Review Article

Stem Cell INVESTIGATION

Into the eyes of bone marrow-derived mesenchymal stem cells therapy for myocardial infarction and other diseases

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Abstract: Applications of bone marrow-derived mesenchymal stem cells (BM-MSCs) have been documented for diseases occur in the sports system, the central nervous system, the cardiovascular system etc. However, poor viability of donor stem cells after transplantation limits their therapeutic efficiency. Although the autophagy theory has been reported, the underlying mechanisms are still poorly understood. Isolation and culture methods of mesenchymal stem cells are currently concentrate on four ways. Overall, BM-MSCs have both important research significance and clinical application value in cell replacement therapy, gene therapy and reconstruction of tissues as well as organs especially for myocardial infarction (MI). In this article, we review the biological characteristics of BM-MSCs and its research progress especially in MI.

Keywords: Autophagy; bone marrow-mesenchymal stem cells (BM-MSCs); apoptosis; hypoxia; signal transduction pathways; myocardial infarction (MI)

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Introduction

Bone marrow mesenchymal stem cells (BM-MSCs) are mesoderm derived stem cells, which mainly exist in the interstitial connective tissue. Bone marrow tissue has the most abundant content of BM-MSCs. Due to characteristic of self-renewal, proliferation and multi-directional differentiation in appropriate micro environment, BM-MSCs have the potential to promote the repair of tissue injury. In view of the advantages of BM-MSCs which are easy to obtain, cultivate, and they have low immunogenicity, which can survival for a long-term in the host and easy for exogenous gene transfer as well as long-term expression, BM-MSCs have been widely used in the field of tissue engineering, cell transplantation, gene therapy, and organ transplantation. Studies showed that the surface antigen phenotype of mesenchymal stem cells was not single but had the characteristics of mesenchymal, endothelial and muscle cells. Besides, immunohistochemistry and flow cytometry revealed that SH2, SH3, CD71, CD29, CD44, CD90, and CD120A were all positive expressed, which can be generally used to identify and amplify the mesenchymal stem cells (1). Recent studies showed that BM-MSCs could be used in the clinical treatment of autoimmune diseases, degenerative diseases and hypoxic ischemic brain damage (2,3). Bone marrow not only contains hematopoietic stem cells which can develop and differentiate into all types of blood cells but also has mesenchymal stem cells which can produce non hematopoietic tissues. Some of articles also called them stick wall cells or fibroblast colony forming units as they relatively easy to adherent and form into fibroblast like clones. Moreover, as BM-MSCs come from the supporting structure of the bone marrow, they can act as feeder layer to support growth of hematopoietic stem cells. Therefore BM-MSCs are also called bone marrow stromal cells. In view of the following features of

bone marrow which has aroused people's interest (1,4,5). Furthermore, BM-MSCs can act as support hematopoietic cells, promoting the growth of hematopoietic stem cells. Above all, BM-MSCs have broad application prospects in tissue engineering, cell transplantation and gene therapy because of the advantages of easy separation, amplification and easy operation *in vitro* and *in vivo* (6-9). Taken together, BM-MSCs have important research significance and clinical application value in cell replacement therapy, gene therapy and tissue regeneration. In this article we review the latest progress, limitation as well as clinical application of BM-MSCs.

Isolation of BM-MSCs

BM-MSCs are obtained mainly from bone marrow aspiration, while human BM-MSCs are generally drawn from the anterior superior iliac spine (10). They are also available from the tibia, femur, sternum, lumbar spine. The acquisition sites of BM-MSCs in large animals are the same as humans, however, rabbits' BM-MSCs need to be extracted in the middle of the tibia or femur bone marrow (11-13). The proportion of BM-MSCs nucleated cell population accounts for less than 0.0001% of them, however they can easily be isolated and expanded by using certain cell culture techniques (10). Stro-1 monoclonal antibody is usually used to isolate BM-MSCs which grow by attaching to the wall in laminin adhesion culture plate with low concentration of serum and CD45-/A-glycoproteins (14). In the past, BM-MSCs isolation methods were mainly concentrated on density gradient centrifugation method, differential adherence screening method, flow cytometry sorting method as well as immune beads method (15). However, high purity of BM-MSCs cannot be obtained by the four kinds of separation methods as described above. Nowadays, selecting the appropriate factor based on different reactivity of BM-MSCs to growth factors, to stimulate the proliferation, obtaining a higher proportion the mesenchymal stem cells has been regarded as a more accurate isolation method. Meanwhile, the new method of using 3 microns diameter plastic petri dish to screen BM-MSCs, whose homogeneity are greater than 98%, with capacity of proliferation, self-renewal and have the potential to differentiate into bone, fat, cartilage tissue differentiation nature (6,16-20). Overall, currently methods are various among laboratories in the world and further standardization of the BM-MSCs' separation process is still needed in-depth study according to their biological characteristics and mechanisms.

Application of BM-MSCs: update

Based on its far-reaching biological effects, there are increasingly number of researches and exciting discoveries since 1999 (21) (*Figure 1*). Up to now, applications of BM-MSCs towards cells, animals and clinical tests have been came down to diseases occurred in the sports system (21), the central nervous system (4), the cardiovascular system (21), the respiratory system (21), the digestive system (22), the urinary system (21) etc. (*Figure 2*). Among these systems, researches about the sports system and the central nerves system account for a significant proportion. It's interesting to note that there is one paper tried to treat cancer by using BM-MSCs, which has the great significance as most therapies toward cancers have various kinds of severe complications in patients (23).

Autophagy and apoptosis in the BM-MSCs therapy towards myocardial infarction (MI)

Autophagy is a process of intracellular bulk degradation in which cytoplasmic components including organelles are sequestered within double-membrane vesicles that deliver the contents to the lysosome/vacuole for degradation (24,25). There are three primary forms of autophagy: chaperone-mediated autophagy, microautophagy and macroautophagy (24-28). During the process of macroautophagy, the sequestering vesicles, termed autophagosomes, fuse with the lysosome or vacuole resulting in the delivery of an inner vesicle (autophagic body) into the lumen of the degradative compartment (29-31).

Nowadays, one of the highest incidence and fatality rate of clinical disease is MI (32-35). Numerous studies have been proved BM-MSC is an emerging effective therapy to the disease. However, poor viability of donor stem cells after transplantation limits their therapeutic efficiency, whereas, the underlying mechanism is still poorly understood (36). Autophagy, a highly conserved process of cellular degradation, is required for maintaining homeostasis and normal function including MI (37).

Actually, when it comes to the role of autophagy on cell, it is still a controversial issue according to the present study (11,38-41). There is evidence demonstrated that autophagy can either protect cells or contribute to cell death depend on the intensity of stimulus. Autophagy at basal levels is involved in maintaining normal function in various

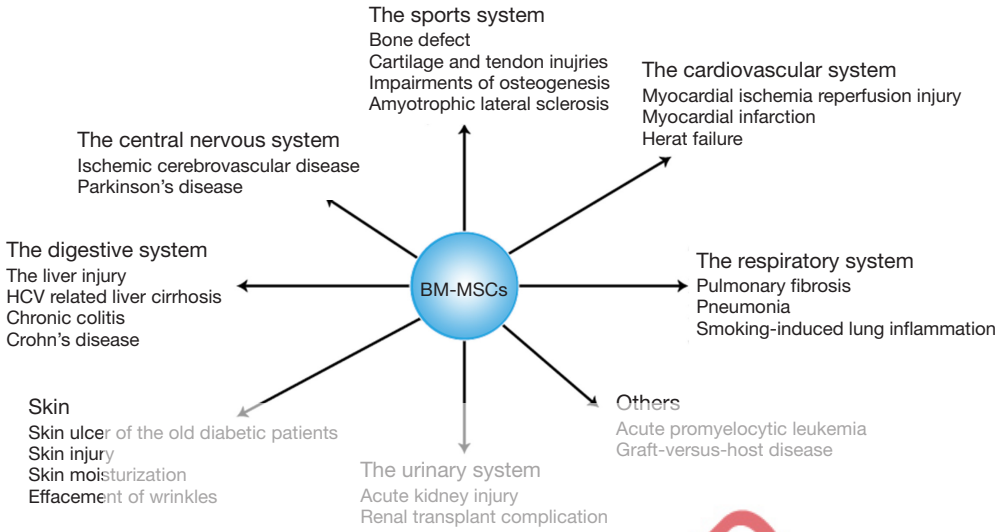

Figure 1 Summary of potential of various preventive and therapeutic effects of BM-MSCs. BM-MSCs, bone marrow-mesenchymal stem cells.

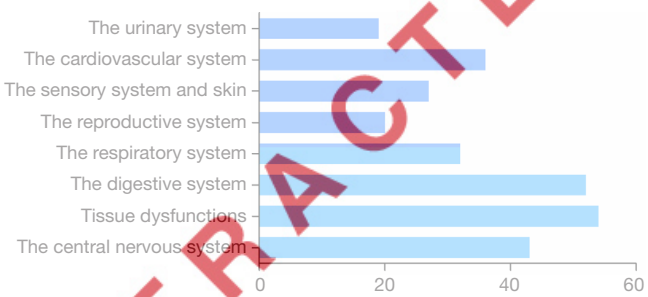

Figure 2 Number of papers that report effects of BM-MSCs in various systems between 2012 and 2016. BM-MSCs, bone marrow-mesenchymal stem cells.

organisms. Hence, autophagy has been generally considered as a protective cellular response against various stresses. Previous studies have demonstrated that modest autophagy induced by sublethal hypoxic preconditioning can increase cell survival and inhibit extensive apoptosis (41,42).

Conversely, other studies also suggested that extensive and prolonged autophagy may be a promoter of apoptosis, leading to cell death as type II programmed cell death. Such discrepancy may be attributed to differences in hypoxic treatment protocol. Our previous studies adopted hypoxia (1% O_2)/serum deprivation injury for 24 h to mimic ischemic microenvironment *in vivo* (43). However, Liu *et al.* performed hypoxic preconditioning with 5% O_2 for 6 h (44). The comparison results showed that autophagy is paradoxical that can both protect and impair cell survival depending on the environment. Therefore, the different stress or anaerobic injury may result in the disparate effects of autophagy on MSCs.

Regulating autophagic activity may be a potential optimizing target for promoting BM-MSCs based cellular therapy for MI (43). Thus, many signaling pathways have been suggested to participate in autophagy regulation. As the main problem of stem cell therapy is that the survival ability of implanted stem cells is poor, the survival mechanism and related regulation are more and more concerned by people. Until now, there are some potential signal transduction pathways such as PI3K/Akt/nuclear factor-kappa B, MEK/ERK and SCF/c-kit which participate in the relationship between autophagy and apoptosis has been reported to participate in autophagy. Besides, autophagy plays a key role in promoting the survival of transplanted stem cells in MI and it may provide a new

therapeutic approach for stem cell therapy and regenerative medicine (45).

Remaining problems and future directions

In recent years, studies of BM-MSCs have been made great progresses, but there are still some problems to be solved. Firstly, no standard method has been putted forward about isolation, purification and specific marker molecules for the identification of BM-MSCs. Secondly, the efficiency of BM-MSCs differentiation is not ideal, which is currently one of the research focus on how to induce BM-MSCs to differentiate to the single specific tissue and cells (46-49). Thirdly, the signal transduction mechanism and the molecular basis of BM-MSCs' differentiation such as which transcription factors or gene were activated to make it for some specific differentiation is still not clear though it is generally considered to be related to reprogramming of BM-MSCs. Fourthly, whether the induced cells have real structure and function, homing to the corresponding organization are need to be further investigated. Lastly, although there is no report on the transformation of BM-MSCs into malignant cells and the production of abnormal extracellular matrix, the safety of BM-MSCs is also worth noting.

On the other hand, BM-MSCs have important clinical application value in cell replacement therapy, gene therapy and tissue regeneration. Bone marrow collection is also convenient, safe and cause less injury, especially has no obvious complications to the donor. Therefore BM-MSCs is conducive to the expansion and autologous transplantation *in vitro*, thereby becoming the promising source of tissue engineering. BM-MSCs were amplified *in vitro*, which can directly carry on cell transplantation or implant biomaterials, and then transplanted into the body to repair tissue defects. In addition, retroviral vector, adenovirus vector which carry the target gene can be also successfully transfected into BM-MSCs, and have high expression *in vivo*. Besides, BM-MSCs are relatively primitive cells, whose immunogenicity is weak and can inhibit the mixed lymphocyte reaction. However, previous studies also reported the clinical application of BM-MSCs is not matched with donor, host immune rejection or graft versus host reaction (50-52). Moreover, allogeneic bone marrow transplantation of mesenchymal stem cells in severe idiopathic aplastic anemia patients have also been shown to improve the effect of bone marrow stromal function (53,54). Allogeneic transplantation of BM-MSCs not only has ability of multi-directional differentiation, but also has special immune tolerance, allowing them to survive in allogeneic environment, in which provides a possibility for the application of BM-MSCs MI therapy.

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Footnote

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