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Regenerative Potential of the Brain: Composition and Forming of Regulatory Microenvironment in Neurogenic Niches[1]

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Abstract—An important mechanism of neuronal plasticity is neurogenesis, which occurs during the embryonic period, forming the brain and its structure, and in the postnatal period, providing repair processes and participating in the mechanisms of memory consolidation. Adult neurogenesis in mammals, including humans, is limited in two specific brain areas, the lateral walls of the lateral ventricles (subventricular zone) and the granular layer of the dentate gyrus of the hippocampus (subgranular zone). Neural stem cells (NSC), self-renewing, multipotent progenitor cells, are formed in these zones. Neural stem cells are capable of differentiating into the basic cell types of the nervous system. In addition, NSC may have neurogenic features and non-specific non-neurogenic functions aimed at maintaining the homeostasis of the brain. The microenvironment formed in neurogenic niches has importance maintaining populations of NSC and regulating differentiation into neural or glial cells via cell-to-cell interactions and microenvironmental signals. The vascular microenvironment in neurogenic niches are integrated by signaling molecules secreted from endothelial cells in the blood vessels of the brain or by direct contact with these cells. Accumulation of astrocytes in neurogenic niches if also of importance and leads to activation of neurogenesis. Dysregulation of neurogenesis contributes to the formation of neurological deficits observed in neurodegenerative diseases. Targeting regulation of neurogenesis could be the basis of new protocols of neuroregeneration.

Keywords: neurogenesis in the adult brain, neurogenic niche, microenvironment, dysregulation of neurogenesis

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FEATURES OF NEUROGENESIS IN A POSTNATAL PERIOD

The complex process of morphogenesis is provided by the functioning of stem cells, which contribute to the maintenance of tissue homeostasis and cell regeneration in adult organism. For many years, it was thought, that the brain due to its structure, existence of connection, the complexity and diversity of neuron types, is an exception, and its cells are not renewed, and neural stem cells (NSCs) are presented only during embryonic development [27]. However, hypothesis of the presence of dividing cells in the central nervous system appeared in the early twentieth century, and J. Altman [3, 10] confirmed it in the 60s of the last century.

Neurogenesis in the adult mammalian brain occurs in two main zones, called neurogenic niches [10]. Neurogenic niche is a specialized microenvironment, which plays an important role in maintaining and regulating of neurogenesis [4, 60]. Neurogenic niche responds to activation of various mechanisms, and several cellular components are involved in its construction, the main of them is astroglia, immature and mature neurons. Adult neurogenesis in mammals, including humans, is distingiushed by two specific brain zones the lateral walls of the lateral ventricles (subventricular zone, SVZ) and the granular layer of the dentate gyrus of the hippocampus (subgranular zone, SGZ) [57]. NSCs are formed in these areas [33].

Adult neurogenesis repeats the entire process of neurons development in the embryonic stage [23]. Milestones of neuronal development are highly conservative during embryonic, early postnatal and adult neurogenesis [29]. The distinctive is significantly slower rate of maturation of neurons in the adult compared to embryonic development [68, 103]. The physiological significance of this longstanding development remains unknown, but the accelerated rate of maturation sometimes leads to anomalous integration of newborn neurons in the hippocampus of the adult brain [23, 68]. Subtypes of progenitor cells demonstrate substantial plasticity at the selection of cell fate [37]. It may be noted the similarity of critical periods in adult neurogenesis in the SVZ and SGZ as well. The survival of neurons has two critical periods: the first is at the intermediate (progenitor and neuroblast) stage

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[73, 83] and the second is at the immature neuronal integration stage [91]. Newborn neurons have enhanced synaptic plasticity, associated with glutamatergic transmission [29, 67, 80]. This increase of plasticity may provide new neurons with a competitive advantage against mature neurons for the selective formation and stabilization of afferent and efferent synapses [91, 94].

NEUROGENIC NICHES IN THE BRAIN OF ADULT MAMMALS

As previously noted, there are unique structure in the adult brain neurogenic niches that restrict active neurogenesis in two discrete zones [35, 76]. The major cellular components of neurogenic niches of adult brain are endothelial cells, astrocytes, ependymal cells, microglia, mature neurons and generation of adult neural progenitor cells.

The entire process of hippocampal neurogenesis is physiologically localized in the dentate gyrus. In addition, SGZ is enriched with a diverse nerve endings and is regulated by various neurotransmitters. In contrast, SVZ is not existed in the dense neural network and physically separated from the olfactory bulb, where integration of new neurons occurs [103].

SGZ is a thin layer of cells located between two layers of granule cells of the dentate gyrus and hilus. The main role of the SGZ is to produce new cells that can functionally integrate into the granular layer of the dentate gyrus. It mainly consists of primary excitatory neurons providing the memory function and learning [82, 103]. Development of the granule cells from NSCs is deriving through several intermediate stages [26]. First NSCs give rise to radial astrocytes (I cell type), which, in its turn, generate intermediate neural progenitor cells (the cell type D or of progenitor cells type II) [28]; the last mentioned cells are immature and differentiate into neuroblasts (III cell type). Neuroblasts can be divided into cells type D1 (immature) and D2 (more differentiated) [26, 103], gradually acquiring electrophysiological characteristics of granule neurons. For several days, the new neurons extend dendrites towards molecular layer and spread axons out to a CA3 field [104]. New neurons follow by stereotyped processes of synaptic integration into existing chain [29]. Compared with mature granule cells newborn neurons exhibit hyperexcitability and enhanced synaptic plasticity at certain stages of their development [29, 80]. After a long phase of maturation newborn neurons acquire basic electrophysiological properties, similar to mature neurons, although some differences remain [63].

Neurogenesis in SGZ occurs in parallel with an angiogenesis [69]. Endothelial cells serve as a template for NSCs, providing signals and causing the release of soluble factors that promote neurogenesis and angiogenesis [76].

The molecular mechanism, underlying the neurogenesis in the dentate gyrus, is not fully understood. It is obvious that transcriptional cascade of events controls specification of neuronal identity in the dentate gyrus [42, 88, 100], but the details of the expression nature and the function of each transcriptional factors remain unknown.

SVZ is located on the lateral side of the two lateral ventricles. The formation of the niches starts from neuroepithelial cell of embryonic zone of ventricular, where the radial glial proliferation occurs during development. As the SGZ, SVZ is characterized by a heterogeneous population of stem and progenitor cells [10]. There is neural stem cells (I) in SVZ, in a quiescent state. NSCs (type of cell B1 and B2) are slow-dividing precursor cells, which have the potential to self-renew and functions typical for astrocytes [19, 48]. They give rise to actively proliferating cells (II), representing intermediate progenitor cells in a transit stage of terminal differentiation (cell type C, or transit amplifying cells) [18]. Cells of type C differentiate into neuroblasts (III) (immature cell types, type A cells) [48], which migrate through the rostral migratory stream to the olfactory bulb, where they become mature granule cells [5, 53].

SVZ can be anatomically divided into three main structural domains. Domain I (wall of ventricle) contains ependymal cells [10], which are single-layer epithelium, lining the wall of the lateral ventricle. Recently it was shown that the NSCs (B1-type of cells) contain primary cilium, which acts as a sensor for different signals [31, 62, 84]. Since the primary cilium of NSCs protrudes into lateral ventricle lumen, it is thoroughly possibly that the cerebrospinal fluid may also contain important signals to control cell fate. Since the choroid plexus of the lateral ventricle is the main source of cerebrospinal fluid [39], the epithelial cells of the choroid plexus may also be considered as a cellular component subventricular niche. Domain II (below the wall of ventricle) contains the cells of type A, B, C, neuronal endings and other accessory cells. In domain III there are type B cells, which form endings to contact with the blood vessel [27]. Due to the anatomical location of SVZ stem cells are located inside the brain. On the one hand, they are in direct contact with the cerebrospinal fluid, on the other hand, they are tightly connected to blood vessels, forming a kind of "periventricular" blood-brain barrier (BBB). Thus, NSCs of SVZ are in direct contact with two different microenvironment [62, 78]. It is believed that periventricular has high permeability, facilitating the delivery of molecules, that regulate self-renewal and differentiation of cell types B and C. In addition to contact with the blood vessels, SVZ is also very close to the critical areas of the forebrain (basal ganglia, striatum), which contain GABAergic neurons capable of modulating the relationship between cortical and subcortical areas [45]. NSCs in the SVZ are separated from the caudate nucleus and

the striatum with only a layer of myelin and they are in close contact with the surrounding glia and blood vessels [4, 18]. This special situation in SVZ makes NSCs susceptible to the action of neurotransmitters, such as GABA [73], glutamate [73] ATP [2] and acetylcholine [102]. It is very possible that NSCs of SVZ may directly depend on the activity of neural networks [93]. For example, reduction of NSCs proliferation, observed in Parkinson's disease, is associated with loss of dopaminergic innervation of the SVZ [16].

The vascular network is also a component of the neurogenic niche, neural stem cells and transit amplifying cells are in direct contact with the blood vessels [69, 92]. Endothelial cells release the growth factors, which influence cell fate of NSCs [75, 81]. Astrocytes the most common cell type in the adult mammalian brain provide structural, metabolic and trophic support to neurons and modulate synaptic transmission. Astrocytes may also maintain the proliferation of NSCs and transit amplifying cells in the SVZ and differentiation of neuroblasts in vitro [51].

Some neuroscientists are of the opinion that in CNS of adult mammals the new neurons are formed not only in the SVZ. The presence of markers including label into the DNA of dividing progenitor cells, phenotypically similar to differentiate into neural cells of germinal zones, was demonstrated in the cerebral cortex, amygdala, striatum, substantia nigra. The intensity of neurogenesis in these structures is considerably lower than in the SVZ, olfactory bulb and hippocampus. However, for example, in the substantia nigra of mice the number of newly generated neurons is sufficient to complete renew of their population during the lifespan of the animal [25]. It is believed that neurogenesis in these regions is activated in pathological conditions.

FORMATION OF REGULATORY MICROENVIRONMENT IN NEUROGENIC NICHES OF THE BRAIN

Microenvironment, formed in the neurogenic niches, supports the maintenance of the NSCs population and regulates "decision making" by the cells to differentiate along the neuronal or glial lines through cell-to-cell interactions and microenvironmental signals [15, 30]. Paracrine regulation of cellular functions supports a variety of processes in the neurogenic niche of the brain [74]. Neurogenic niche almost completely braided with blood vessels, and cells in the vessels come into contact with the niche [17]. Vascular microenvironment in neurogenic niche integrated with signaling molecules, secreted from endothelial cells in the vessels of the brain or direct contact with these cells [30, 92]. The relationship between the NSCs and the vessels of the brain plays an important role in the early development of the nervous system and is maintained throughout the lifespan of mammals. Factors, secreted by endothelial cells, regulate not only proliferation and survival/self-renewal, but also differentiation and migration NSCs within niche. Many researchers have identified the effect of paracrine effectors of cerebral vessels at the NSCs in the niche, including vascular endothelial growth factor (VEGF) [81], epidermal growth factor (EGF) [20], the basic fibroblast growth factor (bFGF) [43], brain-derived neurotrophic factor (BDNF) [12, 81] and pigment epithelium-derived factor (PEDF) [75].

Factors, secreted by the endothelium, contribute to the development of neurons [72], while neural progenitors affect the properties of the BBB in the developing brain [97]. Contactless co-culture of endothelial cell with embryonic cortical NSCs have shown the bidirectional effects increased self-renewal of stem cells and neurogenesis with one-time suppressing their differentiation and stimulation BBB formation [97]. It is believed, that intact endothelial secreted factors support stem/progenitor cells of the brain in immature state, but the damaged endothelial cells contribute to migration of neurons and differentiation [72]. Clustering neural progenitor cells, which provide the appropriate level of regulatory molecules and metabolites [98] within the local neurogenic microenvironment, may be important not only for reparative neurogenesis, but also for physiological events, which depend on neurogenesis (e.g., memory consolidation).

The accumulation of astrocytes in the neurogenic niches stimulates the activation of neurogenesis [101]. The effect of cytokine-activated astrocytes on neurogenesis and synaptogenesis was described [14]. Formation joint astroglial network, in which cells are associated with each other by connexin channels, is the basis for generating a local microenvironment, that maximize proliferation of cell clusters in neurogenic niches [1]. On the one hand, neurogenic potential of astroglial cells ensures the implementation of the neurogenesis program in the embryonic and adult periods of ontogenesis, the formation of the microenvironment in the neurogenic niches and migration streams for the new generated cells [65]. On the other hand, astrocytes together with microglial cells play an important role in the local production of gliotransmitter (serine, glutamate, ATP) and cytokines (interleukins, growth factors) [11].

One of the transmitters D-Serine stimulate hippocampal neurogenesis [89] and regulates proliferative activity of NSCs [34]. Disturbance of serine production due to a genetic defect of the product 3-phosphoglycerate dehydrogenase, which expressed in astrocytes and serves to synthesis of L-serine, transported further in neurons [24], leads to disruption of neurogenesis [40].

ATP, performing the function of neuro- and gliotransmitters, interacts with purinergic receptors, expressed by cells in neurogenic niches. An additional source of ATP is stem cells themselves [22]. It is show

in particular, that the activation of P2Y1 and P2Y2 receptors enhances the proliferation of progenitor cells, stimulated by growth factors [102]. Overall, ATP is a mitogenic signal to the cell, which participate in the neurogenesis process [52], but, as a rule, we are talking about the combined effect of ATP and polypeptide growth factors, necessary and sufficient to achieve the mitogenic effect. Taking into account that the amount of extracellular ATP increases significantly diring damaging cells (ischemia, hypoxia, neuroinflammation), the effects of the transmitter in relation to cells of neurogenic niches can acquire particular importance in the implementation of the cerebral reparative capacity.

Astrocytes regulate bioavailability of glutamate, which is released into the extracellular space by neurons and is captured by astroglial cells. Glutamate affects the proliferative and differentiation potential of brain cells [79], showing mainly effective for stimulating neurogenesis and this effect is not only to processes in adult brain but also in respect of embryonic neurogenesis [90].

Thus, the formation of the microenvironment, necessary for the implementation of complex events during neurogenesis, is provided by all cells, component of the structure of neurogenic niches, and endothelial cells of surrounding blood vessels and astrocytes belongs a special role in this context [30, 56].

IMPORTANCE OF NEUROGENESIS IN THE ADULT BRAIN: NEUROGENIC AND NON-NEUROGENIC FUNCTION

Hippocampal neurogenesis is necessary for the formation and maintenance of memory, especially in the early period [36, 86]. The increase in hippocampal neurogenesis is accompanied by improved performance in cognitive tests [77]. Neurogenesis in the hippocampus is a key factor in the gradual extinction of long-term potentiation phenomenon [44]. It has been shown, that the reduction of neurogenesis is accompanied by long period of hippocampus-dependent memory of associative fear. It is believed, that this mechanism plays a role in the removal of unneeded old memory traces to preserve the ability to learn [99].

The functional role of the NSCs, located in the SVZ, is still controversial. As already noted, the newgenerated cells in SVZ migrate along the rostral migratory stream to the olfactory bulb, where they are integrated as the interneurons in the granular layers and glomerular cells. The process is important for the maintenance and reorganization of the olfactory system [36]. The integration of new neurons in the olfactory bulb and dentate gyrus is different. Thus, in the olfactory bulb neurogenesis contributes to the maintenance and reorganizing the whole system, while in the dentate gyrus new neurons integrate for modulation of existing neural networks [36]. Neurogenesis in SVZ of the adult brain does not play a role in preserving the memory of the difference between odors and congenital olfactory preferences [36], but at the same time, it participates in the consolidation of long-lasting olfactory traces [46]. The increase in survival of newborn granule cells leads to better differentiation of related odorants [64]. Recent studies have demonstrated that for the more complex and subtle distinctions of scents modulation of neuronal survival of newborns is necessary [57]. In the past few years it has been found non-neurogenic functions of NSCs in the brain. It was shown, that neuroblasts derived from neurogenic niches exhibit phagocytic activity against apoptotic neuronal precursors. This activity is critical in maintaining neurogenesis in the brain [55].

Apoptotic newborn cells come under elimination by phagocytosis of microglia cells, which are located in the SVZ. Microglia play an important role in maintaining homeostasis of niches [83]. Also, it was shown that NSCs modulate activation of microglia, proliferation, and phagocytosis by secretion of VEGF [66]. It has recently been described another "homeostasis" NSCs function: hypothalamic neurogenesis in adult mice plays an important role in the control and regulation of energy balance and weight [49].

Newborns neuroblasts in the SGZ regulate stress reactivity dynamically as at the endocrine and behavioral levels through regulation of the hypothalamic-pituitary-adrenal system [87]. These data generally support the concept that NSCs besides neurogenesis have a wide range of nonspecific non-neurogenic functions, aimed at maintaining brain homeostasis [58].

DYSREGULATION OF NEUROGENESIS DURING NEURODEGENERATION

Universal factor in neurodegeneration is damage of neurogenesis process. It is characteristic for cerebral development and plays an important role in the initiation and progression of a neurodegenerative process [59]. Chronic neurodegeneration has different implications for stem cell proliferation, migration, survival and functional integration.

Studies, conducted in various animal models of disease, convincingly demonstrated that SVZ and SGZ may respond to adult brain damage by producing new precursors cells and their subsequent migration to the damaged area. In epilepsy, multiple sclerosis and stroke increase the regulation of progenitor cells production, the level of cytokines and migration proteins in the SVZ leads to an increase in the number of neurons "adult" origin. In contrast, in Alzheimer's and Parkinson's diseases the number of proliferating cells decreases in SVZ [50].

Neurogenesis increases after some acute pathological conditions, including post-stroke, epileptic attacks or acute injury [70]. Neurodegenerative dis-

Features of neurogenesis in acute and chronic neurodegeneration

Type of neurodegeneration	Violation of neurogenesis mechanisms
Perinatal hypoxia/ischemia (acute neurodegeneration of developing brain)	Increase regulation of progenitor cell production, cytokine level and migration protein in the SGZ lead to increases the number of "adult" origin neurons, i.e. to the stimulation of neurogenesis
Cerebral ischemia (acute neurodegeneration of young and mature brain)	
Parkinson's disease (chronic neurodegeneration of mature brain)	Reduced neurogenesis in the SVZ. After the destruction of the nigrostriatal pathway some of SVZ precursors begin to express tyrosine hydroxylase and neuronal markers (neurogenesis of dopaminergic neurons in the SVZ), neurogenesis of dopaminergic neurons can also occur in the substantia nigra
Alzheimer's disease (chronic neurodegeneration of mature brain)	At the early stages of degeneration stimulation of neurogenesis, increased number of progenitor cells and their proliferative activity; at the later stages of degeneration the suppression of neurogenesis
Autism (chronic neurodegeneration of developing brain)	Dysregulation of neurogenesis (the intensification of proliferation during disturbances of cell migration), which leads to disruption of brain cytoarchitectonics

eases are chronic and slowly progressing process. Neurons in neurodegenerative diseases are affected at the level of synaptic transmission, synaptic contacts, axons and dendrites. Furthermore, the number of functional neurons in neurogenic regions are reduced and neurogenesis are damaged. It is known, that the brain regions vary in its resistance to aging. Some regions are very sensitive to age and neurodegenerative changes, these include the dentate gyrus of the hippocampus, subiculum [85] and olfactory bulb [8].

Numerous studies have shown that neurogenesis rate in the SVZ and SGZ decreases with age; this allows to explain memory impairment and cognitive disorders in the elderly [41]. The study neurogenesis in the brain of Alzheimer's patients showed increased expression of markers of immature neurons [38], but these observations were challenged in recent years [6]. Other results indicate that with age in Alzheimer's disease there is a significant reduction in the degree of proliferation of progenitor cells and their amount [9].

The difficulty of understanding neurogenesis in Alzheimer's disease is that it is necessary to consider many variables that influence the process. Most studies that investigate neurogenesis in the hippocampus or in the SVZ of transgenic mice, expressing the APP gene mutation, show proliferative disorder progenitor cells and/or disturbance of neuronal differentiation. Thus, in these animals was observed decrease in the number of new cells and the number of surviving cells in the SGZ. These abnormalities were apparent in the age of one year after the start of the formation of amyloid plaques, but not in the earlier two months age [21, 47].

Study of new neuroblasts showed a decline their amount in subgranular layer simultaneously with the increase in their number in the granular layer. It underlines the need to concrete analysis of specific brain regions in the evaluation of the number of new generated cells in the hippocampal microenvironment, as well as the need for specific markers of cell lines for a thorough analysis of neurogenesis. Injection of β-amyloid in the lateral ventricle decreases cell proliferation in the SVZ for the next 5 days [32]. It was shown that abnormal oligomeric forms of β-amyloid increases neuronal differentiation of embryonic and postnatal cells in vitro [54]. S. Mirochnic et al. (2009) found an increase in cell proliferation in the hippocampus of transgenic mice with Alzheimer's disease, but eventually reducing the number of new differentiated neurons [61]. Profound changes of adult neurogenesis processes in transgenic animal models of Alzheimer's disease have been shown by others [13, 21, 32, 47, 54, 61, 71, 95, 96].

Dysregulation of neurogenesis contributes to the formation of neurological deficits observed in neurodegenerative diseases. Features of neurogenesis in various forms of acute and chronic neurodegeneration are shown in table.

Analysis of neurogenesis in the adult brain is the ability to analyze the biology of neural stem cells in the

pathological environment and targeted regulation of neurogenesis can be the basis of new neuroregeneration protocols.

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