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REVIEW

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The role of adipose tissue-derived stromal cells, macrophages and bioscaffolds in cutaneous wound repair

S. Gandolfi^{1,2*}, A. Sanouj¹, B. Chaput², A. Coste¹, B. Sallerin^{1,3} and A. Varin¹

Abstract

Skin healing is a complex and dynamic physiological process that follows mechanical alteration of the skin barrier. Under normal conditions, this complex process can be divided into at least three continuous and overlapping phases: an inflammatory reaction, a proliferative phase that leads to tissue reconstruction and a phase of tissue remodeling. Macrophages critically contribute to the physiological cascade for tissue repair. In fact, as the inflammatory phase progresses, macrophage gene expression gradually shifts from pro-inflammatory M1-like to pro-resolutive M2-like characteristics, which is critical for entry into the repair phase. A dysregulation in this macrophage shift phenotype leads to the persistence of the inflammatory phase. Mesenchymal stromal cells and specifically the MSC-derived from adipose tissue (ADSCs) are more and more used to treat inflammatory diseases and several studies have demonstrated that ADSCs promote the wound healing thanks to their neoangiogenic, immunomodulant and regenerative properties. In several studies, ADSCs and macrophages have been injected directly into the wound bed, but the delivery of exogenous cells directly to the wound raises the problem of cell engraftment and preservation of pro-resolutive phenotype and viability of the cells. Complementary approaches have therefore been explored, such as the use of biomaterials enriched with therapeutic cells to improve cell survival and function. This review will present a background of the current scaffold models, using adipose derived stromal-cells and macrophages as therapeutic cells for wound healing, through a discussion on the potential impact for future applications in skin regeneration. According to the PRISMA statement, we resumed data from investigations reporting the use of ADSCs and bioscaffolds and data from macrophages behavior with functional biomaterials in wound healing models. In the era of tissue engineering, functional biomaterials, that can maintain cell delivery and cellular viability, have had a profound impact on the development of dressings for the treatment of chronic wounds. Promising results have been shown in pre-clinical reports using ADSCs- and macrophages-based scaffolds to accelerate and to improve the quality of the cutaneous healing.

Keywords Chronic wounds, Cellular therapies, Bioscaffolds

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Background

Skin healing is a physiological, complex and dynamic process, which follows a mechanical alteration of the skin barrier. Local and/or general conditions of the patient can alter this sophisticated mechanism, leading to the development of chronic wounds, instead of following the physiological healing cascade [1–3]. Accordingly, chronic wounds represent a major health problem with related



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costs to healthcare system, affecting patient's quality of life, and not far from serious health complications as septic phenomena or secondary malignant transformation such as squamous cell carcinomas [4]. Despite recent advances in comprehension of the pathophysiology of wound healing and the development of new therapeutic methods [5–7], the treatment of many chronic wounds remain still unsatisfactory and traditional therapies have shown some limited effectiveness. Therefore, there is a constant need of therapeutic innovations in chronic wound care. Indeed, cell transplantation therapies have been widely explored as an alternative method for skin regeneration [8]. However, the direct administration of stromal cells or blood cells can be defective, creating problems of cell viability and functionality [9, 10]. In this concept, bioactive scaffolds, made up of functional biomaterials and enriched with therapeutic cell, are thought to be preferential in guiding cutaneous regeneration by providing not only a support for therapeutic cell colonization, migration and growth, but also by providing a suitable structure for cell survival. This review will present a background of the current scaffold models, using adipose derived stromal-cells and macrophage as therapeutic cells for wound healing, through a discussion on the potential impact for future applications in skin regeneration.

Chronic wounds pathophysiology

Soft tissue healing process is a dynamic process involving soluble mediators, blood cells, extracellular matrix, and parenchymal cells, creating a cascade of events leading to the reconstitution of the skin layers barrier.

In a normal condition, this process undergo three distinct and subsequent phases of inflammation, cell proliferation, and scar remodeling [11].

After a vascular phase, leading to the formation of the hemostatic clot by platelets [12], numerous vasoactive mediators and chemotactic factors are generated and activated complement pathways. These substances recruit inflammatory leukocytes to the site of injury to promote a detersive inflammatory phase, characterized by a significant release of pro-inflammatory cytokines and factors as tumor necrosis factor-alpha (TNF- α), interleukin 1-beta (IL-1 β), or matrix metalloproteinases (MMPs) [13]. Neutrophils, recruited in the wounded area, clean up foreign particles, cell debris and bacteria.

Simultaneously, skin macrophages originate from yolk sac-derived primitive hematopoiesis, are involved in this process [14]. Macrophages exhibit various functional phenotypes in response to microenvironmental stimuli, a phenomenon known as macrophage polarization [14–16]. This polarization can either promote or inhibit the inflammatory phase of wound healing. During wound

healing macrophages develop a range of phenotypes and functions from (i) "classically-activated" pro-inflammatory or "M1" macrophages, which release pro-inflammatory cytokines such as IL-12, IL-1 β , IL-6, TNF α , reactive oxygen species (ROS) and inducible nitric oxide synthase (iNOS), and are involved in pathogen elimination, inflammatory cytokine release, and inducing a Th1-type response; to (ii) "alternatively-activated" anti-inflammatory or "M2" macrophages, which promote angiogenesis, extracellular matrix repair, release of anti-inflammatory cytokines, and resolution of inflammation [15].

During the inflammatory stage of wound healing, macrophages migrate to the wound site, and immediately mature into pro-inflammatory M1 macrophages (M1-M ϕ) [15]. As the inflammatory phase progresses, macrophage plasticity enables them to gradually shift from pro-inflammatory M1-like to pro-resolutive M2-like, which is critical for entry into the repair phase [16–18]. This phase of resolution is conditioned by the macrophages' efferocytosis of the apoptotic neutrophils. This phenomenon favors the transition from the M1 to the M2 phenotype, leading to the shift from a pro-inflammatory environment to a pro-resolving environment. This process culminates in a proliferative phase with the development of a granulation tissue in order to fill and stabilize the soft tissue defect.

Under the stimulus of anti-inflammatory cytokines and factors such as the IL-4, IL-10 and tumor growth factor-beta (TGF- β), pro-resolutive macrophages (M2-M ϕ) induce proliferation of fibroblasts and stimulate their production of new extracellular matrix. Moreover, the presence of proangiogenic factors in this anti-inflammatory microenvironment will promote neoangiogenesis and neovascularization, facilitating the delivery of oxygen, nutrients, and restoring cells to the wound site [19]. Pro-resolutive macrophages (M2-M ϕ) and these mediators are necessary for the initiation and propagation of the wound repair mechanism, leading then to the re-epithelization of the tissue and the remodeling of the newly produced tissue. In fact, pro-resolutive macrophages (M2-M ϕ) are highly immunosuppressive and secrete multiple angiogenic and growth factors, cytokines and chemokines as metalloproteinases (MMPs), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), IL-8, TGF- β , IL-10, which are essential for the proliferation and the differentiation of endothelial cells and keratinocytes, and for the recruitment of fibroblasts in order to reconstruct the skin's integrity [20]. During the proliferation phase, the secretion of PDGF- α and TGF- β by macrophages induce fibroblast proliferation and differentiation into myofibroblasts [21], responsible of the wound contraction as well as collagen synthesis

and deposition. Characteristics to distinguish between M1-like and M2-like activation states of macrophages are resumed in Table 1 [22]. For a normal healing process, all of the above stages must function in a proper sequence and on specific times [1, 19] (Fig. 1). As described above, macrophages have a central role in the transition between the inflammatory and the repair phase demonstrating that macrophage plasticity is crucial for wound [23]: it appears that in most chronic wounds, tissue regeneration is arrested in the inflammatory phase, which leads to a pathological inflammation and the inability of the endogenous repair response to progress to the advanced stages of wound healing. The ongoing inflammatory phase leads to abnormal production of inflammatory cytokines and abnormal degradation of the extracellular matrix due to increased secretion of matrix metalloproteinases [24]. Some local or systemic factors, resumed in Table 2, can participate in chronic wounds, and given the high inflamed environment, these wounds fail to respond to conventional therapies [25].

Table 1 Characteristics of pro-inflammatory-like and pro-resolutive-like macrophages

	Pro-inflammatory like Mφ	Pro-resolutive like Mφ
Activation signals	LPS TNF-α	IL-13 IL-4 IL-10
Activation markers	ROS IL-1β IL-8 IL-12	IL-10 IL-1RA; IL-1R2 CD36 CD206
Functions	Inflammation Immunogenicity	Inflammation resolution Tissue repair

Table 2 Local and systemic factors favoring the development of chronic wounds

Local factors	Systemic factors
Infections	Nutritional deficiencies
Foreign materials	Smoking
Ischemia	Neuropathies
Arterial/Venous insufficiency	Hormonal contextes
Radiations	Uremia
Cancer	Immunitary diseases
Bone/tendon/articular exposition	Diabetes mellitus

Current treatments for chronic wounds

Clinical treatments for chronic cutaneous wounds include the use of specific dressings or surgical coverage as skin grafts, dermal substitutes or reconstruction by flaps. Debridement is the first preliminary phase in preparing chronic wound beds. It corresponds to the removal of necrotic tissue from the wound. Before debridement, the wound is generally filled with a non-vascularized fibrinous tissue (Fig. 2A) or dry necrosis (Fig. 2B). The presence of necrotic tissue not only prevents the wound repair cascade but also can cause local or even systemic infections [26, 27]. Debridement can be chemical or mechanical, obtained respectively by specific dressings or surgery.

In case of a though necrosis, hydrogel dressings achieve debridement by rehydration, molting, and removal of inactivated and necrotic tissue [28, 29]. The choice of a suitable dressing depends on several factors: wound’s origin and location, its appearance (dry, fibrinous, necrotic, exudative), the depth and the surface area, the quality of the peripheral skin or the presence of infection [26]. A

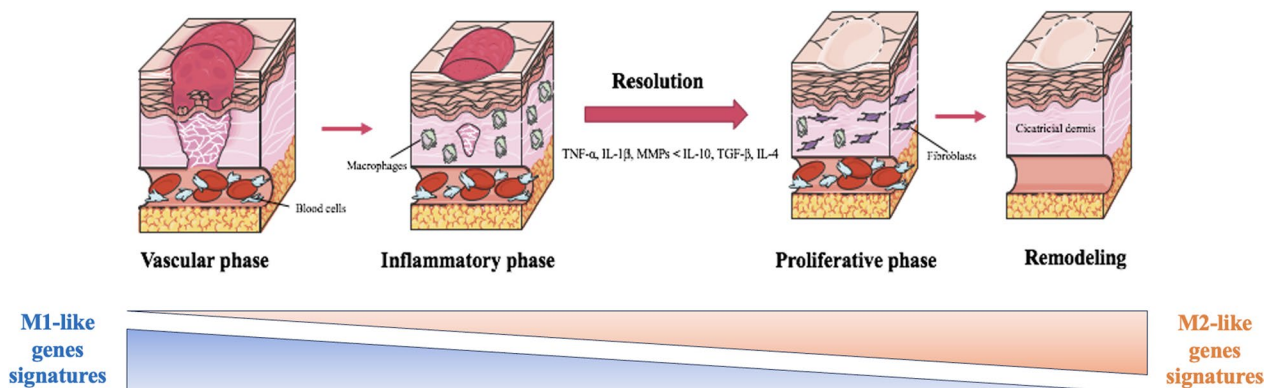


Fig. 1 Schematic representation of the normal healing process. Under the effect of anti-inflammatory cytokines (IL-4, IL-10, TGF-β) produced by the anti-inflammatory macrophages M1-Mφ, the resolution of the inflammatory phase proceeds to enhance the proliferative phase of the healing process

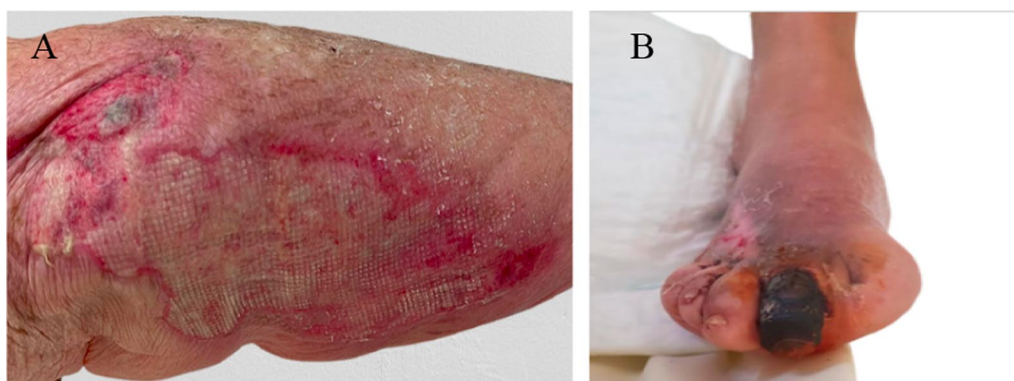


Fig. 2 **A** Fibrinous wound in a posterior forearm after a thermic burn; **B** toe dry necrosis secondary of a vascular insufficiency

thorough semiotic examination of the wound is necessary in order to prepare the best treatment protocol (Fig. 3).

The different classes of dressings explain the multitude of products available on the market that have been shown to have therapeutic potential [30, 31]. Hydrocolloid occlusive dressings composed by carboxymethyl cellulose and polyurethane are suitable in case of exudative wounds. When the hydrocolloid dressing comes into contact with the wound exudate, the matrix forms a gel layer promoting debridement and the formation of a granulation tissue [32, 33]. Alginates are natural polysaccharides extracted from brown algae and characterised by their absorption capacity and their haemostatic properties. In addition, they have anti-bacterial properties and promotes neovascularization by enlarging

calcium after contact with saline solution [34, 35]. Hydrofibers have a high exudate absorption capacity, approximately 30 times their weight. On contact with the exudate, this dressing retains the fluid and maintains a moist environment [36]. Table 3 resumes the main dressings characteristics.

Other technique to accelerate wound healing process is the negative-pressure therapy. This technique accelerates the proliferative stage of wound healing and favor the collection of secretions [36, 37]. The use of hyperbaric oxygen therapy promotes healing in certain complex situations of extensive skin damage or in serious soft tissue infections such as necrotizing dermo-hypodermis. [38]. Very effective on anaerobic germs, this method ensures a good local oxygenation of the tissues [39].

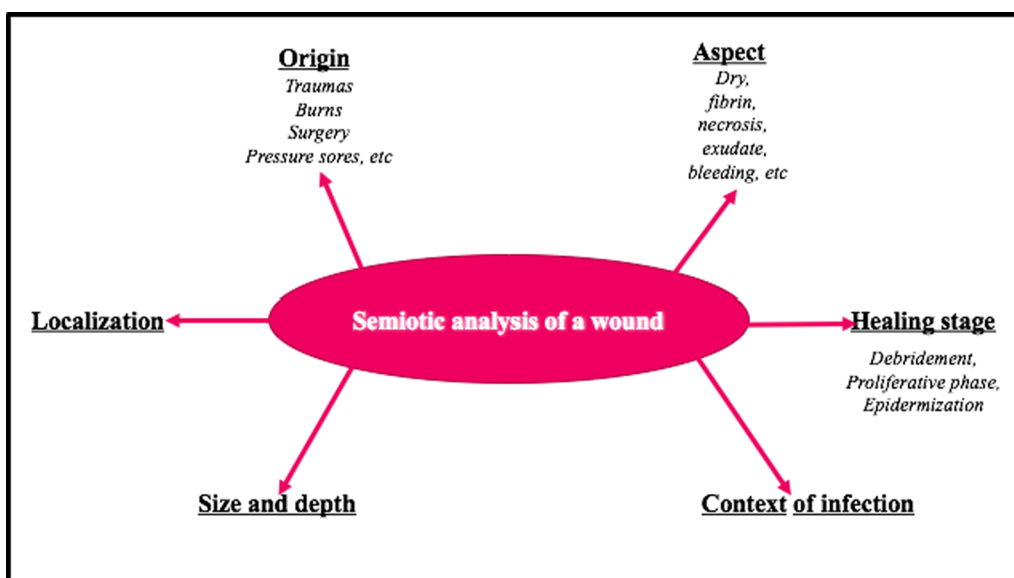


Fig. 3 Characteristics to be considered for a proper semiotic analysis of a wound

Table 3 Characteristics of the most common dressing in clinical practice

Dressing	Composition	Properties	Indications
Hydrocolloide	CMC + polyurethane	<ul style="list-style-type: none"> • Maintains a moist wound environment • Turns to gel on contact with exudate • Produces a "pus-like" substance • Adheres to healthy skin but not to the wound • Impermeable to liquids (showering authorized) 	<ul style="list-style-type: none"> • Can be used at all stages of healing • Poorly exuding wounds
Hydrocellular	polyurethane foam	<ul style="list-style-type: none"> • High absorption • Promotes healing and drainage of exudates 	<ul style="list-style-type: none"> • Exudative budding phase • Post-surgical dressing
Hydrogel	H ₂ O in gel form, translucent sheets or compresses	<ul style="list-style-type: none"> • Stimulate the autolytic detersion process • Absorb exudates and fibrino-leukocyte debris 	<ul style="list-style-type: none"> • Detersion and healing of dry wounds • Softening of necrotic plaques
Alginate	Polysaccharides extracted from brown seaweed, immersed in a calcium solution	<ul style="list-style-type: none"> • Na⁺Ca²⁺ in contact with exudates: gelling of alginate fibers + activation of platelet plug 	<ul style="list-style-type: none"> • Absorption of exudates • Promotes detersion • Treatment of hemorrhagic or bleeding wounds
Hydrofiber	CMC fibers	<ul style="list-style-type: none"> • Absorption of exudates • Controls bacterial contamination 	<ul style="list-style-type: none"> • Absorption of exudates • Detersion and budding
Charcoal dressing	Charcoal and metal (Cu ²⁺ , Ag ⁺) layers dressing	<ul style="list-style-type: none"> • Retains odors • Absorption numerous compounds (bacteria) • Removes wet necrosis and fibrin 	<ul style="list-style-type: none"> • Smelly and exuding wounds • Infected wounds

CMC carboxymethylcellulose

In case of extensive skin wounds or a stagnant healing process, surgery can be indicated. To cover a soft tissue defect, surgery includes the realization of autologous skin grafts or flaps (Figs. 4, 5), the implantation of keratinocytes after cultures, or the use of dermal substitutes [40]. Autologous skin grafts are a common way to treat full-thickness wounds, where harvested skin (epidermis or epidermis with dermis) is transferred from a sane site of the body to the injured area. Autologous keratinocytes

produced in vitro have been used to treat serious burns for a long time in human patients [41], but recently, focus has shifted to regenerate the dermal component of the skin to overcome the lack of dermis in skin grafts [42]. For this reason, at the date, there are several commercialized dermal matrices differing essentially in the involvement of a single or two operative steps. Numerous animal studies have been carried out to determine which product provides the best graft or the best functional result,

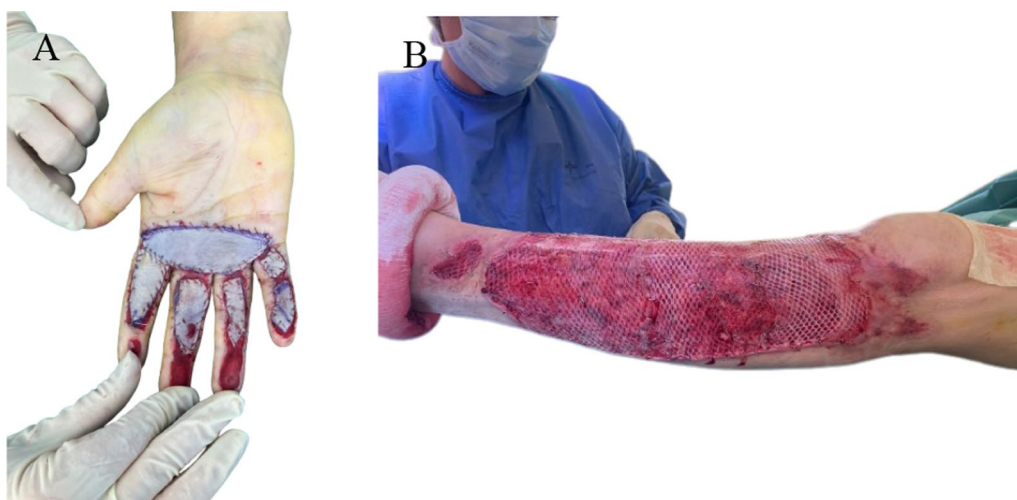


Fig. 4 Skin grafts, immediate post-operative aspects. **A** Total skin graft realized; **B** thin meshed skin graft



Fig. 5 Skin flap. A flap is a vascularized tissue that is transferred to a loss of substance. Black arrow points to the vascular pedicle

but, there does not seem to be any significant difference between products [43]. The main advantages of artificial dermis are dominated by the quality of the functional and aesthetic results (better elasticity, less retraction, tendon gliding plane). The disadvantages are above all the costs and the high susceptibility to infections requiring a perfect decontaminated operating site.

Cell therapy as an innovative treatment in wound healing: focus on Adipose derived stromal cells and macrophages

Adipose derived stromal cell: history and characteristics

At the end of the nineteenth century, the German surgeon Gustav Neuber first described the technique of autologous adipose tissue graft reporting successful outcomes after transplanting fat beneath atrophic scars in orbital frame [44]. For a long time, this autologous fat transfer procedure proved to be defective: the re-injected fat tended to resorb significantly, with unpredictable results.

It was not until the end of the twentieth century that this practice spread to the field of cosmetic surgery, with more stable and more reproducible results, thanks to the introduction in 1995 by Doctor Coleman of a rigorous procedure for purifying the lipoaspirate before reinjection [45].

With this technique, the surviving grafted adipocytes continue their development cycle in the recipient site, and the graft of surviving adipose tissue generates adipocytes by induction [46].

The ultimate aim of the current fat grafting technique is therefore to create adipose tissue from the adipose tissue.

This technique is extensively used in reconstruction, especially to fill a loss of substance, but also in cosmetic surgery, where the aim is to create a volumizing filling effect. Over the years, the democratization of this

Table 4 ADSC markers

	ADSC markers
MSC markers	CD10, CD13, CD34, CD44, CD54, CD71, CD73, CD90, CD105/SH2, CD106, CD117
Differentiation capacity markers	CD201, CD36
Wound healing markers	CD66, CD271, CD248
Immune regulation markers	CD29, CD200, CD274

procedure has led surgeons to conclude that in addition to the volumizing effect of the adipose tissue injection, there was also a trophic effect, significantly improving the quality of healing of the surgical site.

Adipose tissue gained widespread popularity among researchers, surgeons and physicians when Zuk and colleagues identified in 2001 the presence of mesenchymal stromal cells (MSCs) in adipose tissue [47]. Zuk hypothesized that adipose stromal cells were perhaps a variant of the mesenchymal stromal cells population from bone marrow (BMSCs), located within the adipose compartment. Therefore, they could be used as an alternative therapy cell to MSCs, which, at that time, had been almost exclusively isolated from bone marrow [47, 48].

A consensus in 2004 by the International Federation for Adipose Therapeutics and Science (IFATS) indicated the acronym “ADSCs” to refer to adipose-derived stem cells [49].

Nowadays, liposuction is the most frequently performed aesthetic surgery procedure in Western Countries [5], with over a million procedures per year performed worldwide [11]. Thus, due to its abundant availability, cells derived from adipose tissues are being heavily considered and used as a source of mesenchymal stromal cells (MSCs). Compared with bone marrow (BMSCs) or umbilical cord stem cells (UMSCs), ADSCs shared the same characteristics exhibiting in vitro self-renewal, capacity for multipotential differentiation, plastic adherence and fibroblast-like morphology [12, 13, 13, 48, 50].

They are found within a larger component known as the stromal vascular fraction (SVF) and have immunomodulatory, pro-angiogenic and antifibrotic properties that make them interesting new tools from regenerative therapies [51, 52]. ADSCs show similar properties to BM-MSCs and exhibits similar cells markers such as CD90 and CD73 [48, 53–55] (Table 4). They have the ability to differentiate in other mesodermal lineages [47–49] or to be reprogrammed to behave like cells of different ectodermal lineages [56–58]. They also promote angiogenesis and grow factors secretion under appropriate stimulation [59].

The role of the adipose derived stromal cell in cutaneous regeneration

In response to an injury, ADSCs may migrate and differentiate into skin cells to repopulate the injured skin or activate the dermal fibroblasts and keratinocytes to accelerate the wound healing. Thanks to their plasticity, in response to a cutaneous damage, ADSCs can differentiate to fibroblasts exhibiting morphological similarities and expressing vimentin, fibronectin [60], and into keratinocytes (expressing K5 and K14) [60]. Furthermore, ADSCs can also differentiate in endothelial cells into the walls of the newly formed blood vessels [61]. In addition, ADSCs may enhance the process of wound healing through their paracrine factor secretion that promote not only their differentiation and their proliferation but also the recruitment of neighboring cells in the wound. Indeed, by secretion of several growth factors including fibroblast growth factor 2 (FGF-2), insulin-like growth factor 1 (IGF-1), hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), and transforming growth factor- β 1 (TGF- β 1), ADSCs stimulate the proliferation of fibroblasts, keratinocytes and endothelial cells [62–64]. Neovascularization is also enhanced in the injury site due to the presence of anti-inflammatory cytokines and proangiogenic factors as the production of keratinocyte growth factor (KGF) and VEGF to surrounding cells [61]. An additional interesting point to observe is that local hypoxia in the wound bed (1–5% of oxygen concentration), as observed in several clinical cases of chronic wounds, is the preferable condition for ADSCs to migrate, proliferate and differentiate [62]. Hypoxia improves ADSCs functions increasing the up-regulation of certain genes, as the hypoxia-induced factor-1 α , mainly angiogenic (VEGF, HGF, FGF2) [65–67] and anti-apoptotic [68, 69]. Other potential properties of ADSC favoring cutaneous regeneration include their response to oxidative stress and their antibacterial properties. It was shown that ADSCs express heat shock protein 47 [70], protecting existing fibroblasts from free radicals [71], and showing a remarkable resistance against bacterial cytotoxic effects [72].

Macrophages dysfunction in chronic wounds

As previously shown, macrophages critically contribute to the succession of the physiological cascade for tissue repair.

Persistent hyper-inflammation is a hallmark of chronic wounds, and macrophage dysfunction is considered as a main contributor thereof. Their dysregulation leads to the persistence of the inflammatory phase, resulting in a deficit of the resolution phase, and thus participating in the pathophysiological mechanism of chronic wounds.

During wound healing, the fine regulation of the transition of macrophage phenotype from M1 (pro-inflammatory) to M2 (anti-inflammatory and pro-healing) is crucial for the progression of the repair process [73]. However, in pathophysiological conditions (obesity, infection, diabetes) M1 macrophages in wounds are prevented from switching completely to the M2 phenotype, resulting in blockage of the repair process at inflammatory phase [74].

The distinct and complex microenvironment of chronic wounds prevents the activation of macrophages from the inflammatory to the reparative phenotype. As a result, the inflammatory phase of wound healing cannot progress to the proliferative phase, and the proliferation of connective, endothelial and epithelial tissues cannot be achieved [75].

The key-role of macrophages in cutaneous regeneration is particularly observed in diabetic ulcers where macrophages present a downregulation of the expression of anti-inflammatory M2-like genes such as the CD36, CD206 and the peroxisome proliferator-activated receptors (PPARs), while pro-inflammatory M1-like factors such as IL-1 β , and the Inducible nitric oxide synthase (iNOS) are upregulated [75–80]. Reduced PPAR- γ expression induces dysfunctional efferocytosis, leading to enhanced accumulation of apoptotic cells at the wound site leading to the augmentation of pro-inflammatory activity and sustains the inflammatory phase [81].

In addition, several studies have shown that macrophages dysregulation under pathophysiological conditions like diabetes occurs not only at wound sites but also in the bone marrow and blood circulation. Changes in the number and function of macrophages in chronic wounds are closely linked to hematopoietic disruption, resulting in elevated levels of circulating monocytes and then an accumulation of macrophages in diabetic wounds [82].

In a recent study conducted by Pang et al., it was shown that macrophages present in diabetic ulcers share expressed more M1-like markers and characteristics and less M2-like markers [83].

In chronic venous ulcers, an interesting point is the observation of the stagnation of the inflammatory environment, due to the liberation of a large amount of free radicals and oxygen species (ROS), due to the Fenton reaction caused by the iron's macrophage phagocytosis [77, 84]. This was sustained in a hemochromatosis mouse model by Silandrilaru et al. [77], where macrophages in wound tissue of iron overloaded mice presented uncontrolled pro-oxidant and pro-inflammatory M1-like signatures with increased expression of CD36, CD206 and with and accumulation of ROS and TNF α in the wound tissue.

Targeted control of dysregulated macrophage activation in chronic wounds, could, therefore, represent a promising approach for the treatment of chronic wounds. In fact, the progression of the polarization from M1-like to M2-like phenotypes can be controlled at different steps, by the delivery of bioactive signals or cells, able to interrupt or reduce the inflammation cascade, or by cytotherapy approaches, when exogenous pre-activated macrophages are delivered into the tissue to re-establish functions [85, 86].

The era of the tissue engineering in cutaneous wound healing

Cutaneous tissue engineering has been heralded as the alternative strategy of the twenty-first century to accelerate wound healing in chronic wounds. The field of regenerative skin tissue engineering has had several advancements to facilitate faster wound healing. In this concept, scaffolds are defined as the best materials to restore, maintain and improve tissue function [87]. They provide a suitable structure, permitting cells survival, proliferation and differentiation [88].

Several natural, synthetic or composite biomaterials have been used for skin tissue engineering. There are some factors usually considered in the design of an ideal biomaterial enhancing wound healing: the hemostatic and antimicrobial properties, a good absorption of wound exudates and a gas permeability, an easy sterilization and use, and biodegradability, non-toxicity and non-immunogenicity [89].

Several techniques are described to permit scaffold's construct, including the use of the ECM secreting cell sheets [90], permitting cells to secrete ECM facilitating cell growth and proliferation; the construct of porous scaffolds biomaterials [91]; the decellularized ECM scaffolds [92]; and the fabrication of cells entrapped in hydrogels [93]. Various natural, synthetic and biodegradable materials are used for generation of highly porous scaffolds, providing a suitable environment for cell growth and proliferation, and specific pore sizes are required to the cell types preventing cluster formation and avoiding necrotic center formation [91, 94]. In the acellular scaffolding approach, a complete de-cellularization of the organ is realized to create extracellular (ECM) based matrix where the specific cells of interest can be then effectively grown [92, 95, 96]. In hydrogel approach a mixture of a polymeric solution is mixed with skin cells to generate injectable hydrogels at the wound sites, facilitating then the skin regeneration. However, this last procedure has a limited mechanical strength due to its soft structure [93].

Scaffolds can be made up with natural, synthetic or composite polymers.

Due to their resemblance to the natural extracellular matrix (ECM), natural biomaterials are chosen most of all for their biocompatibility, and biodegradability and they are absorbed in vivo [97]; synthetic materials are fabricated, therefore with controlled characteristics about structure and properties [98, 99].

Biomaterials

Natural biomaterials can be made up from natural proteins, or polysaccharides. Natural proteins include collagen, gelatin, silk and fibrin.

Since its first use in 1881 by the surgeons Joseph Lister and William Macewen [100] with the development of a collagen coat suture, collagen started to be used in medical practices, because of its biocompatibility, versatility and mechanical properties. Being an integral part of the ECM, collagen offers tensile strength for tissue growth and promotes cell adhesion and proliferation [101–104], stimulating thus the healing process. Different types of collagen dressing formulations are existing and include collagen-based skin substitutes [105], collagen membrane [106] or composite films [107], micro- [108] or nanofiber scaffolds for cellular support [109]. Gelatin is a natural origin protein derived from collagen hydrolysis, extensively used in regenerative medicine, thanks to its cell-responsive properties and its capacity to deliver a wide range of biomolecules [110]. It can attract fibroblasts during the wound healing process [111] and compared to collagen, gelatin could be preferred given its low cost and its low antigenicity, and with a robust hemostatic effect [112]. Various formulations are existing, including films [113], sponges [114] or hydrogel [115]. Gelatin owns common arginyl-glycyl-aspartic acid (RGD) sequence, allowing certain cellular activities such as attachment, spreading, and cell differentiation and matrix metalloproteinase (MMP) sequences supporting a key-role in dermal wound healing, tissue regeneration and remodeling [104, 116, 117].

Silk is a biocompatible material produced by a variety of insects such as flies or spiders [117], widely used for tissue engineering in wound healing applications [118–120]. It provides cell adhesion and migration, mechanical strength and hemostatic properties with a minimal inflammatory reaction [121]. Other protein used for healing process is the fibrin, formed by the polymerization of fibrinogen and thrombin in blood plasma. It is a biomaterial widely investigated for tissue regenerations due to its biocompatibility, biodegradability, and easy production. Natural scaffolds made up of fibrin and anti-inflammatory bandages composed of thrombin and fibrinogen are used for wound dressing and skin regeneration applications [122, 123].

Finally, polysaccharides-based biomaterials are subdivided as homoglycan polysaccharides such as glucans, cellulose, dextran and chitosan; and heteroglycan polysaccharides such as alginates, agarose, pectins, gums or glycosaminoglycans. The most used in biomedical fields are alginates, chitosan and glycosaminoglycan as hyaluronic acid (HA), having an important interest in various biomedical fields [124].

Synthetic and composite materials

Synthetic biomaterials have to share bio-mimetic characteristics but they can be either biodegradable or non-biodegradable. Among the biodegradable biomaterials, aliphatic polyesters, as polylactic acid (PLA), polyglycolic acid (PGA) and polycaprolactone (PCL), are the most common materials used in skin regeneration, given their mechanical strength property, and their easy fabrication [125]. Other synthetic polymers include poly(vinyl pyrrolidone) (PVP), poly(ethylene oxide)(PEO)/poly(ethylene glycol) (PEG), Poly(hydroxyethyl methacrylate) (PHEMA), poly(vinyl alcohol) (PVA) and polyurethanes (PUs) [125]. Generally, synthetic polymers are usually cross-linked with natural polymers to enrich mechanical properties and tensile strength and to form composite materials [126]. Composite materials can be constituted by natural and synthetic materials, or either different natural polymer. Several composite biomaterials suitable for skin regeneration include chitosan- and fibrin-based composites [127], poly(*N*-vinyl caprolactam)-calcium alginate (PVCL) hydrogel films [128] or different alginate- or chitosan- based materials [129], and cellulose-based composite that have strong antibacterial properties [130].

Current cutaneous tissue engineering models: a retrospective analysis on biomaterials used in combination with ADSC and modulating macrophages for cutaneous wound repair

Scaffolding provides a suitable three-dimensional environment for the cells' growth, proliferation and differentiation. In the era of tissue engineering and bioscaffolds promoting skin repair by adjusting the wound's microenvironment [131], it was shown that ADSCs and macrophages, when combined with different scaffolds, may improve wound healing [59, 75]. Several studies employing locally transplanted ADSCs or macrophages to accelerate wound healing by taking advantage of their differentiation, and pro-resolution abilities in addition to the secretion of paracrine factors. ADSCs and macrophages were applied directly into the wound bed requiring a considerable number of cells which may have lost their vitality and function, and the delivery of the transplanted cells can also be severely limited [131–134]. To overcome

the disadvantages associated with a direct administration, a suitable biomaterial could be used as a preferable vehicle during cells transplantation to maintain the cell viability. Therefore, complementary approaches such as using bioactive scaffolds may govern a better cellular microenvironment, thereby survival and function of macrophages or ADSCs can be improved. Hence, there is an urgent need for a cell delivery approach that can deliver cells to the wound bed to maximize their therapeutic potentials [135]. In this concept, functional materials could play a crucial role in enhancing the debridement phase, controlling the bacterial colonization, and participating to the local immunoregulation and angiogenesis. In this systematic review, carried out according to the PRISMA statement [136], we resumed data from investigations reporting the use ADSCs and bioscaffold and data from the macrophage behavior with functional biomaterials in wound healing models.

ADSC and bioscaffolds in healing animal models

The wound healing capacity from ADSCs is synergistically regulated by direct interaction with their microenvironment. Therefore, the local microenvironments in which ADSCs reside plays a crucial role in their phenotypic expression and their wound healing capacity [137].

Several researches focused on biomaterials to create a favorable microenvironment for ADSCs in order to maximize their therapeutic potential. Many studies investigated the efficacy of ADSCs in cutaneous wound healing when implanted in collagen-based scaffolds [138–144]. In these reports, ADSCs populated collagen gel [138], 3D-collagen based-scaffold membrane [139, 140, 142, 143], collagen hydrogel [141] or bilaminar devices coupled with Polyactiglycolic acid (PLGA) [144]. *In vitro* results confirm cell viability and proliferation, positive expression of CD90 and CD105 and an up-regulation of VEGF expression [141, 142, 144]. In histological analysis, the dermal portion of wound scars populated with these devices was thicker than collagen-based scaffold wound scars without ADSCs and with an acceleration in granulation tissue and capillary formation. In their study, Barrera et al. [141] demonstrated also an improvement in scar quality with a more reticular collagen pattern compared to wound control. Similar results were found in Domingues et al. research [144], where the bilaminar device (PLGA/collagen/ADSC) showed a reduced granulosomatous reaction to collagen scaffold alone.

Other natural proteins used in association with ADSCs include gelatin-based scaffold [145–148] and silk-based scaffold [149, 150]. In these reports, it was found that stromal cell retention is significantly improved *in vivo* with vehicle-mediated delivery.

The ADSC-gelatin-based treatment decreases inflammatory cell infiltration, enhances neovascularization, and remarkably accelerates wound closure in diabetic mice [145, 146].

In Hsieh et al. [147], and Cheng et al. [148] researches, gelatin was coupled with hyaluronic acid and fibrous polymers to overcome the water-solubility of these natural materials in order to maintain the delivery of ADSCs and the morphological cellular stability [147]. ADSCs were found to proliferate in gelatin-based scaffold while preserving their phenotype in addition with fibrous polymer. Furthermore, genes associated with skin regeneration were upregulated increasing the growth factor secretion by ADSCs to collectively enhance their functions [146–149]. An interesting point investigated by Hsieh et al. [147] is the increased number of pro-inflammatory CD68⁺ macrophages after 3 days of treatment with PGH (Polymer-Gelatin-HA)/ADSCs device, and the number of the pro-resolutive CD163⁺ macrophage on day 7. This study demonstrate that ASDCs-scaffolds can recruit macrophages in the wound bed and can switch to a pro-resolutive phenotype.

ADSC is also associated with polysaccharides-based biomaterials as well as Hyaluronic acid (HA) or chitosan, to treat chronic wound [151–158].

Hyaluronic acid (HA) as one of the main components of the extracellular matrix (ECM), participates in the processes of adhesion, migration, and proliferation of fibroblasts and keratinocytes. It can be prepared in association with ADSCs in gel [151–154, 183] or scaffold form [153–155]. HA gel encapsulating ADSCs have demonstrated promising regenerative capabilities such as the maintenance of ADSCs' stemness and secretion abilities.

Gel methods involve the use of ADSCs spheroids implanted in a syringe filled with HA. This method could be very simple to use in the future, being the HA commonly used as injectable material by several physicians. On the other hand, the development of injectable material remains a great challenge due to the restriction of crosslinking efficiency or mechanical properties. To overcome these problems, other authors have added additional polymers to stabilize mechanical properties and to reduce to reduce swelling and fouling properties [153–155].

Decellularized adipose tissue (DAT) enriched with ADSCs in wound healing was explored in three studies [159–161]. In these reports, it was shown that incorporating ADSCs mediated the inflammatory response and promoted pro-resolution macrophage phenotype in addition to induce a strong angiogenic response. However, ADSCs incorporated in DAT tend to have an adipogenic differentiation, more suitable for deep soft tissue defect than skin reparation. On the contrary, when ADSCs were

implanted in acellular dermal matrix [162, 184] or in acellular skin graft [163], it was observed an enhanced stimulation and migration of fibroblasts as well as an increasing in granulation tissue formation, re-epithelialization and neovascularization in *mouse* models.

Just one study evaluated the utilization of an alternative natural product as Aloe vera hydrogel enriched with ADSCs in a rat model [164] as several previous works have shown promising effectiveness of herbal extract in differentiation and proliferation of human mesenchymal stromal cells (hMSCs) [165, 166]. Authors found that combination of ADSCs and Aloe vera can effectively improve wound healing by stimulating mesenchymal cell proliferation, angiogenesis and re-epithelialization, and by reducing scarring through the lowering TGF- β 1 and bFGF expression level. However, authors incorporate the Aloe vera/ADSCs hydrogel in a decellularized bone matrix with no specific investigation on the effect of the complex Aloe vera/ADSCs alone.

In addition, mesenchymal stromal cells, have been loaded to biomaterials in order to investigate the macrophage function in wound healing [147, 167, 168]. Lin et al. [168] demonstrated that mesenchymal stromal cells (MSC) loaded in bioactive fish scale scaffolds converted activated M1-macrophages into an M2 phenotype reducing inflammation and promoting cutaneous healing. In Zomer et al. study, mesenchymal stromal cells from dermal and adipose tissues implanted in collagen-based scaffold induced macrophage polarization to a pro-repair (M2) phenotype and improve skin wound healing [169]. Moreover, in a burn murine model, ADSCs were tested in combination with injectable hydrogels resulting in a reduced inflammatory response and with an enhanced macrophage M2 polarization [170].

Studies investigated the properties of ADSCs in association with biomaterials are resumed in (Table 5).

Regulation of macrophage functions by bioactive scaffolds

Cellular therapies involving the direct administration of macrophages can be defective, creating problems of cell viability and functionality [10], and different strategies have been explored to regulate macrophage functions by bioactive scaffolds for wound healing. Physical properties of bioactive scaffolds, as well the incorporation of immunomodulatory agents or stem cells, have been considered as important factors influencing macrophage functions, especially their polarization. Several studies have shown that the pore size of the scaffold and the diameters of the fibers could modulate macrophage behavior [171–173]. Scaffolds with a larger pore size tend to polarize macrophages toward a pro-resolutive phenotype while smaller pores shift macrophages to a pro-inflammatory phenotype [174, 175]. Sussman EL et al. demonstrated

Table 5 Pre-clinical studies focused on ADSCs and bioscaffolds

References	Year	Country	Model	ADSC-scaffold
Altman et al. [149]	2009	USA	Murine healing model	Silk fibroin-chitosan scaffold
Nambu et al. [139]	2007	Japan	Murine healing model	Atelocollagen scaffold
Nambu et al. [140]	2009	Japan	Murine healing model	Atelocollagen scaffold
Lee et al. [138]	2011	South Korea	Murine healing model	Collagen gel
Huang et al. [162]	2012	Taiwan	Murine healing model	Acellular dermal matrix
Han et al. [159]	2015	Canada	Rat healing model	Decellularized adipose tissue (DAT)
Yu et al. [160]	2013	Canada	Rat healing model	Decellularized adipose tissue (DAT)
Altman et al. [70]	2008	USA	Murine healing model	Acellular dermal matrix
Kaisang et al. [183]	2017	China	Diabetic rat	Injectable hydrogel
Xu et al. [153]	2018	China	Diabetic mouse	Injectable hydrogel
Wu et al. [156]	2018	China	Diabetic rat	Chitosan film
Dong et al. [151]	2020	China	Burn murine model	PEG-HA-RGD hydrogels
Barrera et al. [141]	2021	USA	Burn murine model	Collagen hydrogel
Oryan et al. [164]	2019	Iran	Burn murine model	Aloe vera hydrogel
Alemzadeh et al. [152]	2020	Iran	Rat healing model	HA-hydrogel
Guo et al. [142]	2018	China	Diabetic mouse	Collagen scaffold
Dong et al. [145]	2018	China	Diabetic mouse	PEGDA and gelatin scaffold
Jin et al. [146]	2020	China	Diabetic rat	POLY, HA, gelatin scaffold
Xu et al. [153]	2018	China	Diabetic rat	HA-PEGDA scaffold
Feng et al. [154]	2017	Japan	Diabetic mouse	HA scaffold
Da Silva et al. [155]	2017	Portugal	Diabetic mouse	Gellan gum -HA scaffold
Chen et al. [161]	2020	China	Diabetic mouse	Acellular adipose matrix
Navone et al. [150]	2014	Italy	Diabetic mouse	Silk fibroin scaffold
Nie et al. [163]	2015	China	Diabetic rat	Decellularized skin graft
Hsu et al. [157]	2015	Taiwan	Rat healing model	Chitosan-hyaluronan membranes
Feng et al. [154]	2017	Japan	Diabetic mouse	HA gel
Hsieh et al. [147]	2022	Taiwan	Rat healing model	PLGA/gelatin/HA (PGH) membrane scaffold
Shokrgozar et al. [143]	2012	Iran	Rat healing model	Collagen/chitosan scaffold
Cao et al. [184]	2022	China	Diabetic rat	Acellular dermal matrix
Cheng et al. [148]	2022	Taiwan	Rat healing model	HA + collagen + gelatin matrix
Nishiwaki et al. [185]	2019	Japan	Diabetic mouse	Porous nanosheet
Domingues et al. [144]	2016	Brazil	Wound pig model	PLGA + collagen membrane
Burmeister et al. [186]	2018	USA	Wound pig model	PEG hydrogel + skin graft
Shen et al. [158]	2013	China	Diabetic mouse	PLGA + chitosan

PEG polyethylene glycol, HA hyaluronic acid, RGD arginylglycylaspartic acid, PEGDA polyethylene glycol diacrylate, PLGA poly(lactic-co-glycolic acid)

that porous implants with a pore size of 34 μm reduced fibrotic reaction after subcutaneous implantation in mice, which was related to the shifting of macrophages to a pro-resolutive phenotype [176]. Diameter fibers was investigated by the study of Horii et al. [177]. They showed that too thick and too thin fibers caused a continuous inflammatory response with massive M1 macrophages infiltrate, whereas a fiber diameter between 0.9 and 3.0 μm inhibited the inflammation with a more powerful M2-macrophages response [177]. Furthermore, the macrophage behavior in relation with biomaterials can be controlled by adding immunomodulatory agents

or chemicals. Zhang et al. demonstrated that IL-4-loaded hydrogel beads promoted M2 macrophage polarization with an increased expression of TGF- β 1 in vitro [178]. In another study by Xuan et al. [179], an injectable bFGF-loaded chitosan- silver hydrogel was developed for the treatment of infected wounds. The in vivo results demonstrated that bFGF-loaded hydrogel enhanced the repair of infectious wounds, in relation of the augmentation of pro-resolutive macrophage polarization [180]. Many chemical compounds with the ability to modulate macrophage functions have been incorporated into wound dressings. Moura LI et al. incorporated Neurotensin

(NT) in a collagen matrix to promote diabetic wound healing resulting in a reduction of the production of TNF- α and IL- β by the macrophages [180]. Similarly, Wu et al. [181] reported that a prolonged release of the amino acid taurine in a collagen sponge, improved the healing of full-thickness skin wounds, which was related to the stimulation of M2 macrophage polarization and a decreased inflammatory response [181]. Peng et al. [182] constructed a polylactic acid glycolic acid/silk fibroin membrane loaded with artemisinin, a compound extracted by *Artemisia annua*, and tested it in a full-thickness skin wound model. This bioactive scaffold shortened the period of inflammation and enhanced skin regeneration through the downregulation of pro-inflammatory cytokines, IL-1 β and TNF- α [182].

Future perspectives and conclusion

With the economic and patient care impacts of wound healing, it comes as no surprise that the field of wound healing research is incredibly prosperous. In this regard, in the past two decades, fundamental research initially focused on cell therapies with good preliminary results, which has gained widespread popularity among researchers and physicians. Subsequently, methods to better govern viability and cell function were developed. In the era of tissue engineering, functional biomaterials, that can maintain cell delivery and cellular viability as well as change the wound microenvironment, have had a profound impact on the development of dressings for the treatment of chronic wounds. Promising results have been shown in pre-clinical reports using ADSCs-based scaffolds to accelerate and to improve the quality of the cutaneous healing. Indeed, ADSCs-based scaffolds can be used as a vehicle for therapeutic cell delivery but most of all to increase the cell proliferation rate of wound and cell function by upregulating the expression level of key-genes for wound healing and neo-angiogenesis. In addition, by accommodating the survival and the proliferation of ADSCs, followed by the delivery of ADSCs to the wound site, bioactive scaffolds treatments have showed equally to modulate inflammation through the recruitment and polarization of macrophages. In fact, in cutaneous wound healing the plasticity of macrophages, more specifically, the different phenotype of macrophages after polarization, plays a key role. In vivo researches, studying the polarization of macrophages in relation to bioscaffolds in cutaneous wound healing, confirm the importance of this macrophagic behavior. In this concept, it could be interesting, in the next future, to study the dialogue between ADSCs and macrophages in a unique bioactive scaffold in order to promote wound healing.

Abbreviations

ADSCs Adipose derived stromal cells

BMSCs	Bone marrow mesenchymal stromal cells
CMC	Carboxymethylcellulose
DAT	Decellularized adipose tissue
ECM	Extracellular matrix
FGF	Fibroblast growth factor
HA	Hyaluronic acid
HGF	Hepatocyte growth factor
hMSCs	Human mesenchymal stromal cells
IL	Interleukin
iNOS	Inducible nitric oxide synthase
IGF	Insulin-like growth factor
LPS	Lipopolysaccharides
KGF	Keratinocyte growth factor
MMPs	Matrix metalloproteinases
MSCs	Mesenchymal stromal cells
PCL	Polycaprolactone
PDGF	Platelet-derived growth factor
PEG	poly(ethylene glycol) (PEG)
PEO	poly(ethylene oxide)
PGA	Polyglycolic acid
PGH	Polymer-gelatin-HA
PHEMA	poly(hydroxyethyl methacrylate)
PLA	Polylactic acid
PPARs	Peroxisome proliferator-activated receptors
PU	Polyurethane
PVA	poly(vinyl alcohol)
PVCL	poly(<i>N</i> -vinyl caprolactam)-calcium alginate
PVP	poly(vinyl pyrrolidone)
ROS	Reactive oxygen species
SVF	Stromal vascular fraction
TGF- β	Tumor growth factor-beta
TNF- α	Tumor necrosis factor-alpha
UMSCs	Umbilical cord mesenchymal stromal cells
VEGF	Vascular endothelial growth factor

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Author contributions

GS: design of the work, acquisition and analysis of data, drafting the work. SA: acquisition and analysis of data. CB: substantial revision. CA: analysis of data and substantial revision. SB: design of the work and substantial revision. VA: design of the work, data analysis, substantial revision. All authors read and approved the final manuscript and have agreed both to be personally accountable for the author's own contributions.

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Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

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No datasets were generated or analysed during the current study.

Competing interests

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