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Review

The Research Progresses of Mesenchymal Stem Cells Therapy in Hematological Diseases

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Received: 10 June 2024; Accepted: 25 June 2024; Available online: 30 June 2024

ABSTRACT: Hematopoietic diseases are characterized by the high heterogeneity of associated hematopoietic cells, which mainly affect the homeostasis of the hematopoietic system. Due to their potential for multilineage differentiation and expected immunomodulatory properties, mesenchymal stem cell (MSC) based therapies have demonstrated significant promise in treating hematologic diseases. They have been successfully applied in various conditions, including aplastic anemia, refractory/relapsed myeloid leukemia, immune thrombocytopenic purpura, etc. Therefore, the purpose of this article is to review the biological characteristics, clinical applications, and related mechanisms of MSCs in hematopoietic diseases.

Keywords: Mesenchymal stem cell; Immune thrombocytopenic purpura; Aplastic anemia; Leukaemia

1. Introduction

According to the International Statistical Classification of Diseases (ICD), blood diseases are divided into three categories: red blood cell diseases, white blood cell diseases, and hemorrhagic diseases. Aplastic anemia (AA) is a disease of red blood cells. According to the World Health Organization (WHO), anemia affects 40% of children aged 6 to 59 months, 37% of pregnant women, and 30% of women aged 15 to 49 years globally. Leukemia, a disease affecting white blood cells, has an overall survival rate of around 61%. However, survival rates differ by type; for example, the five-year survival rate for chronic lymphocytic leukemia is as high as 85%, while it is approximately 27% for acute myeloid leukemia (AML). Immune thrombocytopenic purpura (ITP) is classified as a hemorrhagic disease, with 25–50 cases per million people globally. Current treatments for these three types of diseases include drug therapy, bone marrow transplantation, and radiotherapy. However, drug therapy can result in drug tolerance and side effects, while radiotherapy can cause immune damage, hair loss, and other issues, ultimately impacting the long-term quality of life for patients. Bone marrow transplantation has a wide range of applications and can fundamentally reshape the hematopoietic environment, which is a promising therapeutic method [1]. Immune rejection has long been a challenging issue, but the current use of stem cells may help mitigate this problem.

Stem cells are a kind of cell population with self-renewal and multi-directional differentiation potential [2]. According to the developmental stage of stem cells, they can be divided into embryonic stem cells and adult stem cells. Embryonic stem cells are highly undifferentiated cells with developmental totipotency and can be induced to differentiate into almost all cell types of the body. Adult stem cells refer to undifferentiated cells existing in differentiated tissues, which are distributed in various tissues and organs of the body, and they are sourced widely, including bone marrow, retina, umbilical cord, peripheral blood, dental pulp, etc. They could produce specific precursor

https://doi.org/10.70322/BG20240110001

cells in certain tissues, whereas the differentiation potential is less potent than embryonic stem cells [3]. Mesenchymal stem cells (MSCs) and hematopoietic stem cells are types of stem cells. MSCs can be categorized based on their sources, such as bone marrow mesenchymal stem cells (BMMSCs), adipose mesenchymal stem cells (Ad-MSCs), umbilical cord mesenchymal stem cells, and others [4]. Hematopoietic stem cells mainly exist in bone marrow, and a small part can also exist in peripheral blood and umbilical cord blood. They can differentiate into various blood cells, including red blood cells, white blood cells, platelets, etc. In 2006, the International Association of Cellular Therapy (ISCT) made the minimum identification standard for MSCs. Presenting an adherent growth state under standard *in vitro* culture conditions; More than or equal to 95% of the cells expressed CD105, CD73, and CD90, and no more than 2% of the cells expressed CD45, CD34, CD14, CD11b, CD79a or HLA class II molecules; They can differentiate into osteoblasts, chondrocytes, and adipocytes under *in vitro* induction conditions [5].

As of April 2024, there were 1272 clinical trials using MSCs worldwide (www.clinicaltrials.gov). Most of these studies (57.7%) were phase I studies, which involved cardiovascular diseases, diabetes, graft-versus-host disease (GVHD), neurological and immune systemic diseases, etc. Globally, the use of MSCs for treating various diseases has emerged as one of the most prominent and innovative areas in medical research today, showing tremendous potential for future development.

2. Biological Characteristics of MSCs

2.1. Proliferation Ability and Multi-Directional Differentiation Ability

MSCs are also known as "seed cells", and could maintain the renewal demand of the human body for a lifetime because of their strong proliferation ability. Since MSCs are derived from the mesoderm, they also keep a strong multi-directional differentiation potential. Under specific stimulation conditions, MSCs could differentiate into osteoblasts, chondrocytes, neural cells, etc. The multi-directional differentiation ability makes them more widely used in clinical practice [6].

2.2. Low Immunogenicity

Immunogenicity refers to the ability of antigens to stimulate specific immune cells, triggering a series of immune responses that ultimately lead to antibody production and lymphocyte sensitization. It is well known that GVHD is caused by a mismatch of human leukocyte antigens (HLA) between the recipient and the donor, which induces a strong immune response in the host body. The ability of MSCs to express low levels of MHC class I antigens and not express MHC class II antigens allows them to have immune tolerance. Therefore, even when allogeneic MSCs are used clinically, they generally do not elicit immune responses in the host [7].

2.3. Homing Effect

"Homing" refers to the tendency of lymphocytes circulating in the blood to migrate to certain sites where they were originally derived, such as lymph nodes. The homing process of MSCs is that MSCs captured in the vascular system migrate across the vascular endothelial cells and go to the target tissues where they are needed. The microenvironment is the initial factor in the homing process of MSCs, as various microenvironments release different signaling molecules. Certain signaling molecules bind to specific receptors on the MSC membranes, guiding them to targeted locations [8].

2.4. Immunomodulatory Effect

MSCs have a certain immunomodulatory function on innate immunity or acquired immunity through direct cell-cell contact or secretion of anti-inflammatory cytokines. Lymphocytes, macrophages, and neutrophils are all target cells of MSC action. The immunomodulatory effects of MSC mainly involve promoting the polarization of macrophages towards the M2 type, inhibiting the activity of T lymphocytes, stimulating the proliferation and activation of regulatory T cells (Tregs), and suppressing the activation of natural killer (NK) cells [9].

2.5. Different MSCs, Different Characteristics

Although MSCs can be isolated from different tissues of the same body, there are also different characteristics among MSCs from different tissues, showing different proliferation ability, immunomodulatory ability, and cytokine-production ability. BMMSCs are the most extensively studied, but they exhibit telomere shortening by the 18th passage, and with increasing age, the proliferative capacity of BMMSCs also decreases, while the umbilical cord MSCs (UC-

MSCs) maintain a stronger proliferation inhibiting at the 30th generation. In addition, BMMSCs have high immunogenicity and high expression of HLA-DR and are affected by the inflammatory environment, while MSCs derived from the umbilical cord have low immunogenicity and low expression of HLA-DR and are not affected by the inflammatory environment. The immunoregulatory ability of adipose-derived MSCs is significantly better than that of BMMSCs. It has a more powerful regulatory ability on dendritic cells. BMMSCs secrete higher levels of vascular endothelial growth factor (VEGF), which has certain advantages in promoting angiogenesis, while umbilical cord-derived MSCs secrete much higher levels of cytokines (such as IL-6, IL-8, and IL-11) than BMMSCs. UC-MSCs highly express stem cell growth factor (HGF) and low-expressed VEGF. Ad-MSCs secrete more brain-derived neurotrophic factor (BDNF) than BM-MSCs. This demonstrates that MSCs from various sources have distinct characteristics, aiding in the selection of the most suitable MSC source for treating different diseases [10].

3. Mesenchymal Stem Cell Therapy in AA/ITP/Leukemia

3.1. Aplastic Anemia

Aplastic Anemia (AA) is a rare, life-threatening, heterogeneous syndrome of bone marrow failure, which is characterized by the loss of function of hematopoietic stem cells in the bone marrow, leading to pancytopenia in the peripheral circulation, accompanied by the reduction of bone marrow cells. Recent clinical studies showed that the pathogenesis of AA may be related to abnormal hematopoietic microenvironment, hematopoietic stem cell defects, and imbalance of the immune system [11]. The first-line treatment for patients with AA depends on its severity, age, and donor availability. Generally, immunosuppressive therapy (IST) and bone marrow transplantation (BMT) are the mainstay of treatment for AA.

In the 1990s, it was demonstrated that anti-thymus/lymphocyte globulin (ATG/ALG) combined with cyclosporine (CSA) immunosuppressive therapy could achieve a hematologic response rate of about 70% [12]. However, despite 30 years of continuous optimization, the hematologic response rate has remained unchanged. The primary limiting factor is the lack of residual hematopoietic stem cell progenitor cells. A higher number of residual hematopoietic stem cell progenitor cells results in a better therapeutic effect of IST. Therefore, if IST is performed on the basis of hematopoietic stem cell transplantation, the efficacy will be improved. Hematopoietic stem cell transplantation requires HLA matching between the donor and the recipient, but this matching is difficult and expensive in China, and 5–15% of patients suffer from adverse quality of life due to GVHD. Therefore, a new approach to the treatment of AA is urgently needed. As mentioned above, MSCs have low immunogenicity, which helps to avoid the body's immune response. Consequently, a new treatment concept was born: combining MSCs with hematopoietic stem cell transplantation [13] so as to achieve the purpose of increasing the residual hematopoietic stem cell progenitor cells of patients. In an experiment investigating the efficacy of UC-MSCs intravenous infusion in the treatment of refractory severe aplastic anemia (SAA), 106 patients with severe aplastic anemia were selected as the subjects. Peripheral blood Th1, Th17 levels, blood cell changes, and adverse reactions were measured before treatment at month 1, month 2, and month 3 post-treatment. The results showed that among the 106 patients, there were no significant adverse reactions during the infusion process or within 24 h post-infusion. After one year of treatment, follow-up results showed that 31 patients had complete remission (CR) (29.25%), 44 patients had partial remission (PR) (41.51%), 19 patients had no response (NR) (17.92%), and 12 patients died (11.32%), with 75 cases having a good prognosis and 31 cases having a poor prognosis. Additionally, there were no significant changes in peripheral blood Th1 and Th17 levels at month 1 after treatment ($P > 0.05$), while Th1 levels gradually increased and Th17 levels decreased at month 2 and month 3 post-treatment ($P < 0.05$). Furthermore, white blood cells and neutrophils significantly increased at month 1, month 2, and month 3 post-treatment ($P < 0.05$), while platelets and hemoglobin levels showed slow recovery at month 1 ($P > 0.05$) but gradually increased at month 2 and month 3 post-treatment ($P < 0.05$), which showed that the treatment was effective and safe [14]. In another retrospective study, 27 patients with severe aplastic anemia were treated with MSCs combined with haploidentical allogeneic hematopoietic stem cell transplantation. The results showed that the incidence of II–IV and III–IV acute GVHD was 40.7% and 22.2%, respectively, and the 2-year overall survival rate was 76.3% [15]. Therefore, this treatment method is feasible and effective for the treatment of aplastic anemia without matched relatives or unrelated donors.

Hence, utilizing the low immunogenicity of MSCs to combine with hematopoietic stem cell transplantation has a practical and effective therapeutic effect, which provides a new possibility for the treatment of aplastic anemia.

3.2. Immune Thrombocytopenic Purpura

Immune thrombocytopenic purpura (ITP) is an acquired autoimmune blood disease characterized by a platelet count below 10^5/μL. Patients with ITP may be asymptomatic or present with varying degrees of bleeding symptoms, such as ecchymosis, purpura, oral and nasal bleeding, urinary tract and mucosal bleeding, or menstrual bleeding. In a small number of cases, intracranial hemorrhage can also occur [16,17]. Clinical studies showed that children with ITP usually showed spontaneous remission, whereas adults presented with a chronic progressive disease. The pathogenesis of ITP is still unclear. The treatment of ITP is usually divided into three lines. The first-line treatment is glucocorticoid and adrenocortical hormone. The second-line treatment includes thrombopoietic agents, rituximab, or immunosuppressive agents; surgical treatment involves splenectomy. The third-line treatment includes azathioprine, cyclosporine A, vinblastine, and other drugs [18]. Although there are many ways to treat ITP in clinical practice, patients with chronic ITP usually do not respond well to existing therapies or find it difficult to tolerate long-term drug therapy. Therefore, there is an urgent need to explore new therapeutic approaches.

In a study using umbilical cord-derived mesenchymal stem cells (UC-MSCs) intravenously infused to treat 4 patients with refractory ITP, it was found that after infusion of 5×10^6–1×10^7 cells, complete remission of symptoms was achieved within 12 months in 3 patients and within 24 months in 1 patient. Three patients received a second UC-MSCs transplant at the same dose, with a median time of 12.5 days between transplant and response. No serious adverse events occurred during or after the UC-MSCs transplant. Although the number of patients in this study was small, it nevertheless demonstrated, to some extent, the feasibility of using MSCs in the treatment of ITP [19]. In April 2024, a prospective study to evaluate the efficacy and safety of UC-MSCs in the treatment of refractory ITP was conducted. According to the "3 + 3 dose-escalation" design, a total of 18 ITP patients were enrolled. A total of 12 ITP patients were enrolled in the dose-escalation phase, and they were successively enrolled into three dose groups. The dose of UC-MSCs was 0.5×10^6 cells/kg (n = 3), 1.0×10^6 cells/kg (n = 3), and 2.0×10^6 cells/kg (n = 6), respectively, administered weekly for 4 weeks. A total of 6 ITP patients were enrolled in the subsequent dose-expansion phase, and 2.0×10^6 cells/kg was administered weekly for 4 weeks. Adverse events, platelet counts, and changes in peripheral blood immune indicators were monitored and recorded throughout the administration and follow-up periods. The results showed that 13 patients (13/18, 72.2%) experienced one or more adverse events. Four patients (4/18, 22.2%) had gastrointestinal bleeding, menorrhagia, or acute myocardial infarction, with the Common Terminology Criteria for Adverse Events (CTCAE) being grade 3. In the dose-escalation phase and dose-expansion phase, the effective rate was 41.7% (5/12) and 50.0% (3/6), respectively, and the total effective rate was 44.4% (8/18). The results showed that UC-MSCs were effective and safe in the treatment of refractory ITP, which provided a new treatment option for ITP patients [20].

It can be seen that UC-MSCs are effective in treating refractory ITP and are well-tolerated, and it is believed that there will be more clinical trials in the future to support this view.

3.3. Leukemia

Leukemia originates from the malignant clone disease, where hematopoietic stem cells transform into leukemia cells that proliferate uncontrollably, fail to differentiate properly, resist apoptosis, and accumulate in large numbers in the bone marrow and other hematopoietic tissues, thereby inhibiting normal bone marrow hematopoietic function and infiltrating lymph nodes, liver, spleen and other tissues and organs of the disease [21]. Leukemia can be classified into acute leukemia (AL) and chronic leukemia (CL) based on the degree of cell differentiation and the natural progression of the disease. AL may manifest with high fever or severe bleeding, whereas CL progresses more slowly and may present with anemia, bleeding symptoms, enlargement of lymph nodes and spleen, and abnormal proliferation of lymphocytes.

At present, there are various methods for the treatment of leukemia in clinical practice. Chemotherapy is the most used therapy, along with radiotherapy, bone marrow transplantation, and targeted therapy [22]. Since 2017, the U.S. Food and Drug Administration (FDA) has approved a total of 8 targeted drugs for the treatment of AML [23]. Although targeted drugs can be used for treatment, the long-term prognosis is still not ideal, so a new therapeutic regimen is urgently needed. The latest research advances in the use of haploidentical HSCT for leukemia patients have greatly improved the possibility of a cure because almost every patient has at least one related haploidentical donor. In addition, the low immunogenicity and immunomodulatory characteristics of MSCs may also contribute to preventing the occurrence of GVHD.

In 2017, a retrospective clinical study report was published domestically, which included 36 patients with refractory or relapsed myeloid leukemia. They underwent UC-MSCs combined with haploidentical allogeneic

hematopoietic stem cell transplantation therapy. The study evaluated the incidence and severity of graft-versus-host disease (GVHD) and the 2-year overall survival rate. The results showed that the time of leukocyte and platelet engraftments in 36 patients was 12 days and 14 days, respectively. The incidence of III–IV aGVHD was 13.8%, and the incidence of cGVHD was 37.5%, while the incidence of extensive cGVHD was only 6.25%. The two-year overall survival rate was 76.9%. It shows that this method does provide new possibilities in the treatment of leukemia [24]. Although there are some clinical cases of HSC transplantation combined with MSCs, in these instances, MSCs serve to rebuild the microenvironment that supports HSC function, promote HSC proliferation, and reduce the incidence of GVHD.

Consequently, the application of MSCs in leukemia treatment remains limited, necessitating further clinical studies in the future.

4. Mechanisms of MSCs in Hematologic Disease Treatment

Aplastic anemia is a rare disease in the blood system, with pathogenesis that can be broadly divided into four aspects. Abnormalities of hematopoietic stem cells, which are manifested as a reduction in the number of hematopoietic stem cells; abnormalities of hematopoietic microenvironment; abnormalities of immune mechanisms; and genetic factors.

Abnormal immune mechanisms are as follows. (1) Th1/Th2 imbalance. Th0 mainly polarizes to Th1, and the number of regulatory T cells (Tregs) decreases in AA patients. (2) The number of $CD8^+$ T cells increases in AA patients, which has a killing effect on HSCs. (3) The ratio of myeloid dendritic cells (mDC) to lymphoid dendritic cells (pDC) increased. The increased proportion of activated dendritic cells suggests that the patient's immune system is hyperactive. The increase of mDC will lead to the increase of IL-12 and T-bet, both of which can further cause Th1/Th2 imbalance and then attack HSCs [25].

The therapeutic effect of MSC on AA may be related to the following aspects. (1) The improvement of hematopoietic microenvironment: the hematopoietic microenvironment of bone marrow is composed of bone stromal cells, extracellular matrix, and some cytokines. As key precursor cells of the bone marrow microenvironment, BMSCs play a key role in the process of blood cell formation. MSCs differentiate into a variety of stroma cells to form the HSCs niche and promote the hematopoietic function of HSCs [26]. (2) The effect on dendritic cells (DCs): the maturation of DCs is inhibited, reducing their ability to activate T cells, which also regulates the signals produced by DCs to decrease pro-inflammatory signals and increase anti-inflammatory signals, making the immune response gentler and reducing the attack of the immune system on HSC [27]. CCR7 plays an important role in the migration of DCs to lymph nodes. Under inflammatory stimulation, mature DCs express CCR7 and guide the lymph nodes for antigen presentation by binding ligands CCL21 or CCL19 [28]. In 2018, researchers demonstrated that extracellular vesicles secreted by mesenchymal stem cells (MSC-EVs) can impair the antigen uptake capability of immature DCs and prevent their maturation. This resulted in reduced expression of maturation markers CD83, CD38, and CD80 on DCs, decreased pro-inflammatory cytokines IL-6 and IL-12p70, and increased anti-inflammatory cytokine TGF-β. This study also pointed out that after stimulating DCs with lipopolysaccharide (LPS), the secretion of CCR7 by DCs in the MSC-EV-treated group decreased threefold compared with the control group. The efficiency of its migration towards CCL21 also reduced significantly and further identified MicroRNA-21-5p as one of the most abundant miRNAs in MSC-EVs [29]. (3) The effects of T lymphocyte: MSCs can promote the generation of TregS to regulate the activity of T lymphocytes. In 2021, researchers showed that MSCs regulate the balance between Th17 and Treg mainly through the secretion of indoleamine 2,3-dioxygenase (IDO), and TGF-β, and the decrease of Th17 levels leads to the increase of Treg levels, thereby restoring the immune response ability [30]. In 2023, it was reported that MSC-derived exosomes could improve the survival and functional stability of Tregs *in vitro* by activating autophagy and phosphorylating Stat5 to maintain the expression of FOXP3 in Tregs. The increase in Treg reflected a rise in $CD4^+$ T cell levels, thereby reducing the levels of $CD8^+$ T cells and decreasing their attack on HSCs. This helps restore the levels of HSCs in patients, leading to the alleviation and treatment of AA [31].

The pathogenesis of ITP involves multiple immune dysregulation mechanisms resulting from the collaborative action of various immune-related factors and effector cells. On one hand, B cells and plasma cells are abnormally regulated, leading to the production of autoantibodies. These autoantibodies bind to specific glycoproteins on platelet membranes, and platelets are then cleared through phagocytosis mediated by Fcγ receptors on macrophages, leading to increased platelet destruction. Autoantibodies can also bind to megakaryocytes, interfering with their maturation and resulting in decreased platelet production. On the other hand, immune dysregulation mediated by Th cells and Treg

cells may lead to the overactivation of the immune system, increasing the production of autoantibodies. In addition, $CD8^+$ T cell mediated cytotoxicity can also directly destroy platelets and make the megakaryocyte impair platelet production. These mechanisms eventually lead to the destruction of platelets and the reduction of platelet production [32].

The possible mechanisms of MSC infusion in the treatment of ITP are as follows. (1) The effect on B lymphocytes. It can slow down the proliferation rate of B cells and affect their development into a mature state. At the same time, it can also produce regulatory B cells (Bregs) to maintain the balance of the immune system and prevent overreaction. In 2019, a study found that MSC-EVs induced B cells to down-regulate the PI3K/Akt signaling pathway through miR-155-5p, inhibiting B cell proliferation and reducing the activation ability of B lymphocytes, thereby reducing the extent of the immune response [33]. (2) Effects on macrophages. MSCs can secrete molecules such as IL-10, which promote the polarization of macrophages to M2, reducing antigen presentation and the destruction of platelets. In 2019, researchers stimulated macrophages toward M1 polarization by using PLS and detected a significant increase in the expression of IL-6, IL-1β, CD86, and iNOS. In the group treated with MSCs, the expression levels of CD86 and iNOS decreased, while the expression level of the M2 surface marker CD206 increased, suggesting macrophage polarization towards M2. The team further proved that TGF-β secreted by MSCs plays a crucial role in promoting macrophage polarization. They also discovered that the Akt/FoxO1 signaling pathway is activated in TGF-β-induced macrophages to transform into an M2 phenotype. The latest research discovered that MSC-derived exosomes (MSC-Exos) could also promote macrophage polarization towards M2 by mediating the MAPK/NF-kb signaling pathway to achieve this goal [34,35].

In the bone marrow microenvironment (BMME), MSCs modulate the self-renewal of healthy and cancerous hematopoietic stem/progenitor cells (HSPCs). Previous studies have shown that MSCs abnormality is also a pathogenic factor of leukemia, which could promote the development of leukemia mainly through (1) promoting the colonization, growth, and proliferation ability and inhibiting the apoptosis of leukemia stem cells (LSCs); (2) long-term inflammatory stimulation from MSCs which could drive HSCs' unbalance and stimulate the occurrence of leukemia [36].

Nowadays, the possible mechanisms of MSCs infusion in the treatment of leukemia are as follows: (1) inducing the differentiation process of AML cells in AML disease. In 2023, a study demonstrated that umbilical cord mesenchymal stem cells (UC-MSCs) presented the neutrophil elastase (NE)-encapsulated extracellular vesicles (EVs) to AML cells, Vitamin D receptor (VDR) activation in UC-MSCs increased the release of NE-packaged EVs, which could promote the differentiation of AML cells more effectively and inhibit the development of leukemia [37]; (2) restoring the bone marrow microenvironment by reorganizing host macrophages. A 2020 study suggested that hematopoietic ability was rebalanced and Arg1-related macrophage remodeling was enhanced following MSC infusion in leukemia mice [38].

5. Limitation

Although the therapeutic potential of MSCs is promising, they still have certain limitations, which bring great challenges to the clinical work.

5.1. Senescence of MSCs

During the process of *in vitro* culture, MSCs inevitably undergo cellular senescence, accompanied by genomic instability. The characteristics of MSCs senescence include cellular enlargement and flattening, slow proliferation, and increased expression of β-galactosidase. Different cultivation methods may result in MSCs showing signs of senescence at different generations, with some reaching senescence at the 7th generation and others at the 10th generation. An increase in the number of replication cycles can lead to a decrease in their viability and functionality. Therefore, the long-term culture of MSCs can affect their therapeutic efficacy, emphasizing the importance of precise cultural guidelines during their cultivation [39].

5.2. Heterogeneity of MSCs

Due to variations in donor gender, age, and health, the function of MSCs also exhibits significant differences. Additionally, even MSCs from the same donor can be heterogeneous due to differences in extraction techniques and *in vitro* cell culture conditions. However, the human MSCs community standards issued in 2021 gave standards for extraction technology and culture conditions to control its heterogeneity [40]. In addition, to solve the problem of heterogeneity, there are two acknowledged solutions. One solution is to continue exploring the specific surface markers

of MSCs from different tissues and organs and use these markers to distinguish MSCs subsets. It was reported that $CD105^+$ MSCs isolated from bone marrow showed a better myogenic potential in repairing myocardial infarction, while $CD106^+$ MSCs showed more pluripotency and immunosuppressive ability. However, the screening of these markers has mostly remained at the animal experiment stage, and more studies are needed in the future. The other solution is to define the differentiation direction of MSCs *in vitro* by exploring the developmental origin of MSCs, to obtain source-limited MSCs and improve the homogeneity of MSCs [41].

5.3. Distribution of MSCs after Infusion

The infused MSCs do not directly reach the target area as expected, and they cannot survive in the body for an extended period. When MSCs are intravenously infused, the first barrier they need to overcome is the lungs. However, due to the characteristics of the pulmonary vascular system, the majority of MSCs are retained in the lungs [42,43]. Therefore, to ensure clinical efficacy, multiple infusions are needed. However, MSCs infused at different times may have distinct characteristics. Moreover, the initiating factor for the homing properties of MSCs is the alteration of the microenvironment, which requires the binding of signal molecules released from the altered microenvironment with MSC surface receptors for homing to occur. We cannot guarantee that MSCs, once inside the body, will naturally migrate towards areas where the microenvironment has changed. Consequently, more therapeutic targets need to be explored [8].

6. Summary and Prospect

In summary, MSCs have the potential to treat hematological diseases such as aplastic anemia, immune thrombocytopenic purpura, and leukemia due to their low immunogenicity and immunomodulatory capabilities. On one hand, MSCs can be infused to enhance the hematopoietic microenvironment *in vivo*. On the other hand, they can also improve the body's immune function. MSC-EVs are the future direction of stem cell research. Numerous studies have shown that MSC-derived vesicles can conditionally improve bone regeneration situations, the treatment effect of liver diseases, as well as the therapeutic effect of immunomodulatory therapy. It is believed that in the future, we will overcome the difficulties of MSCs therapy and truly achieve widespread clinical applications, benefiting society.

Author Contributions

Writing—Original Draft Preparation, Y.W.; Literature Collection, X.Y. and S.L.; Writing—Review & Editing, X.C. and G.T.

Ethics Statement

Not applicable.

Informed Consent Statement

Not applicable.

Funding

This research was supported by the Project of Nanjing Medical Science and Technology Development Foundation (No. YKK21152).

Declaration of Competing Interest

The authors declared no conflict of interests.

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