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MODERN STRATEGIES FOR THE PREVENTION AND TREATMENT OF POST-BURN SCARS (A SYSTEMATIC REVIEW)

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Despite advancements in modern reconstructive surgery, preventing the formation of thick scar tissue that impairs limb function or causes cosmetic defects remains a critical challenge. Equally important is the effective correction of existing scars to optimize both functional and aesthetic outcomes. Severe functional impairment of the upper limbs can result in disability. A combination of surgical and nonsurgical interventions is essential to enhance functionality while minimizing the risk of scar recurrence. Platelet-rich plasma injections, stem cell therapy, adipose tissue transplantation, and a combination of negative pressure wound therapy (NPWT) with traditional flap reconstruction and other transplantation methods are gaining popularity in modern reconstructive surgery. NPWT plays a crucial role in preparing the wound bed for subsequent tissue reconstruction and serves as an effective alternative to traditional dressings. The vacuum created over the wound after closure with a skin autograft helps prevent inflammation at the graft base, reduces excessive granulation tissue formation, and minimizes the risk of rough scar development in the long term. The mechanisms of formation of hypertrophic scar and keloids have not yet been completely understood. However, research indicates that bone marrow-derived cells, including fibrocytes and keratinocyte-like cells, contribute to the inflammatory cell infiltrate during wound healing, and can play a role in cutaneous fibrosis, especially in cases of impaired healing. Several pathophysiological and biochemical processes involved in the repair of extensive and deep wounds have been established. Additionally, the role of keratinocytes within hair follicle bulbs in promoting epithelialization of post-burn wound surfaces, particularly in areas with preserved skin appendages, has been recognized. Studies indicate that stromal-vascular fraction of adipose tissue plays a positive role in various stages of wound healing, including keloid and hypertrophic scar formation. Adipose-derived stem cells can be used in combination with hydrogel. The hydrogel base of dressings maintains a moist environment in both burn wounds and wound surfaces following tangential or radical excision of burn scab. This promotes faster wound healing, reduces the risk of scar hyperplasia, and enhances the sustained release and effectiveness of medications applied to the hydrogel base. Prompt surgical intervention, including early excision and grafting, along with modern treatment methods in the early postoperative period for deep burns, can significantly reduce the risk of hypertrophic and keloid scar formation.

Keywords: burns, scars, cell technologies, biomedical cell products.

INTRODUCTION

Advancements in surgical techniques, resuscitation protocols, and the overall management of deep burns have led to significant improvements in survival rate of patients with acute thermal injuries. However, it should be emphasized that research into the long-term functional outcomes for burn survivors remains an ongoing area of study.

Patients with severe post-burn scarring, particularly in the upper extremities, often experience a substantial reduction in functional capacity [1].

The type of surgical intervention significantly impacts the likelihood of contracture development. In this context, the preference for reconstructive surgery aims to improve limb function and reduce the risk of contracture recurrence [2]. Ongoing research focuses on improving long-term surgical outcomes by integrating time-tested technologies with established surgical techniques. dermal tissue substitutes and platelet-rich plasma (PRP) are gaining traction as promising regenerative therapies for tissue repair and functional restoration.

The application of autologous PRP therapy, stem cells, adipose tissue autotransplantation, negative pressure wound therapy (NPWT), traditional flap reconstruction, and other transplantation techniques is becoming increasingly common in burn treatment. Dermal scaffolds and split-thickness skin grafts (STSG) are among the options that enhance skin quality, flexibility, and overall patient quality of life.

NPWT plays a crucial role in improving graft fixation by minimizing displacement and reducing the risk of complications. It also stimulates granulation tissue formation, accelerates revascularization, and supports successful graft integration into the wound bed. NPWT has been shown to effectively enhance the engraftment of both split-thickness and full-thickness skin grafts

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(FTSGs) [3–7]. This technique provides an almost ideal interface between the graft and the recipient site [8, 9], preventing the accumulation of seromas and hematomas, as well as the onset of infections – key contributors to graft loss during the early postoperative period [10].

Acellular dermal matrix (ADM) is a single-layer dermal component composed of bovine collagen and hydrolyzed elastin. This material transforms into a highly viable neoderm, both functionally and morphologically, facilitating adhesion between the skin epidermis and underlying bone tissue [11]. A one-stage ADM grafting procedure, combined with overlapping skin grafts of varying thicknesses (STSG), has been reported in clinical practice. After a few weeks following surgery, an ADM integrates into the recipient's tissue, developing vascular and nerve connections, effectively functioning as the patient's own tissue. This unique characteristic of ADM contributes to complete assimilation of the graft. The minimally invasive procedure has yielded results that are either excellent or comparable to those achieved with more complex skin or skin-fascial flaps, without resulting in donor site morbidity [1, 11].

PRP is an autologous blood-derived product where plasma, rich in platelets, growth factors, and cytokines, is concentrated. Since the 1970s, PRP has been used for tissue repair [12]. PRP injections, stem cell injections, and NPWT all promote tissue regeneration and enhance integration within the recipient skin area.

According to Karakol and Bozkurt [1], the combined use of surgical techniques with advanced approaches – such as ADM, PRP therapy, and NPWT for wound management – has been shown to be effective in achieving both functional and aesthetic outcomes for patients suffering from severe burn contractures.

In each of the aforementioned therapeutic approaches and disease prevention strategies, biotechnologies play a central role, with a focus on stimulating the body's natural recovery processes. The research methods discussed for both autologous and xenobiomaterials can be applied in the development and implementation of biomedical cellular products aimed at preventing post-burn scars. This direction holds significant promise and is supported by scientific justification and potential.

RESEARCH METHODS

A literature review was conducted using specialized scientific databases, including MEDLINE, Google Scholar, EMBASE, and PubMed. The efficiency in selecting relevant scientific papers was enhanced by using targeted keywords and phrases in search queries, such as "burns," "scars," "post-burn scars," and "post-burn scar prevention techniques". The inclusion criteria for publications in the review involved an initial screening of titles and abstracts to assess their relevance to the research topic. Additionally, a supplementary search method was employed, where the reference lists of the selected papers were reviewed to identify other significant sources. The final step involved a comprehensive full-text analysis and systematic evaluation of the chosen studies, enabling the extraction of key information for incorporation into the preparation of this research article.

An information search using the outlined strategy yielded a dataset of 2,335 scientific articles. During the initial screening, in which irrelevant materials were excluded, the number of articles was reduced to 238. A subsequent detailed full-text analysis identified 152 articles that did not meet the established criteria. Consequently, the final selection consisted of 86 articles that fully met the search parameters.

RESULTS

Factors causing hypertrophic and keloid scars

While research continues, the exact biological mechanisms behind the formation of hypertrophic and keloid scars are not fully understood. However, studies by Curran and Ghahary have identified a link between delayed re-epithelialization and enhanced extracellular matrix production. Recent research indicates that bone marrow-derived cells, especially fibrocytes and keratinocyte-like cells (KLCs), may contribute to the inflammatory infiltrate during wound healing [13, 14]. These findings underscore the potential role of these cells in the re-epithelialization process and their critical role in stimulating skin fibrosis when healing is impaired [14, 15].

Fibrocytes and KLCs are products of transdifferentiation from $CD14^+$ adherent monocytes, a specific subset of mononuclear stem cells found in peripheral blood [15, 16]. This process allows $CD14^+$ monocytes to transform not only into myofibroblasts [17], but also into osteoblasts, skeletal myoblasts, chondrocytes, adipocytes [18], and cardiomyocytes [19], depending on the surrounding environmental conditions. This discovery highlights the remarkable plasticity and potential of peripheral blood monocytes in regenerative processes and tissue repair. Fibrocytes were first described in 1994 by Richard Bucala and colleagues [16], who identified a large number of adhesive, fibroblast-like, spindle-shaped cells that infiltrated wound cavities shortly after implantation, serving as a model for tissue reparative reactions *in vivo*. These cells, which exhibit adhesive properties and the ability to migrate to sites of tissue damage, exhibit unique characteristics, including expression of collagens I and III, vimentin, and CD34. These markers suggest their multipotent stem cell potential and their ability to differentiate into various mesenchymal cell types depending on local conditions [16]. Over time, as fibrocytes mature, a loss of CD34 expression is observed, which may serve as a marker of their differentiation into mature cellular forms during tissue repair and regeneration [20].

Transformation of $CD14^+$ monocytes into fibrocytes *in vitro* can be induced by cultivating them in a specialized fibroblast culture medium [13, 21].

In vivo, fibrocytes can be found in areas of injured tissue by day 4 after injury, appearing simultaneously with the influx of inflammatory cells. Fibrocyte migration is believed to be driven by the activation of CCR7 chemokine receptors on their surface, enabling them to interact with chemokines present in lymphoid tissues. Accumulation of fibrocytes in the wound area continues until the day 9 or 10 after injury [22, 23].

Exposure of $CD14^+$ monocytes to a specialized keratinocyte-enriched culture medium or to bone morphogenic protein-4 (BMP-4) can initiate their transdifferentiation into KLCs after about 7 days in culture [14, 24]. These KLCs morphologically resemble native keratinocytes, characterized by enlarged elliptical nuclei, and express specific keratinocyte markers such as stratifin, keratin-5, and 14-3-3σ protein [14, 15]. While "keratinocyte-like cells" was coined by the research teams of Curran and Ghahary, other labs refer to them as bone marrow-derived keratinocyte precursors, obtained through transdifferentiation protocols from various stem cell populations.

Curran and Ghahary's research demonstrated that, in addition to the previously understood pathway from $CD14^+$ monocytes, KLCs can also be directly derived from $CD34^+$ bone marrow cells, bypassing the need for $CD14^+$ intermediates [17, 24, 25]. Identifying keratinocyte-like differentiation involves two key indicators: checking for the expression of keratin-14, and the absence of CD45, a marker specific to hematopoietic lineage cells.

The recruitment of mononuclear cells, including $CD14^+$ monocytes, from peripheral blood to sites of tissue injury is mediated by fibroblast-derived chemokines and cytokines like CXCL5 and fibroblast growth factor beta [26]. Resident keratinocytes also actively contribute to directed migration of mesenchymal stem cells (MSCs) by releasing the secondary lymphoid chemokine (CCL21), which interacts with CCR7 receptors on these stem cells, enhancing their movement [24].

While fibrocytes constitute a small fraction (about 0.5%) of circulating leukocytes, they can make up a significant portion (up to 10%) of cells within subcutaneous implantation chambers in mice, highlighting their crucial role in tissue healing and regeneration [16]. Fibrocytes can also act as antigen-presenting cells by expressing class II MHC molecules, costimulatory molecules (CD80, CD86), and adhesion molecules (CD11a, CD54, CD58) [27], unlike mature fibroblasts that require interferon-γ stimulation to achieve similar levels of antigen expression. The transdifferentiation of $CD14^+$ monocytes into dendritic-related (DR) fibrocytes appears to be dependent on the presence of $CD14^+$ cells and can be induced by conditioned medium, even in their absence. However, this process is inhibited by antibodies against transforming growth factor-β1 (TGF-β1), underscoring the pivotal role of TGF-β1 in promoting this transdifferentiation [29]. In burn patients, elevated serum levels of TGF-β1 are correlated with a higher number of fibrocytes observed in their peripheral blood mononuclear cell (PBMC) cultures compared to healthy controls [29].

The plasticity of fibrocytes is evidenced by their ability to adapt fibrogenic activity in response to environmental cues. These cells play an active role in the regulating and transmiting genetic information, producing substantial amounts of mRNA required for the synthesis of key fibrogenic growth factors, particularly platelet-derived growth factor A (PDGF-A) and transforming growth factor-β1 (TGF-β1). Beyond their role in fibrogenesis, fibrocytes contribute to hematopoiesis and immune responses by producing mRNA for macrophage colony-stimulating factors (M-CSF) and proinflammatory mediators like macrophage inflammatory protein-1α (MIP-1α) and related chemokines [22]. Even at low levels, interleukin-1α (IL-1α) and tumor necrosis factor-α (TNF-α) cytokines play a crucial role in maintaining a regulated inflammatory response.

Fibrocytes, derived from PBMCs, can influence fibroproliferative activity by modulating matrix metalloproteinase-1 (MMP-1) expression, even in the absence of TGF-β signaling [14, 15, 27]. This suggests that they may not always contribute to pathological scar formation but can also participate in matrix remodeling under certain conditions. Collectively, these findings support the hypothesis that fibrocytes, when activated at an injury site, transform functionally and collaborate with other cell types to perform diverse roles in tissue repair and remodeling.

To test this hypothesis, Medina and Ghahary [13] injected bone marrow-derived stem and progenitor cells into rat inguinal fascial-fat flaps. Some of these flaps treated to inhibit TGF-β signaling using an antibody targeting the TGF-β type II receptor, aiming to induce immunological resistance to the transplanted cells. Flaps with mock cells and untreated bone marrow exhibited increased density, weight, and stronger fibrotic adhesion compared to flaps treated with a TGF-β antagonist. Histological analysis further revealed that flaps treated with synthetic or bone marrow-derived cells exhibited significantly higher collagen deposition compared to those treated with a TGF-β inhibitor. The collagen architecture in the TGF-β-exposed group closely resembled that of native fascial-fatty tissue harvested from the contralateral thigh of the rat.

Evidence suggests that an overpopulation of fibrocytes in the wound bed can lead to excessive tissue repair and fibrotic outcomes like hypertrophic scarring and keloid formation [13, 16, 30]. Fibrocytes, which migrate to injury sites alongside inflammatory cells, are highly responsive to the local inflammatory environment, influencing their function. *In vitro* studies show that interleukin-1β (IL-1β), a key mediator in tissue re-

generation, suppresses the synthesis of type I collagen [31]. Concurrently, IL-1β, stimulates the production of various pro-inflammatory and pro-fibrotic cytokines, including macrophage inflammatory protein-1α (MIP-1α), MIP-1β, monocyte chemoattractant protein-1 (MCP-1), interleukin-8 (IL-8), oncogene-related growth factor-α, interleukin-6 (IL-6), macrophage colony-stimulating factors, TGF-β1, and TNF-α. These mediators further amplify the inflammatory response and may contribute to dysregulated wound healing and fibrosis.

Patients with extensive burns exhibit increased fibrocyte differentiation compared to non-injured individuals, which contributes to the sustained presence of these cells at the injury site and perpetuates the inflammatory response [32]. This prolonged inflammation, a characteristic of severe burn injuries, promotes greater fibrocyte differentiation and retention within the wound area. In PBMC cultures, burn patients exhibit a higher proportion of collagen-producing fibrocytes compared to healthy controls [29]. Moreover, inflammatory microenvironment significantly impacts fibrocytes, altering their morphology and gene expression, which in turn influences their behavior and function [16, 22]. Leukocyte-specific protein 1 (LSP-1), a protein highly expressed in fibrocytes and associated with type I procollagen, has been identified as a reliable biomarker for detecting and characterizing fibrocytes [33]. Elevated LSP-1 expression in fibrocytes suggests an adhesive phenotype, differentiating them from surrounding leukocytes in inflamed tissue, and persistent inflammation promotes fibrotic activity, with fibrocytes abundant in hypertrophic scar tissue after burns compared to non-hypertrophic scar tissue (Fig. 1) [33].

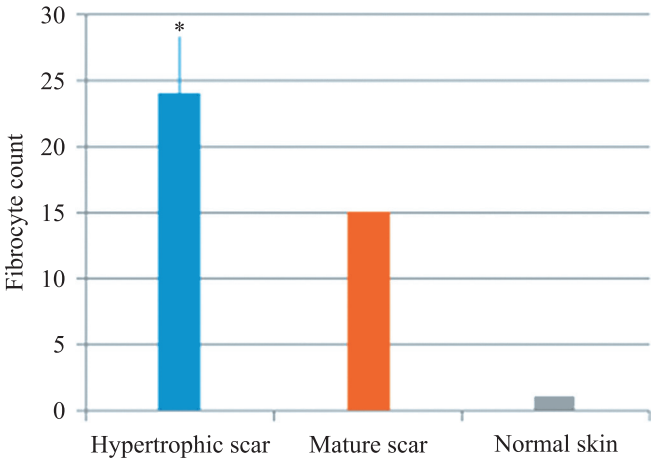

Fig. 1. Fibrocyte count (immunofluorescence staining) in cryosections of a hypertrophic scar, mature scar, and normal skin collected from 10 burn patients. The number of double-labeled fibrocytes per high-power field (HPF) in the dermis was compared using one-way analysis of variance (ANOVA). (* $P < 0.5$)

Consequently, unchecked expansion of fibrocytes contributes significantly to hypertrophic scar development and persistence by differentiating into collagen-producing fibroblasts and stimulating collagen synthesis in resident fibroblasts through paracrine signaling [19, 33].

In a wound scenario, PBMC (specifically $CD34^+$ cells) migrate to the injury site and are stimulated to differentiate into KLCs through interaction with the chemokine ligand CCL27, which attracts skin T-cells and whose activation occurs in the tissue affected by the wound, as well as through binding to the CCR10 receptor [25].

Bone marrow-derived keratinocyte precursors ($CD34^-$ cells) migrate to injury sites, in part, via interaction with the chemokine CCL21, which is typically expressed in secondary lymphoid tissues [24, 25]. In parallel, $CD14^+$ monocytes have also demonstrated the capacity to transdifferentiate into KLCs when exposed to a specialized microenvironment enriched with keratinocyte-specific factors [23, 24]. The cellular environment conditioned by these KLCs influences dermal fibroblast activity through the secretion of exosomes, which in turn enhance the production of matrix proteins. This environment promotes increased synthesis of matrix metalloproteinase-1 (MMP-1) compared to that observed in fibroblasts cultured with keratinocyte-conditioned medium alone (Fig. 2) [15].

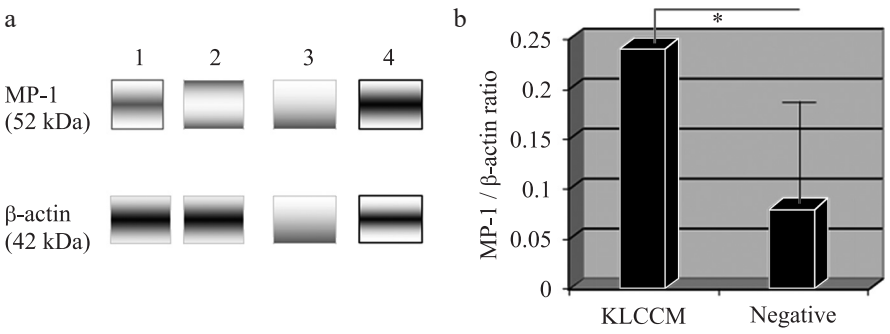

Fig. 2. Matrix metalloproteinase-1 (MP-1) expression in dermal fibroblasts treated with keratinocyte-like cell (KLC)-conditioned medium. a, showed MP-1 expression in dermal fibroblasts after 24 hours in each case: 1 = KLC-conditioned medium from day 28 of cell transdifferentiation, 2 = Dulbecco's modified Eagle medium + 2% fetal bovine serum (FBS; negative control), 3 = blank, 4 = dermal fibroblasts treated with recombinant stratifin (positive control); b, densitometric analysis of MP-1/β-actin ratio. (n = 4)

It was found that decreased levels of 14-3-3 proteins under these conditions lead to a decrease in the described effect, indicating the critical role of these proteins in modulating the antifibrotic response when interacting with dermal fibroblasts [15]. In addition, it has been found that keratinocytes from hair follicles are able to migrate to wound areas, actively contributing to re-epithelialization, especially between days 2 and 4 after injury [11]. These data are supported by the observation that wounds where hair follicles have been destroyed heal significantly slower, confirming the crucial role of keratinocytes within follicles in the healing process [34].

Recent advancements show that bone marrow, peripheral blood, and umbilical cord blood sources are increasingly used in local skin wound treatments, particularly for accelerating healing and converting chronic wounds to acute ones [35–37]. These materials stimulate the healing response by modulating cellular activity, including fibrocytes and KLCs, which are specialized subsets of stem cells derived from these sources. This stimulation leads to the chemotaxis of PBMCs to the injury site, where chemokines in the wound bed activate the transdifferentiation of $CD14^+$ mononuclear cells into fibrocytes or KLCs. The outcome of this transdifferentiation is heavily influenced by the local environment, which can fluctuate, particularly in burn wounds with varying depth and lesion area. Although the precise mechanisms remain incompletely understood, it is known that these cell subpopulations are more prominent in hypertrophic scars than in normotrophic scars, suggesting they may play a role in modulating fibrosis in affected tissues. Further research is needed to fully determine the role of these cells in wound healing.

Application of stromal-vascular fraction of adipose tissue

One of the emerging trends in the treatment of burns, post-burn scars, and other complex wounds is the use of adipose tissue. Adipose-derived stem cells (ADSCs) are increasingly used for regenerative purposes. These cells possess the ability to differentiate into various tissue types, including adipose, bone, cartilage, and muscle, with potential for even broader tissue differentiation. ADSCs are also rich sources of regenerative and metabolic factors, secreting growth factors like epidermal growth factor (EGF), TGF-β, hepatocyte growth factor (HGF), platelet-derived growth factor (PDGF), and basic fibroblast growth factor (bFGF). Adipose tissue, harvested via liposuction, can be processed using physical or chemical methods to separate its components (like stromal vascular fraction) either at the point of care or in a lab [38–44].

The Coleman technique is widely burn in the treatment of burn injuries, involving cyclic injections at intervals of two to four weeks until the wound is completely healed or a specific medical procedure, such as wound closure, skin grafting, or skin flap placement, is performed. For ongoing scar management, injections are administered under the scar every three months, following the Coleman's procedure [45–48].

Fat grafting, used as an adjunct in treating acute and subacute burn wounds, and chronic vascular wounds (e.g., venous insufficiency or diabetic arterial disease), harnesses the regenerative and metabolic properties of fat tissue to enhance vascularization and accelerate tissue regeneration. When used in repeated sessions (15–21 days apart), autologous fat grafting can promote healing and aid in wound recovery [48–50].

The primary goals of burn scar therapy are to reduce tissue hypertrophy (fibrosis), decrease scar thickness, and increase scar elasticity. Therapeutic techniques aim not only to improve the appearance of the affected area but also to address functional impairments caused by excessive fibrotic activity. These methods are also widely applied in treating fibrosis that arises in the joint area after trauma or surgery, as well as in preventing the formation of adhesions following tendon surgeries [51–54].

For open wounds, injections are typically administered under general anesthesia at intervals of 15 to 21 days. In patients with hypertrophic scars after burn healing or keloids of any origin, repeated injections (up to four injections in total) are administered at intervals of 8 to 12 weeks.

Fat is most commonly harvested from the abdomen, thighs, or lateral surfaces of the upper buttocks, with shaving of the pubic area or proximal thigh performed in the operating room if necessary just before the procedure. For liposuction cannula insertion, puncture incisions are typically made along the midline in the suprapubic crease, medial to the femoral artery pulse, in the inguinal crease, or along the mid-axillary line, extending towards the superior border of the iliac spin

While previously viewed as a passive energy storage and insulation tissue, contemporary science recognizes adipose tissue as a significant endocrine organ, playing a crucial role in regulating various physiological processes. Adipose tissue contains a diverse range of cellular components, offering promising opportunities in regenerative medicine. Adipose tissue, while primarily composed of adipocytes (one-third of the tissue's volume), also contains a complex stromal-vascular fraction (SVF) including preadipocytes, fibroblasts, MSCs, endothelial cells, and immune cells, forming a complex network [47]. The enzymatic breakdown of adipose tissue yields a cellular precipitate, the SVF, containing a heterogeneous population of progenitor cells.

The International Federation of Adipose Therapy and Science (IFATS) and the International Society for Cellular Therapy (ISCT) have defined the cellular composition of adipose tissue's SVF as a mixture of cells including stromal cells (15–30%), endothelial cells (10–20%), lymphocytes (10–15%), granulocytes (10–15%), monocytes

(5–15%), pericytes (3–5%), and stem and progenitor cells (<0.1%) [55]. This diverse cellular population of adipose tissue-derived SVF has garnered significant interest for its potential therapeutic applications in regenerative medicine. More specifically, MSCs within the SVF, also known as adipose-derived stem cells (ASCs), have been identified as a key cell type responsible for the therapeutic effects of SVF. *In vitro* studies demonstrate that ASCs enhance human skin fibroblast proliferation, migration, and collagen production through both direct cell-to-cell contact and paracrine signaling [56]. However, it remains to be determined whether these beneficial effects can be harnessed for the development of effective therapies for chronic and non-healing wounds.

Adipose tissue is classically categorized into two types: white adipose tissue (WAT) and brown adipose tissue (BAT) [57]. WAT primarily functions in energy storage, storing triglycerides, and providing thermal insulation and physical cushioning for the body. In contrast, BAT is specialized for energy dissipation by generating heat [58]. WAT is the dominant form of adipose tissue in humans, while BAT is less abundant, typically found in specific areas such as the supraclavicular, periadrenal, and paravertebral regions of the body [47].

Fibroblasts at the dermis-hypodermis interface play a crucial role in wound healing due to their unique characteristics, differing from adipogenic stem cells derived from adipose tissue and fibroblasts from the papillary and reticular dermis. These cells contribute to tissue repair in distinct ways. While adipose tissue plays a role in regeneration, obesity significantly impairs natural healing processes. This is primarily due to alterations in adipose tissue metabolism, including hypertrophy and hyperplasia of adipocytes, making them less functional [58]. These changes disrupt angiogenesis, as the rate of new vessel formation becomes mismatched with the increased demand from the growing adipocytes, resulting in hypoxia and delayed healing [59]. Moreover, obesity is linked to reduced adiponectin levels, a cytokine produced by fat cells, and this reduction can complicate tissue regeneration [42].

Adiponectin, a key mediator, plays an essential role in skin damage repair by promoting the growth and migration of keratinocytes in a concentration-dependent manner, as observed in mouse cell cultures. This effect occurs through activation of the extracellular signal-regulated kinase (ERK) pathway, as confirmed by various studies [60]. These findings highlight the importance of understanding the role of adiponectin in skin repair mechanisms, which is crucial for developing more effective treatments aimed at minimizing side effects and complications.

Table summarizes the paracrine factors produced by adipose tissue stem cells that stimulate the functional activities of dermal fibroblasts.

While research into the regenerative potential of adipose stem cells is ongoing, pioneers of autologous adipose tissue transfer have demonstrated the significant therapeutic potential of this technique. Adipose tissue transplantation has shown promise in improving both the appearance and function of scars, particularly in areas with abnormal healing and scarring. Concurrent laboratory studies using *in vitro* cultures suggest that adipose-derived stem cells (ASCs) play a crucial role in the therapeutic effects observed.

Application of hydrogel dressings in the treatment of burn wounds and scars

In burn treatment, ASCs are often combined with hydrogels containing hyaluronic acid, Aloe vera extract, and other beneficial components. Skin repair is typically sufficient when the intensity of the injury is within the skin's regenerative capacity. The healing process involves three main interrelated phases: the inflammation, proliferation, and extracellular matrix (ECM) reconstruction [66]. However, when the damage surpasses the skin's regenerative threshold, the healing process becomes more complicated. The final stage, which is particularly crucial, involves fibroblast activation, collagen

Table

Regulation of dermal fibroblast activity by adipocyte stem cell secretion: significance for effective wound healing

Stimulatory effect of ASC secretion on dermal fibroblast function	Paracrine factors secreted by ASCs	References
Increased proliferation	Fibroblast growth factor (FGF-2)	[37, 59, 60]
	Hepatocyte growth Factor (HGF)	[61]
	Exosomes	[62, 63]
	Microvesicles	[64]
Increased migration	FGF-2	[4, 37]
	Exosomes	[4, 62, 63]
	Microvesicles	[64]
Matrix remodeling (increased production of collagen I and III, TGFβ, FGF2 and MMP1)	Adiponectin	[65]
	Exosomes	[62, 63]

deposition, and new blood vessel formation. In response to critical injuries, macrophages release cytokines like fibroblast growth factor-2 (FGF-2), transforming growth factor-β (TGF-β), and insulin-like growth factor, which subsequently stimulate fibroblast migration, proliferation, and intensive collagen production. The formed collagen undergoes further reconstruction for up to two years. In addition, the regeneration process involves a complex interplay of a variety of components, including cellular elements, growth factors, cytokines, and ECM. An imbalance in this process can lead to uncontrolled repair and hypertrophic scarring.

Hypertrophic scars, resulting from increased fibroblast proliferation and excessive collagen production, are characterized by a range of properties that distinguish them from healthy skin. These include visible thickening, loss of elasticity, a firm texture upon palpation, and a color change to an abnormal purple-red hue. In the early stages (4–8 weeks), these scars are often accompanied by intense pain and itching. Over time, they gradually mature, transforming into atrophic scars over a period of weeks to two years, which can significantly impact both the physical and psychological well-being of patients. In industrialized countries, approximately 4 million individuals suffer from hypertrophic scarring annually, with the numbers in developing countries reaching up to 5 million, highlighting the need for effective treatment methods. Contemporary treatments for hypertrophic scars include surgery, laser therapy, and drug treatments, but challenges persist with large scars, where complete wound healing after surgical intervention or closing skin defects can be difficult, limiting easy suture closure [68].

Alongside other leading techniques, carbon dioxide laser therapy is widely employed in burn treatment centers alongside other leading techniques to address hypertrophic scars. This method effectively induces fibroblast apoptosis and eliminates excess collagen, making it a highly targeted and efficient treatment. In addition, corticosteroids are commonly used to enhance therapeutic outcomes in scar management [69, 70].

Beyond the direct application of medications to the affected area, scar healing can also be facilitated through the use of drugs incorporated into hydrogels. Hydrogels are an innovative type of wound dressing that has gained popularity due to their exceptional ability to absorb moisture and deliver pharmacological agents directly to the wound site. Hiwatashi et al. developed collagen-gelatin matrices saturated with basic fibroblast growth factor, demonstrating the ability to reduce the accumulation of dense collagen and having a positive therapeutic effect on vocal cord scars [71]. Le Wang et al. created a PCL/gelatin scaffold by electrospinning, saturated with small molecule inhibitors of TGF-β1 signaling, which inhibits the growth of fibroblasts, the main cells contributing to scar formation, and effectively prevents hypertrophic scars in wound healing [70]. Bu et al. successfully developed a nanoliposomal gel with 5-aminolevulinic acid applied by photodynamic delivery, which changes the structure of collagen fibers and accelerates the apoptosis of fibroblasts in scar tissue [71]. The introduction of skin grafts and their substitutes has had an encouraging effect on the healing process, but also comes with potential difficulties in the field of dermal restoration, for example, increasing the size of the graft correlates with the duration of re-epithelialization, which may promote scar formation [72]. This suggests the need to develop new strategies for the prevention of hypertrophic scars characterized by minimal side effects.

Papain, a cysteine protease derived from the immature milk of Carica papaya, is known for its high enzymatic activity, excellent heat stability, and safety profile, making it widely used in medical applications [73]. This proteolytic enzyme plays a crucial role in preventing the formation of granulation tissue (GR) during wound healing by affecting various cell types involved in tissue regeneration. Papain exerts anti-inflammatory, antibacterial, and antioxidant functions while also degrading proteins and collagen [73–75].

For example, papain strongly inhibits the angiogenic effects induced by vascular endothelial growth factor (VEGF) in human umbilical vein endothelial cells (HUVECs) by blocking AKT, MEK1/2, and SAPK/JNK phosphorylation. Moreover, papain is known to degrade proteins involved in tight junctions, including ZO-1, claudin-4, and occludin, in keratinocytes [76]. It has also been observed that papain effectively suppresses monocyte activation, particularly that induced by monocyte-derived pro-inflammatory cytokines (MPAs), by inhibiting the MAPK and PI3K/Akt signaling pathways [77]. Even papain pretreatment at a concentration of 10 mg/mL also inhibits T-lymphocyte activation induced by islet allografts [78].

Papain actively suppresses the expression of TGF-β1 protein and the phosphorylation of Smad-3, key components of the TGF-β signaling pathway. This suppression effectively controls cell proliferation, cell-cell interactions, and ECM remodeling by modulating the TGF-β/Smad signaling cascade. It also contributes to reducing collagen and keratin formation in the dermal layer [79]. In scar tissue compared to healthy skin, elevated NF-κB p65 protein levels contribute to excessive fibroblast activity, leading to uncontrolled collagen production and abnormal ECM accumulation. Papain significantly lowers NF-κB p65 levels, thereby promoting the healing of hyperplastic scars by regulating the NF-κB pathway. However, topical papain application *in vivo* faces challenges due to difficulties in maintaining consistent contact with the wound, potentially limiting its therapeutic benefits.

Hydrogels offer a promising alternative for pharmaceutical delivery, enabling precise and controlled release of active ingredients. Chitosan, a natural bio-

polymer derived from chitin through deacetylation, is widely used in this context due to its biocompatibility, non-toxicity, and biodegradability. This polysaccharide is known for its enhanced bioactivity, stability *in vivo*, and affordability, and it is obtained from renewable natural sources. As a result, it has extensive applications in the medical field, particularly in the development of hydrogels for various therapeutic purposes when combined with other natural or synthetic polymers [80]. For instance, hydrogels containing poly (γ-glutamic acid) and chito-oligosaccharide, enriched with the enzyme papain (G/C/P hydrogels), show potential in regulating skin repair and preventing formation of hypertrophic scars.

Hydrogels are increasingly used for local and transdermal drug delivery of bioactive molecules, as well as effective wound dressings because of their ability to create an optimal microenvironment that promotes cell growth and differentiation [80]. Specifically, chitosan-based hydrogels have demonstrated unique therapeutic properties: they activate macrophages and gradually degrade to release N-acetyl-β-D-glucosamine. This metabolite stimulates fibroblast proliferation, promotes angiogenesis, normalizes collagen deposition, and enhances natural hyaluronic acid synthesis at the wound site, thereby accelerating healing and reducing scar formation [81, 82].

Furthermore, hydrogel bases are widely used to prolong the therapeutic effects of the drugs they deliver. This property is particularly valuable in applications like hydrogel-based antibacterial dressings for burn treatment, enabling controlled, sustained release of antimicrobial agents directly into the wound, improving efficacy and reducing dressing changes [83].

An innovative, multifunctional macroporous antimicrobial hydrogel has been developed to combat bacterial infections and promote skin regeneration by modulating cytokine production from the body's own stem cells. This advanced hydrogel is created using a cryogenic gelation technique, forming a hyaluronic acid-based cryogel with a macroporous architecture. The surface of the cryogel is then functionalized via dopamine oxidative polymerization, enabling the immobilization of the antimicrobial peptide DP7, resulting in the DA7CG construct. Placenta-derived MSCs are subsequently introduced into this cryogel (DA7CG@C).

The DA7CG@C hydrogel, according to *in vitro* and clinical trial data, exhibits stage-specific actions during wound healing, with DP7, during the inflammatory phase, suppressing infection and modulating the inflammatory response. In the proliferation phase, the presence of placenta-derived MSCs supports the regeneration of skin, vasculature, and hair follicles. In the remodeling phase, DP7 enhances paracrine secretion of stem cells, facilitating extracellular matrix remodeling and promoting scar-free healing.

Due to its multifunctional properties, this hydrogel presents a promising alternative to traditional dressings for the treatment of burn wounds [84].

Hydrogel dressings provide optimal wound hydration for both burn injuries and wounds following the removal of necrotic burn tissue via tangential or full-thickness excision. This moist environment facilitates accelerated re-epithelialization and significantly reduces the risk of hypertrophic scar formation [84].

Despite their proven efficacy in wound management, hydrogel dressings may not be suitable during certain healing phases. Their limited absorbency makes them unsuitable for wounds with heavy exudate, as they can reduce effectiveness. Furthermore, a common challenge with hydrogel drug delivery systems is the rapid release of incorporated drugs, with a large portion of the active compounds being released within the first few hours post-application. This can increase the risk of local toxicity and reduce sustained therapeutic efficacy. In contrast, advanced hydrogels and xerogels incorporating nanocomponents offer enhanced wound healing potential. Their mesoporous architecture enables better control over the release of bioactive substances, making them potentially more preferable in certain clinical scenarios [8].

In modern wound care, two primary types of hydrogel dressings are used, each with distinct structural and functional characteristics. The first type comprises hydrogels with a stable three-dimensional macroscopic structure formed through molecular cross-linking. These dressings typically appear as elastic, transparent sheets of variable thickness. They maintain their structural integrity during exudate absorption, although they may swell as fluid is absorbed. This swelling continues until the gel reaches its saturation point, achieving equilibrium with the wound microenvironment.

The second type includes amorphous hydrogels, which lack a fixed structure and adapt dynamically to the wound surface upon contact with moisture. These hydrogels fill all irregularities and contours of the wound bed, conforming to its shape. As they absorb increasing volumes of exudate, their viscosity decreases, eventually transforming into a more fluid-like solution that becomes fully integrated into the wound environment. The most advanced developments in this field are third-generation hydrogel dressings, which provide an optimal moisture environment for wound healing. These dressings actively absorb exudate while preventing fluid accumulation through their evaporative properties. In addition, they promote the formation of a natural protective protein layer – rich in endogenously produced growth factors – on the wound surface, a critical factor in accelerating tissue regeneration [47, 85].

Silicone-based formulations, particularly siloxane polymers, are a widely recommended, non-invasive first-line treatment for preventing and treating hypertrophic

and keloid scars. These agents are considered among the most effective nonsurgical interventions available, with their efficacy well supported by extensive scientific research [86].

CONCLUSION

The formation of hypertrophic and keloid scars following deep burns and severe skin trauma remains a complex and not fully understood process. Emerging evidence suggests that bone marrow-derived cells, like fibrocytes and keratinocyte-like cells, may contribute significantly to skin regeneration and potentially to the development of fibrotic responses during aberrant wound healing. Recent research has identified specific pathophysiological and biochemical mechanisms that become activated in tissues during the healing of extensive and deep wounds. In particular, hair follicle keratinocytes have been shown to play a critical role in promoting epithelialization of wound surfaces following burn injuries.

In the early post-injury phase, negative pressure wound therapy (NPWT) has been shown to significantly reduce infection risk, promote granulation tissue, and prepare the injury site for reconstruction, whether through autologous skin grafting or transplantation of composite tissue flaps. Incorporating pharmacological agents into hydrogel dressings at specific stages of healing creates a microenvironment that promotes tissue regeneration. This therapeutic approach supports repair in both open wounds and beneath the "living protective layer" formed by repositioned skin flaps.

Adipose tissue has emerged as a promising therapy for burn wound healing, scar reduction, and complex wound management. The therapeutic efficacy of adipose-derived stromal-vascular fraction (SVF) has been validated through numerous animal studies and is increasingly used clinically.

Adipose-derived SVF is a heterogeneous mix of cells capable of differentiating into various tissues including adipose, bone, cartilage, and muscle. These cells also play a vital role in tissue repair and metabolic regulation, primarily through secretion of growth factors. Recognized as one of the body's highly active endocrine organs, adipose tissue is a readily available source of regenerative cells, with wide-ranging applications in both regenerative medicine and aesthetic dermatology. Unlike mesenchymal stem cells, the clinical use of SVF is already supported by an established regulatory framework and is facilitated by relatively simple and accessible extraction and processing methods. Burnazyan Federal Medical and Biophysical Center is actively developing innovative methods for targeted delivery of regenerative cells to injury sites, including intra-articular injections. A key focus of this research is the long-term preservation of cell functionality through the use of hydrogels and other high-viscosity carriers with enhanced adhesive properties. This integrated approach holds significant promise for advancing the development of next-generation biomedical cell-based therapies specifically tailored for burn treatment.

The accumulated medical knowledge and clinical experience enable the integrated treatment of patients with burns and wounds, including the restoration of skin defects. Optimizing the healing process and enhancing the quality of scar tissue formation, along with preventing scar contractures in areas near joints, ultimately contributes to improved long-term quality of life for the burn victims.

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