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Potential benefits of allogeneic bone marrow mesenchymal stem cells for wound healing

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Abstract

Introduction—It is becoming increasingly evident that select adult stem cells have the capacity to participate in repair and regeneration of damaged and/or diseased tissues. Mesenchymal stem cells have been among the most studied adult stem cells for the treatment of a variety of conditions including wound healing.

Areas covered—Mesenchymal stem cell features potentially beneficial to cutaneous wound healing applications are reviewed.

Expert opinion—Given their potential for in vitro expansion and immune modulatory effects, both autologous and allogeneic mesenchymal stem cells appear to be well suited as wound healing therapies. Allogeneic mesenchymal stem cells derived from young healthy donors could have particular advantage over autologous sources where age and systemic disease can be significant factors.

Keywords

Cell therapy; Chronic wounds; Dermatology; Mesenchymal stem cell; Stem cell; Tissue repair; Wound healing

1. INTRODUCTION

Stem cells promise to herald in a new era in therapeutic options for disorders not currently amenable to treatment and may provide a unique the opportunity to rebuild aged, damaged tissues. Bone marrow transplantation is perhaps the earliest and most successful example of stem cell therapy[1, 2]. This work has been greatly advanced by the identification of select bone marrow cells, which have the capacity to reconstitute the hematopoietic system of an individual[3]. Bone marrow is particularly unique for it's varied population of stem and progenitor cells including hematopoietic, mesenchymal and endothelial precursors. We and others have demonstrated that bone marrow cells have the capacity to differentiate into tissues not previously thought to be of bone marrow origin[4–7]. These findings have lead many to postulate that bone marrow may be responsible for delivering (through the circulatory system) stem and progenitor cells throughout the body in response to injury and

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Declaration of interest

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in maintenance of homeostasis. Since then, several laboratories including ours have been involved in therapeutic trials and preclinical studies examining the effect of delivering bone marrow stem and progenitor cells for the treatment of disorders including heart disease, stroke, spinal cord injury, diabetes, lung disease and wound healing[8–18].

2. MESENCHYMAL STEM CELLS

While several types of mature, progenitor and stem cells are present in bone marrow. Mesenchymal stem cells (MSC's), found in the stromal component of bone marrow, are of particular interest to many investigators due to several unique characteristics[19–21]. MSC's are multipotent cells capable of differentiation into bone, adipose, cartilage and fibroblastic lineages. While more controversial, other reports describe the ability of these cells to differentiate in to non-mesenchymal tissues[20, 22–24]. Aside from their potential of being a substrate material for tissue, MSC's also appear to be important in the orchestration of tissue repair[25–30].

Orchestration of tissue repair appears to be possible even at distant sites. In animal models of myocardial infarction MSC's infused intravenous or into skeletal muscle have shown benefit in repairing the cardiac tissue despite the fact that few MSC's reach the heart[25, 31, 32]. When MSC's were infused intravenously, most cells became trapped in the lung where they began production of several cytokines including Tumor Necrosis Factor-Stimulated Gene 6 protein (TSG-6), an anti-inflammatory factor[25]. Human studies of intravenously administered MSC's have also supported their benefit in myocardial infarction[16] perhaps by similar mechanisms. These benefits have been observed with both autologous and allogeneic MSC's, in humans and animal models, and with xenogeneic MSC's in animal models (human MSC's delivered to mice)[5]. The ability to use allogeneic cells would provide significant advantage in availability.

From a manufacturing aspect, MSC's can be substantially expanded in culture using relatively simple methods and do well with cryopreservation. Manufactured cells are easily characterized by cell surface markers, leading to greater uniformity of products derived from different sources. This, in turn, allows for more accurate comparison of products from a variety of samples. The ease with which these cells can be stored facilitates extensive testing prior to use in clinical studies. We have also found that unlike some other bone marrow cells, MSC's are readily transducible with lentiviruses, and therefore have important potential for manipulation in preclinical studies and future gene therapy trials.

Among the most unique and prospectively useful aspects of MSC's are their low immunogenicity and immune suppressive features, which are mediated by a variety of mechanisms[33]. Their lack of immunogenicity may arise from low levels of expression of MHC class II antigens and their immunosuppressive properties appear to be due to secretion of substances such as nitric oxide, TGF-β, TSG-6, and indoleamine 2,3-dioxygenase (IDO). IDO seems to have a substantial role in human models[34]. MSC's may also exert a greater immune suppressive effect when exposed to proinflammatory cytokines and therefore could provide additional benefit in the treatment of inflammatory conditions[35]. Additionally, previous investigations suggest MSC's are capable of altering T-cell interactions and suppressing antigen-presenting cells[36–38]. The compatibility of MSC's with several commonly used immunosuppressive agents may make utilization of allogeneic MSC's even more feasible[39–42]. An allogeneic source may prove critical when considering bone marrow cells for the treatment of patients with chronic wounds, autoimmune disease, and other disorders where the bone marrows derived from these individuals have been show to have less than normal function and/or growth characteristics as compared to normals [10].

Numerous animal and human studies have examined the safety and role of MSC's in the treatment of several disorders [15, 16, 43–51]. Clinical studies investigating allogeneic MSC's in the treatment of cardiac disease[15, 16], graft versus host disease following bone marrow transplantation[44, 52–56], and autoimmune disease have been reported[47, 48, 57–62]. MSC's have been delivered (sometimes in multiple doses) by several routes of administration including systemically, intrathecally, and intraosseously[13,15,16,58,63,64]. Both autologous and allogeneic MSC's have been delivered to patients and in some cases have been delivered with other bone marrow cells in the setting of bone marrow transplantation, [45]. Substantial immunologic or severe adverse events have not been reported in the literature for patients treated with either autologous or allogeneic MSC's.

3. MESENCHYMAL STEM CELLS AND WOUND HEALING

Several wound healing studies have been conducted in animals and humans using both autologous and allogeneic MSC's[5,57,65–77]. MSC's likely contribute to cutaneous wound healing by several mechanisms. Due their multipotential properties, they may differentiate in to skin structures such as muscle[78,79], dermal stromal cells[80], adnexal structures[81] or perhaps even epithelial cells[82]. Many cytokines beneficial to wound healing have been shown to be secreted by MSC's including epidermal growth factor, Insulin-like growth factor-1, keratinocyte growth factor, hepatocyte growth factor, stromal cell-derived growth factor-1, vascular endothelial growth factor-α and angiopoietin 1[32,67]. MSC's are also quite responsive to a stimuli commonly found in wounds. Chronic wounds are often subject to poor vascularization with localized hypoxia. Under hypoxic conditions, MSC's are rapidly mobilized[83,84] and are stimulated to secret increased levels of cytokines involved in tissue growth and angiogenesis[32,85]. In fact preconditioning MSC's in hypoxia has been shown to enhance their tissue regenerative properties[84,86].

Reports of autologous MSC's for the treatment of wounds in patients illustrate the efficacy of these cells for non-healing and/or difficult to heal wounds[57, 65, 68,69, 72, 77]. Dosing in these protocols vary from single to multiple applications with doses up to 2×10^8 cells per administration. In one report where up to 4 administrations of autologous MSC's were delivered topically with fibrin, the authors commented that dosages of greater than 1×10^6 cells per cm^2 were strongly correlated with increased wound closure[69]. The exact method of administration of autologous MSC's to patients in these reports varied from topical application (with a solid substrate or fibrin) to local injections. We have been using cultured autologous bone marrow cells to treat chronic wound patients via local injection and topical application in saline[9, 10]. While most cultured cells we have been delivering are a mixed population of bone marrow cells, they clearly include MSC's. We also have seen evidence of healing after administering cultured bone marrow cells[9, 10] and have not observed a related significant adverse event to date due to their administration. In our investigational therapies with autologous cultured bone marrow cells, we have also noted that patients with non-healing wounds of long duration tend to respond slowly and require repeat treatments. Given the chronic nature of these wounds and often associated co-morbidities seen in these patients, it is not surprising that rebuilding of affected tissues will take considerable time. Stem cell based treatments for chronic wounds, whether autologous and/or allogeneic, will then likely require multiple applications to rebuild the wound bed and achieve eventual wound closure.

Animal studies of allogeneic MSC's in wound healing have also been performed[66, 71, 73, 75, 76, 87]. The route of administration in these studies has been topical[71, 73] (combined with a matrix in some protocols), intravenous[87], and by local injection[66, 75, 76, 87], sometimes with multiple doses[87]. Allogeneic lineage negative bone marrow cells have been shown to be effective in a murine diabetic wound-healing model,

with all studies reporting improvement in healing without significant adverse effect[88]. In addition, xenogeneic (human) MSC's delivered to immune competent diabetic (*db/db*) mice have shown effectiveness in wound healing, also without adverse effect[5].

Several authors have reported near equivalency when comparing allogeneic MSC's to autologous or syngeneic MSC's in wound healing models [66, 71, 87]. While allogeneic MSC's showed virtual equivalency to autologous/syngeneic MSC's in their wound healing benefits and lack of significant immunogenicity, allogeneic fibroblasts were less effective in their wound healing effect with evidence of an immune response[66]. These findings should be viewed within the context that allogeneic fibroblasts are routinely delivered to patients with acute and chronic wounds, mostly in the form of approved bioengineered skin equivalents. Bioengineered skin equivalents have been designed using allogeneic dermal fibroblast and/or allogeneic keratinocytes (mostly from neonatal sources), which were chosen in part due to their limited immunogenicity as compared to other skin cells89. While one could argue that these cells are delivered topically, evidence of retained allogeneic cells has been detected in treated wounds for up to 28 weeks[90–92]. Repeat application of bioengineered skin is also commonplace in the clinical management of chronic wounds and is not associated with significant adverse effects. As allogeneic MSC's have consistently shown low levels of immunogenicity comparable with their autologous/syngeneic counterparts and with less immune stimulatory properties than cells that are commonly retained in skin following treatment with approved bioengineered constructs[66, 71, 87], it appears that allogeneic mesenchymal stem cells may be ideal candidates in the treatment of wounds and skin disorders.

Importantly, there is evidence to support that an allogeneic source for MSC's may be a better than an autologous one for the treatment of diseased tissue. Abnormalities in bone marrow cells, including MSC's, have been demonstrated in chronic disorders associated with non-healing wounds such as diabetes and autoimmune disease[93–97]. We have demonstrated that bone marrow derived from chronic wound patients consistently exhibits reduced growth in culture compared to normals[10]. Further evidence that bone marrow derived MSC abnormalities are involved in these conditions is illustrated by the observation that administration of allogeneic MSC's can ameliorate these disorders[95, 98]. It is reasonable to then presuppose that allogeneic MSC's from healthy donors may have substantial therapeutic benefits beyond autologous MSC's derived from chronic wound patients, since they lack the functional impairment seen in the cells of afflicted persons. This question is best suited for study in humans as it may not be readily amenable to study in animal models. Animal models of chronic wounds have deficiencies, many with critical shortcomings[99–101]. Wounds in humans that are 5 cm^2 or greater with a duration of greater than six months have a very poor prognosis for healing and this scenario cannot be duplicated in animals[102,103]. Numerous age related changes and chronic disorders commonly seen in chronic wound patients also cannot be reproduced in animals[104]. Immune dysregulation in older individuals (who are most often afflicted with chronic wounds) could actually make these individuals more amenable to allogeneic-based cell therapies[105]. Because of these factors, commonly used animal models for chronic wounds are in reality delayed healing models, with notable differences in pathophysiology that point to the necessity of further study in humans. Furthermore, there are subtle but potentially significant differences in MSC's derived from humans and animals. Porcine derived MSC's have been reported to not have equivalent immune modulatory effects as human derived MSC's with potentially greater immunogenicity[106]. Murine MSC's call for hypoxic conditions to ensure consistent growth while human MSC's, although growth enhanced by hypoxic conditions, are not routinely grown in hypoxia. Human MSC's are likely to play unique roles in delivery to non-healing wounds that cannot be fully duplicated in animal models. These important differences

between human and animal MSC's, combined with the imperfections inherent to animal model of chronic wounds, show the importance of more extensive investigation in humans.

4. CONCLUSION

Many unique features appear to make MSC's an ideal source of materials for cell-based wound healing therapies. Among these features are ease of propagation, storage and availability of MSC's from adult tissues. The immune modulatory properties of MSC's allow for an allogeneic source to be an option when autologous cells are not available. Autologous cells, when available, may also not be an optimal choice for therapy in cases where systemic disease and age impact cell function. Future investigation is needed to determine when and if autologous cells are not the prime therapeutic option. Given the safety profile of MSC's, variability of several MSC properties between humans and animals and the limited availability of animal models for wound healing, human studies will be critical in examining these questions.

5. EXPERT OPINION

Stem cells provide a means to rebuild a variety of tissues damaged by disease, trauma and the aging process using methods previously unavailable to clinicians. In order for stem cell to achieve these goals however, one will need to; *i.)* have a readily available source of stem cells that can easily be screened and tested during manufacturing, *ii.)* have access to stem cells that themselves are not damaged due to disease or the aging process and *iii.)* be able to utilize stem cells from other sources that do not cause an immune reaction or other adverse event. MSC's appear to meet these requirements in particular due to their derivation from available adult tissues, ease of propagation and storage, and immune modulatory effects allowing their potential use from allogeneic sources. The ability to use of allogeneic stem cells would provide patients with the opportunity to overcome defects commonly found in stem cells derived from patients with chronic wounds, autoimmune disease and likely other disorders. Apart from their role in tissue repair and regeneration, MSC's might have their greatest potential in modulating inflammatory states that lead to disease. While further investigation is needed, MSC's appear compatible and sometimes synergistic with several approved immune suppressive agents[40–42]. MSC's might then be easily integrated into current treatment regimens, as combined immune modulatory drug therapy is a mainstay in the management of several inflammatory and autoimmune disorders involving the skin. The use of MSC's as drug-sparing agents could lower the risk of toxicity associated with currently used immune suppressive agents. This could be of great benefit when immune suppressive agents known to interfere with wound healing and maintenance of skin tissues, such as corticosteroids, are used. In addition, a cell-based agent would represent an entirely new class of therapeutics with unique functions and the capacity for tissue regeneration, which could represent a very significant treatment advance. Wound healing studies are especially well suited to test these possibilities as wounds (particularly chronic wounds) exemplify the interplay between inflammation and repair. Currently the best expected outcome in the treatment of chronic wound is often closure of the wound with limited functional repair due to scarring, long-standing co-morbidities and age related changes. MSC based therapies hold the promise of addressing many, if not all, of these issues by orchestrating regeneration of aged and/or diseased tissues. Given the limitations of animal models, human studies will be necessary to answer some of these questions and assess the full therapeutic benefit of both autologous and allogeneic MSC's. Safety data from clinical trials have thus far indicated that expanded studies are reasonable. This could permit MSC therapy to reach clinical practice for the treatment of wounds and other skin disorders much more rapidly. As techniques advance, these emerging cellular based therapies are expected to become commonplace. The literature reflects the rapidly increasing interest in examining

MSC's a therapeutic agent for many disorders. With the current pace of new studies planned and in progress, both autologous and allogeneic MSC based treatments should become more widely accessible to clinicians within the next decade, or perhaps even sooner. They will offer new opportunities for the treatment of disorders not currently amenable to current methods.

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Article Highlights

- Bone marrow derived cells including MSC's are capable of differentiation into structures found in skin tissue.
- MSC's do not need to engraft into wounded tissue to exert a healing effect.
- Paracrine properties of MSC's are important in orchestrating repair.
- The immune modulatory features of MSC's are mediated by a variety of mechanisms.
- MSC's appear compatible with currently used immune modulatory drugs.
- The use of allogeneic donor MSC's for therapy is possible due to their immune modulatory properties.
- Bone marrow cells function has been reported to be adversely altered by age and systemic disease processes. Allogeneic cells may provide a better alternative for treatment as they can be derived from young healthy donors.
- MSC's are commonly derived from bone marrow and can be easily stored. This makes them amenable to a variety of therapeutic applications.
- Several wound healing studies support the use of MSC's.
- Animal models for chronic wounds are lacking and MSC's derived from different species may not be equivalent. Human studies will be necessary to fully examine cell based treatments for chronic wounds.