REVIEW

Innervated Biomaterials for Improved Cutaneous Wound Healing: A Review of Recent Advancements and Future Prospects

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Abstract: Cutaneous wound healing remains a significant clinical challenge, particularly for chronic and large-scale injuries, where functional recovery—especially sensory reinnervation—is often inadequate. Recent advances highlight the pivotal role of innervation in regulating tissue repair through neuropeptide signaling, immunomodulation, and angiogenesis. Despite progress in biomaterial-based therapies, most existing solutions focus on structural repair while neglecting neural regeneration, leading to suboptimal functional outcomes. This review explores emerging biomaterial strategies that integrate neuroregenerative capabilities with wound healing properties, including electroconductive scaffolds for bioelectric stimulation, neurotrophic factor-releasing matrices, and bioengineered constructs. We critically evaluate their mechanisms in promoting axonal regrowth, macrophage polarization, and vascular network formation, while addressing challenges in long-term functional integration. This review outlines the mechanisms of wound healing, existing treatments, and the vital role of nerves in the healing process. It also highlights materials that promote skin neuralization in cutaneous wound healing, aiming to inspire further research into these materials and the underlying mechanisms involved. By bridging the gap between neural and cutaneous regeneration, this work provides a roadmap for developing next-generation wound therapies that restore both structural integrity and sensory function. Future directions emphasize the need for standardized neuroregenerative assessment criteria and clinically translatable designs.

Keywords: cutaneous wound, innervation, neuro regenerative materials

Introduction

The skin is the largest organ in the human body and performs functions such as mechanical protection, immune regulation, fluid regulation, temperature regulation, and sensing external stimuli.[1,2] Treating large and chronic wounds caused by accidents or diseases on any part of the body remains a challenge. Autografts and allografts are common in clinics, but they have issues like re-traumatization, infection risk, immune rejection, and limited availability.[3] Various materials have been developed to address these issues with anti-infection, inflammation modulation, and angiogenesis-promoting effects.[4–7] These innovations, ranging from natural polymer-based systems to synthetic nanocomposites, have been shown to improve wound closure rates compared to traditional treatments.[8–11] Nonetheless, most of these studies overlook the recovery of the sensory function of the skin. Incomplete sensory recovery, chronic neuropathic pain, and itching are frequent in healed wounds and have a significant impact on the quality of life of patients.[12]

Emerging evidence suggests that innervation is one of the master regulators of skin repair. Sensory neurons and Schwann cells coordinate healing through mechanisms such as neuropeptide release and neurotrophic factor signaling.[13] Injury receptors regulate macrophage polarization through the IL-10/TGF-β pathway, whereas autonomic fibers regulate

Graphical Abstract
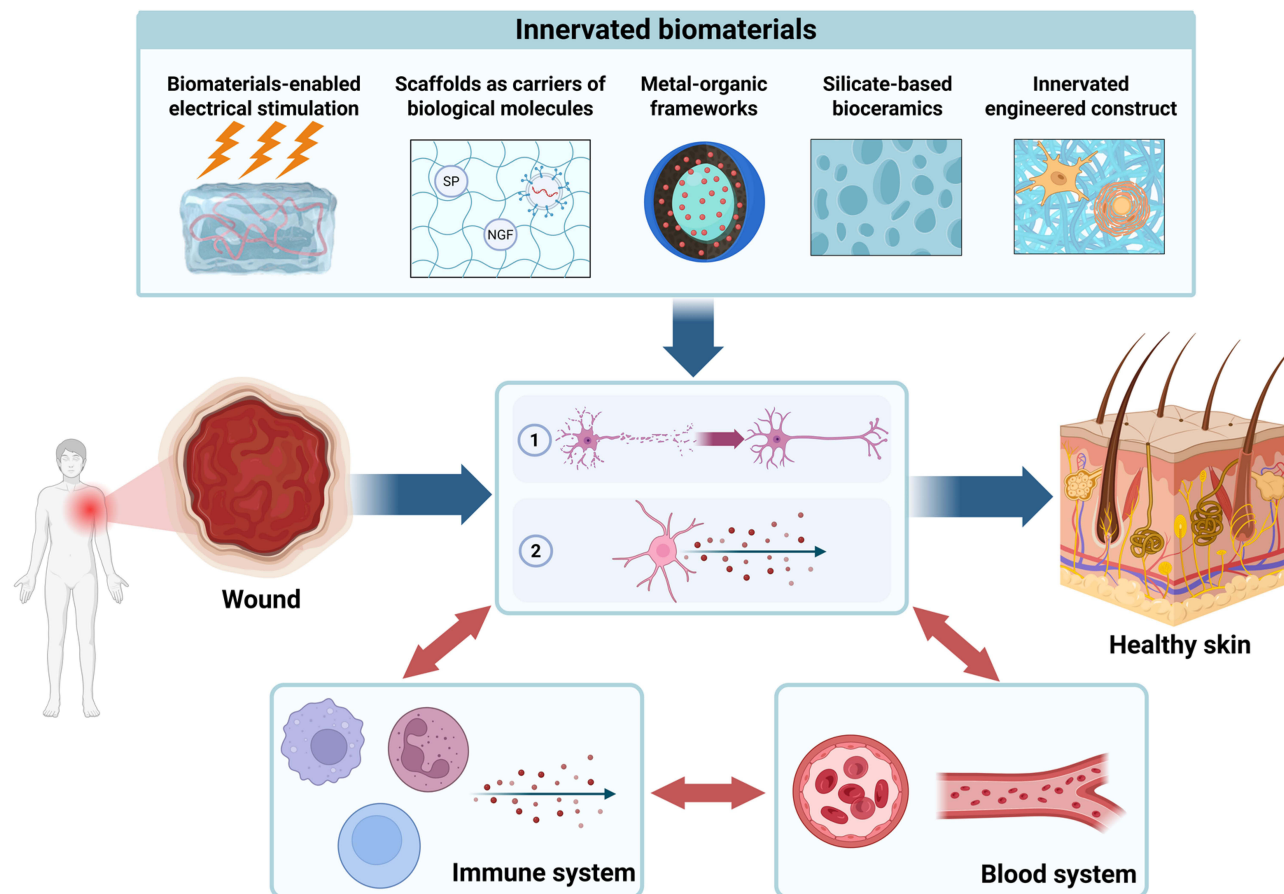
perfusion through VEGF-dependent angiogenesis.[14,15] Critically, denervated wounds exhibited delayed healing and reduced tensile strength, confirming that nerves are active participants in tissue regeneration rather than passive bystanders.[16] Therefore, to create ideal materials for treating skin wounds, we need to emphasize the role that nerves play in the healing process as well as the restoration of perceptual function after healing.

Recently, a series of materials exhibited both tissue-induction activity and neural induction activity that had been explored for innervated skin regeneration. These materials can be categorized according to functional mechanism and material type as biomaterials-enabled electrical stimulation, scaffolds as carriers of biological molecules, metal-organic frameworks, silicate-based bioceramics, and innervated engineered constructs. However, few reviews have focused on the role of materials that promote cutaneous wound regeneration through nerve action. As the important role played by nerves in wound healing is gradually being elucidated and related materials research continues to make progress, a systematic summary of the applications of innervated biomaterials in skin wound treatment is timely and necessary.

This review aims to provide an overview of current approaches for treating and repairing cutaneous wounds through material-based therapies. It highlights various materials that promote skin nerve reinnervation and enhance cutaneous wound healing by facilitating nerve regeneration. The review summarizes and discusses the latest research advancements in this field. It is hoped that this review will inspire further development of materials that support neuroregeneration in cutaneous wound healing.

Cutaneous Wound Healing

Skin wound healing is a complex process of overlapping yet coordinated cellular and molecular events that repair tissue damage and restore function through interactions among various cell types and systems (Figure 1).[17] Cutaneous wound healing is conventionally divided into four overlapping stages: hemostasis, inflammation, proliferation, and dermal remodeling.[18,19] The hemostasis phase involves vasoconstriction, activation of the intrinsic coagulation cascade leading to clot formation, and subsequent scab development. These processes collectively prevent hemorrhage, protect against microbial infiltration, and provide a microenvironment rich in immune cells and cytokines.[20,21] The inflammatory phase typically begins within minutes to hours after injury. The key inflammatory cells include neutrophils, macrophages, and monocytes, which work together to lay the foundation for the subsequent wound-healing process.[22,23] The proliferative phase involves the migration and proliferation of fibroblasts, keratinocytes, and endothelial cells alongside extracellular matrix components. Together, these processes form granulation tissue, restore the epithelial layer, and repair tissue.[24,25] The remodeling phase of cutaneous wound healing, lasting weeks to years, determines wound healing quality. It involves tissue reorganization, contraction, collagen maturation, and the transition from type III to type I collagen.[26,27]

Most cutaneous wounds heal naturally without external intervention. However, deep wounds, large wounds, severe burns, and chronic wounds often require medical treatment to ensure proper healing and restore function. Deep cutaneous wounds, or those that extend into the dermis, are difficult to heal and are more likely to result in scarring. Studies suggest that this situation is related to a threshold for wound depth, which is associated with the effects of epidermal-dermal interactions.[28,29] In addition, large-area cutaneous wounds may also require medical intervention in some cases. Large-area cutaneous wounds require extensive angiogenesis and tissue repair, making complete regeneration difficult. The activation of inflammation and the enhancement of fibrosis are the main obstacles.[30] Similarly, large-area cutaneous wounds are also
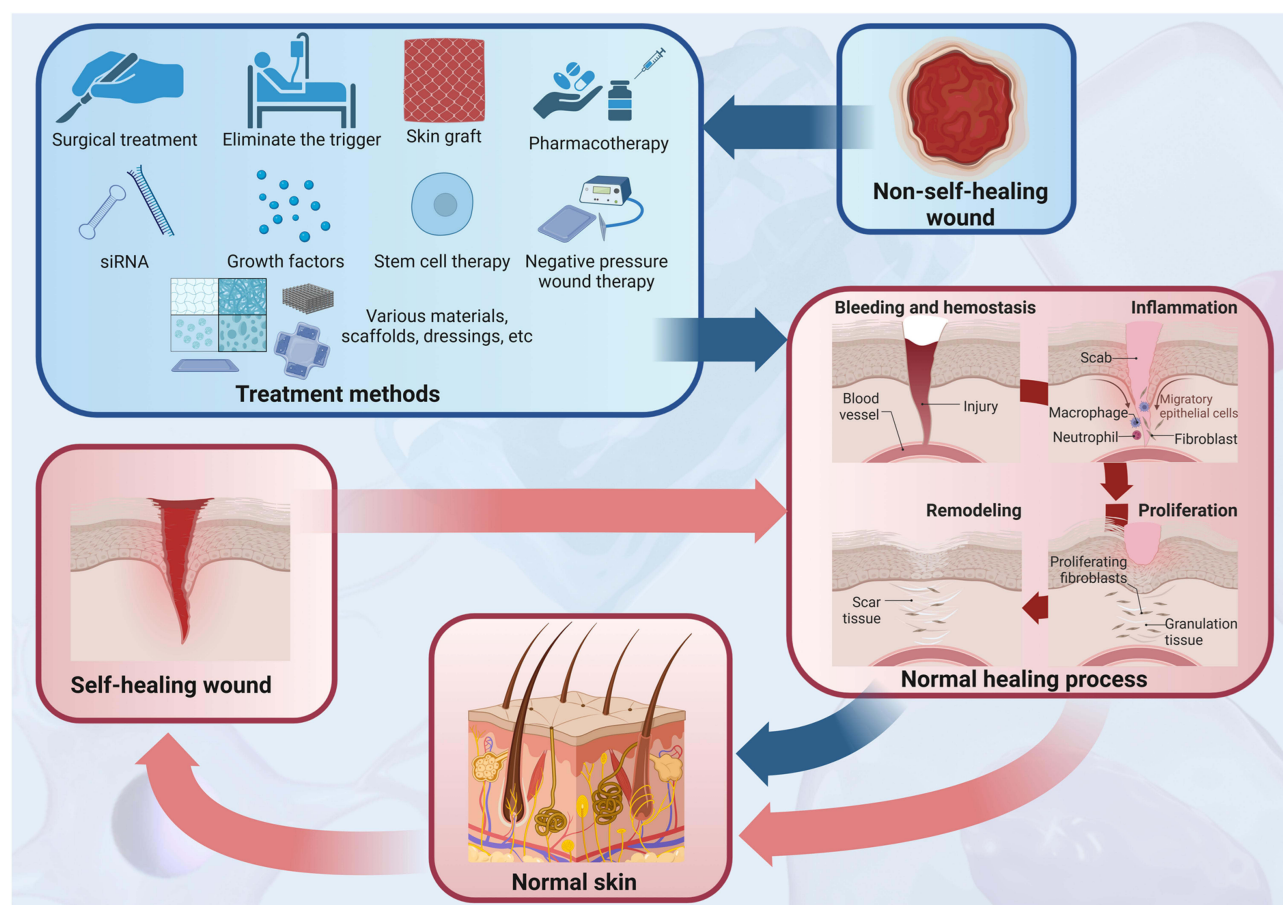
Figure 1 Cutaneous wound healing and current treatment methods. Created in BioRender. SZ. (2025) https://BioRender.com/q5d0dl2.

more prone to infection, which makes wound healing more difficult. In addition, the difficulty in healing large-area burns is due not only to the risk of infection but also to an abnormal inflammatory response. Severe burns initiate an uncontrollable inflammatory process, causing excessive inflammation that hinders healing and induces a hypermetabolic state.[31] Chronic cutaneous wounds constitute another type of wound that necessitates medical intervention. A chronic wound is defined as a break in the skin that lasts for a long time (>6 weeks) or recurs frequently.[32] In recent years, it has become widely accepted that the presence and persistence of wound infection are the primary causes of chronic wound development.[33] The microenvironment of the wound is of critical significance to the success or failure of cutaneous wound healing. Chronic wounds are frequently associated with substantial inflammatory stimuli, such as bacterial colonization, necrotic tissue, foreign bodies, and localized tissue hypoxia.[34] This infection may trigger abnormal inflammation. Research indicates that excessive inflammatory responses play a key role in wound pathology. Such persistent inflammation damages tissue repeatedly, creating a cycle of chronic inflammation that drives chronic wound formation.

Large and chronic wounds, which are difficult to heal naturally, often necessitate grafts or supplementary materials to support recovery. As the gold standard for treating large areas of skin loss or chronic wounds, autologous skin grafting has a lower risk of rejection and better healing outcomes. However autologous skin grafting has drawbacks, including the need for incisions to obtain graft material, long culture times, donor site morbidity, nerve damage, and the risk of infection.[35] Using dressing materials to treat chronic wounds is also a popular area of research. Traditional dressings are mainly used for early hemostasis, as well as for cleaning and drying wounds. However, the performance of traditional dressings is also less than ideal.[36] Their fibers tend to adhere to granulation tissue, causing pain when the dressing is removed, disrupting newly formed tissue, and delaying healing. The inflammatory phase of wound healing is often stalled in chronic wounds. The wound should be clean, have a healthy base of granulation tissue, and be free of infection to optimize cutaneous wound healing. The choice of dressing should be such that the wound is neither too moist nor too dry, and the dressing should maintain moisture in the wound.[37] Factors typically considered in the design of an ideal wound dressing include hemostatic activity to stop bleeding, prevention of microbial infection, effective absorption of wound exudate, ease of sterilization, and promotion of cutaneous wound healing. The dressing should also be gas-permeable, easy to use, biodegradable, and non-toxic.[38]

In addition, various modern dressings for wound repair have been developed and studied. Nowadays, the types of dressings used for wound repair include hydrogels, hydrocolloids, foams, and semipermeable films.[39] The main types of these dressings are natural materials, synthetic polymer materials, biological dressings and skin substitutes, and tissue-engineered skin (TES). First, natural materials are a hot topic in skin wound healing research and clinical applications, mainly including chitosan, cellulose, collagen, and hyaluronic acid. Natural macromolecular compounds offer excellent biosafety and degradability with strong physicochemical properties that promote cell growth and differentiation, regulate the wound microenvironment, and are cost-effective for wound healing and tissue repair applications.[40] In addition, studies have shown that many synthetic polymer materials and composite materials are also used in skin wound repair, such as polyvinyl alcohol, polyethylene glycol, and gelatin methacrylate acid. Moreover, biological dressings and skin substitutes are prominent research areas. Current studies focus on synthesizing and modifying biocompatible materials.[41] These materials, often derived from biopolymers such as collagen and gelatin, are engineered to enhance cutaneous wound healing by leveraging the beneficial properties of these biopolymers. Another area of research for skin repair materials is the use of TES. Bioengineered artificial skin substitutes may be able to overcome graft rejection and provide local delivery of mesenchymal stem cells (MSCs) to reduce inflammation and speed up the healing process.[42] In addition, these substitutes can facilitate the delivery of various biomolecules and cells to promote wound repair.[43,44] Furthermore, bioactive dressings can also facilitate targeted drug delivery (such as antimicrobials, anti-inflammatories, growth factors, and other bioactive substances) to specific tissues or organs.[39] In the treatment of cutaneous wounds, bioactive materials can release factors that promote skin regeneration and interact with receptors in the skin, thereby enhancing wound healing. In addition to materials such as polylactic-co-glycolic acid, polyvinylpyrrolidone, and hydrogels, nanomaterials have also gradually been applied in controlled and targeted drug delivery due to their excellent antimicrobial properties.[45,46] In addition, sustained delivery of growth factors, siRNA delivery, microRNA targeting, and stem cell therapy are new potential interventions for wound healing.[47] Although significant progress has been made in these areas, the current therapeutic outcomes remain suboptimal, possibly owing to the neglect of the important role of neurogenesis in cutaneous healing.
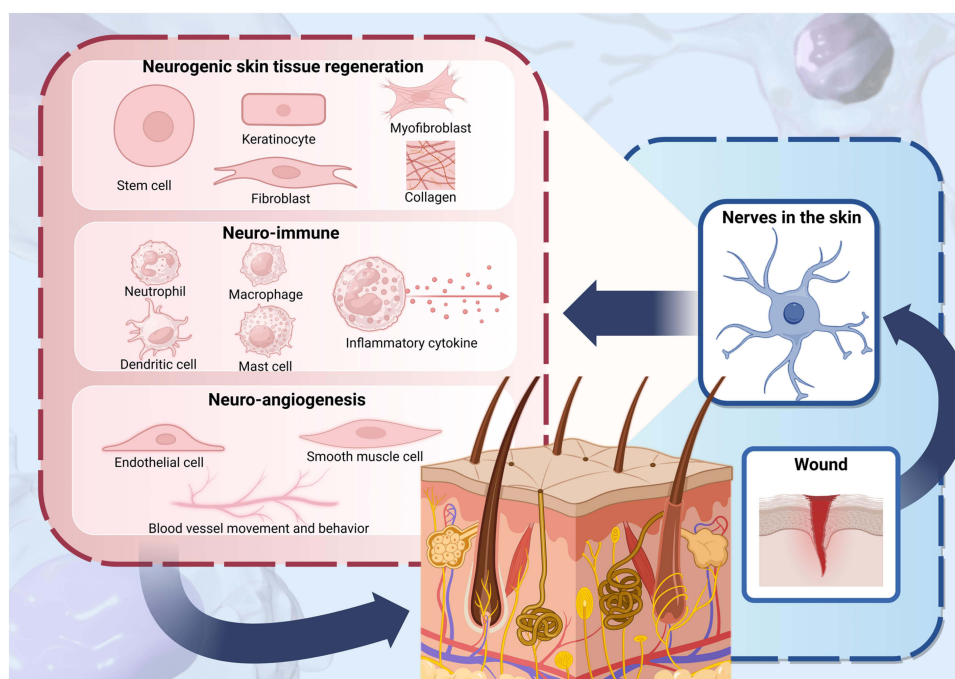
Neural Repair in Cutaneous Wound Healing and Its Functions

The skin is densely innervated by the peripheral nervous system, including afferent somatosensory and efferent autonomic components. The somatosensory system, composed of neurons in the dorsal root and trigeminal ganglia whose axons form connections between peripheral tissues and the central nervous system, detects external stimuli and transmits this sensory information. The autonomic nervous system, comprising the sympathetic and parasympathetic divisions, controls involuntary physiological functions. Its serial organization involves preganglionic neurons from the central nervous system synapsing with postganglionic neurons in the sympathetic ganglia (near the spinal cord) or parasympathetic ganglia (close to target organs).[35] The skin is densely populated with sensory nerves, categorized by diameter and conduction velocity into Aβ, Aδ, and C fibers, ranging from the largest and fastest to the smallest and slowest. These fibers enable the skin to perceive various sensations.[48–52]

The process of nerve regeneration in cutaneous wound healing involves the coordinated action of various factors and cells.[53–55] Remodeling of regenerating nerve fibers and alterations in nerve fiber density have been observed during cutaneous wound healing.[56] However, the underlying mechanisms of nerve regeneration remain unclear. Nerve regeneration is a crucial aspect of cutaneous wound healing and plays a pivotal role in regulating the process. During cutaneous wound healing, nerves, blood vessels, and the immune system interact in a triangular relationship. Nerves can directly regulate cutaneous wound healing by conducting electrical signals or by releasing relevant neurotransmitters, neuropeptides, and other substances. They can also influence cutaneous wound healing by modulating related blood vessels and the immune system (Figure 2).

Nerves or Nerve-Associated Mediators Directly Regulate Cutaneous Wound Healing

Nerves are critical to the regulation of skin functions. First, the regulation of various stem cells in the skin is under the influence of nerves. Capsaicin-induced denervation hinders the expulsion of stem cell progenitors from hair follicles, which is associated with stronger epidermal activation. These may explain the prolonged healing time in denervated skin. Thus, during cutaneous wound healing, sensory innervation might contribute to the regulation of the physiological functions of hair follicle stem cells.[16] Moreover, Chéré et al discovered that dorsal root ganglia and neuro mediators promote fibroblast and keratinocyte proliferation while modulating the collagen type I/type III expression ratio, shifting it

Figure 2 The role of nerves in cutaneous wound healing. Created in BioRender. SZ. (2025) https://BioRender.com/2h4o3hd.

toward collagen I, thereby enhancing cutaneous wound healing and restoring its original strength.[57] Additionally, tissue-resident stem cells located within the skin basement membrane exhibit significant regional heterogeneity, characterized by unique anatomical structures, transcriptional profiles, and diverse markers, while sensory innervation is crucial for establishing their diverse molecular characteristics and lineage potentials.[58] During acute wound healing, the release of pain mediators facilitates the initiation and progression of the inflammatory phase, while also promoting the migration of various cells and collagen production, thereby accelerating wound healing.[59] These studies demonstrate that nerves play a crucial regulatory role in skin homeostasis and post-traumatic repair, with specific mechanisms related to the actions of nerve cells and associated neurotrophic factors.

Nerves and nerve-related cells can directly regulate the healing of cutaneous wounds. Neurons contribute to the regulation of collagen formation and alignment in the skin. Through interactions with fibroblasts, they influence fibroblast differentiation into myofibroblasts and modulate collagen dynamics.[60] Schwann cells (SCs) are essential for myelination and nerve repair in cutaneous wounds. They promote fibroblast generation and myofibroblast differentiation via TGF-β signaling. Additionally, glial cells support repair through paracrine signaling, influencing ECM remodeling, angiogenesis, and immune cell chemotaxis, all of which are crucial for wound healing.[61]

Neurotransmitters, neuropeptides, neurotrophic factors, and related neuroactive substances contribute to the regulation of cutaneous wound healing. Vasoactive intestinal peptide (VIP), calcitonin gene-related peptide (CGRP), neurotrophic factors such as nerve growth factor (NGF) and brain-derived neurotrophic factor, and neurotrophins are reported to enhance fibroblast functions under in vitro conditions, in skin explants, and in vivo studies of wound healing.[62] CGRP has been demonstrated to facilitate cutaneous wound healing.[13] CGRP and endothelin's receptor, Calcrl, is expressed in dermal basal layer stem cells in a nerve fiber-dependent manner, which highlights a significant interaction between neuronal components and the epidermis.[63] In an innervated skin model, human CGRP significantly enhanced keratinocyte proliferation and epidermal thickness, indicating its crucial role in regulating epidermal morphogenesis, while substance P (SP) had a minimal effect.[64] Additionally, CGRP promotes the production and release of mature and immature NGF in cultured human keratinocytes, indicating its role in regulating cell survival during wound healing.[65] Besides CGRP, VIP and NH-2 VIP derivatives promote human keratinocyte proliferation and migration through a cAMP-dependent signaling pathway.[61] NGF also plays a regulatory role in cutaneous wound healing. NGF regulates cutaneous wound healing by exerting various biological effects through its receptors, such as stimulating keratinocyte proliferation, inducing wound contraction and extracellular matrix remodeling, and accelerating wound closure.[66] NGF promotes dose-dependent keratinocyte proliferation and enhances their migration at the wound margins. Additionally, keratinocytes secrete active NGF, establishing an autocrine regulatory mechanism.[55] Furthermore, NGF induces myofibroblast differentiation and collagen synthesis through the NGFR-F-actin-MRTF-A signaling pathway, facilitating tissue contraction and matrix reorganization.[67] Other studies indicate that the use of NGF-incorporated collagen as a localized treatment accelerates excision wound recovery.[68] SP promotes neurite extension, increases vascular permeability and dilation, drives new blood vessel formation, and supports endothelial cell differentiation and growth. Moreover, it enhances the proliferation of human and murine keratinocytes through NGF release, acting through both direct and indirect mechanisms.[13] SP has a significant promoting effect on skin healing.[69] SP and neurokinin A have been shown to directly upregulate NGF mRNA expression and promote the secretion of bioactive NGF in human and mouse keratinocytes. Neurokinin A further amplifies NGF expression and release in both in vitro and in vivo models, contributing to the formation of a positive feedback mechanism.[70] The delay in cutaneous wound closure caused by morphine is attributed to the suppression of SP and neurokinin A release at the wound site, a process associated with decreased NK-1R expression.[71] Besides, SP influences collagen breakdown in wounds by enhancing matrix metalloproteinase-2 (MMP-2) function within fibroblasts, thereby participating in the process of cutaneous wound healing.[72] Neurotrophin-3, a critical "epi heliotropin" in the human epidermis, functions through both paracrine and autocrine mechanisms, playing a key role in maintaining skin homeostasis and facilitating cutaneous wound healing.[13] In addition, 5-hydroxytryptamine significantly contributes to promoting cutaneous wound healing. The role of neuro-related factors, however, may differ depending on wound conditions. For instance, extensive research highlights the role of SP in impaired cutaneous wound healing in diabetic individuals, whereas CGRP appears to exert no significant effect on this process.[73]

Sensory neurons contribute significantly to cutaneous wound healing, although their role is not indispensable, even in the absence of the immune system.[69] However, innervation can make the cutaneous wound healing process optimal, improve the quality of healing, and restore more skin functions.

Nerves Promote Cutaneous Wound Healing by Neuro-Immune Regulation

Inflammation is crucial for normal cutaneous wound healing, with nerves modulating the inflammatory response to impact the healing process. Cutaneous nerve fibers engage with the immune system by releasing neurotransmitters, which bind to specific receptors on skin target cells, including mast cells, macrophages, neutrophils, and dendritic cells. These interactions affect various processes, both physiological and pathological, involving cellular behavior, immunity, and leukocyte recruitment, ultimately promoting cutaneous wound healing.[74] Transient receptor potential vanilloid 1 (+) and voltage-gated sodium channel nav1.8-positive nociceptors (+) nociceptors modulate the IL-23/IL-17 pathway and regulate skin immune responses by interacting with dendritic cells.[75] CGRP modulates neutrophils and macrophages via receptor activity-modifying protein 1, inhibiting recruitment, promoting cell death, enhancing phagocytosis, and polarizing macrophages for tissue repair through thrombospondin-1 release and autocrine/paracrine effects.[76] SP facilitates the synthesis and release of pro-inflammatory cytokines (IL-1, IL-6, TGF-α) by keratinocytes, stimulates mast cell degranulation and TNF-α release, enhances IL-8 release from endothelial cells, and increases the production of cytokines in leukocyte subpopulations, with many effects reliant on the nitric oxide pathway, which is vital for effective cutaneous wound healing and repair.[13] Acetylcholine acts as an immune modulator, inhibiting macrophages via cholinergic anti-inflammatory pathways. Several nicotinic acetylcholine receptor (nAChR) agonists have been developed to treat subcutaneous inflammation, as nAChRs on macrophages influence immune regulation and inflammatory processes, while keratinocytes produce non-neuronal acetylcholine.[49] Another study demonstrates that non-peptidergic Gα-inhibiting protein interacting protein-positive skin sensory neurons regulate immunity during tissue repair by producing TAFA4, which enhances IL-10 production in dermal macrophages, supports the survival of TIM4+ macrophages, and inhibits inflammatory macrophage amplification, ultimately promoting cutaneous wound healing.[15]

Nerves Promote Cutaneous Wound Healing by Enhancing Angiogenesis

Angiogenesis is vital for the regeneration of new tissue in wound beds and is a key factor in the wound healing process. First, the arrangement of blood vessels is related to nerves. A study reveals that neurovascular alignment depends on the G protein-coupled receptor signaling pathway involving the neurogenic ligand Cxcl12 and its receptor Cxcr4, with genetic inactivation of this pathway disrupting neurovascular alignment and abolishing angiogenesis. In vitro experiments further demonstrate that Cxcl12 recruits blood vessels to nerves, while VEGF-A facilitates arterial differentiation.[14] Another study revealed that VEGF is essential for sensory neurons or SCs to induce arterial marker expression in isolated embryonic endothelial cells. This indicates that peripheral nerves serve as a blueprint for the organotypic organization of vascular branching and arterial development in the skin through localized VEGF secretion. Neuro-related substances can also directly regulate the formation of blood vessels. For example, NGF modulates VEGF expression via the PI3K/mTOR signaling pathway in human HaCaT keratinocytes.[77] NGF stimulates VEGF production through TrkA receptors in endothelial cells. It enhances endothelial cell invasion and cord formation by upregulating matrix MMP-2 and the activating protein-2 transcription factor via the PI3K/Akt pathway, thereby promoting angiogenesis.[78] CGRP promotes angiogenesis and prolongs vasodilation in cutaneous wound healing, enhancing dermal endothelial cell proliferation and acting as a potent vasodilator with lasting effects across species, including humans.[13] Interestingly, some neuro-related substances have a dual role in blood vessel formation, such as dopamine. This difference is likely related to the type of dopamine receptor that is activated in target cells.[79] In summary, neurovascular interactions play a critical role in angiogenesis and wound healing, with nerves providing templates for vascular branching and neuro-related substances, such as VEGF, NGF, and CGRP, regulating blood vessel formation through diverse signaling pathways. These findings highlight the complex interplay between the nervous and vascular systems in tissue regeneration.

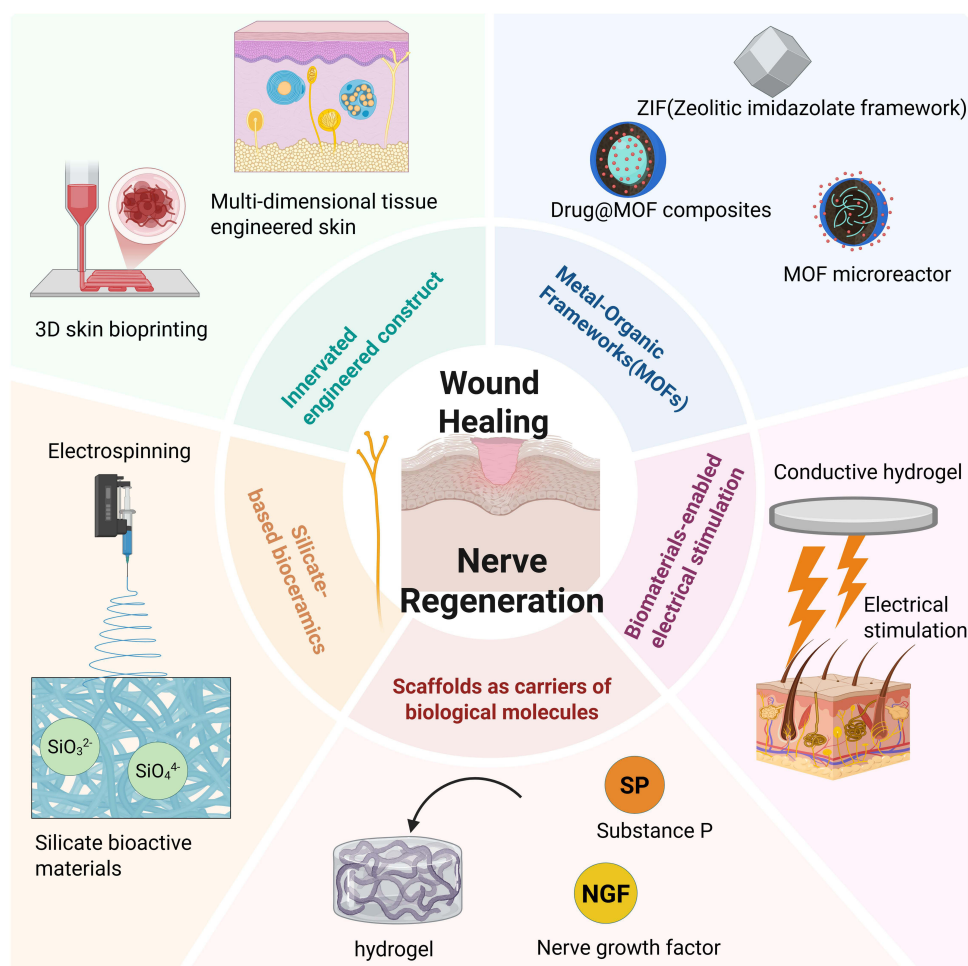# Innervated Biomaterials for Improved Cutaneous Wound Healing

Large and chronic wounds often struggle to heal on their own due to continuous inflammatory stimulation. Currently, the repair of nerves and their role in facilitating wound healing are frequently overlooked.[1] However, as previously discussed, nerve repair in the skin may promote cutaneous wound healing remarkably by regulating inflammation or vascularization.[80] Consequently, an increasing number of researchers are focusing on wound healing materials that can promote neurogenesis, including materials capable of generating electrical stimulation, metal-organic frameworks (MOFs), scaffolds as carriers of biological molecules, innervated engineered construct, and silicate-based bioceramics (Figure 3). Table 1 summarized representative innervated materials and their effects on cutaneous wound healing.

Biomaterials-Enabled Electrical Stimulation for Cutaneous Wound Healing

Biomaterials-enabled electrical stimulation is beneficial to wound healing and can stimulate neurite extension and nerve formation.[100,101] There are different types of biomaterials-enabled electrical stimulation such as conductive materials and electroactive materials. A wealth of researchers have reported the use of biomaterials-enabled electrical stimulation as a potential wound-healing material in both preclinical and clinical cases, especially in large and chronic wounds.[84,102,103]

External Electrical Stimulation Treatment Devices

During cutaneous wound healing, researchers demonstrated that external electrical stimulation can expedite the proliferation and migration of fibroblasts, augment nerve regeneration, and thereby enhance functional restoration post-injury. A conductive hydrogel combined with external electrical stimulation was developed by Guan et al, which significantly

Figure 3 Innervated biomaterials for improved cutaneous wound healing. Created in BioRender. ab, i. (2025) https://BioRender.com/vgw2cpt.

Table 1 A Summary of Innervated Materials and Their Effects on Cutaneous Wound Healing

Type		Components	Biological Effects	Advantages and Disadvantages	Refs
Biomaterials-enabled electrical stimulation	External electrical stimulation treatment devices	AgNPs@PDA, CNC/PPy, and polyvinyl alcohol	Antibacterial activity, nerve repair, M2 macrophage polarization, angiogenesis	• Allows precise control of electrical parameters • Suitable for large and chronic wounds • Promotes cell proliferation and migration effectively • Bulky and inconvenient to transport • Limited to specific treatment locations	[81]
	Conductive materials	AgNPs@PDA, CNC, PPy, PVA	Schwann cell proliferation, macrophage phenotype restoration, ROS scavenging, antibacterial efficacy	• Promotes efficient cell communications • Mimics endogenous bioelectric fields • Suitable for nerve regeneration • Potential biocompatibility risks • Requires power sources for operation	[82]
		GelMA, OCS, OCS-PPy NPs	Neurovascular regeneration, Collagen synthesis		[83]
	Electroactive materials	Flexible TENG, Bioadhesive	Nerve stimulation, accelerated cell migration and proliferation, and hemostasis	• Self-powered and biocompatible • Enables non-invasive or minimally invasive treatments • Can be used for precise wound healing benefits • Limited penetration depth for light-based materials • Unpredictable output in static wounds • Long-term effects and scalability need further research • Complex biological systems may affect energy control	[84]
		PVDF-TrFE electrospun scaffolds	Promotes SCs elongation and sensory neuron extension		[85]
		One-dimensional TiO_2/Bi_2S_3 QDs nanotubes	Nerve reinnervation, immune modulation		[86]
		Flexible piezoelectric generator and conductive gel	Nerve regeneration, sensation restoration		[87]
		Microporous structure scaffolds, Nanosheets	Macrophage phenotype, angiogenesis, ROS scavenging, tissue remodeling		[88]
Scaffolds as carriers of biological molecules	SP	Chitosan hydrochloride conjugated with SP	Neurite outgrowth, nerve regeneration, extracellular matrix deposition and remodeling	• Enables precise delivery and sustained release of multiple bioactive substances • Mimics natural extracellular matrix • Enhances cell adhesion and proliferation • Needs to address the stability of incorporated factors • Require complex fabrication processes • Degradation byproducts that may affect healing • Potential for fibrosis or tissue overgrowth at the scaffold site	[89]
	NGF	NGF-β fused with CBD	Nerve growth, re-epithelialization, capillary lumen formation		[90]
		PEI-plasmid NGF/ANG nanoparticles	Nerve regeneration, angiogenesis, and functional skin repair		[91]
	Exosomes	Chitosan/silk hydrogel sponge loaded with GMSC-derived exosome	Re-epithelialization, collagen deposition and remodeling, enhances angiogenesis and neuronal ingrowth		[92]
	Other Growth Factors	Collagen-chondroitin sulfate scaffold functionalized with SDF-1α gene	SCs differentiation, neuroregeneration, and endothelial angiogenesis		[93]
		CBPGCTS–SF@PRP hydrogel	Proliferation of repair cells, collagen deposition, angiogenesis, and nerve repair		[94]

(Continued)

Table 1 (Continued).

Type	Components	Biological Effects	Advantages and Disadvantages	Refs
MOFs	MOF, neuroblastoma cell membrane, neural-associated intracellular proteins	Peripheral nerve regeneration, hair follicle niche formation, and suppressed local inflammation	• Exhibits multifunctionality in treatment approaches • Offers high porosity and surface area for therapeutic proteins loading • Potential issues with biocompatibility and biodegradability • Complex synthesis and functionalization processes • Limited understanding of long-term effects in vivo	[95]
	NGF/Ce-UiO-66	ROS scavenging, reduced inflammation, recovery of skin neuroendocrine system, and nerve recovery		[96]
Silicate-based bioceramics	CuCS/Cur	Nerve-related factor expression, neural network reconstruction, angiogenesis stimulation	• Promotes rapid wound healing through bioactive ion release • Integrates well with host tissues for long-term functional recovery • Possible immune responses to degradation products • Challenges in achieving uniform ion release over time	[97]
	Bioactive nanofibrous scaffolds and Zn_2SiO_4 nanoparticles	Angiogenesis, neurogenesis, re-epithelialization, and vascularization		[98]
Innervated engineered construct	iPSC-derived sensory neurons, SCs, and innervated TES	Neurite network formation, axonal migration, and cutaneous neuroinflammation study	• Provides a platform for studying skin neuroinflammation and neuronal roles in skin physiology/pathology • Potential to create skin models with neural networks • Allows for precise control over cell differentiation and tissue formation • Limited clinical translation • Potential variability in tissue regeneration. • Research is still inadequate.	[99]

promotes neuroregeneration in diabetic wounds.[81] However, external electrical stimulation treatment devices are bulky and inconvenient to transport, limiting treatment to specific locations like hospitals.

Conductive Materials

Numerous studies have adequately demonstrated that hydrogels that can conduct electricity help cells send signals to each other more easily, which speeds up the healing of large and chronic wounds and injuries to peripheral nerves.[104,105] The combination of conductive polymers with hydrogels enables the development of conductive hydrogels that possess tissue-matched conductivity and mechanical properties, making them suitable for nerve regeneration. Bi et al developed a versatile hydrogel that combines antioxidant properties, photothermal therapy, curcumin release, and electrical conductivity. This hydrogel releases curcumin that can enhance the migration and proliferation of Sc, and also facilitate myelin regeneration in diabetic wounds by regulating SOX10 and myelin-forming genes, thereby promoting the overall repair process.[82] In another study, conductive hydrogels boost neuronal and vascular regeneration by elevating intracellular Ca^{2+} and stimulating PI3K/AKT and MEK/ERK pathways (Figure 4F and H). They accelerated full-thickness diabetic wound healing within 14 days via neuronal and vascular regeneration and collagen deposition (Figure 4G).[83]

Conductive materials could mimic endogenous bioelectric fields and showed significant wound healing potential, highlighting their suitability for wound treatment. Nevertheless, the incorporation of conductive components (carbon nanotubes, polypyrrole et al) might have potential biocompatibility risks. Meanwhile, the conductive materials require power sources, which is inconvenient. To overcome these limitations, electroactive materials such as photoelectric, triboelectric, and piezoelectric materials have been engineered to facilitate electric stimulation, offering a more convenient and accessible treatment option.

Electroactive Materials

Firstly, triboelectric nanogenerators are recognized for their biocompatibility, miniaturization, and ability to produce stable electrical outputs, making them ideal for energy harvesting medical healthcare. Qian et al designed a bioadhesive triboelectric nanogenerator that possesses the potential to be utilized not only in wound treatment but also for nerve regeneration.[84]

Secondly, low-intensity pulsed ultrasound-based electrical stimulation, a non-invasive approach, offers precise wound healing benefits. In the study by Westphal et al, ultrasound was used to enhance SC elongation and sensory neuron extension in skin-tissue engineering.[85] In another study, Wang et al employed ultrasound to rapidly eliminate 94.2% of Staphylococcus aureus and utilized piezoelectric microfibers to promote wound healing and promote nerve vascularization.[103] Besides, a recent study demonstrated that low-frequency ultrasound-driven MXene/PVDF films can enhance axonal regeneration and promote M2 macrophage polarization in diabetic wounds, accelerating healing and restoring sensory function through neuro-immune regulation.[106]

Subsequently, the photoelectric effect is utilized to precisely treat wounds and promote nerve repair by adjusting the intensity and frequency of light to act on specific areas.[107,108] Qiao et al proposed one-dimensional TiO_2/Bi_2S_3 QDs nanotubes with high photoelectric properties excited by visible red light.[86] This photoelectric therapy offers an advantageous electrophysiological milieu conducive to neuronal differentiation and axon growth. In the TBCHA+L phototherapy group, a significant expression of β-3 tubulin and α-smooth muscle actin markers was observed on day 14, indicative of nerve fiber regeneration and the re-establishment of the epithelial neural network.

In addition, Tan et al developed a self-powered patch using a flexible piezoelectric generator and conductive gel (Figure 4A), which can foster skin repair and nerve regeneration by delivering biological-electrical signals in the program.[87] This advancement was attributed to the synergistic interplay between neuro-directed glial cell-derived exosomes and electrical stimulation (Figure 4B and C). The combination of these elements fostered an environment conducive to the substantial promotion of MSC differentiation towards a neuronal lineage and the generation of new neurons (Figure 4D and E).

Finally, leveraging intrinsic bioelectric fields offers a self-sustaining approach for chronic wound management. Liu et al developed an MXene-integrated decellularized scaffold that established a neuro-immunoregulatory microenvironment through endogenous ion flow.[88] It achieving 96.9% diabetic wound closure within 14 days via macrophage
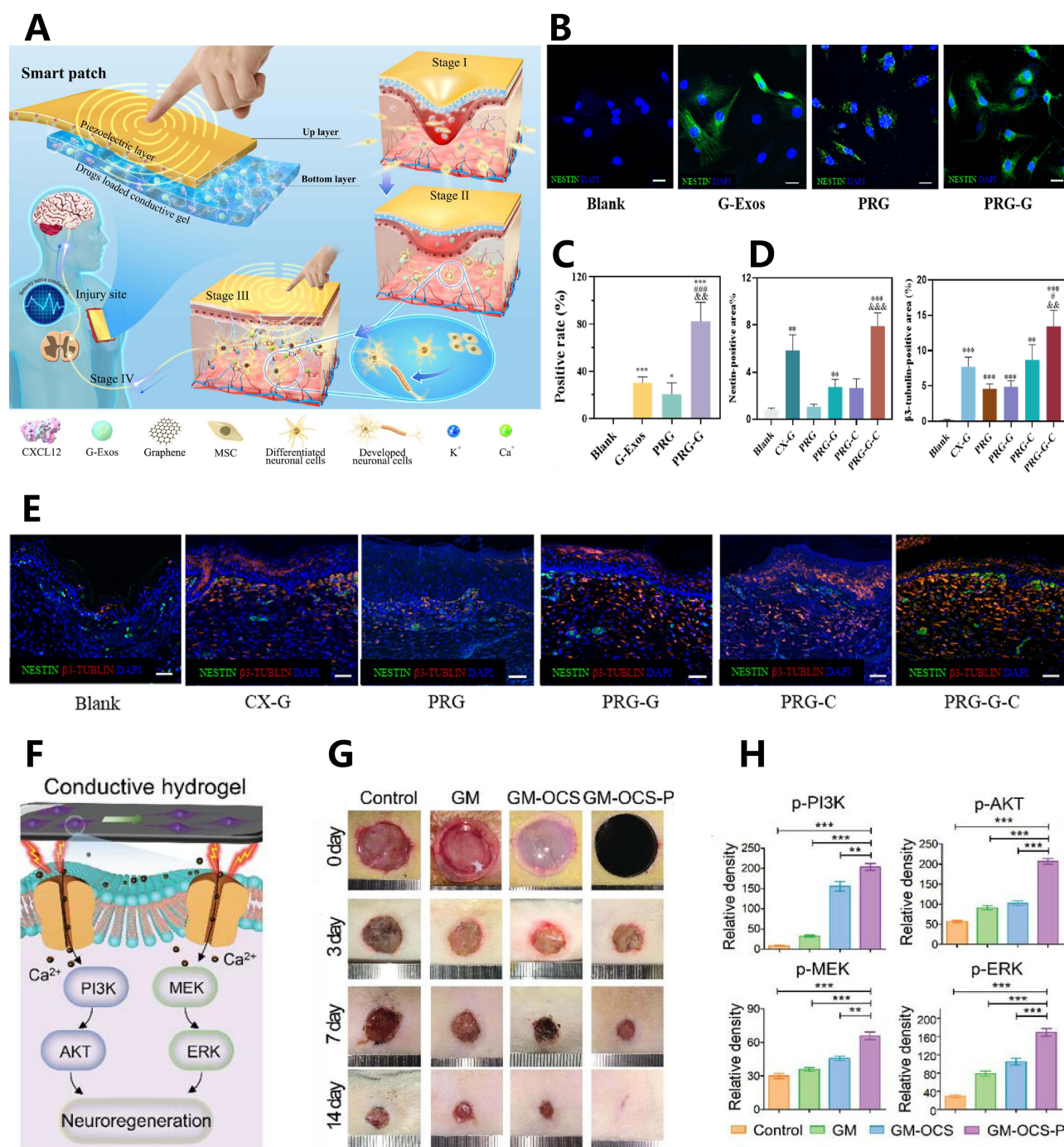
Figure 4 (**A**) Hierarchical architecture of PRG-G-C and its stimulation in endogenous stem cells based neural restoration and sensory function recovery. (**B**) Immunofluorescence staining of nestin expression (green fluorescence) by bone mesenchymal stem cells cultured with PBS (Blank). Scale bars indicate 10 μm. (**C**) for 7 days and semi-quantification of nestin-positive cells. (**D**) Semi-quantification of nestin and β3-tubulin expression rates in the healed skins. (**E**) Immunofluorescence staining of nestin (green) and β3-tubulin (red) in healed skins on day 15 post-treatment. Scale bars indicate 50 μm. Statistical significance is indicated as * p < 0.05, **p < 0.01, ***p < 0.001 Blank group. #p < 0.05, ##p < 0.05, ###p < 0.001 versus G-Exos group. & p < 0.05, && p < 0.01, &&& p < 0.001 versus PVDF group. Adapted from *Biomaterials*, volume: 283. Tan MH, Xu XH, Yuan TJ, et al. Self-powered smart patch promotes skin nerve regeneration and sensation restoration by delivering biological-electrical signals in program. 121413. Copyright 2022, with permission from Elsevier.[87] (**F**) Schematic illustration of the mechanism of conductive hydrogel promoting neuroregeneration. (**G**) Photographs of skin wounds at days 0, 3, 7, and 14 in different groups. (**H**) Quantitative analysis of protein expression (n = 3) (* p < 0.05, ** p < 0.01, *** p < 0.001). Adapted from Fan L, Xiao C, Guan P, et al. Extracellular matrix-based conductive interpenetrating network hydrogels with enhanced neurovascular regeneration properties for diabetic wounds repair. *Adv Healthc Mater*. 2022;11(1):e2101556. © 2021 Wiley-VCH GmbH.[83]

reprogramming, ROS clearance, and angiogenesis activation. This endogenous electrotherapy bypasses the need for external devices while facilitating neural-immune crosstalk, presenting strong translational potential for electrosensitive tissue regeneration through autonomous bioenergy utilization.

These innovative biomaterials and therapeutic approaches leverage physical stimuli like triboelectricity, ultrasound, photoelectric effects, piezoelectricity, and intrinsic bioelectric fields to enhance wound healing and nerve regeneration. Key features include biocompatibility, precise electrical signal generation or delivery, and sometimes self-powering capabilities, enabling non-invasive or minimally invasive treatments. But visible/NIR light cannot reach deep wounds, which might have limited photoelectric effect. Charge generation depends on unpredictable wound movement, which might resulted in unreliable output in static wounds. Furthermore, these methods promote tissue repair by influencing cell behavior, further research is necessary to fully understand long-term effects, improve scalability and cost-effectiveness, and achieve precise energy control within complex biological systems.

Scaffolds as Carriers of Biological Molecules

Bioactive molecules such as neurotrophins, and growth factors within the neural tissue exert their effects through complex signaling pathways, which in turn enhances the nutritive supply and repair processes at the wound site.[80,109] However, due to the transient half-life of these molecules, many studies have employed scaffolds to deliver these factors effectively.[110,111] Scaffolds provide not only structural reinforcement at the wound site but also serve as vehicles for sustained delivery of growth factors and cytokines, thus creating a conducive atmosphere for tissue regeneration. Neurotransmitters, neuropeptides, neurotrophic factors, and other neuro-related substances that could play regulatory roles in cutaneous wound healing were fabricated into scaffolds to achieve enhanced cutaneous wound healing.

Substance P (SP)

Accumulating evidence has supported that SP stands as a prominent neuropeptide among those secreted by nerve fibers in reaction to damage, which accelerates wound healing by regulating the inflammatory phase.[112] Whereas the application of SP is significantly hindered by its low stability and susceptibility to oxidative degradation during manufacturing, transit, and preservation processes. Therefore, the incorporation of SP into scaffold materials, such as hydrogels, can enhance their bioavailability.[111,113] A multifunctional SP-conjugated chitosan hydrochloride hydrogel was designed by Li et al and used for the loading and release of SP.[89] In vivo, the material significantly enhances vascularization, extracellular matrix deposition and remodeling, and nerve regeneration, thus facilitating effective healing of full-thickness skin defects. Moreover, the hydrogel formulated with 10^{-5} M SP facilitated 98% wound closure within 16 days, whereas the comparator sample failed to achieve complete re-epithelialization during the same period.[114]

Nerve Growth Factor (NGF)

NGF plays a crucial role in the differentiation, regeneration, and repair of both the central and peripheral nervous systems. Consequently, numerous researchers have developed materials loaded with NGF, aiming to facilitate neural repair and regeneration. Furthermore, researchers have discovered that NGF may accelerate wound healing by promoting angiogenesis, stimulating keratinocyte proliferation, and enhancing neuroregeneration.[115]

So far, several works have been done about the application of NGF for angiogenesis to the wound. Keykhaee et al have fabricated a multifunctional hydrogel combining alginate, gum arabic, and specially designed mesoporous silica nanoparticles loaded with NGF, forming SiNGF.[116] The hydrogel, AG-Car/SiNGF, sustains NGF release over 21 days, ideal for diabetic wound healing. Histological results show it improves re-epithelialization, collagen deposition, and neovascularization, with enhanced TGF-β expression and nerve neurofilament. This composite system holds promise for treating large and chronic wounds. Furthermore, with peripheral nerve growth, scaffolds impregnated with collagen-binding human NGF-beta effectively expedite ulcer repair.[90] Recent advancements in NGF-based therapies demonstrate enhanced neurovascular regeneration through biomaterial innovation. Yang et al developed a dual-gene activated dermal scaffold delivering NGF/ANG via PEI-chimeric plasmid nanoparticles in PLGA/collagen-chitosan scaffolds. This system achieved 3.9× greater nerve density and complete wound healing within 10 days by synergistically upregulating β3-tubulin/PGP9.5 neural markers and CD31/α-SMA vascular markers. Notably, it restored physiological sensory

thresholds through Piezo2-mediated mechanotransduction, outperforming single-factor systems by addressing neurovascular interdependence - a critical advancement for functional tissue regeneration.[91]

Exosomes

Exosomes secreted by cells are vesicles with a variety of functions. Research has shown that somatic stem cells can promote wound healing and skin regeneration by facilitating the proliferation and migration of epithelial cells, enhancing angiogenesis, and aiding in neural repair.[117–121]

In the study of Shi et al, they extract exosomes originating from gingival mesenchymal stem cells (GMSCs) and incorporate these GMSC-derived exosomes into the hydrogel for the purpose of administering them directly to wounds.[92] In diabetic rats, GMSCs embedded within the hydrogel secrete NGF, thereby enhancing neuronal growth and regeneration, and increasing neural density. Simultaneously, GMSCs foster angiogenesis and collagen regeneration, collectively contributing to accelerated chronic and large wound healing.

Other Growth Factors

Among growth factors, VEGF plays a pivotal role in promoting angiogenesis and is one of the extensively studied stimulatory factors in the wound healing process.[122] Recent research underscores the importance of considering the angiogenic potential of nervous system cells, such as Schwann cells (SCs).[93] By genetically activating SCs on scaffolds with stromal cell-derived factor-1α (SDF-1α), SCs overexpressing SDF-1α subsequently produce higher levels of VEGF, enhancing endothelial angiogenesis and promoting a repair phenotype in SCs. These findings suggest that neuronal system cells can facilitate comprehensive vascular formation and regeneration through the expression of angiogenic factor genes, thereby accelerating the healing of large and slow-healing wounds.

Besides, platelet-rich plasma hydrogel (PRP gel), made from fibrin glue mixed with PRP and thrombin/calcium, treats diabetic wounds. Extracted from whole blood, it contains platelets and bioactive molecules like exosomes, NGF, and Platelet-derived growth factor, aiding wound healing.[123–125] Due to PRP gel's instability and rapid degradation, its efficacy in treating chronic diabetic wounds was limited. Therefore, Qian et al developed a self-healing, injectable hydrogel (CBPGCTS-SF@PRP) combining chitosan, silk fibroin, and PRP. This hydrogel protects PRP from degradation, enabling sustained release and enhancing MSC chemotaxis.[94] It accelerated collagen deposition, angiogenesis, and nerve regeneration in skin defect rat models, enhancing wound healing.

Metal-Organic Frameworks (MOFs)

MOFs have emerged as promising tools in promoting wound healing through their versatility.[126,127] In the context of deep burns, a neuro-inspired biomimetic microreactor, termed Neuro-MOF, has been designed to emulate the outer membrane of neuroblastoma cells that enables immune evasion, as well as neural-related intracellular proteins.[95] This microreactor, mounted on a MOF and coated with a membrane of neuroblastoma cells, effectively triggers the release of therapeutic proteins upon near-infrared light excitation. These proteins help compensate for enduring skin neurological damage, initiating peripheral nerve regeneration and hair follicle niche formation. In mouse models, Neuro-MOF demonstrated significant functional skin regeneration effects, especially in the restoration of sensation and hair follicle neogenesis, highlighting its potential in large and chronic wound therapy targeting sensory nerves.

Moreover, MOFs have also shown efficacy in treating diabetic ulcers, where peripheral neuropathy and extreme ROS due to diabetes hinder wound healing.[96] A nanoscale MOF loaded with nerve growth factor (NGF/Ce-UiO-66 or NGF/CU) has been created to address this issue. The Ce-UiO-66 component acts as an oxidation Inhibitor, scavenging ROS and reducing inflammation, while NGF aids in nerve regeneration in the skin. Experiments confirmed the efficacy of NGF/CU in promoting diabetic ulcers healing in vivo and in vitro. RNA sequencing analysis further showed that NGF/CU improves wound healing by suppressing the NF-κB signaling route and restoring the neuroendocrine system of the skin.

In conclusion, MOFs exhibit neuro-inspired potential in wound healing through targeted delivery of therapeutic proteins and antioxidants, enhancing nerve regeneration and reducing inflammation.[128] These findings open new avenues for the treatment of burns and diabetic ulcers, offering promising strategies for neural regulation in wound management.

Silicate-Based Bioceramics

Silicate-based bioceramics represent a promising category of materials for wound dressings, owing to their ability to expedite wound healing processes through the modulation of endothelial cells, dermal fibroblasts, macrophages, and epidermal cells. Notably, silicate-based bioceramics can undergo further functional enhancement through specific structural designs or the incorporation of functional components.[129–131]

Zhang et al developed a wound dressing, created through electrospinning, comprised of calcium silicate enriched with copper and Cur, referred to as CuCS/Cur.[97] The Cu^{2+}-Cur chelate exhibited exceptional neuro-inductive properties, facilitating the transformation of neuronal cells derived from hair follicles into fully functional neural networks. Furthermore, the Cu^{2+}-Cur chelate demonstrated remarkable angiogenic potential and provided abundant nutrition for wound regeneration, hair follicle regeneration, and neural regeneration.

In another research, the treatment of severe burn injuries, was addressed through the use of Zn_2SiO_4 nanoparticles-incorporated bioactive nanofibrous scaffolds.[98] The Zn_2SiO_4 nanoparticles, synthesized via a facile hydrothermal way and incorporated into the scaffolds, exhibited excellent angiogenic and neurogenic activities in vitro. Results further demonstrated that these scaffolds, through Zn_2SiO_4 nanoparticles releasing bioactive Zn and Si ions, promoted wound healing with skin regeneration, nerve repair, and vascularization in vivo.

Innervated Engineered Construct

Engineered construct is composed of an artificial extracellular matrix as a scaffold, and cells are mounted on it. Through the incorporation of cytokines and stem cells, tissue-engineered skin(TES) facilitates optimal tissue repair and regeneration of full-thickness wounds. Studies showed that in vitro, SCs significantly enhance sensory neuronal outgrowth in 3D dermal models, doubling that of controls. SCs spontaneously co-localize with neuronal outgrowth and form myelin sheaths, observed via transmission electron microscopy. In vivo, reconstructed skin enriched with SCs, transplanted onto nude mice, increased neuronal migration by 1.8-fold and 1.7-fold at 60 and 90 days, respectively. These SC-enriched reconstructed skin samples exhibited similar current perception thresholds for large myelinated Aβ sensory fibers to normal skin, unlike controls. This suggests that SCs in engineered skin enhance neuronal migration, promote myelination, and restore neural function in vivo.[132]

To further investigate, researchers developed neuronal TES models initially using murine sensory neurons. To create fully human TES, they differentiated induced pluripotent stem cells (iPSCs) from human skin fibroblasts. After 19 days, differentiated sensory neurons expressed markers like BRN3A and β3-tubulin, and responded to stimuli by releasing neuropeptides. SCs, essential for neuronal function, were also differentiated from human iPSCs. In TES models with additional month-long culture, iPSC-derived neurons formed neuronal networks spanning the entire TES to the epidermis, only when combined with mouse or iPSC-derived SCs. This human TES model is significant for studying skin neuroinflammation.[99]

In conclusion, by utilizing SCs and iPSC-derived neurons, researchers can create skin models with neural networks, crucial for studying skin neuroinflammation and neuronal roles in skin physiology/pathology. With further research, neuronal TES could emerge as a novel treatment for large and chronic wound healing.

Conclusions and Future Prospects

Innervated biomaterials serve as an effective method capable of improving cutaneous wound healing.[111,128] This review briefly demonstrates the course of cutaneous wound healing and the materials commonly applied for cutaneous wound healing in medical practice. By emphasizing the function of nerve repair in wound healing, it highlights the potential role of innervated materials in wound healing. This review summarizes the design of innervated wound healing biomaterials by researchers in the areas of electrical stimulation, biomolecule delivery, MOFs, silicate-based bioceramics, and engineered constructs.

Despite promising preclinical results in select innervated biomaterial systems for accelerating cutaneous wound repair, significant translational barriers persist, including unresolved biocompatibility concerns, inconsistent neuromodulatory efficacy, and limited mechanistic understanding of neuro-immuno-regenerative crosstalk, which collectively underscore the imperative for systematic multidisciplinary investigations to advance these technologies toward clinical viability. Future research can be conducted in the following aspects:

1. The development of cutaneous wound healing materials with desirable therapeutic effects requires an in-depth understanding of several important issues. Current research mainly centers on materials that can simultaneously promote neurogenesis and wound healing. However, there is insufficient evidence to show how these materials facilitate the wound-healing process through neuronal pathways. It is important to gain a deeper understanding of the specific mechanisms by which nerves promote cutaneous wound healing. Therefore, future studies are required to provide more detailed proof of how innervated biomaterials accelerate wound healing. Meanwhile, although regeneration of cutaneous sensory nerves is essential to restore sensory function, regeneration of tactile and pain nerves also contributes to enhancing the quality of patients' lives. The precise mechanism by which tactile and pain nerves contribute to the improvement of wound healing remains unknown.

2. While innervated biomaterials hold promise for enhancing cutaneous wound healing by mimicking neural-electrical microenvironments, their biosafety remains a critical concern. Current biocompatibility evaluations often focus on short-term in vitro cytocompatibility and basic inflammatory responses in vivo. However, comprehensive assessment of their long-term biosafety in physiological environments is still lacking. Beyond localized inflammation and histological analysis of major organs, the fate, distribution, and degradation behavior of these materials—particularly conductive or piezoelectric components (eg, polymers or ceramics used to enable neural interfacing)—must be rigorously evaluated. For instance, piezoelectric additives or electroactive polymers, though beneficial for electrical stimulation, may raise concerns about chronic toxicity, bioaccumulation, or adverse immune reactions if degradation products persist in tissues. Advanced characterization tools, such as high-throughput screening and real-time biodistribution tracking, could provide multidimensional insights into systemic biosafety. Additionally, the interplay between material properties (eg, stiffness, electrical cues) and neural tissue remodeling requires careful optimization to avoid unintended neurotoxicity or dysregulated regeneration. Addressing these challenges will bridge the gap between innovative design and clinical translation, ensuring that innervated biomaterials achieve both therapeutic efficacy and long-term safety in wound healing applications.

3. Despite their potential to revolutionize cutaneous wound healing, innervated biomaterials face significant barriers in clinical translation. A primary challenge lies in the complex synthesis and scalability of components (eg, piezoelectric ceramics or conductive polymers) often integrated into these systems. Developing low-cost, eco-friendly synthesis strategies to ensure reproducible physicochemical properties is critical for regulatory approval and commercialization. From a translational perspective, most studies on innervated biomaterials are confined to small animal models (mice, rats), which fail to replicate human anatomical complexity, biomechanical stresses, or chronic wound healing dynamics. Transitioning to large-animal preclinical trials (eg, porcine models) is essential to validate safety, dosing, and functional efficacy under clinically relevant conditions, including surgical implantation and long-term biosafety monitoring.

In conclusion, innervated biomaterials represent a transformative frontier in cutaneous wound healing, offering unprecedented potential to restore both structural integrity and sensory function by bridging neural regeneration with tissue repair. While innervated biomaterial systems have demonstrated remarkable preclinical success in enhancing neuro-integrated healing, critical challenges persist in elucidating mechanistic neuro-immuno-regenerative crosstalk, ensuring long-term biosafety, and achieving scalable clinical translation. Future efforts must prioritize mechanistic exploration, eco-friendly synthesis, and rigorous preclinical evaluation in large-animal models to address regulatory and translational barriers. By uniting materials science, neurobiology, and clinical expertise, this emerging field can unlock innovative therapies that not only accelerate wound closure but also restore sensory fidelity, ultimately improving patient outcomes. We envision that this review will inspire collaborative advancements, driving innervated biomaterials from conceptual innovation to clinical reality in regenerative medicine.

Abbreviations

TES, Tissue-engineered skin; MSCs, Mesenchymal stem cells; SCs, Schwann cells; VIP, Vasoactive intestinal peptide; NGF, Nerve growth factor; CGRP, Calcitonin gene-related peptide; SP, Substance P; MMP-2, Metalloproteinase-2; nAChR, Micotinic acetylcholine receptor; MOFs, Metal-organic frameworks; Cur, Curcumin; GMSCs, Mesenchymal stem cells; SDF-1α, Stromal cell-derived factor-1α; PRP gel, Platelet-rich plasma hydrogel; iPSCs, Induced pluripotent stem cells.

Acknowledgments

Disclosure

The authors report no conflicts of interest in this work.

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