CLINICAL MANAGEMENT extra

Mesenchymal Stem Cell Therapy and Delivery Systems in Nonhealing Wounds

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All staff, authors, and planners, including spouses/partners (if any), in any position to control the content of this CME activity have disclosed that they have no financial relationships with, or financial interests in, any commercial companies pertaining to this educational activity. The authors have disclosed they intend to discuss the off-label usage of fibrin sealant, hemostatic matrix, basement membrane matrix gel, and surgical sealant in stem cell therapy.

To earn CME credit, you must read the CME article and complete the quiz and evaluation on the enclosed answer form, answering at least 13 of the 18 questions correctly.

This continuing educational activity will expire for physicians on November 30, 2012.

PURPOSE:

To enhance the learner's competence with knowledge of mesenchymal stem cell (MSC) therapy and delivery systems in nonhealing wounds.

TARGET AUDIENCE:

This continuing education activity is intended for physicians and nurses with an interest in skin and wound care.

OBJECTIVES:

After participating in this educational activity, the participant should be better able to:

1. Apply knowledge of the physiology of wound healing to the use of MSCs to improve the wound healing process.

2. Analyze research investigating the use of MSC with a variety of delivery systems for enhanced wound healing.

ABSTRACT

OBJECTIVE: The objective of the study was to inform wound care practitioners of mesenchymal stem cell application for nonhealing wounds. Recent advances in delivery systems are also discussed in order to highlight potential improvements toward clinical application of stem cell therapy for chronic wounds.

DATA SOURCES: MEDLINE and PubMed Central were searched for scientific studies regarding the use of mesenchymal stem cells and delivery systems in wound healing.

STUDY SELECTION: Preclinical studies using stem cells as therapeutic modality for chronic wounds were selected for this review.

DATA EXTRACTION: Information on study design, sample size and characteristics, stem cell source, type of delivery systems, and rate and time of wound closure was abstracted.

DATA SYNTHESIS: Application of mesenchymal stem cells improved wound healing in experimental and clinical settings. Advances in stem cell therapy and delivery vehicles offer promising alternatives to current limited therapeutic modalities for chronic wounds.

CONCLUSIONS: Stem cell therapy has recently emerged as a promising therapeutic strategy for nonhealing wounds. Further research is needed to evaluate the relationship between the various delivery systems and stem cells in order to maximize their therapeutic effects. Development of novel delivery vehicles for stem cells can open new opportunities for more effective cell therapy of chronic wounds.

KEYWORDS: mesenchymal stem cell therapy, nonhealing wounds, hydrogel fibrin sealant

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INTRODUCTION

An estimated 7 million people per year in the United States are treated for nonhealing or chronic wounds at an annual cost of $25 billion.[1] These wounds, regardless of their etiology, are characterized by a pathological healing process that is physiologically impaired at all stages.[2] Despite many advances in wound repair, such as dermal substitute application and growth factor therapy, chronic wounds still achieve only a 50% healing rate.[3,4] As a result, a large segment of this population is at risk for infection, sepsis, and amputation, not to mention the incalculable psychological impact of physical disfigurement.[5] In light of this epidemic, novel therapeutic modalities are needed in the clinician's armamentarium to aid patients with chronic wounds. Stem cell therapy has recently emerged as a promising therapeutic strategy for nonhealing wounds. This article will help clinicians to interpret the role of mesenchymal stem cells (MSCs) in wound healing, as well as the available and potential delivery systems.

STEM CELLS IN WOUND HEALING

Wound healing requires a tightly orchestrated integration of cell migration, proliferation, differentiation, extracellular matrix (ECM) deposition, and angiogenesis.[6] In normal circumstances, this process results in re-epithelialization (ie, a stratified epithelium is laid over a provisional wound bed of collagen-rich granulation tissue).[7] Angiogenesis ensues, which supplies a self-sustaining vasculature in the newly formed tissue and promotes its complete closure.[8,9] These steps involve multiple cellular and molecular events, well controlled in acute wound healing, but dysregulated in nonhealing wounds.[10–12] The role of stem cells as a therapeutic strategy in wound healing is thought to have multiple applications in all stages of the healing process from angiogenesis to re-epithelialization.

This literature review aimed to summarize strategies for the treatment of nonhealing wounds using MSCs, focusing on delivery system parameters that maximize wound closure. MEDLINE and PubMed Central were searched for English-language literature describing human or animal studies published between 2000 and 2010. The search utilized the following keywords in the title or abstract: ''nonhealing wounds'' or ''chronic wounds'' or ''wound healing'' and ''mesenchymal stem cells'' or ''stem cells'' or ''MSC.'' Studies utilizing non-MSCs were not included in this review. A total of 7 studies were identified—5 described murine models, and 2 described human studies.

RESULTS OF LITERATURE REVIEW

Recent studies have shown that the bone marrow–derived stem cells (BM-SCs), particularly MSCs, contribute significantly to skin regeneration[7,13–15] and its vasculature.[16] Furthermore, it has been suggested that these cells home to tissue shortly after injury to participate in the repair process.[10,17,18] Mesenchymal stem cells are self-renewing, multipotent, plastic-adherent, fibroblast-like cells with an ability to differentiate into osteoblasts, adipocytes, and chondroblasts.[19] In an effort to categorize the MSC surface markers, the International Society for Cellular Therapy proposed the following criteria: (1) greater than 95% of the population must be positive for CD105, CD73, and CD90; and (2) greater than 98% must be negative for CD45, CD34, CD14, CD11b, CD79a, CD19, and HLA-DR.[19,20] Mesenchymal stem cells are most commonly isolated from bone marrow aspirate, but they are also frequently derived from adipose tissue and a number of other organs.[21,22] Multiple studies have demonstrated that topical application of BM-SCs to cutaneous wounds promotes their repair in mice[10,23–26] and humans.[23,27] These

studies demonstrated that wounds treated with MSCs undergo accelerated repair as defined by enhanced epithelialization,[10,11,28] granulation tissue formation,[28–30] and angiogenesis[10,11,28] (evidence summarized in Table 1). Adding to their therapeutic appeal, autologous BM-MSCs are nonimmunogenic and easily accessible and proliferate rapidly in culture.[31] Importantly, a limitation to the studies described in Table 1 is that none have been verified in blinded studies.

Table 1.
SUMMARY OF PRECLINICAL DATA

Reference	Stem Cell Source	Delivery System	Total Cells	Wound Closure	n *P* value Time	Control Intervention	Other Outcomes
Kim et al,[36] 2007	Human ADSCs	Collagen gel	1×10^6	↓Wound area 34% ± 15%	n = 6 $P < .05$ t = 7 d	Collagen gel (vehicle control)	1. ↓Time to closure 2. ↑Secretion: type I collagen 3. ↑mRNA: type III collagen, fibronectin 4. ↓mRNA: MMP-1
Sasaki et al,[11] 2008	Mouse BM-MSCs (femur, tibia)	Intravenous (PBS)	1×10^6	↓Wound area 59.6%	n = 10 $P < .05$ t = 8 d	PBS (vehicle control)	None
Javazon et al,[28] 2007	Mouse BM-MSCs (femur, tibia)	Topical (PBS)	7.5×10^5	↓Wound area 25%–45%	n = n/a $P < .001$ t = 7 d	1. Filtered bone marrow 2. PBS (vehicle control)	1. ↑Granulation tissue 2. ↑Angiogenesis
Chen et al,[31] 2009	Mouse BM-MSCs (femur, tibia)	Subcutaneous (PBS) + topical basement membrane matrix gel	1×10^6	↓Wound area 20%–40%	n = 21 $P < .01$ t = 14 d	1. Dermal fibroblasts 2. Subcutaneous PBS + topical basement membrane matrix gel (vehicle control)	1. ↓Time to closure 2. ↑Cellularity 3. ↑Cell engraftment
Wu et al,[10] 2007	Mouse BM-MSCs (femur)	Subcutaneous (PBS) + topical basement membrane matrix gel	1×10^6	↓Wound area 20%–40%	n = 17 $P < .01$ t = 14 d	1. Dermal fibroblasts 2. Subcutaneous PBS + topical basement membrane matrix gel (vehicle control)	1. ↑Angiogenesis 2. ↑Cellularity 3. ↑Cell engraftment
Falanga et al,[23] 2007	Mouse BM-MSCs	Fibrin spray	1×10^6	↓Wound area 20%–40%	n = n/a $P < .01$ t = 10 d	Fibrin spray (vehicle control)	MSCs engraftment in blood vessels
Falanga et al,[23] 2007	Human MSCs (iliac crest)	Fibrin spray	$1 \times 10^6/cm^2$	↓Wound area 30%–50%	n = 6 $P = .0058$ t = 20w	Fibrin spray (vehicle control)	Reduction in wound area is dose dependent (MSCs)

Abbreviations: ADSCs: adipose-derived stem cells; BM-MCSs: bone marrow-derived mesenchymal stem cells; PBS: phosphate-buffered saline.
Most of these studies utilized a variation of the wound model described by Galiano et al.[32] Falanga et al[23] used an alternate full-thickness tail wound. See references for wound model details.

Given MSCs' therapeutic potential in wound healing and other clinical arenas, several studies have been undertaken to evaluate their safety. Ra et al[33] observed stable karyotype and immunophenotype in culture-expanded human MSCs over 12 passages. Furthermore, they observed no adverse effects or mortality during 13 weeks of observation after infusing SCID mice with high doses (10^8 cells/kg body weight) of human MSCs. The same group undertook a phase 1 clinical trial of 8 patients with spinal cord injuries in which they administered high doses (4×10^8 cells) intravenously. During the 3-month follow-up period, there were no clinically significant adverse events or complications.[33]

Mesenchymal stem cells' multidifferentiation potential and participation in the neovascularization process have raised concerns in the literature regarding their tumorigenicity. Muehlberg et al[34] demonstrated that MSCs injected locally and at distant sites promote progression of existing breast cancer in mice. That group recently demonstrated, however, that soft-tissue wounds are able to retain MSCs and do not permit their migration to distant tumor sites; no tumor-promoting effect was observed.[35] Furthermore, Ra et al[33] found no evidence of tumor development during 26 weeks of observation after injecting immunodeficient mice with high doses (2×10^8 cells/kg) of human MSCs.

Results from preclinical in vivo studies demonstrate that autologous MSCs are safe and effective as treatment for chronic wounds. Although the bone marrow harvest or liposuction performed to access MSCs is uncomfortable, patients may elect to undergo these procedures if they reliably offer relief from a painful and disfiguring chronic wound. Investigation into alternative, less invasive methods of MSC isolation is ongoing, but the topic is beyond the scope of this discussion.

Ongoing studies of this therapeutic strategy generally seek to answer 2 major questions: (1) By what mechanism do BM-MSCs promote wound healing? (2) What is the best way to apply the stem cells to the wound?

MSC MECHANISM OF ACTION

Investigations into the mechanism of stem cell–promoted wound repair suggest that application of ex vivo expanded MSCs results in both their differentiation into resident cells and stimulation of regenerative paracrine signaling.[10,20,25] The relative contributions of these 2 mechanisms, however, remain to be determined. Mesenchymal stem cells administered to whole-thickness wounds become locally engrafted and differentiate into various cutaneous phenotypes (keratinocytes, endothelial cells, pericytes), which results in improved healing.[10] At the same time, the mere addition of MSC-conditioned medium yields accelerated wound repair,[25,30,36] suggesting that paracrine signaling is the predominant mechanism by which these stem cells ameliorate the healing process.[20] However, studies using MSCs for brain and heart repair demonstrated a direct relationship between delivery method and cell engraftment efficiency.[37] Put simply, there is insufficient evidence to conclude whether cell differentiation or paracrine signaling is predominantly responsible for enhancing wound healing.

MODALITIES FOR TOPICAL STEM CELL APPLICATION

Delivering stem cells to the wound remains a formidable technical challenge. In order to optimize MSCs' therapeutic potential, the delivery medium should support cell adhesion, proliferation, migration, and differentiation.[38] The hostile nonhealing wound environment, characterized by increased proteolytic activity and chronic inflammation,[39] presents additional challenges to cell viability after delivery. The ideal delivery system would enable MSCs' therapeutic mechanism(s), conform to the irregular shape of the wound, have a simple preparation and application procedure, and demonstrate a significant cost-benefit ratio to the patient. The most widely available stem cell delivery materials are hydrogels, specifically fibrin sealants.

Hydrogels

Hydrogels are 3-dimensional insoluble polymer networks capable of absorbing and maintaining large amounts of water or biological fluids many times their solid weights.[40] They can be formulated such that their precursors are injected into the wound and cross-link under physiological conditions.[21] Once congealed, the hydrogels provide the proper physiomechanical properties to support local tissue. These flowable and injectable in situ gel systems are particularly useful because they could circumvent the need for surgery.[41] Hydrogels fully conform to the irregular shapes of wound beds and can also be engineered to degrade at a rate that is compatible with the healing process.[21] Because they resemble biological tissues, hydrogels could be formulated to mimic the ECM and have been rigorously investigated as a potential delivery system for stem cell therapy. Commercially available fibrin sealants have thus far been the most widely used hydrogel technology.

Fibrin Sealants

Fibrin sealants that are currently approved by the Food and Drug Administration for surgical hemostasis have been used off-label for the delivery of keratinocytes[42] and fibroblasts[43] in wound healing. They have been extensively studied as a delivery system for MSCs (preclinical observations summarized in Table 2). Commercially available fibrin sealants consist of 2 separate chambers of fibrinogen and thrombin, which when

Table 2.
SUMMARY OF HUMAN CELL BEHAVIOR IN FIBRIN GELS

Reference[a]	Model	Cell Behavior	Observations
Bensaid et al,[45] 2003	In vitro	Adherence Spreading Proliferation	1. Low fibrinogen concentration promotes MSC proliferation 2. MSCs have longer lag phase, but shorter doubling time, than in culture 3. MSC proliferation is accompanied by cell elongation/spreading
Bensaid et al,[45] 2003	In vivo	Migration	1. Implanted MSCs demonstrate robust migration to local tissue
Catelas et al,[46] 2006	In vitro	Viability Spreading Proliferation Differentiation	1. MSCs are viable in, and migrate through, a fibrin scaffold 2. Low fibrinogen concentration promotes MSC proliferation and elongation 3. High fibrinogen concentration promotes MSC differentiation
Ho et al,[44] 2006	In vitro	Spreading Proliferation	1. Low fibrinogen concentration promotes MSC proliferation 2. Thrombin concentration does clearly affect MSC proliferation 3. MSC proliferation is accompanied by cell elongation/spreading
Park et al,[64] 2010	In vitro	Spreading Proliferation Differentiation	1. Fibrin more strongly promotes MSC proliferation than collagen or HA 2. Fibrin promotes MSC differentiation when component of hydrogel 3. Fibrin can differentially impact cell morphology and ECM deposition when in co-gel with other scaffolds (collagen, HA)

[a]All studies used human MSCs cultured from bone marrow.

combined, mimic the coagulation cascade. Cross-linked fibrin forms a biopolymeric hydrogel matrix resembling biological fibrin clots.[44]

An early in vitro study by Bensaid et al[45] indicated that fibrin supports the adherence, proliferation, and migration of MSCs. Cell proliferation in the 3-dimensional fibrin scaffold demonstrated an increased lag phase (9 vs 3 days), but a decreased doubling time (54 vs 84 hours) when compared with MSCs in 2-dimensional culture on plastic. Analysis of proliferation at varying concentrations of fibrinogen and thrombin showed that MSCs proliferated only when the concentration of fibrinogen was no greater than 18 mg/mL.[45] Subsequent work by Catelas et al[46] supported this finding but also demonstrated that such conditions inhibit cell differentiation. Interestingly, it has been consistently shown that thrombin concentration has a negligible effect on MSC proliferation, even though it is a known mitogen.[47]

Fibrinogen concentration may affect cell proliferation and viability by altering both the extracellular microstructural and biochemical environments. Higher concentrations of fibrinogen result in a more densely cross-linked scaffold that impedes cell spreading intrinsic to proliferation.[48] Fibrin's affinity for fibronectin, a circulating ECM glycoprotein to which cells adhere, provides the cell-matrix interactions that are critical for their viability.[44,49] Fibrin also plays a role in facilitating cell migration by supporting the emigration from the implanted scaffold to the surrounding tissue. Both in vitro and in vivo studies indicate that MSCs readily migrate out of a fibrin scaffold, particularly in response to a nutrient or oxygen gradient.[45,46]

The results of investigations by Falanga et al[23] supported earlier reports that fibrin promoted MSC viability and migration *in vitro* and demonstrated that application of BM-MSCs in a fibrin hydrogel spray improves wound healing in mice and humans. Because the improvement was dose dependent (application of more cells resulted in greater wound closure), the investigators concluded that accelerated wound healing resulted from the application of at least 1×10^6 cells/cm^2. No adverse effects were observed when this fibrin system was used to apply MSCs to human wounds. However, the authors were unable to show that MSCs were engrafted when applied to human wounds, despite demonstrated modest engraftment in mice.[23]

Increasing fibrinogen concentration results in a more rigid fibrin gel structure with a longer degradation time.[44] Cells incorporated/dispersed within the fibrin gel can secrete plasmin and matrix metalloproteinases (MMPs) that digest the cross-linked fibrin, thereby promoting its degradation.[50,51] Although the effects that fibrin concentration exerts on cell proliferation, differentiation, migration, and viability have been demonstrated, the influence of cell encapsulation on delivery system properties has not been fully characterized.

FUTURE DIRECTIONS

Extracellular Matrix Components as MSC Delivery Vehicles

The ECM is a heterogeneous network of macromolecules that provides the mechanical and biochemical cues involved in regulation of cell growth, proliferation, movement, and differentiation.[52] The ECM binds cells, organizes them into tissue, and provides their characteristic mechanical properties.[38,52] Functional ECM is a corequisite for wound healing because it provides the adherence scaffold necessary for keratinocyte migration and successful epithelialization.[6] Given that ECM is the anatomical niche for stem cells and that cell-ECM interactions play a key role in regulating cellular activity, its components have been studied for their potential as delivery systems.[21] The ECM macromolecules under investigation include collagen, elastin, glycosaminoglycans (GAGs), and adhesion components.

Collagen is an attractive vehicle for MSC delivery, as it is the predominant ECM component[52] and is proangiogenic.[53] In addition, its mechanical stiffness confers the functional rigidity necessary to reconstitute tissue deficits.[21] Collagen-based vehicles have been successfully used for differentiation of MSCs to chondrocytes for cartilage regeneration.[54–56] More recently, Wang et al[57] synthesized collagen-containing hydrogels to which MSCs adhered, enabling their proliferation and multipotent differentiation in vitro.[57] Another type of MSC, adipose-derived stem cells (ADSCs), accelerated repair of mouse wounds when applied in a collagen gel.[22,36,58] Furthermore, the abundance of endogenous collagenase means the scaffold is biodegradable and will yield to the angiogenic processes that proceed during wound healing.[56,59] However, using collagen for delivering MSCs to wounds raises a number of technical and logistical problems. Soluble collagen that could suspend MSCs and conform to the shape of a wound is very costly and thus rarely used. Furthermore, soluble collagen is less rigid[60] and must undergo a caustic cross-linking reaction,[61] which may impede the biochemical processes involved in wound healing.

Hyaluronic acid (HA) is one of the GAGs found in the ECM that can be extensively hydrated and serves to absorb large compressive loads. Hyaluronic acid is nontoxic, and its retention of large amounts of water makes it a particularly effective facilitator of cell migration.[62] The demonstration that culture of ADSCs in HA results in collagen deposition, cell engraftment, and angiogenesis[63] suggests that HA has the potential to be formulated into an effective delivery system. However, further studies are needed to determine the extent to which the proteoglycan facilitates MSC proliferation, as 2 recent investigations of ADSC proliferation in vitro yielded conflicting results.[63,64] Moreover, the resulting cell population expressed significantly more CD44 and CD105 than those cultured in collagen or fibrin, as described above, suggesting that they were less differentiated.[64] The finding that HA putatively inhibits MSC differentiation reinforces the need for a defined mechanism of MSC-promoted wound repair; it is possible that HA's preclusion of differentiation will have no bearing on its therapeutic potential as a delivery system.

To address the challenge of MSC-synthetic hydrogel attachment, investigators are attempting to incorporate adhesive components into the network, particularly those from ECM.

Lastly, an ECM-like material is commonly used to mimic the basement membrane in tissue culture. Although not identical to the heterogeneous and dynamic in vivo ECM, the basement membrane matrix gel contains many of the same components, enabling its complex interaction with cells.[65,66] Importantly, application of MSCs to wounds in a basement membrane matrix gel scaffold in conjunction with subcutaneous injection of MSCs suspended in phosphate-buffered saline resulted in accelerated wound closure.[10,31] However, there is a paucity of literature to rigorously evaluate the mechanistic aspects of a basement membrane matrix gel as a stem cell delivery system.

Synthetic and Semisynthetic Delivery Vehicles

Theoretically, synthetic polymers are an ideal alternative MSC delivery system because they can be custom designed with properties optimal for MSC delivery. In addition, they can be manufactured in industrial quantities with great consistency.[38] Polyethylene glycol has been considered for MSC encapsulation because it is porous, immunogenically nonreactive, and able to absorb large amounts of water, and its cross-linking density can be easily controlled.[38,67]

The major limitation of MSC encapsulation within synthetic materials is the cells' tendency to undergo anoikis (apoptosis resulting from lack of cell-ECM interactions), representing a major drawback on cell viability and therapeutic potential.[68–71] As described earlier, cell-ECM interactions initiate many of the biochemical events responsible for functions related to cell proliferation, differentiation, and migration.[72,73] Although these commercially available materials have been used to deliver other human cells,[74] they are less successful with MSCs because they lack a domain to which the adherence-dependent MSCs can attach. Degradation of the synthetic polymers is another challenge; disintegration rate is a static intrinsic property of fabricated gels, whereas ECM component degradation is subject to the needs of local cells.[38]

To address the challenge of MSC-synthetic hydrogel attachment, investigators are attempting to incorporate adhesive

components into the network, particularly those from the ECM. Cell attachment to ECM adhesive components is principally mediated by integrins (transmembrane heterodimeric surface receptors), which play a major role in cell survival and migration.[75] Fibronectin, as described above, is one such adhesive component that has been integrated into synthetic gels to maintain cell survival.[69,76,77] Karoubi et al[68] demonstrated that immobilization of fibronectin and fibrinogen in an agarose gel capsule aids human MSCs in evading anoikis and increases cell engraftment in vivo. However, the incorporation of large proteins into commercially available hydrogels like PEG can alter the structure and mechanics of the gel and may distribute nonuniformly throughout the network.[21]

Accordingly, researchers looked to include only the adhesive domains (small polypeptides) of the large ECM proteins, such that they might be less disruptive to the polymer and more homogeneously distributed. Indeed, incorporation of the RGD tripeptide (arginine-glycine-aspartate), the major adhesive domain on fibronectin, promoted fibroblast attachment and proliferation. In addition, RGD inclusion did not impede gelation, swelling, or other measurable mechanical properties.[78]

Ideally, a synthetic MSC hydrogel scaffold would break down as resident cells proliferate and begin to deposit their own ECM. This nascent ECM is subject to remodeling by cell surface MMPs and other proteases that cleave their substrates at specific target motifs. Researchers have begun to incorporate these target domains into PEG hydrogels to render the synthetic scaffold biodegradable. These cleavage sites have been identified from a variety of ECM components, including type I collagen,[79,80] type II collagen,[81] and fibronectin.[67,82]

CONCLUSION

Preclinical studies suggest that BM-MSCs represent an effective and safe therapeutic strategy in the treatment of nonhealing wounds. Significant investigation remains to be undertaken to (1) define the mechanism by which these cells induce repair and (2) determine the medium in which stem cells should be delivered to achieve optimal therapy.

Currently, fibrin sealants possess many of the attributes that constitute the ideal stem cell delivery system. Its commercial availability and frequent use are additional advantages. However, fibrin sealants have not been compared with other potential stem cell delivery systems in preclinical or clinical study. Therefore, it remains to be elucidated which delivery system will prove to be the most efficient and cost-effective modality. Although MSCs are able to interact biochemically with ECM components such as collagen and HA, it has not yet been shown that either constituent can functionally replace the diversity and complexity of the endogenous ECM. Alternatively, synthetic hydrogels promise custom-designed structural properties and physical consistency, but significant provisions must be made to ensure their support of cell viability and function.

Although the current data suggest that delivery vehicles can facilitate MSCs' therapeutic efficacy in chronic wounds, further exploration is needed. This discussion emphasized the biochemical and microstructural properties of various materials that influence cell behavior. However, the extent to which each of these criteria should be maximized to attain optimal therapy for nonhealing wounds can be derived only from future clinical studies.

PRACTICE PEARLS

- Mesenchymal stem cells are pluripotent, self-renewing, fibroblast-like cells with an ability to differentiate into osteoblasts, adipocytes, and chondroblasts.
- Mesenchymal stem cells have been shown in both preclinical and clinical investigations as a promising therapy to promote healing of chronic nonhealing wounds.
- The 2 primary mechanisms by which mesenchymal stem cells promote wound healing appear to be through differentiation into resident cells and stimulation of regenerative paracrine signaling.
- The ideal delivery system for mesenchymal stem cells has yet to be developed; however, a vehicle that serves as a functional extracellular matrix is achievable, especially through formulating it as hydrogels.
- Synthetic hydrogels are promising delivery vehicle under development as they can be modified with components of the extracellular matrix to enhance mesenchymal stem cell performance.

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