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Neuronal reprogramming: approaches, challenges, and prospects

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ABSTRACT

The development of technologies and methods for reprogramming cells at different stages of differentiation *in vitro*, *ex vivo*, and *in vivo* has become one of the most significant scientific and technological advances of recent decades. Each year, an increasing number of experimental studies report successful direct reprogramming of differentiated cells, including the generation of specialized neurons from glial cells *in vivo*. These technologies hold the potential to advance regenerative medicine to a fundamentally new level. However, despite the growing understanding of differentiation mechanisms and phenotypic plasticity, as well as expanding capabilities to guide these processes, the clinical application of cellular reprogramming remains a major challenge. This review discusses the definitions of cellular plasticity, recent advances in neuronal cellular reprogramming approaches using direct and indirect methods, and the key barriers to their clinical implementation.

Keywords: genetic engineering; gene therapy; direct cellular reprogramming; induced pluripotent stem cells; neurons; glial cells.

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Пронейрональное репрограммирование: подходы, проблемы и перспективы

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АННОТАЦИЯ

Разработка технологических подходов и методов, позволяющих осуществлять репрограммирование клеток разной степени дифференцировки *in vitro*, *ex vivo* и *in vivo*, стала одним из важнейших научно-технических достижений последних десятилетий. С каждым годом публикуется всё больше экспериментальных данных об успешном прямом репрограммировании дифференцированных клеток, включая получение специализированных нейронов из глиальных клеток *in vivo*. В перспективе такие технологии позволят вывести возможности регенеративной медицины на качественно новый уровень. Однако несмотря на постоянно углубляющееся понимание механизмов дифференцировки и фенотипической пластичности клеток, а также на расширение возможностей направления этих процессов, практическое применение клеточного репрограммирования пока остаётся нереализуемой задачей. В обзоре обсуждаются определения клеточной пластичности, передовые достижения в области пронейронального клеточного репрограммирования с помощью прямых и непрямых методов, а также сложности, препятствующие их внедрению в клиническую практику.

Ключевые слова: генная инженерия; генная терапия; прямое репрограммирование клеток; индуцированные плюрипотентные стволовые клетки; нейроны; глиальные клетки.

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前神经细胞重编程：方法、挑战与前景

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摘要

近几十年来，开发在in vitro、ex vivo和in vivo条件下对不同分化程度细胞进行重编程的技术手段，已成为生命科学领域的重要突破之一。近年来，关于通过直接重编程将分化细胞转化为特化神经元的实验数据逐年增加，包括在in vivo条件下由胶质细胞生成神经元的研究成果。未来，这类技术有望将再生医学的潜力提升到一个全新水平。尽管我们对细胞分化和表型可塑性机制的理解日益深入，且调控这些过程的手段不断丰富，但细胞重编程在临床中的实际应用仍面临诸多挑战。本文综述了细胞可塑性的概念，介绍了前神经细胞重编程的最新研究进展，包括直接和间接重编程方法，并分析了阻碍其转化为临床实践的主要难点。

关键词：基因工程；基因治疗；细胞直接重编程；诱导多能干细胞；神经元；胶质细胞。

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INTRODUCTION

Recent advances in the technology and methods for reprogramming of cells of various differentiation stages represent one of the most important scientific and technological achievements of the last decades. Each year, an increasing number of experimental papers describe direct cellular reprogramming *in vitro*, *ex vivo*, and *in vivo* [1–4]. In the future, such technologies will potentially reach a higher level of regenerative medicine including neuroregeneration. Global trends toward lifespan extension and a growing population of elder people are leading to an increased incidence and prevalence of age-related diseases, including neurodegenerative diseases such as Alzheimer disease for which there is no effective cure so far [5]. So, many researchers and investors consider replacement of dysfunctional neurons by *in situ* reprogramming or by intracranial delivery of *in vitro* reprogrammed cells to be an extremely promising technology. The potential of using proneural reprogramming, e.g., for glial cells, is being evaluated in experimental models of traumatic spinal cord and brain injury [6, 7], stroke [8], retinal neuron regeneration [9, 10], Parkinson disease [11], and Huntington disease [12].

However, the rapid and widespread practical application of this technology remains an unrealistic task, despite continuously growing understanding of the mechanisms of cell differentiation and phenotypic plasticity, and the emergence of novel technological capabilities for cellular reprogramming, including *in situ*.

The aim of this review was to summarize the results of recent studies regarding direct and indirect proneural reprogramming and to elucidate the barriers to clinical implementation of these technologies.

DEVELOPMENT OF THE CENTRAL NERVOUS SYSTEM AT DIFFERENT ONTOGENETIC STAGES

The development of the nervous system, or neurulation, begins with the formation of the gastrula at the beginning of embryogenesis. The neural plate formed by a thickened portion of the ectoderm endures a ventromedial turnover to form neural folds and a groove that constitutes the neural tube during neurulation. Further differentiation of the neural tube leads to the development of the brain and spinal cord. The neural tube is formed from the neuroectoderm, so all multipotent progenitor cells in the central nervous system (CNS) are neuroepithelial or neural stem cells (NSCs) [13]. They can divide in two ways. Symmetrical division is needed to form a pool of NSCs, whereas asymmetrical one yields cells that retain NSC properties and postmitotic neuronal progenitor cells which cease to divide any longer [14]. Subsequently, most NSCs differentiate into radial glial cells (RGCs). RGCs are characterized by high expression of specific transcription factors: *Pax6* (Paired box gene family), a tissue-specific coordinator of embryonic development of the nervous system and eyes; *Sox2* (SRY-related HMG box family), one of the major regulators of pluripotency maintenance in stem cells; *Ascl1/Mash1* (Achaete-scute family bHLH transcription factor 1/Mammalian achaete-scute homolog 1); *Dlx* (Distal-less homeobox genes) and NEUROD (neurogenic differentiation factors) gene families encoding proteins that regulate neuronal migration and differentiation. Cells expressing RGC markers [15] appear at days 8–10 of embryogenesis in rats [14] and at weeks 5–8 of prenatal development in humans [16]. The bodies of these cells are predominantly located in brain regions formed during forebrain development: subventricular zone (SVZ) in the lateral walls of the lateral ventricles and the subgranular zone (SGZ) of the dentate gyrus [17]. RGCs can also divide symmetrically and asymmetrically to develop into intermediate progenitor cells (IPCs). They are the main source of all major CNS cells such as neurons, astrocytes, and oligodendrocytes, as well as highly specialized populations such as Müller cells which are the most abundant glial cells in the retina [18] and Bergmann gliocytes in the cerebellum [19]. In contrast to neurons, glial cells do not generate action potentials, but perform essential support functions. They regulate synaptogenesis, maintain synaptic plasticity and myelination of nerve fibers; for rapid conduction of nerve impulses, produce neuroprotective compounds and factors vital for proliferation, survival, migration and differentiation of neurons, provide neuronal trophism and brain tissue regeneration [20]. IPCs continuously migrate to the cortex during the embryogenesis to secure the formation of the neocortical histoarchitecture and the interneuron network. By the end of embryonic development, most RGCs not yet differentiated leave the ventricular zone and migrate to the cortex where they differentiate to astrocytes [13] (Fig. 1).

However, the SVZ and SGZ remain and secure the pool of quiescent RGCs and NSCs [21]. These populations of multipotent cells maintain neurogenesis, the process of mature neurons differentiation from progenitor cells throughout the entire postnatal ontogenesis [22].

Neurogenesis in the fully formed brain is required to regenerate olfactory cells. They are sensory neurons located in the olfactory region of the nasal mucosa and first ones of the cranial nerve I [23]. Neurogenesis is vital for neuroplasticity maintenance, replacing neurons in the structures responsible for memory and other cognitive processes [24]. In adult rodents, the SVZ is primarily responsible for the formation of olfactory interneurons in the olfactory bulb (OB). It was also reported that small populations of neuroblasts might be able to migrate to the prefrontal cortex and striatum [25]. However, the canonical rostral SVZ-OB migratory stream and the less studied medial migratory stream directing neuroblasts to the prefrontal cortex appear to exist only for the short neonatal period in humans [26]. The SGZ is responsible for hippocampal neuroregeneration [22]. SGZ-derived neurons are involved in spatial and social memory functions in adults,

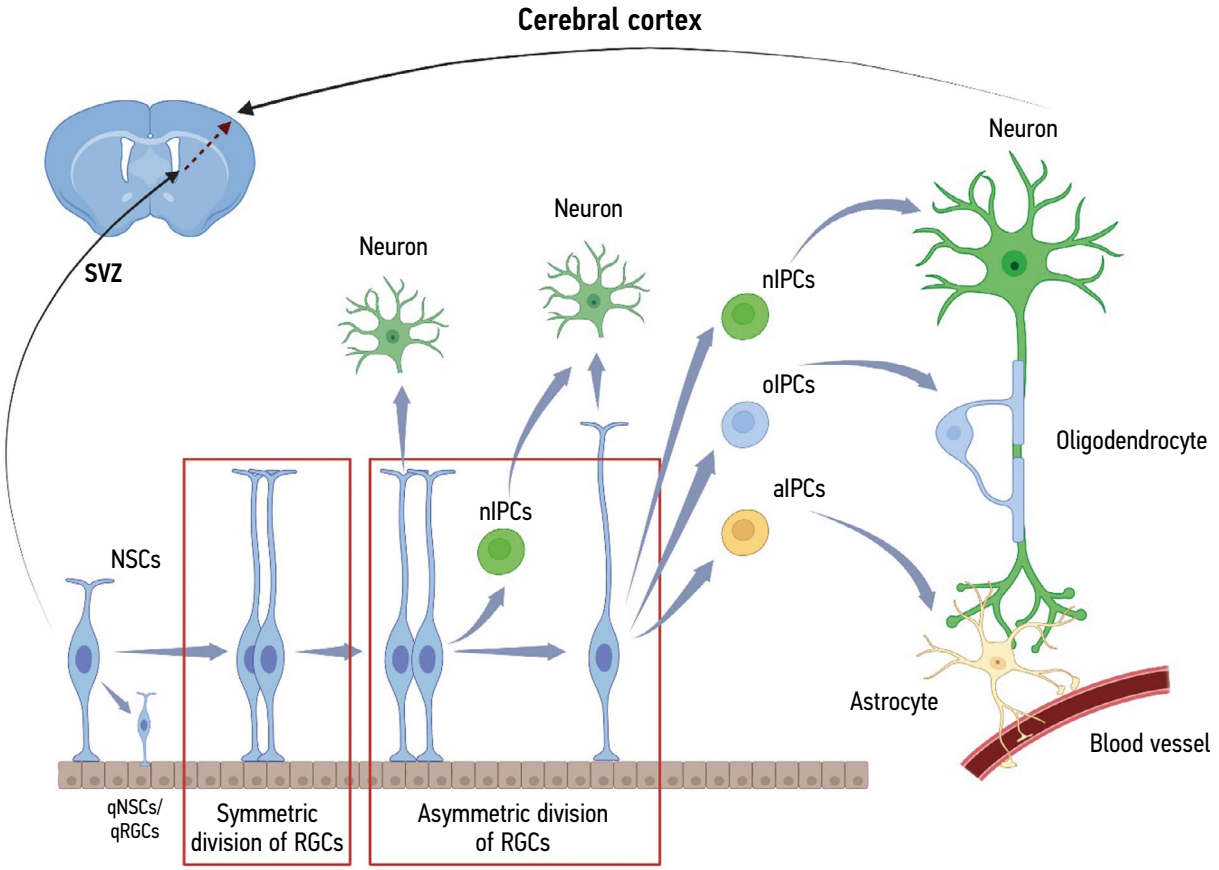

Fig. 1. Schematic representation of embryonic brain development. Neural stem cells (NSCs) in the subventricular zone (SVZ) divide symmetrically, generating a pool of radial glial cells (RGCs). Through both symmetric and asymmetric division, RGCs give rise to intermediate progenitor cells: neuronal intermediate progenitor cells (nIPCs), oligodendrocyte intermediate progenitor cells (oIPCs), and astrocyte intermediate progenitor cells (aIPCs). As differentiation progresses, these cells migrate from the neurogenic SVZ, contributing to neocortical histoarchitecture (indicated by the red dashed arrow) and maturing into neurons, oligodendrocytes, and astrocytes. During the earliest stages of embryogenesis, a niche of quiescent NSCs and RGCs (qNSCs/qRGCs) is established, which contribute to neurogenesis in the adult brain.

Рис. 1. Схема эмбрионального развития головного мозга. Стволовые нейроэпителиальные клетки (NSCs) в субвентрикулярной зоне (SVZ) делятся симметрично и формируют пул клеток радиальной глии (RGCs). В результате симметричного и асимметричного деления RGCs образуются промежуточные клетки-предшественники — нейрональные (Neuronal intermediate progenitor cells, nIPCs), олигодендроцитарные (Oligodendrocyte intermediate progenitor cells, oIPCs) и астроцитарные (Astrocyte intermediate progenitor cells, aIPCs). По мере дифференцировки клетки мигрируют из нейрогенной области SVZ, формируют гистоархитектонику неокортекса (обозначено красной пунктирной стрелкой) и становятся зрелыми нейронами, олигодендроцитами и астроцитами. На самых ранних этапах эмбриогенеза формируется ниша покоящихся NSCs и RGCs (Quiescent NSCs/RGCs, qNSCs/qRGCs), за счёт которых происходит нейрогенез во взрослом головном мозге.

provide the ability to distinguish similar events, and support stable encoding of information to consolidate short-term memory into long-term memory [27].

During postnatal neurogenesis, quiescent RGCs become activated under the influence of the surrounding glial cells and resume symmetric and asymmetric cell division to yield required progenitor cells. As they migrate to different parts of the brain, they differentiate into neuroblasts, then into immature neurons and finally into differentiated neurons. The spectrum of genes expressed in progenitor cells changes significantly throughout their development which make it possible to distinct the maturation stage of particular progenitor cells. However, it is not an easy task as multiple markers are common for different stages of progenitors' development [28] (Fig. 2).

REGENERATIVE POTENTIAL OF THE ADULT BRAIN

Being multipotent cells, RGCs simultaneously express markers of various differentiation stages of progenitors— PAX6, DLX, ASCL1, and NEUROD1— and mature astrocyte-specific proteins, including glial fibrillary acidic protein (GFAP), astrocytic glutamate transporter (GLAST), and brain lipid binding protein (BLBP) [29]. In adult mice, neurogenesis is regulated by *Pax6, Dlx, Ascl1* and *Neurod1* genes just as in embryogenesis [30]. However, as RGCs divide, neurons are formed both as primary cells and from progenitor cells during embryonic development. In the postnatal brain, new neurons might only be formed from intermediate progenitors and due

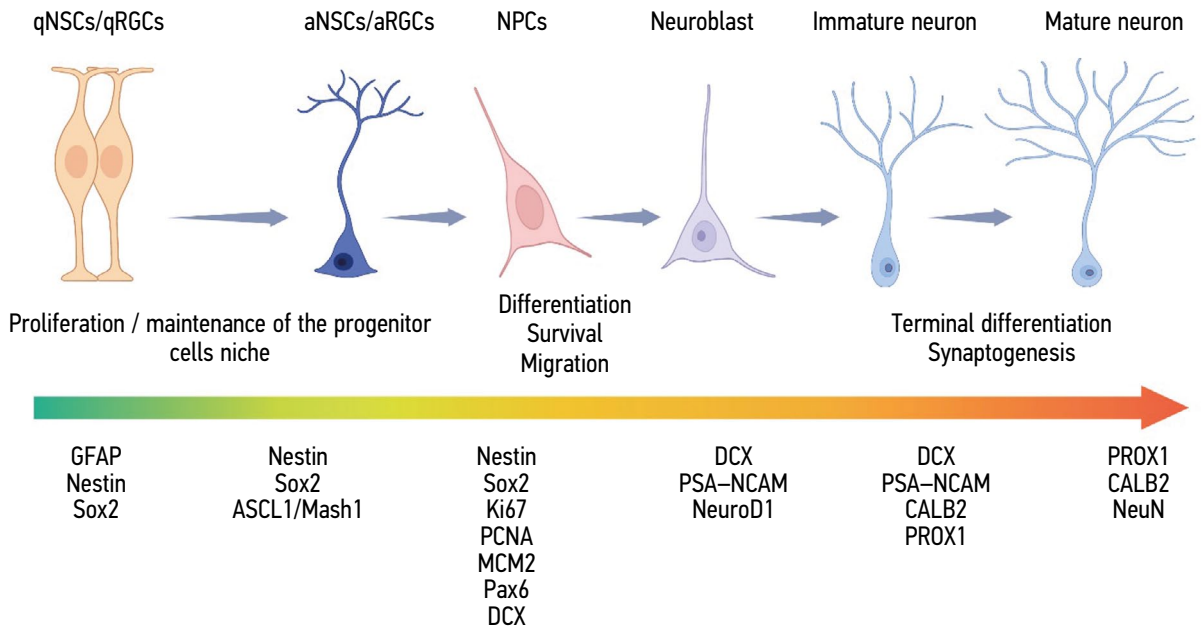

Fig. 2. Stages of neurogenesis in the adult brain of rodents and humans. Quiescent neural stem cells and radial glial cells (qNSCs/qRGCs) become activated (aNSCs/aRGCs) in response to microenvironmental signals and resume asymmetric division. Unlike embryonic neurogenesis, postnatal neurogenesis does not involve the direct generation of new neurons from radial glial cells (RGCs). Instead, a sequential differentiation process occurs, giving rise to neuronal progenitor cells (NPCs), neuroblasts, immature neurons, and finally, functionally active, mature neurons that integrate into the existing neuronal network. The lower part of the figure (below the arrow) indicates key genes expressed at different stages of cell differentiation during neurogenesis.

Рис. 2. Этапы нейрогенеза во взрослом мозге грызунов и человека. Покоящиеся стволовые нейроэпителиальные клетки и клетки радиальной глии (qNSCs/qRGCs) под воздействием сигналов от микроокружения активируются (aNSCs/aRGCs) и возобновляют асимметричное деление. При постнатальном нейрогенезе новые нейроны не образуются напрямую из клеток радиальной глии (RGCs), что отличает его от эмбрионального нейрогенеза. Происходит последовательная дифференцировка в нейрональные клетки-предшественники (NPCs), нейробласты, незрелые и дифференцированные нейроны, которые функционально активны и способны встраиваться в существующую нейронную сеть. В нижней части рисунка, под стрелкой, обозначены основные гены, экспрессирующиеся на разных стадиях дифференцировки клеток при нейрогенезе.

to the secretory context of the mature glia microenvironment, primarily astrocytes and ependymocytes [31]. As a result, RGCs are prone to gliogenesis rather than neurogenesis. The formation of new functional neurons from these progenitor cells, require the much higher expression of proneural factors (*Pax6, Dlx, Ascl1, Neurod1,* etc.) than it is needed for gliogenesis. Expression of proneural factors, as well as the transition of progenitor cells from a quiescent to an activated state, are strictly regulated processes. These physiological mechanisms presumably occur to prevent accelerated exhaustion of the NSC and RGC pool in the neurogenic niches. At the same time, a depletion of the pool of stem and progenitor cells in neurogenic zones progresses with age and negatively regulates neurogenesis. The fewer quiescent NSCs and RGCs remain, the lower the potential of their activation and the efficiency of differentiation into mature neurons [32]. Kalamakis et al. [33] showed that the number of NSCs in the SVZ in C57Bl/6-TLX-CreERT2YFP mice, in which NSC marker proteins was visualized *in vivo* via fluorescent imaging was significantly reduced in 7-month-old (m.o.) mice compared to 2 m.o. ones. There also was no differences found between the animals of 7 m.o. and 22 m.o. groups. Similar changes were observed in the subpopulation of activated NSCs, which were stimulated to resume the division for further neurogenesis initiation. Their number was significantly reduced at 7 m.o. compared to one of 2 m.o. mice [33]. Inflammaging, the age-related pro-inflammatory background plays a critical role in suppressing progenitor cell activation as well. In this study, it was found that the pro-inflammatory cytokines IL-33 and IFN-γ along with the chemokine CXCL10, whose upregulated expression is often observed with aging, inhibit the Wnt-dependent pathway, which is one of the main mechanisms maintaining neurogenesis processes [33].

Notably, that the new neurons of the SVZ and SGZ origin are markedly different despite the similarity of neurogenesis processes in these neurogenic regions. In contrast to the SVZ, NSCs and RGCs in the dentate gyrus are located deep in the brain parenchyma and surrounded by mature neurons and glial cells. This layer is far from the ventricular walls and cerebrospinal fluid flow, but close to blood vessels [34, 35]. As mentioned above, in humans, new neurons are not likely to appear in the olfactory bulb at postnatal period. NSCs and RGCs in this region differentiate predominantely into oligodendrocytes [25]. The published data on the duration of hippocampal SGZ neurogenesis are controversial. Some researchers found differentiating immature neurons in children

aged 7–13 years, but did not observe them in adults [36]. Others reported the presence of RGCs with neurogenic potential and progenitor cells of more differentiation stage in middle-aged and older subjects [37, 38]. However, it is quite reasonable to assume that neurogenesis in the SGZ continues effectively even at the late postnatal period due to the close proximity of this neurogenic niche of the SGZ to mature hippocampal structures. Differences in the data are likely depend on the spatial and secretory context of the microenvironment as well as its epigenetic changes that make progenitor cells prone to acquire a particular phenotype in different brain regions.

The neurogenic potential of the progenitor niche is maintained throughout the entire life. NSCs and RGCs proliferation and differentiation into neurons are strictly regulated to happen only when needed. Some non-genetic diseases and CNS injuries are associated with the death of a significant number of neurons at once which results in cognitive impairment, neurological deficits, and a consequent reduction of life quality and longevity. Such events occur instantly: traumatic injury, ischemic stroke caused by thrombosis and disruption of brain blood flow, and hemorrhagic stroke, which involves bleeding in the brain tissue, between its membranes, or within the ventricles [39]. In a mouse model of transient ischemic attack, it was showed that stroke might activate neurogenesis, migration, and differentiation of neuroblasts, and the treatment with the pro-inflammatory cytokine IL-1β, which enhances the acute inflammatory response, promoted the survival of new neurons in these mice [40]. In addition, the differentiation of progenitor cells into glia might activate angiogenesis processes, which are also required for neuroregeneration [41]. Activation of quiescent progenitor cells and initiation of their differentiation were also reported in traumatic brain injury, both in the SGZ and in single quiescent cells of the cerebral cortex, where they were apparently in a quiescent, immature state [42, 43]. The effectiveness of neurogenesis in traumatic brain injury and stroke of various origins depends on a variety of factors, including the location and volume of brain tissue damage, age of the patient, comorbidities, their monitoring and treatment. For example, the suppression of hippocampal neurogenesis was reported in neuropsychiatric disorders such as mixed anxiety-depressive disorders [44].

A decline in the number of functioning neurons in certain brain areas might be gradual and take a long time to become clinically apparent. This is primarily common in age-related neurodegenerative disorders such as Alzheimer disease and Parkinson disease. Manifesting as mild cognitive impairment, at the age of 60 years and older and gradually progresses, leading to dementia in such patients [45]. Neurodegenerative diseases that are more of the genetic origin include Huntington disease [46], frontotemporal dementia, and amyotrophic lateral sclerosis. However, age is also a risk factor for their clinical manifestation. The depletion of the pool of progenitor cells in the neurogenic niches and the reduced effectiveness of neurogenesis due to aging are important features of these diseases. However, the brain adapts to a gradual reduction in the number of properly functioning neurons over time. As a result, more progenitor cells have to differentiate into mature neurons to maintain stable cognitive function. However, this is prevented by the pro-inflammatory state of inflammaging, a higher activation threshold for quiescent NSCs and RGCs, and a lack of neurotrophic factors caused by aging and senescence of glial and resident immune cells such as astrocytes and microglia [38, 47, 48].

Therefore, despite the enormous adaptive regenerative capacity of the brain, a wide range of CNS disorders leads to the extensive neuronal loss that cannot be restored by the body's own resources. However, it is likely that treatment approaches designed to stimulate current neurogenic potential or to replace lost neurons with new ones derived *in vitro* or *in situ* would have significant clinical efficacy.

CELLULAR REPROGRAMMING: DEFINITIONS AND MECHANISMS

Metaplasia is the process whereby differentiated cells and tissues acquire characteristic of other differentiated cells and tissues. It was described and discussed by Rudolf Virchow and his successors in the 19th century [49, 50]. In modern cell biology and histology, metaplasia is described as a potentially reversible change in the phenotype of differentiated epithelial tissue, i.e., the appearance of features physiologically typical of another type of epithelial tissue [51]. The corresponding intracellular processes are called transdifferentiation or cellular metaplasia [52]. Abnormal and usually adverse stimuli make differentiated cells adapt by changing their phenotype and so might initiate or accelerate metaplastic processes [53]. Such stimuli may include harmful external chemical agents: acids or bases that mediate pH changes [54]; tobacco or alcohol use [55–57]; elevated levels of hormones or hormone-like substances such as bisphenol A and its derivatives [58, 59]; viral infections; chronic inflammation; oxidative stress [60–62]. There is still no consensus on whether cells and tissues can revert to the normal type of differentiation for their location after the harmful stimulus is removed and how long adverse environmental conditions should persist to result in dysplasia and increase the risk of malignancy [63]. It is not possible to determine the exact prevalence or incidence of any type of tissue metaplasia in the general population because most population studies include only a few of the most common diseases. For example, intestinal metaplasia of the esophageal epithelium, also known as Barrett esophagus, often accompanies gastroesophageal reflux disease. Constant reflux of gastric acid into the esophagus initiates the replacement of the squamous epithelium of the esophagus to single-layered cylindrical epithelium. Previously, patients diagnosed with Barrett esophagus were thought to have a 30 to 125 times higher relative risk of

esophageal adenocarcinoma than the general population with an average annual risk of malignancy of 0.5% (range: 0.1%–3.5%). However, subsequent studies estimated a lower annual risk of adenocarcinoma ranging from 0.12% to 0.18% [64]. Metaplastic lesions of various types in some locations may regress after the irritating stimuli cease to exist. However, in the case of Barrett esophagus epithelial cells remain a phenotype of prismatic intestinal epithelium and do not revert to squamous epithelial phenotype even with effective treatment [65].

In human tissues, metaplasia is mainly considered for several epithelial types and is categorized as squamous, intestinal, or acinar–ductal metaplasia [63]. The processes occurring in the human tissues are related to direct metaplasia, in which phenotypic changes in cells are not accompanied by the stage of differentiation decrease. Such phenotype shifts are the result of the activation and/or deactivation of genes in combinations that are not typical of a particular type of epithelium under physiological conditions. The same mechanisms underlie direct reprogramming *in vivo*, or so called induced metaplasia. The absence of dedifferentiation stage is a key difference between direct reprogramming and the approaches of induced pluripotent stem cells (iPSCs) yielding and further regulation of their differentiation to obtain cells with the desired phenotype [66]. In terms of their morphofunctional and molecular biological properties, iPSCs are closest to embryonic stem cells, which have the lowest degree of differentiation [67]. Most somatic cells can be reprogrammed into iPSCs, such as keratinocytes [68], melanocytes [69], adipose tissue-derived stem cells and adipocytes [67], neural progenitor cells (NPCs) [70], etc. However, fibroblasts are most commonly used to obtain human iPSC populations [71, 72]. Hundreds of protocols for the differentiation of iPSCs into various cell types have been developed and performed with varying efficacy. They are based on the overexpression of transcription factors that are only active in poorly differentiated cells, or the co-cultivation with proteins and small molecules typical of pluripotent cells. As a result, the processed cells lose their signs of differentiation and revert to the stem cell state. After that, the *in vitro* iPSCs undergo all differentiation stages that cells of the target phenotype do under physiological conditions in the body by regulating the expression of different genes or by culturing with specific proteins and low-molecular compounds typical of the microenvironment of the target cells.

Neurons can be obtained via both the direct reprogramming and dedifferentiation into iPSCs from non-neuroectodermal cells, such as fibroblasts and peripheral blood monocytes. Whether this process can be considered as an example of mesenchymal–epithelial transition remains a matter of discussion [73, 74]. Embryonic ecto-, meso-, or endodermal cytogenesis appears to be a limiting but not prohibitive factor for reprogramming into cells of another germ layer. This may be due to the loss of unique epigenetic properties by the cells subjected to controlled exposure during culture, more in iPSC obtaining and less in direct reprogramming protocols, especially at late passages (⩾10) [75]. However, several papers reported that some epigenetic changes are still preserved, which might keep cells to be prone to more successful reprogramming within the tissue of origin [67, 76]. This also applies to neurons. As shown by Hargus et al. [77], iPSCs derived from fetal NSCs and dermal fibroblasts differ significantly in the levels of expression of neuronal markers. iPSCs derived from low-differentiated neuroectodermal cells were significantly closer to neurons in the spectrum of expressed genes, and demonstrated significantly higher survival rates after the intracranial injection into the cerebral cortex of mice [77].

Differentiation and proper function of cells, especially neurons, highly depends on the microenvironment, including the changes in its spatiotemporal and secretory context over time. It defines the unique epigenetic changes of cells in a particular type of differentiated tissue [78]. The loss of these modifications, the need to extract cells from the body for *in vitro* reprogramming, and the reinjection of the reprogramed cell population are factors that make iPSCs potentially less practical for widespread clinical use than direct *in situ* reprogramming methods [79]. Although the use of iPSCs is not yet brought in practice, studies are underway using extracellular vesicles isolated from iPSCs to stimulate neurogenesis or neuroregeneration [80]. However, this is a complicated technological task that has not yet been tested in a clinical setting.

PRONEURAL REPROGRAMMING: METHODOLOGY AND TECHNOLOGICAL APPROACHES

Viral vectors carrying plasmids with genes of classical OSKM reprogramming factors (*Oct4*, *Sox2*, *Klf4* and *c-Myc*) in different combinations is one of the most effective and widely used techniques to induce the transition of differentiated cells to a pluripotent state. Lentiviral or retroviral delivery of plasmids is characterized by their integration into the cell genome, which potentially should secure stable expression of genes required for iPSC induction [66, 81]. However, such viral integration into the cell genome might lead to insertional mutagenesis and unwanted transgene reactivation in differentiated cells [82]. An alternative way is the use of non-integrating viral vectors such as adenovirus, adeno-associated virus (AAV), or Sendai paramyxovirus [83]. The development of malignant neoplasms was reported in only a few experimental studies with AVV vector-based gene delivery systems in newborn mice and in dogs with hemophilia. The risk of insertional mutagenesis can be minimized by improving reprogramming protocols and selecting the optimal dose of viral particles [82]. Non-integrating viral vectors are gradually removed from the proliferating and maturing iPSCs. It allows achieving the reprogramming goals

without permanent OSKM integration into the cell genome. OSKM factors can also be delivered into cells using non-viral vectors such as transposons [84], episomal plasmids [85], mRNA [86], etc. In addition, pluripotency can be induced using siRNA [87] and chemical compounds [88–90] both without OSKM. Such approaches increase the efficiency of dedifferentiation and subsequent reprogramming. As mentioned above, the effectiveness of reprogramming highly depends on the ecto-, meso-, or endodermal origin of the cells transfected into iPSCs, as well as the basal expression level of the genes used to induce pluripotency. Mouse and human iPSCs can be derived from NSCs using only *Oct4* and *Klf4*, or even *Oct4* alone, because the basal expression of *Sox2*, *c-Myc* and some other genes is sufficiently high in NSCs and does not require stimulation [70, 91, 92].

The same approaches and techniques are frequently used for direct reprogramming except for the dedifferentiation step. Using various combinations of transcription factors, small molecules, mRNA, miRNA, and other inducers, it is potentially possible to derive cells of any differentiation stage, except embryonic stem cells, from any cell. Currently, this technique is used to derive progenitor cells at different stages of embryonic and adult neurogenesis such as NSCs [93, 94], intermediate progenitors [95, 96], and RGCs [97] from mouse and human fibroblasts and monocytes *in vitro.*

Protocols for direct *in vitro* and *in vivo* reprogramming of various cells into specialized neurons (induced neurons, iNs) like glutamatergic, serotonergic, acetylcholinergic, motor ones and others are described in detail and systematized [98, 99]. For example, human fibroblasts were transdifferentiated *in vitro* into cells that demonstrated morphological features, gene expression, protein secretion, and electrophysiological properties typical of dopaminergic neurons. This result was achieved using a combination of several lentiviral vectors carrying the *hAscl1*, *hNurr1*, *hLmx1a,* and *hmiR-124* genes [100]. Dopaminergic neurons were derived from human fetal fibroblasts without using viral vectors by culturing the cells in the presence of small molecules and growth factors such as Valproic acid; aromatic heterocyclic compounds including Repsox (transforming growth factor beta receptor 1 (TGFβR1) inhibitor), kenpaullon (glycogen synthase kinase 3β inhibitor), forskolin (adenylate cyclase activator), purmorphamine (Sonic hedgehog (Shh) pathway activator); proteins such as Wnt1, Wnt5a, fibroblast growth factors, and the protein encoded by the *Shh* gene [101]. Human embryonic lung fibroblasts from 7–9 weeks of development were successfully reprogrammed *in vitro* into cortical glutamatergic neurons using a lentiviral vector carrying the *Fezf2*, *Ctip2*, *Ngn2,* and *NeuroD1* genes. Reprogrammed cells were identified as iNs, namely cortical neurons, based on electrophysiological activity and levels of the neuronal markers SOX5, FEZF2, CTIP2, OTX1, TBR1, and SATB2. The generated iNs formed synaptic contacts when co-cultured with cells from a primary culture of human cortical neurons, as confirmed by the detection of formed dendritic spines and the presence of the postsynaptic structural protein PSD95 associated with excitatory potential generation [102].

Induced neurons can be obtained either directly or by pre-generating iPSCs both via *in vitro* delivering a vector carrying target genes into somatic cells. The resulting reprogrammed cells are being inoculated directly into the target area to integrate. In gene therapy, viral vector-based agents could require local or systemic administration depending on the disease (Fig. 3). Only animal models have been brought in trials of *in vivo* cell reprogramming so far. However, the advantages and disadvantages of both local and systemic administration of the viral vector have been under investigation.

Transdifferentiated iNs of different subpopulations as well as cells with a lower level of differentiation could be obtained from somatic cells as well as from progenitor and glial cells by direct reprogramming. For example, Rivetti di Val Cervo et al. [103] obtained induced dopaminergic neurons from human astrocytes both *in vitro* and *in vivo* in a mouse model of Parkinson disease [103]. The modelling was performed via an injection of 6-hydroxydopamine into one hemisphere of mice brain to cause death of dopaminergic neurons in the ventral midbrain of the ipsilateral hemisphere, as well as denervation and reactive gliosis. A viral vector containing a plasmid with *Neurod1*, *Ascl1,* and *Lmx1a* genes, as well as the miRNA miR218, which can only be expressed by GFAP-positive cells, was injected transcranially into the ipsilateral striatum. Todd et al. [9] performed *in vivo* reprogramming of Müller glia cells into neuron-like retinal cells in mice by intravitreal inoculation of a lentiviral vector with a plasmid carrying *Atoh1:Ascl1* genes [9].

In addition to direct vector delivery to a specific brain region, intrathecal and intraventricular injections of viral vectors-based agents carrying transcription factors genes were quite effective [104]. The possibility of systemic delivery of the plasmid on AAV-vectors and reaching the CNS was also evaluated. An intravenous administration of viral particles that could be activated only by interaction with specific markers for radial glia and astrocytes (GFAP) and neurons (synaptophysin) resulted in transgene expression, monitored via GFP fluorescence, was detected only within the CNS, albeit in a small number of target cells [105].

There is a wide range of approaches and methods available for the direct proneural reprogramming. This type of reprogramming is widely investigated, improved and applied as protocols for preclinical experimental studies. AAV vectors as gene delivery systems offer most available high short-term safety and stability compared with other viral and non-viral systems for reprogramming. However, clinical trials of therapeutic systems based on direct neuronal reprogramming are still not possible due to some serious limitations.

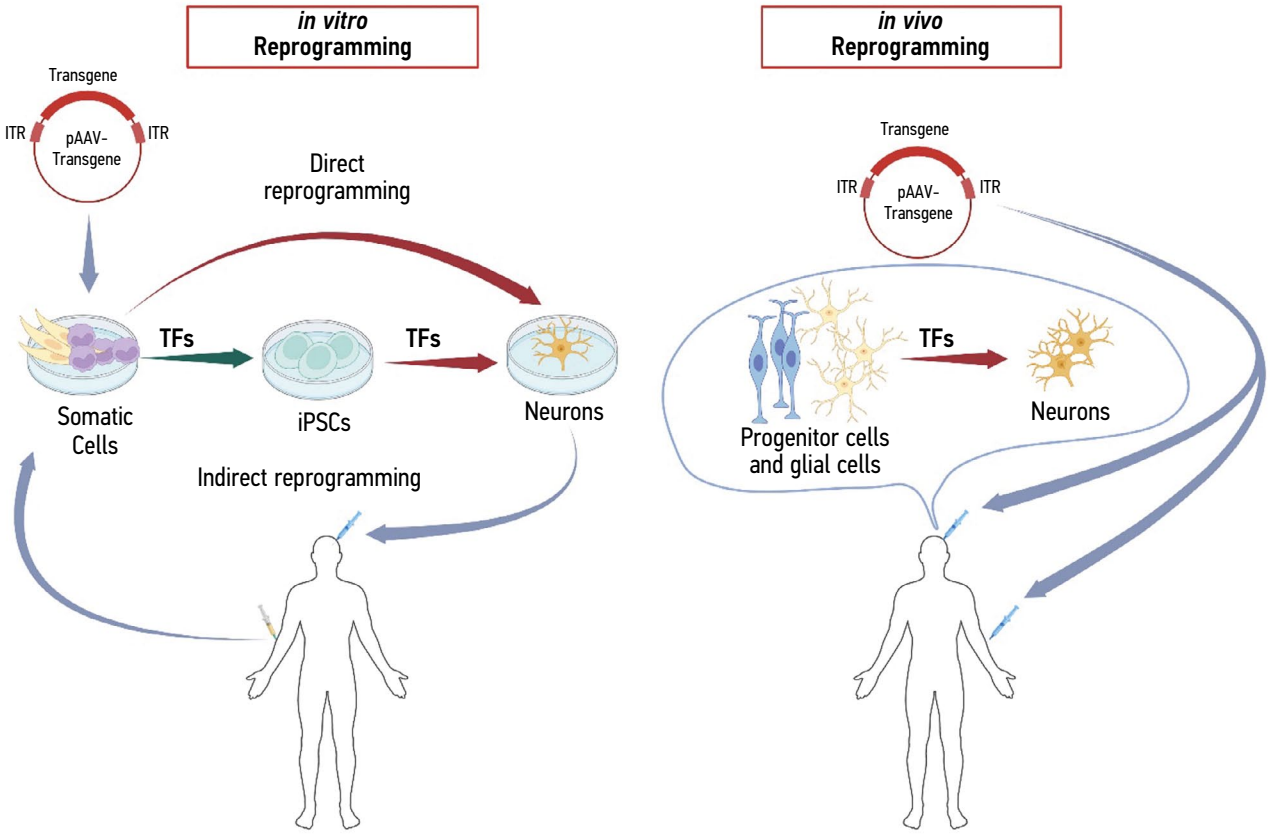

Fig. 3. Schematic representation of cellular reprogramming *in vitro* and *in vivo*: TFs, transcription factors; pAAV-transgene, viral vector carrying target genes; iPSCs, induced pluripotent stem cells.
Рис. 3. Схематичное изображение клеточного репрограммирования в условиях *in vitro* и *in vivo*: TFs — факторы транскрипции (Transcription factors); pAAV-transgene — вирусный вектор с таргетными генами; iPSCs — индуцированные плюрипотентные клетки.

LIMITATIONS OF *IN VIVO* CLINICAL USE OF DIRECT PRONEURAL REPROGRAMMING

Gene therapy, including those based on AAV vectors, is already used in clinical practice. Currently, 26 viral vector-based agents are approved for *in vivo* use by the U.S. Food and Drug Administration (FDA) and other regulatory agencies [104]. All of these agents insert functional nucleotide sequences into the DNA of patient's cells to replace defective ones in rare genetic diseases, including those affecting the nervous system. For example, Solgensma (onasemnogene abeparvovec) uses AAV serotype 9 capsids with plasmids containing a copy of the survival of motor neuron (*SMN*) gene, which dysfunction leads to spinal muscular atrophy manifestation [106]. Similarly, Upstaza (eladocagene exuparvovec[1]) has been developed for gene therapy of aromatic L-amino acid decarboxylase (AADC) deficiency. The absence of AADC disrupts the synthesis of serotonin and dopamine and results in death in early childhood [107]. However, none of the approved agents affect the degree of cell differentiation and cell phenotype. Despite a growing understanding of mechanisms of proneural reprogramming and the development of new protocols, including suitable for *in situ* use, there are still some fundamental issues to be resolved before clinical trials would become feasible.

Many papers described the *in vivo* direct proneural reprogramming using transgenic mouse lines with cells expressing Cre-loxP or Flp-FRT recombinases. These recombinases trigger expression of plasmid-embedded target genes [108]. Activation of the recombinases also induces the synthesis of the fluorescent GFP, which make it possible to detect cells expressing target genes and synthesizing the necessary proteins using *in vivo* imaging systems [109]. However, it is not always successful even in mice [110]. Similarly, *in situ* expression of direct reprogramming factors could theoretically be initiated in humans. However, it is not currently possible to assess the efficiency of reprogramming *in vivo* using available imaging systems designed for cell lines and small organisms such as mice.

In addition, there are still no completely safe methods for the delivery of gene constructs. As mentioned above, the risk of malignancies after AAV vector-based gene therapy is

[1] The product is not approved in the Russian Federation

quite low. However, adverse reactions are common with both local and systemic administration of such agents. Preclinical studies in mice, rats, and primates displayed damage to neurons in dorsal root ganglia (DRG), accompanied by ataxia and proprioceptive sensory impairment [111–113]. A case report describes dorsal root gangliopathy following intravenous administration of AAV-miR-SOD1 to two patients for the treatment of amyotrophic lateral sclerosis caused by a mutation in the superoxide dismutase 1 gene. One patient reported tingling in the hands and severe shooting pain in the left foot after drug administration, which correlated with electrophysiologic changes and DRG contrast enhancement on magnetic resonance imaging. The second patient had previously received immunosuppressive therapy and showed no clinical manifestations of DRG damage [114]. Toxic liver damage of varying severity may occur in 60% of cases during systemic gene therapy with AAV vector-based agents [115]. Thrombotic microangiopathy (TMA) is also a common complication (8.2%; 0.5%-75.0%), which can lead to death in the short term, and 1-year survival after therapy with relief of TMA symptoms varies from 16% to 80% [116, 117]. Such adverse reactions are frequently associated with a systemic immune response to the administration of large numbers of viral particles. The vast majority of people are infected with a variety of different viruses during their lifetime, requiring careful multi-step testing for antibodies to AAV capsids prior to treatment. If a patient has antibodies to certain types of viruses, the adaptive immune response is activated before the agent will be able to induce any therapeutic effect [118].

Available viral vector-based gene therapy agents are primarily used in early childhood to treat severe congenital diseases. Up to six months of age, infants may have antibodies that are transplacentally transferred from the mother. However, the older the patient, the higher the possibility of having antibodies to adenoviral capsids [119]. However, the administration of large numbers of viral copies inevitably activates innate and adaptive immunity even in the absence of such antibodies prior to therapy. It correlates with the development of side effects as well. Advances in gene therapy regimens may reduce the incidence and severity of side effects, including by reducing the number of viral copies in a dose of the agent and increasing the number of doses administered [120]. However, this approach significantly increases the financial cost of treatment. Intensive immunosuppressive therapy is still required to achieve the necessary therapeutic effect on the underlying disease. At the same time, immunosuppressive agents such as corticosteroids, sirolimus, tacrolimus, complement inhibitors, and various monoclonal antibodies [114, 117, 121] cause a variety of systemic side effects themselves and have many contraindications for use. Given the high incidence of chronic diseases in the older population and the need for treatment to control the symptoms and progression of medical conditions, it is unlikely that the use of AAV vector-based agents for proneuronal reprogramming of glial cells will be approved for clinical trials in the near future, particularly in patients with neurodegenerative diseases.

Notably, it is not currently possible to precisely and reproducibly direct differentiation towards the desired subtype of differentiated cells. The use of Sox2, one of the key transcription factors in reprogramming, was reported to obtain low differentiated RGCs, NPCs, and neuroblasts in brain and spinal cord tissues, including *in vivo* [53, 74–76]. Although the outcome of reprogramming depends on the number of copies of vector administered, it is difficult to say with high certainty which specific cell population will be obtained *in situ* and in what quantity because different differentiation stages express many identical markers [28]. The division cycle of neural stem cells is extremely short in embryogenesis and lasts 10–18 hours [122], whereas the maturation of a neuron from NSCs or NPCs can take up to two weeks in the adult brain under physiological conditions [123, 124]. Therefore, the formation rate of mature specialized neurons from glial cells *in situ* and the effectiveness of their functional integration to restore lost neuronal connections will be extremely difficult to predict and regulate in pathological conditions, especially in neurodegenerative diseases.

Most experiments reported so called *leaky expression*, which is detectable expression of target genes by non-target cells [125]. When transcription factors with activity limited to the initial stages of cell differentiation are administered externally, a complex cascade of processes involving DNA unfolding and interaction with enhancers and promoters of target genes appears to be initiated in cells that need to be reprogrammed. In addition, Katsuda et al. [126] reported hepatobiliary metaplasia in mice after systemic administration of an AAV vector carrying the genes of *Sox4* and *Sox9* transcription factors [126]. Similar changes occur with toxic damage to the organ and can lead to adenocarcinoma [127]. Spontaneous metaplasia of glial cells has not been described in mammals, and the long-term consequences of their reprogramming into neurons have not been studied *in vivo*. Given the uncertain probability of metaplasia transition to dysplasia with subsequent malignancy, especially in older patients with comorbidities and an age-related increased risk of cancer, the potential side effects outweigh the potential therapeutic benefit at the current stage of research and development of AAV vector technologies.

Epigenetic changes inevitably acquired by people throughout their life might have a significant impact on the effectiveness of reprogramming as well. Some single-cell transcriptomic studies of iPSCs derived from commercial cell lines of mature fibroblasts reported the expression of molecular genetic signatures typical of NSCs [128]. However, direct reprogramming has shown that transdifferentiated iNs derived from cells of young and old people retain transcriptional signatures of aging due to unique epigenetic changes [129]. Therefore, given the influence of aging and the associated inflammaging that inhibits neurogenesis, there is a high probability that even successful direct reprogramming

of astrocytes into neurons *in situ* in humans with age-related neurodegenerative diseases may be therapeutically ineffective due to the senescent phenotype of glial cells.

Many of the methodological and therapeutic issues described are likely to be resolved in the near future. However, it is necessary to integrate new neurons not only in close proximity to neurogenic zones such as the hippocampus, but also at a great distance from them in order to achieve a significant and lasting therapeutic effect in the treatment of various CNS diseases. Neurogenesis is a complex process that is tightly regulated by the internal genetic programs of progenitor cells and mature neurons, as well as by external microenvironmental factors. As neurons differentiate, they lose the ability to extend axons due to selective inhibition of migration factors and integrins that were highly expressed during embryogenesis [130]. Attempts to use bone marrow stem cells and embryonic CNS cells to treat spinal cord injury have been successful in rodent experiments [131], but clinical trials have not reported any significant efficacy [132]. Some other clinical trials assessed an effect of intracranial injection of embryonic dopaminergic neurons into the basal ganglia region of patients with Parkinson disease. Despite the high survival rate of the implanted cells, clinical improvement was either absent or unstable [133, 134]. It is clear that targeting a specific pathway will not be sufficient to fully regenerate damaged axons in the adult mammalian CNS, and manipulating a large number of genes at once is an extremely complex task with a high risk of adverse consequences. Therefore, effective proneural reprogramming is still not possible, especially in older patients with comorbidities and a senescent cell phenotype.

CONCLUSION

The integration of multi-step and mutually regulated genomic, epigenomic, and biochemical pathways involved in cell plasticity processes, provides the basis for adaptation and normal function of tissues, organs, and systems. Numerous signaling pathways with similar functions form a complex, self-sustaining, and self-regulating system that ensures the stability of the entire organism when one or more pathways are blocked. The short- and long-term consequences of external interference with the histogenetic signatures of cells, especially when elements of such a complex structure as the human brain are affected, are still poorly understood. In addition, there are a number of fundamental barriers that need to be overcome, such as a lack of ability to ensure the growth of axons to CNS regions that are significantly distant from neurogenic zones. Further studies are warranted to better understand the fundamental cellular and molecular biological processes underlying cellplasticity and transdifferentiation under physiological and pathological conditions. In addition, available gene therapy methods need to be continually improved to secure the safety and efficacy of direct reprogramming approaches.

ADDITIONAL INFORMATION

Author's contributions. A.V. Sentyabreva: literature review and analysis, illustration creation, manuscript writing and editing. The author approved the manuscript (final version for publication) and agreed to take responsibility for all aspects of the work, ensuring proper investigation and resolution of any issues related to accuracy and integrity.

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Вклад авторов. А.В. Сентябрева — сбор и анализ литературных источников, создание иллюстраций, написание текста и редактирование статьи. Автор одобрил рукопись (версию для публикации), а также согласился нести ответственность за все аспекты работы, гарантируя надлежащее рассмотрение и решение вопросов, связанных с точностью и добросовестностью любой её части.

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