Skin Wound Healing Assisted by Angiogenic Targeted Tissue Engineering: a Comprehensive Review of Bioengineered Approaches

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ABSTRACT

Skin injuries and in particular, chronic wounds, are one of the major prevalent medical problems, worldwide. Due to the pivotal role of angiogenesis in tissue regeneration, impaired angiogenesis can cause several complications during the wound healing process and skin regeneration. Therefore, induction or promotion of angiogenesis can be considered as a promising approach to accelerate wound healing. This article presents a comprehensive overview of current and emerging angiogenesis induction methods applied in several studies for skin regeneration, which are classified into the cell, growth factor, scaffold, and biological/chemical compound-based strategies. In addition, the advantages and disadvantages of theseangiogenicstrategiesalong with related research examples are discussed in order to demonstratetheir potential in the treatment ofwounds.

KEYWORDS

Skin tissue engineering, Angiogenesis, Wound healing, Chronic wound, Biomaterials.

1. INTRODUCTION

Skin is the largest organ in the body, which serves numerous vital functions including acting as a physical barrier, energy storage, and controlling bodytemperature [1]. Various factors such as diseases and trauma can damage the integrity of the skin. Upon wound creation, depends on influential pathological factors (i.e., severity or thickness of the wound), the natural healing process would be compromised. According to the reports, about 6.5 million Americans suffer from chronic wounds, which costs more than US$25 billion for medical care, annually [2]. It is expected that due to the vast increase in the rate of people suffering from diabetes, obesity, chronic infections, etc., these numbers will remarkably raise up in the future [3].

Despite the great efforts and advances in wound healing researches and developed products, the management of chronic and full-thickness wounds is still a big challenge. The major obstacles in the process of healing include prolonged infection, continuous inflammation, and particularly, impaired angiogenesis. Furthermore, injured skin provides a rich environment for the growth and

proliferation of bacteria in deep wounds and the loss of vascular bed causes chronic damage or even loss of skin and its underlying tissues [4–6].

Angiogenesis is a key factor in the healing process and tissue regeneration and impaired angiogenic response results in several healing disorders which can be observed for example indiabetic foot ulcers and non-union bone fractures. Regarding the oxygen requiring nature of thecells and the prolonged hypoxic condition in severe and full-thicknesswounds, angiogenic induction approaches can recruit healing promoting cells to restore both the normal structure and function of the damaged skin [7,8].

Evidence from numerous studies suggests that induction of angiogenesis can be categorized into four main strategies: cell-based, growth factor-based, scaffold-based, and biological/chemical compound-based strategies. This review aims to provide a comprehensive discussion of the main bioengineered approaches used for angiogenic induction through the wound bed with a focus on non-healing and chronic wounds with a look at physiological and pathological angiogenic signaling pathways.

2. ANGIOGENESIS DURING WOUND HEALING

Designing approaches for the chronic wound repair or developing healing products with the ability of angiogenesis induction requires deep understanding of the physiological and pathological mechanisms involved in angiogenesis process. Vasculogenesis, is the formation of new vessels from endothelial progenitor cells (EPCs) which usually occurs during stages of embryogenesis. On the other hand, angiogenesis is the process of growing new blood capillaries

from the pre-existing vessels which were formed during the early steps of vasculogenesis. This process can be impaired as a consequence of diabetes, infection, aging, etc. [9,10].

The angiogenesis is a multiple phase process. After the expression of Hypoxia-inducible factor-1 (HIF-1) in the wound bed due to the hypoxic condition, cascades of the angiogenic factors are secreted in order to build and stabilize the new vessels. Briefly, during the healing, migrating platelets secrete angiogenic factors such as fibroblast growth factor-2 (FGF-2) and vascular endothelial growth factor (VEGF), which can recall endothelial cells and also enhance expression of protease enzymes substrates. On the other hand, the gradient of angiogenic factors stimulates endothelial cells presenting in existing peripheral vessels. After migration of cells, including tip endothelial cells towards the wound bed, tube formation occurs. Moreover, the inflammatory cells such as neutrophils secrete a significant amount of angiogenic growth factors and cytokines, which synergistically lead to improvement of the vessel formation. Finally, pericytes and smooth muscle cells (SMCs) maturate the vascular networks by secretion of matrix protein and deposition of the basement membrane, which leads to inhibition of the angiogenesis process as well [11–15].

Thus, a chronological pattern of migration, growth, and maturationis required for the formation of physiologically functional vessels. The role of different factors in angiogenesis is briefly summarized in **Table 1**. Although there are numerous pathogenic and nonpathogenic factors responsible for impaired angiogenesis in chronic wounds, diabetes is considered the most prevalent risk factor in incomplete wound healing. To be more specific, diabetic wounds suffer

from increases in inflammation, excessivematrix metalloproteinase (MMP) secretion, oxidative stress, free radicals, and a decrease in growth factors expression [9,15,16].

As a major process in the developmental process and also wound healing, angiogenesis is assisted by complex interactions and cross-talks, which are activated by several genes through different signaling pathways including HIF[17–19], Sonic Hedgehog (Shh)[20–23], and inflammatory pathways [24]as summarized in **Figure 1**. In addition to the expression of angiogenic growth factors, these signaling pathways pave the way for the proceeding healthy angiogenesis process, controllingthe expression of growth factors, arteriogenesis and transition of small arteries to large ones which is essential in the improvement of blood circulation around chronic wounds [25,26].

Table 1. Role of different biological factors in angiogenesis process[17].

While several studies revealed that the inhibition of these signaling pathwayscan lead to some complications in wound healing and angiogenesis (for example by decreasing the NO function) [27,28], their associated response (specially in the inflammatory pathway) should be controlled for maturation and stability of the vessels. Such regulation in tissue response is usually impaired during chronic wound healing[29,30].

2.1 Regulation of angiogenesis: a necessary step

During wound healing, several fluctuations occur in levels of angiogenic factors. In other words, in early phases the concentration of angiogenic factors increases which leads to the growth of capillary content in the wound bed. However, in the late phases, the level of angiogenic factors is

decreased significantly which contributes to the regression of several blood vessels. This step followed by maturation and stabilization of other capillaries (for example by pericytes), in order to adjust the vascular density similar to the normal skin [31].

The robust presence of angiogenic response in the wound site can lead to scar formation and in severe cases, the formation of keloids. Thus, in order to improve wound healing outcomes, anti-angiogenic therapy, or suppression of angiogenesis should be considered. In fact, partial inhibition of angiogenesis, particularly in the late phase of healing, is required to facilitate vascular maturation and wound closure while minimizing vigorous scar formation [32,33].

Figure 1. The diagram of 3 major signaling pathways of angiogenesis.HIF pathway: During wound healing and after hemostasis, the HIF complex is activated which resulted in the invasion of capillary sprouts through the fibrin clot. After a few days, an organized microvascular network is formed in granulation tissue[17]. Shh pathway: Shh proteins can activate angiogenesis in multiple ways, including expression of pro-angiogenic cytokines in fibroblasts, induction of proliferation and migration of endothelial cells,and also they are essential in the stabilization of vascular bed[30]. Inflammatory pathway: M1 macrophage (pro-inflammatory), which is responsible for the secretion of inflammatory cytokines, can also secrete high levels of the angiogenic growth factors such as VEGF recruiting endothelial cells. Concurrently, M2 macrophage (pro-healing) stabilizes the new vessels and remodels the structure by secretion of PDGF-BB and metalloproteinase enzymes, respectively [34].

3. IMPAIRED WOUND HEALING IN CHRONIC WOUNDS

Typically, a normal wound healing occurs through a well-orchestrated procedure in which myriad of cells and factors are activated in order to regenerate damaged skin tissue and restore its integrity. Accordingly, wound healing process can be classified into 4 major overlapping stages including hemostasis/coagulation, inflammation, proliferation, and remodeling/maturation

[35,36].

The main role of hemostasis and inflammatory phases is to cease the bleeding, clear foreign materials and counteract the invasion of pathogens at the wound site which are respectively, carried out by function and secretion of platelets, neutrophils and macrophages [37]. Owing to the secreted growth factors, cytokines and provisional matrices, along with increase in vascular permeability and edema, recruitment of endothelial cells as well as epidermal and dermal cells into the wound site is facilitated leading to the upcoming proliferation [36]. Still affected by secreted factors, the proliferative phase is progressed towards angiogenesis, increasing the population of fibroblasts and collagen production which result in formation of granulation tissue [38]. Finally, after about 1-3 weeks, remodeling of the tissue occurs by differentiation of fibroblasts to myoblasts, restoration of extracellular matrix (ECM)through increase of collagen type I and its full cross-linking. The new formed vascular network rapidly regresses and a matured tissue construct with low structural strength and decreased resident cell population is created as scar tissue (**Figure 2, normal**) [37,39–41].

Therefore, for an ideal and normal wound healing, the physiological conditions in the wound's environment should be tolerable for cells where the repair process can occur at the highest rate and provide the integrated and functional skin. However, due to the underlying pathologic factors mainly such as diabetes-induced neuropathies and decreased angiogenesis, the normal healing process is impaired and leads to formation of non-healing chronic wounds [20,38].

Such wounds usually exhibit some common features including constant or protracted inflammation, persistent edema and infections which result in formation of microbial biofilm and consequently tissue necrosis due to antimicrobial drug-resistance (**Figure 2, chronic)**[38,41,42].

The microenvironment of a normal wound is known with the presence of responsive cells and their regulated matrix/factors secretions along with sufficient and accurate vascular formation. In chronic wounds, however, the tissue degradation and proteolysis exceed matrix synthesis and the skin cells loose their ability to respond to the environmental stimuli[2,37]. In addition, poor blood circulation and impaired angiogenesis in the wound site lead to insufficient nutrients and oxygen supply. Due to the reduction of oxygen in the environment, a series of proteinases are secreted and toxic oxygen metabolites add further damage to the endothelial cells[43]. As mentioned before, the excessive activity of inflammatory cells (which produce reactive oxygen species (ROS)) and the imbalance in the secretion of MMPs and other enzymes, play a crucial role in failure of chronic wounds to heal [5,41]. Indeed, a viscous circle is present in chronic wounds whereby in spite of the increase in growth factor production their availability and quantity dramatically decreased due to the aggressive environmental conditions[36].

Hence, all chronic wounds require serious medical interventions consisted of accurate diagnosis, proper treatment and effective preventive measures of wound reoccurrence to improve the patient's health conditions.

Figure 2. The comparative illustration of wound healing in normal and chronic wounds. The persistent edema, continuative inflammatory phase, and lack of angiogenesis are significant in chronic wounds. Reproduced with permission.[41]Copyright 2014, Mary Ann Liebert, Inc.

4. TREATMENT OF CHRONIC WOUNDS USING ANGIOGENIC APPROACHES

Nowadays, using tissue-engineered scaffolds and wound dressings are considered as a critical solution for addressing wound healing complications.As mentioned in the previous sections, vascular supply is impaired in chronic wounds that manifest in tissue ischemia and subsequently, the native regenerative ability of the tissue and its healing process would be compromised [2]. In this regard, bioengineering-based technologies attract much more research attentions which offers an alternative for the regeneration of damaged tissue and restoration of its normal function [2,44]. However, such strategies face same critical challenge which finites their usage in clinical application [45]. Indeed, the major obstacle is the lack of adequate vascular supply, which makes the engineered structure to rely on passive diffusion of oxygen and nutrients and consequently, severely limit its function and result in cell necrosis [46,47].Undoubtedly, successful engineered construction should be able to expose all cells to nutrient supply as well as oxygen to maintain viability [12]. For this reason, induction of angiogenesis can be considered as a crucial step toward high functionality of the scaffold and also improvement of regeneration, which is essential in chronic and full-thickness wounds such as diabetic wounds [48,49].

Different strategies have been used for the induction of angiogenesis, predominantly based on two logics: pre-vascularization and *in-situ* angiogenesis induction. The aim of pre-vascularization is to create a tissue construct containing the capillary networks either *in-vitro* or *in-vivo*, which then integrates with the host tissue after implantation. Due to the complications of

this method, such as demanding multiple microsurgeries for the vascular anastomosis, the *in-situ* angiogenesis induction approaches are more applicable and have gained more attention [11,50].

Regarding the *in-situ* angiogenesis, the angiogenesis induction approaches can be classified in the following categories:

- Angiogenesis using cells (including genetic manipulation and co-culturing)
- Angiogenesis using angiogenic growth factors
- Angiogenesis using scaffolds (including modification of physical, chemical, biological properties and use of novel fabrication methods)
- Angiogenesisusing angiogenic compounds (such as drugs and nature-inspired biomaterials)

It is worth mentioning that researchers occasionally combine the mentioned approaches in order to reach desirable results.

4.1 Induction of angiogenesis using cells

Considering the pivotal role of cells in tissue regeneration, induction of angiogenesis using cell delivery approaches, either in the form of cell-loaded scaffolds or scaffold-free systems are attractive areas of studies in wound healing application. Some appropriate cell types, suggested by studies are listed in the following section [11,16].

4.1.1. Endothelial cells

Mature endothelial cells can be extracted either from the skin capillary bed or the umbilical vein. However, cells isolated from the latter are not suitable for the application of skin tissue

engineering, due to their phenotypic heterogeneity to the dermal vascular cells. In addition, numerous complications may face the single culture of the endothelial cells on the scaffolds, which includes the inability to form the tubular structure, lack of donor sites or cell sources, poor proliferation, and viability in a long period. Moreover, the environment-sensitive nature of these cells makes them quickly susceptible to apoptosis in 3D structures. To overcome this problem, several approaches are recommended. One is to transfer genes expressing a caspase-resistant form ofBcl-2 protein, which can inhibit the endothelial apoptosis and increase both their viability as well as angiogenic function[16,51].

Co-culturing of the endothelial cells with other vascular cells, such as SMCs, skin cells (e.g. fibroblasts), or mesenchymal stem cells (MSCs), which play an important role in cell signaling and also stimulating the secretion of angiogenic factors, including VEGF, PDGF, etc. is one of the interesting methods for induction of angiogenesis [52].

One of the important factors in the co-culture of the endothelial cells with vessels supporting cells (e.g. SMCs) is a priority in the cell culture. Studies have shown that the simultaneous culture of these cells would not result in the formation of a functional vessel structure. To address this problem and have an ordered structure with a supportive matrix, SMCs can be initially cultured on the desired scaffold and endothelial cells should be co-cultured thereafter [16,50].

4.1.2. Endothelial progenitor cells (EPCs)

Endothelial progenitor cells (EPCs) are bone marrow-derived cells that can stimulate angiogenesis and wound repair through the expression of several angiogenic markers. It should

be noted that the amounts of EPCsare decreased in diabetic wounds. Thus, the delivery of EPCs either in the form of topical administrationon the wound bed or encapsulated in bioactive materials can significantly increase vascular density, while promoting macrophage recruitment, re-epithelization and wound closure [53].

Because of the convenient isolation procedure from the blood and high proliferation rate, EPCs would be a better cellular option compared to endothelial cells in co-culturing with skin cells. Indeed,not only can they increase both angiogenesis and epithelialization, but also their co-culture with fibroblasts would lead to scarless wound healing without any contraction as well [16,54]. As an example, Wang et al. studied the efficiency of the delivery of EPCs using collagen-polycaprolactone (PCL)-bioactive glass hybrid nanofibrous scaffold. Such cell-loaded construct promoted angiogenesis (by overexpression of VEGF and stromal cell derived factor (SDF)-1), increased formation of granulation tissue and collagen synthesis [55].

4.1.3. Mesenchymal stem cells (MSCs)

MSCs can secrete several growth factors such as VEGF, SDF, and FGF, which promote angiogenesis. Moreover, MSCs have a high potency of proliferation and vascular differentiation[56]. Considering the variety of donor sites for extracting these cells (e.g. adipose tissue, bone marrow, the dermis of the skin, sweat glands, amniotic membrane, etc.), deriving MSCs from patient adipose tissue is a convenient and rich cell source for skin tissue engineering [57,58]. Bone marrow mesenchymal stem cells (BMSCs) are the most common MSCs with high plasticity which can differentiate into endothelial cells, pericytes, and keratinocytes. Moreover, owing to increase in the secretion of erythropoietin (EPO), macrophage inflammatory proteins,

SDF, VEGF, epidermal growth factor (EGF), keratinocyte growth factor (KGF), and other bioactive molecules, BMSCs attracted much attention in promotion of neovascularization, re-epithelialization, and skin regeneration without causing any immunogenicity[11,59].

In some cases, during the extraction of MSCs from connective tissues, stromal vascular fraction (SVF), a natural co-cultured complex consisted of endothelial cells, is also extracted which is significantly effective in clinical wound treatment. Such a supportive structure is usually grafted to the wound site and indeed, provides the required signaling for neovascularization within the tissue [16,50].

4.1.4. Adipose-derived stem cells (ADSCs)

Many researches have demonstrated that stem cells are promising cell sources in the treatment of tissues that are damaged by diabetic ischemia. ADSCs as multipotent stem cells have multiple advantages, including high bioavailability (ability to readily extract from excess human lipid layer), ease of culture, high proliferation, self-renewal, and ability to differentiate to different cell types, such as endothelial cells and vascular myocytes. In fact, ADSCs are adipose-derived mesenchymal cells, which can improve re-epithelialization and angiogenesis. Hence, they have frequently been employed in wound healing and skin damage treatments. In addition, allogeneicADSCs do not cause immunogenic reactions, and can meanwhile secrete numerous angiogenic factors as well [50,60,61].

Since ADSCs extracted from a diabetic patient are poor in their ability to induce angiogenic response compared to healthy cells, the use of the autologous source of cells may not be

effective. Preconditioning of these cells with angiogenic compounds and drugs is suggested as a promising way for the restoration of their actual ability [60].

On the other hand, some studies focused on the fabrication of ADSC-laden scaffolds for wound treatments. For example, Lin et al. used the temperature-sensitive polymer,*N*-isopropylacrylamide (PIPAAm), in order to form a cell sheet by culturing ADSCs on it which can easily be detached from the culture surface [62]. In addition, the study of Jiang et al. has demonstrated that a combination of collagen scaffolds with ADSCs significantly enhancesVEGF expression, angiogenesis, cell proliferation, and wound closure in comparison with topical application of ADSCs alone on a diabetic porcine wound model [63].

4.1.5. Inflammatory cells

Meanwhile, there are some studies indicated the significant role of the immune system and inflammatory cells in the process of tissue angiogenesis. Neutrophils, as the first cells responding to the implanted biomaterial, and macrophages are now found to play an integral role in angiogenesis in multiple tissues and exhibit considerable potential for angiogenic-based tissue regeneration [64–66]. In terms of biomaterial-guided *in-situ* tissue regeneration, application of the pro-angiogenic potential of the neutrophils with biomaterial carrier/scaffold due to their robust secretion of matrix metalloproteinase-9 (MMP-9) can improve biomaterial performance by initiating matrix reprogramming. In fact, such an angiogenic effect is a mutual regulated event occurred between neutrophils and biomaterial. Thus, *in-situ* tissue angiogenesis as a novel and attractive approach can be provided through the design of immunomodulatory biomaterials which harness the pro-angiogenic potential of neutrophils to drive matrix reprogramming

[65,67].

In order to increase the transformation of macrophages to the M2 phenotype (i.e. pro-healing macrophages), genetic manipulation of the immune cells (e.g. macrophages) has attracted the attention of researches [68,69]. For instance, a study confirmed that the release ofsmall interfering RNAs (siRNAs) inhibiting interleukin-6 (IL-6) translation led to a decrease in M1 macrophages (i.e. pro-inflammatory cells) and helped in the angiogenesis [34]. Thus, regulation of the inflammatory pathwayin tissue and immunomodulation for induction of angiogenicresponse is a hot topic in tissue engineering and gene therapy, which needs more attention[30,59].

4.1.6. Induced pluripotent stem cells (iPSCs)

Recent studies used induced pluripotent stem cells (iPSCs) as a promising cellular source for induction of healing and augmentation of revascularization [53,70]. Using the strategy developed by Takahashi et al in 2006, somatic and differentiated cells, harvested from for example patient/donor's skin, hair, or fat, can be reprogrammed to pluripotent states, differentiated to the vascular cells, and re-implanted in patient's body [71,72]. In this regard, iPSCs provide several advantages compared to other cellular sources and stem cells mainly such as avoiding immunogenicity and bioethical concerns. In addition, although adult-derived stem cells (e.g. MSCs) have exhibited outstanding results in clinical trials and commercially available products, their process of isolation is more invasive and have limited differentiation potency compared to iPSCs[73–77].

So far, there are myriad studies confirmed improved wound healing and angiogenesis via sole- or co-delivery of human iPSCs (hiPSCs)-derived endothelial cells (ECs), SMCs, MSCs with or without fibroblasts [78–85]. As an example, it was reported in the study of Shen et al. that hiPSC-derived vascular cells increased vascular formation during wound healing in Diabetic foot ulcer patient due to their high capability of differentiation to the 2 major vascular cell populations of endothelial cells and pericytes[86]. Another important study by Gorecka et al. investigated the therapeutic effectiveness of using hiPSC-derived SMC embedded in 3D collagen scaffold in diabetic wound healing. After 72 h *in-vitro* culture, the scaffold applied *in-vivo* on a diabetic wounded nude mouse model. Results showed increased concentration of pro-angiogenic cytokines along with enhanced number of M2 macrophages which promoted angiogenesis and accelerate wound healing compared with using hypoxia-activated murine ADSCs in the scaffold[87].

However, the process of reprogramming routinely requires viral vectors which increase the risk of undesired genetic manipulations, mutations and teratogenesis[88]. Moreover, most of the current reprogramming techniques are time-consuming and yield to relatively low cellular quantity. Therefor, it is vital to develop efficient and non-viral- mediated methods for improving the outcome of this therapeutic cell [72].

There are several limitations associated with using cells to induce angiogenic response including lack of cell source availability and difficult extraction procedures from the donor site, having

various degrees of potency and immunogenicity, and complicated culture conditions. To address these problems, genetically modified cells are regarded as one of the alternative approaches.

Indeed, skin is an appropriate and safe target tissue for gene therapy because of the convenient availability for genetic-based therapeutic delivery and almost fast visibility of the results. Moreover, gene therapy of the damaged skin is a permanent treatment, in which side effects like hyperplasia or teratoma can be prevented [89].

In this regard, some researches have focused on genetic manipulation of the cells (e.g. MSCs, iPSCs or EPCs) cells using micro RNAs (miRNAs or miR) and siRNAs, which could turn cells into a factory of secretion of angiogenic growth factors, and then transplantation of them into the patient's body [59,90].For example, studies have shown that the transfection of the allogeneic endothelial cells with miR-132 and miR-126 has a striking impact on the proliferation and migration of endothelial cells, as well as capillary density [90–92].

Other strategies aimed to the delivery of the angiogenic genes such as VEGF expressing nucleotides using different vectors encapsulated in either scaffolds or controlled release particles.For example, Won et al. have added oxygen-dependent degradation sequences into the VEGF plasmid in order to be stimulated in hypoxia and form the vessels without apoptosis [93]. The role of growth factors, biomaterial scaffolds and their combinations in angiogenesis induction will be addressed further in the following sections.

4.2 Angiogenesis induction using angiogenic growth factors

As mentioned in the previous sections, the normal wound healing process highly depends on the sequential and controlled secretion of growth factors, cytokines, and other biochemical components required for the cell functions [59,90]. Considering the important role of growth factors in the improvement of angiogenesis, re-epithelialization, the formation of granulation tissue, and regulation of inflammatory response, their administration is necessary, especially in chronic wounds with a decreased level of growth factors. In the following section, the role of important factors in angiogenesis and regeneration will be discussed.

4.2.1. Vascular endothelial growth factors (VEGF)

VEGF family includes VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placenta growth factors. Among these members, VEGF-A has a pivotal role in the healing process, because it initiates the angiogenesis and assists in the migration and proliferation of endothelial cells. There are 2 types of genes which express VEGF-A receptors: KDR and Flt-1. While the former is associated with endothelial cells'behavior, the latter is responsible for vessel formation, vascular permeability, anti-apoptotic proteins, and expression of MMPs in SMCs[94].

Since the main stimulator of the VEGF-A release in wounds is hypoxia, a gradient of VEGF-A concentration is shown to parallel the hypoxic gradient. VEGF-A also affects lymphangiogenesis, the formation of lymphatic vessels from pre-existing lymphatic vessels. Although VEGF-A is a therapeutic option in the treatment of diabetic foot ulcers, sole delivery of this factor may cause leaky vessels and loss of integration between the vessel and lymph [95].

VEGF-C and placental growth factor are also pro-angiogenic molecules increased in wound healing, which regulate inflammation and increase blood diffusion to the underlying tissues, migration of EPCs, and granulation tissue formation. The level of these factors dramatically dropped in adults with diabetic chronic wounds [93].

Alternatively, administration of these angiogenic factors can also be achieved using genetically transfected cells or their encapsulation into biodegradable polymers (e.g., poly(lactic-co-glycolic acid) (PLGA) or poly-L-lysine (PLL)). These transfected cells or polymer-based carriers can provide a sustained release of the desired factors[96–98].

4.2.2. Fibroblast growth factors (FGF)

Among the 23 members of the FGF family of growth factors, FGF-2, FGF-7, and FGF-10 are mainly involved in wound healing. FGF is primarily released from keratinocytes, fibroblasts, endothelial cells, SMCs, and mastcells, and its receptors are often conjugated to the proteoglycans, such as heparin, in order to be activated.Typically, in acute wound healing, the level of FGF-2 is increased which plays an important role in formation of granulation tissue, tissue regeneration, and epithelialization. Moreover, regulation of the ECM secretion, stimulation of fibroblasts and keratinocytes migration, and induction of collagen synthesis are other effects of this factor.Notwithstanding, in chronic wounds the level of FGF-2 plummetsdue to its fast degradation in the harsh environment of these wounds (such as diabetic foot ulcers) which resulted in impaired healing. On the other hand, FGF-7, another member of FGF family, is generally present in the last steps of angiogenesis and is considered critical for lumen formation. In addition to reducing the amounts of ROS in the wound environment, FGF-7 has a

synergisticeffect on the VEGF expression and epithelialization as well. In fact, FGF as a heparin-binding growth factor, can initiate angiogenesis in collaboration with VEGF, and induce proliferation and migration of endothelial cells [57,99].

In some research, hydrogels have been used to improve the efficiency of FGF delivery [100]. For example, Zhao et al. used specific peptides (fibrin-binding peptide kringl) to attach FGF to fibrin hydrogels. They reported that these FGF bonded fibrin hydrogel can significantly improve therapeutic angiogenesis and wound repair [101].

4.2.3. Platelet derived growth factors (PDGF)

In addition to platelets, other cells, such as fibroblasts, keratinocytes, and also vascular endothelium secrete PDGF. The activation of PDGF's receptor as a consequence of ligand-receptor binding, along with its dimerization and phosphorylation results inrunning a signaling pathway forrecruitment of neutrophils, macrophages, and SMCs towards wound bed as well as granulation tissue formation.The mechanism of angiogenic effect of PDGF is tissue-specific. In case of wounded skin, secreted PDGF promotes the HIF complex formation leading to the increased expression of VEGF and its receptor. PDGF is also necessary for maturation of new vessels. In particular, this factor recruits pericytes towards the capillary region and also recalls SMCs, which results in the integrity and functionality of the vascular structure, respectively. Moreover, PDGF plays an important role in increasing the proliferation of fibroblasts, ECM secretion, differentiation to myofibroblasts, migration of keratinocytes, and epithelialization [102,103].Since chronic wounds suffer from low level of PDGF, promoting PDGF expression and release could be significantly helpful in their healing process [103].

In a study done by Xie et al., the dual release of VEGF and PDGF were accomplished by the fabrication of chitosan combined with polyethylene oxide (PEO) nanofibers containing VEGF and PDGF-loaded PLGA nanoparticles. Early release of VEGF followed by a sustained release of PDGF resulted in the creation of functional vascular networks, accelerate healing, and re-epithelialization[104].

4.2.4. Transforming growth factor-β (TGF-β)

Since TGF-β is secreted from macrophages, fibroblasts, platelets, and keratinocytes, it plays a role in inflammation, angiogenesis, epithelialization, and connective tissue regeneration[105]. This factor eliminates pathogens and peroxide free radicals, increases expression of VEGF and ECM proteins (e.g. collagen, fibronectin), and inhibits MMP-1 and MMP-3 enzymes which can result in fast wound closure. Moreover, it paves the way for the stabilization of new vessels through ECM deposition [48,106].

For example, in the study by Miscianiovet al., the critical role of TGF-βpathway in regulation of the endothelial cell homeostasis and vascularization in skin wound healing was investigated. Their results demonstrated that overexpression of miR-148b which regulates TGF-βsignalling, resulted in increased migration and proliferation of endothelial cells. Moreover, *in-vivo* wound healing in mouse model revealed the therapeutic effects of miR-148b in treatment of impaired wounds through enhanced endothelial-to-mesenchymal transition and angiogenesis[107]. Another study by Riedel et al. assessed the effect of TGF-βtargeting using antisense oligonucleotides on improvement of angiogenesis via expression of VEGF in chronic dermal

wounds. For this reason, human endothelial cells were cultured in the conditioned medium of treated keratinocytes with antisense TGF-βoligonucleotide. They reported that using antisense TGF-βoligonucleotide upregulatedVEGF secretion, increased endothelial cell migration and tube formation in chronic wounds [108].

However, the release of TGF-β should be controlled because it can cause hypertrophic scars.Overall, studies indicated that while exogenous addition of TGF-βcan promote wound healing through stimulation of angiogenesis, its endogenous diminishing would reduce scar formation without hindering wound healing [109].

Due to the short half-life (about hours) of growth factors and loss of bioactivity in the biological environment and in particular enzymatic and inflamed environment of chronic wounds, a sustained release manner is required for at least a month for the formation of stable and functional vessels until vascular sprouting. Although the fast delivery rate of a specific growth factor like VEGF can increase capillary density, these vessels are usually unstable and leaky [95,103]. Thus, researchers have utilized scaffolds and micro/nanocarriers for encapsulation and controlled delivery of such therapeutics to mimic their spatiotemporal release and avoid the negative side effects caused in their supraphysiological concentrations.

4.3 Angiogenesis induction approaches using scaffolds

Undoubtedly, providing a suitable niche for cells, which supports their functions and normal behavior, is considered as the most vital merits of scaffolds. Similarly, scaffolds substituting the

nativedermal layers should contain vascular network for better nourishing the cellular population. Accordingly, it is now well recognized that the scaffold micro/nanostructure and physicochemical properties can be tuned to facilitate the vascular network formation inside the structure, improve the host response and also direct the cell behavior. Therefore, modification of the scaffold properties using either biochemical or biophysical cues can be a promising approach towards angiogenesis that may be useful to address the complications of previous induction methods (i.e. cell- and growth factor-based methods) [35,110,111].

Regarding biophysical modification of scaffolds,in order to improve angiogenic response of the tissue, the modulation of scaffold itself without using any bioactive additive is underscored. Such modulation can include but not be limited to modification of porous structure (e.g. size, shape and interconnectivity), surface pattern, etc.On other hand,application of biochemical cues in forms of fabrication of biomaterial based scaffolds, grafting/immobilizing bioactive motifs, encapsulation of therapeutics, etc. is another promising approach for mimicking the native cellular niche and stimulation of desired vascular formation within the scaffold[53,86,112,113]. As mentioned, there are numerous strategies used for the induction of angiogenesis in the scaffold structure, which are discussed in the following sections.

4.3.1. Structural modification

Angiogenesis induction in the scaffolds is dependent on the morphological/structural features such as pore diameter and also their connectivity. Based on the evidences, scaffolds with pore diameter larger than 200 μm, can stimulate the formation of the vascular network with large

vessels and low densities. Nevertheless, scaffolds having pores smaller than 200 μm, can lead to small vessels with high densities, which are suitable for skin tissue engineering applications [114]. For example, a commercial double-layer skin substitute named Integra™ has pore diameter distribution from 20-125 μm. Moreover, studies have documented that in addition to the pore size, pore connectivity significantly affects the induction of angiogenesis, so that scaffolds with inter-connective pores in the range of 150 μm can improve vessel formation [16,115].

Consequently, ideal angiogenic scaffolds should provide proper porosity in order to fabricate hierarchical interconnected porous structures in different shapes and sizes. There are several methods such as electrospinning, rapid prototyping, and solid free form (SFF) fabrication, including stereolithography, selective laser sintering, and 3D printing, which can be tailored to form an accurate microstructure of a skin substitute [116,117].

Nanofibrousdressings/scaffolds can be regarded as promising structures in skin tissue engineering due to their ability to simulate the native microenvironment of cells, improvement of cell adhesion, and physical-mechanical properties as well[118].

However, due to the small pore size and 2D architecture of electrospun scaffolds, the cell infiltration and vessel formation into the scaffold structure are limited. To overcome this limitation, the electrospun scaffolds have been modified by various methods such as ultrasonication, bubble formation, the combination of micro and nano spinning, charge repulsion of electrospun fibers, and also wet electrospinning aimed to expand the compact 2D fibrous

structure [119–122]. For instance, Sheikh et al.reported that expanding the 2D structure of silk fibroin to 3D structure with highly interconnected pores resulted in better cell infiltration and consequently more proper angiogenesis. Such a nanofibrousscaffold with improved 3D porousstructure can providebetter conditions for full-thickness wound regeneration with perfused vascular structure [121].In another example,Chen et al. developed a 3D expanded nanofibrous scaffold with radially or vertically aligned nanofibers in combination with BMSCs and evaluated wound healing in type 2 diabetic mice wound model. In addition to customizable geometry and shape-recoverable properties, BMSCs-laden 3D scaffolds promoted angiogenesis and collagen deposition. Such a 3D porous structure supported the in-depth vascular formation and thus could be effective for the treatment of diabetic wounds[122](**Figure 3A, B**).

Taking advantage of rapid prototyping methods, such as 3D printing, and also microfluidics, researchers can create a vascular network with a specific pattern and desired structure. For example, in using the 3D printing approach, incorporation of a combination of endothelial and parenchymal cells along with the growth factors, in an injectable hydrogel led to the production of the in-situ formed structure with specific shapes and a high degree of interconnectivity in pores. On the other hand,studies also used microfluidic systems in order to monitor the differentiation and migration of vascular cells and create a suitable bioreactor system for vessel-like tissue formation. The main advantage of these microfluidic systems was thelaminar flow in the microfluidic channels combined withcell-laden hydrogels coated on the surface of the channels [92,123]. As an example, in Skardal et al.'s study, a fibrin/collagen hydrogel in

combination with a microfluidic system has been used for improvement of the angiogenesis. Hydrogel incorporating amniotic fluid-derived stem (AFS) cells, fibroblasts, and keratinocytes, were printed on the surface of Matriderm, a commercial acellular dermis, and led to new functional skin [124](**Figure 3C, D**).

Figure 3. Fabrication of 3D scaffold with fine cellular distribution and infiltration.(A) Thetrichrome staining and enhanced granulation tissue formation of wound area ofRAS (radially aligned scaffolds), VAS (vertically aligned scaffolds), RAS+BMSCs (BMSCs loaded radially aligned scaffolds), and VAS+BMSCs (BMSCs loaded vertically aligned scaffolds) groups compared to control group after 3 and 7 days postsurgery. Green and blue arrows indicate newly formed blood vessels and newly formed collagen fibers, respectively, and (B) Macroscopic view of 3D scaffolds consisting of radially or vertically aligned nanofibers with different sizes. (C) A schematic of bioprinting of AFS cells in a full-thickness skin wound with (D) confocal images of green fluorescent protein-tagged AFS cells laden deposited gels 24 hours post-printing from above view. Reproduced with permission.[122,124]Copyright 2012, Wiley and 2020, Elsevier.

4.3.2. Physicochemical modification

Since the cells contact the surface of the biomaterial, its chemical and physical modifications should be highlighted for the regulation of the cellular behaviorwhich is crucial in healing. Studies have demonstrated that providing specific surface micro/nanopatterns in the biological structure, such as nano/microfiber, nanopit, nanopillar/post, and nanogrooves can influence the migration, alignment, and adhesion of the endothelial cells through contact guidance phenomenon [125] (**Figure 4**).

Indeed, biophysical factors are broadly involved in orchestrating morphogenesis, angiogenesis, and tissue remodeling by modulating cell function and fate.Cells can convert the biomaterial'sbiophysical features into intracellular biochemical signals via for example

mechanosensing resulted in ultimate gene expression [126]. Therefore, the creation of specific morphologies and surface patterns along with optimization of pore size and pore morphology has been shown to influence the growth of interconnected blood vessels within the scaffold and also the degree of vascularization through the mechanisms involving the body's immune system [127,128]. In this regard, using biomaterials containing microchannelarchitecture, expanded fibrous morphologies, and 3D bioprinting systems can be considered as promising approaches due to their ability to 3D mimicking the native microenvironment of cells[35,64,127–130].As an example, Tang et al. studied the effect of microchannels on the integration and vascularization of host tissue into the 3D porous silk scaffolds containing 508 μm diameter microchannels. The *in-vivo* test results (at 6 and 14 weeks) showed the formation of perfused and functional blood vessels within the microchanneled scaffold which were connected to the animal's cardiovascular system demonstrated by smooth delivery of either the contrast agent or dye through the vessels inside the scaffold[128] (**Figure 4F, I**).

Interestingly, in the wound healing process, although the migration of fibroblasts occurs under a concentration gradient of growth factors (usually named chemotaxis), its direction and path are guided by ECM topography (known as contact guidance). However, it has been shown that a high density of growth factors (such as TGF-β) in the wound site may result in scar formation. Therefore, improvement of the wound healing and also angiogenesis is dependent on the surface topography [131](**Figure 4A**).

Regarding the natural skin morphology and basket-weave fibrous network structure of the dermis, electrospun scaffolds can be served as ideal skin dermis substitutes. For example, Sun et al. mimicked the basketweave-like pattern of collagen fibrils in native skin and investigated its effect on chronic wound healing in diabetic rats. Despite most nanofibrous scaffolds, which are randomly oriented, crossed fiber organization caused the best healing outcome with an increase in migration of fibroblasts and keratinocytes as well as induction of angiogenic response [132].

More interestingly, wounds formed in the same direction of parallel tension lines of skin ECM can heal with fewer scars which indicate to the importance of substrate patterning in regeneration potential. In fact, surface patterns and topography play an important role in the migration of skin cells, specially fibroblasts, which ultimately leads to accelerated healing [131]. For instance, Xie et al. showed that radially aligned PCL nanofibers fabricated by ring-and-dot collector significantly enhanced the migration of fibroblast cells from the periphery towards the center of the scaffolds compared with random fibers. Moreover, results confirmed secretion of type I collagen with a high degree of organization which might induce functional wound closure without scarring (**Figure 4C, D**) [133].

On the other hand, grafting/immobilization of functional groups on the biomaterial's surface, via various techniques such as surface plasma treatment, are considered as an effective chemical modification. Immobilization of the proteins or peptides on the scaffolds for angiogenic tissue engineering is regarded as an efficient method for sustained and combinational delivery of numerous angiogenic growth factors. The active peptide sequences can be derived from cell

adhesion proteins, such as fibronectin (e.g. RGD and REDV), laminin (e.g. YIGSR), or even glycosaminoglycans (GAGs) (e.g. heparin), which contain growth factor binding sites and can support attachment and migration of the vascular cells. For instance, the combinational release of VEGF with angiopoietin-1, IGF, or SDF from either a scaffold or micro/nanoparticle represented promising angiogenic results [50,134].Some studies used the angiogenic effects of endothelial cell's secreted factors in combination with adhesion protein-based scaffolds for wound healing applications [135,136]. For example, Losi et al. evaluated angiogenic effects of fibrin scaffolds containing fibrin microspheres loaded with endothelial nitric oxide synthase enzyme (eNOS) on the diabetic wounds of rabbits. The results represented an induction of angiogenesis via the release of eNOS and an increase in the number and length of vascular branches up to more than 3 fold. Moreover, in the control group (i.e. the fibrinous scaffold without factor), the increase in the vascular branches is observed to some extent, which proved the regenerative and angiogenic nature of fibrin [137].

There are also several studies that used ECM's derivatives such as proteoglycans and their GAGs as hydrogels or bioactive molecules immobilized onto scaffolds to bind a range of growth factors, cytokines, and chemokines through their GAG chains [126,138]. Among these proteoglycans, research findings confirmed that perlecan, or heparan sulfate proteoglycan 2 (HSPG2), has major roles in tissue and organ development and wound healing by orchestrating the binding of morphogens and delivery of angiogenic factors to cells in a spatiotemporal and dynamic manner [139,140].

Recently, the use of methacrylic acid **(**MAA)-based biomaterials in either scaffold fabrication or modification has attracted much attention in wound management. This compound showed an increase in angiogenesis without the need for cell or growth factor incorporation. One of the main capabilities of MAA- based biomaterials is the improvement of angiogenesis and wound healing in either diabetic or non-diabetic individuals [141].There are various reasons documented for such angiogenic effect in these biomaterials which can be categorized into twomain mechanisms. First, the preferential adsorption of complement proteins (e.g. C1q and Factor H) toMAA-based biomaterials may trigger endothelial cell migration and the local inflammatory response in the tissue. This can result in macrophage polarization to M2 type and upregulation of the expression of inflammatory genes such as osteopontin, tumor necrosis factor (TNF) and IL-1. The other effects of MAA-based biomaterials which can be regarded as one of the most critical mechanisms for their angiogenic and wound healing responses, is associated with activation of Shh signaling pathway along with upregulation of Shh and Gli3 genes. Interestingly, Gli3 as the main Shh transcription factor plays an important role in regulation of endothelial cell function and vascularization[30,142,143].

TheMAA-based biomaterials can be fabricated into the various forms of beads, 3D scaffolds, films, or injectable hydrogels and comprise porous topography and a negative charge, which is important for tissue integration, vascular formation and also acting as a growth factor reservoir [144]. In a study comparing the potential of MAA and methyl methacrylate (MM) beads as skin grafts for the use of healing injured albino rats, it was shown that in the MAA sample, the

number of blood vessels was more than 40% after 11 days, in comparison with MM. Moreover, the thickness of the skin stromal layer in the MAA group was thicker and healthier, indicating the normal vascular function [144].The regenerative effect of MAA-beads was also investigated in another study on the diabetic mouse model. Histological examination results indicated an increase in the angiogenesis on the seventh and fourteenth day with a significant difference in the number of vessels on day seven [30,145].Indeed, studies have suggested that the negative charge of MAA beads can absorb the cationic growth factors, and slowly release them. Consequently, they can be considered as growth factor reservoirs for long-term release in the cellular environment [146,147].

It is worth mentioning that using a composite structure in order to produce an essential concentration gradient for cell growth and also resembling the vascular tissue has been applied in many scaffolds, including chitosan/gelatin, chitosan/collagen, fibrin/gelatin, etc.[125].

Figure 3. The effect of biophysical cues on healing and angiogenesis.(A) Schematic of dependency of fibroblast's migration on surface topography and the orientation of nanogrooves. (B) Macroscopic and (C) SEM images of radially aligned nanofibers deposited on the collector. Fluorescence micrographs comparing the migration of fibroblasts on radially aligned (D) and random (E) nanofibers after seeding at day 0 with magnified views of the center portion of radially aligned fibers (Dashed circle line indicates the border of cells). (F) Histological analysis of H&E stained cross-sections of silk scaffolds without (-channels) or with (+channels) hollow microchannels at week 6 post-implantation with their schematic shapes and histological analysis of tissue morphology in channeled silk scaffold at week 6 post-implantation. In the presence of microchannels, vascular tissue ingrowth was observed throughout the entire construct. Analysis of blood vessel perfusion in silk scaffolds with: (G) ΔR maps of MRI imaging showed the relative blood volume inside the channeled scaffold implanted subcutaneously in mice for 6 weeks, (H) ΔR map overlaid over a corresponding histological section, and (I) Fluorescent images of lectin- perfused blood vessels (red) inside a silk scaffold (green) implanted subcutaneously in mice for 6 weeks and imaged via light-sheet microscopy (Dashed line: scaffold boundary, White arrow points to the silk scaffold, Scale bar is 1 mm).Reproduced with permission.[128,131,133]Copyright 2018, Royal

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4.3.3. Biological activation

Incorporation of the angiogenic growth factors (e.g. VEGF, PDGF, and FGF) into the scaffolds structure serves as an important method for the induction of vessel formation. To expand the short half-life of blood vessels and reduce the chance of leaky vessel formation, sustained delivery systems are suggested. Therefore, a variety of polymers such as gelatin, chitosan, alginate, fibrin, polyesters, etc. have been studied for designing the sustained release systems [148]. Due to the supportive role of GAGs, specially heparin, which serve as a reservoir of growth factors *in-vivo*, they have attracted much more attention for the fabrication of the GF releasing scaffolds [50,115].

On the other hand, nano/microfibers can be loaded by several therapeutic substances (e.g. drug, growth factors, etc.), and support their releasing over time [117]. Moreover, a combination of nano/microcarriers with nano/microfibers has a noticeable impact on the stimulation of angiogenesis in damaged tissue, particularly in the case of drug/growth factor delivery. However, the proper sequential delivery of different therapeutics should also be considered [99,115,149].

For example, in the study by Lai et al., the sequential delivery of four growth factors (including VEGF, PDGF, bFGF, EGF), was achieved following the encapsulation of the two factors in gelatin nanoparticles and other two factors blended in nanofibers' polymer solution. The collagen-hyaluronic acid nanofibrous scaffolds incorporating the nanoparticles were then implanted into the animal model (**Figure 5A**). Based on their results, the burst release of bFGF and EGF from the nanofibers caused capillary sprouting, epithelialization, and delayed release of

PDGF and VEGF from gelatin nanoparticles in the fibrous scaffold, helped the functional blood vessel formation [150].

Considering the effective mimicking of natural ECM with the preserved 3D interconnected porous structure containing vessel networks, biologically-derived scaffolds are another suitable candidate for angiogenesis induction[151–153]. After the de-cellularization procedure, the re-cellularization of the construct with the desired cell types is carried out. One of the useful de-cellularized tissues in this regard is small intestinal submucosa (SIS), which is enriched in collagen and elastin fibers, as well as perfusable capillary networks [4,116]. For instance, Fercana et al. evaluated the angiogenic capacity of ECMbioscaffolds derived from decellularized human, porcine aortic adventitia (hAdv and pAdv, respectively), and porcine small intestinal submucosa (pSIS). They revealed that AdvECM hydrogels resembled the microarchitecture of the matrix fiber presented in native vessels, while maintained the angiogenic and bioactive factors (such as FGF2) in their bioactive form and this supported their use in microvascular regeneration applications[154] (**Figure 5D, E**). In another study, Kim et al. tested the functionality of a hybrid scaffold consisted of electrospunpoly(l-lactide-co-caprolactone) (PLCL) membranes containing heart decellularizedECM (hdECM) as a wound dressing. Their results confirmed the presence of pro-angiogenic factors in this porous hybrid structure led to enhanced angiogenesis, effective wound healing and reduced scarring in a rat excisional wound-splinting model [151].

Figure 5. Some examples of biological activation of scaffold for angiogenesisinduction.(A) Illustration of loading four different growth factors in hyaluronic acid (HA) and collagen (Col) nanofibers with or without encapsulation of factors in gelatin nanoparticles (GN). (B) Fluorescent (fluorescein and rhodamine b) and scanning electron microscopy (SEM) images of Col-HA-GNnanofibrous scaffold (Arrows indicate gelatin nanoparticles; the scale bar in (B) 5 μm and (C) 6μm). Angiogenic effect of ECM-derived bioscaffolds*in-vivo*: (D) Bright-field images of scaffolds on the chorioallantoic membrane (CAM) of the chick embryo (incubated for 72 h). The angiogenic response to pSIS and pAdvECM-containing fibrin scaffolds (250 mg/mL), scaffolds loaded with digestion buffer (1% (w/v) pepsin in 0.1 N HCl) andDMSOare represented. Addition of the FGF2 inhibitor PD173074 (100 nM) compromised the angiogenicability ofpAdvECM. (E) Histological cross-sections of CAM assay containing scaffolds in which the vasculatureisvisualized using tomato lectin-Dylight® 650 (red) and nuclei are labeled with Hoechst dye (blue). The angiogenic capacity of different concentrations of pAdvECM scaffolds obeys from a dose-dependent manner. (F) Addition of DMSOand FGF2 inhibitor PD173074 to the pAdvECM scaffolds. (G) Chemoattraction of lectin-negative cells in the avascular zone adjacent to invading lectin-positive cells in pAdvECM-loaded fibrin scaffolds in two concentrations.Dashed white lines and arrowheads indicate the scaffold/CAM interface and invasion of new vasculature (lectin-positive vascular cells) towards the scaffold, respectively. All scale bars in panels D= 5 mm, E and F= 500 mm, and G= 20 mm, *= Avascular zone). Reproduced with permission.[150,154] Copyright 2014 and 2017, Elsevier.

4.3.4. Cell sheet engineering

Cell sheet engineering is one of the alternative methods of providing skin substitutes with various thicknesses and morphologies. Considering the native structure of skin tissue,typically, a combination of keratinocytes and fibroblasts(as ECM secreting cells) sheetsis used for the new cell sheet engineering approach. In this case, the epidermal sheet containing cultured keratinocytes on the polymeric substrate is placed on a full-thickness wound coated with the fibroblast sheet[155]. However, this approach also faces limitations concerned with wound dressings/scaffolds such as delayed epithelialization, poor mechanical properties, poor nutrients supply and lack of functionality. In order to make a vascularized skin substitute, a double layer graft containing endothelial cells coated on polymeric substrate can be applied for the deep

wound treatment. Nevertheless, the more different cells are recruited, the more time is needed for the sheet fabrication and culturing[50,156]. To facilitate sheet fabrication, the culture of the cellular monolayer is conducted on the surface of temperature-sensitive polymers, such as PIPAAm. In such polymers, the formed cell sheet can be detached by changing the gelation properties of the substrate in decreased temperature. In the case of PIPAAm, changing the water absorption and swelling properties of the polymeric sheet at a temperature lower than 32℃, results in removing the whole cultured cell layer, while the cell-cell contacts and secreted ECM were preserved as well [157]. Due to the presence of secreted ECM proteins and the resultedadhesive properties of this new-formed sheet, different cell sheets co-cultured with the endothelial cells can be easily stacked to form a 3D vascularized structure.Cerqueira et al. investigated the effects of a double layer skin substitute incorporating the endothelial cells on the treatment of full-thickness wounds and revealed that new skin formed with similar mechanical, morphological, and biological properties to the natural skin with functional vessels. In this research, after extraction of keratinocytes, fibroblasts, and endothelial cells from adipose tissue, they were cultured on a temperature-sensitive polymer coated dish, and then 3D scaffold was formed by stacking the keratinocyte layer on the fibroblast co-cultured with endothelial cell layer [156].

4.3.5. Green photosynthetic scaffolds

Even in the best circumstances, induction of angiogenesis with the aforementioned methods is time-consuming (usually needs several days), which can lead to the early death of the cells present in the center of the scaffold from hypoxia. Therefore, supporting the loaded cell

oxygenation seems necessary. Interestingly, Hofner et al. have offered a new method of scaffold synthesis, incorporating a natural oxygen supply, named HULK (from the German abbreviation of HyperoxieUnterLichtKonditionierung) (**Figure 6**). HULK is attributed to providing local oxygen in the dermis scaffold, using natural photosynthesis. For this purpose, single green cells of microalgae, named "Chlamydomonasreinhardtii", which are biocompatible and have a high photosynthetic function under photo radiation, cultured on the Integra^{TM} wound dressing. These algae can initiate the HIF-1α pathway, stimulate penetration of the nearby vessels, and consequently lead to the formation of the new vascular network [50,158,159].

Figure 4. HULK scaffold: macroscopic view (A) and SEM (B,C) images of Chlamydomonasreinhardtii algae seeded on Integra show the incorporation of the microalgae even in the inner cavities of the scaffold. (D) implanted HULK scaffold in full-skin defects of nu/nu mice after 5 days with *ex-vivo* visualization of infiltrating microvessels through the scaffold (E) (Scale bars: A= 10 mm; B= 200μm; C= 50 μm D= 4 mm; E= 1mm). Reproduced with permission.[159] Copyright 2015, Wiley.

Undoubtedly, application of advanced micro/nanofabrication techniques, biophysical and biochemical cues to engineer cell fate and generate vascularized and functional scaffolds has been progressed considerably. In addition, cell sheets and photosynthetic scaffolds are another alternative approaches exhibited great promises for effective wound healing. Interestingly, the ability of loading various angiogenicstimulants including growth factors, bioactive compounds, drugs, small molecules, genes, or even cells in a single scaffold is the major advantage of this approach. Despite having such diversity in mechanism of the angiogenic induction, optimization of scaffold's characteristics is required to develop a reproducible and desired result. In fact, the more sophisticated system is, the more figuring out the optimal conditions would be challenging.

Moreover, since the underlying effect of the biophysical factors in *in-vivo* environment is not fully understood, further studies in the future is crucial.

4.4 Induction of angiogenesis using biological/chemical compounds

In the light of the diversity in material selection, cost-effectiveness, easy processability, and also regenerative effects, incorporation of biological/chemical compounds into the scaffolds is preferred for induction of vessel formation. These compounds can be utilized either in the form of bioactive therapeutics (such as natural products and chemical drugs) or angiogenic polymers, used for scaffold fabrication.

4.4.1. Chemical therapeutics

4.4.1.1. Deferoxamine

Deferoxamine (DFO) is the FDA approved iron-chelating drug that is prescribed for the treatment of hemochromatosis and metal poisoning. Iron chelators are chemical compounds, which can form a metal complex that is used to trap Fe^{3+} ions. Studies have demonstrated that DFO has angiogenic effects. This drug consists of several carbonyl and hydroxyl groups, which can provide electrons for Fe^{3+} ion and help inhibit its catalyst role. Thus, by inhibition of the activity of iron ions and eventually inhibition of prolyl hydroxylase enzyme degradation, DFO can support HIF-1α expression and promote angiogenesis and vascular formation [160]. For this reason, DFO has attracted much attention for the treatment of chronic wounds such as diabetic wounds [161,162]. In addition to the inhibition of ischemia, DFO as an antioxidant agent can protect tissue from the free radical attacks, which results in higher cell proliferation and promote

healing. Due to the short half-life and chance of toxicity in intravenous administration, transdermal delivery of DFO is used for skin regeneration applications. However, due to the high molecular weight (560 Da) and hydrophilicity, DFO cannot penetrate freely through the stratum corneum of the skin. Hence, encapsulation of DFO within lipophilic carriers (such as liposomes and niosomes) or polymeric hydrogels are suggested for facilitating its absorption as well as controlling the release rate [60,163]. As an example, Duscher et al. have encapsulated DFO in inverse micelles and then loaded them into the ethylcellulose foam. Results of skin penetration and *in-vivo* tests (carried out on diabetic wound of rats) have demonstrated proper passing and releasing of the drugs through the skin layer after 2 days, and also the formation of the new capillary networks [164]. In another study, Chen et al. investigated the angiogenic properties of gelatin-methacrylate (GelMa) hydrogel containing DFO for treatments of diabetic wounds, which were safe, reliable, and highly effective [165]. In addition, Rassu et al. loaded DFO in PLGA particles embedded in alginate/chitosan hydrogel, and they showed a significant increase in drug absorption and effectiveness [166].Studies have suggested that 10% DFO can lead to angiogenesis, increasing dermis thickness, decreasing cell apoptosis, inhibition of free oxygen radicals, promote healing, and has a prophylactic effect [164]. It is worth mentioning that the topical administration of DFO at a concentration of 100-folds lower than the therapeutic dosage prescribed parenterally in hemochromatosis shows a better safety profile [52].

4.4.1.2. Simvastatin

As an oral drug synthesized from a fungus named “Aspergillusterreus”, simvastatin is an inhibitor of the co-enzyme controlling rates of the cholesterol synthesis metabolic in the body

[3,167].Despite being prescribed for either blood cholesterol reduction or treatment of cardiovascular diseases, studies have documented that simvastatin can significantly affect healing and have anti-inflammatory and angiogenic properties [168][169].Studies have shownthat simvastatin is able to improve the pattern of VEGF production, enhance the content of NOin the wound, and also increase the proliferation of keratinocytes [167].

Asai et al. showed that the topical application of simvastatin has resulted in wound healing in diabetic mice through angiogenesis and lymphangiogenesis. In fact, statins can treat ischemic damage by stimulation of vasculogenesis followed by direct regulation of proliferation of the endothelial cell, inhibition of apoptosis, and capillary formation [170].

4.4.1.3. Erythropoietin

Erythropoietin (EPO), also called hemopoietin, is a glycoprotein controlling red blood cell production. Precisely, erythropoietin is a specific cytokine of red blood cells or erythrocytes presented in the bone marrow and is produced by the interstitial kidney fibroblasts [171].

In addition to the production of red blood cells, EPO has a potentially significant effect on the vascular stiffening in hypertension, stimulation of angiogenesis, increasing cellular viability through activation of anti-apoptosis genes in ischemic tissue and also shows the neuroprotective effect in the diabetic neuropathy [171,172].

Recent research suggests that EPO leads to angiogenesis through the inflammatory responsepathway and the overproduction of M2 macrophages [173]. A study done by Elsherbiny et al. demonstrated that the use of adipose-derived stem cells cultured in erythropoietin-supplemented culture medium improved wound healing in a mouse model by enhancing

angiogenesis, proliferation, and migration of both endothelial cells and endothelial progenitor cells [172].

4.4.1.4. Melatonin

Melatonin is a tryptophan-based hormone, which is secreted from the pineal gland, skin, retina, and the digestive system and acts as a neurotransmitter. Melatonin stimulates the production of IL-1, TNF-α, and TGF-β. Moreover, it regulates the immune response, increases proliferation of fibroblasts, secretion of cytokines from monocytes, and stimulates angiogenesis [174].

The *in-vivo* study onmurine animal models with full-thickness wounds showed that regular injection of melatonin could increase angiogenesis, collagen fiber formation, and level of hydroxyproline in the treated group. Moreover, an increase in the macrophages on the third day after treatment together with the proliferation of fibroblast and formation of skin appendages on day 21 noticeably healed the wounds [174]. Melatonin has a high affinity for binding to T-helper lymphocytes, which stimulates IL-4 and eventually releases the growth factors from bone marrow. This protein has antibacterial and antioxidant effects as well [102,175].

In one of the studies conducted by Jin et al. the major mechanism of melatonin-induced angiogenesiswere found. They showed that treatment of EPCs derived from mural bone marrow with melatonin could decrease advanced glycation end product (AGE)-induced apoptosis and cellular dysfunction. In other words, by stimulation of autophagy flux through the Adenosine monophosphate activated protein kinase(AMPK)/mammalian target of rapamycin (mTOR) signaling pathway, melatonin provides defense against apoptosis and impaired function of EPCs which is occurred in diabetic wounds [176].In addition, Song et al. study on the culture of the

keratinocyte cellular model in the presence of melatonin has revealed low levels of inflammatory cytokines and oxidative stress which resulted in increased proliferation, migration, and wound healing [175].

4.4.2. Natural and biological compounds

4.4.2.1. Aloe vera

Aloe barbadensis, which is commonly named "Aloe vera", is one of the ancient herbs used for the treatment of burns, wounds, and anti-inflammatory applications in old China and Egypt. This plant tends to cure various wounds in a dose-dependent manner and can reduce the pain and edema, as well [177–179].

Considering its several valuable properties, such as being antifungal, antiviral, antibacterial, anti-inflammatory, antidiabetic, antioxidant, biodegradability, oxygen permeability, low toxicity, and cost-effectiveness, aloe vera can be a useful material for scaffold fabrication or other tissue engineering applications [178].

Aloe vera contains a cellulose-like substance called "Lignin", which gives it the ability to penetrate into the skin. Anthraquinones are the antibacterial and antifungal components of aloe vera inhibiting the synthesis of bacterial proteins. In addition, saccharide compounds of aloe vera, such as Acemannan, Mannose-6-phosphate, and Glucomannan, play an important role in creating an anti-inflammatory response, tissue regeneration, stimulating macrophages and control the immune system activity. Additionally, Aloesin, a glycoprotein present in aloe vera gel, results in proliferation of fibroblasts, production of collagen type I and epithelialization via the proliferation of keratinocytes [180–182].

The study by Moon et al. on the angiogenic effect of aloe vera has demonstrated its regenerative properties through the presence ofβ-sitosterol compound, as a herbal steroid,which can stimulate the endothelial cell migration towards the wound and promote new vessel formation[183].

Moreover, aloe vera can increase levels of hyaluronic acid and dermatan sulfate, inhibit the activity of MMPs,and promote growth factor production (such as bFGF and TGF-β1) leading to angiogenesis [181,184].

4.4.2.2. Black raspberry

The black raspberry, called *Rubusfruticosus*, is a plant with a permanent root, wooden and spiny branches, containing white flowers and black fruits. It contains isocitric acid, malic acid, pectin, monoglucosidecyanidin, tannins, alkaloids, flavonoids, ascorbic acid, iron, magnesium, sodium, and vitamin A. Flavonoids found in the black raspberry, inactivate free radicals and prevent cardiovascular diseases, oxidative stresses and damage to the cell membrane. Anthocyanidin is another important compound found in raspberries that shows antioxidant, antimicrobial, angiogenic, and antidiabetic properties, and is suitable for diabetic wound healing [178,185]. Moreover, phenolic and anthocyanin compounds of berries play a crucial role in promoting angiogenesis via modulation of migration in endothelial cells [186,187].

Research findings confirmed that the local administration of black raspberry extract can reduce average wound area and accelerate healing through increasing collagen synthesis and other extracellular matrix components, recreation of skin appendages, reducing inflammation and more importantly, promoting angiogenesis through HIF pathway in diabetic rats [188,189].

4.4.2.3. Grape seed’s extract

Grape seeds contain a combination of lipids, proteins, carbohydrates, and polyphenols, the percentages of which depend on the type of grapes. Polyphenols presented in the grape seed include tannins, gallic acid, monomeric flavan-3 catechin, epicatechin 3-galit, and dimeric, monomeric and polymeric proanthocyanidin which can mitigate the chronic wounds complications[190–192].

In particular, the incorporation of grape seed's proanthocyanidin into a scaffold's structure can regulate the tissue angiogenesis and improve wound healing[193].The study of Locilento et al. incorporated grape seed extract in an electrospun wound dressing consisted of a blend of polylactic acid (PLA) and PEO. Their results showed a significant proliferation of fibroblasts as well as rapid wound healing owing to the antioxidant activity of grape seed extract [194].

In addition, *in-vivo* studies have indicated positive effects of the grape seed extract on diabetic wound healing. Specifically, the presence of phenolic compounds and flavonoids leads to an increase in wound closure, epithelialization, capillary formation, proliferation of fibroblasts, and thus healing of chronic wounds. Moreover, tannin, which is also found in this extract, helps wound healing via contraction and antimicrobial effects. In fact, inhibition of the expression of inflammatory cytokines results in a decrease of inflammation and improvement of angiogenesis, which is then followed by fast healing of the chronic wounds [191,195].

4.4.2.4. Egg white

Egg white as an active protein that can form a gel network and increase the viscosity and stability of the emulsion and foams, is among the best sources of natural proteins that can be used to make scaffolds. Egg white has been employed to treat various disorders, including

wound healing since it has shown to have regenerative, antibacterial, anti-inflammatory, and proliferative properties [196,197].

Egg white consists of three main proteins: Conalbumin, Ovalbumin, and Lysozyme[196].Egg white ovalbumin is one of the family members of albumin glycoproteins and has the ability to bind to the angiogenic growth factors and compounds, which are very important in diabetic wound healing [198].

A review of the literature shows that instead of using whole egg white, specific protein components such as lysozyme and albumin, which are commercially available, are usually used to make scaffolds [199–201]. However, the whole egg white possesses noticeable angiogenic and regenerative capacities and for this reason, can be used as a potential biomaterial in scaffold preparation [202]. For instance, in a study carried out by Jalili et al., after providing freeze-dried foam from whole egg white (E2), it was subcutaneously implanted in the nude mice and its angiogenic response was examined and compared with the collagen scaffold (Col) (**Figure 7**). In addition to the proper tissue integration and formation of functional vascular tubes, the scaffold acts as a storage site for cytokines and growth factors and helps in the polarization of macrophages to the M2 type [198].

Figure 5. Scaffolds interaction with *in-vivo* environment and angiogenesis evaluations. Images of H&E, Masson's Trichrome, CD31, and CD206 staining show the development of new vessels in the scaffolds (Scale bar: 100 μm). Reproduced with permission.[198] Copyright 2015, Wiley.

4.4.2.5. Platelet-rich plasma (PRP)

Platelet-rich plasma (PRP) is a fraction of blood plasma that contains several growth factors and cytokines secreted from alpha granules of platelets. This bioactive complex can modulate angiogenesis, enhance proliferation and differentiation of stem cells, and ultimately accelerate wound healing. According to the study by Etulain et al., the induced angiogenic response of PRP is due to the presence of PDGF, VEGF, and bFGF that results in tube formation and vascular development, as well as skin regeneration in mouse. In spite of the minimal risk of immune rejection and economical means of treatment, PRP confronts some limitations in efficacy owing to the short half-life of its protein content [203,204].

Another source of angiogenic growth factors is Leukocyte- and Platelet-Rich Fibrin (L-PRF). Based on research done by Ratajczak et al. it suggested that L-PRF induce endothelial migration and proliferation due to the presence of several CXCR-2 (IL-8 receptor) and EGFR ligands, which can eventually result in tissue regeneration and revascularization [205].

Considering the significant healing effect of platelet concentrates, several studies have applied them in delivery vehicles to prolong their effect and this area is still in progress.

4.4.2.6. Colostrum

Colostrum is a viscous fluid secreted at the beginning of lactation. It has a variety of clinical applications, including the treatment of bacterial and viral diarrhea, joint inflammation, sinusitis, pulmonary inflammation, and allergies. It has a range of antibacterial, antiviral, and anti-inflammatory factors suitable for tissue repair and growth [206].Among the growth factors presented in the colostrum, TGF-β, PDGF, FGF, TGF-α, and EGF, are effective in the process of

wound healing and angiogenesis. Additionally, immune factors such asimmunoglobulin G(IgG), immunoglobulin A(IgA), lactoferrin, and defensine, along with neutrophils and macrophages, make this material suitable for local administration on ulcers [207].

Research has shown that colostrum, in addition to accelerating wound healing, can contribute to wound closure via promoting granulating tissue formation, angiogenesis, increasing collagen synthesis, and proliferation of fibroblasts. Studies on the effect of localadministration of colostrum ointment on the ulcers proved that it can accelerate the wound repair andwound closure, increase collagen synthesis, andvascularization[206,207].

4.4.2.7. Honey

Honey has a long history of application for treatments of the wound, burns, acute and chronic injuries, going back to ancient Greece, Egypt, and India [208,209]. Honey is found to prevent infection and inflammation and can lead to anti-oxidant effects. Moreover, itprotects the wounds against gram-positive and gram-negative bacteria and is also resistant to fungi [206,208].Honey contains active biological agents, such as melitin, apamin, and adolapin, which could increase membrane permeability and affect the production of growth factors such as VEGF, TGF-β1, and collagen synthesis [208–210].

Animal studies have documented that owing to enhanced cell proliferation, angiogenesis, and collagen synthesis, honey decreases the formation of scar and improves the healing response [49,206].Honey-incorporated dressings, in comparison with colostrum, results in better healing, faster hemostasis, angiogenesis, less inflammation, more anti-bacterial and anti-oxidant activity,

collagen production, proliferation of fibroblasts, epithelialization, and contraction of the ulcer [206,209,210].As acommercial dressing, Medihoney® (Derma Sciences Inc., Canada) is a hydrocolloid dressing made of alginate containing at least 70% honey, which according to the FDA, can be used to treat full-thickness, diabetic and burn wounds [49,211].

4.4.3.1. Dextran

Dextran is a hydrophilic branchy polysaccharide derived from the microbial origin (i.e., lactobacillus)which is biocompatible, degradable, and inert in the biological environment. Dextran facilitates the infiltration of inflammatory cells and stimulates the migration of angiogenic cells to the ulcer. Applying dextran-based wound dressing on diabetic wounds can lead to rapid wound closure within 8 days without causing pain, edema, and secondary damage, and improve the healing through antibacterial effect [145].In a study conducted by Sun et al., dextran resulted in the recruitment of endothelial progenitor cells and SMCs, which created the vascular network and treated burn wound within a week [212]. Recreation of skin appendages, epidermal maturity, and the rapid penetration of neutrophils into the site of the ulcer for the secretion of the angiogenic factors are other effects of dextran based skin substitutes [213].

Among the mentioned compounds,natural compounds (such as medicinal plants) have attracted increasing interest because of theircost-effectiveness, high availability and low side effects.However, considering the possible variations in properties of these compounds derived

from different species, their usage in wound treatment is still in premature levels and requires more researches.

5. CONCLUSIONS AND FUTURE DIRECTIONS

Skin ulcers are one of the most serious and prevalent injuries in the world. In spite of the presence of various wound healing products in the market (e.g. in the forms of ointments, films, foams, sponges, hydrocolloids, and hydrogels dressings), efficient management and treatment of chronic and full thickness wounds still encounter several challenges. Considering the severity of damage, persistent inflammation andimpaired healing in such ulcers, the use of ordinary dressings will no longer be effective.Reducing the number of reactive oxygen species, subsiding formation of the granular tissue, stimulating re-epithelialization, and improvement of angiogenesis in the biomaterial structure, are the main goals in chronic deep wounds.In this regard, angiogenic targeted tissue engineering can be suggested as the key approach toward efficient healing. Indeed, creating a vascular support plays a crucial role in nourishing and improving the function of cells responsible for healing.As listed in **Table 2**, there are several angiogenesis oriented methods based on the different strategies, which in this review were categorized into several groups:

- Angiogenesis induction using cells
- Angiogenesis induction using angiogenic growth factors
- Angiogenesis induction using a modification of scaffold’s properties

- Angiogenesis induction using angiogenic compounds

One of the most important methods for stimulating tissue repair and angiogenesis in the wound substrate is to use cell-based strategies including co-culturing with vascular cells and genetic manipulation of the cells. However, these methods meet some difficulties such as unwanted genetic changes and the complication of providing suitable conditions for the simultaneous culture of different cell types.

Table 2. Summary of some combinational wound healing approaches assisted by angiogenic induction.

Incorporation of the angiogenic agents, such as growth factors or angiogenic compounds, for local healing in the injured site, serves as an applicable strategy. Notwithstanding, in growth factor delivery approach, in addition to the challenges facing the controlled release of growth factors, their negative side effects in supraphysiological concentrations as well as the loss of their bioactivity in bioenvironment can cause serious disadvantages.

In addition, modification of the scaffold physicochemical properties can be a promising approach towards angiogenesis, even without the incorporation of specific angiogenic compounds. Nevertheless, this approach usually suffers from the difficulties attributed to the design of scaffolds with ideal regenerative and angiogenic features. Moreover, there are still concerns about the release of by-products resulting from scaffold's degradation which can stimulate undesired immune system reactions.

On the other hand, usingnatural compounds that induce angiogenesis is not only economically appropriate, but also because of their biocompatibility and having several active molecules, the

wound healing process can be significantly accelerated. However, their probable sensitization and unpredictable side effects due to unclear mechanism of actionsin some of these compounds is a major drawback. Nowadays, studies use a mixture of natural and synthetic materials to enhance the controllability of the skin tissue-engineered construct's properties.

Looking forward, use of smart oxygen delivery systems, on-demand design of interconnected porous scaffolds by application of additive manufacturing techniques and in particular 3D printing, recombinant proteins and genetic engineered cells are more likely to be successful in accelerated wound healing. The employment of the state of the art technology in scaffold fabrication will pave the way for engineering improved vascular networks by accurately controlling the biophysical and biochemical features of the structure. On the other hand, advancement in genetic engineering and biotechnology, specially in the fields of creating growth factor/exosome releasing cells, generation of recombinant growth factors with higher half lives, and immunoengineering by recruiting M2 macrophages and neutrophils is another decisive factor in future perspective of vascularization techniques. It is worth mentioning that due to the slow and insufficient growth of blood vessels, *in-vitro* or *in-vivo* pre-vascularization in combination with previous methods is required, particularly in extensive defects, for better engrafting new formed vessels to the host vasculature.

Finally, although the field of skin tissue engineering and the use of biomaterials have progressed far more than other tissues so far, focus on angiogenesis and the creation of a functional tissue similar to the primary tissue should be further investigated. Undoubtedly, the ultimate goal in the

engineering of most tissues is to create a complete 3D structure containing healthy cells, and this will only be achieved by providing adequate food and oxygen through the use of angiogenic induction techniques in the scaffold.It is worth mentioning that no single vascularization technique has proven effective across multiple applications. Therefore, more studies should be carried out to combine the mentioned approaches and utilize the multiple vascularization cues in order to reach desirable outcomes in wound healing application.

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CONFLICT OF INTEREST

Authors declare no conflict of interests.

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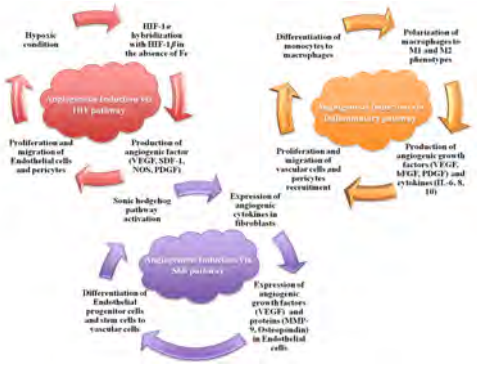

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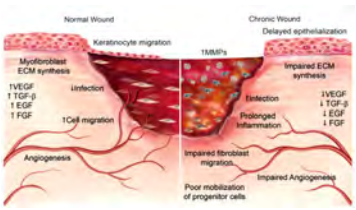

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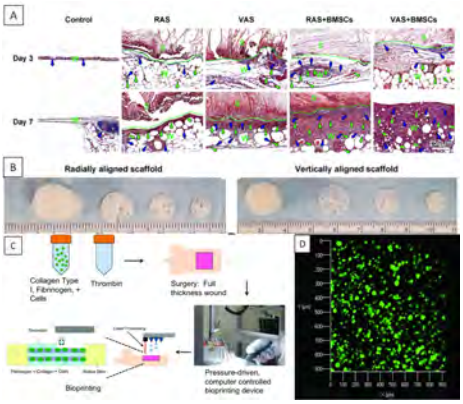

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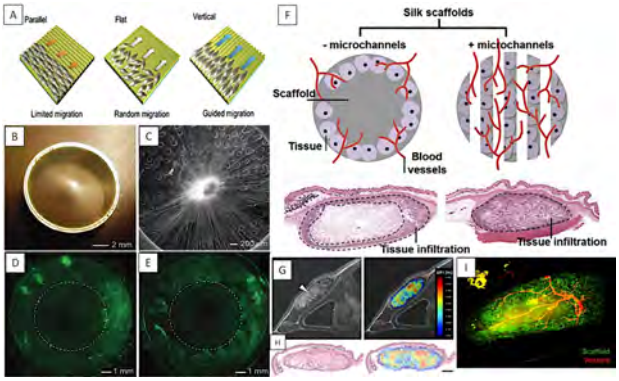

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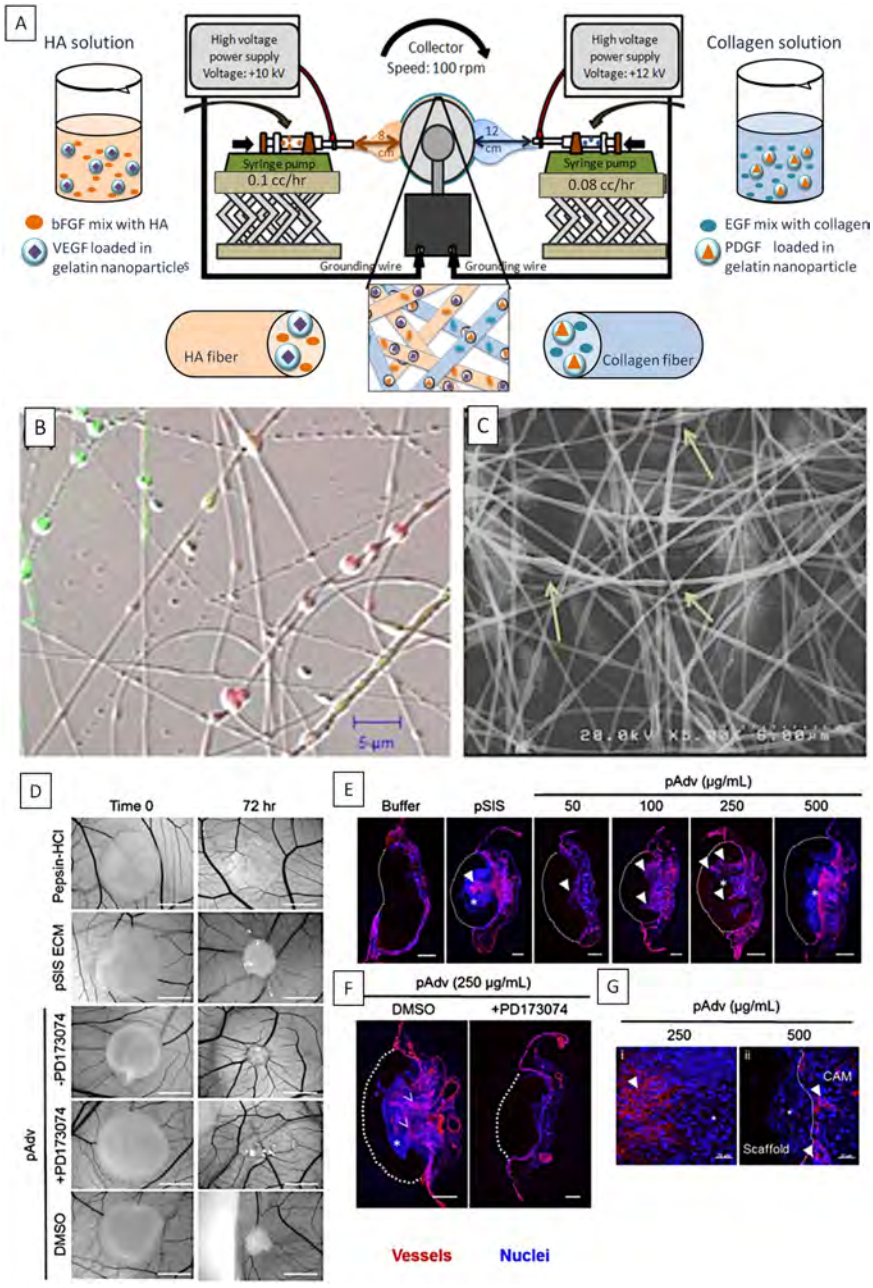

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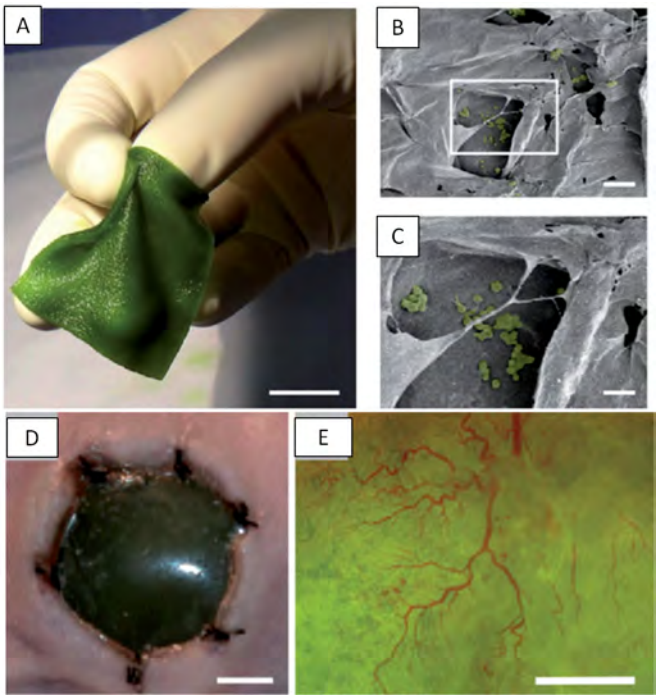

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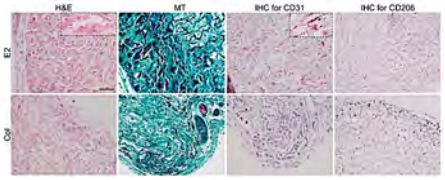

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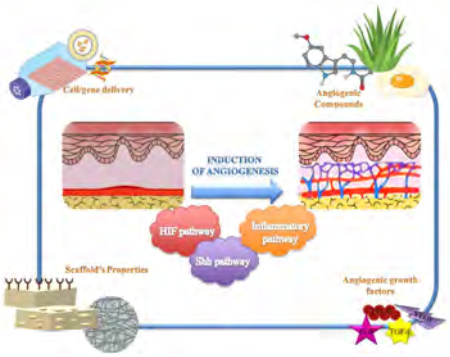

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Table 2. Summary of some combinational wound healing approaches assisted by angiogenic induction.

Angiogenic induction approach	Experiment	Significant results	Reference
Genetic manipulation	Controlled release of siRNA inhibiting prolyl hydroxylase enzyme from polymeric nanocarrier loaded in urethane scaffold	Enhance angiogenesis and secretion of VEGF by 2 folds	Martin et al. [214]
Genetic manipulation and cell therapy	Releasing IL-10 expressing plasmids from polymeric carrier embedded in collagen scaffold containing MSCs	Increase in M2 macrophages, wound healing and angiogenesis	Alvarez et al. [29]
Angiogenic factor and genetic manipulation	Using adenovirus vector for delivery of PDGF genes	Promising treatment in diabetic wound healing	Lee et al. [103]
Angiogenic factor and scaffold modification	Dual delivery of VEGF and PDGF using PLGA nanoparticles loaded in chitosan-PEO nanofibrous scaffold	Early release of VEGF with sustained release of PDGF leads to angiogenesis and re-epithelialization	Xie et al. [104]
Scaffold modification with biological agent	Hybrid wound dressing consisted of electrospun PLCL membranes and hdECM	Enhanced angiogenesis and reduced scarring	Kim et al. [151]
Angiogenic factor and scaffold modification	FGF immobilized to PEG hydrogel	Induction of migration and alignment of SMCs	DeLong et al. [100]
Angiogenic factor and scaffold modification	FGF attachment to fibrin hydrogel via fibrin binding peptide kring1	Improve angiogenesis and wound repair	Zhao et al. [101]
Angiogenic factor and scaffold modification	Sequential delivery of 4 growth factors using gelatin nanoparticles loaded in collagen/hyaluronic acid nanofibrous scaffold	Improvement of epithelialization, capillary sprouting, and functional blood vessel formation	Lai et al. [150]
Cell therapy and scaffold modification	3D expanded nanofibrous scaffold with radially or vertically aligned nanofibers in	Promoted collagen deposition and angiogenesis with in-depth vascular	Chen et al. [122]

	combination with (BMSCs)	formation in of diabetic wound model	
Cell therapy and scaffold modification	Fibrin/collagen hydrogel with in-situ layer by layer bioprinting of amniotic fluid derived stem cells, fibroblasts and keratinocytes in the wound site	Promote wound healing, and formation of new skin with functional vessel	Skardal et al. [124]
Scaffold modification	3D porous silk scaffolds containing 508 μm diameter microchannels	Formation of perfused and functional blood vessels within the microchanneled scaffold	Tang et al. [128]
Cell therapy and scaffold fabrication	Combination of collagen scaffold with ADSCs	Enhanced angiogenesis, cell proliferation and wound healing than cell delivery	Jiang et al. [215]
Cell therapy and scaffold fabrication	Delivery of EPCs using collagen-PCL-bioglass nanofibrous scaffold	Overexpression of VEGF and SDF-1, granulation tissue formation, and collagen deposition	Wang et al. [216]
Novel scaffold fabrication and cell therapy	Cell sheet scaffold containing fibroblasts, keratinocytes, and endothelial cells cultured on temperature sensitive polymer	Resulted in full-thickness wound healing, and formation of functional vessels	Cerqueira et al. [156]
Novel scaffold fabrication	Incorporation of microalgae in wound dressing	Provide oxygen supply for the cells, induce angiogenesis, formation of new vessels, and skin regeneration	Hopfner et al. [158]
Angiogenic compound: drug	Encapsulated deferoxamine in inverse micelles and loaded in ethyl cellulose foam	Proper skin penetration of the drug, fast wound healing and capillary network formation	Duscher et al. [164]
Angiogenic compound: drug	GelMa hydrogel containing deferoxamine	Enhance diabetic wound healing, promote angiogenesis and in-situ filling the	Chen et al. [165]

		wound cavity	
Angiogenic compound: drug	Topical application of simvastatin on diabetic wounds	Induction of angiogenesis, lymphogenesis, and proliferation of endothelial cells	Asai et al. [170]
Angiogenic compound: drug	Adipose-derived stem cells cultured in erythropoietin media	Improved wound healing by enhancing angiogenesis, proliferation and migration of EPCs and endothelial cells	Elsherbiny et al. [172]
Angiogenic compound: drug	Culture of keratinocyte in presence of melatonin	Increased wound healing and cellular proliferation, reduced oxidative stress	Song et al. [175]
Angiogenic compound: natural biomaterial	Aloe vera incorporated biomimetic nanofibrous scaffold	Increase level of hyaluronic acid and dermatan sulfate, inhibit MMPs activity and stimulate migration of epithelial cells	Suganya et al. [181]
Angiogenic compound: natural biomaterial	Effect of aloe vera on the expression of wound healing factors in mouse embryonic fibroblast cell	Promote angiogenesis and affect fibroblasts via production of bFGF and TGF-β	Hormozi et al. [184]
Angiogenic compound: natural biomaterial	Lyzosyme loaded chitosan/PVA electrospun scaffold	Represented antibacterial properties, wound healing, and improve fiber morphology	Charernsriwilaiwat et al. [201]
Angiogenic compound: natural biomaterial	PVA/egg albumin electrospun wound dressing containing tetracycline hydrochloride	Controlled release of drug, improve fiber morphology and effective wound healing	Zahedi et al. [200]
Angiogenic compound: natural biomaterial	Egg white freeze-dried foam implanted subcutaneously in mouse model	Proper tissue integration, formation of functional vessels, and polarization of macrophages to M2 type	Jalili et al. [198]

Angiogenic compound: natural biomaterial	Application of colostrum and honey on diabetic wound	Fast wound closure, promote angiogenesis, increase collagen synthesis, and proliferation of fibroblasts	Tanideh et al. [206]
Angiogenic compound: natural biomaterial	Honey incorporated wound dressing	Proper wound healing, fast hemostasis, induce angiogenesis, and reduce bacterial infection	Oryan et al. [209]
Scaffold modification with biological agent	Fibrin microsphere loaded with eNOS	Increase angiogenesis and vascular branches more than 3 fold	Losi et al. [137]
Scaffold modification with biological agent	Hybrid collagen/PCL scaffold combined with hyaluronic hydrogel containing VEGF and PDGF	Continuous controlled release of factors for up to 5 weeks, improve angiogenesis, and formation of 3D structure	Ekaputra et al. [51]
Scaffold modification with biological agent	Cross-linked GAG hydrogel film as wound dressing	Increase epithelialization, creation of hydrated environment, and fibrovascular tissue formation	Kirker et al. [217]
Angiogenic compound: natural biomaterial	Dextran based skin substitute	Recruitment of EPCs and SMCs, creation of vascular network, epidermal maturity, and burn wound healing	Sun et al. [212]
Angiogenic compound: synthetic biomaterial	MAA-based scaffold with optimum porosity	Improve angiogenesis and reduce scar formation	Lisovsky et al. [141]

Table 1. Role of different biological factors in angiogenesis process [17].

Angiogenesis phase	Inducing factor
Vessel expansion and vasodilation	Nitric oxide (NO)
Increase vessel permeability	VEGF
Migration of plasma protein	VEGF
Endothelial sprouting	Angiopoetin-2
Extra cellular matrix degradation	MMPs
Growth factors recruitment	Insulin-like growth factor-1 (IGF-1), basic fibroblast growth factor (bFGF), VEGF
Endothelial proliferation and migration	FGF, Platelet derived growth factor (PDGF), VEGF, Angiopoetin
Pericytes and SMCs recruitment	PDGF
Formation of endothelial layer and lumen	VEGF, Angiopoetin-1
Vascular stabilization	Plasminogen activator inhibitor-1 (PAI-1)
Maintenance, differentiation and remodeling of vascular structure	Angiopoetin-1
Inhibition of angiogenesis	Angiostatin, Endostatin, Thrombospondin

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