oxygen as possible, i.e., to increase the P/O coefficient. In other words, the ratio between synthesized ATP and oxygen intake should be maximal. The efficiency of such feed consumption was shown in experiments with ruminants [43]. In light of this, the P/O coefficient becomes an important indicator of the aging rate, since the P/O rise with age related to glycolysis activation can indicate the intensification of defence mechanisms inhibiting the development of age-related impairments of the cell structures, in particular, mitochondria.

As for a low-calorie diet, there is an opinion that certain food intake limitations are useful at a younger age, but at an older age they are not and can even be harmful [44]. If this is the case, then it should be acknowledged that free radical lipid oxidation is mostly dangerous at a younger age, when defence antioxida-tive mechanisms are not formed, while at an older age, there can be problems associated with oxidative phosphorylation. So, the intensification of metabolism can be more useful for older individuals.

POSSIBLE ROLE OF EPIGENETIC MECHANISMS

We can conclude from the published data, that more attention is paid to genetic impairments, i.e., changes in the DNA structure of the nucleus or mitochondria, than to possible epigenetic disturbances associated with changes in the intensity of repression/expression of somatic genes. At the same time, it is obvious that these processes are more mobile, regulated and conditioned than the changes in the genome structure itself. Oxidative damage can make an impact on transcription process rather than on the DNA nucleotide sequence [26]. In addition, epigenetic processes can be involved in the formation of many irreversible reactions connected with the action of adaptive hormones, mediators, and other substances influencing cell metabolism. Hence, epigenetic mechanisms can be responsible for recording life history, which undoubtedly, will be reflected in their impact on the rate of aging.

We discussed similar mechanisms based on the modified Jacob-Monot model, when considering a possible basis for the formation of life-long types of long-term memory [45]. They can be applied to explain aging based on epigenetic processes.

METHODS OF EVALUATING THE RATE OF AGING

In summarizing the existing concepts on aging mechanisms, we can conclude that the mutation accumulation theory has advantages over the concept of programmed development which is clearly defined in the theory of antagonistic pleiotropy, although reasons for accumulation and localization of mutations remain unclear. However, the main principles of this theory provide starting points for studying aging and allow us to define the set of methods, which can be used to evaluate the aging rate. First of all, the method of repair activity evaluation.

Taking into account the principal role of free radicals, namely oxygen, and of lipid peroxides in the origin of cell damage, we should focus our attention on the assessment of cell reaction to oxidative stress and on the balance of oxidation/phosphorylation ratio estimated based on the P/O coefficient and intensity of anaerobic glycolysis.

It is important that aging be connected not only with the accumulation of somatic genetic mutations, but also with changes in the epigenetic mechanisms. Therefore, when analyzing these processes, the possibility of non-active gene expression or, to the contrary, the repression of active genes [46], estimated by the cell ability to synthesize new aminoacid sequences, should be taken into account.

Mitochondrial morphology and cell membrane permeability can serve as efficient indicators of biological age. Changes in cell membrane permeability can be one of the first consequences of an intensification of lipid peroxide oxidation; this is supported by the data [47] that the membrane transport function of aging hepatocyte is impaired, but other intracellular structures remain relatively stable.

It is clear that, due to many obscurities and contradictions in the aging theories, a complex evaluation of organism based on different parameters should be used to assess the rate of aging.

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