García-Guillén AI, et al., J Stem Cell Res Dev 2020, 6: 037
DOI: 10.24966/SRDT-2060/100037

HSOA Journal of
Stem Cells Research, Development and Therapy

Review Article

Wharton´s Jelly Mesenchymal Stem Cell Therapy for Skin Wound Healing

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Abstract

The management of chronic wounds still remains an important unsolved problem in clinical practice. Different therapeutic approaches, including regenerative medicine or tissue engineering strategies, have been used to ameliorate this pathology to achieve skin regeneration. Mesenchymal stem cells represent a potential therapeutic option for chronic wounds due to their differentiation, proliferation, and immunomodulatory properties. Among them, Wharton's jelly mesenchymal stem cells from the umbilical cord are a type of extraembryonic stem cells that have been proven to be very effective for treating chronic wounds. These cells possess some advantages when compared to adult mesenchymal stem cells such as higher proliferation rate, multipotency, and low immunogenicity. They act as potent immunomodulators during the inflammation phase of wound healing and are also involved in replacing the damaged skin tissue. In this review we will discuss the findings obtained in different preclinical and clinical studies performed with Wharton´s jelly mesenchymal stem cells systemically administered, implanted on a biocompatible scaffold, or using mesenchymal stem cell-derived extracellular vesicles or their conditioned medium as possible treatments for chronic wounds

Keywords: Chronic wounds; Mesenchymal stem cells; Wharton´s jelly; Wound healing

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Citation: García-Guillén AI, Millán-Rivero JE, Martínez CM, Moraleda JM, García-Bernal D (2020) Wharton´s Jelly Mesenchymal Stem Cell Therapy for Skin Wound Healing. J Stem Cell Res Dev Ther 6: 037.

Received: May 11, 2020; **Accepted:** May 20, 2020; **Published:** May 28, 2020

Introduction

The skin is one of the most important protective organs in humans. When the skin is injured a wound healing process starts in order to regenerate the normal structure of skin and adnexal appendages. When the damage is too extensive or there is an alteration of the regenerative process, the healing process can progress to develop chronic wounds or leading the induction of a fibrotic response which induce scar formation and loss of skin adnexal, a major problem in some kind of pathologies (i.e., extensive burns).

Chronic wound healing represents a major public health issue [1], especially when patients have other underlying diseases. Some chronic wound treatments pursue to control the causative factors, but those based on the use of skin substitutes have been suggested as the most effective choices [2].

Actually, stem cell-based therapy is an effective alternative to treat skin diseases because of their regenerative potential [3-6]. The ability of Mesenchymal Stem Cells (MSCs) to mediate tissue regeneration through different mechanisms such as transdifferentiation into multiple skin cell types, mesenchymal-epithelial transition, direct cell-to-cell contacts, production of extracellular vesicles, and secretion of a large number of soluble molecules (i.e., chemokines, cytokines, growth factors, and extracellular matrix components) make them useful in the treatment of many pathological skin conditions [7-12]. MSCs can be isolated from different sources, both adult and fetal tissues. The fetal MSCs come from tissues such as the placenta, amniotic membrane, amniotic fluid and Wharton´s jelly from the umbilical cord stroma (Wj-MSCs) [13]. Among them, Wj-MSCs present some advantages compared to adult MSCs because they retain characteristics of embryonic stem cells such as higher expression of pluripotency markers including Nanog, Oct4, Sox2 and c-Kit [14]. The use of these fetal MSCs does not have ethical concerns because they come from extraembryonic tissues that are discarded after birth. In addition, they are obtained without using invasive procedures, and they present a greater multipotentiality, better proliferative rate and lower capacity to form teratomas upon transplantation as compared to adult bone marrow or adipose tissue-derived MSCs [15-21]. Furthermore, some fetal MSCs, mainly the Wj-MSCs, have demonstrated less immunogenicity and better immunomodulatory properties than their adult's counterparts by secreting a significant number of anti-inflammatory molecules such as TGFβ, IDO, IL-10, PGE_2 and TSG-6 [22,23]. Many studies, most of them preclinical, show the advantages of the employment of adult and fetal MSCs for the treatment of several diseases; however, more mechanistic studies are needed to translate this therapeutic tool to a clinical phase [8,19,24-28].

In this review, we will summarize some of the most relevant findings obtained in this research area.

Wound Healing

The skin is the largest structure of the organism and acts as a barrier, regulating water and electrolyte balance, and protecting the organism from microbes and other harmful external agents [29]. When the integrity of the skin is disrupted, a cutaneous wound appears [1]. The wound healing is a complex process and consists of three different sequential and overlapping stages: the inflammatory phase, proliferative phase (i.e., neoangiogenesis, granulation tissue formation, and re-epithelization), and the extracellular matrix remodeling phase. In all these stages, different soluble mediators and blood cells, extracellular matrix components, and parenchyma cells are involved [1,30].

This progression may be sometimes disrupted due to the presence of underlying comorbidities or other secondary factors such as neuropathies, vasculitis, or extensive burns. All of them can cause the loss or delay of the restitution ad integrum progression of the skin and induce the appearance of a chronic, non-healing wound [1,31], and keloids or scars instead of healthy skin [32]. Additionally, this situation may get worse with the appearance of opportunistic infections which aggravate the progression of these pathologies [33].

To date, there are only partial remedies for this condition, and it is an unmet clinical need to develop new therapeutic strategies to avoid a state of chronic, non-healing wounds and to promote proper skin re-epithelization.

Mesenchymal Stem Cells

MSCs are defined as undifferentiated cells with self-renew potency and the capacity to differentiate into various cell types [34], following the minimum criteria established by the International Society for Cellular Therapy [35]: 1) MSCs must possess plastic adherence in culture conditions; 2) 95% of the cells must express the markers CD105 (endoglin), CD73 (ecto-5'-nucleotidase) and CD90 (Thy1), and no more than 2% of the cells must be positive for CD45 (pan-leukocyte marker), CD34 (hematopoietic and endothelial progenitor cells marker), CD14 or CD11b (expressed on macrophages and monocytes), CD79a or CD19 (B cells markers) and HLA class II; and 3) they must be able to differentiate in culture into osteoblasts, adipocytes, and chondroblasts under specific differentiating conditions.

MSCs possess potent immunomodulatory properties since they can inhibit the proliferation and function of different immune cells such as $CD4^+$ and $CD8^+$ T lymphocytes, B lymphocytes, Dendritic Cells (DC), or natural killer (NK) cells [36-40]; and they also can reduce immune cell cytokine secretion [41]. MSCs are involved in the macrophages phenotype switch (from pro-inflammatory M1 phenotype to an antiinflammatory M2 phenotype) [42], and stimulate T lymphocytes to change into an anti-inflammatory Th2 phenotype [43]. Furthermore, MSCs can induce immunomodulatory effects by secretion of various anti-inflammatory cytokines such as TGFβ, IDO, PGE_2, nitric oxide, IL-6, semaphorin-3A, or galectins Gal-1 and Gal-9 [44-50].

A variety of studies have demonstrated that MSCs migrate to inflamed tissues following signals such as growth factors, cytokines, and chemokines. Also MSCs display paracrine mechanisms of action in the tissues, and some of their beneficial effects seem to be mediated by the secretion of trophic factors (e.g., VEGF, angiopoietin, FGF, CNTF, GDNF, HGF and IGF) [51]. Secreted bioactive factors can stimulate the regeneration and repair of injured tissues by inducing migration and proliferation of circulating stem cells and other resident tissue-specific cells [52], can present immunomodulatory effects in the site of action and/or present anti-apoptotic and pro-angiogenic capacity [53]. Importantly, some studies have indicated that in wound healing MSCs increase the response of many cell types in the wound area including epithelial cells, endothelial cells, keratinocytes and fibroblasts as a result of their trophic-mediated effects [54].

Wound Healing and Wj-MSC Treatment

The role of MSCs in the treatment of chronic wound and non-healing ulcers has been demonstrated in both preclinical and clinical studies as a strategy to repair and restore the function of the skin [2,3,55-57]. Treatments with MSCs have resulted in clinical improvement of chronic wounds in some patients and mice, accelerating the time of reepithelization of the wound without scarring [58,59].

In some studies, MSCs were administered intravenously or delivered on a biocompatible scaffold, showing no signs of immune rejection, skin retraction, or scar formation [59-64]. The delivery of the MSCs on a biological scaffold seems to have some benefits compared to systemic administration or locally implanted around the wound [65,66], since these routes of administration limit the engraftment and the survival of the cells. The use of a scaffold provides cell support and chemical and structural signals that help MSCs in their regenerative or reparative role in the wound [67]. It was demonstrated that the employment of Wj-MSCs in combination with decellularized amniotic membrane as scaffold showed better results than the direct injection of Wj-MSCs, with less formation of scars, and better regeneration of the skin [17,68]. Other studies combined the use of Wj-MSCs-laden collagen scaffolds with hyperbaric oxygen therapy resulting in improved wound healing progression in diabetic mice [69]. Recent work by our group showed that the administration of Wj-MSCs on a silk fibroin scaffold on the wound beds promoted a decrease of the inflammatory infiltrates, diminished fibrotic progression, improved neoangiogenesis, and accelerated skin regeneration [60].

Apart from direct intercellular interactions within the tissues, MSCs can exert part of their pivotal trophic and immunomodulatory function by secretion of a large number of soluble molecules. Thus, some researchers have used the Wj-MSC-conditioned medium, which contains all of these factors, for the prevention and treatment of skin ulcers. Some studies showed that the use of this conditioned medium was able to accelerate wound closure and enhance the wound healing process [70,71].

On the other hand, Extracellular Vesicles (EVs) (i.e., microvesicles, exosomes, and apoptotic bodies) are lipid bilayer particles containing mRNAs, microRNAs, lipids and proteins released by cells that can interact with neighbouring cells and influence their behaviour [72]. The potential role of the MSC-derived Extracellular Vesicles (EVs) in the wound healing process has also been investigated. Preliminary results showed that EVs have also displayed angiogenic, immunomodulatory, and immunosuppressive activity. These important properties make them a useful therapeutic approach, also in wound healing [12]. Some recent findings showed that Wj-derived EVs were also able to stimulate the wound healing process [73,74]. Wj-MSC-mediated effects on wound healing, or by their related cellular products (i.e., conditioned medium or EVs) are summarized in table 1.

Cell-based therapy	Effects on wound healing	References
Only Wj-MSCs	Accelerate formation of the epithelial sheet	[60]
	Increase wound contraction and improve epithelization, neovascularization and collagen characteristics	[61]
	Accelerate wound closure by enhancing collagen deposition and angiogenesis	[62]
	Stimulate higher re-epithelization and newly formed capillary vessels in the skin wounds	[64]
Wj-MSCs combined with biocompatible scaffolds	Reduce scar formation with hair growth and improve biomechanical properties of regenerated skin	[17]
	Induce formation of well-organized and vascularized granulation tissue, enhance re-epithelization, and reduce formation of fibrotic scar tissue	[60]
	Induced a faster healing and a higher number of blood vessels in the wound	[63]
	Decrease wound healing time and wound size in chronic diabetic wounds	[68]
	Accelerate healing effect in chronic diabetic wounds	[69]
Wj-MSCs-derived conditioned medium	Enhances normal skin fibroblast proliferation and migration, and stimulate wound healing	[66]
	Regenerates sebaceous glands and angiogenesis, without scar formation	[70]
	Enhances re-epithelization, increases angiogenesis and stimulates sebaceous gland and hair follicle formation	[71]
Wj-MSCs-derived extracellular vesicles	Produce higher collagen deposition and stimulate wound healing	[68]
	Attenuated full-thickness skin wounding by enhancing epidermal re-epithelialization and dermal angiogenesis	[74]

Table 1: Summary of therapeutic effects of Wj-MSCs in skin wound healing.

Due to the large number of preclinical studies carried out to study the therapeutic effect of Wj-MSCs on wound healing, and the mostly beneficial results obtained, different clinical trials have been recently implemented in order to study the safety and therapeutic efficacy of Wj-MSCs for the treatment of acute burns (ClinicalTrials.gov Identifiers: NCT01443689 and NCT03237442), large area skin lesions (NCT02669199 and NCT02672280), and chronic diabetic foot ulcers (NCT04104451).

Conclusion

The choice of Wj-MSCs as the therapeutic option for wound healing has been demonstrated as a suitable cell therapy alternative to stimulate skin repair. There are many experimental studies showing the anti-inflammatory, immunomodulatory and regenerative/reparative properties of Wj-MSCs. Although more preclinical and clinical research is necessary to optimize the route of administration, dose, or the best way to deliver the cells into the wound, with or without scaffold, Wj-MSC and their related cellular products (i.e., conditioned medium or EVs) seem to be a really compelling strategy for the treatment of ulcers and chronic, non-healing wounds in the clinical practice.

Funding

This work was supported by Instituto de Salud Carlos III (ISCIII) and the Spanish Network of Cell Therapy (TerCel), RETICS subprogram of the I+D+I 2013-2016 Spanish National Plan, project "RD16/0011/0001" funded by ISCIII and co-founded by European Regional Development Funds "una manera de hacer Europa".

Competing Interest

The authors declare that they have no competing interests.

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