

Mesenchymal Stem Cells in Ischemic Wound Healing

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Background: Regenerative medical strategies using adult stem cells promise to revolutionize the treatment of a variety of diseases and conditions for which effective therapies are currently lacking. Recent advancements in the field of regenerative medicine have highlighted the potential of mesenchymal stem cells (MSCs) as a potential source of cells capable of differentiating and mediating repair of a variety of tissues, including the skin.

The Problem: Despite an increasing awareness of the pathophysiologic events that occur in the development of chronic wounds of various underlying etiologies, chronic wounds remain a burdensome problem for more than 5 million patients and the healthcare providers that treat them in the United States each year. The impact of ischemia on the process of dermal healing is profound and has been considered one of the most significant contributing factors in the development of chronic wounds.

Basic/Clinical Science Advances: Regenerative medicine was in its infancy almost two decades ago when MSCs were targeted to improve orthopedic repair in a variety of preclinical models. Continued advances in our understanding of the importance of the stem cell niche, mechanisms by which MSCs mediate tissue repair and optimization of their cellular delivery have further contributed to the expansion of their use in regenerative therapies for many tissues. Most recently, MSC-based therapies have been shown to improve healing of chronic cutaneous wounds including ischemic ulcers.

Clinical Care Relevance: The ability of MSC-based therapy to overcome the detrimental effects of ischemia in the wound healing process may provide innovative approaches to chronic wounds secondary to a variety of underlying etiologies.

Conclusion: Cellular-based therapies using MSCs offer significant promise as a novel approach to restore healing to chronic wounds and deservedly are the focus of intensive research efforts in the field of wound bioscience.

BACKGROUND

For wounds to progressively heal, inflammatory, vascular, mesenchymal and epithelial cells must coordinate production of a variety of growth factors, cytokines, ECM and the enzymes necessary to modify this ECM. Ischemia induces a loss of the balanced activities of these cellular components and leads to chronic, impaired wound healing.¹ Although it has been known for more than 30

years that oxygen tension is a key regulator in wound repair,² ischemic wounds remain a burdensome challenge to the health care industry. Ischemia, a major factor of which is tissue hypoxia, has been shown to decrease granulation tissue formation, impair epithelialization and diminish biomechanical strength parameters in wounds.^{3,4} Decreased tissue oxygen tension has been shown to diminish collagen production in

Abbreviation list

α SMA: alpha smooth muscle actin
 bFGF: basic fibroblast growth factor
 CTGF: connective tissue growth factor
 EGF: epidermal growth factor
 HB-EGF: heparin binding-epidermal-like growth factor
 KGF: keratinocyte growth factor
 MSC: mesenchymal stem cells
 PDGF-B: platelet-derived growth factor-B
 TGF α : transforming growth factor- α
 TGF β : transforming growth factor- β
 VEGF: vascular endothelial growth factor

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wounds, increase matrix metalloproteinase activity and cause aberrant expression of a variety of growth factors and cytokines within the wound.^{2,5-7} These quantitative and qualitative differences in growth factors and ECM components further contribute to diminished proliferative and migratory capacity of key cellular components (fibroblasts, endothelial cells and keratinocytes) within and recruitment into the wound.⁸⁻¹⁰ Unless sufficient cell numbers can be generated within the wound from existing precursors or progenitors enter the wound from distant sites, these wounds will remain unhealed.

- MSCs are attractive candidates for cell-based therapies because of their relative ease of isolation, broad differentiation potential, and ability to be expanded *in vitro*.
- Bone marrow-derived MSCs are capable of homing to sites of injury, including cutaneous wounds, and participate in dermal repair.
- Application of MSCs to ischemic wounds led to improved reepithelialization and increased granulation tissue formation.

Therefore, chronic wounds appear to be appropriate targets for regenerative medical strategies which seek to heal the body either by stimulation of endogenous cells to repair damaged tissues or through transplantation of cells or engineered tissues to replace injured or diseased ones. Regenerative medicine is an emerging field of wound biomedicine that promises to provide new and exciting therapeutic modalities.

CLINICAL PROBLEM ADDRESSED

Chronic wounds are a formidable clinical challenge that is associated with significant social and economic consequences. Ischemia has been implicated as one of the most serious contributing factors leading to the development of chronic wounds.¹¹ Chronic nonhealing wounds, including ischemic ulcers, plague more than 5 million Americans each year with an estimated financial burden of more than \$20 billion.¹²

BASIC SCIENCE CONTEXT

Cellular therapy is an emerging therapeutic strategy for cutaneous wounds. In addition to skin-derived cells (fibroblasts and keratinocytes), the bone marrow

provides another source of cells that contribute to normal wound repair. Although bone marrow-derived inflammatory cells have long been recognized to play a critical role in wound repair, the mesenchymal stem cell (also referred to as marrow stromal cells or MSCs) is another component of the bone marrow which has exceptional potential to improve healing of chronic wounds, particularly those with an ischemic component. Recent investigations have begun to elucidate the role of MSCs in response to dermal injury. Bone marrow-derived MSCs are capable of homing to sites of injury, including cutaneous wounds,^{13,14} and are thought to contribute to healing through a variety of mechanisms. MSCs may participate directly in wound closure through progenitor cell proliferation and differentiation, as well as production of an extracellular matrix (ECM) by these cells.¹⁴⁻¹⁶ Alternatively, MSCs may indirectly participate in the healing process through the production of paracrine growth factors that would result in proliferation and improved function of resident cell populations, i.e. fibroblasts, endothelial or epithelial cells.

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- Application of MSCs to ischemic wounds led to improved reepithelialization and increased granulation tissue formation.
- Implanted MSCs provide cellular precursors that are capable of engrafting and directly contributing to dermal repair.
- The production of a rich extracellular matrix by transplanted MSCs may contribute to wound repair by improving mechanical properties of the wound as well as modulating activity of other cells within the wound through cellular-matrix interactions.
- The expression of trophic factors and chemokines by MSCs is an important mechanism by which cutaneous wound repair is enhanced in MSC-based therapies.
- The robust expression of various angiogenic factors by MSCs is thought to be the primary mechanism by which MSCs increase neovascularization of damaged tissues. This property of MSCs makes them highly attractive candidates for repair of ischemic tissues, including ischemic dermal wounds.

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The effect of paracrine factors may go beyond the wound to recruit additional regulatory cell populations such as monocytes and macrophages from distant sites. Wound tissue may be particularly suitable for MSC-based therapeutic strategies, as the granulation tissue bed is produced within a defect, unlike other damaged tissues which may require repopulation of existing tissues with MSCs. Collectively, these results suggest that, although current knowledge about vulnerary effects of MSC for chronic wound therapy is just beginning to be understood, MSCs may be particularly suited to promote repair of nonhealing wounds through a variety of mechanisms which target many of the cellular and growth factor alterations present within the chronic wound.

EXPERIMENTAL MODEL

Although there is currently no ideal model of the chronic wound, the rabbit ischemic ear model developed by the Mustoe laboratory³ has been considered the gold standard in the investigation of ischemic wounds for many reasons. This model, in which two of the three major arteries to the ear are ligated and divided, provides significant and prolonged ischemia to the ear (at least 14 days). Secondly, healing occurs with minimal contraction due to the adherence of soft tissues to underlying auricular cartilage, thus more closely approximating distal extremity wounds in people where chronic wounds tend to occur. Lastly, the size of the rabbit allows for multiple wounds to be created on the same ear (ischemic or non-ischemic), creating intraanimal controls and therefore increasing statistical power of studies. To address the relative lack of molecular tools available in the rabbit, several rodent models have been devel-

oped. Both a modified ischemic ear and a dorsal pedal model have been described in the rat, as well as several other models in which ischemia is created on the dorsum of the animal using implants to prevent neovascularization and/or contraction.^{6,17-19} Although rodent models allow for a more efficient mechanistic dissection of therapies for ischemic wounds and are less costly, the smaller size limits both size and number of wounds possible on each individual which does diminish their usefulness in the assessment of therapeutic strategies for ischemic wounds.

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Delivery of MSCs to cutaneous wounds created in other animal wound models has been by injection into the wound periphery or application onto the wound bed in a simple cellular suspension or within a variety of matrices or biosynthetic materials.^{15,20-22} The latter approach may help retain cells within the wound and influence their fate within the wound.

DISCUSSION OF FINDINGS AND RELEVANT LITERATURE

MSCs have received tremendous attention regarding their clinical potential in regenerative medicine, particularly for orthopedic and ischemic myocardial diseases, but also in neurologic, renal, and hepatic diseases.²³⁻²⁶ They have been shown to accelerate dermal repair in not only acute wounds but also when applied to chronic wounds in both animal models and humans patients.^{15,16,20,22,27} The ability of MSCs to treat ischemic wounds has been assessed using allogeneic MSCs in the rabbit

TAKE HOME MESSAGE—CLINICAL SCIENCES

- Therapeutic application of MSCs to ischemic wounds has been shown to reverse the detrimental effects of ischemia on wound healing parameters in the ischemic rabbit ear model.
- MSC based therapeutic strategies have been shown to be effective in improving dermal healing in several animal models of chronic wounds as well as in several studies examining their efficacy in treating chronic wounds in human patients.
- Delivery of MSCs for wound therapy may be by direct application to the wound bed, injection into the periphery of the wound, or within a variety of matrices or biosynthetic materials. The latter of which may assist in cellular retention as well as direct differentiation capacity within the wound.

Table 1. *This is a sample for table caption.*

Method	Technique–Description	Processing Time & Costs	Advantages	Disadvantages	Practice Implications
Qualitative Cultures	Swab culture of wound taken from debrided surface. Standard bacteriology culture	1 hour for Gram stain; 1-3 days for culture results	Inexpensive, widely available	Low sensitivity, especially for fastidious organisms; not quantitative	Useful to identify presence of specific organisms, such as MRSA or Pseudomonas
Quantitative Culture	Tissue specimen homogenized. Organisms identified and quantitated. 10^5 CFU/Gm is empiric threshold for invasive infection	3-4 days for speciation and quantitation; Requires rapid processing Expensive	Provides accurate and reproducible measure of organism burden within wound	Labor Intensive, requires specialized facilities, Long lag time until results are available, which impacts clinical utility. Unknown if infection threshold varies by organism	Widely used in Burn units, but clinical correlation not well defined.
Nucleic Acid Amplification-PCR	DNA is extracted from specimens and amplified, using organism-specific primers	Processing time can be 4-6 hours; moderate cost	Rapid turnaround. Assays can be highly sensitive	Requires testing against probes for known organisms. Not useful for identifying “unknowns”. Not clinically standardized. Will also identify DNA from non-viable organisms	Research settings largely. Increasing use to quantify organisms load and to identify MRSA in surveillance settings.
Metagenomic Methods	DNA is extracted from wound specimens, amplified and sequenced. Different sequencing approaches include clone libraries and pyrosequencing	Multiple steps involved, processing takes several days, requires extensive lab and informatics support, expensive	Method can identify all of the bacterial sequences within a specimen, including fastidious organisms, organisms in low numbers. Can identify unknown organisms	Expensive, long turnaround time, not standardized. Sequences identified may include surface contaminants, and non-viable organisms	Research settings, to particularly identify non-viable organisms

ischemic ear model.¹⁵ In this study, topically applied bone marrow-derived MSCs were capable of reversing the detrimental effects of ischemia on wound repair by promoting both an increase in granulation tissue formation as well as reepithelialization. Mechanistic dissection suggested that the ability of MSCs to improve dermal healing in the face of ischemia is multifactorial, including both direct and indirect mechanisms. Applied MSCs were found to persist in the granulation tissue of the wound bed, contributing to the increase seen in granulation tissue of ischemic wounds compared to vehicle- or bone marrow mononuclear cell-treated ischemic wounds. Additional data support that these cells may assume a myofibroblast phenotype in granulation tissue based upon their expression of the myofibroblast marker alpha smooth muscle actin (aSMA) and their constitutive expression of type I and III collagens in culture. The production of a rich extracellular matrix by MSCs is likely to contribute to wound repair by improving mechanical properties of the wound as well as modulating activity of other cells within the wound through cellular-matrix interactions.

Although other studies have suggested that MSCs are capable of differentiation into epithelial

and/or vascular endothelial cells,^{16,28,29} there was no evidence for these events within the ischemic wounds.¹⁵ This discrepancy could be explained by differences in wound microenvironments, as both lactate and oxygen levels have been shown to regulate MSC properties and may potentially limit differentiation potential.^{30,31} Rather than trans-differentiation, the positive effects of applied MSCs on both reepithelialization and neovascularization in the ischemic wounds appear to be through the production of multiple paracrine mediators. To explain the observation that MSC application to ischemic wounds was able to increase vascular density within the newly formed granulation tissue six-fold compared to control wounds without directly contributing to vascular progenitors, an examination of soluble mediators of angiogenesis by MSCs was performed. MSCs were found to express several important angiogenic cytokines, particularly bFGF and VEGF, as well as PDGF and CTGF, which have been shown to promote endothelial cell recruitment and modulate vascular remodeling. The powerful ability of MSCs to improve angiogenesis within ischemic tissues through the production of soluble factors is consistent with results of other studies examining MSC-based therapeutic

strategies for ischemic myocardial disease, as well as renal and neurologic injury.^{24,26,32}

Similarly, several growth factors important to keratinocyte proliferation and migration, such as HB-EGF, TGF α , EGF, KGF and bFGF were found to be expressed by MSCs and provide a mechanism by which MSCs improve reepithelialization in the absence of their epithelial transdifferentiation in ischemic wounds. The ability of conditioned media from MSC cultures to promote keratinocyte proliferation and outgrowth from epidermal explants supported this hypothesis of indirect participation by MSCs on reepithelialization of the ischemic wounds. MSCs were also found to express CTGF, bFGF, and PDGF-B which may function in both an autocrine or paracrine role within the wound to positively regulate ECM production, as well as proliferation and chemotaxis of other mesenchymal progenitors within the wound. These combined observations in this preclinical model support the further development of MSC-based therapeutic strategies for ischemic wounds and elucidate several mechanisms by which MSCs may be able to initiate healing in these problematic wounds.

Caution, Critical Remarks and Recommendations

Although MSC treatment has been shown to positively influence healing of chronic wounds due to a variety of underlying etiologies, it should be remembered that the particular microenvironment of an individual wound may influence both the differentiation potential of delivered MSCs as well as

their activity within the wound (proliferative capacity, migration, apoptosis and secretion of paracrine factors). Therefore, the response to MSC therapy may vary in wounds of differing etiologies as well as with the chronicity of individual wounds. It is also important to note that MSC application and systemic administration for regenerative therapies in rodent models has revealed MSC differentiation to undesirable phenotypes, including dystrophic mineralization associated with osteogenic differentiation within cutaneous wounds³³ and malignant transformation.^{34,35} Evolution of our understanding of both the cues required by MSCs, as well as the responses elicited in MSCs, to facilitate cutaneous wound repair will improve our ability to harness the potential of these cells and avoid complications associated with therapies.

FUTURE DEVELOPMENT

Regenerative medicine and tissue engineering strategies that seek to harness the potential of MSCs for treatment of chronic cutaneous wounds are still in development; however, initial basic and clinical studies have shown they offer tremendous promise for a clinical problem in desperate need of effective therapy. To reap their clinical benefits will require an improved understanding of the biology of these cells as well as the development of technologies for delivery or endogenous recruitment of MSCs to sites of repair.

SUMMARY ILLUSTRATION

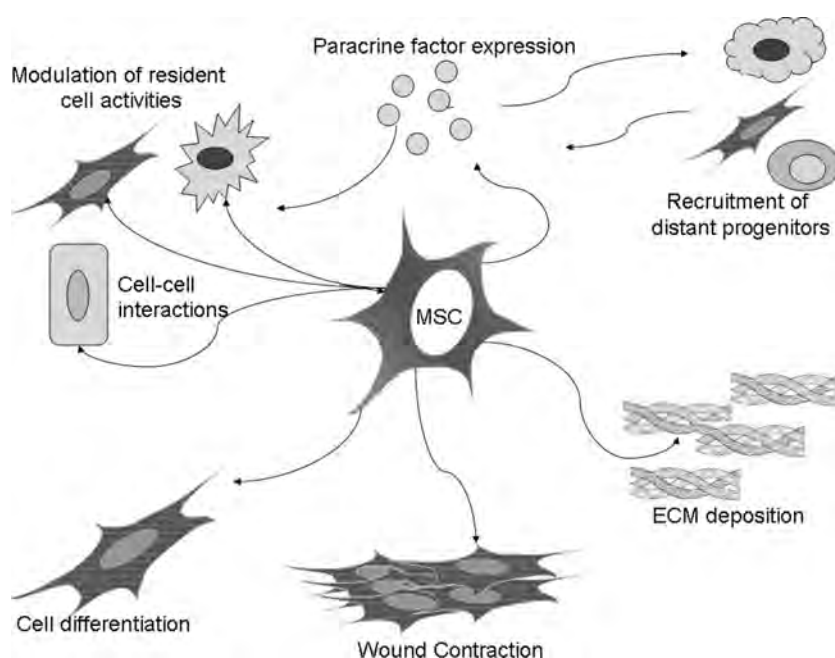


Figure 1. MSCs may improve ischemic wound healing by a variety of mechanisms. MSCs may directly improve wound healing by providing progenitor cells that engraft and differentiate into fibroblasts/myofibroblasts (potentially additional cell types in other chronic wounds). These cells may elaborate a rich extracellular matrix and participate in wound contraction. Activities of resident cells in the wound may be influenced by direct contact with the MSCs or their differentiated cell types as well as through the effects of paracrine growth factors secreted by the MSCs. Expression of chemokines by MSCs may also be responsible for the recruitment of distant progenitors to or migration of local cells within the wound bed.

AUTHOR DISCLOSURE STATEMENT

No conflict of interest disclosed.

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