Advanced Studies in Biology, Vol. 8, 2016, no. 1, 17 - 25
HIKARI Ltd, www.m-hikari.com
http://dx.doi.org/10.12988/asb.2016.612

Systemic Structural Hypothesis of Aging

A.K. Kolomiytsev

Department of Pathology, RostGMU, Nakhichevanshi 29, Rostov-na-Donu, Russia

Aleksandrovskaya 97-5, Taganrog Rostovskaya oblast, 347935, Russia

Abstract

Phenomenon of aging came to existence simultaneously with formation of cell associations and multicellular organisms and played an adaptive role at the early stages of evolution. This phenomenon may be the result of formation of mechanisms that control cellular growth in compliance with nutrient factors limit. Multicellular organisms function as complex systems where the cell division is regulated both by intracellular processes and general systemic organization. The developmental process is determined by a kinetic curve of population growth, which is typical of every cell association. The systemic structural hypothesis considers every multicellular organism as a system that consists of various cellular associations in symbiotic interaction. One of these associations limits the developmental kinetics of the whole organism. Life duration is determined by potential of limiting cell association stem cells. It is offered to introduce a special term – regeneration submodule - a unit that consists of cells and tissues which have a general regeneration complex – a group of stem cells that renovate strictly these cells and tissues. Such regeneration submodules are formed within organs and systems; one of them is a dominating unit which determines the life duration.

Keywords: aging, aging hypothesis, loss of neurons, brain aging

1. Introduction

Although with recent advances in biology and medicine the average life duration has substantially increased it is now reaching a level which may be considered as a biological limit of life. Despite all scientific achievements of the past decades humanity is still far from resolving the problem of the origin of aging. New advances in aging control may be provided by recent research in genetics of aging (van de Lagemaat et al. 2014; . Spinner et al. 2014). However, these studies revealed

a great number of genetic associations with human aging, but contrary to expectations these associations did not result in revealing the mechanism of aging regulation (de Magalhaes 2014). The systemic organization of any living organism is supposed to present the basis for any aging research. The systemic structural hypothesis is aimed at better understanding of the phenomenon of aging.

2. Hypothesis

We hypothesize that systemic organization of any living organism presents the basis for any aging research. Our systemic structural hypothesis was presented for better understanding of phenomenon of aging. This conjecture does not contradict either the evolutionary or the molecular theories of aging. It may be considered as an attempt to produce a comprehensive view of how aging developed in complex organisms. This is an instrument which allows to understand how aging arose at all and estimate every multicellular organism as a system where aging process starts from a definite structure.

It is highly probable that aging comes to existence at the stage of formation of multicellular organisms. When single-cell organisms unite in associations – colonies – the presence of the developmental process resulting in deterioration becomes obvious. The problem of aging in single-cell organisms is not resolved yet. Numerous studies, however, confirm its existence (Stewart et al. 2005). The fact that the results of these studies were obtained in bacterial colonies and cell cultures is of particular significance as the regulative features of this environment are obvious. The perfect conditions for aging study in unicellular organisms hypothetically should be the following: a single-cell organism divides, and the daughter cell is removed mechanically while the observation is carried out constantly. But it should be a very complex experiment as the result of cell division is formation of two identical cells.

The most profound research that has been carried out concerns growth of single-cell organisms in symbiotic associations. The features of growth of bacterial associations consisting of two or three species of microorganisms were studied. As became evident, the type of microorganisms that limits the process of colony growth determines the kinetics of the development of association. If one of the microorganism species is strictly limiting, the kinetics of growth and deterioration of such a population is highly dependent on the kinetics of the development of this microorganism. Thus, the principle of limitation of growth of symbiotic populations by means of limiting features of one of the species comes to existence already on the level of bacterial populations (Pechurkin 1978).

Thus, we conjecture that the phenomenon of aging may occur as a result of formation of mechanisms that control cellular growth in accordance with nutrient factors limit; it had been developed at the very early stage of evolution, even at the level of bacterial colonies.

Since multicellular organisms function as complex systems, the life of cells is determined both by cellular molecular processes and also by system organization. The developmental process of organism possibly depends on a kinetic curve of population growth, which is typical of every cell association (tissue culture, cell culture, colony of microorganisms, etc.). It includes phases of induction, exponential growth, linear growth, deceleration, a stationary and an atrophy phase (Khokhlov et al. 1987).

Systemic structural hypothesis considers every multicellular organism as a system that consists of various cellular associations in symbiotic interaction. One of these associations determines the developmental kinetics of the whole organism. We propose that it is the nervous system that may play the role of such a cellular association and determine the life span in animals and human beings due to its restricted regeneration capabilities. As is well-known, there are two main types of regeneration in human or animal organism: cellular and intracellular. The former exists due to the ability of cells to divide. The latter occurs in the case when cells lose their capability to proliferate. Its essence is hypertrophy and hyperplasia of intracellular components. All the cells of a human organism may be divided into 3 groups: labile cells (continue to divide throughout life under normal physiologic conditions), stable cells (decrease their capability to multiply under normal conditions but retain the capacity to proliferate in response to stimuli) and permanent cells (lose their ability to proliferate constantly). The last group includes neurons, skeletal muscle and cardiac muscle cells. Such cells regenerate only by means of intracellular hypertrophy which is expressed enough in muscular cells but restricted in neurons. It is obvious that regeneration capabilities of the nervous system are restricted, which may have certain repercussions, such as continuous damage of regulatory functions of nervous system and therefore the persistence of dysregulation pathologic processes. Being a main regulation unit in a human or animal organism this system may determine the duration of its life.

Although there is a certain amount of neural stem cells in the human nervous system, they are unable to generate enough new nerve cells to restore functional damages completely. This is an evolutionary conditioned feature. This means that an organism may be theoretically regarded as a "neuronal cell culture" that develops on the "medium" (the other tissues which make up the body).

Constant alterations in neural tissue may result in persistence of a number of pathologic processes as an expression of dysregulation pathology and result in a decrease of life duration. The theories of life span gene regulation may be explained by means of our theory. Even the limit to cell division (Hayflick 2002, 2007) may be considered a compensatory feature that arose as a result of cellular development in complex systems where nutritional competition occurs as well as the accumulation of destructive products.

This rule can also be applied to plants, even though there is no nervous system in their structural organization. For instance, apical meristems in plants play the role of organogenesis units. Since organs need to be produced continuously during the life cycle, the apical meristems have to maintain a pluripotent stem cell population (Bowman et al. 2000; Thomas et al. 2009). Thus, apical meristems may play a dominant role in plant maintenance and development. Apical meristem control in plants is carried out by means of hormones (Khan et al. 2014). Plants may be regarded as modular organisms (as well as some animals, primarily invertebrates). The body plan of modular organisms is based on an indeterminate structure composed of iterated modules arrayed in various levels of complexity (leaves, twigs, and branches). Every module (unit) consists of various tissues, one of which is dominating in the developmental process. Each module undergoes individual senescence. Thus, senescence occurs in the units of a modular organism but systemic ageing is not obvious in some species.

It seems to be convenient to introduce a special term – regeneration submodule. This term will be used to indicate a unit that consists of cells and tissues which have a general regeneration complex, the latter meaning a group of stem cells that renovate strictly particular cells and tissues. The formation of such regeneration submodules occur within organs and systems. One of them happens to be a dominating unit that determines the life duration.

3. Study Design

The main aim of the research was to reveal a correlation between age-related loss of neurons in autonomous nervous system centers and development of pathologic processes which can be estimated as dysregulation pathology.

4. Morphologic Evidence for the Systemic Structural Hypothesis

1. As a preliminary step, we examined the state of neurons in the human brain centers responsible for gastrointestinal system innervation- dorsal nuclei of n. vagus. We used chronic gastric and duodenal ulcers as models for study. The aim of the study was to reveal possible neurotrophic mechanism of ulcer disease persistence related to autonomous nervous system disorder- loss of neurons in nucleus dorsalis n. vagi. Age-dependent loss of neurons was not studied at this stage.

The research was undertaken on autopsy material derived from patients. This approach is useful to reveal the changes to the neural centers that have accumulated within the span of an individual's life. Fragments of human medulla oblongata were fixed in 10% formaldehyde and underwent standard histological processing which included dehydration of specimen in ethanols of ascending concentrations and infiltration with paraffin. Cross-sections of medulla oblongata 10 microns in thickness were prepared. This thickness of preparations corresponds to the mean diameter of neurons within the dorsal nuclei. The cross-sections were stained by means of standard histological and histochemical methods: hematoxylin and eosin,

toluidine blue. The calculation of numbers of neurons in the right and left dorsal nuclei of n. vagus per field of vision (280x) was undertaken with mean number identification. The diameter of field of vision was 0.45 mm. This method was applied to standardize the research as in this case we are able to estimate the number of neurons in a certain volume of brain tissue. As we cannot visualize the exact borders of every nucleus within the brain stem due to irregular location of neurons, we applied cell counting per field of vision of the central part of nucleus (45 mm in diameter). Additionally, we estimated neurons' nuclear and cellular volumes.

96 autopsies were studied: in 50 cases chronic gastric or duodenal ulcer was revealed, while 46 cases formed a control group of autopsies demonstrating cardiovascular pathology instead. The age of the subjects varied from 28 to 90 years both in main group and from 31 to 87 years in control groups.

Main group. Chronic peptic gastric or duodenal ulcer was considered as a principal disease in 41 cases (82%). In 9 cases ulcer disease was considered as attendant disease (18%), the principal disease was the ischemic heart disease. Age groups: 21-30 years- 1 case, 31-40 years- 0, 41-50 years- 12, 51-60 years- 15, 61-70 years- 16, 71-80 years- 5, 81-90 years-1. Sex groups distribution: male- 30 (60%), female- 20 (40%).

Control group. Acute myocardial infarction (32 cases- 69.6%) and chronic ischemic heart disease (24 cases- 70.4%) were considered as a principal disease in this group. Age groups: 31-40 years- 1, 41-50 years- 4, 51-60 years- 9, 61-70 years- 17, 71-80 years- 11, 81-90 years-4. Sex groups distribution: male- 22 (47.8%), female- 24 (52.2%).

The results revealed a decrease in neuron numbers in transversal sections of the n. vagus dorsal nuclei, which made up 22.9% (mean number) in cases of gastric of duodenal ulcer persistence compared with control cases- 27.42. Morphometry also revealed a decrease of 14.9% in cellular and nuclear volumes compared with controls.

We also observed the presence of chronic atrophic pyloric gastritis in cases where the decrease of mean number of neurons was obvious. This type of gastritis was common in all the cases of ulcer persistence, i.e. of the main group where the decrease in neuron numbers was revealed. On the other hand, the structure of control group was found heterogeneous: in 35 cases the mean number of neurons in dorsal nuclei of n. vagus exceeded the mean number for this group and was at the level of 29.31. In 11 cases the mean number of neurons was approximately as in the main group – 22.05 and in all these cases atrophic pyloric gastritis was found. So these cases formed an "additional" group inside control one. The main parameters for this group were the decreased mean number of neurons in dorsal nuclei of n. vagus, chronic atrophic pyloric gastritis, absence of ulcer disease. Thus, we revealed the strict correlation between the decrease of number of neurons in dorsal nuclei of vagus nerve and persistence of chronic atrophic pyloric gastritis which forms the conditions for ulceration which may occur when additional aetiological factors take place.

Statistics.
The results presented are statistically significant. We calculated Student criterion ($P<0,01$) and Pearson X^2 which reflected the significance of distinction of parameters of the main group. This criterion provides methods that estimate the significance of difference between the obtained values and theoretical values. As the result it is possible to test a consent, i.e. to compare the experimental and theoretical data distribution. We used Pearson X^2 for comparison of various conditions of the same qualitative indication: presence and absence of neuronal loss correlating with ulcer and chronic atrophic pyloric gastritis persistence. Criterion X^2 equals 80.92; this result exceeds critical meaning $X^2= 10.82$ for 0.1% level of significance.

The study revealed morphological evidence of a correlation between the alterations in nucleus dorsalis n. vagi and chronic gastric and duodenal ulcer persistence. These changes occur consistently in chronic atrophic gastritis, chronic peptic gastric and duodenal ulcer, and may be estimated as dysregulation pathology.

2. We further examined age-dependent loss of neurons in various brainstem structures. The research was undertaken on autopsy material. We studied the state of nucleus dorsalis n. vagi and brainstem reticular formation.

Reticular formation plays a significant role in brain functions. This structure is a set of interconnected neural cells that are connected with other brain structures. Vital regulatory centers that control visceral functions are located in the brainstem reticular formation: cardiac and vasomotor center and respiratory center. Morphologic changes in brainstem reticular formation as the result of senescence are not studied yet although these changes may result in functional damages of vasomotor and respiratory centers.

Fragments of human medulla oblongata were fixed in 10% formaldehyde and underwent standard histological processing. Cross-sections of medulla oblongata were prepared and stained by means of standard histological and histochemical methods. The calculation of neurons was undertaken with mean number identification. The method of calculation was the same as in the previous study.

60 autopsies were studied, from subjects varying in age from 34 to 80 years. Acute myocardial infarction (30 cases- 50%), chronic ischemic heart disease (26 cases- 43.3%) and idiopathic restrictive cardiomyopathy (4 cases- 6.7%) were considered as a principal disease in this study. Age groups: 31-40 years- 6, 41-50 years- 9, 51-60 years-19, 61-70 years- 16, 71-80 years- 10. Sex groups distribution: male- 32 (53.3%), female- 28 (46.7%).

The study revealed an 18% decrease in the mean number of neurons in n. dorsalis n. vagi in the age group from71-80 years as compared with the age group of 31-40 years. We also observed a strict correlation between the persistence of chronic atrophic gastritis and loss of neurons. The age-related decrease of neurons in reticular formation revealed in the same age groups was 33.58%.

5. Discussion

Thus, our study revealed the age-dependent loss of neurons in autonomous nervous centers- dorsal nuclei of vagal nerve and brainstem reticular formation. Although this process is dependent from age, the deterioration is not occur linearly, it may develop in different time units in various brain structures. Therefore dysregulation pathology that develops due to the damages in regulatory centers and neurotrophic innervation deterioration may be expressed irregularly in various organs and systems. The failure in "regeneration submodule" function therefore results in atrophy persistence in corresponding organs as an expression of senescence and development of various pathologic processes.

6. Conclusion

1. Aging is a universal phenomenon. It can be observed not only in mammals and human beings but also in plants and even bacteria.
2. Aging came to existence at the same time as cell associations and multicellular organisms started to form. On the early stages of evolution it played the adaptive role.
3. Multicellular organisms function as complex systems. The cell division in them is regulated by both, intracellular processes and general systemic organization. The developmental process is determined by a kinetic curve of population growth, which is typical of every cell association (cell culture, colony of microorganisms, etc.).
4. Systemic structural hypothesis regards every multicellular organism as a system that consists of various cellular associations in symbiotic interaction. One of these associations determines the developmental kinetics of the whole organism.
5. Life duration is determined by potential of limiting cell association stem cells.
6. It is convenient to introduce a special term – regeneration submodule. This term will be used to indicate a unit that consists of cells and tissues which have a general regeneration complex, the latter meaning a group of stem cells that renovate strictly particular cells and tissues. The formation of such regeneration submodules occur within organs and systems. One of them happens to be a dominating unit that restricts the life duration.
7. The nervous system is the dominant cellular association in animals and human beings. The duration of its development is restricted by low capacity of neural stems to divide and to take part in nervous tissue regeneration. Therefore age-related alterations progress in nervous system structures that result in dysregulation pathology, aging and death.

Funding. This research received no grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests. The author declares no conflicts of interest.

Ethics approval. RostGMU Bio-Ethical Committee.

References

[1] J.L. Bowman, Y. Eshed, Formation and maintenance of the shoot apical meristem, *Trends in Plant Science*, **5** (2000), no. 3, 110-115.
http://dx.doi.org/10.1016/s1360-1385(00)01569-7

[2] J.P. de Magalhaes, Why genes extending lifespan in model organisms have not been consistently associated with human longevity and what it means to translation research, *Cell Cycle*, **13** (2014), no. 17, 2671-2673.
http://dx.doi.org/10.4161/15384101.2014.950151

[3] L. Hayflick, DNA replication and traintracks, *Science*, **296** (2002), no. 5573, 1611-1612.
http://dx.doi.org/10.1126/science.296.5573.1611

[4] L. Hayflick, Biological aging is no longer an unsolved problem, *Annals of the New York Academy of Sciences*, **1100** (2007), 1-13.
http://dx.doi.org/10.1196/annals.1395.001

[5] M. Khan, W. Rozhon, B. Poppenberger, The role of hormones in the aging of plants- a mini review, *Gerontology*, **60** (2014), no. 1, 49-55.
http://dx.doi.org/10.1159/000354334

[6] A.N. Khokhlov, M.E. Golovina, E.I. Chirkova, T.L. Nadzharian, Analysis of the kinetic growth patterns of cultured cells. III, The effect of inoculation density, of a geroprotector-antioxidant and of stationary-phase aging, *Tsitologiia*, **29** (1987), no. 3, 353-357.

[7] N.S. Pechurkin, *Population Microbiology*, Novosibirsk, Nauka, 1978.

[8] N.B. Spinner, L.K. Conlin, Mosaicism and clinical genetics, *Am. J. Med. Genet. C: Semin. Med. Genetics*, **166** (2014), no. 4, 397-405.
http://dx.doi.org/10.1002/ajmg.c.31421

[9] E.J. Stewart, R. Madden, G. Paul, F. Taddei, Aging and death in an organism that reproduces by morphologically symmetric division, *PLoS Biology*, **3** (2005), no. 2, e45.
http://dx.doi.org/10.1371/journal.pbio.0030045

[10] H. Thomas, L. Huang, M. Young, H. Ougham, Evolution of plant senescence, *BMC Evol. Biology*, **9** (2009), 163.
http://dx.doi.org/10.1186/1471-2148-9-163

[11] N.L. van de Lagemaat, B. Nijhof, D.G. Bosch, M. Kohansal-Nodehi, S. Keerthikumar, J.A. Heimel, Age-related decreased inhibitory vs. excitatory gene expression in the adult autistic brain, *Front Neurosci*, **8** (2014), 394. http://dx.doi.org/10.3389/fnins.2014.00394

Received: February 15, 2016; Published: February 25, 2016