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Editorial

Stem Cells to Improve Burn Wound Healing

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Abstract

Burn injuries are a common and highly lethal trauma causing immense pain, suffering, disability, and unfortunately death. The secondary contracture can lead to loss of function and furthermore lifelong disability both physically and mentally. Stem cells have been used in a variety of clinical applications to repair and regenerate chronic wounds. However the use of stem cells in burns has just recently been applied to the field. Besides showing the power to promote better and faster healing of the burn wounds, stem cells have also showed the ability to decrease inflammation and the degree of scarring and fibrosis. This mini review aims to highlight the recent studies that have shown the therapeutic effect of mesenchymal stem cells (MSCs) in burn wound healing and to further discuss the many different strategies of application of such cells to a burn wound.

Introduction

The research of stem cells has allowed us the ability to treat certain debilitating conditions that traditional treatments could not address. Conditions such as diabetes, chronic renal failure, arterial or venous insufficiency, radiation-induced tissue damage, thermal injuries are among the processes that contribute significantly to dysfunctional wound healing [1], [2], [3]. These complex wounds are categorized by inhibition of the inflammatory response, dysfunctional macrophages leading to an inability to combat infection, impaired vasculogenesis, accumulation of fibrous tissue, and aberrant extracellular matrix accumulation [4]. Numerous therapies have attempted to treat chronic wounds but have shown to be of limited use [3]. Recent studies have shown the ability of stem cells to promote the healing of such chronic wounds [4].

Mesenchymal stem cells (MSC) have the ability to rebuild the dermis by differentiating into many cell types such as fibroblasts, cartilage, and muscle by releasing many growth factors and cytokines that are necessary for wound repair [3]. MSC's have already been used in a variety of animal models to treat specific conditions such as Parkinson's disease [5], stroke [6], cardiovascular conditions [7], and spinal cord injuries [8]. In recent years the safe and efficient delivery of MSC's to humans in the treatment of healing and scarring in chronic wounds has proven to be successful [1, 2, 9].

However the use of stem cells to improve the treatment of burns is unparalleled.

Burn injuries can be quite devastating from a functional and/or cosmetic standpoint. They cause a great source of pain, suffering and death during times of war and accidents occurring in daily activities of life. Although many burns are not life threatening they can cause significant distress and impairment. Healing of burn wounds can often times lead to hypertrophic scaring further leading to scar contractures [10]. These contractures can limit the normal function of the body and represent a great source of disability and morbidity for burn patients [10]. Treatments to lessen the effects of hypertrophic scarring including scar massage, topical treatments, steroid injections, and compression garments have not consistently shown desired results [11, 12]. Thus application of stem cell therapy to severe burn wounds as well as scar contractures from burns provides an opportunity to increase morbidity and mortality in situations where alternate therapies are limited and often ineffective.

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Use of Mesenchymal Stem Cells in Burn Wound Healing

Shumakov et al. was one of the first to apply the concept of using MSCs in burn wound healing [13]. An accelerated formation of new vessels and granulation tissue was seen in the burn wounds of rat models [13]. Rasulov et al. also used rat models to show the beneficial use of MSCs by comparing the effects of fetal fibroblasts and fibroblast-like MSCs on burn wounds [14]. The study showed a reduction in cell infiltration and the formation of vessels and granulation tissue [14]. Rasulov et al. also used bone marrow mesenchymal stem cells in a female patient with extensive skin burn and confirmed regeneration of the wound by active neoangiogenesis [15]. Francois et al. found success in the use of MSC injections in radiation burns, induced in mice [16]. Lataillade et al. and Bey et al. used similar novel approaches by combining surgical and cellular therapy with adult stem cells in victims of radiation burns to promote tissue regeneration[17, 18]. Furthermore their studies showed favorable healing progression, decrease in radiation pain and no recurrence of radiation inflammatory waves [17, 18]. Agay et al. conducted experiments using minipigs that were induced with radiation burns and intradermally injected with MSCs in the affected areas [19]. Their study showed that MSCs led to local accumulation of lymphocytes and improved vascularization [19]. In 2012, Riccobono et al. studied the role of adipose tissue derived stem cells in the treatment of radiation burns [20]. They determined that autologous derived stem cells had superior burn wound healing with no necrosis and decreased pain versus allogenic stem cells [20]. Xue et al. investigated the effect of MSCs on the improvement of burn wound healing in mouse models [21]. They found that wound surface healing was significantly accelerated and interestingly they found that body weight and activity were restored in the MSC treated mice and no tumor growth was found [21]. In 2014, Liu et al. used human umbilical cord MSCs (hUC-MSCs) to investigate wound healing in severely burned rats [22]. They discovered that wound healing was significantly accelerated in the group treated with hUC-MSCs and showed a remarkable decrease in inflammatory cells levels of IL-1, IL-6, TNF-alpha and increased levels of IL-10 and TSG-6 in wounds [22]. Furthermore, increased levels of VEGF and neovascularization in wounds were seen when compared to the control groups [22].

The use of MSCs has also recently been taken to the next level with the combination of other factors that also promote wound healing. For example Yan et al. examined the effects of using marrow-derived mesenchymal stem cells (BMSC) in combination with skin-derived keratinocytes to promote healing in irradiated skin using porcine models [23]. Pathologically, they revealed better granulation formation and re-epithelialisation, and collagen deposition in the combination therapy compared to the other groups [23]. Xia et al. transfected human vascular endothelial growth factor and human beta-defensin 3 into rat derived MSCs and injected this combination into the sites of induced radiation burn injuries on rats [24]. This combination showed significant proliferation and cell migration of human endothelial cells [24]. A shortened wound-healing time was seen as well as an increase in granulation tissue formation/maturation, skin appendage regeneration and collagen deposition [24]. Mansilla et al. used a novel approach by applying intelligent acellular dermal matrices (IADMs) coated with anti-CD44 monoclonal antibody to promote homing and attachment of the stem cells in a deep large burn of a pig model [25]. They further loaded the IADMs with granulocyte-macrophage colony-stimulating factor, epidermal growth factor, and MSCs to investigate the effects in a deep large burn of a pig model [25]. The wound completely closed, total regeneration of the skin was seen, hair follicles and skin appendages developed despite the severity and deep nature of the burn [25]. Surprisingly, even the burned muscles and ribs underwent regeneration [25]. Yang et al. experimented with a fibrin glue and MSC mixture to treat inflicted scald wounds on the backs of rats [26]. In the group that received the combination they saw faster healing and on histopathological analysis they saw proliferation of sebaceous glands and the appearance of hair follicle-like structures [26]. The addition of the fibrin glue allows a quick formation of a film-like gel over the scald wounds, which can potentially be useful in emergency treatment and skin-grafting operations [26]. The use of stem cells in the treatment of burn wounds is an active field that is still undergoing heavy research.

Conclusion

The potential impact of mesenchymal stem cell therapy to regenerate burn wounds is promising and will have a profound impact on the lives of many burn victims. Many different approaches and strategies can be used to help in the healing of burn wounds as outlined above. Stem cells can be used from emergent settings to the healing of scar contractures. The use of stem cells to heal burn wounds is groundbreaking and will finally bring a safe and effective treatment to an area that has not seen much improvement in quite some time.

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