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THE CURRENT STATE OF STEM CELL THERAPY FOR SPINAL CORD INJURY AND OTHER SYSTEMIC INJURIES

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ABSTRACT

The pathomechanism of many diseases affecting the human brain and spinal cord has not been fully elucidated. Some organs of the human body have the ability to rebuild and regenerate in the event of apoptosis or necrosis of some cells. An organ with a high self-regeneration capacity is, for example, the liver. In this respect, the human nervous system is its opposite. This is related to the strict functional specialization of neurons and the fact that the function of the nervous system is influenced not only by the operation of individual cells, but also by efficient transmission in often huge and complex networks of neuronal connections, the damage of which is practically impossible to repair. This limited regenerative capacity is why cell loss and nerve fiber disruption are irreversible losses. This constitutes a significant problem in the treatment of patients with spinal cord injuries or suffering from diseases involving rapid (stroke) or constantly progressive (neurodegenerative diseases) loss of nerve cells.

The aim of this work: This work presents the current and most interesting directions of research on the possibility of using stem cells in attempts to regenerate spinal cord and brain injuries.

Methods: Selected articles from Pubmed and specialist textbooks were analyzed in detail. We focused on

selected disease states in which stem cells may have therapeutic possibilities.

Conclusion: Currently, cell therapies are mainly used in bone marrow diseases such as leukemias and myelodysplastic syndromes. If our level of knowledge allows it, in the future stem cells may become a tool in the fight against numerous diseases currently considered incurable and help in the regeneration of organs with a low degree of self-renewal, such as the spinal cord and brain, but also the heart, pancreas and many others.

Keywords: Stem cells, spinal cord, stroke, multiple sclerosis, neurodegenerative diseases.

INTRODUCTION

Unlike other tissues, such as skin, intestinal epithelium or blood, there are tissues whose regeneration does not occur or is only slightly dependent on factors influencing this process. Each cell has mechanisms that work in two ways: either the selected cell retains the ability to divide throughout its life, or it loses this ability, which is an adaptation to the function performed by the cell in the tissue that constitutes the organ. Stem cells (SC) can be classified in terms of their origin (embryonic and tissue - somatic cells), or their functionality due to their different ability to differentiate (totipotent, pluripotent, multipotent, unipotent). The first of them are characterized by the ability to differentiate into all types of body cells and into extraembryonic tissues, so they can build a complete, living organism [1]. They are created as a result of the union of an egg cell and a sperm cell, from the first divisions of a fertilized egg cell [2]. Pluripotent cells, which are descendants of totipotent cells, differentiate into all types of body cells [1, 3]. However, multipotent cells are able to produce several types of cells, usually within the same tissue, while unipotent cells maintain the ability to divide, but differentiate into only one type of cell [3].

Stem cells	
Embryonic	**Fetal**
cells of the inner layer of the blastocyst	amniotic fluid cells
	placental cells
	cord blood cells
	tissue-specific cells (liver, bone marrow)

Fig. 1. Division of stem cells according to their origin.

In order for a stem cell to be used for therapeutic purposes, it must have several features, the key among them being a high level of safety after transplantation, the possibility of obtaining the appropriate amount and the credibility of the therapeutic effect in preclinical studies. However, the most important feature of the cell is the ability to self-renew and proliferate for a sufficiently long time [4]. Cells that build organs, e.g. the heart or kidney, undergo narrow specialization to perform a selected function, while the stem cell remains unspecialized until it receives an appropriate signal that sets it to specialization [5]. Stem cells circulate in the blood throughout the body. Their characteristic place of residence is the bone marrow. Cell migration is regulated by the interactions of chemotactic compounds with appropriate cell receptors [6, 7]. Under the influence of physical activity, trauma or inflammation, the pool of stem cells circulating in the blood may increase. During a stroke stem cells are released from distant places, primarily from the bone marrow, which is their largest reservoir [6, 7, 8]. Substances such as, among others: cytokines, interleukins, chemokines released from damaged tissue are a kind of lure for stem cells. Attempts were made to take advantage of this possibility by using pharmacological agents that could mobilize stem cells to appropriate places in the body [9].

The bone marrow is the home of mesenchymal stem cells (MSCs). These non-hematopoietic cells are currently of interest to scientists because they are the least known [10]. There is no doubt that specific targeting of cell differentiation could help people with various types of diseases, including patients with neurological diseases [6]. MSCs can also be found in the muscles and liver, where they provide structural support for these organs, but are also a reservoir from which adipocytes, osteocytes and chondrocytes derived from the mesoderm can arise [11]. MSCs are also known to be heterogeneous and express high levels of pluripotent markers compared to other types of stem cells such as embryonic stem cells [12].

In vitro culture can use clonogenic tests and assess single cells for their ability to differentiate and self-renew [13, 14]. Stem cells can also be isolated by using a characteristic set of surface markers. But in vitro culture conditions can change the behavior of cells, making it possible for a different type of behavior to occur in vivo. There is ongoing debate about whether some adult cell populations are actually stem cells

[15]. The mentioned in vitro cell culture often raises ethical controversies. Human stem cells can be obtained from: embryos obtained by in vitro fertilization, embryos obtained by cloning, fetal tissue after miscarriage or abortion, umbilical cord blood during childbirth, and the human body which is a source of mature stem cells [6, 16]. The latest reports indicate the possibility of collecting stem cells by autopsy [17].

Umbilical cord blood (UCB), obtained from puncture of the umbilical artery after delivery, is a source of hematopoietic stem cells (HSC), hematopoietic progenitor cells that constitute 0.02-1.42% of the total number of cells and are found in occurs in the G0 phase of the cell cycle [18, 19]. MSCs are also present among these cells. Cardiomyocytes were obtained from in vitro cultures of human MSCs, and mononuclear cells differentiated towards neurons [18, 20, 21]. Cord blood may also be a source of hepatocyte precursors, glial cells, and in vitro may be the basis for the formation of a structure similar to pancreatic islets producing insulin [18, 22, 23, 24].

METHODS

The paper presents current and most interesting research on the use of stem cells in the study of spinal cord and brain injuries based on carefully analyzed selected articles from Pubmed and specialist textbooks. We focused on selected disease states in which stem cells may have therapeutic potential.

RESULTS AND DISCUSSION

Spinal cord injury (SCI) is a condition involving impairment or loss of motor, sensory and autonomic functions [25]. The pharmacotherapy, surgery and rehabilitation therapy used provide poor results [26]. It is crucial to obtain an effective and, equally important, safe method that can improve the condition of a patient with SCI. Relatively recently, stem cells have become a therapeutic option in regenerative medicine [27].

In preclinical studies conducted on animal models of SCI, stem cell therapy resulted in increased motor activity and improved neurological functions [28]. Spinally injured rats showed significant improvement on day 5 after UCB transplantation [29]. UCB transplantation improved sensory perception and mobility in the hip and thigh area in animals with spinal cord injury, which was associated with noticeable cord regeneration at the site of injury visualized using computed tomography and magnetic resonance imaging techniques [18]. Regeneration can also be attributed to neural stem cells and MSCs, such as bone marrow MSCs (BM-MSCs), adipose tissue-derived MSCs (AT-MSCs), and umbilical cord MSCs (UC-MSCs), most likely capable of regenerating damaged neural pathways, as demonstrated in several in vivo studies using experimental models of SCI [30, 31].

Neural stem cells are multipotent cells isolated from the lateral ventricle, hippocampal gyrus and spinal cord canal, which can differentiate into neurons, oligodendrocytes and astrocytes [30, 32].

A preclinical study showed good survival and differentiation ability, which favors the restoration of lost functions [33]. Additionally, the administration of neural stem cells accelerated the growth of axons in the injured area and slightly improved axonal conduction [30, 34]. NSCs secrete many growth-stimulating factors including: BDNF (brain-derived neurotrophic factor), GDNF (glial-derived neurotrophic factor), IGF-1 (insulin-like growth factor 1) [35]. The therapeutic effect of neural stem cells is related to their immunomodulatory effect by affecting T cells and macrophages, i.e. cells responsible for the processes of inflammation and demyelination [36]. It has also been shown that UCB transplantation after spinal cord injury increases the concentration of metalloproteinase 2 (MMP-2) and reduces the formation of glial scar, providing an appropriate environment for endogenous repair mechanisms [18, 37].

Stem cell therapies do not always bring the expected results, as they may be associated with complications such as: neuropathic pain [38]. As the above information shows, stem cells can play a significant role in the therapeutic, regenerative and repair processes in spinal cord injuries, therefore it is necessary to implement further research on their role and effectiveness.

APPLICATIONS OF STEM CELLS IN THE TREATMENT OF OTHER DISEASES OF THE NERVOUS SYSTEM

The good results of research using stem cells carried out on animals over the last several decades have meant that scientists are now looking for new applications for this form of therapy and are trying to use the knowledge acquired in laboratory tests in clinical trials with patients. In addition to the spinal cord therapy described above, much attention is also paid to other diseases of the nervous system.

ISCHEMIC STROKE

Ischemic stroke is a disorder of brain function caused by insufficient blood supply to a given area of nervous tissue, most often as a result of occlusion of an arterial vessel by an embolic material. Ischemia quickly leads to irreversible damage to a certain population of nerve cells, which increases until normal blood flow is

restored [39]. For this reason, it is very important to diagnose and start treatment as soon as possible.

Mesenchymal stem cells have the ability to differentiate into many types of cells, including neurons, glial cells and endothelial cells, i.e. groups of cells that are damaged in cerebrovascular accidents. An additional advantage of MSCs is that they can be obtained relatively easily, stored for a long time, and their use does not raise as many ethical problems as therapies with embryonic stem cells [40]. The positive effects of the use of MSCs in the treatment of stroke are related to their immunomodulatory effect, reduction of inflammation, as well as their impact on the function of glial and nerve cells as well as angio- and neurogenesis. This effect is largely related to compounds secreted by MSCs, such as growth factors (e.g. IGF, BDNF) and other cytoprotective compounds acting paracrine in the area of ischemic damage [41]. Clinical trials using MSCs have shown that the therapy can be safe and highly effective. In most studies, cells were administered intravenously. Direct intracerebral administration is a very invasive procedure and may be dangerous in patients with a severe clinical condition, therefore it is preferable to administer cells intravascularly or into the cerebrospinal fluid. After the introduction of therapy, some patients experienced transient fever [42]. The studies noted a significant improvement in the condition, which was manifested, among others, by: in the form of improved results in scales used to assess post-stroke patients, such as the Barthel scale, the National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin scale (MRS) [43, 44]. It is necessary to conduct further research to better understand the impact of stem cells and the compounds they secrete on the tissue affected by stroke, as well as long-term observation of patients undergoing this therapy to exclude the occurrence of long-term side effects.

MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a chronic inflammatory disease of autoimmune origin, leading to the gradual destruction of the myelin sheaths and axons of nerve cells, resulting in impaired signal conduction within the nervous system. Symptoms vary depending on the location of the inflammatory process and most often concern the optic nerve (vision disorders), oculomotor nerves (double vision), sensory tracts (sensory disorders, paresthesia), corticospinal tracts (weakened muscle strength) and cerebellum (ataxia, balance). The causes of MS are still not fully understood, but the pathogenesis of the disease is probably influenced by both genetic dysfunctions of the immune system and environmental factors triggering a pathological inflammatory response in predisposed people [6].

Currently, pharmacological agents are used in therapy to minimize the inflammatory reaction, but patients' response to treatment is not always satisfactory and the disease often leads to permanent disability. So far, several variants of stem cell therapy have been tested in MS treatment trials [45]. One of them is based on autologous hematopoietic stem cell transplantation (auto-HSCT). These cells are obtained by isolation from peripheral blood after their prior mobilization from the bone marrow using pharmacological agents (cyclophosphamide). Then, after appropriate selection, the cells are administered to the patient who undergoes the so-called conditioning, i.e. a procedure aimed at getting rid of autoreactive cells using immunoablative agents, which include radiation and pharmacological agents [46]. The aim of the method is to eliminate dysfunctional lymphocytes and replace them with normal cells of the immune system. A review of studies conducted since 1995 (15 studies involving 764 patients) using this method indicates its effectiveness, especially in the treatment of relapsing-remitting MS. The best results were achieved by patients in whom the disease had not yet caused a high degree of disability [47]. Over the years, the use of new immunoablative agents has also reduced the toxicity of therapy. Of all the cell therapies tested so far in MS, the use of auto-HSCT seems to be the most promising in terms of reducing symptoms. However, it is not certain whether the good results of therapy are caused by an actual change in the functioning of the immune system after cell autotransplantation or by aggressive immunoablation leading to the inhibition of the inflammatory process [48].

In addition to auto-HSCT, the effectiveness of other cell types was also tested. A potential therapeutic option is the use of mesenchymal cells (MSCs), oligodendrocyte progenitor cells (OPCs) and induced pluripotent cells (iPCs). MSCs are most often administered intravascularly (another option in the treatment of CNS diseases is direct administration into the cerebrospinal fluid), and their positive effect is probably related to their involvement in the repair of damaged tissues by secreting many substances with cytoprotective effects [48]. OPCs and iPCs can differentiate into mature oligodendrocytes and participate in the remyelination of damaged nerve fibers, but there are still many unknowns regarding the migration and maturation process of these cells and the role they play during demyelination occurring in MS, as well as potential side effects, including possible cancer potential of iPSCs [45].

NEURODEGENERATIVE DISEASES

Alzheimer's disease belongs to the group of neurodegenerative diseases and is characterized by progressive dementia caused by the loss of neurons in cortical and subcortical areas. Cell death occurs as a result of the accumulation of insoluble forms of amyloid, creating the so-called senile plaques and the appearance of intracellular neurofibrillary tangles consisting of hyperphosphorylated tau protein [6]. The exact mechanism of the development and progression of the disease is still not fully understood. However, it is known that

many factors contribute to its appearance, including genetic ones. The lack of an effective treatment method and the increase in average life expectancy leading to an increase in the number of diseases (the risk of developing the disease increases with age) motivate us to look for new potential methods of therapy. Promising results of research on animal models encourage attempts to use stem cells in patients with Alzheimer's disease [49]. These studies have attempted to use neural stem cells (NSCs), mesenchymal stem cells (MSCs), embryonic stem cells (ECS) and induced pluripotent stem cells (iPSCs). Each cell type has both advantages and disadvantages, and further tests are needed to answer the question of which cells could be the most optimal in possible future therapy [50]. Another problem is the fact that there is a huge difference between rodent and human neurons in terms of functioning and the pathomechanism of damage, which means that the results obtained in laboratory tests are often not confirmed in clinical tests with patients [49]. Cells were tried to be administered to patients not only intravenously, but also directly to the hippocampus and neocortex using a stereotaxic frame. This method turned out to be safe and well tolerated [51].

Attempts to develop an effective cell therapy for Parkinson's disease have been ongoing for many years. Animal studies show the great potential of MSCs, or rather the compounds secreted by them [52]. Substances such as cystatin C, vascular endothelial growth factor, brain-derived neurotrophic factor, or interleukin-6 synthesized by MSCs may have cytoprotective and trophic effects, which is particularly desirable in the treatment of diseases involving excessive cell loss, such as Parkinson's disease [53] Due to the high therapeutic value of these compounds, attempts have been made to administer them directly without injecting the MSCs that synthesize them [52,53,54]. The results of these studies show that the administration of compounds alone may be as effective, and in some cases even more effective, than the administration of MSC in terms of improving motor functions [53, 54]. However, there is still not much evidence of effectiveness in human studies.

In the future, induced pluripotent stem cells (iPSCs) may also play an important role in the treatment of Parkinson's disease. Attempts to treat patients using these cells include, among others: in Japan [55]. Clinical trials involve implanting stem cells directly into structures in the central nervous system related to the pathomechanism of Parkinson's disease using stereotactic neurosurgery. The method seems to be a step in the right direction and if long-term observation of patients undergoing this therapy does not reveal any undesirable side effects, this method has a chance in the future to become, next to pharmacotherapy and DBS, another therapeutic option in the treatment of Parkinson's disease.

RESTATEMENT OF THE MAIN POINTS

Over the last few years, the possibility of using various types of stem cells in the treatment of spinal cord injuries and brain diseases involving the loss of nerve cells has been intensively researched. The results of this research are promising and give hope for the future. The cell populations administered to patients can not only try to replace those lost (e.g. iPSCs), but also protect the cells of the recipient body through secreted substances and limit the extent of damage in the course of ischemia, inflammation or injury (MSC). We should also not forget about neural stem cells (NSCs) present in the vicinity of the brain ventricles or hippocampal formations, which have the ability to differentiate into neurons, oligodendrocytes or astrocytes.

Currently, animal experiments dominate the field of stem cell research, but the number of clinical trials is still growing. The biggest barrier here are the differences in the functioning of the nervous system and its greater degree of complexity in humans compared to the rodents studied. This means that the good results of some animal-assisted therapies are not reflected in the improvement of the clinical condition of patients. It is therefore important to look for appropriate therapy parameters in humans and find out what are the most optimal routes and places of cell administration and their doses, as well as which types of stem cells provide the best therapeutic effects in the treatment of a given disease. Ethical dilemmas that have arisen with the use of cells of embryonic origin can be resolved by using cells obtained from niches, such as bone marrow, found in the adult body.

Another option is to produce iPSCs from mature somatic cells by changing the expression of certain genes. Currently, cell therapies are mainly used in bone marrow diseases such as leukemias and myelodysplastic syndromes. If our level of knowledge allows it, in the future stem cells may become a tool in the fight against numerous diseases currently considered incurable and help in the regeneration of organs with a low degree of self-renewal, such as the spinal cord and brain, but also the heart, pancreas and many others.

CONCLUSIONS

To sum up, although all the above studies provide opportunities to confirm the therapeutic possibility of using stem cells, the safety of the procedure necessitates conducting more extensive multicenter studies. Although a small series of patient experiments suggest improved motor and sensory function after MSC administration, significant hurdles remain before these findings can be translated into new therapies. For patients who have hope, this is a good chance. For scientists, it is a huge challenge, which involves hours spent in laboratories. In particular, we need to better understand the mechanisms of action of MSCs and the

behavior of transplanted stem cells in the pathological environment of the CNS. To enable better evaluation of stem cell treatments, more clinical trials with larger and more homogeneous patient groups and longer follow-up periods are needed.

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