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Neurogenesis and brain aging

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Abstract: Human aging affects the entire organism, but aging of the brain must undoubtedly be different from that of all other organs, as neurons are highly differentiated postmitotic cells, for the majority of which the lifespan in the postnatal period is equal to the lifespan of the entire organism. In this work, we examine the distinctive features of brain aging and neurogenesis during normal aging, pathological aging (Alzheimer's disease), and accelerated aging (Hutchinson-Gilford progeria syndrome and Werner syndrome).

Keywords: aging; Alzheimer's disease; brain; Hutchinson-Gilford progeria syndrome; stem cells.

Introduction

Aging is associated with a gradual reduction in the effectiveness of mechanisms involved in the maintenance of homeostasis of the organism and its organs and tissues, which leads to an increased risk of various pathologies and death. Currently, there are several dozen theories of aging, but all of them can be divided into two groups: aging is a genetically programmed process and aging is a random process caused by a gradual damage of the organism over time as a result of its vital activities. Human aging affects the entire organism, but aging of the brain must undoubtedly be different from that of all other organs, as neurons are highly differentiated postmitotic cells, for the majority of which the lifespan in the postnatal period is equal to the lifespan of the entire organism (Isaev et al., 2013). Using single-cell whole genome sequencing, the accumulation of somatic mutations with age has been observed in single postmitotic human neurons of the prefrontal cortex and hippocampus (Lodato et al., 2018). There is no large loss of neurons in the process of normal aging, but the number, diameter, length, and branching of the dendrites as well as the density of the dendritic spines in the neurons may decrease with aging (Page et al., 2002; Duan et al., 2003). It should be taken into account that the structure of these changes is very heterogeneous in different regions of the brain, and the decrease in the number of neurons is very local (Smith et al., 2004). As the intensity of neuronal death is varied in different regions of the brain, the decrease in volume of the brain also varies in its different departments and structures. The greatest shrinkage occurs in the frontal and temporal cortex, putamen, thalamus, and nucleus accumbens (Fjell and Walhovd, 2010). It should be noted that, in the hippocampus (perhaps in other regions of the brain as well), neuronal death could be partially compensated as a result of neurogenesis. However, with age, neurogenesis is significantly impaired. In recent years, accumulated evidence has shown that neurogenesis can restore a more youthful state during aging. An important objective for the coming years will be to find ways to intervene in this process to slow the aging of the brain. There are already some data that suggest that it may be possible to influence lifespan and aging through genetic manipulations. One of the genes that are of interest in this regard is the *Klotho* gene. The Klotho protein is involved in the regulation of phosphate and calcium metabolism, protects cells from oxidative stress and apoptosis (Duce et al., 2008), and suppresses the intracellular signal transduction pathways of insulin and insulin-like growth factor-I (IGF-I; Kurosu et al., 2005). The overexpression of this protein increases the lifespan of female mice by 19% and that of males by 30% compared to normal mice. The disrupted expression of the Klotho gene in mice causes a syndrome that resembles human aging and results in a shortened lifespan, development of infertility, arteriosclerosis, skin atrophy, osteoporosis, and emphysema (Kuro-o et al., 1997). Notably, the expression of the Klotho protein in the mammalian brain decreases during normal aging (Duce et al., 2008), whereas mice with a mutation of this gene exhibit cognitive impairment and accumulation of lipid peroxide in the brain (Nagai et al., 2003). A high level of expression of the *Klotho* gene was detected in the brain, which suggests that the *Klotho* gene is involved in the regulation of brain aging. This assumption is supported by the fact that the Klotho protein is involved in the regulation of neurogenesis in the brain of adult animals. The overexpression

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of the *Klotho* gene has been found to enhance neurogenesis at least in early adulthood, whereas Klotho-deficient brains undergo a rapid collapse of the hippocampal neurogenic niche (Laszczyk et al., 2017). It should be noted that accelerated aging of the organism is observed not only as a result of mutation of the *Klotho* gene but also accompanies a number of other genetic pathologies. Therefore, one of the approaches to the problem of aging is studying genetic pathologies leading to accelerated aging, such as the Hutchinson-Gilford progeria syndrome (HGPS), Werner syndrome (WS), and Down syndrome. This approach can also be used to investigate the neuronal mechanisms underlying normal and pathological brain aging (Isaev et al., 2018).

Brain neurogenesis in normal aging

Neurogenesis is the process of the formation of new neurons from their precursors – stem cells. Stem cells in various tissues are located in a special microenvironment – niche of stem cells. The concept of neurogenic niches is becoming widely accepted due to the growing evidence of the important role of the microenvironment created in the close vicinity of stem cells in establishing adequate control of cell proliferation, differentiation, and apoptosis (Pozhilenkova et al., 2017). All cells that are in the niches of stem cells and in their immediate vicinity affect the level of neurogenesis. The main components of the niche are mature neurons, neuronal progenitors, endothelial cells, ependymal cells, astrocytes, and microglia. This microenvironment is necessary not only for the normal functioning of the stem cells but also for the coordination of their behavior and interaction with the environment of the organism.

Neural stem cells (NSCs) transplanted beyond the neurogenic niche lose their ability for self-renewal and formation of new neurons (Suhonen et al., 1996). This is likely to happen because of the lack of necessary signals from the microenvironment (Apple et al., 2017). In adult primitive vertebrates, such as zebrafish, the zones of NSC niches are located along the entire rostrocaudal axis of the brain (Kizil et al., 2012). The ability of fish, frogs, and salamanders for regeneration in the brain is apparently associated with the presence of extensive germinative regions in their central nervous system (Tincer et al., 2016). In the brain and spinal cord of zebrafish, stem cells retain their ability to reactivate the molecular programs required for central nervous system regeneration (Ceci et al., 2019). However, in the adult mammalian brain, NSC niches are located only in the subventricular zone (SVZ) of the lateral ventricles and in the subgranular zone (SGZ) of the dentate gyrus of the hippocampus (Ming and Song, 2011). It should be noted that whereas the neurogenic ability of stem cells in SVZ niches in rodents is retained throughout the adult life, the formation of new neurons in SVZ in humans is greatly reduced 2 years after birth (Sanai et al., 2011; Conover and Todd, 2017). New neurons not only maintain the structural integrity and regeneration of brain tissue, but they are also necessary for learning and memory (Snyder et al., 2005; Aimone et al., 2006; Lledo et al., 2006). However, it should be noted that there is still a lot of controversy about the direct involvement of newly formed neurons in learning and memory. According to one hypothesis, neurogenesis is more crucial for more complex tasks, such as pattern separation and cognitive flexibility, rather than for direct learning and direct recollection. But undoubtedly, a reduction of neurogenesis in the adult brain results in the disruption of vital physiological processes (Cameron and Glover, 2015). Neurogenesis in mammals goes on throughout the entire life, but as the animals age this process is significantly diminished (Enwere et al., 2004; Ahlenius et al., 2009; Schouten et al., 2012; Cameron and Glover, 2015); however, the ability for synaptogenesis in newly formed hippocampal neurons varies little with age (Schouten et al., 2012). A number of studies have shown that a reduction in the level of hippocampal neurogenesis correlates with the development of deficiency in memory and learning (Drapeau et al., 2003; Driscoll et al., 2006). It should be noted that the administration of fibroblast growth factor-2 and heparin-binding epidermal growth factor to old mice restores the number of newly formed neurons in SVZ and SGZ to the level observed in young animals (Jin et al., 2003). In addition, an understanding of the age-dependent changes in proteostasis in the NSC pool could help identify ways to enhance the function of old NSCs and maintain the brain health. In the adult brain, the NSC pool comprises quiescent and activated populations with distinct roles. During aging, quiescent NSCs accumulate defects in their lysosomes, which leads to an increased formation of protein aggregates and the ability of NSCs for activation decreases. Restoring the lysosomal pathway in old quiescent NSCs helps clear cells from protein aggregates and improve the ability of NSCs to activate, allowing them to regain a more youthful state (Leeman et al., 2018).

The level of neurogenesis in old animals can be maintained by means of enriching their environment. In mice that lived in an enriched environment from age 10 to 20 months, adult hippocampal neurogenesis was fivefold higher than in the controls. Such cellular plasticity was observed in the context of significant improvements

in learning parameters, exploratory behavior, and locomotor activity. Mice that lived in an enriched environment also had a reduced lipofuscin load in the dentate gyrus, which indicates decreased nonspecific age-dependent degeneration. Therefore, signs of neuronal aging in mice can be diminished by a prolonged active and challenging lifestyle even if this stimulation started only at the middle age. The activity exerts not only a short-term but also a long-term effect on brain plasticity (Kempermann et al., 2002). These data support the hypothesis that the rate of aging is determined by a number of factors and in particular by psychological and social aspects of people behavior; these factors affect the brain, which, depending on the signals received, can accelerate or slow down the work of the aging program (Skulachev et al., 2014; Isaev et al., 2015).

It should be noted that recent studies have demonstrated that brain injury is capable of activating an endogenous program of neurogenesis that results in the replacement of neurons in various cerebral regions of rodents and primates (Yamashima et al., 2007). Brain ischemia may be an example of such injury. In ischemia, endogenous neural precursors located in different regions of the adult primate brain are differentially activated. In the adult macaque monkey brain, a limited endogenous potential for postischemic neuronal repair exists in the neocortex and striatum but not in the hippocampus *per se* (Tonchev et al., 2007). The authors believed that the presence of putative parenchymal progenitors and sustained progenitors in germinative centers provides new opportunities for precursor cell recruitment to sites of injury. The molecular manipulation of this process could make it possible to employ brain progenitor cells for the treatment of human neurological diseases. The possibility of stimulation of early stages of neurogenic response was also shown in a diffuse brain injury model (Bye et al., 2011).

Very interesting data have been obtained by studying cultured progenitor cells derived from murine SVZ. The authors have shown that primary NSC cultures from adult and old animals form fewer neurospheres than those from embryonic ones, but with prolonged cultivation this difference disappears. Moreover, aging results in the reduction of the proliferation of NSCs and their survival during their differentiation *in vitro*. However, with further cultivation, the remaining living cells have retained their ability to actively proliferate and differentiate. Thus, old NSCs can differentiate into functional neurons that are indistinguishable in their electrophysiological properties from neurons derived from NSCs of young animals (Ahlenius et al., 2009). These results demonstrate that the age-related mechanisms leading to a reduction in neurogenesis do not affect the morphofunctional properties of newly formed neurons. This is also confirmed by the fact that the density of dendritic spines in new neurons in young and old animals is the same despite the decrease in neurogenesis in the hippocampus of old mice (Morgenstern et al., 2008). At the same time, the pyramidal neurons of the cerebral cortex of old animals are characterized by not only age-related selective elimination of small, thin spines but also by a decrease in the density of axo-spine synapses (Dumitriu et al., 2010).

Apparently, unlike stem cells that can differentiate into other specialized cells (not neurons), the functions of NSCs of old animals are largely restored at the conditions *in vitro* (Ahlenius et al., 2009), which implies the influence of epigenetic factors on the formation of the age-related phenotype of these stem cells. Indeed, heterochronic parabiosis restores levels of IGF-I, growth hormone, Wnt3, transforming growth factor-β, or GDF11 in old mice and improves neurogenesis (Schultz and Sinclair, 2016).

Stem cells of the lateral ventricle of the brain are in contact with the cerebrospinal fluid and bloodstream that can affect the state of these cells. One of the negative regulators of adult neurogenesis and an inducer of microglial reactivity is the vascular cell adhesion molecule 1; its systemic blockade with antibodies prevents the inhibitory effect of the old environment on neurogenesis and microglial reactivity (Yousef et al., 2018).

Summarizing, the function of NSCs of old animals is largely restored not only when they are transferred to the conditions *in vitro* but also *in vivo*, when the animals are kept in the enriched environment or subjected to heterochronic parabiosis or the treatment resulting in the intensification of the lysosome work. This implies that the age-related mechanisms leading to a decrease in neurogenesis in normal aging do not affect the morphological and functional properties of newly formed neurons.

Brain neurogenesis in pathological aging: Alzheimer's disease (AD)

In the contemporary aging society, cognitive dysfunction is one of the most serious issues that need to be urgently addressed (Iwamoto and Ouchi, 2014). Aging of the brain can follow the pathological pathway with the development of AD. Diagnostic signs of AD arise very slowly and sequentially, as if the disease develops according to a specific program (Isaev et al., 2015). The population frequency of this disease steadily increases with age and comprises 0.7, 4.6, 16.5, and 18.2% in the age groups 60–69, 70–79,

80–89, and 90+ years, respectively (Kalyn and Bratsun, 1999). In contrast to normal aging, AD is accompanied by a progressive impairment of cognitive functions, synaptic degeneration, an increase in the expression of the active form of the apoptotic enzyme caspase-3 and procaspase-3 in the synapses, and the massive death of neurons (Louneva et al., 2008). Especially significant is the loss of neurons in the cerebral cortex, cerebellum, and cholinergic basal nuclei and degeneration of synaptic contacts (Bertoni-Freddari et al., 1996; Kerbler et al., 2014). The main initiators of cognitive impairment and synaptic degeneration followed by neuronal loss in patients with AD are currently believed to be the β-amyloid peptide and the hyperphosphorylated intracellular protein τ, the accumulation of which leads to mitochondrial damage and development of oxidative stress (Schmitt et al., 2012). Mass death of neurons in this neurodegenerative disease causes the disintegration of various parts of the brain and the complete disruption of its functions, whereas in normal aging the disruption of connections in the brain can be partially compensated by the delocalization of activity, i.e. by the involvement of additional brain regions in cognitive activities, which can significantly prevent the deterioration of cognitive abilities (Bishop et al., 2010).

In recent years, accumulated evidence has shown that the symptoms of AD may be partially associated with the impairment of the neuron's formation from NSCs, which is necessary to maintain the function of learning and memory (Li et al., 2016). However, a complete clarity about the changes in the process of neurogenesis in the human brain in AD is still missing. Rather contradictory data have been obtained in the animal models of this disease as well (Chuang, 2010). For most mouse AD models that are based on mutations of the APP protein, the precursor of the β-amyloid peptide, a decrease in neurogenesis has been shown, whereas in transgenic mice with different mutations of preselenin, neurogenesis could either increase or decrease (Zhao et al., 2008). Enriching the environment with various devices to provide extensive physical and learning activities (tunnels, houses, hammocks, stairs, boxes, and wheels) restores neurogenesis affected by the toxic action of β-amyloid peptide in animal AD models (Salmin et al., 2017).

It should be noted that the modeling of sporadic form of AD by the administration of streptozotocin into the lateral ventricles of the rodent brain (Mayer et al., 1990; Hoyer et al., 1994) is accompanied not only by the impairment of animals' ability to learn and memorize but also by a significant decrease in neurogenesis in the lateral ventricles of the brain and the hippocampus (Sun et al., 2015; Mishra et al., 2017). It is interesting that when modeling AD by administering β-amyloid peptide into the brains of old zebrafish, the activation of NSC proliferation and neurogenesis has been observed (Bhattarai et al., 2017). According to some data, in the hippocampus of patients with AD, there is an increase in cell proliferation as well, but this process is apparently associated with glial cells rather than neurogenesis (Boekhoorn et al., 2006). It is interesting that the dentate gyrus is the most resilient area of the hippocampus to many pathological conditions including AD (Parent et al., 2013).

Summarizing the available data, we can conclude that, despite the large amount of research performed in animal models of AD, it remains unclear how this pathology affects hippocampal neurogenesis (Martinez-Canabal, 2014). At the present time, possible approaches to AD therapy, such as transplantation of various types of stem cells, are being actively discussed and developed, but it is too early to talk about the actual progress made in this direction.

Brain neurogenesis in accelerated aging

Another form of pathological or rather accelerated aging is progeria, or the HGPS, in which the typical signs of aging begin to appear in early childhood. The average life expectancy of patients with this disease is 14.6 years (Gordon et al., 2003). In children with this pathology, growth retardation after birth, loss of subcutaneous fat, sclerotic skin with pigmentation spots, alopecia, atherosclerosis, and anomalies in the development of the skeleton are observed (Coutinho et al., 2009). The development of the disease is associated with a mutation of the *LMNA* gene on the chromosome 1 encoding lamin A, a fibrillar structural protein that is part of the nuclear lamina and is involved in the regulation of transcription in the cell nucleus. At the ultrastructural level, the nuclear lamina is a protein network adjacent to the inner membrane of the nuclear envelope and involved in maintaining the shape, size, and integrity of the nucleus and the pore complex of the nuclear envelope. Mutant lamin A, also called progerin, is capable of binding to the transcription factor NRF2 that is activated by the exposure of the cell to oxidative stress and induces the expression of antioxidant enzymes. Binding of NRF2 leads to a disruption of its transcriptional activity, which in turn causes chronic oxidative stress (Kubben et al., 2016). Despite accelerated aging, patients with HGPS do not have cognitive impairments and symptoms typical of AD (Ullrich and Gordon, 2015; Isaev et al., 2018).

It is possible that progerin is involved in the process of normal aging as well, as nuclei of fibroblasts from

old people express progerin and have defects similar to those in cell nuclei of patients with HGPS (Scaffidi and Misteli, 2006; Cao et al., 2007). Moreover, the content of this protein in the coronary vessels has been shown to increase with age (Olive et al., 2010; Graziotto et al., 2012).

There is currently no evidence of changes in neurogenesis in patients with HGPS. However, interesting results have been obtained in the modeling of this disease in transgenic mice expressing a mutation of the *LMNA* gene (Baek et al., 2015). The mutant progerin protein has been found in the skin, heart, brain, and kidneys of the animals, but the adverse effect of progerin in the brain has been less pronounced than expected. Although the synthesis of ATP by the mitochondria of fibroblasts of mice expressing progerin or prelamin A was significantly reduced, no such impairments were found in the mitochondria of the brain. Long-term expression of the mutant gene did not cause pronounced neuropathological defects despite serious disruptions in the ultrastructure of the nuclei of hippocampal neurons. A study of the process of neurogenesis in the brain of animals with *LMNA* gene mutation showed that the fractions of newly formed and immature neurons as well as the numbers of proliferating cells in the SGZ of the dentate gyrus of the hippocampus are similar in mutant and wild-type animals (Baek et al., 2015). The authors concluded that nerve cells are less sensitive to progerin expression, although it has a long-term effect on the adult organism.

It should be noted that, in comparison to peripheral tissues, neurons and glial cells in the murine brain have rather low levels of lamin A and its precursor prelamin A, whereas the C form of lamin is predominant. Moreover, in knockout mice expressing progerin in peripheral tissues, the level of this mutant protein in the brain is also very low and the regulation of its decrease at the transcriptional level is associated with brain-specific miR-9 microRNA (Jung et al., 2012; Nissan et al., 2012). Recent studies of induced pluripotent stem cells derived from patients with HGPS confirmed the absence of lamin A expression in neurons derived from these cells (Nissan et al., 2012). In addition, these studies showed that protection of neurons from the negative effect of progerin in HGPS is realized via a physiological limitation of expression of this protein by means of miR-9 microRNA.

To explain the selectivity of the manifestation of HGPS in different tissues, a hypothesis has been proposed that progeria syndromes manifest themselves mainly in tissues that are more susceptible to mechanical stress (for example, blood vessels and joints) or are necessary to maintain continuous growth (hair follicles and nails) and in which the replacement of cells and depletion of the pool of progenitors occur more rapidly. Therefore, diseases associated with tissues that are protected against mechanical stress (the brain) are mostly absent in HGPS. However, there are some facts that contradict this hypothesis. For example, there is practically no change in skeletal muscles in progeria (Halaschek-Wiener and Brooks-Wilson, 2007).

It is interesting that patients with HGPS have normal cognition and do not show signs of memory impairment or cognitive problems that are often observed during normal aging. However, vascular changes occurring in HGPS cause neurological disorders. Thus, although neuronal cells do not appear to be negatively affected by progerin expression, many patients with HGPS have problems such as headaches, muscle weakness, or convulsions resulting from circulatory disorders (Ullrich and Gordon, 2015).

Another disease with signs of premature aging is WS or 'adult progeria' caused by mutations of the *WRN* gene. This gene encodes a multifunctional nuclear protein with exonuclease and ATP-dependent helicase activities. The mean age of death is 40–50 years; the mean age of diagnosis is 15–20 years (Huang et al., 2006). Based on presently available limited data, it was suggested that the symptoms of accelerated aging in WS are much less pronounced in the brain than in other organs (Isaev et al., 2018). This is confirmed by the fact that WS patients exhibit premature aging predominantly in mesenchyme-derived tissues, but not in neural lineages, which may be a consequence of telomere dysfunction and accelerated senescence. Indeed, telomerase activity was found to be higher in neural progenitor cells (NPCs) than in mesenchymal stem cells derived from induced pluripotent stem cells. The activity of telomerase in normal NPCs and in NPCs from patients with WS did not vary significantly. Similarly, the length of telomeres in WS NPCs was comparable to that in normal NPCs. WS NPCs actively proliferate in cell culture and include bromodeoxyuridine at a speed similar to that of normal NPCs. In the cultures of WS NPCs, premature aging was not observed. Based on these data, there is no impairment of proliferation and telomere function in WS, which is consistent with the clinical phenotype of WS (Cheung et al., 2014). These data demonstrate that in pathologies associated with accelerated aging, NPCs and the whole brain are generally less affected than other tissues and organs.

Conclusion

Apparently, aging is not a simple accumulation of errors; rather, it is a gradual impairment of the work of a multifactorial program responsible for the prevention and repair

of the damages in genome, proteins, and lipids. Therefore, mutations of individual genes involved in the implementation of this program can cause pathologies manifested in accelerated aging. Human aging affects the entire organism; however, the above data demonstrate that the brain has a number of distinctive features and the age-related mechanisms leading to a decrease in neurogenesis do not have an effect on the morphological properties of the newly formed neurons. In addition, unlike other stem cells, the function of NSCs of old animals can largely be restored in conditions *in vitro* and *in vivo*. Probably, one of the factors that protect the brain during accelerated and normal aging is a low level of lamin A and its precursor prelamin A in neurons and glia. All of this suggests that the brain has additional antiaging systems; without them, normal aging could have a much higher rate.

Thus, the presented facts indicate that aging is not necessarily a permanent state but may be susceptible to treatment and that finding ways to interfere in the intrinsic cell machinery to slow down or even reverse this process will be the challenge for years to come (Katsimpardi and Lledo, 2018).

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