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REVIEW

Regulation of neurogenesis and cerebral angiogenesis by cell protein proteolysis products

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Annotation. Brain development is a unique process characterized by mechanisms defined as neuroplasticity (synaptogenesis, synapse elimination, neurogenesis, and cerebral angiogenesis). Numerous neurodevelopmental disorders brain damage, and aging are manifested by neurological deficits that are caused by aberrant neuroplasticity. The presence of stem and progenitor cells in neurogenic niches of the brain is responsible for the formation of new neurons capable of integrating into preexisting synaptic assemblies. The determining factors for the cells within the neurogenic niche are the activity of the vascular scaffold and the availability of active regulatory molecules that establish the optimal microenvironment. It has been found that regulated intramembrane proteolysis plays an important role in the control of neurogenesis in brain neurogenic niches. Molecules generated by the activity of specific proteases can stimulate or suppress the activity of neural stem and progenitor cells, their proliferation and differentiation, migration and integration of newly formed neurons into synaptic networks. Local neoangiogenesis supports the processes of neurogenesis in neurogenic niches, which is guaranteed by the multivalent action of peptides formed from transmembrane proteins. Identification of new molecules regulating the neuroplasticity (neurogenesis and angiogenesis). i.e. enzymes, substrates, and products of intramembrane proteolysis, will ensure the development of protocols for detecting the neuroplasticity markers and targets for efficient pharmacological modulation.

Key words: brain, neurogenesis, cerebral angiogenesis, stem cell, progenitor cell, regulated intramembrane proteolysis

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Регуляция нейрогенеза и церебрального ангиогенеза продуктами протеолиза клеточных белков

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Аннотация. Развитие головного мозга представляет собой уникальный процесс, характеризующийся механизмами, определяемыми как нейропластичность (синаптогенез, элиминация синапсов, нейрогенез, церебральный ангиогенез). Многие нарушения развития головного мозга, повреждение головного мозга, а также старение проявляются неврологическим дефицитом, в основе которого — аберрантная нейропластичность. Присутствие стволовых и прогениторных клеток в нейрогенных нишах головного мозга обеспечивает образование новых нейронов, способных интегрироваться в предсуществующие синаптические ансамбли. Определяющими факторами для клеток нейрогенной ниши являются активность сосудистого скаффолда и наличие активных регуляторных молекул, формирующих оптимальное микроокружение. Установлено, что внутримембранный регулируемый протеолиз играет важную роль в контроле процессов нейрогенеза в нейрогенных нишах головного мозга. Молекулы, генерируемые за счет активности специфических протеаз, могут стимулировать или подавлять активность стволовых и прогениторных клеток, их пролиферацию и дифференцировку, миграцию и интеграцию вновь образованных нейронов в синаптические ансамбли. Локальный неоангиогенез поддерживает процессы нейрогенеза в нейрогенных нишах, что гарантируется мультивалентным действием пептидов, формирующихся из трансмембранных белков. Идентификация новых молекул-регуляторов процессов нейропластичности (нейрогенез и ангиогенез) из числа ферментов, субстратов и продуктов внутримембранного протеолиза обеспечит разработку протоколов регистрации процессов нейропластичности и эффективной фармакологической модуляции.

Ключевые слова: головной мозг, нейрогенез, церебральный ангиогенез, стволовые клетки, прогениторные клетки, регулируемый внутримембранный протеолиз

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Neurogenesis and brain plasticity

The brain development is associated with a wide range of cellular and molecular events that determine the neuroplasticity phenomenon. An important role in brain plasticity is played by stem and progenitor cells, which are the base to the cells of neuronal, astroglial and oligodendroglial nature. Stem cells are known to have two basic fundamental properties:

1) self-renewal, which is necessary to maintain a pool of stem cells ready to receive a signal from the microenvironment to proliferate; 2) multipotency, in which the stem cell forms progenitor cells that can differentiate into other cell types. These events occur within clonogenic niches that form the optimal microenvironment for the survival and development of stem and progenitor cells. The concept that stem cells are located in specialized niches was first proposed in the 1970s [1], but only in the 2000s the significant progress in describing both the cellular components of the niches and their functional interactions in various tissues was made [2].

Neurogenesis in mammals is defined as the process that leads to the generation of functional neurons from neural stem cells (NSCs). This process includes the maintenance of stem cells' pool, their entry into the cell cycle, proliferation, differentiation and migration of descendants of stem and progenitor cells, integration of newly formed neurons into pre-existing synaptic ensembles [3]. NSCs and progenitor cells (neural progenitor cells, NPCs) have a fairly high regenerative potential, since they are able to differentiate into three types of CNS cells which are neurons, astrocytes, and oligodendrocytes, but they are, also, a very vulnerable cell population in brain pathology and physiological aging [4—6].

During the embryonic development of mammals, the neural tube consists of a single layer of neuroepithelial cells that can undergo division. In embryonic neurogenesis, neuroepithelial cells can follow a symmetrical division, forming two daughter cells. With further development, the neuroepithelial cells begin to suppress their epithelial properties, and a gradual acquisition of glial properties occurs that eventually become a homogeneous population of radial glia. Radial glial cells are a pool of NSCs with glial phenotype present in the developing brain and preserved in the sub-ventricular (SVZ) and sub-granular (SGZ) zones of the postnatal and adult brain [7], progenitor cells actively proliferate and differentiate. Radial glial cells undergo asymmetric differentiating division, generating a new radial glial cell and a basal progenitor cell [8, 9]. It was found that the basal progenitor cell further divides symmetrically to generate two neuroblasts and eventually differentiates into neurons [10].

In the postnatal development period, the main contribution to neurogenesis is made by populations of stem and progenitor cells located within neurogenic niches, where, due to the microenvironment formed by endothelial and astroglial cells, they can give rise to new neurons. Both in the embryonic and postnatal periods of the body's development, the processes of neurogenesis are closely associated with the mechanisms of cell death (apoptosis), especially at the stage of progenitor cell proliferation.

Currently, it is generally accepted that neurogenesis in the embryonic development period is important for the formation of brain structures, while neurogenesis in the postnatal period is relevant to neuroplasticity: the appearance of new neurons is crucial for the formation of memory with sufficient resolution, learning and emotions. The neurogenesis intensity at different stages of postnatal development can differ significantly, moreover, there is still no consensus about the intensity of postnatal neurogenesis in higher primates and humans. At the same time, the influence of various factors (physical, chemical, biological, including social) on neurogenesis, as well as its disorders in the development of a wide range of diseases of the central nervous system, is indisputable in modern neurobiology and neurology.

Methodological aspects of recording the intensity of neurogenesis *in vitro* and *in vivo*

The study of neurogenesis in the embryonic and adult brain is one of the actively developing areas of modern neuroscience. Methodologically, this is associated with some difficulties, which is due to both the low availability of methods for visualization of events in neurogenic niches in vivo, and the variability of the neurogenesis process under the influence of a large number of external factors affecting the processes of cell proliferation and differentiation.

The most common method of labeling dividing cells involves registering the inclusion of a molecular

probe in the replicating DNA during mitosis. Previously, 3H-thymidine was used for this purpose, which allows radiographic tracking of cells in the tissue, in the 1990s BrdU (bromodeoxyuridine) was first used, later -IdU and ClдU (iodide and chloride equivalents of uridine, respectively), which allowed the immunohistochemical identification of newly formed cells [11].

NSCs/NPCs phenotyping in brain tissue samples or in in vitro culture is performed by evaluating the expression of a large spectrum of molecules (Table 1).

Table 1

Major markers expressed by neural stem cells

№	Marker	Brief description	Reference
1	Nestin	Neuroepithelial stem cell protein that is expressed in NSCs and disappears upon differentiation. It is essential for the survival and self-renewal of NSCs.	[92]
2	Sox2	Transcription factor, has high expression in embryonic stem cells and NSCs of the adult brain during development, as well as in cells that differentiate along the glial pathway.	[93]
3	Notch1	Transmembrane receptor that regulates the formation, migration, and differentiation of neuronal cells.	[3]
4	HES1 and HES3	Transcription factors that support symmetric stem cell division.	[94]
5	Vimentin	Intermediate filament protein that is expressed in glial cells (radial glia, immature astrocytes).	[3]
6	PAX6	Transcription factor that has the ability to determine the development path of cells of a neural nature.	[95]
7	GFAP	Glial fibrillary acidic protein known as a marker of astrocytes and radial glial cells.	[96]
8	Mash1	Transcription factor required for embryonic neuronal differentiation.	[97]
9	GLAST and GLT1	Glutamate transporters are markers of glial cells.	[98]

«Silent» and activated NSCs/NPCs can be phenotyped by the presence of the following antigenic composition: In SVZ, «silent» NSCs have the following expression profile — GFAP+CD133+Nestin-, activated NSCs -GFAP+CD133+Nestin+, and express monocarboxylate transporters MCT1 for active lactate transport. In SGZ, «silent» NSCs have an expression profile of GFAP+Nestin+PCNA -, activated NSCs — GFAP+(–)+Nestin+PCNA++, and have a low level of MCT1 expression due to glycolysis which is already suppressed in them (compared to «silent» cells) and reduced lactate production [12]. Slowly dividing NSCs (so-called the 1st type of cells corresponding to the radial glia, and having two morphological subclasses, one of which is cells with horizontal processes which are known for active proliferation) is characterized by the expression of Pax6 and the absence of expression of NeuroD1, whereas amplifying progenitor cells (the so-called 2nd type cells) are characterized by the simultaneous expression of Pax6 and NeuroD1, while NeuroD1 is co-expressed with Tbr1 on progenitor cells of the 3rd type, which are mitotically active, but express markers of neuronal differentiation [13]. It is noteworthy that morphologically different NSCs may respond differently to mitogenic stimuli (for example, activation of Notch signaling) [14]. It is believed that the neurogenesis suppression in aging is associated with an increase in the relative number of «silent» NSCs and the depletion of their activation resources [15].

During the development from radial glial cells to mature neurons, the expression of various marker proteins, as well as the morphology and cells' activity, change significantly. In particular, in the SGZ of hippocampus, the cells belonging to the NSCs/NPCs group are characterized by the expression of GFAP, Sox2, NeuroD, PSA-NCAM, Nestin, Pax6, have a rounded shape, and do not have electrical excitability. Neuroblasts continue to express NeuroD, PSA-NCAM, DCX expression appears in them, processes are formed,

they show a high level of electrical excitability, and GABA causes an excitatory effect in them. In immature neurons, which demonstrate the ability to migrate, DCX, NeuN, Prox1 are expressed, and their dendrites reach other regions of hippocampus, electrophysiological properties of inter-hippocampal cells' integration appear, GABA begins to show inhibitory activity, and glutamate — stimulating, in these cells the first recorded expression of genes immediate early response (c-fos, jun, Arc, Homer1), which corresponds to the cell response to the stimulating neurotransmitters' effect. In mature neurons, NeuN, Prox1, and calbindin are expressed, the dendrites have a large degree of branching, stably active synapses are formed, all the characteristics of synaptic plasticity are manifested, and the cells respond with the gene expression for an immediate early response to stimulation [16].

Assessment of neurogenesis in vitro can be performed by using real-time cell proliferation analysis technologies, for example, using xCelligence technology [17], but such results should be compared with immunophenotyping data.

A significant limiting factor in the neurogenesis assessment is the difficulty in registering it in vivo. To overcome this limitation, various approaches have been suggested, in particular, positron emission tomography, magnetic resonance imaging, functional magnetic resonance imaging, and magnetic resonance spectroscopy, each of which has its own advantages and disadvantages [18—20].

Neurogenic brain niches

In the adult mammalian brain, neurogenesis is very limited and continues throughout life in the neurogenic niches of two regions: the subventricular zone (SVZ) of the lateral ventricles (LV) and the subgranular zone (SGZ) of the dentate gyrus in the hippocampus [21, 22].

In the SVZ of the adult brain, GFAP-expressing astrocytes are a population of NSCs (so-called B/B1 cells), with B-cells interacting with blood vessels. Formed neuroblasts and immature neurons migrate in mammals (not in higher primates) along the rostral migration pathway to the olfactory bulbs, where they differentiate into mature neurons and remain within the granular and periglomerular layers. It is noteworthy that in higher primates, immature cells also migrate from the SVZ, but most likely they are focused on filling in structural defects in areas of brain damage [23].

In the SGZ of hippocampus of the adult brain, GFAP+Nestin+Sox2+ radial glial (RGL) cells (1st type) are «silent» NSCs which activation leads to the formation of progenitor cells (type 2a, type 2b). Stem and progenitor cells develop to immature neurons (type 3) migrating to the inner granular layer of the dentate gyrus, where they differentiate to mature granular cells. New neurons, characterized by increased excitability, direct their dendrites to the molecular layer and project axons to the CA3 hippocampus' subregion, which ensures their full functional integration, which, starting from the NSCs activation process, can take, according to various data, from 2 to 6 weeks [24]. It is important to note that the formation of type 3 cells (immature neurons) significantly intensifies the process of apoptosis (about 1—2 weeks after the activation of NSCs), which is important for controlling the population of newly formed neurons.

It should be noted that an important difference between immature and mature neurons formed in the dynamics of neurogenesis is their response to the action of GABA. It is known that in the prenatal period, GABA is an excitatory neurotransmitter for the brain neurons, but in the intranatal period, due to the effects of oxytocin, which concentration increases significantly during childbirth, there is a «switch» of the excitatory effect of GABA to an inhibitory one, which persists throughout the life of the body. However, the response of neuroblasts and immature neurons in neurogenic niches also demonstrates the excitatory effect of GABA, which, as in the case of prenatal development, is due to the expression properties of the chlorine transporters NKCC1, KCC2 [25, 26].

A number of experimental studies have shown that various factors and signals regulate the formation, division and migration of progenitor cells, in particular, neurotransmitters, neuropeptides, hormones, cytokines, external stimuli that initiate the processes of learning,

remembering, expressing emotions, as well as complex behaviors and the body's stress response [26—29]. At the same time, there is increasing evidence that the adult mammalian brain contains other neurogenic niches that can generate new neurons and glial cells, especially after damage or after some inductive stimuli, for instance, in areas of increased permeability of the blood-brain barrier (in ischemic brain damage), in some brain regions where cells with proliferative potential are preserved (e.g, in hypothalamus, amygdala, cerebellum) [30—33]. No less significant may be the contribution of neurons with prolonged immaturity, which are found in the cerebral cortex throughout the life of mammals and, potentially, can participate in the formation of new cells of a neuronal nature [34, 35], as well as astrocytes of the brain parenchyma (cortex, striatum), which conversion to stem cells has been experimentally proven [36, 37]. At the same time, the observations that call into question the significance of the neurogenesis processes in the adult human brain cannot be ignored: it is possible that the formation of new neurons is almost completely suspended after the age of 7—13 years [38, 39].

An important component of neuroplasticity is cerebral angiogenesis, which ensures the formation of so-called vascular scaffold for developing neuronal and glial cells, while structural and functional integrity of the endothelial layer dictates the properties of neurogenesis in the neurogenic niches: in the SVZ increased permeability of the blood brain barrier (e.g., due to a lower coverage of the endothelium and pericytes dendrites of perivascular astroglia) is necessary for secretion of growth factors and other regulatory molecules to the niche, whereas in the SGZ, the permeability of the wall of the cerebral microvessels is significantly lower, and the main part of the humoral factors regulating neurogenesis is secreted locally [40, 41].

It is known that cerebral neoangiogenesis is induced after undergoing ischemic brain damage [42] and during neurodegeneration [43], and the permeability of such newly formed vessels is increased, which is probably responsible for the formation of new sites of neurogenesis in the damaged brain, for example, in the wall of the 3rd and 4th ventricles [33]. Later, it was shown that these events are connected to active mechanisms, utilizing Notch signaling: endothelial cells and pericytes of the cerebral microvessels begin expressing of the ligand of Notch receptor — Delta-likeligand –4 (DLL4) — in response to the high level of vascular endothelial growth factor (VEGF) in systemic circulation that leads to the activation of mitotic NSCs and start the process of neurogenesis in the walls of the brain ventricles [44]. It is obvious that neoangiogenesis plays an equally important role in the brain development and in the realization of neuroplasticity: for instance, insulin-like growth factor-1 (IGFR-I) and vascular-endothelial growth factor (VEGF) stimulate both neurogenesis and cerebral angiogenesis during physical and cognitive load [45—47].

The mechanisms of vascular development are based on the divergence of the key properties of the cerebral endothelial cells (tip cells expressing DLL4 and stalk cells expressing the Notch receptor in response to VEGF), this provides the migration, proliferation and differentiation of cells with angiogenic potential to the brain tissue, controlled by the activity of Hes/Hey transcription factors in the cells [48]. In other words, VEGF acts in this context as an important regulator of angiogenic sprouting, being secreted by endothelial cells, astroglia, and neurons in areas of intensive neoangiogenesis, e.g., due to the activity of hypoxia-inducible factor-1 (HIF-1) [48].

An increase in the local concentration of lactate as a product of the metabolic activity of astrocytes in the neurovascular brain unit [49] and the effect of some «non-classical» proangiogenic factors, such as β-amyloid (Aß), may be equally relevant [50]. Endothelial tip cells are characterized by a high level of VEGFR receptors of the second type (VEGFR2) expression compared to the receptors of the first type (VEGFR1 or Flt1), which distinguishes them from the stalk cells following them in the growing vessel [48]. The soluble form of VEGFR1 exhibits an antiangiogenic effect, which is associated with the activity of Wnt signaling initiated by the interaction of the Wnt ligand with the transmembrane receptor of the Frizzled family, followed by the activation of gene transcription via β-catenin migrating to the cell nucleus

[51]. In general, the contribution of mechanisms associated with the activation of angiogenesis and the formation of a vascular scaffold in neurogenic brain niches is so significant that it is known how it is necessary to reconstruct such a scaffold when modeling the neurogenic niche in vitro [52], as well as for the formation of functionally competent brain organoids from induced pluripotent stem cells (iPSCs) [53]. Partially similar problems are solved when creating spheroid models of the blood-brain barrier and the neurovascular brain unit [54].

At the same time, it is still unknown what determines the fate of stem and progenitor cells in the neurogenic niche, how the processes of neurogenesis and cerebral angiogenesis are coordinated with each other. It is obvious that the action of various factors that stimulate (enriched multi-stimulus environment, cognitive training) and suppress (stress, lack of nutrients) neurogenesis ultimately leads to dynamic changes in transcriptional activity in NSCs/NPCs and the parameters of the functioning of vascular scaffold cells in the neurogenic niche.

Proteolysis of cellular proteins and regulation of neurogenesis and cerebral angiogenesis

Over the past two decades, the attention of researchers has been drawn to the mechanisms of formation and implementation of the effects of proteolysis products of membrane proteins. Together, these mechanisms relate to the phenomenon of so-called regulated intramembrane proteolysis (RIP), which provides the generation of peptides with different biological activity. RIP is implemented in cells due to the activity of intramembrane enzymes (presenilin, S2P protease, rhomboid serine protease), other proteases (e. g., sheddases, which generate extracellular fragments of transmembrane proteins), the target of which is transmembrane proteins with different topologies, and the result of the action is the generation of extracellular and intracellular fragments of peptides [55, 56]. The enzyme complex (γ-secretase) consists of 4 proteins (presenilin, nicastrin, Aph-1, Pen-2), the result of this complex is the formation of peptides that can be translocated into the cell nucleus and initiate gene transcription, or bind to other proteins in the cytosol and participate in signal transduction [55]. For now, the role of γ-secretase in (patho) physiology of the embryonic and adult brain (brain development, the mechanisms of synaptic plasticity) is well studied [57, 58]. For instance, suppression of the activity of γ-secretase results in an intensification of NPCs differentiation (β-catenin-dependent form) in vitro [59].

The substrates for RIP enzymes can be the Notch receptor (generated in cells as a result of its binding to the ligands Delta or Jagged and the activity of metal proteinases), the VEGFR-1 receptor (VEGFR1), the amyloid precursor protein (APP), the IGF-I receptor (insulin-like growth factor-I receptor — IGF-IR), the epidermal growth factor receptor (Erb4), cadherins, CD44, other diverse receptor protein kinases, such as VEGFR3, FGFR4, TRKA, MUSK, MER, TYRO3, EPHA2, EPHA5, EPHA7, EPHB3, EPHB4, and EPHB6, and other molecules [55, 60, 61]. In particular, it was found that presenilin catalyzes intramembrane and intracellular proteolys Notch and APP, which is important for the generation of biologically active fragments of these peptides released into the extracellular space (Nß, Aß) or migrating to the cytosol and the cell nucleus (Notch intracellular domain — NICD, Amyloid precursor protein intracellular domain — AICD), as well as participates in the proteolytic degradation of beta-catenin in Wnt signaling [62, 63].

In Notch proteolysis NICD is formed, which moves to cell nucleus and interacts with DNA-binding protein CSL (which, in the absence of NICD is in a complex with the histone-deacetylase HDAC1 and suppresses the transcription of the respective gene) and Mastermind protein starts the transcription of genes, particularly c-Myc, cyclinD1, p21, IL-4, as well as Hes and Hey, which encode transcription factors, preventing differentiation and preserving a pool of NSCs [64]. During the proteolysis of APP, AICD is generated, which translocates into the cell nucleus and, being stabilized in the cell due to interaction with the protein Fe65 or due to the formation of a complex with histone-acetyltransferase Tip60, regulates the

expression of genes, in particular, GSK3ß, p53, Hes1, LRP1, etc. [65].

It was found that Hes1 and Ascl1 gene expression oscillations characterize the conversion of «silent» NSCs into active stem cells entering the cell cycle: high Hes1 expression and low Ascl1 expression characterize the «resting» state of brain stem cells [66, 67]. Taking into account that Ascl1 plays an important stimulating role in Wnt signaling, and Hes1 acts as a Notch effector molecule, it is not surprising that Wnt/Notch signal transduction determines the future fate of NSCs/NPCs, in particular, their development along the neuronal or glial pathway [68]. In general, Notch signaling is an important factor in regulating the activity of neurogenesis processes [69]. Wnt/Notch signaling is also relevant for angiogenesis processes [70], which accompany the neuroplasticity mechanisms. In particular, it was found that the cell's fate in neurogenic niches significantly depends on the vascular scaffold, and the permeability of the vascular wall determines the bioavailability of many molecules with regulatory activity in the niche [41, 49]. Interestingly, there are probably antagonistic relationships between the two pathways associated with proteolysis of Notch and APP: in particular, AICD suppresses the transcriptional activity of NICD [71]. This type of interaction is reflected, for example, in the implementation of the proangiogenic activity of APP and Aß, which is associated with the suppression of Notch signaling in cerebral endothelial cells and pericytes [50].

In addition, NICD acts as an «integrator» of several important signaling pathways (Wnt, HIF-1), which is largely determined by the NICD-controlled expression of Hes transcription factor [72]. Thus, for example, the object of Notch-mediated regulation is the metabolism of stem or progenitor cells. It is known that the activation of NSCs/NPCs is accompanied by significant changes in their metabolic status. In particular, «silent» SVZ stem cells demonstrate dependence on lactate production and fatty acid oxidation, while stimulation of their proliferative activity leads to an increase in the contribution of mitochondrial respiration, intensification of mitochondrial biogenesis, and a decrease in the utilization of fatty acids [73—75]. Genes encoding proteins-glycolysis enzymes, glucose transporters, and Krebs cycle repressors are under positive Notch control, in other words, the activity of Notch signaling contributes to the development of the Warburg effect in tissues [76], which is obviously necessary to maintain the population of «silent» stem cells and their pluripotency. This, in particular, was shown in the activation of Notch-Hes1 signal transduction and corresponded to the activation of the HIF-1 transcription factor [77]. If Notch signaling is suppressed, then NSCs in the neurogenic niches of the adult brain quickly enter mitosis, neurogenesis is intensified, but very soon the stem cell pool is completely depleted [78]. Thus, metabolic changes dictated, among other factors, by the activity of Notch-mediated mechanisms are necessary to maintain an adequate level of «silent» NSCs, which can potentially give rise to new neurons throughout the life of the body. According to the theory of hippocampal clearance, depletion of the neurogenesis process will lead to ineffective extra-hippocampal consolidation of new memories, but will not affect (or even improve) preserving old memories [79].

It is noteworthy that neurogenesis in the striatum and in the cerebral cortex from postmitotic differentiated astrocytes can be initiated by the suppression of Notch signaling in these cells (e.g., after ischemic damage), and the full passage of all stages of neurogenesis from the astroglia of the brain parenchyma requires (at the stage of amplifying neuroblasts) additional action of epidermal growth factor [37, 80].

It is known that another RIP product, AICD, acts as a suppressor of NPCs proliferation and an inducer of neuronal apoptosis, although there is evidence of opposite effects. Extracellular Aß stimulates NPCs' proliferation and the migration of neuroblasts, provides their differentiation into neurons, but shows such effects only in physiological (picomolar), but not in supraphysiological (nanomolar) concentrations [81, 82]. Moreover, it was shown that the suppression of activity of γ-secretase complex disrupts the processes of angiogenesis and barrier formation in the developing brain, while the presence of cerebral endotheliocytes Aß in low concentrations in the culture medium

has a pro-angiogenic effect [83,84]. Acting in high concentrations, Aß provokes the development of aberrant angiogenesis, characterized by excessive formation of a vascular network with pathologically increased permeability [43], probably through interaction with RAGE receptors [85].

The receptors of vascular endothelial growth factor VEGF (VEGFR1, VEGFR3), which is a powerful regulator of neurogenesis and angiogenesis, are also subjected to controlled intramembrane neuroteolysis. VEGFR1 binds VEGF-A with greater affinity, and the formation of an intracellular peptide from VEGFR1, mediated by the activity of γ-secretase, leads to the suppression of angiogenesis and is thus antagonistic to the effects of VEGFR2 activation [86]. Acting through VEGFR1, VEGF-A acts as a proneurogenic factor stimulating proliferation and migration of NPCs and probably neuroblasts [87—89]. Another RIP substrate — VEGFR3 — is expressed on radial glial cells in SVZ and is required for both neurogenesis and cerebral angiogenesis [90]. In the SGZ of hippocampus, VEGFR3 activation is relevant for the conversion of «silent» NSCs to NPCs and the implementation of subsequent stages of neurogenesis [91].

Conclusion

Products of regulated intramembrane proteolysis play an important role in the regulation of neurogenesis. The molecules generated by the activity of RIP proteases can stimulate or inhibit the activity of stem and progenitor cells, their proliferation, differentiation, migration and integration of newly formed neurons into pre-existing synaptic ensembles. Local neoangiogenesis supports the processes of neurogenesis in neurogenic niches, which is guaranteed by the multivalent action of peptides formed from transmembrane proteins (e. g., NICD, AICD). The reciprocal influence of the NSCs/NPCs and microvessels' cells and the presence in the niche of other cells producing factors that control neurogenesis (astrocytes, microglia) allow us to conclude that the neurogenic niche is a unique model that combines activity of vascular scaffold, a pool of cells with high proliferative and differentiation potential (NSCs/NPCs), and other cells and humoral factors regulating development processes. Identification of new regulatory molecules of neuroplasticity processes from among the enzymes, substrates, and RIP products will ensure the development of new recording protocols for neurogenesis, angiogenesis, and their directed pharmacological modulation.

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