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The application of mesenchymal stem cells to treat thermal and radiation burns

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ABSTRACT

Mesenchymal stem cells (MSCs) have been developed for a number of indications due to their regenerative and anti-inflammatory phenotypes and their utility is enhanced by the fact that allogeneic transplant is feasible with this cell type. Animal studies and early human cases indicate that this has the potential to be an exciting new therapy for treating chronic non-healing wounds such as diabetic ulcers, burns and cutaneous radiation burns. This review will focus on the use of MSCs to treat thermal and radiation burns. Large, severe burns are difficult to treat and pose a major public health burden worldwide. They are characterized by an extensive loss of the outer protective barrier, delayed wound healing, increased oxidative stress and a heightened inflammatory state. The breakdown of the protective barrier results in increased susceptibility to fluid loss and bacterial sepsis. In the case of radiation burns, chronic inflammation can result in subsequent waves of tissue injury leading to skin breakdown and necrosis. The aim of this review is to summarize the current knowledge on MSCs in treating thermal and radiation burns along with the specific scope of characterizing the biologic function of MSCs that help enhance wound healing in these chronic injuries.

1. Introduction

Wound healing is a dynamic process which involves a coordinated effort by multiple biological pathways and is broadly classified into the stages of inflammation, angiogenesis, proliferation and maturation. During these stages of tissue repair, there is a complex interplay of signals between various cells types involving the secretion of growth factors, cytokines and collagen matrices [1]. In addition, stem cells also play a crucial role in wound healing. Several studies have shown that cells at the base of the hair follicles are the source of epidermal stem cells and in an injury state they help facilitate the re-epithelialization process [2,3]. While normal wound healing follows these trends, in cases of extreme injury such as thermal and radiation burns, the extent of damage dictates the progress of wound healing. Both thermal and radiation burns have been extensively studied and various modes of treatment have been developed to treat the damage inflicted by these injuries [4,5]. One of the more promising therapies for the healing of these severe injuries are MSCs, either by themselves or in conjunction with other treatments [6,7]. This review will focus on the latest advances that have been made in the realm of MSCs as a treatment for thermal and radiation burns.

2. Thermal and radiation burns: Pathophysiology and current treatments

Burns are difficult to treat and pose a major public health burden worldwide. They are classified based on the depth of the burn and larger burns that cover >20% of the total body surface area have severe systemic effects known as burn shock [8]. They are characterized by an extensive loss of the outer protective barrier, delayed wound healing, hypermetabolism increased oxidative stress and a heightened inflammatory state [4]. In addition, sepsis as a result of inadequate wound healing and lack of a protective barrier followed by bacterial invasion, is a major complication associated with burns [9]. The extent of burns dictates the mode of treatment which includes debridement of injury, antibiotics and fluid/electrolyte replacement [4]. The most common treatment for extensive burns and third degree are early burn eschar excision and autologous skin grafts within 24–72 h post injury, however, in case of extreme injury, this is often not an option due to a lack of donor site [4]. In this case, some of the other options include cadaveric allografts, xenografts or dermal substitutes [4].

The extent of damage due to ionizing radiation exposure depends on the radiation dose and the proportion of the body exposed [10]. Cells that proliferate at a higher rate are more susceptible to the effects of radiation and include organ systems such as the bone marrow, gastrointestinal system, skin and muscle [10]. In skin, the basal layer of the keratinocytes and hair follicle stem cells are damaged by the initial

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radiation, followed by generation of free radicals and DNA double strand breaks which lead to further inflammation and oxidative stress [11,12]. Depending on the dose of radiation, the effects at the wound site can vary from erythema within a few days after exposure, to dry desquamation a month after, to moist desquamation and ulceration >6 weeks after exposure finally resulting in chronic non-healing ulcers and fibrosis [11]. This dose-dependent difference in clinical pattern is one of the major differences in the pathophysiology of radiation burns from thermal burns. In addition, thermal and radiation burns differ significantly in their inflammatory response. Radiation burns are followed by recurring waves of inflammation which further result in erythema at the site of exposure finally resulting in necrotic wounds [13]. Like thermal burns, the frontline treatment for full thickness and severe cutaneous radiation burns are skin autografts [14]. However, due to the constant inflammatory state observed, both at the site of injury and systemically [15], the grafts often lead to non-healing injuries [14].

The lack of wound re-epithelialization after surgery, or pharmacological agents to treat severe thermal and radiation burns has prompted further research to develop better therapeutic options. In recent years, cell based approaches have emerged as a potential treatment for chronic non-healing wounds and MSCs have been shown to be at the forefront of therapeutic efficacy.

3. Biology of mesenchymal stem cells

MSCs are multipotent cells that have been identified in several tissues such as bone marrow, adipose tissue, dermis, brain and spleen [16,17]. They have the ability to differentiate into osteoblasts, adipocytes and chondrocytes [18,19] and more recently, MSCs have been shown to differentiate into cardiomyocytes [20,21] and to have an immunomodulatory function [22,23]. Early studies with MSCs revealed that they can improve the biomechanics and structure of injured tendon [24] and that they may have the ability to home in to the site of injury thus assisting tissue regeneration [25–27]. Since then, several studies have demonstrated the regenerative potential of MSCs in cutaneous wounds [28–31], skeletal muscle [32], cartilage repair [33], diabetic wounds [34], cardiac [35], lymphatics [36] and traumatic brain injury [37]. MSCs achieve this by being immunosuppressive [38,39], pro-angiogenic [40], anti-apoptotic [41], pro-differentiation [40], pro-proliferation [42], anti-oxidative stress [37,43] and by reducing fibrosis and hypertrophic scar formation [44,45]. This multifaceted ability of MSCs has led to their application in a number of injury models.

It is important to note that the age of MSCs plays a crucial role in their functionality. Duscher et al. have compared adipose derived mesenchymal stem cells (ASCs) from 3 (young) and 21 (old) week old C57Bl6 mice. What they found was that while the total frequency and viability of ASCs between young and old mice remained unchanged, ASCs isolated from the older mice had significantly diminished signaling and angiogenic potential which in turn resulted in poor cutaneous wound healing in aged mice [46]. In addition, it has been observed that aged MSCs have reduced migratory and anti-inflammatory properties [47]. Table 1 summarizes the surface markers used to isolate MSCs.

Table 1
Surface markers used to isolate MSCs.

Publication	MSC markers	
	+ve	-ve
Liu et al. 2014	CD73, CD29,CD44, CD105, HLA-I	CD34, CD45, CD31, HLA-DR
Xue et al. 2013	CD73, CD90, CD105, CD106	CD19, CD45
Hu et al. 2013	Sca-1, CD29, CD44	CD117
Van der Veen et al. 2012	CD73, CD90, CD105	CD45, CD31, HLA-DR, CD14, CD79a
Oksuz et al. 2013	CD73, CD90, CD105	CD45
Zhang et el 2015	CD29,CD44, CD90, CD105	CD34, CD45
Caliari-Oliveira 2016	CD105,CD29	CD31, CD45, CD11b
Liu et al. 2008	CD44, CD90	—
Yang et al. 2014	CD29, CD44, CD90, CD106	—
Clover 2015	CD29,CD90, CD105	CD14, CD11b
Francois et al. 2007	CD105, CD73	CD45
Agay et al. 2010	CD90, CD44, CD106	CD45
Jin et al. 2016	CD90	CD45
Horton et al. 2013	Sca-1, CD29, CD44, CD106	CD45, CD11b
Zheng 2015	CD29, CD90	CD34, CD45
Xia et al. 2014	CD44, CD105	CD34
Yan et al. 2011	CD29, CD44, CD90	CD45

3.1. Mesenchymal stem cells and thermal burns

In 2003, Shumakov et al. showed for the first time that MSCs help regenerate deep burn injuries. In this study, Wistar rats were subjected to burns followed by treatment with bone-marrow derived MSCs or embryonic fibroblasts. While both treatment groups resulted in improved wound healing, as observed by formation of new vessels and granulation tissue, rats treated with MSCs healed at a quicker rate as compared to those treated with embryonic fibroblasts or control group [48]. Similar results were observed by Rasulov et al. in a rat burn injury model [49]. In another study by Fu et al., minipigs with deep partial-thickness burns were treated with MSCs along with basic fibroblast growth factor (bFGF) and they showed significantly reduced wound areas as compared to other treatment groups [50]. While MSCs had been studied for a while as agents to promote wound healing, these articles published in the early 2000′s led to a slew of research into MSCs and burns [51]. Human bone marrow derived MSCs used to treat burns in a mouse model of fore-limb burn injury revealed accelerated wound healing and neovascularization as compared to untreated controls [52] further facilitating the development of MSCs as a treatment for burn injuries.

In 2006, Mansilla et al. conducted a study where they collected blood from 15 burn patients and 15 healthy donors. They assessed the presence of cells with a MSC phenotype using flow cytometry. MSCs were identified in samples from both the burn and healthy patients, however, significantly higher circulating MSCs were seen in the burn patients which correlated to the original size and severity of the burn injury [53]. This study showed for the first time that the process of burn wound healing might include a circulatory component. Along the same lines, in a burn–injury animal model, rats were injected intramuscularly with MSCs immediately after induction of the burn. Kidney, lung and liver were collected from the rats 24 h after the injury and assessed for general histology, inflammatory cell infiltration and cell death. Rats treated with MSCs had significantly lower number of inflammatory and dead cells in these organs as compared to the control group [54].These results re-affirmed that MSCs have the ability to home in to the site of injury.

Van der Veen et al. compared MSCs isolated from burn eschar to adipose derived stem cells (ASCs) and dermal fibroblasts by looking at stem cell specific markers and their ability to be multipotent. While the markers between the three groups were similar, only MSCs and ASCs were able to differentiate into adipocytes, osteoblasts and chondrocytes. While the exact source of the MSCs in the burn eschar was unclear, their similarity to ASCs led the authors to speculate that the subcutaneous adipose layer may be a crucial source of stem cells in case of dermal injuries [55].

The role of MSCs in enhancing burn wound healing has been elucidated in a number of studies, but more recently the molecular mechanisms behind their migratory capacity have come to light as well. CXCL12/CXCR4 axis has been shown to play an important role in the migration of human umbilical cord MSC's in vitro [56]. In 2013, Hu et al. published an article on the role of CXCL12/CXCR4 in the mobilization of MSCs to the injury site. In this study, female C57BL6 mice were transplanted via tail-vein injection with MSCs derived from male green fluorescent protein (GFP) transgenic mice. 21 days post transplantation, the female mice received a burn injury on the dorsum and the injured tissue was collected at various time points after until day 28 for further analysis. Their results indicated that transplanted cells

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