International Journal of Biology and Life Sciences
ISSN: 2957-9511 | Vol. 6, No. 3, 2024

Advances in Adipose-derived Mesenchymal Stem Cells for Burn Wound Healing

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Abstract: Burn injuries are under-appreciated injuries that involve tissue destruction associated with physiological and pathophysiological responses. The use of stem cell-based therapies has expanded in various diseases, particularly in burn wound repair. Adipose-derived stem cells (ADSCs) have recently been revealed as the regeneration medicine that affects ectodermal, mesodermal and endodermal tissue and organs for repairing damaged tissues. ADSCs can be easily harvested from adipose tissue and are widely used as research tools and therapeutics in preclinical and clinical wound healing trials. Based on the pathophysiology of three phases of burn injuries, we discussed various cell-based components and cytokines associated with ADSCs of three phases of burn injuries. In this review, recent research and therapeutic effects of ADSCs in burn wound are covered and stated separately in each phase. Based on the background knowledge, the differentiation potential and therapeutic applications of ADSCs is connected with these growth factors and cells. In addition, future direction and limits for ADSCs are mentioned in the final stage.

Keywords: Adipose-derived Stem Cells; Burn Injuries; Wound Repair; Stem Cell Therapy; Regenerative Medicine.

1. Introduction

Burn injuries are a common type of traumatic injury that impact a substantial number of people globally. Around 6 million patients are estimated to seek medical treatment for burn-related injuries each year.[1] The injuries can be caused by friction, cold, heat, radiation, chemical or electric sources, but the majority of burn injuries are caused by heat from hot liquids, solids or fire [2]. All burn injuries involve tissue destruction with subsequent pain because of the profound nerve injury. A burn injury can result in a wide number of fatal complications, including infection, electrolyte imbalances, emotional distress with long-term therapy, scarring and deformity [3]. Cutaneous burn healing and regeneration involves four phases which are Haemostasis, Inflammation, Proliferation and Remodelling [4]

In the past several decades, the rising complexity in developing new treatment methods is a result of the varied nature of trauma, influenced by factors such as age, gender, existing health conditions, types and severity of injuries, and complex pathophysiology [5].. Many different treatment strategies are applied in burn wound management. This review delves into recent research and the therapeutic effects of adipose-derived stem cells (ADSCs) in burn wound healing, examining each phase separately. It explores the differentiation potential and therapeutic applications of ADSCs in relation to specific growth factors and cells. Furthermore, it discusses future directions and limitations for the use of ADSCs in the final stage of the review.

2. The Biology of Burn Wound Healing

Skin is the layer of soft flexible outer tissue; meanwhile, it includes three barriers, the epidermis, dermis and hypodermis, with the function of self-defence and self-renewing. The epidermis, derived from ectoderm, is the outermost layer as a protective and sensitive barrier with abundant nerve endings and the ability for regenerative healing [6]. The epidermis mainly includes the stratum corneum, stratum granulosum, stratum lucidum, stratum spinosum, and stratum basale. The dermis, divided into two layers, the superficial papillary layer and the deeper reticular layer, which are related to different scarring depending on the depth of burn injury, is rich in fibroblasts and is responsible for maintaining the stability of the skin's structure and elasticity [7]. The hypodermis consists mainly of adipose tissue and blood vessels, which can ensure the life-saving mechanical the thermoregulatory mechanical of the skin [8]. Three components are organized well with different cell types to repair and regenerate the skin during wound healing [9]. The burn injury could affect from the uppermost layer, epidermis, to the full dermis and damage the nerve ending. Further on, the more burn usually involved damage of deeper tissues like the muscle, nerve or bone [2].

The body responses are unique after burn injury that it won't recover quickly [2]. Wound healing consists of hemostasis, inflammation, proliferation, maturation and remodelling stages [10]. Hemostasis occurs immediately after the primary injury to prevent hemorrhage and fibrin clot deposition at the injury site. Hemostasis involves vasoconstriction, platelet activation and aggregation, which are associated with clotting and growth factors such as platelet-derived growth factor (PDGF), epidermal growth factor (EGF) and transforming growth factor-β (TGFβ) in the deposition [11].

In the second phase, inflammation cells, neutrophils and macrophages are recruited to release cytokines, chemokines (including IL-1, IL-8 and tumour necrosis factor (TNF)) and growth factors (such as TGFβ, insulin-like growth factor and vascular endothelial growth factor), to eliminate cellular debris and initiate cellular signaling cascades for sequential healing phases [12]. The proliferative stage usually occurs in 3-21 days after wound injury, including a group of critical steps such as angiogenesis, granulation tissue formation, collagen deposition and epithelialization [13]. As part of the re-epithelialization phase, keratinocytes play a vital role in

both the closure of the wound surface and the recovery of blood flow through angiogenesis [14]. Additionally endothelial cells are stimulated by EGFs, fibroblast growth factors (FGFs), hepatocyte growth factors (HGFs) and multiple cytokines to trigger and promote angiogenesis, which is important in wound healing. Angiogenesis is characterized by de novo vessel formation from preexisting vasculature [15].

Prior studies have shown new blood vessels promote wound healing by transporting nutrients, oxygen, and growth factors to the injured site [16]. For the final stage, remodeling is the crucial stage of wound maturity. Fibroblasts multiple increases collagen production while transforming to myofibroblasts, which contribute to extracellular matrix (ECM) deposition [2]. Appropriate wound maturation and the remodeling will promote wound healing [17], but on the contrary when the physiological repair response in the normal healing process is insufficient, any interruption in the wound healing phases results in either excessive wound healing (hypertrophic or keloid scars) or the formation of chronic wounds (failure to heal) [18].

3. Treatment of Burns

The standard therapies for full-thickness skin defects mainly include autologous skin grafting and flap grafting; notably, autologous skin grafting requires a sufficient volume of skin and the availability of donor sites may be limited by extensive skin defects or pathological skin diseases [19]. An alternative method for treating burns involves a shift from early excision and skin grafting to staged excision and temporary coverage with xenografts or allografts [20-21].. Tissue engineering is an interdisciplinary field that integrates principles from engineering and life sciences to create biological alternatives for restoring, maintaining, or enhancing tissue function [22]. In recent years, skin tissue engineering applications, including tissue scaffolds, have become commonly utilized to restore and maintain the function of damaged tissues [23].

Furthermore, recent research has highlighted the regenerative, immunomodulatory, and anti-inflammatory properties of mesenchymal stem cells, demonstrating their significant benefits for burn patients [24]. Consequently, mesenchymal stem cells have become the subject of numerous preclinical studies in this field. The advancement of stem cell therapies has led to the exploration of therapeutic options for repairing damaged tissues in a variety of diseases. Burn wound repair, in particular, has emerged as a prominent area of research, intertwining with recent progress in stem cell therapy due to the regenerative potential it offers [25].

3.1. Adipose-Derived Stem Cells (ADSCs) in Wound Healing

Stem cells include embryonic stem cells (ESCs) and adult stem cells, induced pluripotent stem cells (iPSCs) and postnatal adult stem cells [26]. However, the utilization of these cells in clinical settings, particularly ESCs and iPSCs, is impeded by challenges such as the development of teratoma-like tumors, the obstacle of tumorigenicity, as well as concerns regarding immune compatibility, ethical considerations, and tumor induction [27]. Studies conducted recently have revealed adult adipose stem cells are an important source of MSC and can be conveniently recovered and efficiently used in regenerative therapies because of their immune-compatible properties meanwhile avoiding these concerns [28].

Multipotent mesenchymal stem cells (MSCs) are non-hematopoietic stromal cells derived from mesodermal that are present in abundant postnatal organs and connective tissues, which belong to postnatal adult stem cells [29]. MSCs proved to be isolated from bone marrow, umbilical cord blood, adipose tissues, trabecular bone, and muscle stem cells from skeletal muscle [30]. Published studies on MSCs are confirmed that differentiate into adipocytes, osteoblasts, chondrocytes, and myocytes [31].

It has been confirmed by previous research that ADSCs are adult stem cells with pluripotent differentiation potential extracted from the adipose tissue [32]. ADSCs are a cell population with characteristics that are similar, albeit not identical, to those of bone marrow derived MSCs [33].

In recent years, because adipose tissue is ubiquitous in large quantities and highly safety coefficient, ADSCs are widely used as research tools and therapeutics in preclinical and clinical wound healing [34-35]. Research has shown that the proliferation, anti-aging ability, antioxidation ability, and chondrogenic differentiation in the infant ADSCs were proved to be better than those in the adult ADSCs [36]

3.2. Therapeutic Potential of Adipose-Derived Stem Cells in Tissue Regeneration

Adipose tissue-derived stem cells are known as adipose-derived adult stem cells, adipose-derived stromal cells, and human multipotent adipose-derived stem cells. Studies have shown that ADSCs have a broad proliferative capacity and multispectral differentiation ability [37-38]. Among the considerable range of stem cell types examined, ADSCs possess many advantages over other types of stem cells, and their safety and efficacy have been confirmed in wound healing [39]. In a previous study, transgenic green fluorescent protein rat ADSCs were implanted into the hearts of rats with acute myocardial infarction and showed enhanced cardiac function and reduced myocardial remodeling in the ADSCs group compared to the control group [40]. Reduced scarring and enhanced cardiac structure compared to untreated controls. In a 2006 report, grown ADSCs were used as monolayers in thin slices for myocardial injury treatment based on regenerative capacity [41]. Furthermore, BADSCs delivered by chitosan hydrogel prevented adverse matrix remodeling, increased angiogenesis, and preserved heart function [42]. Subsequently, researchers have consistently conducted experimental and clinical studies on the treatment of infarcted myocardium using various types of stem cells (SCs). A comprehensive retrospective review has shed light on the potential mechanisms of action and therapeutic benefits of these cell therapies when applied through surgical or interventional approaches [43]. These findings suggest that ADSCs can be integrated in vivo into fully differentiated functional endothelial cells.

Human ADSCs express smooth muscle-associated markers in vitro consistent with a smooth muscle phenotype. In vivo, human ADSCs were present for 3 months to present the morphology of smooth muscle cells in immunodeficient rat urothelium. Expression studies explored the involvement of ADSCs in smooth muscle differentiation [44-45]. With the development of technology, controlled ADSCs can deliver specific smooth muscle differentiated ADSCs to regenerative processes in the cardiovascular [46] and genitourinary systems [47-48]. Meanwhile, a study in 2022 showed that

ADSCs were targeted by several pathways which affected osteogenic differentiation and, as a result, affected bone formation [49]. Mingjiao Chen et al. in 2021 seeded the miRNA-modified ADSCs onto the scaffolds and then implanted the composite scaffolds into the rat calvarial critical-sized defects. And they discovered that MiR-672 serves as a positive regulator in the angiogenesis process of ADSCs, and when miR-672-modified ADSCs are incorporated into calcium phosphate cement (CPC), it can greatly enhance vascularization and bone regeneration [50].

Recently, the use of ADSCs in the reconstruction of soft tissue defects and skin wound healing has been widely used in clinical treatment [51]. Adipogenesis is widely used in soft tissue wound healing because scholars found that adipose-derived stem cells (ADSCs) can promote wound epithelialization and angiogenesis [52]. Not only that, enzyme isolated stromal vascular fraction (SVF) injection significantly improved the areas of hyperpigmentation, pruritus, tenderness, thickness, pain, and vascularization of mature burn scars [53], accelerating the process of post-burn wound healing. Therefore, AD-MSCs have great potential in stem cell-based therapies in wound healing as well as in orthopedic, cardiovascular, or autoimmune diseases and there are many ongoing clinical trials on AD-MSC and in many cases their effectiveness has been proven [54]. Nanofat with ADSCs showed statistically significant aesthetic improvement in facial scars [55-56]. Studies have shown that ADSCs can reduce collagen deposition and scar formation in wounds in vitro via the p38/MAPK signaling pathway [57].

4. The Influence of Differentiation Potential of ADSCs in Each Phase of Wound Healing

Wound healing, aimed at skin barrier restoration, is a complex, dynamic, multicellular and interactive process involving the combined effects of several cell types and complex signaling networks. Major cells, which include keratinocytes, fibroblasts, endothelial cells, macrophages and platelets, as well as the growth factors and cytokines, are accurately regulated and involved in several overlapping stages (hemostasis, inflammation, proliferation and remodeling). Keratinocytes and fibroblasts are activated in the inflammatory phase. These several types of cells releasing cytokines and growth factors maintain a stable efficiency in the proliferative phase on restoring vascular perfusion and encouraging wound healing. Different phases after burn injury are consistent and progressive processes. In detail, we will connect ADSCs with these cells and the growth factors associated with each overlapping stage.

4.1. The Phase of Haemostasis and Inflammation

Immediately after the injury, the vascular endothelium and basal lamina were disrupted and exposed, resulting in the extravasation of blood compounds and activating platelet. The most damage in the central portion coagulated and the outer zone presented as ischaemia and potentially salvageable. The outermost region characterized by the hyperaemia and increased inflammatory vasodialation. At the site of injury, the effect of blood clotting and aggregation is typically associated with the release of TGF-β, PDGF, FGFs and EGFs, which are secreted by platelets, keratinocytes, macrophages and fibroblasts [58].

ADSCs were demonstrated to differentiate into keratinocytes, platelets, macrophages and fibroblasts [59-60]. In the research of ADSCs differentiated into keratinocytes, GFP-positive ADSCs were observed in the epidermis and dermis after cell transplantation and the results indicated that adipocytes would transform into a more functional and dedifferentiated state and reverse dermal fibrosis, by promoting dermal adipose tissue regeneration, improving angiogenesis, suppressing macrophage-mediated inflammation and myofibroblast accumulation [61]. Meanwhile, in vitro, ADSCs exhibited keratinocyte-like morphology when cultured in conditioned media from keratinocytes [62]. This demonstrates that ADSCs play a role in dermal wound healing under both physiological and pathological conditions by promoting reepithelialization and angiogenesis.

After burn injury, the outermost portion of the wound would be hyperemia by invigorating inflammatory vasodilation. The inflammatory phase is switched on the neutrophils and monocytes at the affected part and serves to degrade the necrotic tissue [2]. The wound healing process begins with the disruption of blood vessels and infiltration of microbial pathogens at the wound site, leading to a swift onset of acute inflammation driven by pro-inflammatory cells such as neutrophils and macrophages, along with the secretion of cytokines [63].

Meanwhile, in the chronic wound environment, the ADSCs are proven to interrupt and restore the progression of the proliferation and remodeling phases. It is well known that ADSCs have been demonstrated to induce the macrophage phenotype from the pro-inflammatory M1 to the anti-inflammatory and wound healing M2 phenotype [64-65]. Besides, P38/MAPK pathways, species of highly conserved serine or threonine protein kinase in the cytoplasm, are related to the inflammation response and positive regulated collagen synthesis in dermal fibroblasts [66]. Furthermore, according to Vesna Karic et al., the findings of the present study suggest the potential use of lasers (at wavelengths of 940 nm and 660 nm) to prompt the differentiation of ADSCs into fibroblasts [67].

4.2. Phase of Proliferation

Angiogenesis, collagen deposition, granulation tissue development, epithelialization, and wound contraction are all characteristics of the proliferative phase [68]. Keratinocytes play a role at the wound edge at the primal of epithelialization [69] For instance, angiogenesis may be best studied in a chicken chorioallantoic membrane or rabbit cornea model, whereas reepithelialization might be studied in a rabbit ear model [70].. With EGF and high Ca2+ level culturing, ADSCs differentiate into keratinocytes-like cells releasing keratinocyte markers [71].

Angiogenesis, restoration of blood flow, is characterized by the phase of proliferation. Activation of angiogenesis is activated by growth factors and required to sustain the neo-formed granulation tissue as well as aimed to renovate vascular perfusion and further promote wound healing [2]. The study showed that compared to the control animal group, the group for injuected intravenous of ADSCs increased vessel density and tissue neovascularization [72]. ADSCs trigger neovascularization through differentiating into endothelial cells and secreting factors such as VEGF, SDF-1 and HIF-1α [73]. An et al. discovered that ADSCs secrete exosomes overexpressing miR-21, leading to the upregulation

of HIF-1α, VEGF, SDF-1, p-Akt, and p-ERK1/2, as well as the downregulation of PTEN in response to miR-21 overexpression. These results suggest that miR-21-enriched exosomes induce angiogenesis through the activation of Akt and ERK pathways, as well as the expression of HIF-1α and SDF-1 [74].

On the other side, ADSCs are demonstrated that differentiate into endothelial progenitor cells and interact with endothelial cells as well as macrophages to update MCP-1 and VEGF secretion to adjust and control angiogenesis and participate in new vessel formation [75]. Meanwhile, ADSCs differentiated as well as stimulated dermal fibroblasts cooperating with VEGF secretion to enhance the capillary density and accelerate granulation tissue formation [76, 77].

Furthermore, this process activates the differentiation of ADSCs and the secretion of extracellular matrix (ECM), leading to the release of TGF-β, which facilitates wound healing [78]. The research results, TGF-β would regulate melanin production and the activation of keratinocyte differentiation and maturation. In the same way, GDF11 increased cell proliferation and production, angiogenesis and ECM production, leading to improve tissue repair[79-80]. Simultaneously, GDF11 amplified and upregulated TGF-β, associated with MMP-9 resulting in remodelling and wound closure [81-82].

ADSCs are demonstrated to facilitate wound healing through the paracrine operation of diverse cytokines as well as growth factors, and the release of exosomes; meanwhile the PI3K/Akt pathway may participate in the whole process [83]. ADSC-Exos enhanced the protein levels of p-Akt/Akt. At the same time, the activation of PI3K/Akt is the mechanism underlying, suggesting the ADSC-Exos improved exosome-mediated of PI3K/Akt signaling. Meanwhile, the result demonstrated that ADSC-Exos treatment increased the number of blood vessels at the burn area, indicating that ADSC-Exos could accelerate the angiogenesis during the proliferation phase [84].

4.3. Phase of Remodeling

In the phase of remodeling, collagen and elastin are reserved and transformed into fibroblasts to myofibroblasts continuously [85]. The quality and flexibility of the repaired wound and at what stage of scar formation are determined by a fragile balance between combination of myofibroblast and re-epithelialization. The complex wound regrowth response is targeted at restoring closure of the skin barrier and functionality of the skin with the process of dermal and epidermal regeneration [2].

In the experimental studies conducted in 2020, the distinctive effects of ADSCs on the biological characteristics of hypertrophic scar fibroblasts (HSFs) and keloid fibroblasts (KFs) were elucidated. The findings of this research suggest that ADSCs manifest an inhibitory influence on cellular proliferation and migration, along with the downregulation of extracellular matrix protein expression in both HSFs and KFs in vitro. Mechanistically, these effects may be attributed to the suppression of the TGF-β1/Smad signaling pathway. [86]. Claudio Luciano Franck et al. observed substantial disparities in fibrosis at the initiation of the remodeling phase, marked by a pronounced reduction in fibrotic tissue in the group treated with ADSCs during the inflammatory and proliferative phases of wound healing. [87].

Additionally, overexpression of ColI and ColIII resulted in the deposition of collagen, and the contraction of myofibroblasts is increased through α-SMA expression. Treatment with ADSCs showed a significant statistical decrease in ColIand α-SMA expression, which means ADSCs might promote wound healing and reduce scar formation [88] Through the finding of ADSCs, a culture medium would decrease the expression level of p-p38; the anti-fibrotic effect of ADSCs is demonstrated via the p38/MAPK pathway[89]. In general, the decrease in scar fibrosis and abnormal collagen deposition contributed to the remodelling phase as well as reduced hypertrophic scar formation [90].

5. Application and Future Expectations of ADSCs Issues

Eliminating and preventing scar formation is an integral part of burn injury. Although no therapeutic regimen could eliminate scars completely, ADSCs and ADSC-Exos are broadly applied to affect the behaviour of fibroblasts and myofibroblasts [91], and then further influenced actively participation in the wound management and scar formation [92].

Qian Li et al. used an ideal 3D biological scaffold providing a appropriate environment for ADSCs to improve their proliferation and support their differentiation ability [93]. The current techniques for extracting ADSCs from adipose tissue include the Coleman technique, liposuction and direct extraction. ADSCs can reserve in conventional cryopreservation media, which is 90% FBS and 10% Dimethyl sulfoxide (DMSO) [94]. ADSCs wafers are proven to have the effect of anti-scar formation and optimize the quality of new skin during wound healing. Besides, ADSCs are demonstrated to reverse radiation-induce hypermigration of dermal fibroblasts [95].

However, the mechanism of ADSCs action is little understood in wound healing. There is a lot of work to do as far as possible. Identification of specific contents of ADSC-Exos and controlling and regulating the effective target contents are problems we need to solve. Besides, the short half-life and high clearance rate of exosomes impaired the therapeutic effect. Combining ADSCs and ADSC-Exos with proper biomaterials is an urgent question to be solved. ADSCs-Exos be used as a component to store and represent specific proteins, lipids, genetic materials and preferentially transport them to target tissues or organs due to its inherent homing ability or targeting ability of artificial modification [96-97]. Therefore, how to improve the delivery function of exosomes still needs further study.

Due to the disparate mechanism of action of fibroblasts and myofibroblasts in different phases of wound healing, precision therapy is necessary to clarify and regulate the therapeutic effects of ADSCs and ADSC-Exos. Depending on the study of ADSCs at various sections of scar formation has not been figured out so far; the different characteristics of fibroblasts and myofibroblasts have been undefined during the wound repair process. Regarding the problem, although there are plenty of beneficial properties of MSCs or ADSCs, the appropriate therapy direction and purpose are hard to control.

To sum up, more data is needed to determine the differentiation types of ADSCs as well as the induction factors of ADSCs differentiation.

References

[1] Smolle C, Cambiaso-Daniel J, Forbes AA, et al. Recent trends in burn epidemiology worldwide: A systematic review[J]. Burns, 2017,43(2):249-257.

[2] Jeschke MG, van Baar ME, Choudhry MA, et al. Burn injury[J]. Nat Rev Dis Primers, 2020,6(1):1-11.

[3] Almutlaq BA, Jarman A, Alfraihi R, et al. Skin burns in Saudi Arabia: causes, management, outcomes and quality of life after skin burns[J]. Int J Burns Trauma, 2020,10(2):28-37.

[4] Jara CP, Wang O, Paulino do Prado T, et al. Novel fibrin-fibronectin matrix accelerates mice skin wound healing[J]. Bioact Mater, 2020,5(4):949-962.

[5] Tachino J, Matsumoto H, Sugihara F, et al. Development of clinical phenotypes and biological profiles via proteomic analysis of trauma patients[J]. Crit Care. 2022;26(1):241.

[6] Zou ML, Liu SY, Sun ZL, et al. Insights into the role of adipose-derived stem cells: Wound healing and clinical regenerative potential[J]. J Cell Physiol, 2021,236(4):2290-2297.

[7] Lin H, Cheng KC, Lin JA, et al. Pholiota nameko Polysaccharides Protect against Ultraviolet A-Induced Photoaging by Regulating Matrix Metalloproteinases in Human Dermal Fibroblasts[J]. Antioxidants (Basel), 2022,11 (4):739.

[8] Pan Y, Li Y, Liu P, et al. Metabolomics-Based Frailty Biomarkers in Older Chinese Adults[J]. Front Med (Lausanne), 2022,8:830723.

[9] Strong AL, Neumeister MW, Levi B. Stem Cells and Tissue Engineering: Regeneration of the Skin and Its Contents[J]. Clin Plast Surg, 2017,44(3):635-650.

[10] Gümüş K, Demir M. Effect of Haematological Parameters in the Development of Urethrocutaneous Fistula After Hypospadias Surgery[J]. Cureus, 2023,15(3):e36033.

[11] Lee YK, Wadhwa P, Cai H, et al. Micro-CT and Histomorphometric Study of Bone Regeneration Effect with Autogenous Tooth Biomaterial Enriched with Platelet-Rich Fibrin in an Animal Model[J]. Scanning, 2021,2021:6656791.

[12] Shady NH, Mostafa NM, Fayez S, et al. Mechanistic Wound Healing and Antioxidant Potential of Moringa oleifera Seeds Extract Supported by Metabolic Profiling, In Silico Network Design, Molecular Docking, and In Vivo Studies[J]. Antioxidants (Basel), 2022,11(9):1743.

[13] Li P, Guo X. A review: therapeutic potential of adipose-derived stem cells in cutaneous wound healing and regeneration[J]. Stem Cell Res Ther, 2018,9(1):302.

[14] Morretta E, D'Agostino A, Cassese E, et al. Label-Free Quantitative Proteomics to Explore the Action Mechanism of the Pharmaceutical-Grade Triticum vulgare Extract in Speeding Up Keratinocyte Healing[J]. Molecules, 2022,27 (3): 1108.

[15] Dou B, Zheng X, Tan D, Yin X. The Effect of HRE-Regulated VEGF Expression and Transfection on Neural Stem Cells in Rats[J]. Front Cell Dev Biol, 2020,8:580824.

[16] Zhang Y, Bai X, Shen K, et al. Exosomes Derived from Adipose Mesenchymal Stem Cells Promote Diabetic Chronic Wound Healing through SIRT3/SOD2[J]. Cells, 2022,11 (16): 2568.

[17] Yan ZH, Li ZL, Chen XW, et al. Misdiagnosis of scalp angiosarcoma: A case report[J]. World J Clin Cases, 2023,11 (13): 3099-3104.

[18] Zaharie RD, Popa C, Schlanger D, et al. The Role of IL-22 in Wound Healing. Potential Implications in Clinical Practice[J]. Int J Mol Sci, 2022,23(7):3693.

[19] Jorgensen AM, Varkey M, Gorkun A, et al. Bioprinted Skin Recapitulates Normal Collagen Remodeling in Full-Thickness Wounds[J]. Tissue Eng Part A, 2020,26(9-10):512-526.

[20] Elmasry M, Steinvall I, Thorfinn J, et al. Temporary coverage of burns with a xenograft and sequential excision, compared with total early excision and autograft[J]. Ann Burns Fire Disasters, 2016,29(3):196-201.

[21] Putri NM, Kreshanti P, Syarif AN, et al. Efficacy of tilapia skin xenograft compared to paraffin-impregnated gauze as a full-thickness burn dressing after excisional debridement: A case series[J]. Int J Surg Case Rep, 2022,95:107240.

[22] Zhu T, Jiang J, Zhao J, et al. Regulating Preparation Of Functional Alginate-Chitosan Three-Dimensional Scaffold For Skin Tissue Engineering[J]. Int J Nanomedicine, 2019;14: 8891-8903.

[23] Persinal-Medina M, Llames S, Chacón M, et al. Polymerizable Skin Hydrogel for Full Thickness Wound Healing[J]. Int J Mol Sci, 2022,23(9):4837.

[24] Mazini L, Rochette L, Admou B, et al. Hopes and Limits of Adipose-Derived Stem Cells (ADSCs) and Mesenchymal Stem Cells (MSCs) in Wound Healing[J]. Int J Mol Sci, 2020,21(4):1306.

[25] Jo H, Brito S, Kwak BM, et al. Applications of Mesenchymal Stem Cells in Skin Regeneration and Rejuvenation[J]. Int J Mol Sci, 2021,22(5):2410.

[26] Yi S, Zhang Y, Gu X, et al. Application of stem cells in peripheral nerve regeneration[J]. Burns Trauma, 2020,8: tkaa 002.

[27] Mandal P, De D, Im DU, et al. Exosome-Mediated Differentiation of Mouse Embryonic Fibroblasts and Exocrine Cells into β-Like Cells and the Identification of Key miRNAs for Differentiation[J]. Biomedicines, 2020,8(11):485.

[28] Jurek S, Sandhu MA, Trappe S, et al. Optimizing adipogenic transdifferentiation of bovine mesenchymal stem cells: a prominent role of ascorbic acid in FABP4 induction[J]. Adipocyte, 2020,9(1):35-50.

[29] Mizuno H, Tobita M, Uysal AC. Concise review: Adipose-derived stem cells as a novel tool for future regenerative medicine[J]. Stem Cells, 2012,30(5):804-810.

[30] Song L, Young NJ, Webb NE, et al. Origin and characterization of multipotential mesenchymal stem cells derived from adult human trabecular bone[J]. Stem Cells Dev, 2005,14(6):712-721.

[31] Yi H, Wang Y, Liang Q, et al. Preclinical and Clinical Amelioration of Bone Fractures with Mesenchymal Stromal Cells: a Systematic Review and Meta-Analysis[J]. Cell Transplant, 2022,31:9636897211051743.

[32] Yang G, Wang F, Li Y, et al. Construction of tissue engineering bone with the co-culture system of ADSCs and VECs on partially deproteinized biologic bone in vitro: A preliminary study[J]. Mol Med Rep, 2021,23(1):58.

[33] Chen Y, Li C, Li C, et al. Tailorable Hydrogel Improves Retention and Cardioprotection of Intramyocardial Transplanted Mesenchymal Stem Cells for the Treatment of Acute Myocardial Infarction in Mice[J]. J Am Heart Assoc, 2020,9(2): e013784.

[34] Subhan BS, Kwong J, Kuhn JF, et al. Amniotic fluid-derived multipotent stromal cells drive diabetic wound healing through modulation of macrophages[J]. J Transl Med, 2021,19(1):16.

[35] Yang CH, Lin DY, Lin YS, et al. The Immunological Microenvironment and the Emerging Role of Stem Cells Therapy in Peyronie's Disease: A Systematic Narrative Review[J]. Int J Mol Sci, 2023,24(1):777.

[36] Wu SH, Yu JH, Liao YT, et al. Comparison of the Infant and Adult Adipose-Derived Mesenchymal Stem Cells in Proliferation, Senescence, Anti-oxidative Ability and Differentiation Potential[J]. Tissue Eng Regen Med, 2022, 19(3): 589-601.

[37] Zarei H, Karimpour A, Reza Khalatbary A, et al. Homing of adipose stem cells on the human amniotic membrane as a scaffold: A histological study[J]. Int J Reprod Biomed, 2020, 18 (1):21-32.

[38] Bukowska J, Szóstek-Mioduchowska AZ, Kopcewicz M, et al. Adipose-Derived Stromal/Stem Cells from Large Animal Models: from Basic to Applied Science[J]. Stem Cell Rev Rep, 2021,17(3):719-738.

[39] Zhou Y, Zhang XL, Lu ST, et al. Human adipose-derived mesenchymal stem cells-derived exosomes encapsulated in pluronic F127 hydrogel promote wound healing and regeneration [J]. Stem Cell Res Ther, 2022,13(1):407.

[40] Yamada Y, Wang XD, Yokoyama S, et al. Cardiac progenitor cells in brown adipose tissue repaired damaged myocardium. Biochem Biophys Res Commun[J], 2006,342(2):662-670.

[41] Miyahara Y, Nagaya N, Kataoka M, et al. Monolayered mesenchymal stem cells repair scarred myocardium after myocardial infarction. Nat Med, 2006,12(4):459-465.

[42] Wang H, Shi J, Wang Y, et al. Promotion of cardiac differentiation of brown adipose derived stem cells by chitosan hydrogel for repair after myocardial infarction[J]. Biomaterials, 2014,35(13):3986-3998.

[43] Stougiannou TM, Christodoulou KC, Dimarakis I, et al. To Repair a Broken Heart: Stem Cells in Ischemic Heart Disease[J]. Curr Issues Mol Biol, 2024,46(3):2181-2208.

[44] Abderrahim-Ferkoune A, Bezy O, Astri-Roques S, et al. Transdifferentiation of preadipose cells into smooth muscle-like cells: role of aortic carboxypeptidase-like protein[J]. Exp Cell Res, 2004,293(2):219-228.

[45] Jack GS, Almeida FG, Zhang R, et al. Processed lipoaspirate cells for tissue engineering of the lower urinary tract: implications for the treatment of stress urinary incontinence and bladder reconstruction[J]. J Urol, 2005,174(5):2041-2045.

[46] Constantin A, Filippi A, Alexandru N, et al. Extracellular Vesicles from Adipose Tissue Stem Cells in Diabetes and Associated Cardiovascular Disease; Pathobiological Impact and Therapeutic Potential[J]. Int J Mol Sci, 2020,21(24):9598.

[47] Shrestha KR, Jeon SH, Jung AR, et al. Stem Cells Seeded on Multilayered Scaffolds Implanted into an Injured Bladder Rat Model Improves Bladder Function[J]. Tissue Eng Regen Med. 2019,16(2):201-212.

[48] Zhou Z, Yan H, Liu Y, et al. Adipose-derived stem-cell-implanted poly(ϵ-caprolactone)/chitosan scaffold improves bladder regeneration in a rat model[J]. Regen Med, 2018,13 (3): 331-342.

[49] Gao Q, Ma X, Qi Z. Comprehensive Analysis of Novel Genes and Pathways Associated with Osteogenic Differentiation of Adipose Stem Cells[J]. Dis Markers, 2022,2022:4870981.

[50] Chen M, Zhou M, Fu Y, et al. Effects of miR-672 on the angiogenesis of adipose-derived mesenchymal stem cells during bone regeneration[J]. Stem Cell Res Ther, 2021,12(1):85.

[51] Naderi N, Combellack EJ, Griffin M, et al. The regenerative role of adipose-derived stem cells (ADSC) in plastic and reconstructive surgery[J]. Int Wound J, 2017,14(1):112-124.

[52] El Hage R, Knippschild U, Arnold T, et al. Stem Cell-Based Therapy: A Promising Treatment for Diabetic Foot Ulcer[J]. Biomedicines, 2022,10(7):1507.

[53] Behrangi E, Moradi S, Ghassemi M, et al. The investigation of the efficacy and safety of stromal vascular fraction in the treatment of nanofat-treated acne scar: a randomized blinded controlled clinical trial[J]. Stem Cell Res Ther, 2022,13(1):298.

[54] Czerwiec K, Zawrzykraj M, Deptuła M, et al. Adipose-Derived Mesenchymal Stromal Cells in Basic Research and Clinical Applications[J]. Int J Mol Sci, 2023,24(4):3888.

[55] Bhooshan LS, Devi MG, Aniraj R, et al. Autologous emulsified fat injection for rejuvenation of scars: A prospective observational study. Indian J Plast Surg[J], 2018,51(1):77-83.

[56] Gu Z, Li Y, Li H. Use of Condensed Nanofat Combined With Fat Grafts to Treat Atrophic Scars[J]. JAMA Facial Plast Surg, 2018,20(2):128-135.

[57] Chai CY, Song J, Tan Z, et al. Adipose tissue-derived stem cells inhibit hypertrophic scar (HS) fibrosis via p38/MAPK pathway[J]. J Cell Biochem, 2019,120(3):4057-4064.

[58] Liarte S, Bernabé-García Á, Nicolás FJ. Human Skin Keratinocytes on Sustained TGF-β Stimulation Reveal Partial EMT Features and Weaken Growth Arrest Responses[J]. Cells, 2020,9(1):255.

[59] Zhou ZQ, Chen Y, Chai M, et al. Adipose extracellular matrix promotes skin wound healing by inducing the differentiation of adipose-derived stem cells into fibroblasts[J]. Int J Mol Med, 2019,43(2):890-900.

[60] Goodarzi P, Alavi-Moghadam S, Sarvari M, et al. Adipose Tissue-Derived Stromal Cells for Wound Healing[J]. Adv Exp Med Biol, 2018,1119:133-149.

[61] Wang J, Cai J, Zhang Q, et al. Fat transplantation induces dermal adipose regeneration and reverses skin fibrosis through dedifferentiation and redifferentiation of adipocytes[J]. Stem Cell Res Ther, 2022,13(1):499.

[62] Ebrahimian TG, Pouzoulet F, Squiban C, et al. Cell therapy based on adipose tissue-derived stromal cells promotes physiological and pathological wound healing[J]. Arterioscler Thromb Vasc Biol, 2009,29(4):503-510.

[63] Chen LY, Cheng HL, Kuan YH, et al. Therapeutic Potential of Luteolin on Impaired Wound Healing in Streptozotocin-Induced Rats[J]. Biomedicines, 2021,9(7):761.

[64] Manning CN, Martel C, Sakiyama-Elbert SE, et al. Adipose-derived mesenchymal stromal cells modulate tendon fibroblast responses to macrophage-induced inflammation in vitro[J]. Stem Cell Res Ther, 2015,6(1):74.

[65] Lo Sicco C, Reverberi D, Balbi C, et al. Mesenchymal Stem Cell-Derived Extracellular Vesicles as Mediators of Anti-Inflammatory Effects: Endorsement of Macrophage Polarization [J]. Stem Cells Transl Med, 2017,6(3):1018-1028.

[66] Du QC, Zhang DZ, Chen XJ, et al. The effect of p38MAPK on cyclic stretch in human facial hypertrophic scar fibroblast differentiation[J]. PLoS One, 2013,8(10):e75635.

[67] Karic V, Chandran R, Abrahamse H. 940 nm diode laser induced differentiation of human adipose derived stem cells to temporomandibular joint disc cells[J]. BMC Biotechnol, 2022,22(1):23.

[68] Quazi A, Patwekar M, Patwekar F, et al. Evaluation of Wound Healing Activity (Excision Wound Model) of Ointment Prepared from Infusion Extract of Polyherbal Tea Bag Formulation in Diabetes-Induced Rats[J]. Evid Based Complement Alternat Med, 2022,2022:1372199.

[69] Yang D, Fu M, Zhao Q, et al. α-ionone promotes keratinocyte functions and accelerates epidermal barrier recovery[J]. Ann Transl Med, 2023,11(8):297.

[70] Freedman BR, Hwang C, Talbot S, et al. Breakthrough treatments for accelerated wound healing[J]. Sci Adv, 2023,9(20): eade7007.

[71] Chavez-Munoz C, Nguyen KT, Xu W, et al. Transdifferentiation of adipose-derived stem cells into keratinocyte-like cells: engineering a stratified epidermis[J]. PLoS One, 2013,8(12):e80587.

[72] Ebrahimian TG, Pouzoulet F, Squiban C, et al. Cell therapy based on adipose tissue-derived stromal cells promotes physiological and pathological wound healing[J]. Arterioscler Thromb Vasc Biol, 2009,29(4):503-510.

[73] Vanderstichele S, Vranckx JJ. Anti-fibrotic effect of adipose-derived stem cells on fibrotic scars[J]. World J Stem Cells, 2022,14(2):200-213.

[74] An Y, Zhao J, Nie F, et al. Exosomes from Adipose-Derived Stem Cells (ADSCs) Overexpressing miR-21 Promote Vascularization of Endothelial Cells[J]. Sci Rep, 2019,9 (1): 12861.

[75] Mazini L, Rochette L, Admou B, et al. Hopes and Limits of Adipose-Derived Stem Cells (ADSCs) and Mesenchymal Stem Cells (MSCs) in Wound Healing[J]. Int J Mol Sci, 2020,21(4):1306.

[76] Marfia G, Navone SE, Di Vito C, et al. Mesenchymal stem cells: potential for therapy and treatment of chronic non-healing skin wounds[J]. Organogenesis, 2015,11(4):183-206.

[77] Gaur M, Dobke M, Lunyak VV. Mesenchymal Stem Cells from Adipose Tissue in Clinical Applications for Dermatological Indications and Skin Aging[J]. Int J Mol Sci, 2017,18(1):208.

[78] Kim YJ, Seo DH, Lee SH, et al. Conditioned media from human umbilical cord blood-derived mesenchymal stem cells stimulate rejuvenation function in human skin[J]. Biochem Biophys Rep, 2018,16:96-102.

[79] Bellei B, Migliano E, Tedesco M, et al. Adipose tissue-derived extracellular fraction characterization: biological and clinical considerations in regenerative medicine[J]. Stem Cell Res Ther, 2018,9(1):207.

[80] Idkowiak-Baldys J, Santhanam U, Buchanan SM, et al. Growth differentiation factor 11 (GDF11) has pronounced effects on skin biology[J]. PLoS One, 2019,14(6): e0218035.

[81] Mohan R, Chintala SK, Jung JC, et al. Matrix metalloproteinase gelatinase B (MMP-9) coordinates and effects epithelial regeneration[J]. J Biol Chem, 2002,277(3): 2065-2072.

[82] Kobayashi T, Kim H, Liu X, et al. Matrix metalloproteinase-9 activates TGF-β and stimulates fibroblast contraction of collagen gels[J]. Am J Physiol Lung Cell Mol Physiol, 2014, 306 (11):L1006-L1015.

[83] Kirby GT, Mills SJ, Cowin AJ, et al. Stem Cells for Cutaneous Wound Healing[J]. Biomed Res Int, 2015,2015:285869.

[84] Zhang W, Bai X, Zhao B, et al. Cell-free therapy based on adipose tissue stem cell-derived exosomes promotes wound healing via the PI3K/Akt signaling pathway[J]. Exp Cell Res, 2018,370(2):333-342.

[85] Skowrońska W, Bazylko A. The Potential of Medicinal Plants and Natural Products in the Treatment of Burns and Sunburn-A Review[J]. Pharmaceutics, 2023,5(2):633.

[86] Xie F, Teng L, Xu J, et al. Adipose-derived mesenchymal stem cells inhibit cell proliferation and migration and suppress extracellular matrix synthesis in hypertrophic-scar and keloid fibroblasts[J]. Exp Ther Med. 2021;21(2):139.

[87] Franck CL, Senegaglia AC, Leite LMB, et al. Influence of Adipose Tissue-Derived Stem Cells on the Burn Wound Healing Process[J]. Stem Cells Int. 2019; 2019:2340725.

[88] Li Y, Zhang W, Gao J, et al. Adipose tissue-derived stem cells suppress hypertrophic scar fibrosis via the p38/MAPK signaling pathway[J]. Stem Cell Res Ther, 2016,7(1):102.

[89] Xiao H, Zhang YY. Understanding the role of transforming growth factor-beta signalling in the heart: overview of studies using genetic mouse models[J]. Clin Exp Pharmacol Physiol, 2008,35(3):335-341.

[90] Li Y, Zhang W, Gao J, et al. Adipose tissue-derived stem cells suppress hypertrophic scar fibrosis via the p38/MAPK signaling pathway. Stem Cell Res Ther[J], 2016,7(1):102.

[91] Wu J, Yang Q, Wu S, et al. Adipose-Derived Stem Cell Exosomes Promoted Hair Regeneration[J]. Tissue Eng Regen Med, 2021,18(4):685-691.

[92] Wang T, Li T, Niu X, et al. ADSC-derived exosomes attenuate myocardial infarction injury by promoting miR-205-mediated cardiac angiogenesis[J]. Biol Direct, 2023,18(1):6.

[93] Li Q, Zheng J, Li Z, et al. Drug-free in vitro activation combined with 3D-bioprinted adipose-derived stem cells restores ovarian function of rats with premature ovarian insufficiency[J]. Stem Cell Res Ther, 2022,13(1):347.

[94] Dai R, Wang Z, Samanipour R, et al. Adipose-Derived Stem Cells for Tissue Engineering and Regenerative Medicine Applications[J]. Stem Cells Int, 2016,2016:6737345.

[95] Yu J, Wang MY, Tai HC, et al. Cell sheet composed of adipose-derived stem cells demonstrates enhanced skin wound healing with reduced scar formation[J]. Acta Biomater, 2018,77:191-200.

[96] Xiong M, Zhang Q, Hu W, et al. Exosomes From Adipose-Derived Stem Cells: The Emerging Roles and Applications in Tissue Regeneration of Plastic and Cosmetic Surgery[J]. Front Cell Dev Biol, 2020,8:574223.

[97] Liu Y, Wang H, Wang J. Exosomes as a novel pathway for regulating development and diseases of the skin[J]. Biomed Rep, 2018,8(3):207-214.