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REVIEW
ОБЗОР

Traumatic brain injury: basic cellular mechanisms and new approaches to therapy

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Abstract. *Relevance.* Traumatic brain injury (TBI) is a serious medical problem and one of the leading causes of disability and mortality among military personnel and civilians. It is known that about 1.5 million people in the world die from TBI every year, while about 2.5–3 million lose work capacity. In Russia, one million people are diagnosed with TBI every year, among which one in five gets group I or II disability. Despite significant efforts in research, effective TBI treatment methods are still limited, as TBI leads to a wide range of pathological changes in brain tissues. Primary brain damage is an acute and irreversible mechanical damage to the parenchyma of the nervous tissue. Among subsequent secondary processes are excitotoxicity, mitochondrial dysfunction, oxidative stress, axon degeneration, and neuroinflammation. These processes are often long and can take from several days to several years. Recent advances in cell therapy are opening up new perspectives for the treatment of this condition. The current review examines the main cellular mechanisms of TBI acute and chronic phases, as well as the treatment prospects for the use of stem cells for. Analysis of recent studies on the use of cell therapy in TBI is presented. Various types of stem cells such as neural stem cells, mesenchymal stromal cells and others are considered in the context of their potential to repair damaged brain tissues. Special attention is paid to the cells action mechanisms in the regeneration process, including their effect on inflammation, neurogenesis, and synaptic plasticity. The issue of using paracrine factors secreted by stem cells as a potential drug for traumatic brain injuries treatment is addressed. *Conclusion.* Cell therapy, as well as the use of products secreted by cells, is one of the new and promising ways of treating TBI.

Key words: traumatic brain injury, cell therapy, secretome, extracellular vesicles, neural stem cells, induced pluripotent stem cells, mesenchymal stromal cells

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Introduction

Traumatic brain injury (TBI) pathogenesis is a complex process resulting from primary and secondary injuries leading to temporary or permanent neurological deficits. The blow results in primary damage (acute phase), expressed by a mechanical violation of endothelial cells, neurons and glia integrity. Secondary damage develops in a time interval from several minutes to several days after the primary damage due to the activation of various cascades leading to further brain damage. Damaged cells produce a large number of factors: ions, proteins, signaling molecules that initiate inflammation, apoptosis and oxidative stress processes in the surrounding tissues. The acute phase lasts about 24 hours. After that, the activation of the pro-inflammatory phenotype of microglia (M1) and reactive astrocytes, as well as blood-brain barrier (BBB) damage and the involvement of peripheral immune cells trigger chronic neuroinflammation mechanisms. The chronic phase is long-term [1–4].

Cell therapy is a promising approach in TBI treatment. This method is aimed at restoring damaged brain tissues and improving functions, and has a positive effect on various cellular processes. The use of stem cells, including neural stem cells and mesenchymal stromal cells, is one of the challenging areas, since they have the ability to differentiate into various cell types, which can help replace damaged neurons and maintain cellular homeostasis. At the same time, cell therapy can stimulate regeneration mechanisms, including neurogenesis (formation of new neurons), angiogenesis (formation of new vessels) and synaptogenesis (formation of new synapses). These processes contribute to the restoration of the brain damaged areas functions. Also, stem cells secrete anti-inflammatory factors, which can have an anti-inflammatory effect, reducing the activation of microglia and astrocytes, as well as reducing the levels of cytokines and other inflammatory mediators.

Cellular response to TBI

A large number of cells are activated in TBI in response to brain damage. Astrocytes, oligodendrocytes, NG2+ precursors of oligodendrocytes, neural stem cells (NSCs) and ependymal cells of the ventricular membrane of the brain are the first to react to the destruction of nervous tissue. In addition, the response also occurs in non-neural CNS cells, namely — in microglial cells, perivascular phagocytes, pericytes and endothelial cells. Blood cells such as leukocytes, platelets, fibroblasts and mesenchymal precursors are attracted to the site of inflammation [2].

Mechanical action on brain cells leads to stretched neuronal membranes, their depolarization and influx of calcium ions (Ca2+). In addition, diffuse axon

damage (traumatic axon shift), leads to bending and disintegration of microtubules (MTB). As a result, the occurring structural damage causes disruption of axonal transport, swelling of axons and, subsequently, their degradation [3, 4]. In mild TBI, small cell damage contributes to a slight increase in extracellular concentrations of glutamate and/or ATP. This, in turn, helps to attract microglia without developing an inflammatory reaction. In addition, extracellular ATP can interact with astrocytes, leading to an increase in intracellular Ca2+ and the release of astrocytic ATP through connexins, which increases the possibility of an inflammatory reaction.

Significant disturbances and cell death stimulate the release of cytosolic and nuclear contents: DNA, RNA, potassium (K+), heat shock proteins, and calcium-binding proteins of the S100 family [2]. Subsequent development of inflammation is associated with the release of a large number of neurotransmitters, cytokines and chemokines, which stimulate the activation of glial cells (so-called reactive gliosis), microglia and attract immune cells (Fig.1) [5].

Activation of microglia

Microglia is an important component of the brain immune defense. Normally, M1 (pro-inflammatory) and M2 (anti-inflammatory) phenotypes of microglia work in tandem, supporting both the processes of destruction (removal of damaged cells) and restoration of nervous tissue. In response to various cytokines, especially in response to interleukin-1β (IL-1β) and interleukin-18 (IL-18), secreted both by damaged cells and by the microglia itself, changes occur in the morphology and functional activity of the microglia, as a result of which the latter acquires the M1 phenotype. As a result, the NF-kB signaling pathway and the pathways of mitogen-activated protein kinases (MAPK) are activated in microglial cells. This leads to M1-microglia starting to secrete a large number of such proinflammatory cytokines as IL-1β, interleukin-6 (IL-6), interleukin-8 (IL-8), IL-18, interferon-γ (IFNy) and tumor necrosis factor-α (TNFa, or TNF-α). In addition, M1-microglia has high phagocytic activity: it can mediate the metabolism of extracellular phosphatidylinositol as a source of arachidonic acid for the synthesis of leukotriene [4, 6, 7]. At the same time, M1 microglia can enhance oxidative stress by increasing the expression of NADPH oxidase and inducible NO synthase (iNOS) [8, 9].

It is important to note that during TBI, M2 phenotype of microglia which has three subtypes: M2a, M2b and M2c, is also activated. Activation of M2-microglia most often occurs later than activation of M1-microglia, and can be induced by interleukin-4 (IL-4). It is very important that in response to TBI, the activation of M1 macrophages quickly transitions into a recovery reaction due to the activation of M2 phenotype [10]. To date, it is known that microglia of M2a subtype inhibits inflammation processes, and also stimulates cell proliferation and migration to the site of injury, where it is able to increase the expression of the antagonist of the IL-1 receptor, arginase-1 and the trigger receptor expressed on myeloid cells-2 (TREM2). M2b microglia, in turn, has both pro-inflammatory and anti-inflammatory functions. The expression of IL-1, TNFa, IL-6 and Toll-like receptors (TLRs) is associated with its pro-inflammatory activity, and the expression of arginase-1 is associated with anti–inflammatory activity. At the same time, M2c subtype exhibits anti-inflammatory activity due to the high level of expression of transforming growth factor-β (TGFß), CD206, CD163 and sphingosine kinase-1 [8]. In addition, it has been shown that M2 microglia is able to secrete insulin-like growth factor-1 (IGF-1), which has a positive trophic effect. M2 microglia is also capable of producing nerve growth factor (NGF), brain neurotrophic factor (BDNF) and neurotrophin-3 (NT-3), which stimulate neurons growth and survival [10].

Reactive gliosis

Under normal physiological conditions, glial cells support the functions of neurons, influence neuroglial interactions, and participate in maintaining neurotransmitters synaptic connections and balance. In pathological conditions, the situation is different, in particular, in TBI, the presence of numerous cytokines initiates reactive gliosis. The interaction of astrocyte receptors with IL-1β, TNF-α, and TGF-1β causes morphological and functional changes in cells: astrocytes

become hypertrophied, demonstrating noticeable changes in the level of certain proteins (for example, glial fibrillar acid protein (GFAP), intermediate filaments, vimentin and nestin). The influence of reactive glial cells on the surrounding cells that support normal functioning of neurons can lead to synapse defects, impaired secretion of neurotransmitters and neuronal death. It is generally believed that reactive astrocytes are localized at the site of injury, however, there is evidence describing their ability to migrate to healthy tissues [10, 11]. It is important to note that reactive astrocytes are capable of forming a glial scar (astrocytic scar), which borders the site of injury. On the one hand, scar formation is needed for partial separation of damaged tissue from healthy tissue in order to prevent widespread inflammation; on the other hand, neurogenesis and neurodevelopment processes are often suppressed in the scar area, because the scar forms a structural barrier that constantly secretes axon growth inhibitors [2, 10, 12, 13].

The regulation of reactive gliosis occurs not only due to proinflammatory agents and various molecules produced by damaged cells, but also due to the influence of substances capable of penetrating through the damaged BBB; substances secreted by leukocytes, as well as due to paracrine and autocrine factors. Reactive glial cells specifically alter the expression of different genes, both depending on the activating molecular cascades, and on the type of injury and severity of damage [2].

Involvement of peripheral immune cells

Focal brain injuries exhibit a characteristic inflammatory response with infiltration by peripheral immune cells after injury. It is believed that these cells are important because they are able to secrete many inflammatory mediators associated with increased tissue damage. In addition, a large amount of data obtained in the study of ischemic injuries indicates that inhibition of leukocyte recruitment contributes to a decreased affected area and the development of a favorable outcome [14].

Activation of endogenous neural stem cells

As is known, there are two main localization zones of neural stem cells in the human and rodent brains: the subventricular zone surrounding the lateral ventricles and the subgranular zone of the dentate gyrus of the hippocampus. The latter is especially important for the formation of new neurons and new synapses in already existing neural circuits. In addition, modeling TBI in rodents showed activation of NSCs of the hippocampus subgranular zone. At the same time, an increase in the level of NSCs proliferation, formation of new neurons and their migration to the site of injury is observed. Literature data analysis shows that in TBI the largest number of neurons is formed in the hippocampus, which is especially important for cognitive functions restoration. However, the problem of effective restoration of nervous tissue in TBI is that the survival rate of newly formed neurons is quite low, especially in conditions of progressive neuroinflammation and apoptosis of surrounding cells. Thus, in order to start the process of endogenous brain repair, it is necessary to use a strategy aimed at stimulating the proliferation of NSCs, increasing the survival of neurons and their migration to damaged areas of the brain (Fig. 1) [15].

New approaches to TBI therapy

Currently, the use of stem cells in regenerative medicine is a promising and challenging area. For more than 30 years, the topic of cell transplantation has been actively studied in order to further apply such technology in TBI treatment. To date, two main hypotheses of the effectiveness of such treatment are described. According to the first one, the transplanted cells have the ability to differentiate into functionally active neurons and glial cells in the lesion, thereby contributing to the restoration of damaged tissue integrity and functionality. According to the second, cells produce various factors, which, in turn, contribute to the inhibition of tissue degeneration, stimulate the restoration of the microenvironment of the damaged central nervous system and regeneration [16]. Literature describes the use of NSC, iPSC and MSC for TBI treatment. Preclinical studies also confirmed the effectiveness of the use of any of the above-mentioned cell types [17].

Loss of functionally active nerve tissue is the most common injury in TBI. Given the limited population of endogenous NSCs, transplantation of exogenous stem cells into damaged areas of the brain is a truly promising method of TBI therapy [15]. It is known

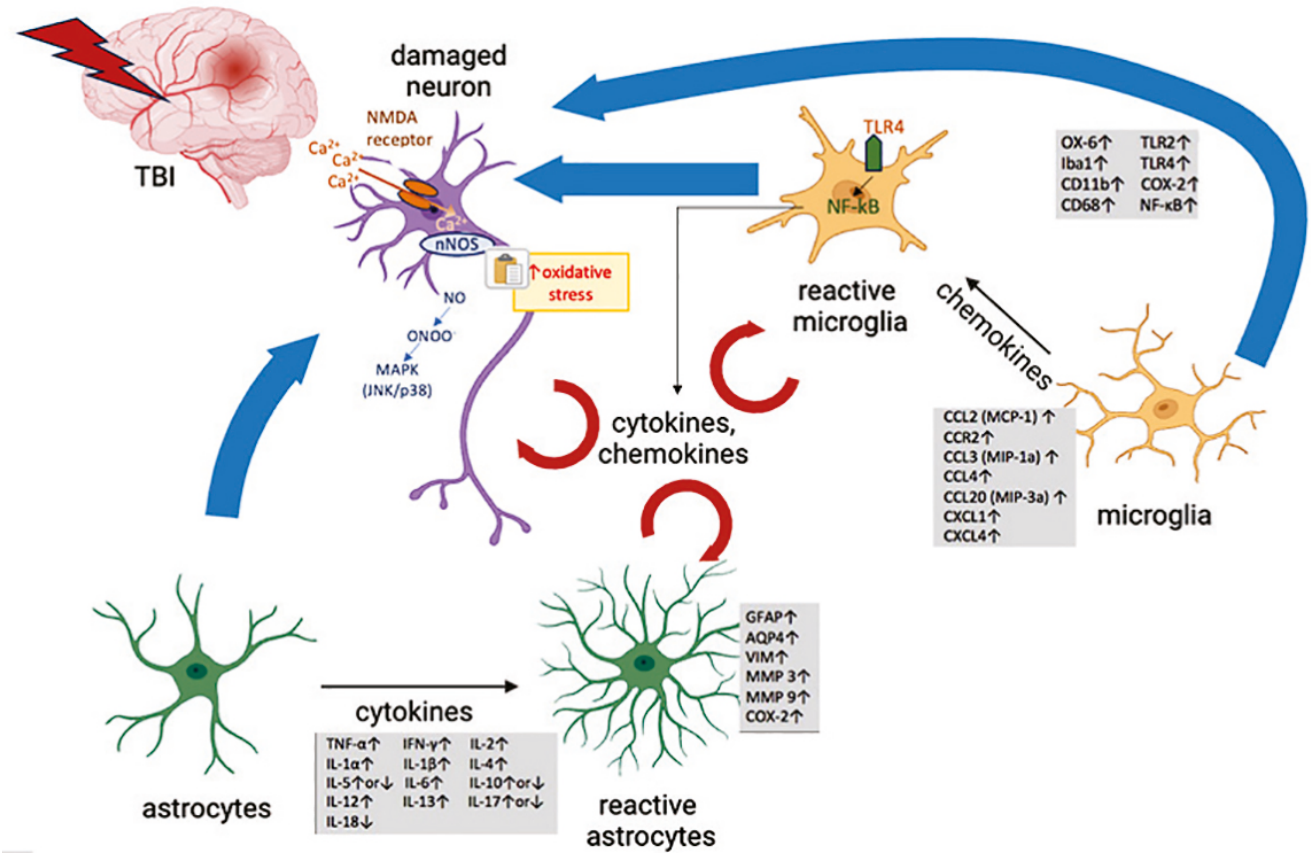

Fig. 1. Cellular response to damage caused by TBI. The red arrows show autocrine and paracrine effects, the blue arrows show the effects of astrocytes and microglia on neurons, according to Chiu et al., 2016, modified [10]

that the implantation of NSCs in the central nervous system stimulates the processes of neurogenesis and regeneration of damaged tissue. Transplanted NSCs are able to self-renew and differentiate into neurons, astrocytes and oligodendrocytes. At the same time, obtained neurons take an active part in the restoration of nervous tissue, while astrocytes and oligodendrocytes are involved in the processes of remyelination, maintaining trophic function and stimulating the restoration of the surrounding neural cells. Improvement of cognitive functions during NSC transplantation is associated with increased synaptogenesis. Implanted NSCs are also able to enhance angiogenesis by increasing the expression of vascular endothelial growth factor (VEGF), reduce astrogliosis and proinflammatory cytokines secretion [18].

Today, embryonic stem cells are considered a promising source for the treatment of various diseases, due to the cells' high plasticity, their ability to differentiate into all three germ sheets (endoderm, mesoderm and ectoderm) and to unlimited self-renewal [19]. One study demonstrated a decrease in the volume of the damaged area, astrogliosis decrease and motor functions improvement during transplantation of embryonic NSCs to rats in a TBI model [20]. In addition, it is interesting to note that human NSCs (hNSC) transplanted to immunodeficient rats are able to survive for six months after administration, differentiating into mature neurons, astrocytes and oligodendrocytes. It is assumed that hNSC transplantation can become an effective therapy for the restoration of cognitive functions after brain injury [21].

As is known, the use of embryonic materials in cell therapy is undesirable for ethical reasons; therefore, special attention of scientists in recent years has been

focused on the study of iPSCs. To obtain iPSCs from somatic cells, the technique described by Yamanaka's group in 2006 is most often used [17, 22]. It is important that iPSCs have a high proliferative potential and are able to give rise to all three germ leaves. It is equally important that iPSCs are ideal candidates for autologous cell therapy, because they can be obtained individually, directly from patients. All this makes it possible to avoid both problems related to immune rejection of the transplant and ethical problems [15]. Literature describes studies where IPSC cell therapy helps to improve motor activity and restore cognitive function in TBI [23, 24]. Nevertheless, the use of iPSCs in cell therapy has its limitations, which are associated with high tumorigenicity, difficulty of obtaining iPSCs and high cost of therapy [16, 17].

As recent studies have shown, MSCs also have potential in the treatment of TBI, due to their anti-inflammatory and anti-apoptotic properties. MSCs are multipotent stem cells with the ability to self-renew and multi-differentiate. Since they are present in many tissues of our body, they can be isolated from various sources: bone marrow, skeletal muscles, adipose tissue, and peripheral blood. In different microenvironments, MSCs differentiate into mesodermal cells and tissues. It is known that MSCs have a number of advantages, the main of which are their easy production, low immunogenicity, high regenerative potential even after freezing, as well as their ability to migrate to the lesion site. These characteristics make MSCs a promising tool for TBI therapy [25]. Studies have shown that when MSCs are transplanted directly into the injury area or using intravenous or intraarterial injections during the acute, subacute or chronic phases of TBI, there is a significant decrease in neurological deficits of motor and cognitive functions [15, 26]. In addition, clinical trials on the use of MSCs as TBI therapy demonstrated that MSCs contribute to the regeneration of brain tissue [27] and improve motor functions [28].

The introduction of stem cells directly into the lesion is an extremely difficult process, which is associated with the complexity of the delivery procedure itself and the risks of systemic side effects. At the same time, the disadvantages of intravenous and intraarterial administration are high risks of a generalized immune response [29].

To date, there is increasing evidence indicating the importance of paracrine signaling by transplanted cells as a mechanism supporting the repair of damaged tissues. That is why the focus of research has shifted to the use of products secreted by stem cells: neurotrophic factors, complexes of biologically active molecules obtained from conditioned media, or extracellular vesicles. This approach avoids both ethical problems of cell transplantation and the problems associated with immune rejection of the injected material [19, 30, 31].

It is interesting to consider the use of the secretome and extracellular vesicles (EV) of stem cells in TBI therapy. There is evidence from literature sources that, for example, in the pig TBI model, the use of extracellular vesicles produced by human MSCs (MSC-EV) helps to reduce edema and partially restore the integrity of the blood-brain barrier [32]. While in the rat model of TBI, the use of MSC-EV improves cognitive and sensorimotor functions, reduces neuroinflammation and death of hippocampal neurons. At the same time, there is a significant increase in the population of endothelial cells in the damaged area, as well as an increase in the number of new immature neurons in the dentate gyrus of the hippocampus, which emphasizes the involvement of EV in the induction of angiogenesis and neurogenesis [33, 34]. In addition, it is known that nanoscale membrane vesicles of MSCs, called exosomes, are capable of having anti-apoptotic, immunomodulatory and neuroprotective effects. The latter, in particular, is due to the induction of the transformation of the proinflammatory phenotype of microglia into an anti-inflammatory one, which is largely due to a decrease in the level of IL-1β [35]. It is important to note that MSC secretome also has a therapeutic effect, which was demonstrated in a rat model of TBI. It has been shown that MSC secretome has an anti-inflammatory effect, due to switching of M1 microglia phenotype to M2, which, in turn, is associated with interleukin-10 (IL-10), being part of the secretome [36].

Literature describes positive paracrine effect not only of MSCs, but also of other types of stem cells. For example, it is known that intravenous administration of extracellular vesicles of NSC (NSC-EV) to rats with

TBI has a neuroprotective effect, promotes restoration of motor function in animals and migration of endogenous NSCs to the lesion [37]. At the same time, the effect of the use of NSC-EV is sex-dependent: males have a much more pronounced therapeutic effect than females [38]. In addition, it is known that NSC exosomes are able to penetrate the blood-brain barrier, inhibit apoptosis, suppress inflammation and regulate autophagy [39]. It has been shown that the target of miR-1246 microRNA included in NSC exosomes is the p53 protein, which, in turn, takes an active part in the regulation of apoptosis and the cell cycle [39, 40]. MiR-21a, another microRNA of NSC exosomes, initiates cell differentiation and promotes regeneration of nervous tissue [41]. In addition to the above, it has been demonstrated that the use of NSC exosomes leads to a decreased affected area of the brain in the rat model of TBI and activates the process of angiogenesis, which is especially noticeable in males [37].

Conclusion

TBI is an important medical problem with serious consequences for health and quality of life. TBI triggers complex cellular mechanisms, including activation of various cell types. Traumatic exposure provokes microglia and astrocytes activation, which leads to the secretion of cytokines, interleukins and other inflammatory mediators. TBI activates a systemic inflammatory response, which is accompanied by the migration of leukocytes, such as neutrophils and monocytes, to the injury area. At the same time, damaging effects can initiate the proliferation of neural stem cells in certain areas of the brain, which can contribute to the formation of new neurons and maintain brain plasticity.

Despite significant advances in the diagnosis and primary therapy of TBI, rehabilitation and recovery methods are still not effective enough. Cell therapy is a promising approach aimed at regenerative processes and restoration of brain functions. However, despite the prospects, additional research is needed to optimize the use of cell therapy in clinical practice. The issues of safety, efficacy and selection of suitable cellular sources require further research.

Summarizing all the above, it can be noted that today profound knowledge of the cellular and molecular processes underlying the pathogenesis of TBI, allows us to consider direct cell transplantation and the use of products secreted by them as a promising method of TBI therapy.

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Черепно-мозговая травма: основные клеточные механизмы и новые подходы к терапии

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Аннотация. Черепно-мозговая травма (ЧМТ) представляет серьезную медицинскую проблему и является одной из ведущих причин инвалидности и смертности среди военнослужащих и гражданского населения. Известно, что ежегодно в мире от ЧМТ погибает порядка 1,5 млн человек, при этом около 2,5–3 млн теряют трудоспособность. В России каждый год ЧМТ диагностируется у 1 млн человек, среди которых каждый пятый становится инвалидом I или II группы. Несмотря на значительные усилия в области исследований эффективные методы лечения ЧМТ до сих пор остаются ограниченными, так как ЧМТ характеризуется широким спектром патологических изменений в тканях головного мозга. Первичное повреждение головного мозга представляет собой острое и необратимое механическое повреждение паренхимы нервной ткани. Последующие процессы вторичного включают в себя эксайтотоксичность, митохондриальную дисфункцию, окислительный стресс, дегенерацию аксонов и нейровоспаление. Эти процессы часто растягиваются во времени и могут занимать от нескольких дней до нескольких лет. Недавние достижения в области клеточной терапии открывают новые перспективы для терапии этого состояния. В данном обзоре рассмотрены основные клеточные механизмы острой и хронической фаз ЧМТ, а также перспективы применения стволовых клеток для терапии данного заболевания. Представлен анализ последних исследований, посвященных применению клеточной терапии при ЧМТ. Рассматриваются различные типы стволовых клеток, такие как нейральные стволовые клетки, мезенхимальные стромальные клетки и другие в контексте их потенциала для восстановления поврежденных тканей мозга. Особое внимание уделяется механизмам действия клеток в процессе регенерации, включая их влияние на воспаление, нейрогенез, и синаптическую

пластичность. Рассматривается использование паракринных факторов, выделяемых стволовыми клетками, в качестве потенциального препарата для терапии черепно-мозговых травм. Выводы. Клеточная терапия, а также использование продуктов, секретируемыми клетками, являются новыми и многообещающими способами лечения ЧМТ.
Ключевые слова: черепно-мозговая травма, клеточная терапия, секретом, внеклеточные везикулы, нейральные стволовые клетки, индуцированные плюрипотентные стволовые клетки, мезенхимальные стромальные клетки

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