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Clinical Treatment and Research Progress of Bone Marrow Mesenchymal Stem Cells

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Abstract

Bone marrow mesenchymal stem cells (MSC) have a high degree of self-renewal and multi-directional differentiation ability, and can be cultured, proliferated and passaged in vitro, and have tumor-tropism and low immunogenicity. At present, researchers at home and abroad have been exploring BMSC more and more deeply. BMSC has become a new hot spot and new direction in basic research and clinical treatment. This article reviews the biological characteristics, isolation and identification methods, clinical treatment, and basic research progress of BMSC.

Keywords

Bone marrow mesenchymal stem cells; clinical treatment; basic research; progress.

1. INTRODUCTION

Mesenchymal stem cells (MSC) have a wide range of sources. They are widely found in various tissues and organs such as bone marrow, fat, umbilical cord, and amniotic membrane. Bone marrow mesenchymal stem cells (BMSC) are the first mesenchymal stem cells found in bone marrow by humans, and are also used to measure stem cells from other sources. Currently, bone marrow is considered to be the best source of stem cells [1]. In recent years, domestic and foreign researchers have explored BMSC more and more deeply, which is a new hot spot and new direction of basic research and clinical treatment. This article reviews the biological characteristics, separation and identification methods, clinical treatment and basic research of BMSC, In order to provide some theoretical basis for the future clinical application of BMSC to treat human diseases and basic medical research.

2. BIOLOGICAL CHARACTERISTICS OF BMSC

BMSC is one of the important primitive bone marrow stromal cells in the stem cell family. It has the characteristics of stromal cells, has the function of supporting hematopoiesis, and can secrete a variety of cytokines [2]. BMSCs are mainly derived from bone marrow, and can also be obtained from a few other tissues and organs. BMSC has strong self-renewal ability and high proliferation ability. Primary BMSC cells were able to adhere to the wall 24 hours after inoculation and grew colony-like. Even cells at the junction of colonies can continue to grow by overlapping and fusing. BMSC can also be subcultured. After the second generation, the cell morphology is elongated spindle-shaped, and the growth mode is monolayer growth [3].

BMSC has multi-directional differentiation ability, and can differentiate into other types of mature tissue cells through different specific induction methods. Previous studies have shown that BMSC differentiates into muscle cells, adipocytes, nerve cells, osteoclasts, osteoblasts, and chondrocytes in different induction environments [2]. The expression level of MHC class I molecules in BMSC is very low, and it does not express MHC class II molecules and T cell

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costimulatory molecules such as B7-1, B7-2, CD40, and CD40L. Therefore, BMSC has weak immunogenicity. Tissue transplantation is not easy to cause immune rejection [4].

Based on these biological characteristics, BMSC is favored by researchers. The research on BMSC basic medicine, translational medicine, clinical treatment and gene tissue engineering has become a hot spot. At the same time, the role of BMSC in clinical treatment is increasingly prominent.

3. ISOLATION, IDENTIFICATION AND CULTIVATION OF BMSC

Research on BMSC requires the preparation of a sufficient number of BMSC. BMSC is mainly derived from bone marrow tissue, but its content is actually very small, and often needs to be collected through invasive operations, so the extraction of BMSC from human bone marrow has some ethical controversy [5].

Extracting BMSC from humans or mammals has certain technical difficulties. There are currently four methods for in vitro separation and purification of BMSC, including density gradient centrifugation, bone marrow adherence screening method, flow cytometer sorting method and immunomagnetic bead method. Among them, density gradient centrifugation is the most classic extraction method. BMSC is separated by the separation liquid. The BMSC obtained by this method has very high purity and strong proliferative activity, but this method is more complicated to operate, and the cell loss during the separation will be more. More [6]; the bone marrow adherence screening method is simple and quick to operate, has little effect on cell activity, and is an ideal extraction method [7]. Flow cytometer sorting method and immunomagnetic bead method are separated by BMSC volume and cell surface antigen. Because of the complicated operation, expensive reagents and consumables, and great influence on cell activity, it is generally not the preferred method for mass production of BMSC [8]. At present, studies have shown that the combination of density gradient centrifugation and bone marrow adherence screening can obtain a large number of BMSCs with high purity and high cell activity [6, 9].

BMSCs extracted from bone marrow are mixed with a variety of other cells, so BMSCs must be purified and identified in experiments and production to determine the proportion of BMSCs in the extracted cells. At present, BMSCs can be identified by morphological characteristics, ultrastructure, surface antigens and multi-directional differentiation ability [10-11]. However, so far, there is no specific antigen that can directly identify BMSC, that is to say, the surface antigen expression of BMSC is non-specific [12]. By reviewing the previous literature, we know that BMSC expresses surface antigens of interstitial cells, and also surface antigens of epithelial cells, endothelial cells, and muscle cells, but does not express surface antigens of hematopoietic cells [13]. BMSC expresses adhesion molecules such as CD106, CD44, CD54, CD102, integrin family such as CD29, CD49, CD104, IL-1R, IL-4R, IL-6R, and other growth factors and cytokine receptor family, interferon receptor, Tumor necrosis factor receptor, etc., but does not express CD34, CD45, CD14 and other surface markers of hematopoietic stem cells.

In basic experiments, the commonly used culture medium of BMSC includes special matrix mesenchymal stem cell culture medium (MSCM) and low sugar DMEM medium. And supplemented with 10% fetal bovine serum in the medium to meet the normal growth of BMSCs. If it is necessary to obtain higher purity BMSCs in a short period of time, the proportion of fetal bovine serum can be appropriately increased [14].

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4. ADVANCES IN CLINICAL TREATMENT AND BASIC RESEARCH OF BMSC IN VARIOUS DISEASES

4.1. Cardiovascular Diseases

Myocardial remodeling after cardiomyocyte injury is one of the main pathogenesis of many cardiovascular diseases. Previous studies have found that BMSCs can spontaneously rhythmically fluctuate under the action of 5-azacytidine, basic fibroblast factor, and histone deacetylation inhibitors, forming myotube-like structures and having actions similar to cardiomyocytes. Potential, also expresses GATA4 and other myocardial specific structural proteins, suggesting that BMSC can induce differentiation into cardiomyocytes, so it can be one of the strategies for the treatment of cardiovascular diseases [15-16]. At present, BMSC transplantation has made more breakthroughs in the treatment of acute myocardial infarction. BMSC transplantation can treat cardiovascular diseases through vascular pathway and myocardial pathway. Vascular route includes coronary artery, coronary vein and peripheral vein injection; myocardial route includes epicardial injection and endocardial injection. The coronary route is mainly injected into the infarct-related coronary artery through a catheter, which can be targeted for delivery and has less trauma; peripheral intravenous injection is the simplest operation, but BMSC may be trapped by the liver, spleen, etc., and may also lead to embolism; epicardial injection The method is accurate in positioning, but it has great damage to the body, and is mainly suitable for patients with coronary artery bypass grafting. Due to the high technical equipment requirements for endocardial injection, there is not much clinical development [17]. Previous studies have found that BMSC mainly induces differentiation into vascular endothelial cells, induces neovascularization, and promotes repair after heart injury. BMSC transplantation can promote the formation of new cardiomyocytes and new blood vessels in the myocardial scars caused by freezing injury [18]. BMSC can also up-regulate the expression of various growth factors in the ischemic myocardium, such as VEGF and insulin-like growth factor-1, so as to promote angiogenesis in the marginal zone of infarcted myocardium and improve the local blood supply of the myocardium [19]. Long-term follow-up found that BMSCs injected via arterial filling had no treatment-related toxicity or treatment-related adverse cardiovascular events, suggesting that BMSC transplantation is safe and effective in treating cardiovascular diseases.

4.2. Cancer Treatment and Cancer Gene Therapy

As mentioned above, BMSC has a high degree of self-renewal and multi-directional differentiation ability, and can be cultured, proliferated and passaged in vitro, BMSC gives a new idea for tumor treatment [20]. Wang et al. Found in vitro that BMSCs can inhibit the proliferation of lung cancer A549 cells and promote A549 apoptosis [21]. Studies by Zhang Hui and others found that BMSCs transplantation can slow the growth rate of lung cancer transplanted tumors, inhibit the proliferation of lung cancer A549 cells, and up-regulate the expression of apoptosis-related genes and promote the apoptosis of lung cancer A549 cells through in vivo studies. However, the current relationship between BMSC and tumor cells is not yet clear, which may be related to the regulation of tumor cell apoptosis by Bax and Bcl-2. BMSCs transplantation upregulated the expression of Bax in A549 cells, and promoting apoptosis of cancer cells through the caspase-3 pathway may be one of the mechanisms [22].

BMSC has tumor-tropism and low immunogenicity. Therefore, BMSC is one of the selectable targeting carrier cells for tumor gene therapy [20]. Introducing the target gene into BMSC by recombinant adenovirus transfection method and letting it express stably is currently the most commonly used method for tumor gene therapy research. Previous studies have used recombinant adenovirus to introduce PEDF into BMSC, and found that PEDF can be continuously and stably expressed in vitro, reflecting the feasibility of BMSC as a gene

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expression vector [23]. Researchers such as Zhang Xia and IL-2 transfected IL-2 into BMSC through recombinant adenovirus and found that they can inhibit the proliferation of ovarian cancer cells and promote the apoptosis of ovarian cancer cells [24].

4.3. Rheumatoid Disease

BMSC only expresses a small amount of MHC-I molecules and does not express MHC-II molecules, so it can escape antigen recognition and has low immunogenicity. In addition, it has a strong immunoregulatory ability, can inhibit T cell proliferation, inhibit B cell differentiation and reduce the synthesis of immunoglobulins, and can also regulate the mature secretion of tumor necrosis factor by NK cells and dendritic cells to inhibit its pro-inflammatory effect [25]. Therefore, cell replacement therapy for immune diseases has great application value. BMSCs in patients with systemic lupus erythematosus have defects in morphology and proliferation. Studies have found that healthy human BMSC transplantation treatment can significantly reduce animal anti-dsDNA antibodies and urine albumin levels, and reduce glomerular complement C3 deposition [26]. Systemic sclerosis is a disease of limited or diffuse skin thickening and fibrosis caused by abnormal activation of the immune system. The pathogenesis is unknown. It has been reported in one patient with systemic sclerosis that the peripheral circulation improved after mesenchymal stem cell transplantation [27]. A meta-analysis showed that 76 patients with rheumatoid disease had improved clinical symptoms to varying degrees after receiving BMSC transplantation, laboratory tests tended to be normal, and no treatment-related adverse reactions and complications have been reported, suggesting BMSC transplantation for rheumatoid Sexual diseases have certain efficacy and high safety [28].

4.4. Ulcerative Colitis

Ulcerative colitis is an immune disease with persistent disease. The pathogenesis of ulcerative colitis is complicated, and the cause is unknown. At present, there is no good treatment for ulcerative colitis. It is mainly symptomatic treatment, relieving symptoms, and controlling the progress of the disease. It cannot be cured fundamentally. At present, in vitro research experiments have found that BMSC can repair and rebuild damaged colonic mucosa. BMSC has low immunogenicity and good immunoregulatory ability, can homing to the damaged colon mucosa surface, and promote the proliferation and differentiation of colon mucosal epithelial cells. Studies have suggested that injection of BMSC can inhibit intestinal cell apoptosis and promote intestinal stem cell regeneration [29]. BMSC can also be induced to form endothelial cells of colon blood vessels, thereby promoting the formation of blood vessels and the repair of colonic mucosa. But the best way to transplant BMSC for ulcerative colitis, the best number of stem cells for treatment, clinical indications and observation of clinical long-term efficacy need to be further explored.

4.5. Chronic Liver Disease

Previous studies have suggested that BMSC transplantation can improve liver function in patients with chronic end-stage liver disease and is a new direction for the treatment of end-stage liver disease. At present, there are three ways for BMSC transplantation to treat liver diseases, including peripheral vein, portal vein and intraperitoneal injection [30]. Some researchers have found that patients with hepatitis B-related cirrhosis can increase the level of inflammatory factors such as TGF-β in serum by autologous BMSC transplantation, thereby inhibiting the differentiation of Th17 and regulating the balance of T cell ratio in patients with hepatitis B-related cirrhosis [31]. In vivo studies by Jin Xiaoya and others have found that BMSC-derived exosomes can improve alcoholic liver injury. The possible mechanism is that BMSC exosome transplantation increases the superoxide in the body by activating the Nrf-2 / HO-l antioxidant pathway The activity of dismutase SOD and the adjustment of the Treg / Thl7 ratio can alleviate the lipid deposition and oxidative stress induced by ethanol and improve liver

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function [32]. In addition, there are studies showing that BMSC can regulate liver immune function and promote liver regeneration [33]. BMSC transplantation can regulate IL-10 through paracrine, activate the STAT3 pathway, regulate immune function changes of Kupper cells, and promote liver cell regeneration [34].

4.6. Orthopedic Diseases

BMSC has the potential for multi-directional differentiation, such as bone, cartilage, tendons, and ligaments, so it has received more and more attention in the treatment of orthopedic diseases. The study of Li Song [35] and others found that autologous BMSC transplantation can effectively treat mandibular radiation necrosis. Ma Weijie found that allogeneic bone BMSC combined with minimally invasive decompression can enhance the osteogenic ability of the femoral head necrosis area, so that most of the femoral head necrosis area is repaired, and the decompression tunnel basically achieves bone healing [36]. Previous studies have shown that vascular endothelial growth factor VEGF and osteogenic protein 2 can induce BMSC differentiation to differentiate into osteoblasts, chondrocytes, and some researchers have transfected osteogenic protein 2 into BMSC and inhibited it to rabbit femoral head by arthroscopy In the necrotic bone marrow cavity, it was found that it can promote the formation of new femurs and promote the rest of bone repair of femoral head necrosis [37].

5. APPLICATION OF BMSC IN CELL ENGINEERING AND TISSUE ENGINEERING

BMSC has the ability of multi-directional differentiation and has the characteristics of "differentiation according to locality". In 1999, Johansson et al. Reported for the first time that BMSC injected into the lateral ventricle of newborn mice can differentiate into neurons and glial cells and can migrate to the hippocampus, olfactory bulb, and striatum [38]. As the research on BMSC becomes more and more in-depth, researchers have found that BMSC in dexamethasone, ascorbic acid, etc. can induce differentiation into osteogenic tissue after class [39], and can be differentiated into endothelial cells under the induction of vascular endothelial growth factor [40], 2-AAD, CCL4 and other conditions can be transformed into hepatocytes [41].

In terms of tissue engineering, the earliest studies reported that red bone marrow transplanted under the skin and muscle can form new bone. In recent years, researchers have discovered that new materials combined with BMSC have good prospects in the treatment of orthopedic diseases. Chen Jiao [42] found that the polylactic acid-glycolic acid copolymer nanofiber membrane has good biocompatibility and ectopic osteogenesis ability in vivo, and can be used as a scaffold material for bone tissue engineering. Can grow well. After combined induction with silk fibroin-chitosan scaffold material, BMSC can repair the defective cartilage tissue in vivo and has good biocompatibility [43].

6. SUMMARY AND OUTLOOK

Although basic research, cell and tissue engineering, and clinical research of BMSCs have made great progress, no specific marker molecules that can clarify the specificity of BMSCs have been found. BMSC has high self-renewal and multi-directional differentiation ability, and can be cultured, proliferated and passaged in vitro. It has tumor tropism and low immunogenicity. However, there are still some difficulties in the actual clinical treatment of diseases, and its application in clinical treatment The security of the system is still an issue that researchers should pay attention to today. In addition, the research of BMSC still has some controversy in ethics, morality and religion. With the continuous exploration and update of research methods and the deepening of understanding of BMSC, these problems will be solved one day, so that BMSC can play a more important role in clinical treatment.

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