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Burn-derived Mesenchymal Stem Cells in Wound Healing

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Abstract

Thermal injury is a severe form of trauma that is accompanied by significant, persistent metabolic and immune dysregulation. The extent of altered post-burn metabolism and inflammation is correlated with severity of injury, with severe burns demonstrating a more significant hypermetabolic, hyperinflammatory response. This in turn delays re-epithelialization and exacerbates poor post-burn wound healing, which is the most important factor in patient mortality outcomes. Recently, stem cells have gained interest in burn wound healing applications due to their capacity to produce multiple cellular subtypes and improve the rate and quality of healing. Here, we focus on applications of mesenchymal stem cells in wound healing. In particular, we highlight the characteristics and efficacy of burn-derived mesenchymal stem cells (BD-MSCs), which improve healing in animal models. Discarded burn tissue is a source of pro-healing BD-MSCs, providing a safe, non-invasive therapeutic option for burn patients.

Burn-Related Complications and Current Standard of Care

Persistent inflammatory derangements are a hallmark of burn trauma that ultimately influences wound healing[1]. Inflammatory mediators such as cytokines recruit immune cells (e.g. macrophages, leukocytes) to the site of injury during the preliminary stage of wound healing. These cytokines in turn recruit keratinocytes and activated fibroblasts to the wound bed, promoting re-epithelialization, which is a key factor in patient outcomes[2-5]. However, while inflammation is likely necessary for healing, excessive, prolonged post-burn inflammation in turn promotes tissue destruction and increases risk of abnormal scarring (e.g. hypertrophic scars)[6-10]. Targeting inflammation with systemic anti-inflammatory agents such as glucocorticoids is detrimental, especially in large burns. Instead, excision and grafting during the inflammatory phase is performed in order to mitigate inflammation and decrease infection, which is another common complication of burn wounds. Burn patients are susceptible to drug resistant infections, which can result in an enhanced immune response accompanied by septic shock, hypotension and poor skin perfusion which ultimately further delays wound healing[11]. Thus, therapeutic strategies that regulate local immune responses to enhance healing are key in preventing scarring and infection.

Standard of care for burn wound management is early excision and debridement (within 72 hours post-injury) followed by autologous split-thickness skin grafting[12-16]. Early excision is associated with decreased blood loss, infection and mortality

coupled with increased graft take[17-20]. However, this poses certain challenges, including creation of a new wound site and complications such as pain, scarring, infection[21,22]. This is in addition to the fact that severe burns (>30% TBSA) require a significant amount of healthy skin for grafting, precluding use of this strategy. Due to these limitations, there is a need for alternative wound coverage strategies, although current options are ineffective secondary to high cost, poor efficacy, and long production time[23,24].

Currently, cell-based techniques for permanent coverage are gaining popularity. Culture-based options include patient-derived keratinocyte isolation and expansion into epidermal autografts, which limits the amount of donor skin need for coverage of large burns. However, keratinocyte-based techniques should be employed carefully since hyperactivation may contribute to pathological scarring[25]. Alternatively, utilizing adult MSCs isolated from bone marrow, hair follicles, adipose tissue, or skin is another viable option. These stem cells promote healing likely via immunomodulation and paracrine activation of host cells, and we discuss characteristics of MSCs in the following section[26].

Characteristics of Mesenchymal Stem Cells

MSCs are classified based on characteristics such as plastic adherence, expression of specific cell surface markers (CD73, CD90, CD105) and lack CD14, CD34, CD45 and HLA-DR, and the ability to differentiate *in vitro* into either adipocytes, chondrocytes or osteoblasts[27]. While the aforementioned characteristics are applicable to all MSCs, there are slight variations depending on the tissue of isolation. MSCs have several beneficial features for skin regeneration such as the capacity for self-renewal, ability to home towards wounds, rapid proliferation and the ability to differentiate into a host of cell types[28]. Importantly, their pro-healing effects can be attributed in part to release of growth, cell recruitment, and immunoregulatory factors in response to inflammatory mediators that accumulate at the site of injury – a process known as 'licensing'[29].

An added advantage over other stem cell types is that MSCs are not immunologically active due to low MHC1 and lack of MHCII and co-stimulatory CD80, CD40 and CD86, which protects MSCs from natural killer (NK) cell lysis[30]. Furthermore, MSCs can inhibit NK and cytotoxic T-cells via various pathways, such as secretion of human leukocyte antigen G5, leukemia inhibitor factor (LIF) and IFNg[31-33]. More specifically, MSCs induce T-cell apoptosis, which enables macrophages to produce TGFb, thus promoting generation of regulatory T-cells and macrophage phenotype switching to anti-inflammatory subtypes[34-36]. These immunomodulatory effects depend on the quantity and type of cytokines present and diminish the risk of immune rejection, making MSCs a viable option in inflammatory conditions and other clinical applications[37,38]. However, intensity of inflammation regulates MSC-mediated immunomodulation, necessitating a strong patient inflammatory status for optimal efficacy[39]. Therefore, burn injuries are a potential application for MSCs. The added advantage of using skin MSCs in particular is that these cells can be easily isolated from debrided burn eschar. In the subsequent section, we discuss the isolation and advantage of utilizing BD-MSCs.

Isolation of Mesenchymal Stem Cells from Burn Skin

Debrided burn skin, which is routinely discarded after excision, contains a host of viable cells that have the potential to be extracted and incorporated into skin substitutes. We previously demonstrated that viable BD-MSCs can be isolated from the dermal component of surgically debrided burn skin (Figure 1). BD-MSCs can be extracted easily

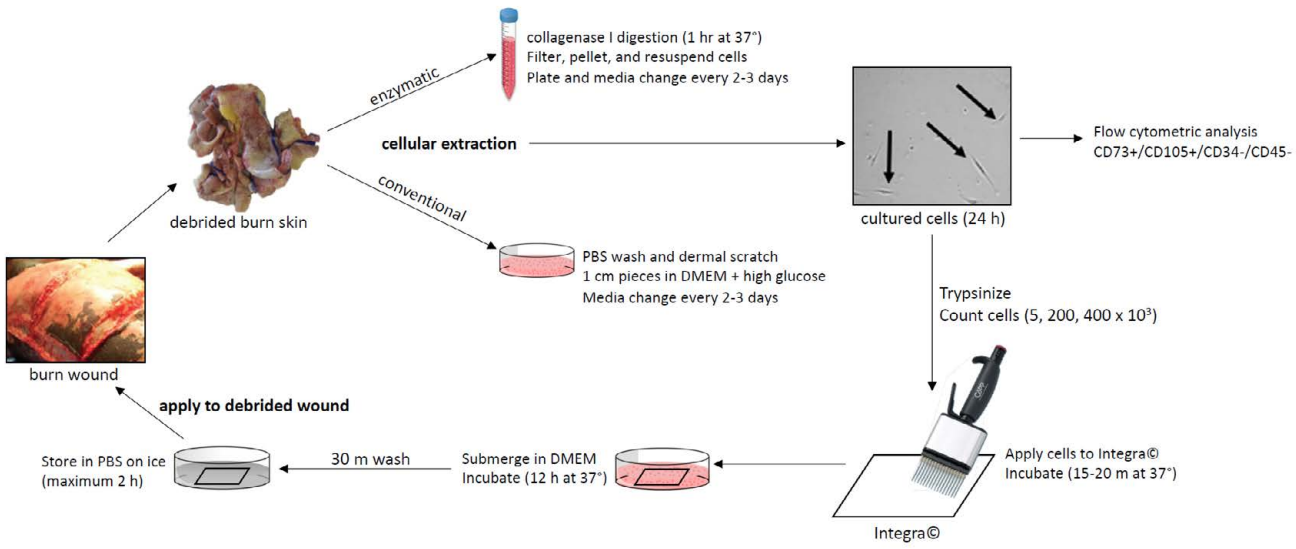

Figure 1. Schematic of the methods and application of BD-MSCs in the clinical setting.

either using an enzymatic or a conventional method. For the former, we homogenized fresh tissue and incubated with collagenase I. For the latter, we washed tissue in PBS with 1% Ab/Am, cut tissue into 1cm squares and placed in high glucose DMEM supplemented with 10% FBS and 1% Ab/Am, and allowed cells to adhere to the surface. Isolated cells were characterized using flow cytometry (CD73+CD105+CD34-CD45-), and multipotency was confirmed by adipogenic, chondrogenic, and osteogenic differentiation. For the *in vivo* murine model, Matrigel containing 110,000 BD-MSCs were applied directly to the full-thickness punch wound and was subsequently covered with Tegaderm. For porcine experiments, we compared wound healing outcomes with Integra or Integra containing 5,000-400,00 BD-MSCs/cm^2 in excised burn wounds.

Outcomes with MSCs

To date, there are several studies investigating applications of locally or systemically injected and topical MSCs in animal burn models[40]. For the purposes of this review, we will highlight studies focused the beneficial effects of MSC-seeded biomaterials (e.g. decellularized tissue extracts, premade porous scaffolds, hydrogel formulations) on burn wound healing as a comparison to our previous work. Several studies in rodent burn models investigated the effect of scaffolds seeded with human MSCs[41-44]. These studies demonstrated accelerated wound closure in full-thickness burns, with enhanced vascularization, granulation tissue formation, and wound maturity – markers for improved healing[40]. Other studies investigating BM-MSC-seeded scaffolds in rodent partial-thickness burns showed similar effects[45,46]. Namely, Guo et al. showed evidence of enhanced re-epithelialization and cellular proliferation coupled with greater blood vessel density, and Yang et al. demonstrated accelerated wound healing and time to closure[45,46]. Similarly, several porcine studies investigated the effect of scaffolds seeded with autologous, allogeneic, or xenogeneic MSCs to treat deep partial- or full-thickness burns. Clover et al. demonstrated evidence of increased collagen content, epidermal area, and dermal thickness by 14 day post-transplantation, while Liu et al. showed enhanced wound area contraction at 4 weeks after management with an autologous BM-MSC seeded scaffold[47,48]. Burmeister et al. also demonstrated increased blood vessel size and percentage of biopsy area represented by blood vessels, providing evidence of enhanced angiogenesis with treatment[49].

We demonstrated similar results with BD-MSCs, with the added advantage that these cells can be isolated directly from discarded burn tissue. In fact, administration of BD-MSCs in Matrigel in immunodeficient mice enhanced wound closure, reduced granulation tissue size, and reduced the thickness of the keratinocyte layer[12]. This indicates a potential anti-scarring effect, which is promising due to the fact that burn patients frequently suffer from abnormal scarring. Furthermore, BD-MSC administration promoted an earlier transition to the remodeling phase of healing. Porcine wound models, which resemble human wounding, similarly exhibited an accelerated epithelialization time and greater dermal blood vessel content, another marker of healing[12]. While this may be a consequence of general wound healing, BD-MSCs may have the potential to directly promote neovascularization. Furthermore, an important consideration of using cell therapy is safety and the potential for tumorigenicity, and we demonstrated no detrimental effects *in vitro* and *in vivo* in both murine and porcine wound healing models over 30 days[12].

To date, there are few studies regarding MSC application in human burn wound healing, and the current studies vary with regards to the time to first MSC administration (five to 29 days). Rasulov *et al*. first described the topical application of allogeneic BM-MSCs for management of a patient with extensive, severe burns, demonstrating enhanced skin graft take and neoangiogenesis[50]. Another case study by Mansilla *et al*. investigated administration of BM-MSCs in a fibrin matrix spray system for a 30% TBSA full-thickness burn[51]. The authors demonstrated early "granulation-like tissue" by day 5 post-treatment, with evidence of epithelialization at the wound margins and almost no scarring during the three-year follow-up. However, it is difficult to determine causality in these case reports due to the lack of controls, although these results suggest that MSC application to human burn wounds may be a potential line of investigation. This is especially promising given the effects on wound contracture and scarring. Abo-Elkheir et al. demonstrated decreased contracture and hypertrophic scarring with locally injected autologous BM-MSCs, in addition to fewer late complications[52].

In addition to improved healing, there are several other advantages to utilizing BD-MSCs. Compared to embryonic stem cells, there are no ethical obstacles to BD-MSC extraction, and discarded tissue provides an ample source of stem cells. Additionally, isolation of BD-MSCs is non-invasive compared to other sources of MSCs and because these are the patients' own cells, there is no added concern of immunological rejection. As we demonstrated earlier, BD-MSCs can easily be incorporated into wound coverage materials or scaffolds, providing an easy, cost-effective method for stem cell delivery to the site of injury. However, there are several limitations in our study and potential issues with the clinical use of cultured autologous cells. Firstly, there are regulatory issues associated with the use of cultured autologous cells in general. Culture expansion of cells is considered to be "more than minimal" manipulation, and these products are classified as medicinal products or biologics that must comply with Good Manufacturing Practice (GMP) guidelines[53]. This introduces additional

Table 1. Advantages and disadvantages of topical cell-based therapies

Cell-Based Therapy	Advantages	Limitations
BD-MSCs	Can isolate easily from discarded tissue[12] Low chance of immunological rejection[12] Same as other sources of MSCs	Need to identify different characteristics from non-burn MSCs[12]
Other sources of MSCs (e.g. bone marrow, adipose)	Multipotent, self-regenerative capacity Easy to isolate and characterize[56] Paracrine secretion of cytokines (e.g. IFNg, TNFa, IL1), growth (e.g. EGF, VEGF) and anti-fibrotic factors[26]	Potentially invasive extraction[12] Need to define long-term safety profile and mechanism of action[56]
Keratinocyte/ Keratinocyte stem cells	Small amount of donor skin needed[25] Easy to isolate and expand Produce various cytokines needed for healing (e.g. IL1, IL6, TNFa)[57]	Hyperkeratosis and scar contracture[25]
Fibroblasts	Maintain cell viability when cryopreserved Produce key ECM* proteins (e.g. collagens, laminins, fibronectins)[57,58] Can be induced into pluripotent stem cells[56]	Heterogenous populations[58] Efficacy not clearly established *in vivo*[59]

**ECM=extracellular matrix*

regulatory challenges prior to clinical implementation, compounded by factors such as variations between clinical sites[53].

Additionally, although we demonstrate no detrimental effects with BD-MSCs, several studies suggest potential adverse affects with MSC treatment[54]. Also, we did not investigate alternate routes of administration such as local subcutaneous or intradermal injection, which shows some promise in several murine and porcine studies[40]. Furthermore, although we detected human BD-MSCs in murine wound tissue after wound closure, it is unclear whether these cells remained in their MSC-state or differentiated into skin cells. While we provided evidence of MSC survival in burn tissue, additional research is needed to determine how these cells survive. We postulate that this population of stem cells may differ due to their ability to resist heat via activation of cellular stress responses. Post-burn changes include altered mitochondrial dynamics (e.g. enhanced uncoupling), and previous studies have shown that mitochondrial function influences cellular renewal and differentiation[55]. In fact, mitochondrial fusion is needed to promote stem cell differentiation and therefore, post-burn mitochondrial dysregulation could promote resistance to differentiation in these populations. Although this is speculative and further work is still needed to elucidate their underlying pro-healing mechanisms, BD-MSC-embedded scaffolds are a promising therapeutic option for burn wound management.

Concluding Remarks

Although advances in wound care have improved burn patient outcomes, severe burns are still associated with significant morbidity and mortality. Currently, excision and grafting is the gold standard for burn patient management. However, a paucity of healthy skin in severe burns limits efficacy of autografting. Therefore, utilizing cell-based therapies such as biomaterial sheets with MSCs may be an attractive option in wound management (Table 1).

Conflict of Interest

The authors declare no conflicts of interest.

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