MESENCHYMAL STEM CELLS: A PROMISING MEANS OF ACTIVATING REPARATIVE OSTEOGENESIS

Abstract. Trauma in everyday life can cause damage to bone tissue and loss of function. One of the consequences of an injury is a fracture, which requires an individual approach in choosing a treatment method, which lasts quite a long time, despite modern advances in medicine. This article analyzes the current literature of the domestic and international scientific community, in which studies describe stem cell therapy as a promising way to improve the results of the restoration of bone tissue that has a poor ability to regenerate. The purpose of the research is to conduct an analysis of scientific literary sources on the use of mesenchymal stem cells to improve bone tissue regeneration. When searching for information on the use of mesenchymal stem cells, their influence on regeneration processes, various combinations of the following keywords were used: "mesenchymal stem cells", "cell therapy", "fracture", "orthopaedics", etc. The survey was carried out for 12 years. After reviewing the abstracts and reading the full text of more than 150 articles, 31 sources of domestic and foreign literature were selected for writing the review. During the performance of the work, the bibliosemantic method of clarifying the status of the outlined issues, studying and analyzing the results of scientific research given in literary sources and electronic resources was used. As a result, it was established that the problem of treating such an injury as a fracture is still acute in medicine and is not only a problem of health care authorities, but also a socioeconomic problem, because it leads to the loss of working capacity of workers and leads to disability. In turn, among the proposed means of treatment of fractures, the use of mesenchymal stem cells is probably the most promising, which will potentially shorten the duration of treatment of fractures, reduce the percentage of complications, which in turn will have positive therapeutic and economic effects. Therefore, in the future, it is important to conduct experimental and clinical research in order to confirm their role in the activation of reparative osteogenesis.

Keywords: trauma, fracture, consolidation, stem cells, bone.

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МАЗЕНХІМАЛЬНИ СТОВБУРОВІ КЛІТИНИ: ПЕРСПЕКТИВНИЙ ЗАСІБ АКТИВАЦІЇ РЕПАРАТИВНОГО ОСТЕОГЕНЕЗУ

Анотація. Травма в повсякденному житті може спричинити ушкодження кісткової тканини та втрату її функції. Одним із наслідків травми є перелом, що потребує індивідуального підходу у виборі методу лікування, яке триває довго, незважаючи на сучасні досягнення в медицині. В даній статті проведено аналіз сучасної літератури вітчизняної та світової наукової спільноти, в яких дослідження описують терапію стовбуровими клітинами, як перспективний шлях для покращення результатів відновлення кісткової тканини, яка має погану здатність до регенерації. Мета дослідження – провести аналіз наукових літературних джерел, які описують терапію стовбуровими клітинами, як перспективний шлях для покращення результатів відновлення кісткової тканини. Під час пошуку інформації з питань використання мезенхімальних стовбурових клітин, їхнього впливу на процеси регенерації, було застосовано різні комбінації таких ключових слів: “мезенхімальні стовбурові клітини”, “клітинна терапія”, “перелом”, “ортопедія” тощо. Огляд проведений на глибину 12 років. Провівши огляд анотацій та ознайомившись з повним текстом понад 150 статей, було відібрано 31 джерело вітчизняної та зарубіжної літератури для написання огляду. Під час виконання роботи використано бібліосемантичний метод з’ясування стану окреслених питань, вивчення та аналіз результатів наукових досліджень, наведених в літературних джерелах та електронних ресурсах. Як наслідок встановлено, що проблема лікування такого виду ушкодження як перелом досі гостро стоїть в медицині і є не тільки проблемою органів охорони здоров’я але і соціально-економічною проблемою, адже призводить до втрати працездатності робітників і призводить до інвалідизації. В свою чергу серед пропонованих засобів лікування переломів, чи не найбільш перспективним є застосування мезенхімальних стовбурових клітин, що потенційно дозволяє скоротити тривалість лікування переломів, зменшити відсоток ускладнень, що в свою чергу матиме позитивний лікувальний та економічний ефект. Тому в подальшому важливим є проведення експериментального та клінічного дослідження з метою підтвердження їх ролі в активації репаративного остеогенезу.

Ключові слова: травма, перелом, консолідація, стовбурові клітини, кістка.

Statement of the problem. The use of stem cells is a relatively new direction in medicine that is currently developing and will likely affect the future of orthopedic surgery. Stem cells are associated with great prospects for medicine. For the orthopedic surgeon, stem cells can change the way orthopedic surgery is performed and the overall approach to treating musculoskeletal disorders. Stem cells can bridge
the field of orthopedics and fields dominated by surgical replacement and reconstruction with the field of regeneration and prevention of complications related to bone tissue. Few tissues and organs can regenerate after disease or injury, and this ability to regenerate diminishes throughout life. Therefore, scientists are developing new methods in the field of tissue engineering, cell therapy and regenerative medicine to promote the regeneration of the musculoskeletal system. The use of stem cells in orthopedic surgery has the potential to change the field of orthopedics from one dominated by surgical replacement and reconstruction to bioregeneration and prevention [1].

Since the first description of mesenchymal stem or stromal cells (MSCs) in the 1960s, research has focused on their potential to differentiate into several tissues such as cartilage, bone, and adipose tissue. This has led to a large number of works devoted to the possibilities of their application in tissue engineering or regenerative medicine related to diseases of the musculoskeletal system [2].

Numerous studies in various animal models of orthopedic diseases have documented the multipotential properties of MSCs, showing their ability to differentiate into a variety of tissues, such as muscle, bone, cartilage, and tendon. However, despite initial suggestions that the therapeutic effects of MSCs depend on their ability to replace cells, recent studies have shown that the paracrine function of MSCs is the main mechanism by which they participate in tissue repair [3].

Most human studies support the view that short-term use of MSCs is safe and feasible; however, further experiments are needed. Importantly, we still need clear evidence to support the efficacy of MSC transplantation in patients. In some randomized controlled clinical trials, the injection of MSCs, which was used in the treatment of injuries, showed its effectiveness [4, 5].

Connection of the publication with planned scientific research works. The article is a fragment of a research topic of the Department of Traumatology and Orthopedics of the National Pirogov Memorial Medical University, Vinnytsya "Complex rehabilitation of patients with injuries and diseases of the musculoskeletal system" state registration number 0115U007095.

The purpose of the article – conducting an analysis of scientific literary sources on the use of mesenchymal stem cells to improve bone tissue regeneration.

Research objects and methods. For the analysis of literary sources, the search scientometric databases Scopus, Web of science, and Google Academy were used. The criteria for including the article in the review were: publication of the article in the period from 2011 to 2023; presence of key words: "mesenchymal stem cells", "cell therapy", "fracture", "orthopaedics", etc.; open and accurate data on research materials and methods; a clear and homogeneous sample in sufficient quantity. After reviewing the abstracts and reading the full text of 156 articles, 31 sources of domestic and foreign literature were selected for writing the review.

During the performance of the work, the bibliosemantic method of clarifying the status of the outlined issues, studying and analyzing the results of scientific research given in literary sources and electronic resources was used.
Presentation of the main material.

Research results and their discussion. Stem cells are heterogeneous and unspecialized cells that are the basis of every organ and cell in our body [6].

Depending on the origin, stem cells are divided into embryonic stem cells, which exist in the inner cell mass at an early stage of development; adult or fetal stem cells that reside in certain tissues and act as a source for repairing damage to their specific tissues; induced pluripotent stem cells, which are adult stem cells that have been reprogrammed into another type of adult stem cell, are among the most important cells that can be used for medical purposes. In addition, there are prenatal stem cells, which are derived from extraembryonic cells of the fetal membrane, umbilical cord, and amniotic fluid, as well as mesenchymal stem cells (MSCs), which are adult stem cells derived from bone marrow and muscle [7, 8].

The International Union of Cell Therapy provides the following recommendations regarding the mandatory criteria for the belonging of cells that exhibit stem activity to a number of multipotent MSCs: adhesiveness to plastic during cultivation under standard conditions; expression of specific surface antigens (CD73+, CD90+, CD105+); the ability to differentiate in vitro into osteoblasts, chondroblasts, and adipocytes [9].

MSCs perform the functions of maintaining tissue homeostasis and have a potential application in regenerative medicine. These cells have been successfully used for clinical purposes such as cartilage and bone repair, skin wound healing, neuronal regeneration, cardiac regeneration, and the treatment of immune disorders, including the treatment of graft-versus-host disease, due to their homing, multilineage differentiation, and immunomodulation capabilities. [10].

As numerous observations have shown, the disability of patients with fractures remains high and amounts to 19–37.9%, therefore there is an obvious need to find new effective methods of treatment and restoration of bone tissue [11].

Bone defects resulting from severe trauma, infection, or tumor removal can pose a significant challenge to mobility, especially if they are of critical size (>2.5 cm) and cannot heal without therapeutic intervention [12]. Cancellous bone from the iliac crest as an autologous bone graft is the gold standard for the treatment of bone defects, but often results in limited tissue availability, donor site morbidity, and lengthy surgeries. Additionally, in the case of large bone defects or open fractures, where the hematoma of the bone and/or fracture is exposed externally, patients may experience complications such as delayed union, nonunion, or infection, which may result in long-term disability. For smaller bone defects, fractures, and some craniofacial defects, the process of distraction osteogenesis to lengthen or reshape the bone, along with bone autograft, is likely to result in successful bone regeneration. However, for larger injuries, this bone graft is insufficient and needs to be supplemented with osteoconductive matrices and/or osteoinductive mediators to ensure bone healing [13].
Nanomaterials are now in the focus of bone regeneration and tissue engineering in general. To date, the biomedical use of nanomaterials has been reviewed in detail [14, 15, 16]. Due to their nanoscale size, nanoparticles exhibit greater availability in biological systems. Rapid advances in biomaterial nanotechnology are helping to address the growing need for functional bone grafts and implants.

Since bone tissue consists of four different cell types: osteoblasts, osteocytes, osteoclasts, and bone-lining cells, which are variously stored in the extracellular bone matrix [17], bone regeneration requires a material that is biocompatible, osteoconductive, osteoinductive, and perceived by the patient's immune system. Cells that mediate the process of osteogenesis, osteoblasts, originate from mesenchymal stem cells [18].

Various immunotherapy and mechanobiology-based therapies are being investigated to promote bone regeneration while providing sufficient local stability to initiate endogenous repair [19].

However, today scientists are very interested in the use of mesenchymal stem cells as the most suitable material for the restoration of bone and cartilage tissues. These cells have the properties of multipotent stem cells that can adhere to plastic surfaces, differentiate into various cells, including chondroblasts, osteoblasts, and migrate to the damaged area [20].

MSCs were isolated and described approximately 30 years ago, and now more than 55,000 publications on MSCs are available [21].

Multipotent mesenchymal stem cells (MSCs) have been thoroughly investigated as an effective means of cell therapy for inflammatory, immune-mediated, and degenerative diseases, due to their immunomodulatory, immunosuppressive, and regenerative potential [22].

Many studies have shown that certain stem cells can be used to treat a variety of human pathological conditions [23, 24, 25]. In clinical studies, significant side effects associated with MSC infusion were not observed [26].

The most widely studied sources of MSCs are bone marrow, adipose tissue, muscle, umbilical cord, umbilical cord blood, placenta, Wharton jelly and amniotic fluid [27], the acceleration of bone healing and good biocompatibility indicate the potential clinical application of this strategy [28].

At the current stage of medical development, other tissues, in addition to bone marrow and adipose tissue, are being investigated as additional sources of MSCs [29]. There is an opinion that umbilical cord MSCs have pluripotency, in contrast to the multipotent stem potential inherent in bone marrow and adipose tissue cells. There are data on the possibility of their expression of the embryonic markers Oct4 and Tra-1-60, Tra-1-81, SSEA-1, SSEA-4. Wharton cells of the umbilical cord (umbilical cord) contain cells that have been preserved from the early stages of embryogenesis, unlike the cells of the bone marrow and adipose tissue, which are mesenchymal stem cells of the adult organism. The use of MSCs from Wharton cord
blood is promising for the latest research, since there are effective cryopreservation methods and there are no legal conflicts regarding obtaining cells from the umbilical cord [30, 31].

Therefore, the analysis of the sources of scientific literature proves that MSCs have quite promising results in the treatment of non-union of bones, and tissue engineering methods using MSCs can be valuable for accelerating the process of bone union. However, the clinical application of MSC as a standard method in such cases requires more clinical trials with a standardized approach to the analysis of results.

**Conclusions.** The conducted analysis shows that today there is a positive result and experience with the use of mesenchymal stem cells in improving the regeneration of bone tissue. However, the lack of thorough research in this field necessitates experimental animal studies, a number of clinical studies involving a sufficient number of patients, the creation and description of clear criteria that define a cell culture as MSC, etc.

We see the prospect of further study of this issue in conducting the studies described above, which will allow us to expand our understanding of the therapeutic effects of the use of MSCs, which can potentially improve the results of treatment of patients with weak consolidation and speed up the fusion of bone tissue.

**References:**


Література:


