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CURRENT PROBLEMS AND PERSPECTIVES OF THE TREATMENT OF CARTILAGE INJURIES USING MESENCHYMAL STEM CELLS

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Annotation. *Since standard methods of treatment of cartilage trauma and inflammatory diseases lack effectiveness, at present one of the most promising strategies is mesenchymal stem cell transplantation. Despite the successes in this field, many issues, such as the selection of the tissue-source of mesenchymal stem cells (MSCs) and their optimization or modification in culture in order to achieve the maximum therapeutic effect, remains an actual task for both global and domestic scientists. The purpose of the study is to prepare a review of literature sources for the period 2004-2022 (in the vast majority on publications of the last five years) and to systematize new data on the biological characteristics of MSCs from various tissue sources, which are used in strategies for the treatment of cartilage lesions tissues, to analyze existing problems and further prospects, as well as potential ways of optimizing MSC cultivation methods to increase their regenerative potential. A study of 49 sources that met the inclusion criteria was carried out. A significant variety of strategies for the use of MSCs in animal models and in clinical practice was revealed. The main mechanisms ensuring the therapeutic effect of MSCs have been determined and can be used as criteria for optimizing cellular material. However, it was found that the question of the effectiveness of the use of differentiated MSCs, the selection of the tissue-source of MSCs, and the specifics of the use of MSCs from neonatal sources remains open. Thus, the analysis of literary sources revealed further promising ways to improve the therapeutic efficiency of MSC grafting in a wide range of cartilaginous lesions. There is a need to research the effects of MSCs from neonatal tissues, and especially the umbilical cord. This will become possible due to experimental research that will be carried out in the future.*

Keywords: *mesenchymal stem cells, cartilage tissue, degenerative diseases, traumatology.*

Introduction

Currently, the full functional restoration of cartilage tissue in traumatic lesions and degenerative diseases is one of the most difficult tasks of modern medicine, despite significant progress in understanding the pathogenesis and key factors necessary for therapy. The central reason for this is the biological properties of cartilage tissue. For example, articular cartilage is known to have a limited and insufficient capacity for self-healing, and to date no standard treatment considered effective can fully restore it after damage [46]. Therefore, cell therapy strategies involving stem cells from a wide range of tissues are attracting increasing attention both in research and when used in clinical practice. Despite significant advances in the study of the effects of stem cells in animal models, and successful application in some patient cases, until now most questions related to the optimal use of stem cells (SC) remain open.

Among the SC populations of an adult organism for use in the therapy of cartilaginous tissue lesions, mesenchymal stem cells (MSCs) from various tissue sources are considered particularly promising. It should be mentioned that the main feature of stem cells is the ability to self-renew and differentiate into specialized cell types. Based on the differentiation potential, they can be divided into totipotent, pluripotent, multipotent, oligopotent, and, finally, unipotent cells. MSCs belong to the group of multipotent stromal cells [20]. They are believed to originate from the mesoderm and neural crest [30, 38]. To date, the isolation of MSCs from various tissues of the adult body has been described, such as bone marrow (BM) [3], adipose tissue [17], dental pulp [47], synovial fluid [36], skin [6], muscle [21], endometrium [5]. Also, MSCs can be obtained from tissues of provisional organs: whole umbilical cord [31], Wharton jelly, placenta [10], amnion [26], and biological fluids, for example, breast milk [16] and menstrual blood [4].

When cultivated in vitro, MSCs are characterized as adhesive cells with a fibroblastic morphology that adhere to culture plastic. These cells do not express hematopoietic SC markers, such as CD45, CD34, and CD14, and express specific mesenchymal markers CD73, CD90, and CD105 [12].

Only recently were the main properties determining the therapeutic effect of MSCs during their transplantation determined. MSCs, regardless of the source tissue, are characterized by the ability to differentiate in the chondrogenic, osteogenic and adipogenic direction - tissue types of mesodermal origin. But, in addition, they can also be differentiated into myocytes and capable of transdifferentiation into ectodermal lineages (for example,

neuroglia cells [15]) and endodermal lineages (hepatocytes and pancreatic islet cells [7, 24]). MSCs secrete a wide range of growth factors and cytokines, such as endothelial growth factor (VEGF), transforming growth factor beta (TGF-β), and interleukins (IL-1β, IL-6, and IL-8) [18]. MSCs have pronounced immunomodulatory properties, which are mediated by both contact interactions with immune cells and paracrine activity. The ability of MSCs to migrate to the foci of inflammation in the tissue along gradients of inflammatory factors is particularly important [44].

All this, taking into account the embryonic origin from the mesoderm, makes them particularly promising for the therapy of a wide range of lesions of the human supporting apparatus.

The purpose of the work is to conduct an analysis of modern scientific sources regarding the role of mesenchymal stem cells in the treatment of cartilage tissue lesions.

Materials and methods

An analysis of scientometric sources from the Scopus, Web of Science databases was carried out to a depth of 18 years using keywords: pathology of cartilage tissue, mesenchymal stem cells, treatment with mesenchymal stem cells, mesenchymal stem cells and cartilage tissue. Criteria for inclusion in the review: availability of statistical data processing, clear criteria for forming the sample and its sufficient volume. Thus, out of 205 articles identified, 49 were included in the review.

Results. Discussion

Analyzing scientific publications, it can be noted that at the present time, among the lesions of the cartilage tissue, for the therapy of which the features of the use of MSCs are being investigated, the most popular is the lesion of the cartilage of the joints, especially osteoarthritis [49], because the ability of the articular cartilage is limited, the ability to regenerate is low, and this type of disease is a serious social and economic problem in countries with an aging population [13].

However, it is worth noting that the simulation of joint cartilage damage in numerous publications is carried out surgically, creating mechanical damage to the cartilage [46]. Therefore, some researchers, considering the prospects of using MSCs in acute cartilage injury, take into account the data obtained in such studies [43]. In contrast to the "dominance" of osteoarthritis among the cartilage lesions described in the scientific literature, a great diversity is observed among the investigated methods of optimizing the cultivation and introduction of MSCs. In this review, we will consider in detail such strategies for the use of MSCs for cartilage therapy, such as, for example, gene modifications to enhance the effects, the use of extracellular microvesicles [19], the introduction of MSCs on specific carriers (in gels and scaffolds, etc.) [23], consider only some aspects of the use of the cells themselves. Until now, a number of questions remain open (the scientific community is conducting an active discussion), which we will dwell on further.

To choose the optimal strategy for obtaining a population of MSCs that would have maximum efficiency, it is important to understand the mechanisms that determine the therapeutic effect. For any lesions of the cartilage tissue, the goal of treatment is its full functional restoration.

It should be remembered that articular cartilage is a highly specialized tissue that lacks innervation and is avascular, receiving nutrients by diffusion from the synovial fluid. The matrix consists mainly of water, various types of collagen (especially type II), proteoglycans and glycosaminoglycans. Chondrocytes are the only type of cells with a low frequency of division, make up 1-2% of the tissue volume and secrete all components of the extracellular matrix. Considering this, the update of the matrix is extremely slow [13]. Therefore, it can be assumed that the presence of cell types and matrix in the newly formed tissue are as close as possible to the physiological norm.

It is also worth outlining the problems that prevent the normal regeneration of damaged tissue, which are especially important in the transplantation of MSCs. It is known that cartilage injury is characterized by an acute process of activation of inflammation and catabolism. Synovial fluid analysis of patients with intra-articular ankle fracture showed the presence of acute, time-dependent fluctuations of pro-inflammatory (interleukin (IL) 1b, IL-6) and anti-inflammatory (IL-4, IL-10) cytokines. As for osteoarthritis, the local microenvironment of osteoarthritic joints is characterized by low-grade chronic inflammation, increased levels of oxidative stress, and activated catabolism. Compared with normal, affected tissues and synovial fluid are highly enriched in inflammatory mediators such as IL-1b, IL-6, tumor necrosis factor (TNF)-a, etc. [40]. Excessive expression of inflammatory mediators and increased reactive oxygen species (ROS) are considered inducers of matrix catabolism, senescence, and chondrocyte death [49]. The central problem in transplanting MSCs into a damaged joint is currently considered to be such a microenvironment, which may be the reason for a decrease in the viability of both chondrocytes and injected MSCs. That is, it can be assumed that native MSCs must have pronounced immunomodulatory properties (especially anti-inflammatory) to be used in the therapy of various joint injuries, which will be especially significant in the first stages of action after transplantation. Taking into account the repeatedly described anti-inflammatory properties of MSCs [34], it can be assumed that the therapeutic effect in inflammation of any genesis will be realized due to similar mechanisms.

Regarding the restoration of the cellular component of damaged cartilage, there are various hypotheses regarding the mechanisms. It is worth noting that the joint tissue has

its own populations of MSCs and their niches, which contribute to the cells being in a dormant, undifferentiated state, and, probably, to their periodic self-renewal. Such resident endogenous MSCs: chondroprogenitor cells, MSCs from the synovial membrane, MSCs from the synovial fluid, etc. have the ability to self-renew, are multipotent, and express typical surface markers of MSCs. Trauma, aging processes in the joint, and inflammatory processes in osteoarthritis attract resident MSCs to the site of injury, during which the cells enter an active state, migrate through the matrix, and "inhabit" the affected areas. In the future, both their differentiation and matrix production, as well as "maintenance" of chondrocyte viability [49] are possible.

There is much evidence that transplanted MSCs not only prevent the death of specialized cells of the affected tissue [33], but also have the ability to interact with the resident stem cells of the affected tissue and attract them to the lesions [45]. The question of the interaction of transplanted MSCs with resident MSCs of cartilage tissue remains open, but given the potential importance of this interaction, it can be assumed that MSCs for transplantation should have significant paracrine potential and the ability to chemoattract.

Some other findings regarding the mechanisms of action of transplanted MSCs are highlighted in the publication of Kangari and colleagues [20]. Currently, paracrine activity is considered one of the central factors of therapeutic effectiveness. Barry's work, for example, examines the role of the secretome, the release of extracellular vesicles, and apoptosis of injected MSCs in enhancing the therapeutic effect [2].

The above-mentioned features can certainly be considered basic for the selection of a population of MSCs or a strategy for optimizing their cultivation. However, it is worth noting that if the strategy is based on the use of autologous MSCs, either native or committed to differentiate into chondrocytes, it will also be important to consider the potential for differentiation and the ability to produce cartilage matrix components that are close to those in intact cartilage (eg, a specific set of collagens and glycosaminoglycans). In view of this, it is possible to dwell on some topical issues of optimizing the selection and preparation of MSCs.

Currently, the effective use of bone marrow MSCs, adipose tissue MSCs, which are generally one of the most researched sources, has been described. For example, injection of bone marrow MSCs into cartilage defects in rats leads to the formation of cartilage matrix [35]. Transplantation of adipose tissue MSCs increases the synthesis of glycosaminoglycans, improves endogenous chondrogenesis, and reduces inflammation [39].

Among the so-called "perinatal" or "neonatal" populations, that is, obtained from provisional organs, we can mention the use of MSCs from amniotic fluid, umbilical cord and umbilical cord blood [41]. It is known from numerous sources about the better paracrine and immunomodulating properties of cells of neonatal sources [1, 8]. In addition, their significant advantage is the non-invasiveness of obtaining the primary material, and a higher proliferative potential compared to that of an adult organism. It is also worth mentioning that compared with BM-MSCs and AD-MSCs, UC-MSCs have the following advantages: the expression of major histocompatibility complex I (MHC I) on the cell surface is low and MHC II is not expressed, so UC-MSCs rarely cause immune rejection [28]. In addition, the composition of the matrix of the umbilical cord is very similar to the composition of the connective tissue of cartilage. Human umbilical cord MSCs have been shown to express aggrecan, collagen type II and SOX-9, as is characteristic of chondrocytes [42].

Some studies have also confirmed the better efficacy of perinatal MSCs compared to MSCs from adult tissues. For example, in the work of Yang and colleagues, it was shown that, in a model of osteoarthritis, after 4 weeks, the content of glycosaminoglycans in the group that was injected with umbilical cord blood MSCs was 10 times higher than that in the untreated group, and in those that were injected with bone marrow MSCs - 8 times.

After 8 weeks after injection, the defect in the MSCs-UB injection group was reduced by 1/2, while in the MSCs-BM group it was reduced by only 1/3 [46].

Unfortunately, in the scientific literature, the cases of using MSCs of the whole umbilical cord, as well as Wharton's jelly MSCs, are insufficiently described. Although some works have shown their effectiveness in animal models, and even in transplantation to patients. In small animal models of osteoarthritis, injection of MSCs-BC into damaged cartilage reduces cartilage fibrillation as well as MMP-1 (metalloproteinase 1, an important enzyme) level and induces a satisfactory reparative effect [48].

It is worth noting that autologous and allogeneic cells have similar immunomodulatory properties [9], and it is believed that they can equally reduce inflammation in the joint. This makes possible the potential use of allogeneic perinatal MSCs for adult recipients.

Until now, the strategy of therapy with the help of MSCs committed to differentiation in the chondrogenic direction, with different degrees of differentiation, has not lost its relevance. It is believed that such methods can have a number of advantages. It is worth mentioning that autologous implantation of chondrocytes has shown high efficiency in "closing" chondral defects [38]. But, for example, it is likely that chondrocytes obtained from patients with late stage osteoarthritis lose the function of cartilage matrix synthesis [14].

MSCs can acquire chondrogenic capacity when cultured under established conditions for differentiation or in ex vivo 3D cultures [22]. During chondrogenic differentiation, MSCs synthesize numerous components of the cartilage matrix, including type II collagen, ACAN, and glycosaminoglycans. The matrix thus reconstructed, with affinity for collagen-binding integrins, can establish connections with chondrocytes or MSCs and further regulate cell viability, differentiation and migration, as well as tissue morphogenesis and subsequent

tissue reconstruction [27, 29].

Preclinical studies in which MSCs differentiated into chondrocytes have been used to treat cartilage repair have shown conflicting results [23]. Dashtdar and co-authors compared the use of pre-differentiated and undifferentiated MSCs for the restoration of full-thickness articular cartilage defects in rabbits, and demonstrated practically the same effectiveness [11]. However, a recent study in an osteochondral defect model in rabbits using constructs of differentiated MSCs on polycarbonate microcarriers showed that implantation of chondrogenically differentiated MSCs led to the best cartilage healing results compared to undifferentiated MSCs [25].

For this strategy, Wharton's jelly MSCs seem particularly promising. For example, in the work of Pelusi, it was shown that umbilical cord MSCs have a higher differentiation potential than bone marrow MSCs [32].

Conclusions and prospects for further development

1. Analysis of literature sources over the past decades has shown the potential advantages of MSCs from neonatal sources, which can be used in traumatic and inflammatory lesions of cartilage tissue. However, a number of questions regarding the optimal strategy for the use of MSCs in therapy remain open, because until now there is a lack of a universal scheme for their use, and ways to optimize these cultures at the in vitro stage. Also, there are only separate data on the specifics of the use of MSCs from certain types of neonatal tissues, for example, Wharton's jelly.

Therefore, the study of these issues remains an urgent task, which can be performed by conducting a series of experiments using a population of MSCs from Wharton's well on a model of traumatic cartilage damage.

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СУЧАСНІ ПРОБЛЕМИ ТА ПЕРСПЕКТИВИ ЛІКУВАННЯ УРАЖЕНЬ ХРЯЩОВОЇ ТКАНИНИ ЗА ДОПОМОГОЮ МЕЗЕНХІМАЛЬНИХ СТОВБУРОВИХ КЛІТИН

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Анотація. *Оскільки стандартні методи лікування травматичних уражень і запальних хвороб хрящової тканини мають недостатню ефективність, на теперішній час однією з найбільш перспективних стратегій вважається застосування мезенхімальних стовбурових клітин (МСК). Незважаючи на успіхи у цій галузі, багато питань, таких як вибір тканини-джерела МСК та оптимізація або модифікація їх у культурі з метою досягнення максимального терапевтичного ефекту, залишається актуальним завданням як для світової, так і для вітчизняної наукової спільноти. Мета дослідження - провести огляд літературних джерел за період 2004-2022 роки (з акцентом на публікації останніх п'яти років) і систематизувати нові дані щодо біологічних особливостей МСК з різних тканинних джерел, які застосовуються у стратегіях лікування уражень хрящової тканини, проаналізувати існуючі проблеми та подальші перспективи, а також потенційні шляхи оптимізації методів культивування МСК для підвищення їх регенеративного потенціалу. Виконано дослідження 49 джерел, що відповідали критеріям включення. Виявлено значну різноманітність стратегій використання МСК на тваринних моделях та у клінічній практиці. Визначено основні механізми, що забезпечують терапевтичний ефект МСК, і можуть бути використані як критерії для оптимізації клітинного матеріалу. Однак, виявлено, що питання ефективності застосування диференційованих МСК вибору тканини-джерела МСК, і особливостей використання МСК з неонатальних джерел залишається відкритим. Таким чином проведений аналіз літературних джерел виявив подальші перспективні шляхи удосконалення терапевтичної ефективності застосування МСК при широкому спектрі уражень хрящової тканини. Існує необхідність у дослідженнях ефектів МСК з неонатальних тканин, і, особливо, пупкового канатика. Це стане можливим за рахунок проведення експериментальних досліджень, які будуть виконані в подальшому.*

Ключові слова: *мезенхімальні стовбурові клітини, хрящова тканина, дегенеративні захворювання, травматологія.*