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Review

Research progress on the role of fascia in skin wound healing

Jiamin Xu, Hongyan Zhang*, Haifeng Ye*,*

Medical Center of Burn Plastic and Wound Repair, The First Affiliated Hospital; School of Basic Medical Sciences; Institute of Biomedical Innovation, Jiangxi Medical College, Nanchang University, Nanchang, Jiangxi 330031, China

*Corresponding author. HY, E-mail: haifeng.ye@ncu.edu.cn; HZ, E-mail: ndyfy00672@ncu.edu.cn

Abstract

The skin, the human body's largest organ, is perpetually exposed to environmental factors, rendering it vulnerable to potential injuries. Fascia, a vital connective tissue that is extensively distributed throughout the body, fulfils multiple functions, including support, compartmentalization, and force transmission. The role of fascia in skin wound healing has recently attracted considerable attention. In addition to providing mechanical support, fascia significantly contributes to intercellular signalling and tissue repair, establishing itself as a crucial participant in wound healing. This review synthesises the latest advancements in fascia research and its implications for skin wound healing.

Keywords: Fascia; Wound healing; Skin; Skin regeneration; Scar tissue

Highlights

- This review summarizes the role of fascia as a critical structural component of the skin in the process of skin wound healing.
- This review examines the relationship between fascia and chronic wounds, with a particular focus on its role in diabetic foot ulcers and scars.
- This review discusses novel therapeutic strategies targeting the fascia and provides an outlook on future research directions.

Background

The skin is a complex, multilayered organ that plays a critical role in separating and protecting the body from the environment, regulating body temperature, and supporting immune responses [1]. As the largest organ in the human body, the integrity of the skin is essential for maintaining overall health. Factors such as trauma, burns, and chronic diseases can severely disrupt the structure of the skin, leading to scar formation, which, in turn, affects individual health and quality of life, while also posing significant economic and social challenges to health care systems worldwide [2,3]. Following skin injury, various intracellular and extracellular signalling pathways are rapidly activated to restore tissue integrity and maintain homeostasis [4]. However, due to multiple factors, the wound healing process may be delayed [5]. Despite significant advances in the understanding of wound healing mechanisms in recent years, issues such as delayed wound healing and hypertrophic scarring persist in clinical practice, with existing treatments and management strategies failing to fully address these challenges.

Fascia, a widely distributed connective tissue, has garnered increasing attention from researchers in recent years. Fascia not only provides structural mechanical support and tension distribution but also plays a crucial physiological role in the wound healing process. Traditionally, research on skin wound healing has focused primarily on the repair mechanisms of the epidermis and dermis, with relatively less emphasis on the fascia [6]. Although existing studies have begun to uncover the potential functions of fascia in wound healing, the mechanisms underlying its role in different types of wounds (such as chronic wounds and diabetic ulcers) remain unclear. Particularly in the context of chronic wound healing, changes in the fascia may affect long-term wound repair, leading to healing complications and disorders. Therefore, a deeper exploration of the specific role of fascia in wound healing and its multidimensional functions in the wound microenvironment is highly important for improving wound healing and developing novel therapeutic strategies.

This review aims to summarize recent research advancements on fascia in skin wound healing, explore its mechanistic role in wound healing, and discuss its potential clinical applications, while also providing an outlook on future research directions, with the goal of offering new perspectives and references for clinical treatment strategies.

Review

Basic structure and function of the skin

Basic structure of the skin

The skin is composed of three layers: the epidermis, dermis, and subcutaneous tissue [7], each with distinct functional characteristics [8] (Figure 1). The epidermis is composed primarily of keratinocytes with self-renewal capacity, which form a lipid-rich stratum corneum during differentiation [9]. Specifically, the epidermis can be divided into the stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum,

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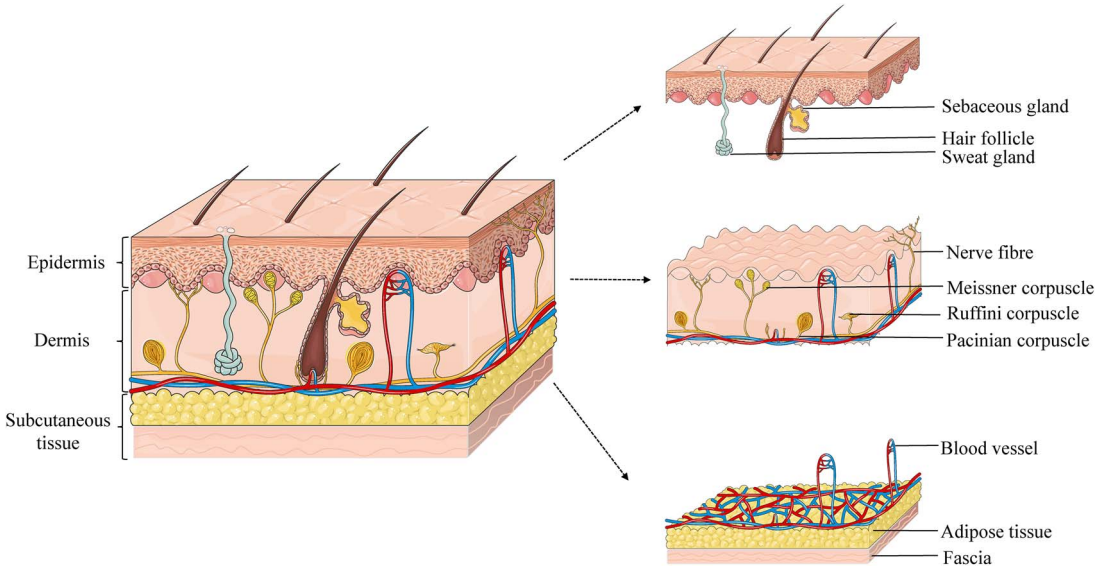

Figure 1. Human skin structure. The skin comprises three primary layers, the epidermis, dermis, and subcutaneous tissue, which are arranged from the outermost layer to the innermost layer. The epidermis can be subdivided into the stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale. The dermis is richly populated with blood vessels, nerve endings, specialised receptors, and accessory structures such as sebaceous glands, hair follicles, and sweat glands. Moreover, subcutaneous tissue consists mainly of connective and adipose tissue. The synergistic interaction among these layers is vital for sustaining skin health and functionality

and stratum basale [8]. The stratum corneum is rich in keratinocytes [10], the stratum lucidum contains eleidin [11], the stratum granulosum is abundant in keratins [12], the stratum spinosum is the thickest part of the epidermis [13], and the stratum basale houses melanocytes and immune cells [11]. The dermis is primarily composed of fibroblasts that synthesize fibres, elastic components, and the extracellular matrix (ECM), including substances such as hyaluronic acid (HA) and proteoglycans (PGs) [9]. It consists of a superficial papillary layer and a deeper reticular dermis layer [14]. The papillary layer interacts with the epidermis through rete ridges, and the anchoring fibrils within the basement membrane tightly connect the epidermis to the dermis [15], which contains numerous capillaries [16]. The reticular dermis layer contains skin appendages such as hair follicles, sebaceous glands, and sweat glands [17]. The subcutaneous tissue is made up of loose connective tissue, providing insulation and protection [6,7], and is rich in glycosaminoglycans and PGs [6]. Adipose tissue stores energy and regulates lipid metabolism [18–20] while also exerting immunomodulatory effects through immune cells [21].

Functions of the skin

The skin is a complex and multifunctional self-regulating organ that plays crucial roles in protection, sensation, immune modulation, absorption, secretion, and thermoregulation [22,23]. As an external barrier, the skin prevents the invasion of harmful factors such as physical, chemical, and microbial agents, while maintaining water and electrolyte balance to stabilize the internal environment [23]. Sensory nerves and specialized receptors within the skin, including Pacinian corpuscles, Meissner corpuscles, and Ruffini endings, are widely distributed and can detect external stimuli, triggering neural reflexes [22]. Additionally, the skin is capable of transdermal absorption through mechanisms such as the stratum corneum, hair follicles, sebaceous glands, and sweat gland ducts, providing the basis for topical drug delivery [24]. The skin also excretes waste products via sweat and sebaceous glands and participates in thermoregulation. It responds to signals from the central nervous system through vasomotion, shivering, and sweating, maintaining thermal balance [25–27]. Furthermore, the skin interacts with the neuroendocrine and immune systems [9], initiating immune responses through the activity of immune cells and molecules, thereby maintaining immune homeostasis [23,28]. Moreover, as a biosynthetic factory, the skin synthesizes and metabolizes various structural proteins, lipids, and signalling molecules, including vitamin D, hormones, and neurotransmitters, demonstrating its multifaceted physiological regulatory functions [9,29–31].

Similarities and differences between human and other mammalian skin

The skin is a crucial barrier against harmful environmental factors, a fundamental function that is universally shared among all species. Nevertheless, notable anatomical differences in skin structure exist across species (Table 1).

Mouse. The mouse model holds significant value in dermatological research, as it can simulate the pathological features of many human skin diseases [11]. Although the skin of mice shares structural similarities with that of humans, both consisting of the epidermis and dermis, there are notable differences in histology and physiology between the two. Mouse skin is thinner, with the dermis typically lacking sweat glands, and there are no distinct Rete ridges (also known as epidermal ridges) between the epidermis and dermis. Additionally, the surface of mouse skin is covered with dense fur, and the hair cycle differs from that of humans [33]. Mice also possess a unique dermal muscle layer—the panniculus carnosus, a thin layer of skeletal muscle found only in the human neck region, associated with the platysma muscle [34].

Table 1. Histological differences in mammalian skin [32]

	Human	Mouse	Rat	Pig
Skin Structure	Tightly attached	Loosely attached	Loosely attached	Tightly attached
Hair	Sparse, primarily concentrated on the scalp	Dense	Dense	Sparse, with bristled hairs
Epidermis	Thick	Thin	Thin	Thick
Dermis	Thick	Thin	Thin	Thick
Panniculus Carnosus	Present only in the neck area, characterised by the platysma muscle	Present	Present	Absent
Sweat Glands	High density of eccrine sweat glands	Limited to foot pads	Limited to foot pads	Few functional sweat glands
Wound Healing	Granulation tissue formation and re-epithelialization	Wound contraction	Wound contraction	Granulation tissue formation and re-epithelialization

Rat. Rats share many physiological and pathological similarities with humans [32]. Their skin, like that of humans, is composed primarily of the epidermis and dermis. However, owing to the high elasticity of rat skin and its relatively weak attachment to deeper structures, it does not fully replicate the structural characteristics of human skin [34]. During the wound healing process, rats primarily heal through contraction rather than re-epithelialization [35]. Furthermore, there are also internal differences between human and rat skin. For example, rat skin contains an enzyme capable of converting L-gluconogammalactone into vitamin C, an enzyme that is absent in humans [36].

Pig. The anatomical and physiological characteristics of pig skin are similar to those of human skin, making pigs an ideal model for studying human skin [37]. The epidermis and dermis of pigs closely resemble those of humans, with the skin firmly attached to the underlying tissues, sparse hair density, and the absence of a widespread panniculus carnosus [33]. Moreover, pigs and humans share many common features in the structures beneath the skin, such as the thickness, orientation, and distribution of blood vessels in the dermis, which are very similar between pig and human skin [37]. Both species also exhibit significant similarities in the composition of keratin, the lipid membrane on the skin surface, the distribution patterns of epidermal enzymes, and the turnover cycle of epidermal cells [34].

Wound healing of skin

Skin wound healing process

Skin wound healing is a finely regulated, complex biological process involving the interaction of various cells and signalling mediators [5]. Typically, wound healing is divided into four sequential and overlapping phases: haemostasis, inflammation, proliferation, and remodelling [38,39]. However, some researchers simplify this process into three phases by combining haemostasis and inflammation [32,40,41]. Regardless of the phase classification, the coordination between these stages is critical for successful healing (Figure 2).

Haemostasis phase. The primary feature of acute wounds is vascular damage and bleeding [5]. Following endothelial injury, platelets come into contact with the vascular endothelium, becoming activated and aggregating at the site of injury [42]. Haemostasis is mediated through both primary and secondary pathways [43]. Primary haemostasis promotes platelet aggregation and thrombus formation through collagen exposure, whereas secondary haemostasis involves the coagulation cascade, which converts fibrinogen into fibrin and forms a fibrin network [44]. This network provides a scaffold for subsequent cell migration and proliferation and serves as a reservoir for cytokines and growth factors [39].

Inflammatory phase. The inflammatory phase begins after haemostasis, with vascular dilation triggered by coagulation and complement cascades, where anaphylatoxins and bradykinin play pivotal roles [45]. Anaphylatoxins increase vascular permeability and recruit monocytes and neutrophils to the injury site [46,47]. Additionally, anaphylatoxins stimulate mast cells to release histamine and leukotrienes, further amplifying the inflammatory response, enhancing skin permeability, disrupting intercellular junctions, and promoting the migration of inflammatory cells to the wound site [48]. Neutrophils are the first cells to arrive at the wound, clearing damaged tissue and infectious agents, and recruiting macrophages through the secretion of chemokines [49,50]. Macrophages further clear apoptotic immune cells and secrete signalling molecules that promote the healing process, including re-epithelialization and dermal repair [41,49,51,52]. Once the inflammatory framework is established, the wound enters the proliferation phase, and new barrier structures begin to form [32,38].

Proliferation phase. The proliferation phase includes angiogenesis, granulation tissue formation, re-epithelialization, and immune regulation [5]. Fibroblasts and other cell types infiltrating the wound site initiate the proliferation phase [53]. Activated fibroblasts produce collagen and replace the temporary fibrin matrix [54,55], secreting cytokines to attract keratinocytes to the wound site, thereby promoting re-epithelialization [47]. During this phase, angiogenesis also occurs [56], with endothelial cells responding to hypoxic conditions and participating in the formation of new blood vessels [57]. As the temporary ECM is degraded, fibroblasts cease migrating and proliferating, marking the conclusion of the proliferation phase [32,41,58].

Remodelling phase. The remodelling phase is the final stage of wound healing, which can last from weeks to years [38]. During this phase, fibroblasts differentiate into myofibroblasts and contract the wound by binding to ECM components such as fibronectin and collagen via integrin receptors [59,60]. The

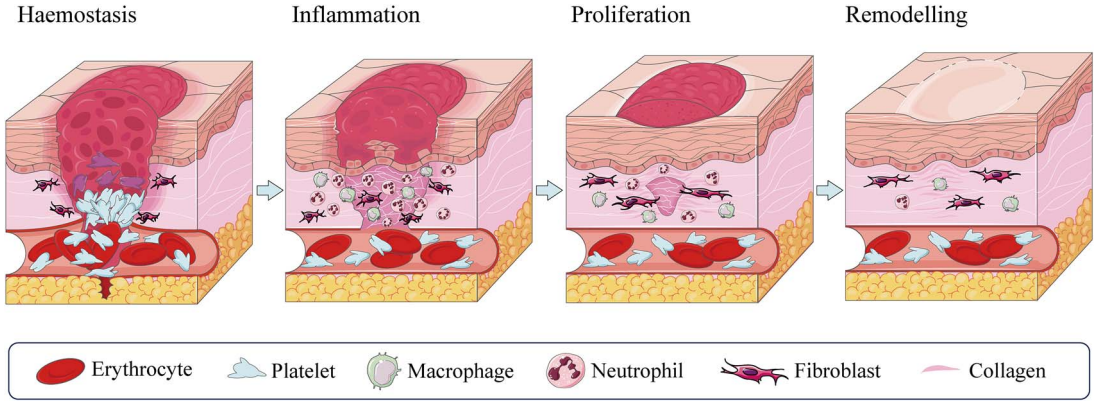

Figure 2. Traditional skin wound healing model. Following the occurrence of injury, blood vessels undergo immediate vasoconstriction to minimise bleeding, while platelets are rapidly activated and aggregate to form a clot that seals the wound. An inflammatory response is subsequently initiated to clear pathogens, necrotic tissue, and cellular debris from the wound site. As inflammation subsides, fibroblasts and endothelial cells begin to proliferate, resulting in the formation of granulation tissue rich in collagen and other ECM components, which serve to fill the wound and provide essential structural support. This granulation tissue is subsequently transformed into scar tissue through remodelling, which involves reorganising and reinforcing collagen fibres. During this remodelling phase, excess collagen is degraded, and new fibres are continuously generated, ultimately allowing the wound appearance to approximate that of the surrounding normal skin. *ECM* extracellular matrix

remodelling process is regulated by matrix metalloproteinases (MMPs), which degrade disordered old collagen, predominantly type III collagen [61,62]. Remodelling occurs when fibroblasts upregulate the expression of type I collagen, and MMPs degrade disorganized old collagen (primarily type III collagen) [39]. Collagen fibres realign and arrange parallel to the tension lines, with type I collagen predominating, resulting in the formation of stable scar tissue [63]. During the remodelling process, newly formed blood vessels exhibit high permeability, facilitating immune cell infiltration that supports healing [5]. Ultimately, vascular pruning stabilizes vascular development, and granulation tissue transitions into collagen-filled scar tissue, completing the healing process [63,64].

Factors affecting skin wound healing

When an acute skin wound fails to heal as expected, it may progress into a chronic wound [65]. Chronic wounds typically remain in the inflammatory phase, where local hypoxia, excessive bacterial load, and impaired host response to stress collectively create a vicious cycle that prevents the wound from entering the proliferation phase, leading to delayed healing and potentially resulting in excessive scarring or tumour progression [65–67] (Figure 3).

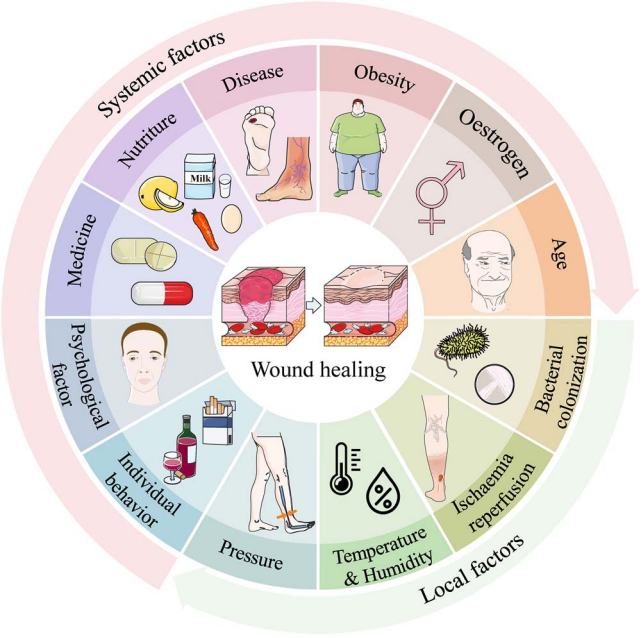

Figure 3. Factors affecting skin wound healing. These determinants of skin healing are multifaceted, encompassing systemic factors such as age, chronic diseases, and nutritional status, as well as local factors such as wound temperature, humidity, ischaemia reperfusion, and bacterial colonization. When acute skin injuries are adversely affected by these factors and fail to heal in a timely manner, they may progressively evolve into chronic wounds

Systemic factors. With the ageing population, age-related factors affecting skin wound healing have gained increasing attention [68]. Ageing results in altered cell adhesion, migration, and function [69], with a decline in tissue regenerative capacity. Elderly individuals exhibit impaired fibroblast and macrophage function [70], reduced collagen production [71], and microcirculatory dysfunction in the skin [72], all of which significantly delay the healing process. As a hormone-sensitive organ, the skin responds to oestrogen, which regulates cytokine levels and modulates the inflammatory response, thereby promoting healing [3,73]. Moreover, nutritional status directly or indirectly influences wound healing. For example, protein deficiency reduces collagen synthesis and fibroblast generation [74]. Vitamin deficiencies, particularly of vitamin C, hinder collagen synthesis by fibroblasts and their transformation into myofibroblasts [8]. Trace elements such as zinc, copper, and iron play crucial roles in wound healing [75], with zinc deficiency notably impairing tissue regeneration and delaying healing [76]. Obesity can also impede wound healing through factors such as increased haematoma formation, reduced oxygen supply, and increased infection risk [77].

Oxygen is essential at all stages of wound healing [78]. Any potential or comorbid conditions that interfere with the body's oxygenation and oxygen transport capacity can significantly affect the healing process [39,79], with diabetes having a particularly marked impact on wound healing, especially

related to specific diabetic complications (peripheral neuropathy and vascular disease) [80,81]. Hyperglycaemia in diabetic patients leads to endothelial dysfunction, reduced blood flow, and microcirculatory impairment, which in turn affects the oxygen and nutrient supplies to the wound site, delaying healing. Diabetes is also associated with impaired immune function, with reduced macrophage and neutrophil activity, decreasing the ability of the local inflammatory response to clear pathogens, thereby increasing infection risk. Furthermore, diabetes-related peripheral neuropathy limits sensory and repair responses to wounds, increasing the likelihood of exposure and damage to the wound site [82]. Medication use can also affect healing [80]. For example, corticosteroids suppress immune responses and inhibit fibroblast proliferation [83], whereas anticancer drugs reduce leukocyte activity, thereby increasing infection risk [81]. Additionally, smoking, excessive alcohol consumption, and other psychological factors (such as anxiety and depression) also have negative impacts on the healing process [80].

Local factors. Studies have shown that maintaining an appropriate temperature and humidity at the wound bed promotes healing [84]. Local pressure, friction, and shear forces can lead to circulatory disruption, impair nutrient supply, and hinder the healing process [80]. Furthermore, ischaemia-reperfusion injury is a common trigger for chronic wounds (e.g. diabetic ulcers, pressure ulcers, and venous ulcers), inducing proinflammatory responses and exacerbating local hypoxia, ultimately obstructing healing and even leading to tissue necrosis [85]. Additionally, bacterial colonization is a critical local factor influencing wound healing [86]. When the bacterial count exceeds 10^5 per gram of wound tissue, it significantly impedes healing [65].

The role of fascia in wound healing

What is fascia?

Fascia is a commonly used anatomical term; however, its definition often suffers from inaccuracies and ambiguities, leading to an incomplete understanding of this essential structure [87,88]. In 2017, the Fascia Nomenclature Committee (FNC) offered a precise anatomical definition: "A fascia is a sheath, a sheet, or any other dissectible aggregations of connective tissue that forms beneath the skin to attach, enclose, and separate muscles and other internal organs [89]". As viscoelastic connective tissue, fascia extensively connects the body's muscles, nerves, skeleton, and visceral organs [90–92], existing within a broader framework referred to as the 'fascia system' [93,94]. The FNC formally defines this system as a 3D continuum of soft, collagen-containing, loose, and dense fibrous connective tissues that permeate the body. It incorporates elements such as adipose tissue, adventitiae and neurovascular sheaths, aponeuroses, deep and superficial fasciae, the epineurium, joint capsules, ligaments, membranes, meninges, myofascial expansions, periostea, retinacula, septa, tendons, visceral fasciae, and all intramuscular and intermuscular connective tissues including the endomysium, perimysium, and epimysium [89]. From an embryological standpoint, fascia primarily arises from the mesoderm; however, some studies suggest that portions of this connective tissue may also originate from the neural crest (ectoderm), particularly in the cervical region [95,96]. Notably, the fascia system is not a homogeneous structure; it comprises multiple functional layers at varying depths, creating a 3D matrix that provides metabolic and mechanical support, which is essential for the strength and flexibility of tissues and organs [97,98].

Functions of fascia

Fascia can be classified into three primary types on the basis of its location and function: (i) subcutaneous fascia (superficial fascia), which exists beneath the skin; (ii) deep fascia, which encompasses and connects muscle fibres; and (iii) visceral fascia, which surrounds internal organs [92,99] (Figure 4).

Superficial fascia. Superficial fascia, commonly called subcutaneous fascia, comprises one or more layers of loose connective tissue, with its specific architecture varying according to the anatomical location of the skin. This layer is vital for preserving skin integrity and supporting underlying structures [100]. Via vertically oriented fibrous septa, distinct layers of superficial fascia are connected to the skin and deep fascia (support bands) [101]. Subcutaneous fascia, along with its corresponding support bands, creates a 3D network connecting the layers of muscle and subcutaneous tissue to the skin, allowing the skin dynamic anchoring [102,103]. Moreover, superficial fascia is instrumental in facilitating movement between the dermis and the deeper muscle and skeletal layers [98]. It also functions as a structural scaffold and protective layer for subcutaneous blood vessels, lymphatic vessels, and nerve networks [92,101]. Additionally, the superficial fascia, which is abundant in autonomic sympathetic nerve endings, provides pathways and safeguards for larger, long-distance nerves, thereby preventing excessive tension on these neural structures [97].

Deep fascia. Muscle bundles are encased in a fibrous layer called the deep fascia [104], which can be divided into two subtypes: epimysial and aponeurotic fascia [105,106]. The former represents the typical deep fascia found in the trunk, as well as the fascia associated with the pectoralis major, trapezius, deltoid, and gluteus maximus muscles, facilitating force transmission between adjacent synergistic muscle fibre bundles [107]. The latter encompasses fascia related to the limbs, thoracolumbar fascia, and rectus sheath [108], allowing for force transmission across various segments of the body [109]. Deep fascia is notably rich in HA, which plays a crucial role in enabling the sliding of fascia relative to the underlying muscle and among different sublayers of fascia [110–113]. Furthermore, aponeurotic fascia layers and HA-enriched spaces between fascia and muscle serve as reservoirs for stem and multipotent cells actively involved in underlying structural maintenance, repair, and regeneration [114]. Furthermore, extensive research has demonstrated that deep fascia is linked to dysfunctions related to proprioception [105,115,116] and motor coordination [117–119], as well as the manifestation of myofascial pain and muscle spasms [120–123].

Visceral fascia. Visceral fascia is defined as the connective tissue intimately associated with individual organs, providing shape and structural integrity. It supports the parenchymal tissue and comprises all fibrous layers that demarcate organ compartments, linking them to the musculoskeletal system [124,125]. This fascia not only offers support and stability to visceral organs but also serves as a buffer against external impacts, reducing the risk of injury and assisting in thermoregulation [126,127]. The mobility of visceral fascia facilitates

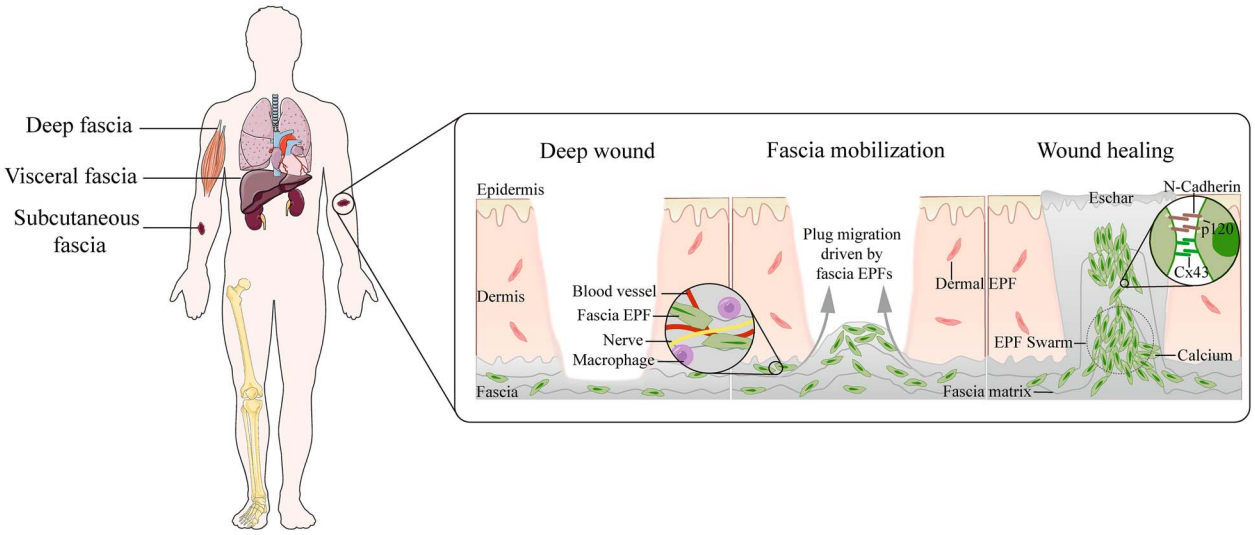

Figure 4. The distribution of fascia and its role in skin wound healing. The fascia is categorised on the basis of its location and function into subcutaneous, deep, and visceral fascia. During deep tissue injury to the skin, fascia is mobilised to close the wound rapidly. EPFs migrate in a swarm-like manner towards the Centre of the wound via cell–cell contact. Notably, N-cadherin and Cx43 play a shared role in cell adhesion during this process. Over time, the fascia matrix that closes the wound undergoes significant remodelling, ultimately resulting in the formation of mature scar tissue. *EPF* engrailed-1 lineage-positive fibroblast. Cx43 Connexin 43

relative movement between organs or between an organ and surrounding tissues, minimising friction and preventing the formation of adhesions [99]. Furthermore, the visceral fascia is richly innervated by autonomic nerve fibres, allowing it to perceive and transmit signals related to pressure, tension, and pain originating from the viscera [125,128,129]. Nevertheless, the specific types of neural innervation present within this fascia remain to be elucidated through further research [124].

Role of fascia in skin wound healing

Traditional wound healing models posit that dermal fibroblasts migrate from the wound periphery into the temporary fibrin matrix, where they differentiate into myofibroblasts to establish granulation tissue, facilitating wound contraction and closure [130–132]. However, recent studies indicate that the repeated removal of granulation tissue does not hinder closure, suggesting that granulation tissue may not be essential for this process [133,134]. Additional evidence reveals that wound contraction predominantly occurs at the wound edges rather than within the granulation tissue [134,135]. An increasing number of studies focused on subcutaneous fascia support these findings, progressively elucidating the role of fascia in skin wound healing [136,137] (Figure 4).

Correa-Gallegos et al. [138] established that fascia serves as the primary source of skin wound natural cells, including fibroblasts, and that the temporary matrix of wounds originates from prefabricated matrices within the fascia. Deep skin injuries trigger the mobilisation of fascia to accelerate wound closure. This mobilised fascial tissue contains both ECM components and fibroblasts, an embedded vascular system, peripheral nerves, and immune cells—all of which are critical for initial wound repair [92,139]. Further investigations demonstrated that resident fibroblasts in the fascia coordinate the movement of connective tissue towards the wound, with mobilisation mediated by a specific fibroblast lineage known as Engrailed-1 (En1) positive fibroblasts (EPFs) [140–142]. Notably, genetic ablation of these fascial fibroblasts impedes the homing of matrix components to the skin, resulting in delayed wound healing. Furthermore, the placement of a membrane barrier beneath the skin that obstructs fibroblast migration to the upper dermis can lead to chronic nonhealing wounds [138]. Researchers have observed the contribution of fascia to the development of large scars and their obstruction, leading to chronic open wounds. They reported that the extent of poor and excessive scarring in the skin, such as in diabetic and ulcerative wounds, as well as hypertrophic scars, particularly keloids, may be attributed to the fascia [138]. This study introduced the concept of the ‘scar primordium,’ suggesting that fascia fibroblasts, rather than dermal fibroblasts, lead to scar formation by guiding matrix deposition from the basal substrate [138].

Jiang et al. [143] further investigated the potential mechanisms of fascia cell mobilization following deep skin injury using a mouse full-thickness wound model. Through *in vivo* and ex vivo real-time imaging, they revealed novel movement patterns of the subcutaneous fascia and key participants, suggesting a mammalian scar model involving N-cadherin expression and cell aggregation towards the scar centre (Figure 4). Their research showed that in skin wounds, a specific group of EPFs mobilize distant fascia connective tissue to repair deep skin wounds via N-cadherin-dependent collective cell migration. This migration occurs through cellular intercontact-mediated swarm behaviour [143–145]. Notably, this swarm migration occurs exclusively in fascia fibroblasts [143]. Moreover, during wound healing and scar formation, fascia EPFs upregulate N-cadherin expression. In tissues without fascia (such as oral mucosa), or when N-cadherin is genetically or chemically inhibited, fascia EPFs swarming is absent, thereby reducing wound contraction and scar formation [143]. In addition to N-cadherin, intercellular communication plays an indispensable role in the patch-like repair of deep skin wounds [4]. Wan et al. [144] further revealed that connexin 43 (Cx43), a gap junction protein, is a key molecular mediator of matrix movement and scar formation and is essential for large wound patch repair. Their study revealed that Cx43 expression is significantly upregulated in the EPF of deep skin fascia, which

is responsible for scar formation. Inhibition of Cx43 expression disrupts calcium signalling oscillation in fibroblasts and inhibits the collective migration of EPFs needed for fascia matrix mobilization. Additionally, after Cx43 blockade, scar formation was reduced, collagen content decreased, and the expression of the fibrosis marker CD26/DPP4 was decreased [144].

Notably, both N-cadherin and Cx43 share cell adhesion functions and mediate cell migration; however, the signalling cascade involving these mediators is not yet fully understood. Cx43 may act as a transcription factor upstream of N-cadherin. Studies have shown that knocking down Cx43 leads to reduced N-cadherin levels [4,146]. Several hypotheses regarding the signal cascade between N-cadherin and Cx43 include the following: first, N-cadherin and Cx43 may physically bind to protein complexes, and the absence of Cx43 may disrupt this complex [147]; second, N-cadherin-mediated adhesion junctions and Cx43-mediated gap junctions are in close proximity, suggesting that adhesion junctions are crucial for promoting the biophysical coupling of adjacent cell membranes, ensuring the correct formation of functional gap junctions between fibroblasts [148]. Clearly, the exact molecular triggers and mechanisms by which N-cadherin and Cx43 upregulation drive fascia mobilization still require further investigation.

Rajendran et al. [149] reported that p120-catenin (p120) plays a pivotal role in fascia mobilization and wound repair. They found that injury triggers p120 expression in the EPF throughout the skin wound healing process, regulating the extent to which the connective tissue matrix and cells are directed to the wound. Silencing p120 modulated the degree of connective tissue matrix and cell migration into the wound, thereby reducing scar severity. When adeno-associated virus was used to silence the p120 gene, the migration of fascia cells and their ECM to the wound was blocked, significantly reducing scar formation and promoting wound healing [92,149]. Furthermore, p120 is crucial for the formation of N-cadherin-based junction complexes and for cell polarity [150]. It can directly bind to and stabilize N-cadherin, and both N-cadherin and p120 are essential for the directed collective migration of fibroblasts.

The latest research by the Rinkevich team revealed the origins of the cellular pathways behind the skin wound healing cascade, identifying multipotent fibroblasts marked by CD201 expression in the subcutaneous fascia. This lineage has been shown to generate all of the specific fibroblast subtypes required for wound repair progress in a spatiotemporally adjusted sequence [151]. Specifically, fascia fibroblasts can differentiate into proinflammatory, primitive myofibroblasts, and myofibroblasts, reflecting the transition between different stages of wound healing. The researchers confirmed the time-dependent expression pattern of fascia fibroblast cluster-specific markers at key time points during the transition from the inflammatory phase to the proliferation phase (Day 3) and from the proliferation phase to the remodelling phase (Day 7). They reported that the number of $PDPN^+$ proinflammatory and phosphorylated activated $STAT3^+$ ($pSTAT3^+$) primitive myofibroblasts peaked on Day 3 and gradually decreased thereafter, whereas the number of $RUNX2^+$ myofibroblasts significantly increased on Day 7 during the remodelling phase. Furthermore, they observed distinct cell distribution patterns across different wound regions: on Day 3, $PDPN^+$ proinflammatory fibroblasts were primarily concentrated in the wound bed and upper regions, whereas $pSTAT3^+$ primitive myofibroblasts did not show a significant spatial preference; on Day 7, $RUNX2^+$ myofibroblasts were predominantly concentrated in the upper wound compartment, with the least distribution in the deeper regions. In summary, the spatiotemporal coordination of fibroblast differentiation during skin wound healing is driven by the differentiation of $CD201^+$ progenitor cells into proinflammatory fibroblasts in the wound bed, which eventually mature into myofibroblasts in the upper wound region [151].

Moreover, the Rinkevich team reported that the spatiotemporal regulation of wound healing in both mouse and human wounds is mediated through the retinoic acid (RA) and hypoxia signalling pathways. These pathways regulate the differentiation of $CD201^+$ fibroblast progenitors into proinflammatory and myofibroblast states, accelerating wound healing [99,151]. Specifically, researchers have observed peak expression of RA pathway genes during the transition from $CD201^+$ progenitors to proinflammatory fibroblasts. RA promotes the recruitment of monocytes and macrophages to fascia-derived proinflammatory fibroblasts by expressing the monocyte chemotactic factor CCL2, thereby supporting the inflammatory phase of wound healing. Notably, while overactivation of this pathway effectively limits the number of myofibroblasts, insufficient downregulation of RA signalling is unable to trigger progression towards a contractile state (proliferation and remodelling phases) [151].

Furthermore, they confirmed that hypoxia-inducible factor-1-alpha (Hif1α) is an upstream regulator of YAP–TAZ mechanotransduction and the TGF-β pathway. Its activity is essential for the transition from proinflammatory fibroblasts to primitive fibroblasts and myofibroblasts, thereby promoting wound closure, tissue contraction, and scar formation [151]. These phenomena are observed in both mice and humans, and this differentiation trajectory has significant implications for the progression of wound healing from the inflammatory phase to the tissue contraction phase. Overall, fascia-related research updates traditional wound healing theories and demonstrates the immense potential of fascia in skin wound healing.

Future perspectives on fascia in skin wound healing

Skin wounds trigger a spatiotemporally synchronized biological cascade aimed at minimizing tissue damage and restoring skin integrity [4]. Current research on fascia in wound healing is still in its early stages, leaving considerable room for exploration [99]. Existing studies highlight a dual mechanism in wound healing: superficial wounds typically prompt dermal fibroblasts to migrate towards the wound, whereas deep skin injuries initiate different repair mechanisms with the fascia as the anatomical centre [92,138]. Fascia is not only a structural bridge connecting the skin to deeper tissues but also a crucial regulatory factor in wound repair.

With the advancement of fascia biology research, fascia-specific therapeutic strategies are gradually emerging as key approaches for enhancing wound healing. Clinical treatments can target fibroblasts in the fascia and their migration processes, particularly through strategies that intervene in fibroblast migration or regulate matrix remodelling. Experimental evidence has demonstrated the potential of these approaches to accelerate wound healing and reduce scar formation. For example, researchers have shown in mouse models that the use of chemical inhibitors to

target N-cadherin or Cx43 or gene ablation of fascia EPF significantly accelerates full-thickness wound healing and effectively reduces scar formation [136,143,144,149,152]. Furthermore, the discovery of $CD201^+$ progenitor cells has opened new therapeutic avenues for skin wound healing. Manipulating each step of this pathway can regulate different fibroblasts at the wound site, offering potential therapies for clinical conditions that modulate skin wound healing and suppress myofibroblast formation to prevent excessive scar formation and wound contraction, without affecting the proinflammatory responses needed during the inflammatory phase [151].

Currently, there is limited clinical evidence directly linking fascia defects with chronic nonhealing wounds. However, existing studies suggest that diabetic foot ulcers are associated with fascia abnormalities, potentially due to impaired local regulation of plantar pressure through fascia tissue [153]. Specifically, prolonged hyperglycaemia leads to the accumulation of advanced glycation end products, causing collagen cross-linking in the fascia, which results in fascia sclerosis and loss of elasticity. Additionally, diabetes can lead to excessive fibroblast proliferation, promoting fascia fibrosis and further exacerbating local tissue stiffness and inflammation. Simultaneously, microvascular complications commonly observed in diabetic patients lead to restricted blood circulation, impairing the blood supply to the fascia's small vessels, which worsens local hypoxia and nutrient deficiency, affecting wound healing. Neuropathy in diabetic patients causes a loss of sensation in the feet, leading to reduced responsiveness to external injuries, whereas fascia sclerosis may increase foot pressure, resulting in foot deformities such as hammertoes or bunions, which further increase the risk of foot ulcers and create a vicious pathological cycle [154]. Studies have shown that excessive pressure on the fascia increases the incidence and recurrence of diabetic foot ulcers, with selective plantar fascia release proven to effectively prevent and manage diabetic foot ulcers [155]. Further investigations into the subcutaneous fascia in chronic wound mouse models are expected to drive progress in understanding how fascia defects impede chronic skin wound healing mechanisms.

Despite the similarities between mouse and human skin wound healing and scar formation, differences in physiology, histology, and wound healing mechanisms exist, and it is currently unclear whether findings in mice reveal general principles applicable to human skin wounds [139]. In fact, the subcutaneous fascia varies across species, anatomical skin locations, ages, and sexes [100]. In scar-prone species such as humans, horses, and dogs, the superficial fascia is relatively thick, whereas in some mammals, the superficial fascia is relatively loose. Additionally, the thickness of the human fascia varies by body part, being thicker in the lower chest, back, and arms, regions that are prone to hypertrophic scarring and keloids [102,156]. Understanding the anatomical location and structure of the fascia layers could help explain the occurrence and severity of hypertrophic scars and keloids. Therefore, while mouse models provide valuable insights into the behaviour of fascia fibroblasts, whether these findings can be directly applied to humans should be approached with caution. To better elucidate the role of fascia in skin wound healing, future research should focus on the similarities and differences in fascia fibroblast function, response, and molecular mechanisms across different species. By exploring these differences, researchers may identify mechanisms of translational relevance for human wound healing, providing new cellular and molecular insights for promoting skin wound healing and preventing excessive scarring.

In the future, in-depth research on the role of fascia in wound healing may lead to a series of innovative therapeutic approaches, especially for treating chronic wounds and challenging conditions such as diabetic foot ulcers. By further understanding the dynamic changes and functional mechanisms of fascia in the wound healing process, more personalized and effective clinical treatment strategies could be developed. Clinically, fascia-targeted therapies could be combined with existing wound care methods to provide more precise and effective treatments for patients, particularly in promoting wound healing, preventing excessive scarring, and reducing chronic wound recurrence. In conclusion, fascia, as a key biological factor in skin wound healing, is increasingly recognized for its role and clinical potential. Through systematic, in-depth research and innovative therapeutic strategies, fascia is expected to become a significant target in clinical wound healing treatments, particularly in chronic wound management and scar prevention, offering more effective treatment options.

Conclusions

Skin injuries initiate synchronised spatiotemporal biological cascades designed to optimise tissue restoration. Even after a great deal of research, the precise mechanisms that promote wound healing are still not fully understood. Impairments in skin wound healing can lead to various complications, including chronic wounds and excessive scarring. Current research has revealed the crucial function of fascia in skin wound healing, emphasising the potential of targeting cellular and molecular pathways to accelerate healing. Future research should further investigate the relationship between fascial defects and chronic wounds and explore the mechanisms of interaction between fascia and other skin layers. Unravelling the dynamics of fascia following skin injuries may be crucial for achieving optimal skin restoration and preventing excessive scar formation in clinical practice.

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Author contributions

Jiamin Xu (Conceptualization [equal], Writing—original draft, Writing—review & editing, Visualization [equal]), Hongyan Zhang (Writing—review & editing, Funding Acquisition [equal], Supervision [equal]), Haifeng Ye (Writing—review & editing, Conceptualization [equal], Funding Acquisition [equal], Supervision [equal]).

Conflict of interest

None declared.

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