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Spinal cord injury: pathogenetic principles of molecular and cellular therapy

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ABSTRACT

Spinal cord injury is a prognostically unfavorable condition due to the subsequent development of primary and secondary damage to the nervous structures, leading to various disorders of motor and sensory capabilities, which is also accompanied by dysfunction of the autonomic nervous system. Considering the initial complexities of regeneration processes in the central nervous system, in order to select treatment tactics for patients with spinal cord injury, it is important for doctors to know the cellular basis of the pathophysiological processes occurring in the spinal cord in the acute and chronic phases after injury, including in order to adequately select cells-targets of pharmacological drugs. Existing methods of treating neurotrauma can still do little to help prevent the death of neurons and the formation of glial scars, which make it impossible for the migration of cells involved in the processes of post-traumatic remodeling of the spinal cord and become an obstacle to the sprouting of regenerating axons. Unfortunately, preventing the formation of a glial scar remains an unsolved problem in clinical practice. In addition, in the case of spinal cord injuries in the clinic, it is extremely important to provide humoral stimulation to maintain the viability of nerve structures, for example, using numerous growth factors that are well known today, which have a beneficial effect on the intracellular regeneration of neurons and other cells involved in these processes, but the methodology for their delivery into the central nervous system has only been tested in animal models. That is why there is an urgent need to develop fundamentally new approaches to the treatment of the consequences of spinal cord injury, including cellular technologies based on transplantation of stem or differentiated cells in order to restore nerve structures and secretion of growth factors, the use of genetic constructs carrying genes for neurotrophic factors that can minimize development of post-traumatic destructive processes in the central nervous system. This review is devoted to these issues.

Keywords: spinal cord injury; neuroglia; neurotrophic factors; gene therapy; cell therapy; review.

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Спинномозговая травма: патогенетические принципы молекулярной и клеточной терапии

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АННОТАЦИЯ

Травма спинного мозга — прогностически неблагоприятное состояние из-за развития после неё первичных и вторичных повреждений нервных структур, приводящих к разнообразным расстройствам двигательных и сенсорных возможностей, что также сопровождается дисфункциями вегетативной нервной системы. Учитывая изначальные сложности процессов регенерации в центральной нервной системе, для выбора тактики лечения пациентов с травмой спинного мозга врачам важно знать клеточные основы патофизиологических процессов, протекающих в спинном мозге в острую и хроническую фазы после повреждения, в том числе и для того, чтобы адекватно выбрать клетки-мишени фармакологических препаратов. Существующие методы терапии нейротравм пока мало чем могут помочь в предотвращении гибели нейронов и образования глиальных рубцов, которые делают невозможной миграцию клеток, участвующих в процессах посттравматического ремоделирования спинного мозга, и становятся преградой для прорастания регенерирующих аксонов. К сожалению, недопущение формирования глиального рубца для клинической практики остаётся до сих пор не решённой задачей. Кроме того, при травмах спинного мозга в клинике чрезвычайно важно обеспечить гуморальную стимуляцию поддержания жизнеспособности нервных структур, например с использованием многочисленных хорошо известных на сегодняшний день факторов роста, благоприятно влияющих на внутриклеточную регенерацию нейронов и других клеток, вовлечённых в эти процессы, но методология их доставки в центральную нервную систему отработана только в моделях на животных. Вот почему существует острая необходимость в разработке принципиально новых подходов к лечению последствий травмы спинного мозга, включающих клеточные технологии, основанные на трансплантации стволовых или дифференцированных клеток, с целью восстановления нервных структур и секреции ростовых факторов, использование генетических конструкций, несущих гены нейротрофических факторов, способных минимизировать развитие посттравматических деструктивных процессов в центральной нервной системе. Этим вопросам посвящён настоящий обзор.

Ключевые слова: травма спинного мозга; нейроглия; нейротрофические факторы; генная терапия; клеточная терапия; обзор.

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Abbreviations

ATP, adenosine triphosphate; GABA, γ-aminobutyric acid; IL, interleukin; UBMC, umbilical cord blood mononuclear cells; SC, spinal cord; SCI, spinal cord injury; CNS, central nervous system; ASIA, Impact scale of the American Spinal Injury Association; BDNF, brain-derived neurotrophic factor; FGF, fibroblast growth factor; GFAP, glial fibrillary acidic protein; VEGF, vascular endothelial growth factor.

BACKGROUND

Spinal cord injury (SCI) is a sudden and unpredictable event that damages part of the spinal cord, causing motor and sensory impairments and autonomic nervous system dysfunction [1]. Such injuries induce debilitating conditions that affect a person's physical, psychological, and social well-being [2].

The effects of SCI largely depend on the severity and level of injury [3]. The irreversibility of functional disorders is due to the initially limited regeneration in the central nervous system (CNS), which is reflected by the lack of neuronal replacement, difficulty in regeneration of damaged axons, and difficulty in restoring damaged functional relationships [4].

Currently, treatment for the consequences of SCI are limited and aimed at surgical intervention at the earliest in the acute phase to limit the loss of neurological functions as feasible. However, increasing negative pathophysiological processes, such as mass death of nerve and glial cells, nerve process demyelination, neuroinflammation, ischemia, hematoma formation, cystic cavities, and glial scars, lead to progressive neurodegeneration and suppress the possibilities for regeneration [3].

Currently, there is no unified and effective method of treating such patients. Thus, new treatment methods aimed at inhibiting the development of the main morphofunctional changes occurring in the spinal cord (SC) after neurotrauma and stimulating post-traumatic neuroregeneration should be established [5].

The consequences of SCI are a devastating neurological condition that often leads to disability, functional impairment in various body systems, and psychological stress in the patient [6]. Long-term treatment, daily care, and financial costs further negatively affect the family, thereby creating significant social problems. More than 50% of patients with such injuries are unable to restore fully impaired functions and return to a full-quality life [7]. According to some data, over the past 70 years, the number of SCI patients has increased 200 times, and 8000 SCI cases are recorded annually in Russia [8].

Depending on its causes, SCI is classified into traumatic and nontraumatic [9]. Traumatic injuries may result from a direct blow to the spine or may be associated with compression, flexion, extension, or rotation of the spine beyond the physiological range [2]. Nontraumatic injuries are due to neurodegenerative diseases, tumors, or infections affecting the SC [9].

The American Spinal Injury Association (ASIA) impairment scale is commonly used in classifying SCI [10]. Using the ASIA scale, based on a standardized examination of SCI patients, which involves testing the dermatomes and myotomes of certain segments of the SC and determining voluntary contraction of the anus and the sensation of anorectal pressure, the level, severity and completeness (complete/incomplete) of damage to the SC are established.

Complete SC injury is characterized by the absence of all motor and sensory functions distal to the injury site, including the sacral roots. In cases of incomplete damage to the SC, motor and/or sensory function below the injury site is partially preserved [11]. Based on time parameters, acute (up to 48 hours), subacute (48 hours to 14 days), intermediate (14 days to 6 months), and chronic (>6 months) phases are distinguished [9].

The pathogenesis of SCI includes the direct impact of injury (primary injury) and development of secondary post-traumatic consequences. Primary injuries resulting from vertebral displacement or spinal fracture lead to compression, the most common manifestation of neurotrauma, or transection (rupture) of SC structures [12]. In this case, violations of the SC integrity are accompanied by bleeding and hematomas, which leads to decreased blood supply, up to its complete cessation in the site of injury with the development of local ischemia of the nervous tissue [13].

The processes described above, as well as blood–spinal barrier permeability impairment and increased edema, enhance negative changes in the gray and white matter of the SC, causing mass death of nerve cells through necrosis or apoptosis. The main causes of neuronal death are physical exposure, hypoxia, and excitotoxicity [12].

Thus, primary injuries trigger a subsequent cascade of irreversible negative changes in the site of injury and SC segments remote from the epicenter of injury (secondary injuries), which lead to further degeneration of nervous tissue and increasing neurological dysfunction [9].

Secondary damage is predominantly associated with neuroinflammation. The migration of macrophages and other leukocytes into the SC tissue is accompanied by an increase in the level of pro-inflammatory cytokines, such as tumor necrosis factor α and interleukin (IL)-1β. The development of inflammation and involvement of macro- and microglial cells in the response prevent the morphofunctional restoration of the SC [9, 13].

The overall negative consequences of secondary injuries significantly aggravate the effect of primary disorders caused by injury, which ultimately leads to irreversible changes in the structural organization of the SC, including the formation of glial scars and cystic cavities. Pronounced pathomorphological changes in combination with unsatisfactory axonal growth and remyelination indicate that the SC has a low potential for independent recovery [14]. In this regard, effective methods are required to stimulate the SC post-traumatic regeneration.

NEUROGLIAL RESPONSE IN SPINAL INJURY

Astrocytes

Astrocytes make up approximately 25%–50% of all the CNS cells and are classified into protoplasmic (located in the gray matter and have several branched short processes) and fibrillar (with numerous long, non-branching processes localized in the white matter) [15]. Astrocytes perform several functions, including maintaining ionic and water homeostasis, utilization of neurotransmitters and metabolic end products in neurons, participating in immune reactions, and regulating synaptic plasticity [16]. Perivascular astrocyte feet, in contact with endothelial cells, are part of the blood–brain and blood–spinal barriers, ensuring their structural integrity and functioning [17].

Astrocytes are activated in response to various stimuli, including inflammation, ischemia, and injury, and are involved in the pathological process in the form of reactive astrogliosis [18]. Many intercellular signaling molecules are capable of triggering reactive astrogliosis or regulating the degree of its manifestation, including growth factors and cytokines such as IL-6, ciliary neurotrophic factor, tumor necrosis factor α, interferon γ, IL-11, IL-10, transforming growth factor β, fibroblast growth factor (FGF) type 2, lipopolysaccharides, neurotransmitters (glutamate and norepinephrine), adenosine triphosphate (ATP), nitric oxide (NO), and neurodegeneration-associated products such as β-amyloid [19].

After SCI, astrocytes, under the influence of signaling molecules, acquire the phenotype of reactive astrocytes [18]. Glial fibrillary acidic protein (GFAP), which is part of the cytoskeleton of astrocytes, is a widely used marker of reactive astrocytes, which degree of the level increase correlates with the severity of SC damage [20]. Moreover, an increase in GFAP expression in astrocytes is accompanied by their characteristic morphological changes [21].

Currently, it is notable that the morphological changes that occur in astrocytes during their transition to a reactive state consist of hypertrophy of the body and processes, but in parallel, there is an increase in both the number of processes and their length. Morphological changes vary depending on the type of astrocytes, their density of distribution, and location at the time of injury [22]. Reactive astrocytes located distant from the injury epicenter have a stellate shape and hypertrophied processes without a predominant orientation, whereas those adjacent to the injury epicenter have longer processes oriented toward the injury [23].

In recent years, numerous studies have shown that activation of astrocytes can lead to changes in their functions and the release of a number of cytokines (tumor necrosis factor α, IL-6, IL-10, IL-1β), chemokines (CCL2, CCL3), neurotrophic factors (brain-derived neurotrophic factor [BDNF], glial neurotrophic factor), amino acids (γ-aminobutyric acid [GABA], glutamate), and extracellular matrix components (e.g., chondroitin sulfate proteoglycans, collagen I, fibronectin, matrix metalloproteinase-9), which are capable of changing the microenvironment of SC neurons after its injury [24]. Thus, chondroitin sulfate proteoglycan secreted by reactive astrocytes inhibits axon regeneration, and bone morphogenetic protein and endothelin-1 have an inhibitory effect on the differentiation of oligodendrocyte precursors, which ultimately reduces the efficiency of remyelination [22].

Moreover, molecules released by reactive astrocytes involve an increasing number of native astrocytes in the process, acquiring a reactive phenotype, which increases secondary damage in the SC [24].

However, reactive astrogliosis can be considered a protective mechanism that limits the site of the epicenter of neurotrauma. In the chronic phase of SCI, reactive astrocytes acquire the phenotype of "scar-forming" cells, which, together with perivascular stromal cells, microglial cells, oligodendrocyte precursors, fibroblasts, and macrophages of bone marrow origin, form the astroglial scar [18, 25].

The formed glial scar forms a dense border structure around the injury epicenter, isolating the damaged site from the surrounding nervous tissue and preventing the migration of leukocytes to the injury epicenter [26]. Thus, one of the crucial functions of the glial scar is delimiting the site of SC damage from healthy tissue to prevent its further secondary damage.

Positive aspects of the involvement of astrocytes in overcoming the consequences of injury include morphogenetic protein Sonic hedgehog secretion, which activates signaling cascades to restore tight junctions between endothelial cells in the blood–brain barrier, and the ability to phagocytose dead cells with the participation of ATP-binding transport proteins (ABCA1) [24].

Microglial cells

Microglial cells represent a heterogeneous group of CNS macrophages and constitute about 10%–15% of all glial cells. The first generation of microglial cells originates from the blood islet cells of the yolk sac, which migrate into the developing brain before the onset of vasculogenesis [27]. In the early stages of prenatal development, microglial cells have an amoeboid (round) shape with short thick processes and immunological, histochemical, and morphological properties common with other tissue macrophages. However, during development, early microglial cell processes elongate and branch, and the cells acquire a shape characteristic of postnatal ramified (branched) microglia [28].

They indirectly participate in CNS development and its homeostasis and secrete neurotrophic factors (BDNF, insulin-like growth factor-1, hepatocyte growth factor) that promote the survival of neurons and significantly contribute to the formation of neural networks [29].

Microglial cells are involved in most processes associated with disorders of the structure and functions of the CNS [27]. One of the earliest functional signals for the activation

of microglial cells is ATP, which is released from damaged cells and identified by specific G-protein receptors P2Y on their membrane [30]. The release of cytokines and other factors, such as IL-1β, tumor necrosis factor α, damage-associated molecular fragment, interferon γ, and nitric oxide (NO), by damaged CNS cells also activates the microglia and increases the rate of their proliferation [31].

When activated, microglial cells undergo specific morphological changes. They acquire a round, amoeboid body with short processes, similar to the structure of tissue macrophages [30]. As part of their homeostatic functions through cytokine secretion, they provide rapid information signaling in response to CNS damage or infection [27].

In the case of SCI, microglia is one of the first types of cells to respond to damage, and the number of activated microglial cells increases maximally by day 7 after neurotrauma [32]. Additionally, it is known that in pathology, monocytes can penetrate the blood–brain barrier and differentiate into microglial-like cells [33].

At the site of SC damage, two types of microglial cells are distinguished, namely, M1 (pro-inflammatory) and M2 (anti-inflammatory), which can participate in SC damage but trigger regeneration mechanisms, whereas the phenotypes of these cells and their functions are relatively dynamic and can change, including depending on the microenvironment in the injury site.

Activated M1 microglia contributes to secondary damage to the SC by releasing pro-inflammatory factors (IL-1β, IL-6, tumor necrosis factor α, CCL5, inducible nitric oxide synthase), which create a neurotoxic environment at the injury site and limit the possibilities of post-traumatic regeneration [34]. Furthermore, M2 microglial cells, which produce transforming growth factor β, IL-10, and IL-1Ra and clear the injury site of cellular debris, create a neuroprotective intercellular environment after SCI [35].

However, the status and functional state of M2 cells is extremely complex. Accumulated research data has revealed various M2 cell phenotypes, such as M2a, M2b, M2c, and M2d, where each phenotype is characterized by unique biological functions that ensure the process of post-traumatic regeneration of the SC, maintaining homeostasis, suppressing inflammation, and producing neurotrophic factors [32].

Oligodendrocytes

Oligodendrocytes are myelin-forming cells of the CNS, which also perform a supporting function and are responsible for axon integrity. In the formed CNS, oligodendrocyte progenitor cells are the main proliferating cell type that maintains oligodendrocyte count, which constitute approximately 5% of all CNS cells. This feature of oligodendrocytes enables the rapid restoration and renewal of myelin, which can be lost as a result of aging/decay or various diseases [36].

Oligodendrocytes are cells that are susceptible to any changes in their microenvironment. As a result of primary damage in SCI associated with ischemia, oxidative stress, and accumulation of cytotoxic metabolites (free radicals and cytokines) in the microenvironment, oligodendrocytes die, and, as a result, the balance of myelination/demyelination of nerve processes is disturbed [37].

The number of oligodendrocytes that have entered into apoptosis is maximum at the injury epicenter, which results in complete demyelination of axons in this site, whereas axons located at a distance from the injury focus remain more intact.

Axon regeneration inhibiting molecules secreted by oligodendrocytes are a crucial negative factor. Neurite outgrowth inhibitor A (Nogo-A), oligodendrocyte-myelin glycoprotein, and myelin-associated glycoprotein cause axonal growth cone damage and concomitant neurite retraction [31]. Long-term loss of oligodendrocytes in the chronic phase of SCI is a main obstacle to effective functional restoration of SC pathways [38].

Ependymocytes

Ependymocytes are neuroepithelial cells lining the SC central canal and cerebral ventricles. They originate from radial glial cells [39]. Cubic-shaped ependymocytes containing microvilli and 1–4 cilia on the apical surface form an epithelial-like layer that performs the delimiting function of the central channel of the SC and ensures the movement of cerebrospinal fluid [40]. Moreover, neuroepithelial cells have pronounced heterogeneity and differ in localization, morphology, surface markers, and functions [39].

Ependymocytes represent a self-renewing population of cells; however, their limited proliferation increases considerably after SCI in animals. Fernandez-Zafra et al. revealed that the lining thickness of the SC central canal in presence of neurotrauma increases due to the proliferation of stem/progenitor ependymal cells, which subsequently migrate from the central canal and participate in brain remodeling [41].

Ependymal progenitor cells migrate to the SC injury site and differentiate into oligodendrocytes and astrocytes, which are involved in the formation of glial scar [42, 43]. The rate of proliferation and differentiation of ependymal progenitor cells depends on damage severity [39]. However, the characteristics of SC ependymocytes vary greatly among different species. Ependymal cells in human SC do not proliferate; however, they exhibit properties of neural stem cells when cultured *in vitro* [44].

Thus, the abovementioned aspects of molecular and cellular changes that occur during primary and subsequent secondary injuries in SCI determine the use of specific pathogenetic therapy for the consequences of spinal cord injury in the acute and chronic phases.

GENE THERAPY

Gene therapy involves the delivery of normal genes into recipient cells to correct the function of similar mutant genes or change the functional activity of cells, providing overexpression of biologically active molecules critical for therapeutic

purposes [45]. Artificial genetic material can be delivered into the recipient's body using plasmid or viral vectors (direct gene therapy) or cellular carriers of the transgene (cell-mediated gene therapy) [46].

Increasing the level of neurotrophic factors in the site of neurodegeneration positively affects SC neuroplasticity. Hence, several studies in the field of gene therapy for SCI focused on the use of various neurotrophic factors [47].

Neurotrophic factors are proteins that regulate neurogenesis, functional activity, synaptic plasticity, and neuronal survival [48]. Selecting neurotrophic factors to control neuronal death in SCI depends partially on the sensitivity of a particular population of nerve cells to a particular factor [49]. In experiments stimulating post-traumatic SC regeneration, factors including BDNF, neurotrophins, glial neurotrophic factor, and vascular endothelial growth factor (VEGF) are widely used [50].

BDNF is secreted by neurons or glial cells and induces a significant effect on brain neuroplasticity under pathological conditions. It binds to tyrosine kinase receptor B and acts through a paracrine or autocrine mechanism [51]. The efficiency of BDNF has been associated with cholinergic, serotonergic, dopaminergic, and GABAergic neurons [52]. In experiments on rats with SCI, BDNF was found to have a neuroprotective effect (reduces the counts of neurons and oligodendrocytes in apoptosis), promote regeneration, and propagate axons after SCI [53].

Neurotrophin-3 is from a large family of neurotrophin proteins and is widely distributed in the CNS. The highest expression of the neurotrophin-3 gene was determined in the motor neurons of the developing SC; however, it decreases in adulthood. This factor ensures the survival of motor neurons and modulates the formation of their synapses with target cells [54]. The positive effect of neurotrophin-3 on axonal growth in the corticospinal tract has been demonstrated in the acute and chronic phases of SCI in rats [48].

Glial neurotrophic factor is a critical growth factor in the CNS and peripheral nervous system, which is revealed in high concentrations during neurogenesis [55]. Moreover, as a neuroprotective agent, glial neurotrophic factor can reduce blood–spinal barrier permeability and nitric oxide synthase levels. These effects reduce cell damage and SC swelling during trauma and provide supportive effect on the functional state of many different types of cells in the nervous tissue [56]. Further, in presence of glial neurotrophic factor overexpression in rats with SC transsection, axonal remyelination was accompanied by an improvement in functional parameters [53].

VEGF is a well-known angiogenic factor, participating in vasculogenesis and angiogenesis [57], and neurotrophic factor [58]. The VEGF family includes VEGF-A (formerly known as VEGF), VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factor. Studies have demonstrated the positive effect of VEGF on neuroplasticity following SCI [59].

The FGF family needs mentioning. Members of this family, including FGF1, FGF2, FGF4, and FGF10, reduce secondary damage after neurotrauma, such as inflammation and astrocyte activation, and can stimulate axonal regeneration and angiogenesis [60]. In several studies, insulin-like growth factor-1 and ciliary neurotrophic factor, which promote oligodendrocyte survival, axonal growth, and myelination, have been used to stimulate regeneration after SCI [61, 62]. Additionally, nerve growth factor can support the survival of neurons and stimulate the growth of their axons, promoting nerve regeneration and motor function recovery after SCI [63].

Most of the listed neurotrophic factors are capable of blocking neuronal apoptosis and maintaining the vital activity of damaged nerve cells; however, they are rapidly destroyed after their direct administration. Thus, to maintain stably the level of neurotrophic factors in the injured SC, gene therapy methods are more advisable [64].

CELL-BASED THERAPY

Over the past decade, significant advances in cell technology have contributed to the introduction of cell therapy for CNS pathology correction [65]. In experiments, cell therapy is actively used in various models for the treatment of post-traumatic and post-ischemic injuries of the CNS and neurodegenerative diseases [66].

The results of SCI are complex, including the simultaneous development of various pathophysiological processes, which involve numerous types of SC cells that die in the acute and/or chronic phases [67]. Therefore, the issue on which type of cells should be transplanted remains to be resolved. Additionally, the survival of transplanted cells and their integration with cells of survivors of traumatic injury remain unclear [68, 69].

For cell therapy of SCI, various stem and mature cells of both allogeneic and autogenous origin are used. The expected effect of cell therapy is determined by the type of transplanted cells [70, 71]. To date, evaluation of the effects of transplantation of several types of cells, including neural stem, mesenchymal stem, Schwann, neuroepithelial ensheathing, and umbilical cord blood mononuclear cells (UBMCs), has shown promising results in overcoming the consequences of SCI [72].

Neural stem cells

Neural stem cells have a high therapeutic potential for restoring damaged SC structures after injury, because they are capable of proliferation and differentiation into neurons and neuroglial cells [73]. Neural stem cell transplantation into the SC following traumatic injury has shown positive effects on cord cell viability, neurite growth, and remyelination. Moreover, young neurons resulting from neural stem cell transplantation after SCI exhibit active axonal growth into the recipient tissue. They potentially act as "mediators" in the restoration of damaged interneuron connections, for example, in the regeneration of the cortical–spinal tract axons [74]. Clinical trial studies using neural stem cells are limited to information about their early termination [75].

Mesenchymal stem cells

Mesenchymal stem cells are attractive candidates for use in cell therapy for SCI owing to the simple and safe procedure for their isolation from various sources (bone marrow, umbilical cord blood, adipose tissue), the possibility of autotransplantation, and the limited risk of tumor development [76].

Previously, it was established *in vitro* that the positive effect of mesenchymal stem cells on neuroregeneration is associated with their ability to differentiate into neuronal or glial cells [77]. However, recent studies have shown that the therapeutic effect is mainly achieved because of their potential to secrete a wide range of biologically active molecules, which, through a paracrine mechanism, influence the functional state of various cells at the focus of injury.

Mesenchymal stem cells are believed to secrete VEGF, hepatocyte growth factor, insulin-like growth factor-1, stanniocalcin-1, transforming growth factor β, and granulocyte-macrophage colony-stimulating factor, which promote the survival of damaged neurons and oligodendrocytes. Together with placental growth factor, monocyte chemotactic protein-1, FGF, and IL-6, they induce a stimulating effect on angiogenesis. Proliferation and regeneration of intact neurons is supported by secreted mesenchymal stem cells, namely, glial neurotrophic factor, BDNF, and nerve growth factor [78].

The ease of obtaining and culturing autologous mesenchymal stem cells and their ability to produce factors crucial for the restoration of SC after injury have become the main reasons for conducting clinical trials with their use [79]. However, most trials only indicated the fact that transplantation of mesenchymal stem cells does not lead to tumor transformation and does not cause any other side effects. In one study, 7 of 14 patients with chronic SCI showed improved ASIA scores; however, this remains to be confirmed in future larger randomized trials [76].

Schwann cells

Schwann cells are responsible for the myelination of nerve processes in peripheral nerves and ensure their regeneration after damage, which was the basis for the use of Schwann cells in cell therapy for SCI [80]. In the Schwann cell transplantation site, a microenvironment is created that is both neuroprotective and beneficial for axonal regeneration through trophic factors (nerve growth factor, BDNF, ciliary neurotrophic factor, and neurotrophin-3), extracellular matrix components (e.g., fibronectin, laminin, and collagen), and adhesion molecules (NCAM and L1) that are produced by transplanted cells.

Clinical trials of cell therapy using autologous Schwann cells in patients with thoracic SCI in the subacute and chronic phases showed that participants did not experience complications associated with autologous Schwann cell transplantation [81].

Neuroepithelial ensheathing cells

Despite the fact that the overwhelming majority of CNS neurons lose their ability to proliferate in adulthood, humans have constantly renewed neurons, for example, the hippocampus and olfactory lining [82].

Neuroepithelial ensheathing cells are specialized glial cells that surround olfactory neurons and their processes [83]. The use of these cells for cell therapy of SCI is based on their properties to stimulate the renewal of olfactory neurons and the growth of their processes in the CNS and beyond it [84]. Neuroepithelial ensheathing cells transplanted into the injured SC synthesize neurotrophic factors (nerve growth factor, BDNF, neurotrophin-3), induce a positive effect on myelination, and increase the density of blood vessels in the site of injury due to VEGF production [85].

A clinical trial demonstrated the safety and absence of complications of autologous ensheathing neuroepithelial cell transplantation in SCI patients; however, larger studies are required to confirm improved neurological outcome [75].

Umbilical cord blood mononuclear cells

UBMCs as a material for cell therapy are attracting increased attention from specialists in the field of regenerative medicine. The cellular composition of the mononuclear fraction includes hematopoietic stem, progenitor endothelial, and mesenchymal stem cells and other stem cells with pluripotent properties; therefore, they can be considered as a potential source for cell therapy for ischemic, traumatic, and neurodegenerative diseases [86].

Additionally, UBMCs synthesize various cytokines, ILs, and growth, angiogenic, antioxidant, and neurotrophic factors, which can also have a stimulating effect on the regeneration of tissues and organs. Moreover, factors such as availability, ease of obtaining and storing, and safety of allotransplantation are attractive [87]. Thus, the International Association of Neurorestoratology recommended UBMCs for clinical use [88].

In clinical trials, UBMCs and mesenchymal stem cells isolated from umbilical cord blood are used for the treatment of SCI. Safety, restoration of sensitivity of the dermatomes near the injury site, and slight restoration of motor activity were established in clinical trials after UBMC transplantation into the SC of patients with chronic SCI [89].

The clinical trial conducted at the N.V. Sklifosovsky Research Institute of Emergency Medicine involved patients with severe SCI (cervical, thoracic, and lumbar) who received intravenous UBMCs (300 million in 100 ml of solution) on day 3 after surgical decompression and/or stabilization of the SCI [90].

Several research groups have transplanted UBMCs + mesenchymal stem cells in SCI patients. Thus, in one trial, after a course of treatment that included four intrathecal infusions with an interval of 1 week, SCI patients achieved improvement in motor and sensory functions and ability to control bowel and bladder functions [91]. In another study, improved autonomic function and restoration of evoked potentials were demonstrated in patients with chronic SCI 12 months after intrathecal and intravenous administration of UBMCs + mesenchymal stem cells [92].

Our studies in rat and mini-pig models with contusive SCI in the thoracic region after intrathecal infusion of genetically

modified UBMCs overexpressing VEGF, glial neurotrophic factor, and NCAM adhesion molecules, in combination with epidural electrical stimulation, revealed restoration of motor activity of the hind limbs and positive remodeling SC in the neurotrauma site [93, 94].

CONCLUSION

SCI remains one of the most serious problems of modern healthcare. It is associated with complex morphofunctional changes that occur in the injured SC during the development of both primary and secondary damage affecting various brain structures and, as a consequence, the ineffectiveness of the applied therapeutic approaches. Therefore, a search for novel treatment methods is required, including modern developments in the field of biotechnology.

Gene therapy and transplantation of cellular material for SCI are considered promising methods for overcoming the consequences of injury. However, to date, despite the presence of convincing evidence of the efficiency of gene and cell therapy in animal models of SCI, clinical studies only confirm the safety of using certain types of cells for the treatment of SCI. However, gene therapy for SCI is not used in clinical trials.

A wide variety of vector systems, therapeutic genes, and their combinations and various methods of delivering transgenes into the body of a SCI patient, timing of gene therapy, and the safety of a gene therapeutic drug are factors that should be considered when developing a method of gene therapy for spinal cord injury.

ADDITIONAL INFORMATION

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REFERENCES

1. Benedetti B, Weidenhammer A, Reisinger M, Couillard-Despres S. Spinal cord injury and loss of cortical inhibition. *Int J Mol Sci*. 2022;23(10):5622. doi: 10.3390/ijms23105622
2. Venkatesh K, Ghosh SK, Mullick M, Manivasagam G, Sen D. Spinal cord injury: Pathophysiology, treatment strategies, associated challenges, and future implications. *Cell Tissue Res*. 2019;377(2):125–151. doi: 10.1007/s00441-019-03039-1
3. Alizadeh A, Dyck SM, Karimi-Abdolrezaee S. Traumatic spinal cord injury: An overview of pathophysiology, models and acute injury mechanisms. *Front Neurol*. 2019;10:282. doi: 10.3389/fneur.2019.00282
4. Zheng B, Tuszynski MH. Regulation of axonal regeneration after mammalian spinal cord injury. *Nat Rev Mol Cell Biol*. 2023;24(6):396–413. doi: 10.1038/s41580-022-00562-y
5. Khan FI, Ahmed Z. Experimental treatments for spinal cord injury: A systematic review and meta-analysis. *Cells*. 2022;11(21):3409. doi: 10.3390/cells11213409
6. Khorasanizadeh M, Yousefifard M, Eskian M, Lu Y, Chalangari M, Harrop JS, Jazayeri SB, Seyedpour S, Khodaei B, Hosseini M, Rahimi-Movaghar V. Neurological recovery following traumatic spinal cord injury: A systematic review and meta-analysis. *J Neurosurg Spine*. 2019;1–17. doi: 10.3171/2018.10.SPINE18802
7. Elliott CS, Dallas KB, Zlatev D, Comiter CV, Crew J, Shem K. Volitional voiding of the bladder after spinal cord injury: Validation of bilateral lower extremity motor function as a key predictor. *J Urol*. 2018;200(1):154–160. doi: 10.1016/j.juro.2018.02.064
8. Novoselova IN. Etiology and clinical epidemiology of spinal cord injury. Literature review. *Russian neurosurgical journal named after professor AL Polenov.* 2019;11(4):84–92. (In Russ.)
9. Ahuja CS, Wilson JR, Nori S, Kotter MRN, Druschel C, Curt A, Fehlings MG. Traumatic spinal cord injury. *Nat Rev Dis Primers*. 2017;3:17018. doi: 10.1038/nrdp.2017.18
10. Van Middendorp JJ, Goss B, Urquhart S, Atresh S, Williams RP, Schuetz M. Diagnosis and prognosis of traumatic spinal cord injury. *Global Spine J*. 2011;1(1):1–8. doi: 10.1055/s-0031-1296049
11. Roberts TT, Leonard GR, Cepela DJ. Classifications in brief: American spinal injury association (ASIA) impairment scale. *Clin Orthop Relat Res*. 2017;475(5):1499–1504. doi: 10.1007/s11999-016-5133-4
12. Anjum A, Yazid MD, Fauzi Daud M, Idris J, Ng AMH, Selvi Naicker A, Ismail OHR, Athi Kumar RK, Lokanathan Y. Spinal cord injury: Pathophysiology, multimolecular interactions, and underlying recovery mechanisms. *Int J Mol Sci*. 2020;21(20):7533. doi: 10.3390/ijms21207533
13. Zhang Y, Al Mamun A, Yuan Y, Lu Q, Xiong J, Yang S, Wu C, Wu Y, Wang J. Acute spinal cord injury: Pathophysiology and pharmacological intervention (review). *Mol Med Rep*. 2021;23(6):417. doi: 10.3892/mmr.2021.12056

14. Shafqat A, Albalkhi I, Magableh HM, Saleh T, Alkattan K, Yaqinuddin A. Tackling the glial scar in spinal cord regeneration: New discoveries and future directions. *Front Cell Neurosci*. 2023;17:1180825. doi: 10.3389/fncel.2023.1180825
15. Gradisnik L, Velnar T. Astrocytes in the central nervous system and their functions in health and disease: A review. *World J Clin Cases*. 2023;11(15):3385–3394. doi: 10.12998/wjcc.v11.i15.3385
16. Giovannoni F, Quintana FJ. The role of astrocytes in CNS inflammation. *Trends Immunol*. 2020;41(9):805–819. doi: 10.1016/j.it.2020.07.007
17. Abbott NJ, Patabendige AAK, Dolman DEM, Yusof SR, Begley DJ. Structure and function of the blood-brain barrier. *Neurobiol Dis*. 2010;37(1):13–25. doi: 10.1016/j.nbd.2009.07.030
18. Okada S, Hara M, Kobayakawa K, Matsumoto Y, Nakashima Y. Astrocyte reactivity and astrogliosis after spinal cord injury. *Neurosci Res*. 2018;126:39–43. doi: 10.1016/j.neures.2017.10.004
19. Sofroniew MV, Vinters HV. Astrocytes: Biology and pathology. *Acta Neuropathol*. 2010;119(1):7–35. doi: 10.1007/s00401-009-0619-8
20. Escartin C, Galea E, Lakatos A, O'Callaghan JP, Petzold GC, Serrano-Pozo A, Steinhäuser C, Volterra A, Carmignoto G, Agarwal A, Allen NJ, Araque A, Barbeito L, Barzilai A, Bergles DE, Bonvento G, Butt AM, Chen W-T, Cohen-Salmon M, Cunningham C, Deneen B, De Strooper B, Díaz-Castro B, Farina C, Freeman M, Gallo V, Goldman JE, Goldman SA, Götz M, Gutiérrez A, Haydon PG, Heiland DH, Hol EM, Holt MG, Iino M, Kastanenka KV, Kettenmann H, Khakh BS, Koizumi S, Lee CJ, Liddelow SA, MacVicar BA, Magistretti P, Messing A, Mishra A, Molofsky AV, Murai KK, Norris CM, Okada S, Oliet SHR, Oliveira JF, Panatier A, Parpura V, Pekna M, Pekny M, Pellerin L, Perea G, Pérez-Nievas BG, Pfrieger FW, Poskanzer KE, Quintana FJ, Ransohoff RM, Riquelme-Perez M, Robel S, Rose CR, Rothstein JD, Rouach N, Rowitch DH, Semyanov A, Sirko S, Sontheimer H, Swanson RA, Vitorica J, Wanner I-B, Wood LB, Wu J, Zheng B, Zimmer ER, Zorec R, Sofroniew MV, Verkhratsky A. Reactive astrocyte nomenclature, definitions, and future directions. *Nat Neurosci*. 2021;24(3):312–325. doi: 10.1038/s41593-020-00783-4
21. Gaudet AD, Fonken LK. Glial cells shape pathology and repair after spinal cord injury. *Neurotherapeutics*. 2018;15(3):554–577. doi: 10.1007/s13311-018-0630-7
22. Li X, Li M, Tian L, Chen J, Liu R, Ning B. Reactive astrogliosis: Implications in spinal cord injury progression and therapy. *Oxid Med Cell Longev*. 2020;2020:9494352. doi: 10.1155/2020/9494352
23. Sonn I, Nakamura M, Renault-Mihara F, Okano H. Polarization of reactive astrocytes in response to spinal cord injury is enhanced by M2 macrophage-mediated activation of Wnt/β-catenin pathway. *Mol Neurobiol*. 2020;57(4):1847–1862. doi: 10.1007/s12035-019-01851-y
24. Wang R, Zhou R, Chen Z, Gao S, Zhou F. The glial cells respond to spinal cord injury. *Front Neurol.* 2022;13:844497. doi: 10.3389/fneur.2022.844497
25. O'Shea TM, Burda JE, Sofroniew MV. Cell biology of spinal cord injury and repair. *J Clin Invest*. 2017;127(9):3259–3270. doi: 10.1172/JCI90608
26. Yang T, Dai Y, Chen G, Cui S. Dissecting the dual role of the glial scar and scar-forming astrocytes in spinal cord injury. *Front Cell Neurosci*. 2020;14:78. doi: 10.3389/fncel.2020.00078
27. Nayak D, Roth TL, McGavern DB. Microglia development and function. *Annu Rev Immunol*. 2014;32:367–402. doi: 10.1146/annurev-immunol-032713-120240
28. Kolos EA, Korzhevsky DE. Spinal cord microglia in health and disease. *Acta Naturae.* 2020;12(1):4–17. doi: 10.32607/actanaturae.10934
29. Abe N, Nishihara T, Yorozuya T, Tanaka J. Microglia and macrophages in the pathological central and peripheral nervous systems. *Cells*. 2020;9(9):2132. doi: 10.3390/cells9092132
30. Kroner A, Rosas Almanza J. Role of microglia in spinal cord injury. *Neurosci Lett*. 2019;709:134370. doi: 10.1016/j.neulet.2019.134370
31. Fan B, Wei Z, Yao X, Shi G, Cheng X, Zhou X, Zhou H, Ning G, Kong X, Feng S. Microenvironment imbalance of spinal cord injury. *Cell Transplant*. 2018;27(6):853–866. doi: 10.1177/0963689718755778
32. Lukacova N, Kisucka A, Kiss Bimbova K, Bacova M, Ileninova M, Kuruc T, Galik J. Glial-neuronal interactions in pathogenesis and treatment of spinal cord injury. *Int J Mol Sci*. 2021;22(24):13577. doi: 10.3390/ijms222413577
33. Andoh M, Koyama R. Comparative review of microglia and monocytes in CNS phagocytosis. *Cells*. 2021;10(10):2555. doi: 10.3390/cells10102555
34. Zhou X, He X, Ren Y. Function of microglia and macrophages in secondary damage after spinal cord injury. *Neural Regen Res*. 2014;9(20):1787–1795. doi: 10.4103/1673-5374.143423
35. Hu X, Leak RK, Shi Y, Suenaga J, Gao Y, Zheng P, Chen J. Microglial and macrophage polarization — new prospects for brain repair. *Nat Rev Neurol*. 2015;11(1):56–64. doi: 10.1038/nrneurol.2014.207
36. Bergles DE, Richardson WD. Oligodendrocyte development and plasticity. *Cold Spring Harb Perspect Biol*. 2015;8(2):a020453. doi: 10.1101/cshperspect.a020453
37. Alizadeh A, Karimi-Abdolrezaee S. Microenvironmental regulation of oligodendrocyte replacement and remyelination in spinal cord injury. *J Physiol*. 2016;594(13):3539–3552. doi: 10.1113/JP270895
38. Plemel JR, Keough MB, Duncan GJ, Sparling JS, Yong VW, Stys PK, Tetzlaff W. Remyelination after spinal cord injury: Is it a target for repair? *Prog Neurobiol*. 2014;117:54–72. doi: 10.1016/j.pneurobio.2014.02.006
39. Deng S, Gan L, Liu C, Xu T, Zhou S, Guo Y, Zhang Z, Yang G-Y, Tian H, Tang Y. Roles of ependymal cells in the physiology and pathology of the central nervous system. *Aging Dis*. 2023;14(2):468–483. doi: 10.14336/AD.2022.0826-1
40. Moore SA. The spinal ependymal layer in health and disease. *Vet Pathol*. 2016;53(4):746–753. doi: 10.1177/0300985815618438
41. Fernandez-Zafra T, Codeluppi S, Uhlén P. An *ex vivo* spinal cord injury model to study ependymal cells in adult mouse tissue. *Exp Cell Res*. 2017;357(2):236–242. doi: 10.1016/j.yexcr.2017.06.002
42. Meletis K, Barnabé-Heider F, Carlén M, Evergren E, Tomilin N, Shupliakov O, Frisén J. Spinal cord injury reveals multilineage differentiation of ependymal cells. *PLoS Biol*. 2008;6(7):e182. doi: 10.1371/journal.pbio.0060182

43. Zhang Y, Yang S, Liu C, Han X, Gu X, Zhou S. Deciphering glial scar after spinal cord injury. *Burns Trauma*. 2021;9:tkab035. doi: 10.1093/burnst/tkab035
44. Dromard C, Guillon H, Rigau V, Ripoll C, Sabourin JC, Perrin FE, Scamps F, Bozza S, Sabatier P, Lonjon N, Duffau H, Vachiery-Lahaye F, Prieto M, Tran Van Ba C, Deleyrolle L, Boularan A, Langley K, Gaviria M, Privat A, Hugnot JP, Bauchet L. Adult human spinal cord harbors neural precursor cells that generate neurons and glial cells *in vitro*. *J Neurosci Res*. 2008;86(9):1916–1926. doi: 10.1002/jnr.21646
45. Dunbar CE, High KA, Joung JK, Kohn DB, Ozawa K, Sadelain M. Gene therapy comes of age. *Science*. 2018;359(6372):eaan4672. doi: 10.1126/science.aan4672
46. Izmailov AA, Sokolov ME, Bashirov FV, Fadeev FO, Markosyan VA, Garifulin RR, Lisyukov AN, Kuznetsov MS, Islamov RR. Comparative analysis of efficiency of direct and cell-mediated gene therapy of rats with contusion spinal cord injury. *Genes & Cells*. 2017;12(4):53–59. (In Russ.) doi: 10.23868/201707030
47. Boyce VS, Mendell LM. Neurotrophic factors in spinal cord injury. *Handb Exp Pharmacol*. 2014;220:443–460. doi: 10.1007/978-3-642-45106-5_16
48. Keefe KM, Sheikh IS, Smith GM. Targeting neurotrophins to specific populations of neurons: NGF, BDNF, and NT-3 and their relevance for treatment of spinal cord injury. *Int J Mol Sci*. 2017;18(3):548. doi: 10.3390/ijms18030548
49. Harvey AR, Lovett SJ, Majda BT, Yoon JH, Wheeler LPG, Hodgetts SI. Neurotrophic factors for spinal cord repair: Which, where, how and when to apply, and for what period of time? *Brain Res*. 2015;1619:36–71. doi: 10.1016/j.brainres.2014.10.049
50. Muheremu A, Shu L, Liang J, Aili A, Jiang K. Sustained delivery of neurotrophic factors to treat spinal cord injury. *Transl Neurosci*. 2021;12(1):494–511. doi: 10.1515/tnsci-2020-0200
51. Liang J, Deng G, Huang H. The activation of BDNF reduced inflammation in a spinal cord injury model by TrkB/p38 MAPK signaling. *Exp Ther Med*. 2019;17(3):1688–1696. doi: 10.3892/etm.2018.7109
52. Gliwińska A, Czubilińska-Łada J, Więckiewicz G, Świętochowska E, Badeński A, Dworak M, Szczepańska M. The role of brain-derived neurotrophic factor (BDNF) in diagnosis and treatment of epilepsy, depression, schizophrenia, anorexia nervosa and Alzheimer's disease as highly drug-resistant diseases: A narrative review. *Brain Sci*. 2023;13(2):163. doi: 10.3390/brainsci13020163
53. Deznabi N, Hosseini S, Rajabi M. Neurotrophic factors-based therapeutic strategies in the spinal cord injury: An overview of recent preclinical studies in rodent models. *Egypt J Neurol Psychiatry Neurosurg*. 2023;59(1):63. doi: 10.1186/s41983-023-00661-3
54. Han Q, Xu XM. Neurotrophin-3-mediated locomotor recovery: A novel therapeutic strategy targeting lumbar neural circuitry after spinal cord injury. *Neural Regen Res*. 2020;15(12):2241–2242. doi: 10.4103/1673-5374.284985
55. Ortmann SD, Hellenbrand DJ. Glial cell line-derived neurotrophic factor as a treatment after spinal cord injury. *Neural Regen Res*. 2018;13(10):1733–1734. doi: 10.4103/1673-5374.238610
56. Rosich K, Hanna BF, Ibrahim RK, Hellenbrand DJ, Hanna A. The effects of glial cell line-derived neurotrophic factor after spinal cord injury. *J Neurotrauma*. 2017;34(24):3311–3325. doi: 10.1089/neu.2017.5175
57. Tsivelekas K, Evangelopoulos DS, Pallis D, Benetos IS, Papadakis SA, Vlamis J, Pneumaticos SG. Angiogenesis in spinal cord injury: Progress and treatment. *Cureus*. 2022;14(5):e25475. doi: 10.7759/cureus.25475
58. Wang L, Shi Q, Dai J, Gu Y, Feng Y, Chen L. Increased vascularization promotes functional recovery in the transected spinal cord rats by implanted vascular endothelial growth factor-targeting collagen scaffold. *J Orthop Res*. 2018;36(3):1024–1034. doi: 10.1002/jor.23678
59. Sundberg LM, Herrera JJ, Narayana PA. Effect of vascular endothelial growth factor treatment in experimental traumatic spinal cord injury: *In vivo* longitudinal assessment. *J Neurotrauma*. 2011;28(4):565–78. doi: 10.1089/neu.2010.1533
60. Zhou Y, Wang Z, Li J, Li X, Xiao J. Fibroblast growth factors in the management of spinal cord injury. *J Cell Mol Med*. 2018;22(1):25–37. doi: 10.1111/jcmm.13353
61. Allahdadi KJ, de Santana TA, Santos GC, Azevedo CM, Mota RA, Nonaka CK, Silva DN, Valim CXR, Figueira CP, Dos Santos WLC, do Espirito Santo RF, Evangelista AF, Villarreal CF, Dos Santos RR, de Souza BSF, Soares MBP. IGF-1 overexpression improves mesenchymal stem cell survival and promotes neurological recovery after spinal cord injury. *Stem Cell Res Ther*. 2019;10(1):146. doi: 10.1186/s13287-019-1223-z
62. Ong W, Pinese C, Chew SY. Scaffold-mediated sequential drug/gene delivery to promote nerve regeneration and remyelination following traumatic nerve injuries. *Adv Drug Deliv Rev.* 2019;149–150:19–48. doi: 10.1016/j.addr.2019.03.004
63. Xu D, Wu D, Qin M, Nih LR, Liu C, Cao Z, Ren J, Chen X, He Z, Yu W, Guan J, Duan S, Liu F, Liu X, Li J, Harley D, Xu B, Hou L, Chen ISY, Wen J, Chen W, Pourtaheri S, Lu Y. Efficient Delivery of Nerve Growth Factors to the Central Nervous System for Neural Regeneration. *Adv Mater*. 2019;31(33):e1900727. doi: 10.1002/adma.201900727
64. Sosnovtseva AO, Stepanova OV, Stepanenko AA, Voronova AD, Chadin AV, Valikhov MP, Chekhonin VP. Recombinant adenoviruses for delivery of therapeutics following spinal cord injury. *Front Pharmacol*. 2021;12:777628. doi: 10.3389/fphar.2021.777628
65. Fischer I, Dulin JN, Lane MA. Transplanting neural progenitor cells to restore connectivity after spinal cord injury. *Nat Rev Neurosci*. 2020;21(7):366–383. doi: 10.1038/s41583-020-0314-2
66. Mahla RS. Stem cells applications in regenerative medicine and disease therapeutics. *Int J Cell Biol*. 2016;2016:6940283. doi: 10.1155/2016/6940283
67. Shinozaki M, Nagoshi N, Nakamura M, Okano H. Mechanisms of stem cell therapy in spinal cord injuries. *Cells*. 2021;10(10):2676. doi: 10.3390/cells10102676
68. Reshamwala R, Shah M, St John J, Ekberg J. Survival and integration of transplanted olfactory ensheathing cells are crucial for spinal cord injury repair: Insights from the last 10 years of animal model studies. *Cell Transplant*. 2019;28(1):132S–159S. doi: 10.1177/0963689719883823

69. Zhou P, Guan J, Xu P, Zhao J, Zhang C, Zhang B, Mao Y, Cui W. Cell therapeutic strategies for spinal cord injury. *Adv Wound Care (New Rochelle)*. 2019;8(11):585–605. doi: 10.1089/wound.2019.1046

70. El-Kadiry AEH, Rafei M, Shammaa R. Cell therapy: Types, regulation, and clinical benefits. *Front Med (Lausanne)*. 2021;8:756029. doi: 10.3389/fmed.2021.756029

71. Zakrzewski W, Dobrzyński M, Szymonowicz M, Rybak Z. Stem cells: Past, present, and future. *Stem Cell Res Ther*. 2019;10:68. doi: 10.1186/s13287-019-1165-5

72. Ashammakhi N, Kim HJ, Ehsanipour A, Bierman RD, Kaarela O, Xue C, Khademhosseini A, Seidlits SK. Regenerative therapies for spinal cord injury. *Tissue Eng Part B Rev*. 2019;25(6):471–491. doi: 10.1089/ten.TEB.2019.0182

73. Guo W, Zhang X, Zhai J, Xue J. The roles and applications of neural stem cells in spinal cord injury repair. *Front Bioeng Biotechnol*. 2022;10:966866. doi: 10.3389/fbioe.2022.966866

74. De Freria CM, Van Niekerk E, Blesch A, Lu P. Neural stem cells: Promoting axonal regeneration and spinal cord connectivity. *Cells*. 2021;10(12):3296. doi: 10.3390/cells10123296

75. Yamazaki K, Kawabori M, Seki T, Houkin K. Clinical trials of stem cell treatment for spinal cord injury. *Int J Mol Sci*. 2020;21(11):3994. doi: 10.3390/ijms21113994

76. Cofano F, Boido M, Monticelli M, Zenga F, Ducati A, Vercelli A, Garbossa D. Mesenchymal stem cells for spinal cord injury: Current options, limitations, and future of cell therapy. *Int J Mol Sci*. 2019;20(11):2698. doi: 10.3390/ijms20112698

77. Kim GU, Sung SE, Kang KK, Choi J-H, Lee S, Sung M, Yang SY, Kim S-K, Kim YI, Lim J-H, Seo M-S, Lee GW. Therapeutic potential of mesenchymal stem cells (MSCs) and MSC-derived extracellular vesicles for the treatment of spinal cord injury. *Int J Mol Sci*. 2021;22(24):13672. doi: 10.3390/ijms222413672

78. Liau LL, Looi QH, Chia WC, Subramaniam T, Ng MH, Law JX. Treatment of spinal cord injury with mesenchymal stem cells. *Cell Biosci*. 2020;10:112. doi: 10.1186/s13578-020-00475-3

79. Sykova E, Cizkova D, Kubinova S. Mesenchymal stem cells in treatment of spinal cord injury and amyotrophic lateral sclerosis. *Front Cell Dev Biol*. 2021;9:695900. doi: 10.3389/fcell.2021.695900

80. Monje PV, Deng L, Xu XM. Human schwann cell transplantation for spinal cord injury: Prospects and challenges in translational medicine. *Front Cell Neurosci*. 2021;15:690894. doi: 10.3389/fncel.2021.690894

81. Fu H, Hu D, Chen J, Wang Q, Zhang Y, Qi C, Yu T. Repair of the injured spinal cord by schwann cell transplantation. *Front Neurosci*. 2022;16:800513. doi: 10.3389/fnins.2022.800513

82. Ernst A, Frisén J. Adult neurogenesis in humans — common and unique traits in mammals. *PLoS Biol*. 2015;13(1):e1002045. doi: 10.1371/journal.pbio.1002045

83. Ahuja CS, Mothe A, Khazaei M, Badhiwala JH, Gilbert EA, van der Kooy D, Morshead CM, Tator C, Fehlings MG. The leading edge: Emerging neuroprotective and neuroregenerative cell-based therapies for spinal cord injury. *Stem Cells Transl Med.* 2020;9(12):1509–1530. doi: 10.1002/sctm.19-0135

84. Hu XC, Lu YB, Yang YN, Kang X-W, Wang Y-G, Ma B, Xing S. Progress in clinical trials of cell transplantation for the treatment of spinal cord injury: How many questions remain unanswered? *Neural Regen Res*. 2021;16(3):405–413. doi: 10.4103/1673-5374.293130

85. Ursavas S, Darici H, Karaoz E. Olfactory ensheathing cells: Unique glial cells promising for treatments of spinal cord injury. *J Neurosci Res*. 2021;99(6):1579–1597. doi: 10.1002/jnr.24817

86. Xi Y, Yue G, Gao S, Ju R, Wang Y. Human umbilical cord blood mononuclear cells transplantation for perinatal brain injury. *Stem Cell Res Ther*. 2022;13(1):458. doi: 10.1186/s13287-022-03153-y

87. Sanchez-Petitto G, Rezvani K, Daher M, Rafei H, Kebriaei P, Shpall EJ, Olson A. Umbilical cord blood transplantation: Connecting its origin to its future. *Stem Cells Transl Med*. 2023;12(2):55–71. doi: 10.1093/stcltm/szac086

88. Ryabov SI, Zvyagintseva MA, Yadgarov MY, Bazanovich SA, Smirnov VA. Comparison of the efficiency of systemic and local cell therapy with human umbilical cord blood mononuclear cells in rats with severe spinal cord injury. *Bull Exp Biol Med*. 2020;168(4):552–555. doi: 10.1007/s10517-020-04751-7

89. Zhu H, Poon W, Liu Y, Leung GK-K, Wong Y, Feng Y, Ng SCP, Tsang KS, Sun DTF, Yeung DK, Shen C, Niu F, Xu Z, Tan P, Tang S, Gao H, Cha Y, So K-F, Fleischaker R, Sun D, Chen J, Lai J, Cheng W, Young W. Phase I–II clinical trial assessing safety and efficacy of umbilical cord blood mononuclear cell transplant therapy of chronic complete spinal cord injury. *Cell Transplant.* 2016;25(11):1925–1943. doi: 10.3727/096368916X691411

90. Smirnov VA, Radaev SM, Morozova YV, Ryabov SI, Yadgarov MY, Bazanovich SA, Lvov IS, Talypov AE, Grin' AA. Systemic administration of allogeneic cord blood mononuclear cells in adults with severe acute contusion spinal cord injury: Phase 1/2a pilot clinical study — safety and primary efficacy evaluation. *World Neurosurg*. 2022;161:e319–38. doi: 10.1016/j.wneu.2022.02.004

91. Liu J, Han D, Wang Z, Xue M, Zhu L, Yan H, Zheng X, Guo Z, Wang H. Clinical analysis of the treatment of spinal cord injury with umbilical cord mesenchymal stem cells. *Cytotherapy*. 2013;15(2):185–91. doi: 10.1016/j.jcyt.2012.09.005

92. Yao L, He C, Zhao Y, Wang J, Tang M, Li J, Wu Y, Ao L, Hu X. Human umbilical cord blood stem cell transplantation for the treatment of chronic spinal cord injury: Electrophysiological changes and long-term efficacy. *Neural Regen Res*. 2013;8(5):397–403. doi: 10.3969/j.issn.1673-5374.2013.05.002

93. Islamov R, Bashirov F, Fadeev F, Shevchenko R, Izmailov A, Markosyan V, Sokolov M, Kuznetsov M, Davleeva M, Garifulin R, Salafutdinov I, Nurullin L, Chelyshev Y, Lavrov I. Epidural stimulation combined with triple gene therapy for spinal cord injury treatment. *Int J Mol Sci*. 2020;21(23):8896. doi: 10.3390/ijms21238896

94. Islamov RR, Izmailov AA, Sokolov ME, Fadeev PO, Bashirov FV, Eremeev AA, Shaymardanova GF, Shmarov MM, Naroditskiy BS, Chelyshev YA, Lavrov IA, Palotás A. Evaluation of direct and cell-mediated triple-gene therapy in spinal cord injury in rats. *Brain Res Bull*. 2017;132:44–52. doi: 10.1016/j.brainresbull.2017.05.005

СПИСОК ЛИТЕРАТУРЫ

1. Benedetti B., Weidenhammer A., Reisinger M., Couillard-Despres S. Spinal cord injury and loss of cortical inhibition // Int J Mol Sci. 2022. Vol. 23, N. 10. P. 5622. doi: 10.3390/ijms23105622
2. Venkatesh K., Ghosh S.K., Mullick M., et al. Spinal cord injury: pathophysiology, treatment strategies, associated challenges, and future implications // Cell Tissue Res. 2019. Vol. 377, N. 2. P. 125–151. doi: 10.1007/s00441-019-03039-1
3. Alizadeh A., Dyck S.M., Karimi-Abdolrezaee S. Traumatic spinal cord injury: An overview of pathophysiology, models and acute injury mechanisms // Front Neurol. 2019. Vol. 10. P. 282. doi: 10.3389/fneur.2019.00282
4. Zheng B., Tuszynski M.H. Regulation of axonal regeneration after mammalian spinal cord injury // Nat Rev Mol Cell Biol. 2023. Vol. 24, N. 6. P. 396–413. doi: 10.1038/s41580-022-00562-y
5. Khan F.I., Ahmed Z. Experimental treatments for spinal cord injury: A systematic review and meta-analysis // Cells. 2022. Vol. 11, N. 21. P. 3409. doi: 10.3390/cells11213409
6. Khorasanizadeh M., Yousefifard M., Eskian M., et al. Neurological recovery following traumatic spinal cord injury: A systematic review and meta-analysis // J Neurosurg Spine. 2019. P. 1–17. doi: 10.3171/2018.10.SPINE18802
7. Elliott C.S., Dallas K.B., Zlatev D., et al. Volitional voiding of the bladder after spinal cord injury: Validation of bilateral lower extremity motor function as a key predictor // J Urol. 2018. Vol. 200, N. 1. P. 154–160. doi: 10.1016/j.juro.2018.02.064
8. Новосёлова И.Н. Этиология и клиническая эпидемиология позвоночно-спинномозговой травмы. Литературный обзор // Российский нейрохирургический журнал имени профессора А.Л. Поленова. 2019. Т. 11, № 4. С. 84–92.
9. Ahuja C.S., Wilson J.R., Nori S., et al. Traumatic spinal cord injury // Nat Rev Dis Primers. 2017. Vol. 3. P. 17018. doi: 10.1038/nrdp.2017.18
10. Van Middendorp J.J., Goss B., Urquhart S., et al. Diagnosis and prognosis of traumatic spinal cord injury // Global Spine J. 2011. Vol. 1, N. 1. P. 1–8. doi: 10.1055/s-0031-1296049
11. Roberts T.T., Leonard G.R., Cepela D.J. Classifications in brief: American spinal injury association (ASIA) impairment scale // Clin Orthop Relat Res. 2017. Vol. 475, N. 5. P. 1499–1504. doi: 10.1007/s11999-016-5133-4
12. Anjum A., Yazid M.D., Fauzi Daud M., et al. Spinal cord injury: Pathophysiology, multimolecular interactions, and underlying recovery mechanisms // Int J Mol Sci. 2020. Vol. 21, N. 20. P. 7533. doi: 10.3390/ijms21207533
13. Zhang Y., Al Mamun A., Yuan Y., et al. Acute spinal cord injury: Pathophysiology and pharmacological intervention (review) // Mol Med Rep. 2021. Vol. 23, N. 6. P. 417. doi: 10.3892/mmr.2021.12056
14. Shafqat A., Albalkhi I., Magableh H.M., et al. Tackling the glial scar in spinal cord regeneration: New discoveries and future directions // Front Cell Neurosci. 2023. Vol. 17. P. 1180825. doi: 10.3389/fncel.2023.1180825
15. Gradisnik L., Velnar T. Astrocytes in the central nervous system and their functions in health and disease: A review // World J Clin Cases. 2023. Vol. 11, N. 15. P. 3385–3394. doi: 10.12998/wjcc.v11.i15.3385
16. Giovannoni F., Quintana F.J. The role of astrocytes in CNS inflammation // Trends Immunol. 2020. Vol. 41, N. 9. P. 805–819. doi: 10.1016/j.it.2020.07.007
17. Abbott N.J., Patabendige A.A.K., Dolman D.E.M., et al. Structure and function of the blood-brain barrier // Neurobiol Dis. 2010. Vol. 37. N. 1. P. 13–25. doi: 10.1016/j.nbd.2009.07.030
18. Okada S., Hara M., Kobayakawa K., et al. Astrocyte reactivity and astrogliosis after spinal cord injury // Neurosci Res. 2018. Vol. 126. P. 39–43. doi: 10.1016/j.neures.2017.10.004
19. Sofroniew M.V., Vinters H.V. Astrocytes: Biology and pathology // Acta Neuropathol. 2010. Vol. 119, N. 1. P. 7–35. doi: 10.1007/s00401-009-0619-8
20. Escartin C., Galea E., Lakatos A., et al. Reactive astrocyte nomenclature, definitions, and future directions // Nat Neurosci. 2021. Vol. 24, N. 3. P. 312–325. doi: 10.1038/s41593-020-00783-4
21. Gaudet A.D., Fonken L.K. Glial cells shape pathology and repair after spinal cord injury // Neurotherapeutics. 2018. Vol. 15, N. 3. P. 554–577. doi: 10.1007/s13311-018-0630-7
22. Li X., Li M., Tian L., et al. Reactive astrogliosis: Implications in spinal cord injury progression and therapy // Oxid Med Cell Longev. 2020. Vol. 2020. P. 9494352. doi: 10.1155/2020/9494352
23. Sonn I., Nakamura M., Renault-Mihara F., Okano H. Polarization of reactive astrocytes in response to spinal cord injury is enhanced by M2 macrophage-mediated activation of Wnt/β-catenin pathway // Mol Neurobiol. 2020. Vol. 57, N. 4. P. 1847–1862. doi: 10.1007/s12035-019-01851-y
24. Wang R., Zhou R., Chen Z., et al. The glial cells respond to spinal cord injury // Front Neurol. 2022. Vol. 13. P. 844497. doi: 10.3389/fneur.2022.844497
25. O'Shea T.M., Burda J.E., Sofroniew M.V. Cell biology of spinal cord injury and repair // J Clin Invest. 2017. Vol. 127, N. 9. P. 3259–3270. doi: 10.1172/JCI90608
26. Yang T., Dai Y., Chen G., Cui S. Dissecting the dual role of the glial scar and scar-forming astrocytes in spinal cord injury // Front Cell Neurosci. 2020. Vol. 14. P. 78. doi: 10.3389/fncel.2020.00078
27. Nayak D., Roth T.L., McGavern D.B. Microglia development and function // Annu Rev Immunol. 2014. Vol. 32. P. 367–402. doi: 10.1146/annurev-immunol-032713-120240
28. Колос Е.А., Коржевский Д.Э. Микроглия спинного мозга в норме и при патологии // Acta Naturae. 2020. Т. 12, № 1. С. 4–17. doi: 10.32607/actanaturae.10934
29. Abe N., Nishihara T., Yorozuya T., Tanaka J. Microglia and macrophages in the pathological central and peripheral nervous systems // Cells. 2020. Vol. 9, N. 9. P. 2132. doi: 10.3390/cells9092132
30. Kroner A., Rosas Almanza J. Role of microglia in spinal cord injury // Neurosci Lett. 2019. Vol. 709. P. 134370. doi: 10.1016/j.neulet.2019.134370
31. Fan B., Wei Z., Yao X., et al. Microenvironment imbalance of spinal cord injury // Cell Transplant. 2018. Vol. 27, N. 6. P. 853–866. doi: 10.1177/0963689718755778
32. Lukacova N., Kisucka A., Kiss Bimbova K., et al. Glial-neuronal interactions in pathogenesis and treatment of spinal

cord injury // Int J Mol Sci. 2021. Vol. 22, N. 24. P. 13577. doi: 10.3390/ijms222413577

33. Andoh M., Koyama R. Comparative review of microglia and monocytes in CNS phagocytosis // Cells. 2021. Vol. 10, N. 10. P. 2555. doi: 10.3390/cells10102555

34. Zhou X., He X., Ren Y. Function of microglia and macrophages in secondary damage after spinal cord injury // Neural Regen Res. 2014. Vol. 9, N. 20. P. 1787–1795. doi: 10.4103/1673-5374.143423

35. Hu X., Leak R.K., Shi Y., et al. Microglial and macrophage polarization — new prospects for brain repair // Nat Rev Neurol. 2015. Vol. 11, N. 1. P. 56–64. doi: 10.1038/nrneurol.2014.207

36. Bergles D.E., Richardson W.D. Oligodendrocyte development and plasticity // Cold Spring Harb Perspect Biol. 2015. Vol. 8, N. 2. P. a020453. doi: 10.1101/cshperspect.a020453

37. Alizadeh A., Karimi-Abdolrezaee S. Microenvironmental regulation of oligodendrocyte replacement and remyelination in spinal cord injury // J Physiol. 2016. Vol. 594, N. 13. P. 3539–3552. doi: 10.1113/JP270895

38. Plemel J.R., Keough M.B., Duncan G.J., et al. Remyelination after spinal cord injury: Is it a target for repair? // Prog Neurobiol. 2014. Vol. 117. P. 54–72. doi: 10.1016/j.pneurobio.2014.02.006

39. Deng S., Gan L., Liu C., et al. Roles of ependymal cells in the physiology and pathology of the central nervous system // Aging Dis. 2023. Vol. 14, N. 2. P. 468–483. doi: 10.14336/AD.2022.0826-1

40. Moore S.A. The spinal ependymal layer in health and disease // Vet Pathol. 2016. Vol. 53, N. 4. P. 746–753. doi: 10.1177/0300985815618438

41. Fernandez-Zafra T., Codeluppi S., Uhlén P. An *ex vivo* spinal cord injury model to study ependymal cells in adult mouse tissue // Exp Cell Res. 2017. Vol. 357, N. 2. P. 236–242. doi: 10.1016/j.yexcr.2017.06.002

42. Meletis K., Barnabé-Heider F., Carlén M., et al. Spinal cord injury reveals multilineage differentiation of ependymal cells // PLoS Biol. 2008. Vol. 6, N. 7. P. e182. doi: 10.1371/journal.pbio.0060182

43. Zhang Y., Yang S., Liu C., et al. Deciphering glial scar after spinal cord injury // Burns Trauma. 2021. Vol. 9. P. tkab035. doi: 10.1093/burnst/tkab035

44. Dromard C., Guillon H., Rigau V., et al. Adult human spinal cord harbors neural precursor cells that generate neurons and glial cells *in vitro* // J Neurosci Res. 2008. Vol. 86, N. 9. P. 1916–1926. doi: 10.1002/jnr.21646

45. Dunbar C.E., High K.A., Joung J.K., et al. Gene therapy comes of age // Science. 2018. Vol. 359, N. 6372. P. eaan4672. doi: 10.1126/science.aan4672

46. Измайлов А.А., Соколов М.Е., Баширов Ф.В., и др. Сравнительный анализ эффективности прямой и клеточно-опосредованной генной терапии крыс с контузионной травмой спинного мозга // Гены и клетки. 2017. Т. 12, № 4. С. 53–59. doi: 10.23868/201707030

47. Boyce V.S., Mendell L.M. Neurotrophic factors in spinal cord injury // Handb Exp Pharmacol. 2014. Vol. 220. P. 443–460. doi: 10.1007/978-3-642-45106-5_16

48. Keefe K.M., Sheikh I.S., Smith G.M. Targeting neurotrophins to specific populations of neurons: NGF, BDNF, and NT-3 and their relevance for treatment of spinal cord injury // Int J Mol Sci. 2017. Vol. 18, N. 3. P. 548. doi: 10.3390/ijms18030548

49. Harvey A.R., Lovett S.J., Majda B.T., et al. Neurotrophic factors for spinal cord repair: Which, where, how and when to apply, and for what period of time? // Brain Res. 2015. Vol. 1619. P. 36–71. doi: 10.1016/j.brainres.2014.10.049

50. Muheremu A., Shu L., Liang J., et al. Sustained delivery of neurotrophic factors to treat spinal cord injury // Transl Neurosci. 2021. Vol. 12, N. 1. P. 494–511. doi: 10.1515/tnsci-2020-0200

51. Liang J., Deng G., Huang H. The activation of BDNF reduced inflammation in a spinal cord injury model by TrkB/p38 MAPK signaling // Exp Ther Med. 2019. Vol. 17, N. 3. P. 1688–1696. doi: 10.3892/etm.2018.7109

52. Gliwińska A., Czubilińska-Łada J., Więckiewicz G., et al. The role of brain-derived neurotrophic factor (BDNF) in diagnosis and treatment of epilepsy, depression, schizophrenia, anorexia nervosa and Alzheimer's disease as highly drug-resistant diseases: A narrative review // Brain Sci. 2023. Vol. 13, N. 2. P. 163. doi: 10.3390/brainsci13020163

53. Deznabi N., Hosseini S., Rajabi M. Neurotrophic factors-based therapeutic strategies in the spinal cord injury: An overview of recent preclinical studies in rodent models // Egypt J Neurol Psychiatry Neurosurg. 2023. Vol. 59, N. 1. P. 63. doi: 10.1186/s41983-023-00661-3

54. Han Q., Xu X.-M. Neurotrophin-3-mediated locomotor recovery: A novel therapeutic strategy targeting lumbar neural circuitry after spinal cord injury // Neural Regen Res. 2020. Vol. 15, N. 12. P. 2241–2242. doi: 10.4103/1673-5374.284985

55. Ortmann S.D., Hellenbrand D.J. Glial cell line-derived neurotrophic factor as a treatment after spinal cord injury // Neural Regen Res. 2018. Vol. 13, N. 10. P. 1733–1734. doi: 10.4103/1673-5374.238610

56. Rosich K., Hanna B.F., Ibrahim R.K., et al. The effects of glial cell line-derived neurotrophic factor after spinal cord injury // J Neurotrauma. 2017. Vol. 34, N. 24. P. 3311–3325. doi: 10.1089/neu.2017.5175

57. Tsivelekas K., Evangelopoulos D.S., Pallis D., et al. Angiogenesis in spinal cord injury: Progress and treatment // Cureus. 2022. Vol. 14, N. 5. P. e25475. doi: 10.7759/cureus.25475

58. Wang L., Shi Q., Dai J., et al. Increased vascularization promotes functional recovery in the transected spinal cord rats by implanted vascular endothelial growth factor-targeting collagen scaffold // J Orthop Res. 2018. Vol. 36, N. 3. P. 1024–1034. doi: 10.1002/jor.23678

59. Sundberg L.M., Herrera J.J., Narayana P.A. Effect of vascular endothelial growth factor treatment in experimental traumatic spinal cord injury: *In vivo* longitudinal assessment // J Neurotrauma. 2011. Vol. 28, N. 4. P. 565–578. doi: 10.1089/neu.2010.1533

60. Zhou Y., Wang Z., Li J., et al. Fibroblast growth factors in the management of spinal cord injury // J Cell Mol Med. 2018. Vol. 22, N. 1. P. 25–37. doi: 10.1111/jcmm.13353

61. Allahdadi K.J., de Santana T.A., Santos G.C., et al. IGF-1 overexpression improves mesenchymal stem cell survival and promotes neurological recovery after spinal cord injury // Stem Cell Res Ther. 2019. Vol. 10, N. 1. P. 146. doi: 10.1186/s13287-019-1223-z

62. Ong W., Pinese C., Chew S.Y. Scaffold-mediated sequential drug/gene delivery to promote nerve regeneration and remyelination following traumatic nerve injuries // Adv Drug Deliv Rev. 2019. Vol. 149–150. P. 19–48. doi: 10.1016/j.addr.2019.03.004
63. Xu D., Wu D., Qin M., et al. Efficient delivery of nerve growth factors to the central nervous system for neural regeneration // Adv Mater. 2019. Vol. 31, N. 33. P. e1900727. doi: 10.1002/adma.201900727
64. Sosnovtseva A.O., Stepanova O.V., Stepanenko A.A., et al. Recombinant adenoviruses for delivery of therapeutics following spinal cord injury // Front Pharmacol. 2021. Vol. 12. P. 777628. doi: 10.3389/fphar.2021.777628
65. Fischer I., Dulin J.N., Lane M.A. Transplanting neural progenitor cells to restore connectivity after spinal cord injury // Nat Rev Neurosci. 2020. Vol. 21, N. 7. P. 366–383. doi: 10.1038/s41583-020-0314-2
66. Mahla R.S. Stem cells applications in regenerative medicine and disease therapeutics // Int J Cell Biol. 2016. Vol. 2016. P. 6940283. doi: 10.1155/2016/6940283
67. Shinozaki M., Nagoshi N., Nakamura M., Okano H. Mechanisms of stem cell therapy in spinal cord injuries // Cells. 2021. Vol. 10, N. 10. P. 2676. doi: 10.3390/cells10102676
68. Reshamwala R., Shah M., St John J., Ekberg J. Survival and integration of transplanted olfactory ensheathing cells are crucial for spinal cord injury repair: Insights from the last 10 years of animal model studies // Cell Transplant. 2019. Vol. 28, N. 1. P. 132S–159S. doi: 10.1177/0963689719883823
69. Zhou P., Guan J., Xu P., et al. Cell therapeutic strategies for spinal cord injury // Adv Wound Care (New Rochelle). 2019. Vol. 8, N. 11. P. 585–605. doi: 10.1089/wound.2019.1046
70. El-Kadiry A.E.-H., Rafei M., Shammaa R. Cell therapy: Types, regulation, and clinical benefits // Front Med (Lausanne). 2021. Vol. 8. P. 756029. doi: 10.3389/fmed.2021.756029
71. Zakrzewski W., Dobrzyński M., Szymonowicz M., Rybak Z. Stem cells: Past, present, and future // Stem Cell Res Ther. 2019. Vol. 10. P. 68. doi: 10.1186/s13287-019-1165-5
72. Ashammakhi N., Kim H.-J., Ehsanipour A., et al. Regenerative therapies for spinal cord injury // Tissue Eng Part B Rev. 2019. Vol. 25, N. 6. P. 471–491. doi: 10.1089/ten.TEB.2019.0182
73. Guo W., Zhang X., Zhai J., Xue J. The roles and applications of neural stem cells in spinal cord injury repair // Front Bioeng Biotechnol. 2022. Vol. 10. P. 966866. doi: 10.3389/fbioe.2022.966866
74. De Freria C.M., Van Niekerk E., Blesch A., Lu P. Neural stem cells: Promoting axonal regeneration and spinal cord connectivity // Cells. 2021. Vol. 10, N. 12. P. 3296. doi: 10.3390/cells10123296
75. Yamazaki K., Kawabori M., Seki T., Houkin K. Clinical trials of stem cell treatment for spinal cord injury // Int J Mo. Sci. 2020. Vol. 21, N. 11. P. 3994. doi: 10.3390/ijms21113994
76. Cofano F., Boido M., Monticelli M., et al. Mesenchymal stem cells for spinal cord injury: Current options, limitations, and future of cell therapy // Int J Mol Sci. 2019. Vol. 20, N. 11. P. 2698. doi: 10.3390/ijms20112698
77. Kim G.-U., Sung S.-E., Kang K.-K., et al. Therapeutic potential of mesenchymal stem cells (MSCs) and MSC-derived extracellular vesicles for the treatment of spinal cord injury // Int J Mol Sci. 2021. Vol. 22, N. 24. P. 13672. doi: 10.3390/ijms222413672
78. Liau L.L., Looi Q.H., Chia W.C., et al. Treatment of spinal cord injury with mesenchymal stem cells // Cell Biosci. 2020. Vol. 10. P. 112. doi: 10.1186/s13578-020-00475-3
79. Sykova E., Cizkova D., Kubinova S. Mesenchymal stem cells in treatment of spinal cord injury and amyotrophic lateral sclerosis // Front Cell Dev Biol. 2021. Vol. 9. P. 695900. doi: 10.3389/fcell.2021.695900
80. Monje P.V., Deng L., Xu X.-M. Human schwann cell transplantation for spinal cord injury: Prospects and challenges in translational medicine // Front Cell Neurosci. 2021. Vol. 15. P. 690894. doi: 10.3389/fncel.2021.690894
81. Fu H., Hu D., Chen J., et al. Repair of the injured spinal cord by schwann cell transplantation // Front Neurosci. 2022. Vol. 16. P. 800513. doi: 10.3389/fnins.2022.800513
82. Ernst A., Frisén J. Adult neurogenesis in humans — common and unique traits in mammals // PLoS Biol. 2015. Vol. 13. N. 1. P. e1002045. doi: 10.1371/journal.pbio.1002045
83. Ahuja C.S., Mothe A., Khazaei M., et al. The leading edge: Emerging neuroprotective and neuroregenerative cell-based therapies for spinal cord injury // Stem Cells Transl Med. 2020. Vol. 9, N. 12. P. 1509–1530. doi: 10.1002/sctm.19-0135
84. Hu X.-C., Lu Y.-B., Yang Y.-N., et al. Progress in clinical trials of cell transplantation for the treatment of spinal cord injury: How many questions remain unanswered? // Neural Regen Res. 2021. Vol. 16, N. 3. P. 405–413. doi: 10.4103/1673-5374.293130
85. Ursavas S., Darici H., Karaoz E. Olfactory ensheathing cells: Unique glial cells promising for treatments of spinal cord injury // J Neurosci Res. 2021. Vol. 99, N. 6. P. 1579–1597. doi: 10.1002/jnr.24817
86. Xi Y., Yue G., Gao S., et al. Human umbilical cord blood mononuclear cells transplantation for perinatal brain injury // Stem Cell Res Ther. 2022. Vol. 13, N. 1. P. 458. doi: 10.1186/s13287-022-03153-y
87. Sanchez-Petitto G., Rezvani K., Daher M., et al. Umbilical cord blood transplantation: Connecting its origin to its future // Stem Cells Transl Med. 2023. Vol. 12, N. 2. P. 55–71. doi: 10.1093/stcltm/szac086
88. Ryabov S.I., Zvyagintseva M.A., Yadgarov M.Y., et al. Comparison of the efficiency of systemic and local cell therapy with human umbilical cord blood mononuclear cells in rats with severe spinal cord injury // Bull Exp Biol Med. 2020. Vol. 168, N. 4. P. 552–555. doi: 10.1007/s10517-020-04751-7
89. Zhu H., Poon W., Liu Y., et al. Phase I–II clinical trial assessing safety and efficacy of umbilical cord blood mononuclear cell transplant therapy of chronic complete spinal cord injury // Cell Transplant. 2016. Vol. 25, N. 11. P. 1925–1943. doi: 10.3727/096368916X691411
90. Smirnov V.A., Radaev S.M., Morozova Y.V., et al. Systemic administration of allogeneic cord blood mononuclear cells in adults with severe acute contusion spinal cord injury: Phase 1/2a Pilot clinical study — safety and primary efficacy evaluation // World Neurosurgery. 2022. Vol. 161. P. e319–e338. doi: 10.1016/j.wneu.2022.02.004

91. Liu J., Han D., Wang Z., et al. Clinical analysis of the treatment of spinal cord injury with umbilical cord mesenchymal stem cells // Cytotherapy. 2013. Vol. 15, N. 2. P. 185–191. doi: 10.1016/j.jcyt.2012.09.005

92. Yao L., He C., Zhao Y., et al. Human umbilical cord blood stem cell transplantation for the treatment of chronic spinal cord injury: Electrophysiological changes and long-term efficacy // Neural Regen Res. 2013. Vol. 8, N. 5. P. 397–403. doi: 10.3969/j.issn.1673-5374.2013.05.002

93. Islamov R., Bashirov F., Fadeev F., et al. Epidural stimulation combined with triple gene therapy for spinal cord injury treatment // Int J Mol Sci. 2020. Vol. 21, N. 23. P. 8896. doi: 10.3390/ijms21238896

94. Islamov R.R., Izmailov A.A., Sokolov M.E., et al. Evaluation of direct and cell-mediated triple-gene therapy in spinal cord injury in rats // Brain Res Bull. 2017. Vol. 132. P. 44–52. doi: 10.1016/j.brainresbull.2017.05.005

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