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Review

Current application of tissue-engineered dermal scaffolds mimicking the extracellular matrix microenvironment in wound healing

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A B S T R A C T

With the continuous advancement of materials science, cell biology, and biotechnology, tissue engineering has introduced novel solutions to traditional wound healing approaches, particularly demonstrating significant potential in addressing complex or non-healing wounds. One of the key technologies in this field, dermal scaffolds, serve as wound coverage materials that mimic the structural framework of the dermis. They primarily assume the function of extracellular matrix, providing space for cell attachment, migration, and proliferation, thus supporting cellular growth and regulating multiple biological processes in healing. Tissue engineering utilizes combinations of natural or synthetic scaffolds, seeded cells, or growth factors to induce distinct effects in angiogenesis, extracellular matrix deposition, and functional recovery. Therefore, various bioengineered dermal scaffolds hold significant potential for clinical translation in wound healing. This review outlines various extracellular matrix molecules utilized in the development of dermal scaffolds, emphasizes recent progress in cell- and growth factor-modified scaffolds, and discusses the challenges and future perspectives in this evolving field.

Contents

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Abbreviations

ECM	extracellular matrix
dFBs	dermal fibroblasts
FGF	fibroblast growth factor
3D	three-dimensional
ADM	acellular dermal matrix
SIS	small intestinal submucosa
AAM	acellular amniotic membrane
DTM	decellularized tendon matrix
DVM	decellularized vascular matrix
ACM	acellular cartilage matrix
FC	fibrinogen concentrate
HA	hyaluronic acid
PGs	proteoglycans
GAGs	glycosaminoglycans
EGF	epidermal growth factor
CS	chondroitin sulfate
sGAG	sulfated GAG
ANGPTL4	angiopoietin-like 4
HDFs	human dermal fibroblasts
MSCs	mesenchymal stem cells
ADSCs	adipose-derived MSCs
rADSCs	rat ADSCs
PADM	porcine ADM
WJ-MSCs	Wharton's Jelly MSCs
MenSCs	menstrual blood-derived stem cells
IGF	insulin like growth factor
PDGF	platelet-derived growth factor
TGF-β	transforming growth factor-β
FGF2	fibroblast growth factor 2
VEGF	vascular endothelial growth factor
CBD	collagen-binding domain
BDDM	book-shaped decellularized dermal matrix
PRP	platelet-rich plasma
GAM	gene-activated matrix

1. Introduction

Progress in medical technology has significantly contributed to the longer average human lifespan. However, as people age, they become more susceptible to various diseases, including diabetes, kidney infections, immunodeficiencies, and nutritional deficiencies. These conditions can hinder the natural healing process and the regeneration of tissues [1]. Extensive or deeper cutaneous wounds require more time to heal and can be complicated by these risks. The wound healing process is widely recognized to involve three distinct yet interconnected phases: inflammation, proliferation, and remodeling [2]. If any of these phases is prolonged, it can result in tissue fibrosis and failure of the ulcer to heal [3], ultimately leading to the development of a chronic wound. The global wound care market size was estimated at USD 20.8 billion in 2022 and is projected to grow at a compound annual growth rate of 5.4% from 2022 to 2027 [4]. Scaffolds, a crucial element in tissue engineering, have transformed from inert structures that offer mechanical support to damaged tissues to composite biomaterials that mimic the natural ecological niche of native tissue cells [5]. Dermal scaffolds, which imitate the structure of dermal tissues, show great potential as materials for fabricating dermal and composite skin substitutes.

The skin consists of the epidermis, dermis, and subcutaneous tissues. The extracellular matrix (ECM) is present in the basement membrane and dermis, playing a crucial role in maintaining structural integrity and creating a favorable microenvironment for cell growth and differentiation. Biochemical and mechanical cues within this microenvironment guide various cellular functions [6]. Hence, natural ECM proteins and their derived components are an essential source for fabricating dermal scaffold materials that can induce specific cell behaviors and growth factor functions. Recent technological advancements have allowed researchers to develop functional complex biomaterials by utilizing natural forms of ECM proteins [7]. Decellularized scaffolds, derived from various somatic membranes, have emerged as a particularly appealing option in this area of study [8]. In order to enhance the performance of conventional decellularized dermal scaffolds, researchers have employed various physicochemical or biological modification techniques. These methods aim to achieve a desirable combination of biocompatibility, bioactivity, degradability, and low immunogenicity. Current methods for modification primarily involve cross-linking, co-culturing autologous or allogeneic cells, and incorporating bioactive substances [9–11].

Dermal fibroblasts (dFBs) are considered the primary cell source of cutaneous ECM. Among all skin cell types, they are the most closely related to ECM and serve an essential part in modifying the dermal scaffold [12]. Different subpopulations of dFBs exhibit distinct local ECM expression profiles, and variations in ECM properties can be observed between the upper papillary layer and the lower reticular layer of the dermis [13]. Seeding dFBs onto dermal scaffolds can result in anisotropic ECM deposition during wound healing. Furthermore, the various layers of human skin consist of distinct cell types, and incorporating cells according to their type can enhance the specialized function of the dermal scaffold [14]. The role of various cytokines, such as fibroblast growth factor (FGF), in wound healing during different stages has also been extensively studied. Researchers have made efforts to incorporate different cytokines into dermal substitutes for simultaneous application [15]. One could argue that dermal scaffolds also

function as delivery systems, transporting growth factors to injured tissues and precisely regulating different stages of wound healing. The prevalence of various skin injury types, including trauma, chronic wounds, and scarring, has led to a growing demand for dermal scaffolds that effectively facilitate wound healing. Factors such as decellularization techniques and sterilization methods significantly influence the characteristics of the final dermal scaffold product [16]. There is an urgent need for innovative modification strategies for dermal scaffolds to enable in vivo application and address specific patient requirements. The ultimate objective of wound healing is to attain the desired outcome of scarless healing and full restoration of skin appearance and function. In this review, we summarized ECM-derived molecules employed in recent years for the fabrication of dermal scaffolds that more accurately replicate the in vivo repair microenvironment. We also discussed the research progress on strategies for modifying scaffolds with cells or growth factors, with the aim of providing valuable guidance and reference for future design of tissue-engineered dermal scaffold properties.

2. Dermal scaffolds mimic the ECM microenvironment to promote wound healing

The ECM consists of macromolecules in the intercellular space, distributed mainly in the interstitial matrix and basement membrane. In contrast to the epidermis, which consists of tightly connected cells, the dermis is primarily composed of ECM and loosely distributed cells. The ECM itself is predominantly made up of five key components: collagen, non-collagen proteins, elastin, proteoglycans, and glycosaminoglycans. ECM provides an ideal microenvironment for cell proliferation, differentiation, and migration in wound healing. The development of skin tissue engineering revolves around three main areas: cells, scaffolds, and bioactive molecules. Of these, scaffolds, as three-dimensional (3D) ECM analogs, primarily mimic the microenvironment posed by the ECM in tissues. ECM-based dermal scaffold biomaterials that have been clinically applied to assist wound repair include acellular dermal matrix (ADM), small intestinal submucosa (SIS), acellular amniotic membrane (AAM), decellularized tendon matrix (DTM), decellularized vascular matrix (DVM), and acellular cartilage matrix (ACM) [17]. They are isolated from human or animal tissues with the primary objective of preserving the macromolecular structure and functional proteins that constitute the ECM, thereby maintaining the specific properties inherent to each protein. Faulk et al. pointed out that some components of the ECM have the potential to form the basis of natural scaffolds [18]. Additionally, numerous studies have reported that the bioactivity of dermal scaffolds can be enhanced by surface modification with ECM molecules [19]. ECM proteins applied in dermal scaffolds can be subdivided into three main groups: fiber-forming structural molecules, nonfiber-forming structural molecules, and matricellular proteins [20] (Fig. 1).

Fiber-forming proteins mainly include collagen, fibrin, elastin, fibronectin, laminin, etc. Among these, collagen is the most commonly used biomaterial in the fabrication of dermal scaffolds [21]. Its development can be traced back to the last century. The employment of collagen as a scaffold was proposed by Yannas and Burke in the 1970s [11]. As early as 1981, Burke et al. employed porous collagen-chondroitin-6-sulfate fiber matrix as a dermal scaffold to fabricate a bilayer epidermal-dermal skin substitute. This innovation was successfully applied in over 90 acute burn patients, offering both physiological function and cosmetic restoration [22]. Along with elastic fibers, fibrin maintains dermal

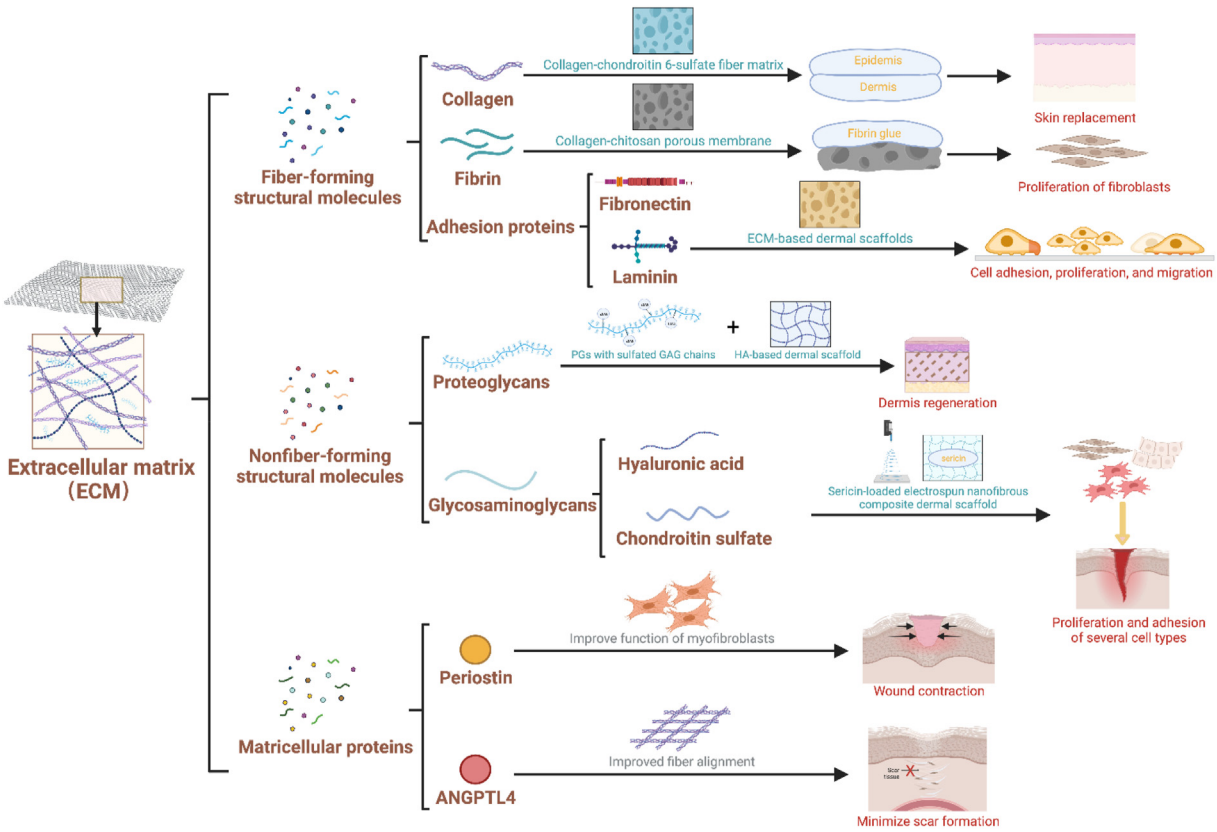

Fig. 1. ECM molecules applied in dermal scaffolds are further categorized into three main groups: fiber-forming structural molecules, nonfiber-forming structural molecules, and matricellular proteins.

homeostasis [12]. In an asymmetric scaffold made from fibrin glue and a collagen-chitosan porous membrane, Han et al. found that fibrin promoted fibroblast proliferation after one week of in vitro testing [23]. In comparison, elastin, which maintains the dermis' structural properties, is expensive and difficult to purify from elastic fibers [1] and prone to contamination. Thus, natural elastin for dermal scaffold modification requires more research. This also suggests that rapid purification of natural ECM molecules used for dermal scaffold functionalization will aid clinical translation. ECM adhesion proteins like fibronectin and laminin mostly regulate cell adhesion, morphology, and migration. In recent years, there has been an increasing amount of research dedicated to these two categories of adhesive proteins, which have been utilized in the study and creation of materials for tissue engineering. Recent studies on adhesins have shown that a dermal scaffold made of human clinical-grade fibrin network, fibronectin, and laminin in fibrinogen concentrate (FC) and exogenous hyaluronic acid (HA), which mimics the ECM, promotes third degree burn wound healing in rabbits [24]. This scaffold demonstrated the clinical translational value of fibronectin and laminin in dermal scaffolds.

The nonfiber-forming structural molecules, mainly proteoglycans (PGs) and glycosaminoglycans (GAGs), provide ECM platforms for charged, osmotically exchanged molecules [25]. Incorporating these proteins into dermal scaffolds more effectively replicates the osmotic balance and hydration environment of the ECM, while simultaneously enhancing biocompatibility. Su et al. loaded HA and epidermal growth factor (EGF) into decellularized porcine peritoneal scaffolds. Animal experiments showed that wounds covered with scaffolds containing HA recovered the best, with a 20th-day wound healing rate of over 85 % [26]. A practical approach to designing new tissue engineering biomaterials is to promote skin cell proliferation and differentiation with PGs and GAGs. HA and chondroitin sulfate (CS), two of the most commonly used GAGs, were used to modify the sericin-loaded electrospun nanofibrous composite dermal scaffold. In vitro experiments showed that modification promotes fibroblasts, keratinocytes, and keratinocyte-human mesenchymal stem cells adhesion and proliferation [27]. The researchers also examined specific ratios of PGs enriched with sulfated GAG (sGAG) chains versus non-sulfated natural HA added to dermal scaffolds, and 90 % HA-enriched versus 10 % sGAG-enriched scaffolds conjugated to fibroblasts were better for dermal repair [28].

Also present in the ECM are matricellular proteins, a recently described group of secreted local proteins [25], such as periostin and tenascin-C. They are mostly expressed transiently after skin injury. Elliott et al. found that periostin-knockout fibroblasts contracted the collagen matrix less than wild-type fibroblasts in full-thickness wound healing, demonstrating the role of periostin in myofibroblast wound contraction [29]. In 2019, it was found that adding angiopoietin-like 4 (ANGPTL4), a matricellular protein, to dermal scaffolds could reverse the phenotypic changes caused by aligned fibers in wound healing and reduce scar formation, suggesting further research on matricellular proteins as scaffold modifiers [30]. In Table 1, critical studies of ECM-based dermal scaffolds were summarized and evaluated, focusing on their efficacy as skin substitutes in various in vitro and in vivo models. Since most of the above experiments used animal models, dermal scaffolds based on ECM molecules may need more clinical translation.

The current methods of tissue engineering used to prepare dermal scaffolds, primarily involving physical methods such as enzymatic decellularization, natural polymeric hydrogel fabrication, collagen self-aggregation, and 3D printing [31], usually unavoidably disrupt the biological tissue structure, thus failing to achieve a complete mimicry of the dermal ECM structure. This leads to inadequate poor mechanical properties, low biocompatibility, and non-degradability of the fabricated dermal scaffolds. In order to overcome these limitations, the functionality of the scaffolds can be optimized by adding bioactive molecules, drugs or cells. In the following two sections, we summarized strategies for co-culturing cells and adding bioactive molecules, respectively (Fig. 2 and Table 2).

3. Dermal scaffolds co-cultured with various skin cells

The skin comprises three layers: the epidermis, dermis, and subcutaneous tissue, with each layer consisting of distinct cell types. The epidermis consists primarily of keratinocytes, melanocytes, and Langerhans cells, whereas the dermal connective tissue predominantly contains fibroblasts and mast cells. Cells play a crucial role in tissue engineering, and dermal scaffolds can serve as carriers to transport cells to the target site of a wound or function as barriers to shield transplanted cells from the host immune response [32]. In addition, the incorporation of cells into dermal scaffolds can introduce distinct characteristics [33]. While

Table 1
ECM-based dermal scaffolds for wound healing application.

ECM molecule	Spatial structure	Model	Performance	Ref
Collagen-C6S	Porous	Patients with severe burns	- Preservation of certain anatomical features - Restoration of physiological function and cosmetic appearance	[22]
Fibrin	Porous	In vitro cell assay	- Promotion of fibroblast adhesion, growth, confluence and differentiation due to smooth interfaces	[23]
Fibronectin Laminin	Porous	Rabbit third degree burn wound model	- Reduction of wound contraction and scarring - Fiber strength for cell adhesion and proliferation	[24]
HA	Sheet-film	Rabbit full-thickness skin wound model	- Stabilized attachment and continuous release of growth factors - Regeneration of skin appendages	[26]
HA CS	Nanofibrous	In vitro cell assay	- Improved adhesion and proliferation of fibroblasts, keratinocytes and mesenchymal stem cells - More efficient wound healing	[27]
PG-sGAG	Porous	In vitro cell assay	- Enhanced expression of specific gene markers - Increased production of tissue ECM proteins - Chemotaxis to target cells	[28]
ANGPTL4	Electrospun fibrous	In vitro cell assay	- Reversal of myofibroblast differentiation - Reduction of scarring	[30]

Abbreviations: ECM, extracellular matrix; C6S, chondroitin-6-sulfate; HA, hyaluronic acid; CS, chondroitin sulfate; PG, proteoglycan; sGAG, sulfated glycosaminoglycan; ANGPTL4, angiopoietin-like 4.

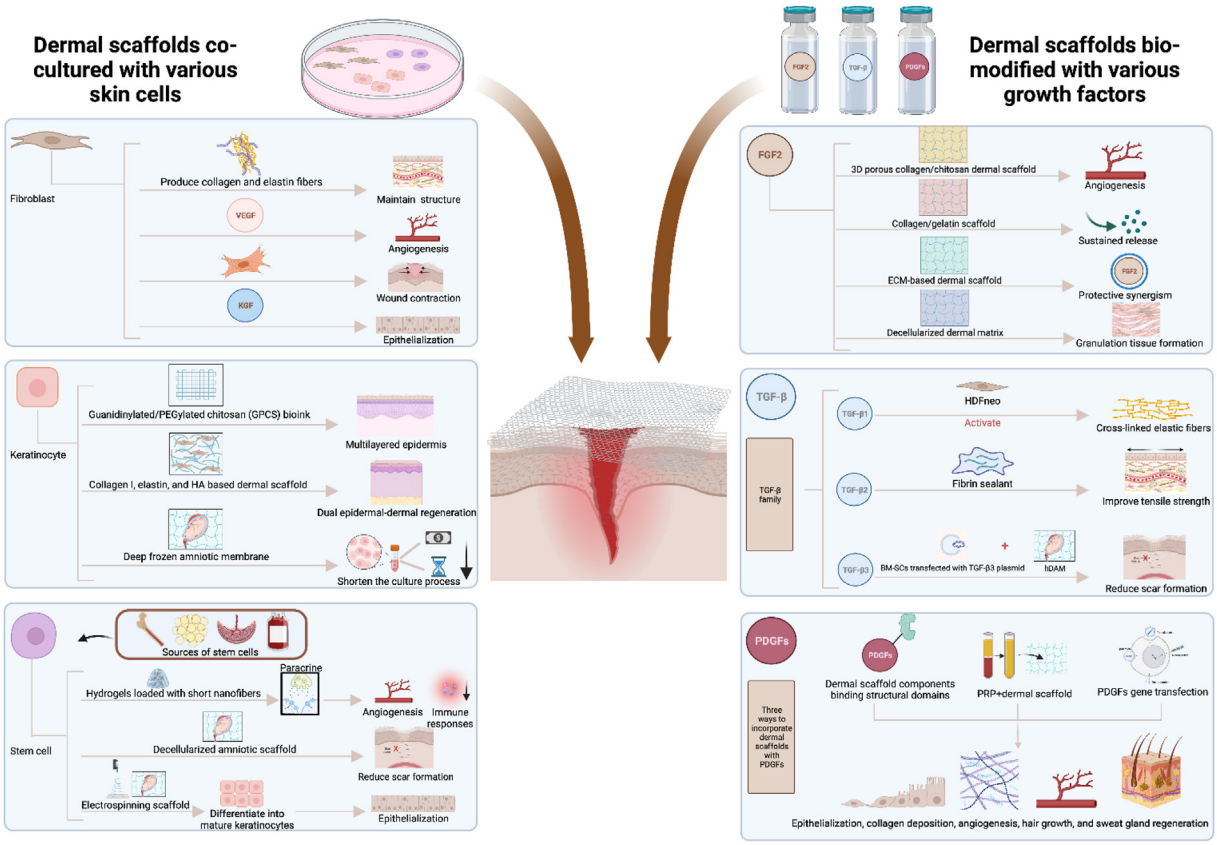

Fig. 2. Strategies for biomodified dermal scaffolds: co-culturing cells and adding growth factors.

conventional dermal scaffolds tend to mimic the native ECM microenvironment, optimal conditions for establishing in vitro skin models may be facilitated by further screening of the cellular microenvironment [34]. We performed a concise overview of three extensively researched cell types employed in dermal scaffolds: fibroblasts, keratinocytes, and stem cells.

3.1. Fibroblasts

The primary cells of the dermis, fibroblasts, are crucial to cell-containing dermal scaffold design. Dermal fibroblasts were the first human somatic cells induced into a pluripotent stem cell lineage [35]. They had a high degree of plasticity, being capable of altering their function and physiology, and even undergoing cellular transformation into new cell types depending on their location in vivo. Fibroblasts coordinate other cell types to heal wounds [36]. As early as 1979, Bell et al. pioneered the use of dermal fibroblasts in treating chronic burn wounds, which laid the cornerstone for the subsequent design of different types of dermal scaffolds seeded with fibroblasts in tissue engineering [37]. Transcyte® and Dermagraft® are commercially available dermal scaffolds supplemented with allogeneic human fibroblasts [38].

Fibroblasts added to dermal scaffolds serve four primary functions in wound healing: (1) Fibroblasts synthesize ECM, especially collagen and elastin fibers, to maintain the biomimetic structural characteristics of the dermal scaffolds. They create a post-traumatic microenvironment suitable for the growth of skin-related cells. By incorporating human fibroblasts in an inert porous dermal scaffold, Mathilde Roger et al. constructed a new full-thickness human skin model that exploits the ability of fibroblasts to secrete their own ECM proteins. No exogenous ECM components were introduced in this model [39]. (2) The pro-angiogenic factors are released and the endothelial cell proliferation is stimulated to enhance the survival of the grafted dermal scaffolds. Importantly, the study showed that when adult human dermal fibroblasts (HDFs) were cultured on silk fibroin dermal scaffolds, they secreted 35 different angiogenic factors. Furthermore, when keratinocytes and adult HDFs were added together to dermal scaffolds made of this material, it enhanced the migration of human dermal microvascular endothelial cells in vitro and promoted angiogenesis more strongly [40]. (3) Migration to the wound periphery at the end of the inflammatory stage of wound healing to further differentiate into myofibroblasts and promote contraction healing. (4) Secretion of keratinocyte growth factor by papillary fibroblasts to control the migration and proliferation of keratinocytes and promote epithelialization. Recent research has demonstrated that when mixed dermal cell suspensions lacking papillary fibroblasts are transplanted, they are unable to reconstruct hair follicles. This suggests that papillary fibroblasts and reticular fibroblasts have distinct transcriptomic and epigenomic profiles, as confirmed by in vitro testing and single-cell sequencing [41,42]. This offers a new avenue for future research on dermal scaffolds that contain various subpopulations of fibroblasts, taking into account their anatomical differences within the dermis.

In specific wounds, like postnatal wound repair, the typical mechanisms of mechanical tension and TGF-β-mediated differentiation of fibroblasts into myofibroblasts are affected by an atypical cytokine and inflammatory environment. Additionally, fibroblasts may play a role in fibrosis and scarring [43]. This enlightens researchers that they should take into account the alterations in the microenvironment around the wound at different stages of healing when adding fibroblasts to dermal scaffolds. Also, maintaining the

Table 2
Cell- or growth factor-modified dermal scaffold.

Types	Biomaterials	Model	Performance	Ref
Cell-modified dermal scaffold				
Fibroblast	Polystyrene membrane	In vitro cell assay	- Formation of highly differentiated epidermis a protective barrier - Synthesis of endogenous human ECM proteins	[39]
	Silk fibroin	In vitro cell assay	- Promotion of the transport of various angiogenic and growth factors - Induction of angiogenesis	[40]
Keratinocyte	Guanidinylated/PEGylated chitosan bioink	In vitro cell assay	- Generation of multilayered epithelial tissue structures that maturely mimic the human epidermis	[47]
	PVA-keratin nanofiber	In vitro cell assay	- Excellent biocompatibility - Simulation of the layered structure of human skin tissue	[48]
	Amniotic membrane	In vitro cell assay	- Reduced incubation time required for cell cultures	[50]
Stem cell	PLCL-ADM nanofiber	Rat full-thickness skin wound model	- Promoted dermal cell proliferation - Vascularization of perigraft tissues	[57]
	Porcine acellular dermal matrix	Rat full-thickness skin wound model	- Induction of angiogenesis - Regulation of immune responses through paracrine signaling	[58]
	Decellularized amniotic membrane	Mouse full-thickness skin wound model	- Reduction of scarring - Hair follicle regeneration	[60]
	Fetal bovine acellular dermal matrix	Rat full-thickness skin wound model	- Promoted wound closure - Anti-inflammatory	[62]
Growth factor-modified dermal scaffold				
FGF2	Collagen/chitosan	In vitro cell assay	- Induction of angiogenesis - Promoted dermal cell proliferation	[76]
	Collagen/gelatin	Rat full-thickness skin wound model	- Induction of angiogenesis - Promoted dermal cell proliferation	[77]
	Decellularized human dermal matrix	Diabetic rat full-thickness skin wound model	- Accelerated formation of granulation tissue	[79]
TGF-β	3D fibrillar matrix from collagen I and fibronectin	In vitro cell assay	- Added at different time points to meet the needs of different stages of wound healing (TGF-β1)	[84]
	Fibrin	Porcine full-thickness skin wound model	- Improved wound tensile strength (TGF-β2) - Optimized local immune environment at the healing interface	[83]
PDGFs	Collagen	Rabbit dermal ischemic ulcer model	- Promotion of re-epithelialization of dermal ulcer wounds - Formation of new capillary lumen	[90]
	ADM-CS	Rat full-thickness skin wound model	- Fixation and sustained release of growth factors - Improvement in the survival rate of autologous skin grafts	[94]
	Polyglycolic acid	Diabetic mouse full-thickness skin wound model	- Accelerated healing	[95]

Abbreviations: ECM, extracellular matrix; PVA, poly(vinyl alcohol); PLCL, poly(l-lactide-co-ε-caprolactone); ADM, acellular dermal matrix; FGF2, fibroblast growth factor 2; TGF-β, transforming growth factor-β; PDGFs, platelet-derived growth factors; ADM-CS, acellular dermal matrix-chitosan.

equilibrium between fibroblasts and myofibroblasts remains a challenge for further investigation. The interaction between scaffolds and cells must be considered when introducing cells, as the matrix stiffness of dermal scaffolds can negatively influence the seeded fibroblasts. Dermal scaffolds fabricated using a bioink consisting of 7.5 % gelatin methacryloyl and 2 % alginate resulted in increased secretion of Pro-Collagen I alpha 1 by the incorporated fibroblasts, alongside reduced levels of MMP-1, while also enhancing their viability and proliferation [34]. Thus, different materials of dermal scaffolds influence the responsiveness of fibroblasts in wound healing.

3.2. Keratinocytes

Prompt epithelialization is critical in the healing of open wounds [44]. Epithelial-mesenchymal transition causes keratinocytes to gradually lose adhesion and transform into a spindle-shaped mesenchymal morphology that migrates and adheres to the wound site, forming an epidermal stratified structure [45]. HaCaT cells have been widely utilized in dermal scaffolds, not only to promote wound re-epithelialization and epidermal stratification but also to enhance the biocompatibility of the dermal scaffolds. Most importantly, this application enables dual regeneration of both the epidermis and dermis.

The addition of keratinocyte cells to conventional dermal scaffolds often ends up in monolayer rather than multilayered epithelial tissue architectures that ideally mimic the native epidermis [46]. To address this issue, Zhu et al. printed dermal scaffolds using biocompatible guanidinylated/PEGylated chitosan as a bioink, and keratinocytes cultured on this material ultimately generated in vitro constructs of 3D structures with multilayered epidermis similar to normal human skin [47]. A similar effect was achieved with the poly(vinyl alcohol)-keratin nanofiber dermal scaffolds constructed by Keshaw R. Aadil et al. Additionally, the 3D co-culture study showed that the infiltration and growth patterns of adjacent HaCaT cells and dermal fibroblasts closely resembled those of epidermal and dermal skin cells [48]. Researchers must also select appropriate materials for dermal scaffolds to co-culture with keratinocytes. A study demonstrated that a biomimetic ECM dermal scaffold composed of collagen I, elastin, and hyaluronan effectively supported the proliferation of human dermal fibroblasts and facilitated the proliferation, differentiation, and stratification of human keratinocytes [49]. This process resulted in the formation of a bilayered hierarchical skin tissue structure, offering significant insights into the selection of matrix for cultured cells on the dermal scaffold. In recent studies, the deep frozen amniotic membrane has emerged as a novel dermal scaffold for keratinocyte culture [50]. The resident cells within the amniotic membrane can function as feeder cells, producing growth factors that support keratinocyte proliferation. Additionally, the amniotic membrane can serve as a carrier for keratinocyte suspension, thus bypassing the traditional monolayer culture steps and significantly shortening the cultivation process. This approach holds considerable translational value in clinical practice.

3.3. Mesenchymal stem cells

Despite the variety of methods for combining allogeneic and autologous cell transplantation and dermal scaffolds, current applications suffer from pathologic scar generation, skin dysfunction, and lack of appendages. Stem cell-related tissue engineering is considered one of the most influential and promising fields in life sciences [51–53]. Significant progress has been made in the application of stem cells to dermal scaffolds over the past few decades. Here, we summarized the combination of dermal scaffolds with different origins of stem cells. Mesenchymal stem cells (MSCs) have the ability to self-renew and differentiate into diverse cell and tissue types [54]. Bone marrow-derived MSCs are the first type of MSCs to be used in combination with skin autografts for burn treatment [55].

Adipose-derived MSCs (ADSCs) are widely used in skin tissue engineering since they can co-produce ECM proteins with fibroblasts and are easy to harvest [56]. ECM-based dermal scaffolds can support ADSCs growth and adhesion, accelerate vascular recanalization at the transplantation site, inhibit grafted stem cell differentiation and apoptosis, and retain therapeutic potential. Ning et al. constructed injectable gelatin methacryloyl hydrogels loaded with PLCL/ADM short nanofibers. This novel material acted as a transplantation vector for ADSCs and effectively promoted the proliferation of ADSCs in vitro by mimicking the natural ECM [57]. Additionally, ADSCs can play multiple roles through paracrine signaling, including promoting angiogenesis and modulating immune responses when heterologous ADM is implanted. In a study on the paracrine function of rat ADSCs (rADSCs) seeded on porcine ADM (PADM), rADSCs seeded on PADM expressed more genes related to inflammation, pro-angiogenic factors, and stemness. The local inflammatory response caused by treated PADM was also reduced [58]. This sheds light on the more effective use of allogenic ADM as dermal scaffolds in repair and reconstruction therapy. MSCs from fetal/perinatal tissues exhibit greater proliferation and differentiation plasticity than adult MSCs [59]. Sabapathy et al. extracted Wharton's Jelly MSCs (WJ-MSCs) from embryonic umbilical cord matrix after artery and vein resection and seeded them on decellularized amniotic scaffolds for scarless wound repair in mice [60]. In a recent study, menstrual blood-derived stem cells (MenSCs) isolated from the menstrual blood of healthy women were seeded onto human amniotic membrane electrospinning bilayer scaffolds. Combining the immunomodulatory potency and specific paracrine effects of MenSCs with the properties of dermal scaffolds was demonstrated by a whole-layer wound model in diabetic mice to attenuate the long-term inflammatory response and promote angiogenesis in diabetic wounds [61]. More importantly, MenSCs even have the potential to differentiate into mature keratinocytes and express a variety of epidermis-specific markers, which provides inspiration for scholars to explore more new origins of stem cells other than MSCs for application in dermal scaffolds. Additionally, Mansour et al. demonstrated that using fetal bovine ADM as a carrier for WJ-MSCs significantly accelerated the healing of full-thickness skin wounds and reduced inflammation [62]. One of the current challenges in stem cell research is determining the optimal source, which should be both abundant and easily isolated. As a result, various categories of stem cell applications are being explored, such as hair follicle bulge stem cells [63], induced pluripotent stem cells [64], and amniotic epithelial cells [65], among others.

4. Dermal scaffolds bio-modified with various growth factors

Growth factors are required in the proliferation and ECM remodeling stages [66]. Especially in wounds such as diabetic ulcers, an imbalance of some inflammatory factors and several growth factors leads to the development of chronic wounds [67]. In contrast, critical cells involved in the healing process, such as fibroblasts and keratinocytes, have a decreased ability to migrate and proliferate, with insufficient secretion of growth factors [68]. While topical administration of growth factors alone may fail to achieve the anticipated efficacy due to various factors such as degradation caused by a short half-life, low absorption in the peri-wound skin, and removal through exudation [69]. Hence, the integration of growth factors with suitable biomaterials can effectively tackle these concerns while concurrently improving the performance of the scaffold. The growth factors commonly utilized for wound healing and skin regeneration include EGF, insulin like growth factor (IGF), FGF, the platelet-derived growth factor (PDGF), and transforming growth factor-β (TGF-β) families [70]. We prioritized summarizing the three groups of growth factors found in biologically modified dermal scaffolds.

4.1. Fibroblast growth factor 2 (FGF2)

FGF is a member of the cell signaling protein family [71]. They promote cell migration and proliferation, angiogenesis, and granulation tissue formation by binding to or activating tyrosine kinase receptors/fibroblast growth factor receptors on the cell surface during the proliferation and remodeling stages of wound healing [72]. Of the 23 members of the FGF family [73], FGF2 is the most widely used factor and has been incorporated into various dermal scaffold carriers. FGF2 is a factor that is more potent in promoting angiogenesis than vascular endothelial growth factor (VEGF) and PDGF [74], potentially creating the conditions for angiogenesis during the initial three days of wound repair [75]. According to Johana Muchová et al., adding thermostable FGF2 (FGF2-STAB®) to naturally crosslinked freeze-dried 3D porous collagen/chitosan dermal scaffolds increased their vasculogenic index in the chick chorioallantoic membrane assay [76]. Dermal scaffold materials must be carefully chosen to accelerate angiogenesis and release FGF2 continuously to overcome its short half-life. A novel collagen/gelatin scaffold containing 10 wt% acidic gelatin sustainably released charged FGF2 for 10 days, inducing angiogenesis and dermal regeneration in inactivated grafts and increasing cultured epidermal autograft application take rate [77]. Additionally, surface modification of FGF2 in dermal scaffolds enhances its stability and prolongs the effective half-life. It has been shown that GAGs such as heparan sulfate bind to FGF2, thereby protecting FGF2 from degradation by dermal scaffolds and promoting chronic wound healing. This protective synergism reduces the amount of FGF2 required, thereby reducing costs [78]. Similarly, Xin Shi et al. fused the collagen-binding domain (CBD), capable of binding collagen, with FGF2. Then it was tethered to collagen fibers of a book-shaped decellularized dermal matrix (BDDM). Not only did they achieve a homogeneous distribution of FGF2 on the dermal scaffold, but they also demonstrated in both in vitro and in vivo experiments that this functional scaffold (CBD-FGF2/BDDM) could sustainably release the tethered FGF2 and promote angiogenesis, granulation tissue formation, and collagen remodeling [79].

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

In recent years, there has been a rise in studies utilizing relevant targets of the TGF-β family-mediated signaling pathway to manipulate cutaneous wound repair [80], with TGF-β1, TGF-β2, and TGF-β3 being the most frequently used members in dermal scaffolds. TGF-β1 and TGF-β2 act as homing factors for inflammatory cells and fibroblasts. Their primary role is to promote the synthesis and deposition of ECM and to trigger fibroblast differentiation and

angiogenesis [81]. Researchers sought to overcome the limited autonomous elastogenesis of ECM-based dermal scaffolds by conducting an in vitro study. They stimulated human neonatal dermal fibroblasts using TGF-β1. Ultimately, within three weeks, these cells synthesized and assembled microfibrils and mature cross-linked elastic fibers, providing a dermal matrix with superior support for wound healing [82]. Furthermore, the application of a fibrin sealant supplemented with TGF-β2 resulted in enhanced tensile strength in treated wounds [83], confirming that TGF-β2 and TGF-β1 have the same promising properties to promote ECM deposition when incorporated into dermal scaffolds.

However, TGF-β1 is a double-edged sword bioactive molecule [84]. In the early stage of wound healing, fibroblasts undergo differentiation into myofibroblasts in response to TGF-β1, subsequently facilitating wound closure. In contrast, excessive TGF-β1 pro-differentiation leads to excessive wound contraction and massive collagen deposition, ultimately resulting in scar healing and fibrosis [85]. Strategies to avoid this result are strongly connected to controlling the timing of TGF-β1 release from the dermal scaffold. Jiranuwat et al. created a biomimetic wound healing model in vitro. This model involved a 3D dermal scaffold made of collagen I and fibronectin, and it was subjected to different time-based stimulation using TGF-β1 and IL-10. The findings suggest that IL-10 should be introduced into the scaffolds to antagonize further proliferation of myofibroblasts at 72 h post-injury, thereby improving the reconstruction of dermal structures [84]. In a study of silver-catechin nanocomposite tethered collagen scaffolds to promote scarless healing of diabetic chronic wounds, immunohistochemical analysis showed downregulation of TGF-β1 expression and upregulation of TGF-β3 expression, which supported the role of TGF-β3 in tissue regeneration without scar in chronic wounds [86]. Samadikuchaksaraei's study showed similar results with dermal scaffolds constructed directly using bone marrow stromal cells transfected with TGF-β3 plasmid and human dehydrated amniotic membrane. Manchester Scar Scale scores showed good wound healing and significantly reduced scar formation in full-thickness excisional skin wounds of rats with the application of such scaffolds [87]. Interestingly, tumor cells are able to evade immune control to some extent by exploiting TGF-β1, while the excessive production of stroma prevents immune cells from accessing the tumor. These findings indicate that TGF-β1 plays a significant role in immunomodulation and could potentially be utilized in the future to modify allogeneic dermal scaffolds, leading to a decrease in immune rejection by the recipient [88].

4.3. Platelet-derived growth factors (PDGFs)

PDGF is produced by platelets, endothelial cells, activated monocytes and macrophages, etc. It is a crucial mitogen that stimulates the division and proliferation of many types of cells, including vascular smooth muscle cells and fibroblasts. It is also the first factor produced after dermal injury and plays a crucial role in wound healing [89]. Nevertheless, achieving sufficient concentrations of PDGFs at the target site poses a challenge in clinical practice, as they tend to rapidly diffuse in the extracellular fluid. To address this difficulty, researchers have used dermal scaffolds as their delivery system, and these two components work in harmony. There are three primary methods to incorporate the scaffolds with PDGFs: (1) using dermal scaffold components binding structural domains to modify PDGFs [90]; (2) dermal scaffolds loaded with platelet-rich plasma (PRP), which contains various active factors including PDGFs [91]; (3) gene transfection of PDGF.

Sun et al. incorporated CBD, TKKTLRT, into native human PDGF-BB, facilitating effective binding of PDGF to collagen-based dermal scaffolds for extended delivery. The composite scaffold was shown to enhance wound re-epithelialization, facilitate collagen deposition, and support the formation of capillary lumens in the newly formed tissue area in a rabbit model of dermal ischemic ulcers [90]. Acellular dermal scaffolds derived from allogeneic skin have been extensively utilized in tissue engineering, as previously outlined. Nevertheless, their application alone continues to be hindered by insufficient remodeling of the non-collagenous matrix and delayed wound vascularization [91]. An ADM/PRP scaffold fabricated by the researchers utilizes the 3D collagen structure of ADM to promote cell adhesion and proliferation. It maintains the sustained release of multiple growth factors, including PDGFs, released by degranulation after platelet activation. The main function is to facilitate collagen synthesis at an earlier stage of the healing process [92]. In addition, the combination of PRP with dermal scaffolds can promote the recruitment and differentiation of dermal-derived stem cells, which in turn promotes hair growth and sweat gland formation. This presents a novel therapeutic approach for functionalized dermal regeneration [93]. Chen et al. emphasized that PRP-loaded scaffolds necessitate meticulous optimization to ensure regulated and prolonged PDGF release. Through heparin modification and the incorporation of polydopamine nanoparticles into ADM-CS scaffolds, they successfully extended PDGF release, promoting angiogenesis, collagen deposition, and attenuated scar formation. This highlights the critical role of scaffold functionalization in modulating the bioavailability of PRP-derived growth factors to enhance therapeutic efficacy in wound healing [94].

In contrast to gene therapy, the first two methods mentioned above, both in the form of PDGFs growth factor proteins incorporated into dermal scaffolds, still suffer from the drawback of high degradation rates. Gene therapy utilizes the dermal matrix to confine the vector to the treatment site, preventing its diffusion to non-target tissues. This approach overcomes the limitations of conventional binding methods, which necessitate high dosages and frequent administration. Adenoviral and retroviral vectors exhibited the highest level of efficiency in transfection. Breitbart et al. used a PDGF-B retroviral vector, transduced fibroblast-seeded polyglycolic acid dermal scaffolds to treat 20-mm full-thickness excisional dorsal skin wounds in diabetic mice. The rise in cellularity and granulation tissue between 7 and 14 days can be attributed to the impact of PDGF on cell chemotaxis, mitogenesis, and granulation tissue deposition, as stated by researchers [95]. Gu et al. used collagen gel (AdPDGF-B/gene-activated matrix, or GAM) to deliver an adenoviral vector encoding human PDGF-B. This treatment significantly facilitated the healing of full-thickness dermal wounds in rabbits when compared to the use of collagen dermal scaffolds alone. Furthermore, repeated administration of AdPDGF-B/GAM showed evidence of immune tolerance [96]. Adenoviral vector-mediated delivery of PDGF effectively sustains its robust chemotactic activity, promoting the recruitment and directional guidance of stem cells to the wound site, thereby accelerating tissue regeneration [97]. A recent study introduced an innovative non-viral CRISPR gene delivery platform utilizing a hydrogel/nanofiber composite scaffold, demonstrating significant efficacy in promoting angiogenesis and wound healing in vivo. While the study primarily focused on activating the VEGF gene via CRISPRa technology, the platform's design and strategy are equally applicable to other wound-healing genes, such as PDGF [98].

Currently, scaffold-mediated growth factor gene delivery in tissue engineering primarily targets cartilage regeneration and oral-maxillofacial defects [99–101]. Future research should focus on applying gene delivery strategies to dermal scaffolds to precisely regulate the distinct phases of wound healing. By leveraging the 3D structure and biological activity of dermal scaffolds, coupled with viral or non-viral gene delivery systems, it may be possible to achieve early PDGF-B release to promote inflammation resolution

and granulation tissue formation, followed by timely delivery of VEGF or TGF-β1 to enhance vascular maturation and collagen remodeling. Developing dermal scaffolds capable of sequential and localized growth factor release will be a key direction for future research.

5. Conclusion and prospects

This review provides a comprehensive overview of the functional patterns and current research landscape of dermal scaffolds in wound healing. We have identified three major research hotspots and emerging topics in this field: dermal scaffolds mimic the ECM microenvironment to promote wound healing, dermal scaffolds co-cultured with various skin cells, and dermal scaffolds biomodified with various growth factors. Furthermore, we thoroughly examined the relevant literature and concluded that dermal scaffolds have evolved from simply covering wounds to mimicking the native ECM structure of the skin. However, further research is necessary to elucidate the fundamental molecular mechanisms underlying wound healing and to explore various modification strategies for scaffolds to attain optimal skin regeneration.

In the last century, researchers, inspired by the clinical treatment of full-thickness burns, realized that dermal healing is crucial to the overall wound healing process. ECM proteins secreted by fibroblasts provide the microenvironmental framework for healing. The initial tissue-engineered skin products were successfully produced during the late 1970s and early 1980s. Additionally, the term "tissue engineering" was first introduced in 1987 by the National Science Foundation at the Bioengineering Panel in Washington, DC [102]. Tissue engineering has seen advancements in dermal scaffolds, which have transitioned from simple mechanical support to more intricate constructs that can partially emulate the structure of human skin. The utilization of suitable dermal scaffolds offers an optimal remedy for the clinical management of severe burns, traumatic skin injuries, and post-surgical scars. The molecular mechanism of ECM in wound healing had consistently been a topic of interest. This can be attributed to the ongoing advancements in sequencing technologies, particularly in single-cell transcriptome sequencing and spatial transcriptome sequencing technologies, which have been progressing since the 21st century. Research on the biological processes and mechanisms by which the ECM regulates cells and factors in wound healing has been a focus of scholars. Modifying dermal scaffolds with tunable components to more accurately regulate healing is a key to clinical translation. The skin differs in ECM composition, mechanical properties, and collagen arrangement across various body sites. Therefore, summarizing and evaluating the current strategies for dermal scaffold construction and their applications will be instrumental in advancing the field towards more personalized and intelligent solutions.

Dermal scaffold grafting is currently used in the treatment of various skin wounds, particularly those involving deep tissue damage or challenging healing processes. For instance, porcine dermal extracellular matrix scaffolds have shown efficacy in the treatment of severe rotator cuff tears, promoting high-quality tissue remodeling, including collagen reorganization and vascular regeneration [103]. The application of ADM as a scaffold graft has also been clinically validated, demonstrating effectiveness in closing chronic wounds, such as diabetic foot ulcers, and reducing postburn scar contractures [104,105]. In scar revision and tumor excision wound repair, dermal scaffolds are widely used [106]. Nonetheless, deficiencies persist in the clinical management and utilization of dermal scaffold grafts for skin wound reconstruction. Further clinical evaluation of ECM-based dermal scaffolds remains to be achieved. The diverse range of products on the market means that the biological properties and functional requirements of scaffolds can vary greatly depending on the specific wound being addressed. Current dermal scaffolds frequently do not offer sufficient customized support to address these variations. For example, scaffolds used for burn wounds may need to possess greater mechanical strength and anti-infective properties, while those used for chronic ulcers may place a greater emphasis on the scaffold's pro-angiogenic and anti-inflammatory characteristics. Managing and establishing treatment consensus can be challenging, potentially resulting in inefficiencies and suboptimal clinical applications. These issues remain to be addressed in the future. This review aims to facilitate researchers' comprehension of the patterns and deficiencies in dermal scaffold research, consequently fostering the advancement of enhanced scaffolds that more effectively fulfill clinical requirements.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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