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Menendez-Menendez Yolanda\*, Alvarez-Viejo Maria\*, Ferrero-Gutierrez Amaia, Perez-Basterrechea Marcos, Perez Lopez Silvia, Escudero Dolores and Otero-Hernandez Jesús

Transplant and Cell Therapy Unit, Hospital Universitario Central de Asturias, Oviedo, Spain

### Abstract

Normal wound healing is a dynamic and complex process involving coordinated interactions between diverse immunological and biological systems. If a wound does not heal in an orderly and timely sequence, or if the healing process does not result in structural integrity, then the wound is considered chronic. It is easy to define a chronic wound, but finding a solution is a complicated matter. Conventional treatment of chronic wounds does not seem to work in several cases, so it is necessary to develop different strategies. Cell therapy constitutes a new alternative to classic methods of wound healing. In this bibliographic review, we present some of the data published up to date on the use of adipose tissue- and bone-marrow-derived Mesenchymal stem cells in patients with chronic wounds caused by several pathologies. Even though cell therapy is a relatively new tool, several studies prove these types of cells may be used safely, and they have demonstrated their efficacy in healing wounds in several cases.

**Keywords:** Wound healing; Stem Cell therapy; Mesenchymal Stem Cells

### Introduction

Skin is the outermost tissue of the body and the largest organ in terms of both weight and surface area. The skin features a very complex structure that consists of many components and adnexa, including hair follicles, sebaceous glands, and sweat glands. The main function of skin is to act as a barrier against environmental aggressions. The skin is formed by two anatomically, functionally, and developmentally distinct tissues: epidermis and dermis. The epidermis is the outermost layer of the skin, mostly composed of a particular kind of epithelial cells known as keratinocytes. The dermis is the living layer that acts as substrate and support network for the epidermis. The essential dermal cell type is the fibroblast, which is responsible for the production and maintenance of the structural elements of the skin [1]. Any disruption of normal anatomic structure with consecutive loss of function can be described as a wound [2]. In everyday pathology, wounds remain a challenging clinical problem, with early and late complications presenting a frequent cause of morbidity and mortality [3,4]. Normal wound healing is a dynamic and complex process involving coordinated interactions between diverse immunological and biological systems. It involves a cascade of carefully and precisely regulated steps and events that correlate with the appearance of various cell types in the wound bed throughout the distinct phases of the healing process [5-8]. The classical model of wound healing is divided into three sequential phases which overlap in the time and space: inflammation, proliferation, and maturation and remodeling (Figure 1).

### Wound Repair Process

#### Inflammation

Just before the inflammation phase is initiated, the clotting cascade takes place. Tissue injury causes the disruption of blood vessels and extravasation of blood constituents. The blood clot re-establishes hemostasis and provides a provisional Extracellular Matrix (ECM) for cell migration [9]. Migratory cells use this matrix as a bridge to crawl across and platelets adhere to it and secrete factors such as Platelet-Derived Growth Factor (PDGF), Endothelial Growth Factor (EGF) transforming growth factor (TGF- $\beta$ ), Fibroblast Growth Factor (FGF), and Vascular Endothelial Growth Factor (VEGF) [10,11]. These factors

act as wound healing mediators. PDGF attracts neutrophils to the wound site to remove contaminating bacteria, foreign particles, and damaged tissue [12] and their main function is to prevent infections [6]. With the help of TGF- $\beta$  monocytes are attracted to the wound site and converted into macrophages. These cells have a longer life than neutrophils and play an important role in augmenting the inflammatory response and tissue debridement. Macrophages provide an abundant reservoir of potent tissue growth factors (TGF- $\beta$ , EGF, PDGF, and FGF) and proinflammatory cytokines (IL-1 and IL-6) which activate keratinocytes, fibroblasts, and endothelial cells [6-8,13-16].

Therefore, inflammation is an essential phase in the healing process because it plays an important role in fighting against infection. Once the inflammation decreases due to the action of neutrophils and macrophage, their number is reduced and, as a result, the proliferation phase is initiated.

#### Proliferation #2

This phase starts few hours after the injury, and it is characterized by fibroblast migration, deposition of new ECM and granulation tissue formation. Fibroblasts migrate into the wound in response to TGF- $\beta$  and PDGF; there, they proliferate abundantly and produce matrix proteins as hyaluronan, fibronectin, elastin, proteoglycans, and type I and type III procollagen [15-17]. Collagens play a key role in wound healing since act as a base for the intracellular matrix formation within

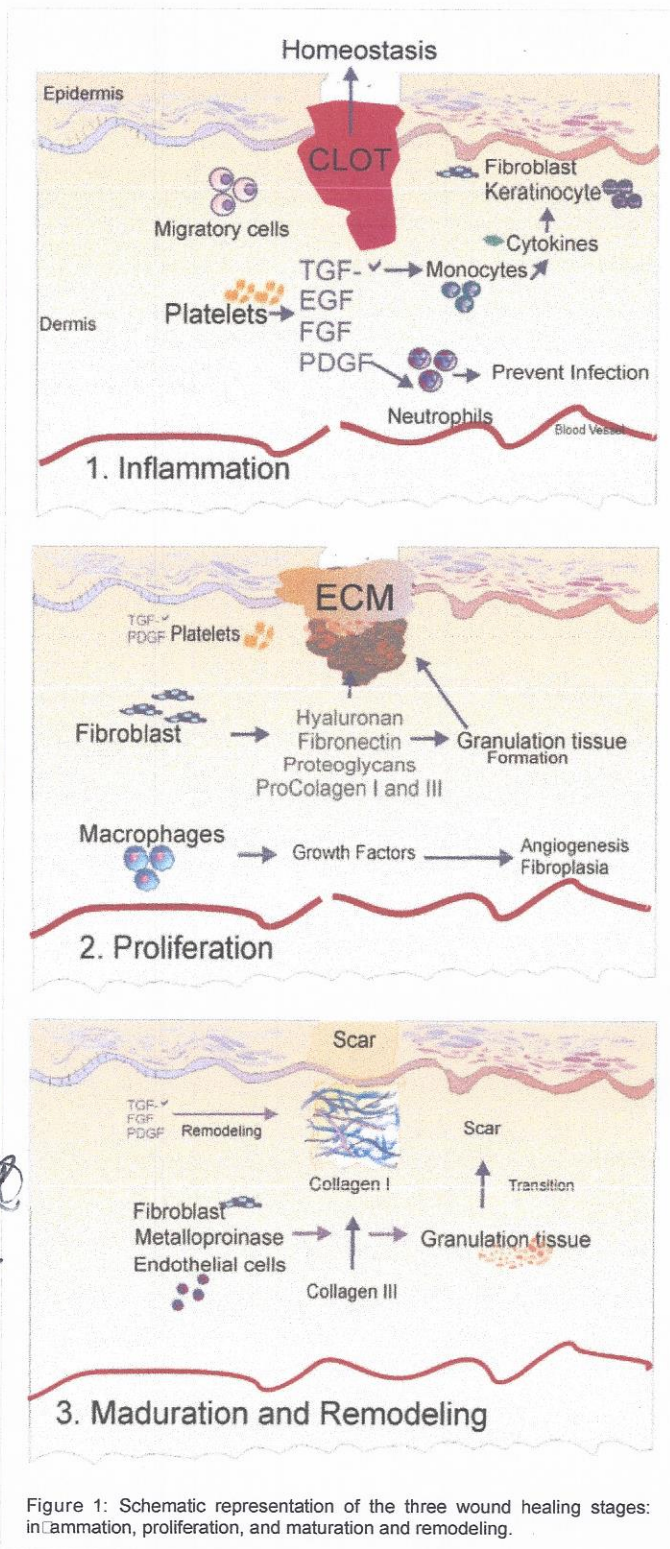
\*Corresponding authors: Yolanda Menendez-Menendez, Laboratorio de Trasplantes y Terapia Celular Edificio Polivalente A, 1 planta, Hospital Universitario Central de Asturias, 33006 Oviedo, Asturias, Spain, Tel: 00 34 985109451; E-mail: [yolanda.menendez@sespa.princast.es](mailto:yolanda.menendez@sespa.princast.es)

Maria Alvarez-Viejo, Laboratorio de Trasplantes y Terapia Celular Edificio Polivalente A, 1 planta, Hospital Universitario Central de Asturias, 33006 Oviedo, Asturias, Spain, Tel: 00 34 985109451; E-mail: [maria.alvarezv@sespa.princast.es](mailto:maria.alvarezv@sespa.princast.es)

Received December 31, 2013; Accepted January 23, 2014; Published January 25, 2014

Citation: Yolanda MM, Maria AV, Amaia FG, Marcos PB, Silvia PL, et al. (2014) Adult Stem Cell Therapy in Chronic Wound Healing. J Stem Cell Res Ther 4: 162. doi:10.4172/2157-7633.1000162

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the wound. Unwounded dermis contains 80% type I and 20% type III collagen, whereas wound granulation tissue expresses 40% type III collagen [18].

At the end of the first week, an abundant accumulation of ECM supports cell migration, which is essential for the repair process [15,18,19]. Moreover, macrophages provide a continuing source of

growth factors necessary to stimulate angiogenesis and fibroplasia. Fibroblasts produce the new ECM necessary to support cell in growth and blood vessels carry oxygen and nutrients necessary to sustain cell metabolism [9]. The structural molecules of the newly formed ECM contribute to the formation of granulation tissue by providing a scaffold or conduit for cell migration [20].

The process of angiogenesis occurs concurrently with fibroblast proliferation when endothelial cells migrate to the area of the wound. These endothelial cells are stimulated by FGF to proliferate and release angiogenic growth factors, such as VEGF, which are responsible for the initiation of this process [21]. Under hypoxic conditions, endothelial cells from uninjured blood vessels are chemotactically attracted to the wound crawling through the ECM in order to form a network of new capillaries [8,17,22]. Once the necessary amount of oxygen and nutrients are achieved at the wound site, angiogenesis ceases and blood vessels that are no longer needed die by apoptosis [23]. Re-epithelialization of wounds begins within hours after injury. The release of growth factors stimulates epithelial cell proliferation and migration through the new tissue. During re-epithelialization, basement membrane proteins reappear in an ordered sequence starting from the edges of the wound. The last step in this phase before maturation is wound contraction, which involves a complex and delicately orchestrated interaction between cells, the ECM, and cytokines. During the second week, a proportion of the wound fibroblasts transforms into myofibroblasts, which express  $\alpha$ -smooth muscle actin and resemble smooth muscle cells in their capacity to generate strong contractile forces [24,25]. The actin in myofibroblasts contracts and, as a result, wound edges are pulled together. Fibroblasts put down collagen to reinforce the wound as myofibroblasts contract [26].

### Maturation and remodeling

The duration of the maturation phase depends on a number of variables including the patient's genetic makeup, age, location of the wound, type of injury, and duration of inflammation. During the maturation phase, type III collagen (which is prevalent during proliferation) becomes gradually degraded and replaced by type I collagen. Collagen remodeling is necessary for the transition from granulation tissue to scar and it relies on the continued synthesis and degradation of collagen. When the balance between collagen synthesis and degradation is achieved, wound maturation begins [26].

The degradation of collagen in the wound is controlled by several proteolytic enzymes called matrix metalloproteinases (which are secreted by macrophages), epidermal cells, endothelial cells, and fibroblasts [27]. During tissue remodeling, PDGF helps to break down old collagen by up-regulating matrix metalloproteinases [28]. Other growth factors which play a role in the remodeling process are TGF- $\beta$  and FGF [29].

With time, the growth of capillaries stops, blood flow to the area declines and metabolic activity at the wound site decreases [29-31], resulting in a fully matured scar with a decreased number of cells and blood vessels and a high tensile strength [31,32].

In summary, successful wound healing depends on the timely and optimal functioning of many diverse processes, cell types, molecular mediators, and structural elements [18]. The outcome of uncomplicated healing is a fine scar with little fibrosis. If a wound does not heal in an orderly or timely sequence, or if the healing process does not result in structural integrity, then the wound is considered chronic [26]. Although, it is easy to define a chronic wound, finding a solution is complicated. Non-healing wounds are stuck in a constant

in inflammatory state because they fail to progress through the normal stages of wound healing [33].

Traditional therapies for the treatment of chronic wounds include debridement of necrotic tissue, minimization of bacterial load, pressure offloading, negative-pressure therapy, biological dressing, skin grafting, and reconstructive tissue flaps [34]. Despite the most recent advances in wound management, up to 50% of chronic wounds still fail to heal [35]. Conventional treatment of chronic wounds does not seem to work in several cases so it is necessary to develop other strategies. Understanding the mechanisms involved in wound healing is of utmost importance for the development of modern wound care. Following this trend, the last decade has seen an increased interest in the use of growth factors. However, on their own, growth factors have proven to be not particularly effective in wound healing [33]. Currently, researchers are focusing their efforts on cell therapy for the treatment of a number of pathologies, including wound healing [36-38].

### Cell therapy

Cell therapy can be defined as a set of strategies which use live cells with therapeutic purposes. The aim of such therapy is to repair, replace or restore the biological function of a damaged tissue or organ. Thus, the use of stem cells in cell therapy is being studied in several areas of medicine. Stem cells are undifferentiated cells capable of auto-renewing and differentiating into progenitor or precursor cells of one or several specific cell types [39,40]. Adult stem cells are the most used in regenerative medicine; they are relatively easy to obtain through in vitro culturing and their use does not raise any ethical concerns as in the case of embryonic cells, although the proliferative ability and differentiation potential of adult stem cells are not as high. Adult stem cells can be collected from almost any tissue; nevertheless, Bone Marrow (BM) is possibly the most common source [41]. Several studies point out that cells obtained from the BM contribute to the regeneration or repair of many tissues, including the myocardium, bone, tendons, cartilage, and skin [42].

### Clinical applications of bone-marrow-derived mesenchymal stem cells (BM-MSCs) in wound healing

The BM is composed of a heterogeneous cell population, including fibroblasts, adipocytes and Mononuclear Cells (MNCs) [43]. BM-MNCs cells include Hematopoietic Stem Cells (HSCs), mesenchymal Stem Cells (MSCs), endothelial progenitors, and cellular precursors [44]. HSCs are responsible for all blood cell lines (erythrocytes, platelets and white cells). MSCs are a group of stem cells originated at the mesodermal germinal layer [45,46] and they are found in very small quantities in the bone marrow (about 0.001-0.01% of mononuclear cells) [47]. In addition, these MSCs can differentiate into osteoblasts, adipocytes and chondrocytes [48].

Once a wound occurs, both HSCs and MSCs mobilize from the BM to the wound site, where they manage and regulate cell proliferation and migration during the inflammation phase of cicatrization [9]. Both cell types feature a high degree of plasticity, and are able to contribute with cell progenitors for hematopoietic and non-hematopoietic tissues [49-51]. Furthermore, recent studies reveal that BM cells, most notably MSCs, play a major role in skin regeneration [52-54] and vascularization [55].

MSCs influence the wound's ability to progress beyond the inflammatory phase and not regress to a chronic wound state. The mechanism of action of these cells is that they directly attenuate

inflammatory response so that they decrease secretion of the proinflammatory cytokines while increasing the production of anti-inflammatory cytokines [56]. These anti-inflammatory properties make them particularly beneficial to chronic wounds by advancing the wound past a chronic inflammatory state into the next stage of healing. Nowadays, it is recognized that MSCs have antimicrobial activity [57]. Furthermore, MSCs secrete several growth factors so these cells promote dermal fibroblast proliferation, angiogenesis and collagen deposition [58].

Diverse mechanisms have been proposed to explain the regenerative properties of MSCs. One would be evidence of MSCs migrating into the wound site and differentiate into cells with the phenotype and function required to repair the damaged tissue [41,59]. This theory constitutes a remarkable foundation upon which cellular theory stands. Other authors in the field favor the idea of a paracrine effect to explain the promising outcomes these therapies are yielding [34,58,60]. These remarkable results obtained by our own group (not yet published) are in agreement with the relevance of the paracrine effect of MSCs, at least when it comes to wound healing.

Several studies have already been published which demonstrate their clinical usefulness (Table 1). Badivas et al. [61] mention that the direct application of autologous Bone Marrow-derived mesenchymal Stem Cells (BM-MSCs) in patients with chronic wounds can achieve the closure of the wound and tissue reconstruction. In this study, they observed that the direct injection of fresh whole BM into the edges of the wound followed by topical application of cultured MSCs managed to completely close chronic ulcers in 3 patients where traditional therapy had failed. Biopsies gathered from these healed wounds revealed the presence of mature and immature inflammatory cells, as well as an increase in vascularization and dermal thickness [61]. In 2009, Dash et al. [62] published the results of a test carried out in 24 patients with ulcers in the lower extremities due to diabetes or vasculitis. These patients received autologous BS-MSCs intramuscularly at the edges of the wound. Twelve weeks after transplantation, in the group treated with MSCs, ulcer size decreased by 73% whereas in the control group the reduction was of just 23%. Biopsy microsection of implanted tissues showed development of dermal cells (mainly fibroblasts), including mature and immature inflammatory cells. This study highlights that autologous implantation of BM-MSCs in non-healing ulcers accelerates the healing process and improves clinical parameters significantly [62]. The clinical benefits of systemic administration of MSCs were also observed in a study carried out by Lu et al. [63] performed on diabetic patients with critical lower limb ischemia. Patients were injected with autologous BM-MSCs or bone marrow mononuclear cells (BM-MNCs) in one of their legs. In the contralateral leg they were injected with saline serum as control. The results at 24 weeks after transplantation showed an improvement in pain and a significant increase of the healing rate of the ulcer. BM-MSC therapy may be better tolerated and more effective than BM-MNCs for increasing lower limb perfusion and promoting foot ulcer healing in diabetic patients with critical limb ischemia [63]. However, in other types of wounds, such as pressure ulcers, BM-MNC administration produced beneficial results for wound closure.

Our group performed a clinical trial on 22 patients with spinal cord injury and grade IV pressure ulcers where conventional treatments had failed. Autologous BM-MNCs were injected topically. In 19 patients (86.36%), the pressure ulcers treated with BM-MNCs were fully healed after a mean time of 21 days. During a mean follow-up of 19 months, none of the resolved ulcers recurred. Our data indicate that cell

Wound type	Cell type	Delivery system	Outcome	Reference
Chronic wounds (n=3)	BM-MNC BM-MSc	BM-MNC, injected into wound BM-MSc, topical application	All wounds healed. Increased inflammatory response and angiogenesis	Badivas and Falanga [61]
Acute surgical wounds (n=4) and Chronic lower limb ischemia (n=6)	BM-MSc	Topical delivery using fibrin spray	Reduction in chronic wound size. BM-MSc engraftment in blood vessels	Falanga et al. [66]
Intractable dermatopathies (n=20)	BM-MSc	BM-MScs on collagen Sponges used as wound dressings	Wound healed in 18 of 20 patients	Yoshikawa et al. [67]
Nonhealing ulcer or Lower extremities (n=24)	BM-MSc	Intramuscular injection and topical application	Improvement in pain-free walking. Ulcer size decreased by 72% in BM-MSc treated group	Dash et al. [62]
Diabetic critical limb ischemia with foot ulcers (n=41)	BM-MNC BM-MSc	Intramuscular injection	Improvement in pain-free walking time and fastest rate of healing in treated group	Lu et al. [63]
Pressure ulcers (n=22)	BM-MNC	Injection into the edges of the wound	Wound healed in 19 of 22 patients	Sarasua et al. [64]
Critical limb ischemia	ASC	Multiple intramuscular injection	Clinical improvement of 66.7%	Lee et al. [74]
Effects of radiation	ASC	Repeated transplants, irradiated areas	Significant clinical improvements. Most patients exhibited no rejection or adverse events, but the fistula remained open	Riggotti et al. [77]
Rectovaginal fistula	ASC, heterologous First case		Effective at inducing healing	Garcia-Olmo et al. [75]
Perianal fistula	ASC	Fibrin glue		Garcia-Olmo et al. [76]

Table 1: Summary of the use of cell therapy in wound healing.

therapy using autologous BM-MNCs could be an option to treat type IV pressure ulcers in patients with spinal cord injury, avoiding major surgical intervention [64].

All these results suggest that cell therapy with BM-MSCs or BM-MNCs applied either topically or systemically yields clinical benefits for the treatment of chronic wounds. Furthermore, some remarkable results can be achieved in the treatment of chronic wounds by combining BM-MSCs with tissular engineering, i.e. application of cells on an adequate support/scaffold which ensures cells remain viable and may efficiently migrate in the wound bed [65]. An example would be a trial performed on 5 patients with acute or chronic wounds which were treated with autologous BM-MSCs applied with a fibrin spray as cell delivery system. The biopsies of these wounds revealed that the MSCs migrated to the wound and stimulated elastin expression, thus improving the structure of the ECM. This trial proved that the use of cultured MSCs is a safe therapy for wound treatment with no adverse events [66]. In another similar study a collagen sponge was used to administer the autologous BM-MSCs to 20 patients with chronic wounds. The results proved that the collagen compound enhanced wound healing in 18 of 20 patients and helped tissular regeneration [67].

#### Clinical applications of adipose-tissue-derived MSCs (ASCs) in wound healing

As previously discussed, MSCs can be harvested from different tissues [68]. Some of these alternative sources are very promising, because bone marrow harvesting is rather invasive and painful. In 2001, Zuk et al. [69] identified and characterized adipose tissue-derived MSCs (ASCs) from lipoaspirates [69]. Adipose tissue appears to be a remarkable source of MSCs, since ASCs are easily isolated from a section of whole fat (biopsy) or lipoaspirate, which means a less aggressive and painful procedure is necessary to obtain the cells. BM-MSCs reside in the BM stroma, but only a very small percentage of the nucleated cells which compose the BM are actually MSCs, whereas the amount of ASCs is approximately 500-fold greater when isolated from an equivalent amount of adipose tissue [41]. ASCs are relatively homogeneous based on their surface immunophenotype, displaying similar, but not identical, surface antigens to those found in BM-MSCs [70]. In vitro, ASCs can differentiate along multiple pathways, including

adipogenic, chondrogenic, adipogenic, and myogenic, among others [60]. Furthermore, they secrete an array of cytokines and growth factors similar (but again not identical) to those released by BM-MSCs [71]. All these features make ASCs an interesting alternative for cell therapy, and they are currently being used for a variety of clinical treatments [72,73], including wound healing. In 2012, Lee et al. [74], published a study in which they applied several intramuscular ASC injections in 15 critical limb ischemia patients. The authors observed clinical improvement in 66.7% of cases, with patients exhibiting a significant decrease in the pain rating scale and improved claudication walking distance. This study concluded that multiple intramuscular ASC injections may be a safe alternative to achieve therapeutic angiogenesis in patients with critical limb ischemia who are refractory to other treatment modalities [74].

In 2008, Garcia-Olmo et al. [75] employed ASCs for treating complex perianal fistula. Cells were obtained from a liposuction procedure and a subsequent expansion process. They were then administered according to a strict protocol which involved infusion of the cells into the target lesion along with fibrin glue. The results obtained comparing ASCs plus fibrin glue application vs. fibrin glue alone reveal ASCs were effective at inducing healing in complex perianal fistulas. In addition, long-term follow-up reaffirmed the very good safety profile of the treatment. Nevertheless, a low proportion of the stem cell-treated patients with closure after the procedure remained free of recurrence after more than 3 years of follow-up [75]. Garcia-Olmo's group published in 2010 the first instance of an application of heterologous ASCs in a rectovaginal fistula. According to the authors, this would be the first time heterologous ASCs were used in humans. No rejections or adverse events were observed, although the fistula remained open. Nevertheless, a great improvement was appreciated. The study concluded that ASC application is safe and adverse effects were not detected, at least in the fistulizing Crohn's disease environment [76].

On the other hand, ASCs were used by Riggotti et al. [77] to treat side effects of radiation treatment in patients with severe symptoms or irreversible function damage (LENT-SOMA scale grades 3 and 4). Purified autologous lipoaspirates were applied to irradiated areas. Ultrastructural tissue regeneration with neovessel formation, as well

as significant clinical improvement was observed in most of treated patients [77].

## Conclusion

Wound repair constitutes a complex process where different cell types and molecules act in an orchestrating way. Any disruption could lead to healing failure, with consequent chronic wound or ulcer development. Current therapies including surgery, dressings, topical negative pressure or skin substitutes among others are not always effective. Cell therapy, specially using adult stem cells, has emerged as a promising tool in those cases where conventional treatments failed. Among adult stem cells, MSCs, both from bone marrow or adipose tissue, have shown to be useful in several clinical approaches. Regardless of the interesting results showed in this review, the use of MSCs for cell therapy requires in vitro extensive expansion, increasing time, budget, and contamination risks. Furthermore, because the precise mechanism which allows this effect is not completely understood, more studies, focused on the role of adult stem cells in wound healing are needed in order to address this question and improve the efficacy of this therapy.

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