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MESENCHYMAL STEM CELLS MIGRATION MECHANISMS AND POSSIBLE STRATEGIES FOR THEIR IMPROVEMENT

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Abstract. In recent decades a lot of data have been accumulated on the mechanisms of tissue renewal and regeneration, which would be impossible without the participation of stem cells. It has been proven that these processes in many tissues are carried out by tissue-specific stem cells (TSCs), but their production, cultivation and administration for therapeutic purposes are extremely difficult. Along with this, mesenchymal stem cells (MSCs) are a promising therapeutic agent that has already proven its clinical effectiveness in various diseases and in tissue engineering. One of the features of MSCs introduced systemically is the ability to find a niche in the affected tissue and remain there, having a significant impact on inflammation, tissue remodeling processes and its regenerative potential. However, the mechanisms of differentiation and migration of MSCs, as well as the factors influencing these processes, are not fully disclosed. This review makes an attempt to summarize the accumulated data on the mechanisms of MSC migration and possible ways to improve it.

Key words: mesenchymal stem cells; tissue regeneration; cell therapy; migration.

МЕХАНИЗМЫ МИГРАЦИИ МЕЗЕНХИМАЛЬНЫХ СТВОЛОВЫХ КЛЕТОК И ВОЗМОЖНЫЕ СТРАТЕГИИ ИХ УЛУЧШЕНИЯ

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Резюме. В последние десятилетия накапливается все больше данных о механизмах обновления и регенерации тканей, которые были бы невозможны без участия стволовых клеток. Доказано, что данные процессы во многих тканях осуществляются за счет тканеспецифичных стволовых клеток (ТСК), однако их получение, культивация и введение с терапевтической целью крайне затруднительны. Наряду с этим наибольший интерес

представляют мезенхимальные стволовые клетки (МСК), которые, благодаря возможности их выделения, экспансии и мультипотентности, являются многообещающим терапевтическим агентом, уже доказавшим свою клиническую эффективность при различных нозологиях, в том числе в вопросах тканевой инженерии. Одной из особенностей МСК, введенных системно, является способность находить нишу в пораженной ткани и оставаться в ней, оказывая существенное влияние на воспаление, процессы ремоделирования ткани и ее регенеративный потенциал. Однако механизмы дифференцировки и миграции МСК, а также факторы, влияющие на эти процессы, раскрыты не полностью. В данном обзоре обобщены современные данные о механизмах миграции МСК и возможных путях ее улучшения.

Ключевые слова: мезенхимальные стволовые клетки; регенерация тканей; клеточная терапия; миграция.

The assumption that there are cells in the body that promote wound healing was made by Cohnheim back at the end of the XIX century [13]. Mesenchymal stem cells (MSCs) were first isolated and cultured in 1968 by Friedenstein, who discovered that transplantation of cell colonies into semi-syngeneic animals could lead to the formation of cartilage and bone tissue containing bone marrow [17]. Years later, it was realized that these works described cells with multipotent ability. Further studies of the heterogeneous population of bone marrow MSCs were carried on by a group of scientists led by Kaplan in the 1980–1990. During this period, the possibility of differentiation of MSCs into various mesenchymal tissues was discovered for the first time, and the first surface markers characteristic of MSCs (CD73, CD105) were identified [21]. The term "mesenchymal stem cells" itself was proposed in 1991 [12]. Since then, the era of cell therapy began.

According to the accumulated data, MSCs show a good safety profile, have multilineage differentiation potential and a low immunogenic profile, which makes them an attractive therapeutic agent [20]. By 2018, estimates of the number of patients who have had experience with the therapeutic use of MSCs ranges from 10,000 to 70,000 people, including children [11]. No serious adverse events associated with MSC therapy and requiring early termination of the clinical trial were reported [11].

FEATURES OF MSC PHENOTYPE

MSCs were initially characterized by their ability to generate colony-forming units, fibroblasts (CFU-Fs). The number of CFU-Fs in the bone marrow is about one cell per 10^4–10^5 mononuclear cells [16]. MSCs are characterized by the expression of various surface markers, but none of them appear to be expressed exclusively by MSCs. In this regard, the International Society for Cell and Gene Therapy (ISCT) proposes at least three conditions that can characterize MSCs [52]:

- adhesion to specialized plastic under standard cultivation conditions;
- expression of surface markers CD105, CD73 and CD90; in this case, CD11b, CD14, CD19, CD34, CD45, CD79α and HLA-DR, which are markers of hematopoietic stem cells, should not be present;
- ability to differentiate into osteoblasts, adipocytes and chondroblasts *in vitro*.

However, controversy remains regarding the ideal set of MSC surface markers, since many of them are expressed by other cell types and may also vary depending on the source, MSC culture method, and number of passages in culture media. For example, a number of surface markers (Oct-4, Nanog, Rex-1, SSEA-3, etc.) are expressed on MSCs, isolated from peripheral blood, liver and bone marrow of a fetus in the first trimester of pregnancy, but are absent on MSCs isolated from the bone marrow of adults [41].

According to the data obtained using multichromatic flow cytometry, MSCs change their immunophenotypic profile depending on the passage number (1–8), although the expression of some markers is variable and independent of time [36]. In particular, during the first passages, high expression of CD29, CD166 and CD201 is observed in addition to the canonical markers CD73, CD90 and CD105. At the same time, by the 8th passage, differences are observed in the expression of CD34, CD200 and CD271 by MSCs, which requires further study, especially in terms of clinical use.

The ability to express surface markers (CD13, CD29, CD44, CD73, CD90, CD105, CD146, CD166) significantly decreases after the 7th passage and beyond, and MSCs themselves enter the aging phase and lose the ability to proliferate [55]. In this regard, for therapeutic purposes it is preferable to use MSCs that have undergone less than 6 passages *in vitro* [1].

STAGES OF MSC MIGRATION TO DAMAGED TISSUE

The therapeutic efficacy of MSCs largely depends on their ability to produce juxtacrine and paracrine factors. For juxta- and paracrine effects to be possible, migration of MSCs into the affected organ/tissue is necessary, which may depend on many factors, including the age of the donor, the number of passages of MSCs, the conditions of their cultivation and the method of delivery to the target organ [3, 4].

It has been shown that when administered systemically, MSCs undergo a multi-stage process of transition from the

bloodstream to the target tissue. Systemic recruitment of MSCs can be divided into five stages: 1) attachment to the endothelial surface; 2) activation; 3) arrest; 4) diapedesis and 5) migration to the target. The initial binding of MSCs to endothelial cells is facilitated by the expression of selectins. MSCs express CD44, which was first identified as a lymphocyte receptor responsible for homing. CD44 interacts with selectins and promotes the process of "rolling" MSCs along the vascular wall [43]. To demonstrate the binding of MSCs to endothelial cells, a parallel plate flow chamber seeded with endothelial cells was created [42]. Antibodies to P-selectin were shown to inhibit the binding of MSCs to endothelial cells, whereas immobilization of P-selectin resulted in rapid binding of MSCs to endothelial cells. As MSCs do not express PSGL-1, it is assumed that they must use another ligand for this purpose. Galectin-1 has been identified as one of these ligands [49]. Another study identified CD24 as a potential P-selectin ligand for MSCs isolated from adipose tissue [7].

The second step (activation) is mediated by G protein-coupled chemokine receptors, usually in response to proinflammatory signals. Expression of stromal cell-derived factor-1 (SDF-1), a ligand for the chemokine receptor CXCR4, is crucial for this stage [30]. Expression of SDF-1 on MSCs has a direct impact on the rate of their migration to the site of damage in a rat model of myocardial infarction [61]. MSCs have also been shown to express CXCR7, which similarly binds to SDF-1 to facilitate homing to various tissues [31]. Overexpression of CXCR4 on MSCs promotes their return to the bone marrow [10]. Along with CXCR4, expression of the chemokine CCL2 on cardiomyocytes of transgenic mice with induced myocardial ischemia is able to enhance the migration of MSCs expressing the corresponding CCR2 receptor due to direct interaction between the ligand and the receptor [8]. A number of studies have shown that MSCs, both freshly isolated and at the cultivation stage, are capable of expressing CCR1, CCR4, CCR7, CCR10, CCR9, CXCR5 and CXCR6 [22, 53], but their role remains to be clarified.

The third stage (arrest) is mediated by integrins. MSCs can express the integrin receptor VLA-4, consisting of α4 (CD49d) and β1 (CD29) chains, which is activated in response to chemokines such as SDF-1. Once activated, VLA-4 binds to VCAM-1 on endothelial cells [47]. It has been shown that neutralizing antibodies to the β1 chain of VLA-4 inhibit the homing of MSCs to the ischemic myocardium, which cannot be said about antibodies blocking the α4 chain [24]. Overexpression of the VLA-4 α4 chain is thought to promote MSC return to the bone marrow [29]. An interesting fact is that MSCs, along with endothelial cells, are capable of expressing cell adhesion molecules VCAM-1 (ligand for VLA-4), as well as ICAM-1 (ligand for the integrin receptor LFA-1) [28].

At the next (fourth) stage, MSCs must pass through the endothelial cell layer and the basement membrane (transmigration) into the extravascular space. To achieve this, MSCs secrete matrix metalloproteinases (MMPs) [47]. A similar mechanism is used by white blood cells and tumor cells for a similar purpose. The expression of MMPs is determined by the secretion of proinflammatory cytokines, which serve as a signal for cell migration into damaged tissue. The maturation and activity of MMPs are regulated by various proteins, most notably tissue inhibitors of metalloproteinases (TIMPs). It is assumed that the balance of MMPs/TIMPs influences the rate of migration of MSCs through the endothelium. When neutralizing antibodies to MMP-2 (an enzyme possessing ability to break down the main component of the basement membrane (collagen IV)) are added to the culture medium, it leads to a significant decrease in MSC migration *in vitro*. A similar result is observed when TIMP3 is added to the culture medium [14]. Neutralization of TIMP1 enhances the migration of MSCs through the endothelium, while neutralization of MMP2, MT1-MMP or TIMP2 reduces it [40]. The question of the participation of various MMPs and TIMPs in MSC migration requires further study.

In the fifth stage, MSCs must migrate to the site of injury, usually in response to signals released from the damaged tissue, such as basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), insulin-like growth factor-1 (IGF-1), platelet-derived growth factor (PDGF) and transforming growth factor β1 (TGF-β1).

Platelet-derived growth factor-AB (PDGF-AB) and insulin-like growth factor-1 (IGF-1) influence MSC migration to a greater extent than the RANTES chemokines, macrophage chemokines (MDC) and stromal-derived factor-1 (SDF-1), which have a limited effect [38]. Preincubation of MSCs with the tumor necrosis factor TNFα increases their migration towards chemokines, probably due to activation of the CCR2, CCR3 and CCR4 receptors. Proinflammatory interleukin-8 (IL-8) can promote the migration of MSCs to the site of injury, as well as their secretion of vascular endothelial growth factor (VEGF), which was shown in a rat model of a stroke [9]. Administration of MSCs treated with IL-8 leads to a decrease in the volume of brain damage and increased angiogenesis in the ischemic border zone compared to MSC therapy without IL-8.

The bFGF factor, being a powerful mitogen, can stimulate the migration of various types of cells, in particular MSCs [33]. A low concentration of bFGF promotes MSC migration, while a high concentration of bFGF inhibits MSC migration, and this contradictory effect of bFGF allows for their directional routing [45]. One of the possible mechanisms for enhancing MSC migration is supposed to be their enhanced expression of αVβ3 integrin and activation of the MEK/ERK signaling pathway. In addition to recruitment, bFGF promotes increased secretion of VEGF by MSCs, which is important in restoring vascular integrity after damage of endothelium [50].

IGF-1, which is actively involved in the regulation of the processes of growth and differentiation of various cells of the body, can also influence the migration of MSCs. Overexpression of IGF-1 on MSCs improves survival and transplant engraftment in a rat model of infarction and promotes MSC recruitment, likely through the paracrine release of SDF-1 [23]. Pre-incubation of MSCs with the addition of IGF-1 to the culture medium improves the migration ability of MSCs in a model of acute kidney injury, with the presence of MSCs promoting rapid normalization of kidney function [57]. IGF-1 increases the migratory potential of MSCs by increasing the expression of the chemokine receptor CXCR4 and its ligand SDF-1. The response to SDF-1 can be attenuated by a PI3 kinase inhibitor, but not by an inhibitor of mitogen-activated protein/ERK kinase, which shows the importance of the PI3/Akt pathway in the response of MSCs to various signaling molecules [32].

TGF-β1 has a broad biological activity, playing an important role in cell growth, differentiation and immune regulation of cells. Remaining in an inactive form in the cell matrix, TGF-β1 is released in an active form in response to mechanical stress or inflammation and is involved in the repair and regeneration of damaged tissues. The expression of TGF-β1 increases during ischemia/reperfusion injury of the myocardium of mice, which enhances the recruitment of MSCs by regulating the expression of CXCR4 [60]. In a mouse model of asthma, it was shown that high levels of active TGF-β1 in their lung tissue were associated with allergen stimulation, and increased migration of MSCs into the lungs was observed. It has also been shown that intraperitoneal administration of both TGF-β1-neutralizing antibodies and a TβR inhibitor to experimental animals leads to a decrease in the migratory ability of MSCs [19].

From the above it follows that chemical factors influencing MSC migration act in a complex manner, activating different signaling pathways. Understanding the molecular events that promote MSC migration has significant implications for strategies to optimize their delivery for therapeutic purposes.

STRATEGIES TO IMPROVE MSC DELIVERY TO TARGET TISSUE

Despite large doses of MSCs when administered systemically (≈1 million MSCs per 1 kg of patient body weight), only a small part of them actually reaches the target tissue [15]. This is believed to be due to several factors. After systemic administration a significant part of MSCs are retained in the capillaries of the lungs [44]. The therapy received by the patient may influence the migratory ability of MSCs. Vasodilators and anticoagulants such as heparin have been shown to reduce the uptake of MSCs into the lungs and increase the number of MSCs in other organs, particularly the liver and red bone marrow [18]. However, the migration process of MSCs is determined, as described above, by the expression profile of specific surface molecules and their receptors, and not simply by passive spread through the vasculature. Another problem is that on MSC after expansion *in vitro*, the expression of molecules required for migration to the target tissue appears to be reduced [22]. There is also heterogeneous expression of homing molecules in MSC cultures from different sources, such as those isolated from adipose tissue versus those isolated from bone marrow [48].

All of these factors necessitate the development of strategies that improve the delivery of MSCs to the target tissue. The most discussed approaches are: *introduction of MSCs into the target tissue, magnetic targeting, pre-treatment of MSCs in the culture or changing the culture conditions, merging the MSC culture with other cell cultures.*

Introduction of MSCs into the target tissue or nearby locations is the simplest and most intuitive strategy to increase the presence of MSCs in the lesion. Unfortunately, there are few studies comparing the effect of different methods of MSC delivery on the results of the therapy; however, there is convincing evidence of some advantages of non-systemic administration compared to systemic administration. It has been shown that transcatheter administration of MSCs in patients with ischemic cardiomyopathy after myocardial infarction increases myocardial contractility in the area of the permanent scar, which influences the subsequent reverse tissue remodeling. However, the study design did not provide for systemic administration [56]. According to the meta-analysis carried out by Vu, in ischemic stroke, intracerebral administration of MSCs appears to lead to a significant improvement in neurological status when compared with intra-arterial and intravenous introduction of MSC [54]. In a porcine model of myocardial infarction, it was shown that transendocardial administration of MSCs reduces the infarct area, while intramyocardial, intracoronary and intravenous administration does not lead to significant improvements [26]. However, another meta-analysis reported that MSC administration improved left ventricular ejection fraction in patients after myocardial infarction in case of intracoronary, intravenous, and intramyocardial administration of MSCs in descending order of effect size [25].

In acute lung injury syndrome, intravenous administration is more effective than intraperitoneal administration [35]. However, the method of administration of MSCs does not influence the results of therapy for traumatic brain injuries [37]. Obviously, one should not assume that direct injection of MSCs into the target tissue will provide the best results.

Another approach to targeting MSCs to target tissue is magnetic targeting, in which cells labeled with magnetic particles are guided to the target organ using an external magnetic field. MSCs labeled with iron oxide were administered intravenously

to rats with a magnet attached to the body in the projection of the liver and to rats without a magnet. In rats that wore an external magnet, 15 days after MSC injection, there were approximately 2 times more labeled MSCs in the liver compared to the control group. In rats that did not wear magnets, MSCs were predominantly localized around the portal triads, and in rats that wore magnets, MSCs were recorded deep in the liver parenchyma [6]. Yanai et al. were able to concentrate MSCs labeled with magnetic particles in the projection of the retina in rats, both when injected into the retina and when administered intravenously using a magnet placed in the orbital area. In rats wearing an external magnet, higher levels of anti-inflammatory factors (IL-10; hepatocyte growth factor (HGF)) were noted, which indicates the therapeutic effect of MSCs [58]. Another study used a magnet to concentrate magnetically labeled MSCs into damaged olfactory bulbs. These cells were detected one week after injection and were present in higher numbers compared to MSCs not treated with magnetic particles. It was noted that magnetic iron oxide particles increased the expression of CXCR4 and SDF-1 on MSCs [59].

Due to the fact that the cultivation of MSCs *in vitro* reduces the expression of surface molecules involved in recruitment on them, *pre-treatment of MSCs in culture or changing culture conditions* is considered to be the simplest and most accessible strategy to enhance MSC migration into target tissues. One way to achieve this goal is to add cocktails with cytokines and other growth factors to the culture medium at the stage of MSC expansion. The combination of the cytokine receptor flt3, stem cell factor (SCF), IL-3, IL-6 and hepatocyte growth factor (HGF) increases both intracellular and membrane expression of CXCR4 on cultured MSCs, which enhances their migratory ability towards SDF-1 [46]. CXCR4 expression can also be enhanced by adding glycogen synthase kinase-3β (GSK-3β) inhibitors to MSC culture, resulting in improved migratory ability *in vitro*, without influencing cell viability [27]. Short-term pretreatment of MSC culture with valproic acid leads to an increase in the expression of CXCR4 and MMP-2 on MSCs and increases their migration towards SDF-1, without influencing the ability of MSCs to differentiate [34].

Culture conditions also influence CXCR4 expression on MSCs. It is believed that this depends on the presence of hypoxia-inducible factor 1α (HIF-1α). Cultivation under hypoxic conditions leads to increased expression of CXCR4 and improved migration of MSCs both *in vitro* and *in vivo*, with this effect being observed both during short-term oxygen limitation and in response to prolonged cultivation under hypoxic conditions [5]. It is worth noting that hypoxia can influence the enhancement of adipogenic and osteogenic differentiation of MSCs in culture, which may be undesirable for further therapeutic use [51].

As noted previously, MSCs express low levels of CXCR4, so a number of researchers have attempted transfection or transduction, in which CXCR4 expression plasmids are delivered into the MSC nucleus using viruses. In approximately 90% of cases after treatment of MSCs with a retrovirus (*ex vivo*) there is overexpression of CXCR4, which leads to phosphorylation of AKT mitogen-activated proteins, as well as an increase in the expression of matrix metalloproteinases (MMPs) after SDF-1 stimulation. MSCs demonstrate enhanced migratory ability towards SDF-1 and homing into the bone marrow of NOD/SCID mice [10]. Viral transduction is the most effective method for obtaining high and stable levels of expression in target cells, but it is associated with the risk of oncogenic transformation and is a rather expensive method.

Fusion of *cell cultures* can be considered within the framework of the approach of enhancing the migration of MSCs, while there are isolated reports on this topic. Co-culture of MSCs derived from amniotic fluid with amniotic epithelial cells enhances the proliferation and expression of CXCR4 [39]. Co-culture of MSCs isolated from rat adipose tissue with Sertoli cells enhances the proliferation and migration of MSCs, apparently due to the activation of the MAPK/ERK1/2, MAPK/p-38 and PI3K/Akt signaling pathways. Treatment of MSCs with conditioned media obtained from endothelial cell cultures increases MSC migration *in vitro*, possibly due to the presence of the cytokines IL-6 and IL-8 [2].

Thus, mesenchymal stem cells have the ability, when administered systemically, to enter the affected tissue and influence inflammation, remodeling processes and regeneration, therefore, further clarification of the mechanisms of differentiation and migration of MSCs, identification of factors influencing these processes will contribute to the expansion of their use in many fields of medicine.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

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