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Review

Experimental stem cell therapies on burn wound: Do source, dose, timing and method matter?

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ABSTRACT

Stem cell therapy has been introduced as a new and promising modality of wound covering in recent decade. It has been used for improvement of burn wound, post burn scar and saving stasis zone of burn with good results. However, there have been some differences between the various experimental burn wound trials in stem cell source, therapeutic dose, delivery method and timing of stem cell delivery. In our study, we aimed to review stem cell biology and investigate discrepancies in animal trials of use of stem cells in burn wound account for the variation in, stem cell source, therapeutic dose, delivery method and timing of stem cell delivery.

Contents

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1. Introduction

Although by the outstanding progress in burn treatment over the past several decades higher survival rates and improved functional recovery of burn victims could be achieved, burn trauma is still one of the important cause of morbidity and mortality even in the developed countries [1,2]. According to the World Health Organization (WHO), an estimated 265,000 deaths occur each year from burn [3]. Burn wound is cause of late onset death and majority of morbidity from burn.

Stem cell therapy has been introduced as a new and promising modality of wound covering in recent decade [4]. It has been used for improvement of burn wound, post burn scar and saving stasis zone of burn with good results. However, there have been some differences between the various burn wound preclinical trials in stem cell source, therapeutic dose, delivery method and timing of stem cell delivery. In our study, we aim to review stem cell biology and investigate discrepancies in animal trials of use of stem cells in burn wound account for the variation in, stem cell source, therapeutic dose, delivery method and timing of stem cell delivery.

2. Method

We searched PubMed (1966 to march 2014) and Google scholar (all times) using the following search terms: (''stem cells'' OR ''stem cell'' OR ''progenitor cell'' OR ''progenitor cells'') AND (''burn'' OR ''burn wound'' OR ''scald''). We also manually searched citation lists and PubMed links to related citations. We included trials that met the following criteria:

- Trial reporting the effect on skin burn wound healing of stem cells in animal studies.
- Trial reporting clearly the source, dose, delivery method, timing of the stem cell application, burn model and wound size in their studies.
- Trial available in full text through our institution.

We excluded trials that met the following criteria:

- Trial reporting in human trails or case.
- Trial reporting chemical burns.
- Trial reporting radiation burn.

3. Stem cell therapy

Stem cell therapy can simply be defined as therapeutic administration of live SCs to promote tissue regeneration by replacing the dead cells and modulation of wound healing processes by secreting various growth factors via injection directly to the circulatory system, application topically to burn wound or implementation by cell containing biomaterials [5].

3.1. *Biologic basis of stem cell*

SCs are immature cells that have multi-differentiative potential which lets them to generate other cell types of the organs [6]. There are two subtypes of SC: adult and embryonic. Embryonic stem cells are derived from newly fertilized egg called blastocysts [7]. They can differentiate any kind of cell lineages and have an unlimited ability to self-renew and be named as totipotent [8]. Unlike embryonic stem cells, adult stem cells (ASCs) can be obtained almost throughout the body. ASCs have limited differentiation potential compared to embryonic stem cell and are called pluripotent [9].

Stem cells take great interest of burn care researchers because of their potential to enhance burn wound healing. SCs not only replace destructed skin cells called as transdifferentiation (fibroblast, keratinocyte) but also modulate all phases of wound healing process [10]. SCs have immunomodulatory, anti-fibrotic and proangiogenic effect on wound healing process [11–13]. Effects of SCs are related to secreted interleukins and proteins (Table 1).

Transdifferentiation of SC is site-specific. The site-specific local delivery of SCs interacts with extracellular matrix (ECM) of burn wound environment. This interaction causes donor site specific expression of cell markers on stem cell and differentiation. SCs have been shown to differentiate into different type of cells, pericyte keratinocyte and fibroblast which are essential for angiogenesis and burn wound healing [14].

Burn injury triggers immunological responses systemically and locally [15]. Main characteristics of systemic immune response are hyper activation of innate immunity and suppression of adaptive immune response that which can produce systemic inflammatory response (SIRS) and multiple organ failure (MOF) in severe cases [16]. Stem cells can serve as an immune modulator in major burn patients.

Local administration of SCs increases the production of the anti-inflammatory cytokines IL-10 and tumor necrosis factor-α (TNF-α)-stimulated protein 6 (TSG-6) which limits macrophages activation and attenuates inflammation, and eventually fibrosis by lowering transforming growth factor β1 (TGF-β1)/TGF-β3 ratio at wound. Diminished fibrosis at wound

Table 1 – MSCs release various cytokines and growth hormones.

MSC related growth factors/cytokines
Transforming growth factor-beta
Transforming growth factor-alpha
Vascular endothelial growth factor
Angiopoietin-1
Epidermal growth factor
Basic fibroblast growth factor
Platelet-derived growth factor
Keratinocyte growth factor
Insulin like-growth factor
Hepatocyte growth factor
Tumor necrosis factor
Insulin-like growth factor binding protein 7
Connective tissue growth factor
Tumor necrosis factor-α (TNF-α)-stimulated protein 6 (TSG-6)
Interleukin-6
Interleukin-8
Interleukin-1
Interleukin-4
Interleukin-10

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