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Review

Recent advances in the role of neuroregulation in skin wound healing

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Abstract

Neuroregulation during skin wound healing involves complex interactions between the nervous system and intricate tissue repair processes. The skin, the largest organ, depends on a complex system of nerves to manage responses to injury. Recent research has emphasized the crucial role of neuroregulation in maximizing wound healing outcomes. Recently, researchers have also explained the interactive contact between the peripheral nervous system and skin cells during the different phases of wound healing. Neurotransmitters and neuropeptides, once observed as simple signalling molecules, have since been recognized as effective regulators of inflammation, angiogenesis, and cell proliferation. The significance of skin innervation and neuromodulators is underscored by the delayed wound healing observed in patients with diabetes and the regenerative capabilities of foetal skin. Foetal skin regeneration is influenced by the neuroregulatory environment, immature immune system, abundant growth factors, and increased pluripotency of cells. Foetal skin cells exhibit greater flexibility and specialized cell types, and the extracellular matrix composition promotes regeneration. The extracellular matrix composition of foetal skin promotes regeneration, making it more capable than adult skin because neuroregulatory signals affect skin regeneration. The understanding of these systems can facilitate the development of therapeutic strategies to alter the nerve supply to the skin to enhance the process of wound healing. Neuroregulation is being explored as a potential therapeutic strategy for enhancing skin wound repair. Bioelectronic strategies and neuromodulation techniques can manipulate neural signalling, optimize the neuroimmune axis, and modulate inflammation. This review describes the function of skin innervation in wound healing, emphasizing the importance of neuropeptides released by sensory and autonomic nerve fibres. This article discusses significant discoveries related to neuroregulation and its impact on skin wound healing.

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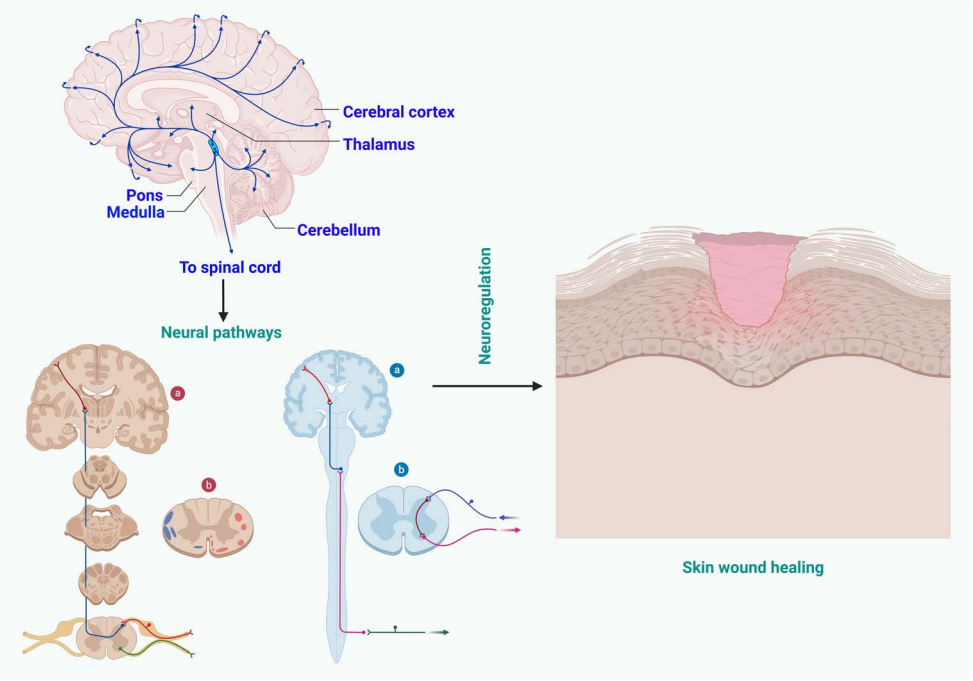
Graphical Abstract



Keywords: Neuroregulation; Skin; Wound healing; Inflammation

Highlights:

- The purpose of this review was to discuss how neuroregulation affects the healing of skin wounds.
- The significant role of neurotransmitters in skin wound healing is discussed.
- This review discusses the role of sympathetic neurotransmitters and angiogenesis in the healing of skin wounds.
- This review focuses on the clinical application of skin wound healing.

Background

Approximately 300 million patients worldwide suffer from chronic wounds, and 100 million suffer from traumatic wounds, making the treatment of cutaneous injuries ubiquitous. Injuries cost health care systems throughout the globe a remarkable amount of money—more than $25 billion annually in the USA alone [1]. The skin, the largest organ in the body, covers the entire body and performs various functions, such as acting as a barrier against contaminants, controlling moisture, and controlling immunological surveillance. Two types of skin exist: hairy and glabrous skin. Wounds, which separate organisms, can have four stages of healing, and two systems must be healed: the epidermis and dermis. Early closure of wounds with sutures and skin replacement is important for wound healing. Re-epithelialization or scarring can result from skin wound healing [2]. Wound healing is a complex process involving neurotransmitters, including serotonin, neuropeptides, dopamine, and epinephrine. These neurotransmitters play crucial roles in wound healing and regeneration. Understanding the molecular pathways through which these neurotransmitters influence the immune system can provide therapeutic interventions to address the increasing prevalence of acute and chronic wounds and improve overall health outcomes [3]. The incidence of chronic wounds is increasing due to type 2 diabetes, peripheral vascular disease, and metabolic syndrome. Treatments for acute and small wounds are effective, but long-term care for large-area burns, infected wounds, and chronic wounds presents challenges. Biomaterial- and nanoparticle-based wound therapeutics focus on infection, burn, and chronic wounds, highlighting their potential for improved healing [4]. The skin plays crucial roles in hydration, protection, vitamin D production, excretion, and thermal regulation. The repair process involves the interplay of cells, growth factors, and cytokines that participate in the closure of the lesion. The challenges arising from injuries, especially persistent wounds, primarily stem from the treatment and management practices that restrict the healing process of the wound rather than the restoration of tissue integrity (known as the 'restitution ad integrum') [5]. Therefore, numerous investigations have focused on achieving more efficient wound treatments to save health care expenses and suggest lasting improvements, ultimately leading to effective scar repair. Skin wound therapy can be categorized as conventional or regenerative. Regardless of aesthetic and potential functional changes, conventional therapy results in the development of scars [6]. Regenerative wound therapy is an emerging field in biomedical research that focuses on repairing damaged skin and cells without leaving scars and restoring the original function of the skin [7]. Skin wound healing involves a unique cellular mechanism involving cells, growth factors, and cytokines. Current research aims to improve wound treatments to reduce costs, provide long-term relief, and promote efficient scar healing. Advancements in wound care include skin regeneration therapy plans,

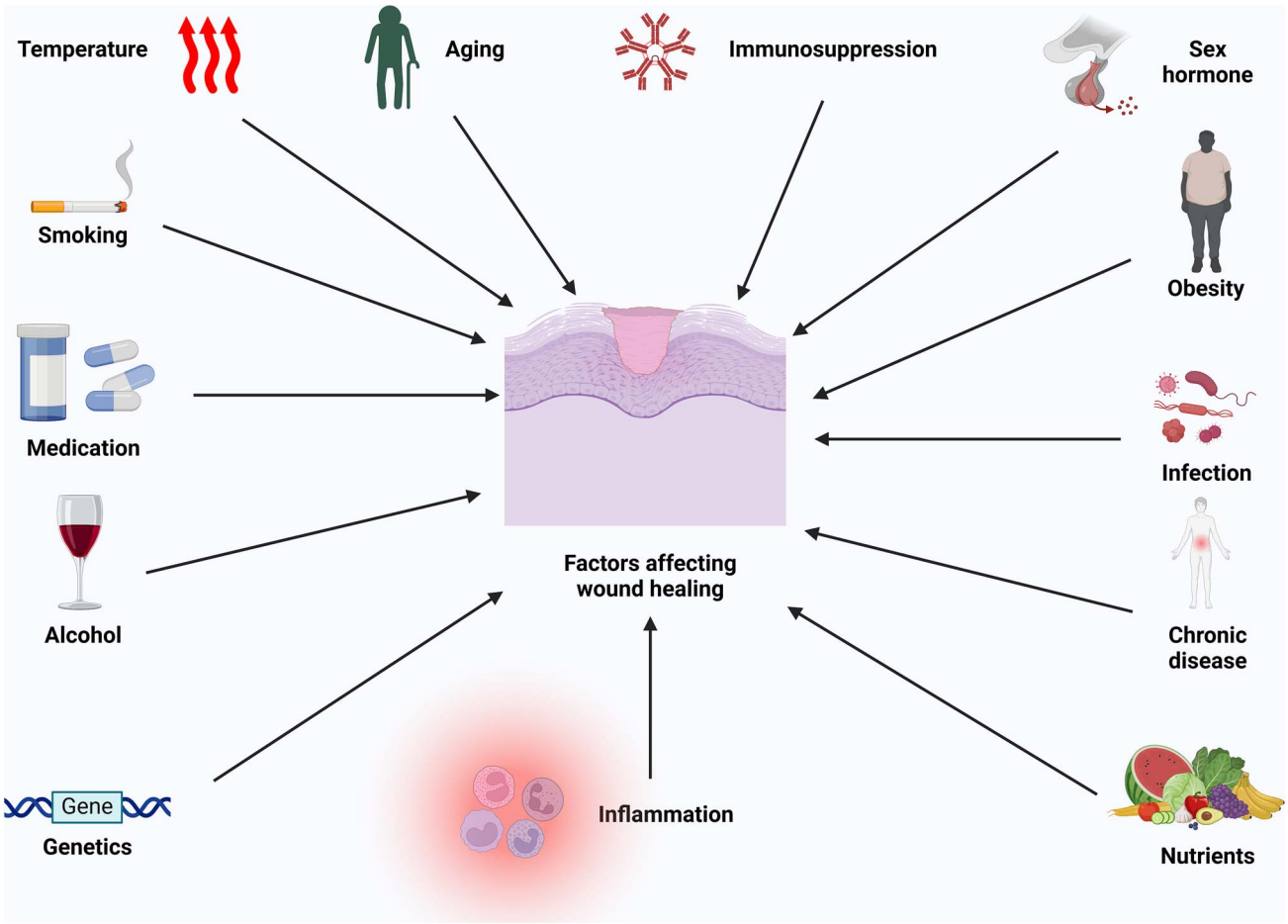


Figure 1. Systemic, local, and chronic factors influence wound healing. Systemic factors include age, nutrition, and health, whereas local factors include wound size, location, and contamination. Lifestyle choices and medications can also affect healing

experimental skin tissue, cellular engineering, and new skin regeneration approaches involving the use of growth factors, bioactive compounds, and genetically modified cells [8]. This study explores efficient techniques for accelerating skin regeneration and wound healing, focusing on design factors, smart technologies, and cellular therapies. The effects of hydrogel formation, electrosprayers, bioprinters, and 3D printing on skin treatments and wound healing are discussed. The study also covers immunomodulation, stromal vascular fraction treatments, small interfering RNAs, and microRNA therapeutics [9]. Wound healing is a complex process that involves various cellular, molecular, and chemical components. The process begins immediately after damage and persists for several months or even years, resulting in a fully healed wound that resembles uninjured skin in both function and appearance. The connections between the central nervous system (CNS) and the skin include many neuromediators, cytokines, hormones, and other substances that exert effects. Therefore, stimuli received at the skin interface can affect the nervous system at both the local and central levels. The brain can regulate skin function in both normal and abnormal states, whereas the skin can impact the pharmacology of the CNS by releasing significant quantities of neuropeptides [10]. Noninvasive transcutaneous electrical nerve stimulation (TENS) can increase the functional capacity of ageing sensory nerves and accelerate tissue healing. A study used rats with sciatic nerve injury and measured hind footpad blood flow responses to assess the effects. The results revealed comparable increases in vascular responses after TENS application, with no evidence that sympathetic fibres influence these responses. The active treatment group achieved a complete recovery at 14.7 days, whereas the recovery time of the placebo group was 21.8 days. These findings suggest that low-frequency TENS can enhance the vascular response in elderly rats [11]. The normal biological process of wound healing in humans involves four perfectly timed steps: haemostasis, inflammation, proliferation, and remodelling. Proper wound healing requires the correct order and duration of all four phases. Different factors can disrupt one or more stages of this process, potentially causing incorrect or compromised wound healing. This study explores key variables influencing cutaneous wound healing and the potential cellular and molecular mechanisms involved. These factors (Figure 1) include oxygenation, infection, age, sex hormones, stress, diabetes, obesity, drugs, alcoholism, smoking, and diet. The influence of these variables on restoration could lead to treatments that improve wound healing and repair damaged wounds [12]. Wound healing is an essential component of survival, as the skin serves as a protective barrier against threats. It involves multiple cell types and mediators interacting in a complex sequence. This study describes the

healing phases and recent advancements and addresses three key topics: scarring, tissue engineering for wound repair, and plasma use in skin wound healing. Healthy skin is crucial for maintaining body homeostasis. Understanding these complex interactions is essential for designing effective wound-healing therapies [13].

The neuroimmunologic characteristics of skin inflammation include the interplay of several systems. The long-standing awareness of the regulatory impacts of autonomic and sensory nerves is well established. Neurokinins originating from these neurons have recently been shown to interact with antigen presentation in dermal Langerhans cells and other crucial mechanisms involved in allergic skin disease. The precise impact of brain signals on the peripheral nervous system remains obscure, despite the ability to process sensory information and recognize local reflexes. Additional factors that have been identified include the role of the brain-derived neurotrophic factor and the involvement of the autonomic nervous system in the response to mental stress [14]. Allergic inflammation triggers neuronal dysfunction, modulating inflammation-related changes in tissues such as the skin. Neurons control inflammatory responses, and structural and invading immune cells release mediators. Skin cells play crucial roles in the allergic response, influencing neuromediators, neurotrophins, and neurotransmitters in inflamed tissue. Peripheral sensory and autonomic nerves are crucial in innate and adaptive immune pathways; further dissection of receptor-mediated and intracellular signalling pathways could lead to more effective therapeutic approaches [15]. This review explores the role of the peripheral nervous system (PNS) in skin biology and pathology. It highlights the network of interactions between cutaneous nerves, the neuroendocrine axis, and the immune system, which impacts physiological and pathological functions such as cell proliferation, immunity, inflammation, pruritus, and wound healing. Neurotrophic factors control nerve growth and regulate skin function through neurohormone receptors and endopeptidases. Understanding cutaneous neuroimmunoendocrinology could lead to novel dermatological treatment approaches [16]. The function of sensory nerves and the impact of ageing on wound healing were enhanced in aged rats. Researchers have used capsaicin treatment and a CO_2 laser to examine the modulatory effects of the interaction between substance P (SP) and calcitonin gene–related peptide (CGRP). The results showed that SP and CGRP effectively accelerated wound healing in older rats. The tachykinin antagonist spantide II was the most beneficial treatment, resulting in faster wound closure. Exogenous treatment with sensory peptides can accelerate wound healing in older rats [17]. Recent advances in understanding the neuroregulation of skin wound healing have focused on the complex relationship between the nervous system and skin repair processes. Research indicates that neuropeptides, neurotransmitters, and neurotrophic factors are crucial for regulating angiogenesis, inflammation, and cell proliferation in wound healing. It has shown positive effects on targeting particular neuromediators to minimize damage and accelerate healing. Novel strategies that have the potential to improve skin regeneration include neurostimulation methods and neuropharmacological therapies. These results indicate the growing importance of neuroregulation as a driving force behind the development of successful wound-healing strategies for dermatology.

Review

Phases of wound healing and the functions of neuromediators

Wound healing involves four phases: haemostasis, inflammation, proliferation, and remodelling (Figure 2). Neuromediators such as cytokines and neuropeptides regulate inflammation, cellular activities, blood flow, and immune responses, influencing cell migration, proliferation, and tissue repair (Table 1).

Inflammatory phase

Haemostasis is a short process that occurs after skin injury and involves the formation of a fibrin plug and the release of proinflammatory substances. Additionally, neutrophils are attracted to chemical signals that promote wound healing [23]. Neutrophils chemically attract other cells involved in the inflammatory phase [24]. They play a significant role in controlling macrophage activity [25]. Macrophages enter the wound and consume infection and cellular debris to aid in healing [26, 27], along with the release of growth factors, chemokines, and cytokines [28, 29]. The inflammatory phase of wound healing is triggered by neuropeptides released by skin nerves, with SP being a significant factor. Other neuropeptides are under investigation. The dorsal root ganglia of the spinal cord produce SP [30, 31]. Human keratinocytes, endothelial cells (ECs), and fibroblasts contain serotonin receptors [32]. NK-1R, a neurokinin G protein–coupled receptor found in peripheral tissues and neurons alike, regulates the activity of SP [33]. The blood arteries, the skin's outer layer, and the tissue that supports and links the body's many parts are all impacted by sphenopalatine ganglion stimulation. Nitric oxide is crucial for optimal wound healing [34]. SP causes blood vessels to widen and improves blood flow through the microvasculature by increasing nitric oxide production and acting directly on ECs [35]. Sphingosine-1-phosphate increases the number of adhesion molecules on ECs, facilitates monocyte migration, and increases the accumulation of inflammatory cells [36–38]. Additionally, SP controls the synthesis and release of proinflammatory cytokines, including transforming growth factor alpha (TGF-α), interleukins, and tumour necrosis factor-α. Inflammatory wound healing is a critical phase of the production of these cytokines [39]. The zinc metalloprotease neuropeptidase (NEP) prevents SP from functioning by degrading SP through its enzymatic activity. NEP and NK-1R struggle to suppress the activity of SP [40]. The interaction between SP and NEP plays an important role in inflammatory signalling during wound healing [41]. After injury, the skin releases neurokinin A, a physiologically active neuropeptide. Its interaction with the neurokinin-2 receptor (NK-2R) affects mainly cutaneous target cells, including keratinocytes and dermal ECs. The interaction between these two factors regulates skin inflammation during the healing process [33]. Immunohistochemistry studies have shown that sensory cutaneous nerves contain corticotropin-releasing hormone (CRH) [42]. CRH stimulates inflammation by increasing the levels of proinflammatory cytokines and opening blood vessels in the skin, promoting angiogenesis and the growth of new blood vessels in the epidermis [16, 43]. CGRP expands blood vessels and allows plasma to leak out [44]. The development of new blood vessels may also be improved by this

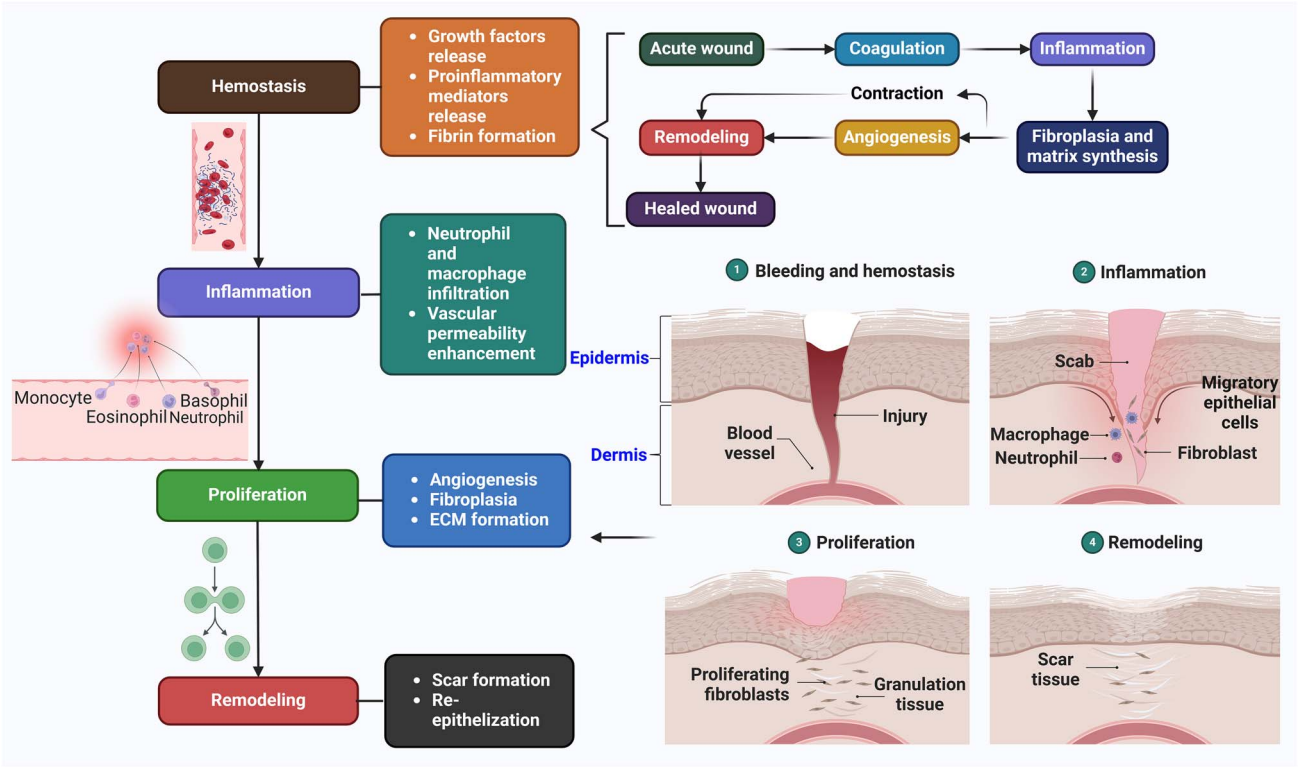


Figure 2. Wound healing involves four phases: haemostasis, inflammation, proliferation, and remodelling. Neuromodulators, such as SP and NGF, play critical roles in influencing inflammation, the immune response, and tissue regeneration, highlighting the vital role of this axis in wound healing

treatment. CGRP increases the inflammatory reactions of other mediators, such as SP [45]. The transforming growth factor beta (TGF-β) superfamily member activin promotes wound healing by increasing CGRP synthesis in sensory neurons that provide nerves to wounds [46]. The regulation of wound healing is evident from these findings. Research has indicated that peripheral nerve terminals release more CGRP when the nerve growth factor (NGF) is present. The NGF regulates the inflammatory phase of wound repair [47]. Wound healing occurs more quickly when the sympathetic nervous system is activated [48]. Neurogenic inflammation is believed to be impacted by stimulation. α1-Adrenoceptors are found in peripheral nerve fibres, and their expression increases after nerve damage, which could worsen neurogenic inflammation [49]. Inflammation during wound healing is the major factor contributing to hypertrophic scarring and keloids, which negatively impact the quality of life of patients. New technologies have shown the effects of inflammatory cells on wound healing and scarring [50]. Hydrogels have shown promise in biomedicine because their anti-inflammatory properties enhance wound healing. Chronic wounds such as those caused by diabetes and severe burns require excessive inflammation to promote healing. Hydrogel dressings work by scavenging free radicals, sequestering chemokines, and promoting the M1 to M2 polarization of macrophages [51].

Proliferative phase

Skin wound healing is primarily attributed to restoring barrier function to prevent further harm or infection. The process requires the distinct interaction and mutual influences of multiple cells and mediators from the outset. The wound-healing process can be hampered or even result in scarring if the healing phases are prolonged or if the organism reacts to damage. Numerous studies are ongoing on the transition from the inflammatory to the proliferative stage of wound healing [52]. The proliferative phase occurs a few weeks after the initial inflammatory phase. The development of granulation tissue is a hallmark of this process, which involves the infiltration of macrophages and fibroblasts into the injured area. Extracellular matrix (ECM) formation occurs when macrophages come into contact with fibroblasts. This ECM supports ECs, angiogenesis, and wound contraction. By increasing DNA synthesis, SP has potent effects on the proliferation of fibroblasts, keratinocytes, and ECs [53, 54]. A key component in the remodelling of granulation tissue is a serine protease. It accomplishes this effect by promoting cutaneous fibroblast growth and migration [55] and the production of relevant receptors and the epidermal growth factor [55, 56]. Peripheral and CNS neurons and other cell types, such as fibroblasts, epithelial cells, keratinocytes, and immunological cells, produce the peptide neurotrophin NGF [57]. The growth, survival, and functionality of sensory and autonomic nerves are significantly influenced by NGF [58]. Additionally, NGF has anti-inflammatory properties [59]. NGFR promotes the proliferation of nearby undifferentiated cells and the growth of excessively growing blood vessels and nerve fibres in wounds [60]. Animal studies and a human case study revealed that NGF promotes angiogenesis and epithelial repair [33]. Neurokinin A induces the secretion of NGF in the outer layer of the skin [33, 61]. The other significant neuropeptides involved in the proliferative phase are CGRP, galanin, vasoactive intestinal peptide (VIP), and pituitary adenylate cyclase-activating peptide (PACAP). GRP is widely dispersed in both the CNS and the PNS. GRP promotes keratinocyte migration, proliferation, and angiogenesis [62]. CGRP stimulates keratinocyte proliferation

Table 1. Functions of extracellular vesicles in various stages of wound healing

Phase	Parental cells	Effects	Recipient cells	Pathway	Finding	Ref.
Haemostasis	Monocytes	Transfer molecules to the platelet membrane	Collagen-activated platelets	TF, PSGL-1	All membrane-bound reactions of the coagulation system can be confined to the surface of activated platelets.	[18]
	Thrombin-activated platelets	The *in vitro* formation of fibrin increases, but the *in vivo* bleeding time and blood loss decrease.	Platelets	Active state of the αIIbβ3 integrin	Activated platelet-derived vesicles (Act-VEs) have been formed as a new haemostatic biomaterial.	[19]
Inflammation	M2 macrophages stimulated by IL-4 generated from bone marrow	Macrophage reprogramming involves a shift from the M1 to M2 phenotype with reduced iNOS levels and increased Arg1 levels, promoting fibroblast migration, endothelial cell tube formation, and wound healing.	M1 macrophages stimulated with IFN-γ generated from bone marrow mouse model exhibiting optimal health in a living organism	CCL24, CCL22, MFG-E8	The transplantation of human cord blood–derived endothelial progenitor cells (EPCs) significantly accelerates wound closure in streptozotocin-induced diabetic nude mice compared to the control group.	[20]
Proliferation	HaCaT cells, HEKa cells, and NHEKs	The upregulation of IL-6, MMP-1, MMP-3, and THBS protein expression leads to increased migration and fibroblast-mediated endothelial tube formation, while decreasing these processes affects TIMP3 and TIMP4 mRNA expression.	Human dermal fibroblasts	ActivatedERK1/2, Smad, p38, and JNK.	Keratinocyte microvesicles exhibit a potent and specific regulatory effect on fibroblasts, potentially impacting various facets of the wound healing process.	[21]
Remodelling	Myofibroblasts derived from healthy skin wounds in humans	Increase migration and collagen I levels	Human skin fibroblasts	PLGF-1, LTA, VEGF, IL-23	The potential roles that myofibroblasts from normal skin wounds and microvesicles may play in mediating the healing of a skin wound were analysed.	[22]

TF, tissue factor; PSGL-1, P-selectin glycoprotein ligand-1; Act-Ves, activated platelet-derived vesicles; CCL24, C-C motif chemokine ligand 24; CCL22, C-C motif chemokine ligand 22; MFG-E8, milk fat globule-EGF factor 8; IL-4, interleukin-4; iNOS, inducible nitric oxide synthase; EPCs, endothelial progenitor cells; HaCaT, immortalized human keratinocyte cell line; NHEKs, normal human epidermal keratinocytes; HEKa, human epidermal keratinocyte line, adult; IL-6, interleukin-6; MMP-1, matrix metalloproteinase; MMP-3, matrix metalloproteinase-3; THBS, thrombospondin; ERK1/2, extracellular signal-regulated kinases 1 and 2; JNK, c-Jun N-terminal kinase; TIMP3, tissue inhibitor of metalloproteinases 3; TIMP4, tissue inhibitor of metalloproteinases 4; PLGF-1, placental growth factor 1; LTA, lymphotoxin alpha; VEGF, vascular endothelial growth factor

and migration [63]. Sensory nerves secrete the peptide galanin, which acts through G protein–coupled receptors. Galanin can inhibit cell growth in tissues [64]. In contrast, a study conducted *in vitro* revealed that galanin increased NGF production [65]. VIPs have been shown to aid in keratinocyte division and movement [66]. VIPs also cause mast cells (MCs) to release histamine, which dilates blood vessels [67]. VIP promotes sciatic nerve regeneration in rats. These findings suggest that VIP may play a role in reneutralizing damaged tissue [68]. PACAP is present in the sensory cutaneous nerves [69]. This substance is a member of the VIP peptide family and exhibits potent vasodilatory characteristics [70]. The C-fibres release PACAP when neurons are activated, resulting in vasodilation and extravasation. PACAP causes MCs to produce histamine, which contributes to cutaneous irritation. Furthermore, PACAP promotes human keratinocyte growth [71]. This study aimed to explore the activation and inhibition of the sympathetic nervous system during the wound-healing phase, specifically through adrenoceptors [72]. The $\alpha 1\beta$- and $\beta 2$-adrenoceptors are activated to promote the growth and migration of fibroblasts [73]. In wound healing models, blocking $\beta 1/\beta 2$-adrenoceptors accelerates the movement and re-epithelialization of human keratinocytes [74]. The balance of various important cytokines, such as TGF-β and insulin-like growth factor-1 (IGF1), impacts the synthesis and restructuring of connective tissues in the skin [75]. Scientists have reported that TGF-β promotes the formation of the ECM [76] and that IGF-1 regulates fibroblast growth and movement in response to chemical signals [77]. Research suggests that the sympathetic nervous system may regulate the production of TGF-$\beta 1$ and IGF-1, cytokine release, ECM synthesis, and migration of fibroblasts in the skin [78]. Neuropeptide Y (NPY) is present extensively in the central and peripheral nervous systems. NPY is expressed in sympathetic nerve fibres in the deep and superficial dermis of the skin [79]. NPY has direct effects on promoting the growth and infiltration of ECs [80, 81].

Stages and difficulties in the healing process of wounds

A brief overview of injuries and their effects

Wounds can be categorized as acute or chronic based on their aetiology and consequences. These injuries can result from several factors, such as injuries, surgical interventions, pathological conditions, pressure, burns, or cuts [82]. The gradual healing process after an acute wound can restore anatomical and functional integrity, whereas chronic wounds cannot reach optimal outcomes. Healing can be influenced by various systemic factors, such as age, vascular conditions, metabolic disorders, autoimmune diseases, and medications [83]. The optimal wound healing outcome is characterized by complete recovery of the original anatomical structure, function, and appearance after an injury. Partially healed wounds maintain anatomical continuity but do not achieve long-term functional outcomes, which increases the possibility of injury recurrence. Both noninvasive and invasive techniques are used to evaluate and categorize wounds and measure their perimeter, maximum length, surface area, volume, deterioration, and tissue viability [83]. Several qualities can characterize a wound, such as blood circulation, oxygenation, infection, swelling, inflammation, repeated injury or insult, nerve supply, wound metabolism, dietary habits, medical history, and systemic factors. These characteristics can indicate a wound's nature, cause, and condition [12]. Wounded patients must be evaluated according to their condition and system. The healing process is complex and requires ongoing investigation. Persistent wounds negatively impact quality of life; increase care costs, psychological effects, hospitalization, morbidity, and mortality; and earn the label of a 'silent epidemic' [84]. Most of the financial expenses pertain to hiring health care staff, the duration and costs of hospital stays, and the selection of materials and treatments. The development of new technology to improve the healing process is complicated by several variables [85].

Phases of wound healing

Wound healing after severe injury can lead to cutaneous fibrosis, affecting movement and patient recovery. Current research focuses on molecular regulators of the inflammatory, proliferative, and remodelling phases of wound healing. A multimodal strategy is necessary to reduce fibrosis by targeting inflammatory mediators, the epithelial-to-mesenchymal transition, and myofibroblast development [86]. Keratinocyte desquamation in the stratum corneum causes skin cell loss, which is replaced in the basal layer through stem cell proliferation. Numerous factors may impact cellular regeneration, such as injuries, hormones, skin diseases, and personal health [87]. The process consists of several steps triggered by biochemical pathways involving cellular components such as the coagulation cascade, inflammatory mechanisms, and immune system cells such as fibroblasts, keratinocytes, and macrophages [88]. Gene expression, either through autocrine or paracrine pathways, controls the progression of the regeneration process. Gene silencing is responsible for terminating active pathways throughout regeneration [89]. Human wound healing is a complex process that requires precise timing and location management between the inflammatory phase and tissue regeneration. Several factors are involved in the inflammatory phase after a harmful event, including the coagulation cascade, the immune system, and the inflammatory pathway [90]. Haemostasis is a complex process that involves the development of a fibrin matrix. This matrix contributes to the infiltration of cells and activates the complement system, which facilitates the entry of neutrophils. This process is triggered by platelet degranulation, signals from necrotic tissue, and components released during bacterial breakdown [91]. During injury, macrophages are responsible for managing all reactions. In addition to eliminating fibrin and cell debris, these cells release monocyte-derived growth factor (MDGF), which promotes the growth of fibroblasts and ECs [92]. Tissue regeneration usually occurs within 2–10 days following injury and involves cell proliferation and migration processes. Granulation tissue forms due to the expansion of fibroblasts, myofibroblasts, and ECs. This highly vascularized tissue plays crucial roles in wound healing and the development of new blood vessels [93]. During the re-epithelialization phase, keratinocytes undergo rapid cell division and movement towards the centre of the wound, while granulation tissue forms at the base and edges of the incision [92]. The sliding and rolling models explain the structural organization of skin re-epithelization. The sliding model proposes that keratinocytes in the basal layer change their anchoring junctions, allowing them to migrate horizontally towards the centre of the lesion. Conversely, the rolling model indicates that these cells migrate towards basal keratinocytes [94]. Keratinocytes

undergo proliferation and vertical differentiation to regenerate the basal layer, restoring the integrity of the epithelial tissue. The remodelling phase, which spans more than a year, prevents prior activity and induces apoptosis or migration away from the wound. The epidermis and dermis maintain the integrity of the skin, with Type III collagen being replaced within 6–12 months [95].

Healing of acute and chronic wounds

Acute wound healing is influenced by the immune response, whereas chronic wounds are caused by immune system dysregulation, inflammatory mediators, and bacterial biofilms [96]. Acute wounds, such as those caused by trauma or surgery, undergo the normal phases of wound healing, resulting in a predictable and organized tissue-rebuilding process [97]. On the other hand, vascular ulcers (such as venous and arterial ulcers), diabetic ulcers, and pressure ulcers are the main types of chronic wounds that are distinguished by an aberrant healing process [98]. This review investigates the regulatory properties of the neuropeptide SP in wound healing, specifically under diabetic conditions. SP plays a key role in regulating cell growth and restoring communication between skin cells. Additionally, SP governs the immune system, offering the potential for wound healing and treating diabetic foot ulcers [99]. Chronic wounds exhibit a continuous inflammatory phase, attracting bacteria, enhancing biofilm formation, and producing TGF-β and ECM components. Long-term activation of the proinflammatory cytokine cascade, comprising TNF-α and interleukin-1β, leads to a significant accumulation of proteases in the wound bed. When chronic wounds occur, more protease enzymes than inhibitors are present. These enzymes degrade the ECM and promote the growth and inflammatory phases [100, 101]. Reactive oxygen species (ROS) levels increase when inflammatory cells are present in a chronic wound bed. ROS damage ECM proteins accelerate the ageing process of cells [102]. Abnormalities in the cells and dermis, such as a decrease in the density of growth factor receptors and a reduction in the capacity to stimulate cell division, further distinguish chronic injuries. These abnormalities delay the ability of local cells to respond appropriately to signals that promote wound healing [103–105].

Epithelialization in skin wound healing

Skin wounds involve tissue remodelling, cellular proliferation, and inflammatory cell infiltration. Epithelialization, a process involving the restoration of the keratinocyte layer, is crucial. Growth factors or proinflammatory cytokines regulate epidermal stem cell migration, proliferation, and differentiation. Treating skin wounds that target these cytokines may be beneficial [106]. The techniques for healing cutaneous wounds are contraction and epithelial resurfacing. Depending on the species, one or more mechanisms dominate the wound-healing process. Rats heal mostly via contraction, whereas in humans, epithelialization is responsible for up to 80% of wound closure [107]. Wound healing depends on several factors: the location, depth, size, and microbial contamination. Patient health, genetics, and epigenetics determine skin appendage preservation and the primary goal of partial-thickness wound healing. However, full-thickness wounds are identified by the total obliteration of the epidermis, dermis, and underlying tissues. Granulation tissue is produced as the first step in healing lost tissue and fills the defect before the epithelial covering appears. The third phase of healing is often complicated, similar to septic conditions, in which wounds are left open and remain so until the inflammatory and potentially life-threatening situation subsides [108]. Wound healing involves various stages, with superficial wounds having a brief haemostatic phase and clean wounds having a longer haemostatic phase. Profound wounds require more time due to extended first stages, including haemostasis and elimination of cellular waste. Epithelialization begins shortly after injury, and keratinocytes transform into migratory cells [109]. Hair follicle regeneration involves how the epidermis, or the outermost layer of skin, regenerates through apocrine gland ducts [109–111] and the margin of the wound. Pilosebaceous units, eccrine sweat glands, and the outer root sheath of the hair follicle appear to be the initial stages of this process in humans. The skin adnexa seem to be arranged particularly for wound healing. Rittié and coworkers [109] described a phenomenon where no extension must travel more than half the distance between adjacent structures before encountering another moving in the opposite direction. Human partial-thickness wounds typically require cells to travel $\sim$500 μm and achieve complete epithelialization within 8–10 days [110]. 'Leapfrogging cells' was the original term for keratinocyte migration to heal an epidermal wound. These cells gradually move over each other and onto the wound bed without specific migratory activity [112, 113]. A previous study showed that leader cells or complete rows of cells exert force on other cells, causing them to crawl over the wound [114–116]. In addition, three more mechanisms may be involved: extension of the membrane or epidermal tongue, lamellipodial crawling, and shuffling [117, 118]. The first line of keratinocytes close to the injury site forms the epidermal tongue. Activated keratinocytes undergo cytoskeletal reorganization [109]. The first line of activated keratinocytes uses lamellipodial crawling to move them away from fibrin, fibronectin, and vitronectin produced by the blood clot and forwards over the wound matrix [117]. Contact inhibition causes keratinocytes to stop moving once they reach the centre of the wound, which results in the wound being covered [119]. Strong interactions between cells are formed again, and keratinocytes take on their inactive cobblestone-like appearance, creating layers in the epidermis. The main goals are to promptly and effectively close the wound and prevent further fluid loss or infection. The ECM that promotes keratinocyte movement is an essential component of epithelialization. The dermis, fascia, and muscles are ideal for the healing of wounds, despite the presence of even small amounts of adipose tissue. The development of granulation tissue ensures the movement of epithelial cells in connective tissues outside the dermis. Granulation tissue consists of macrophages; fibroblasts; blood vessels; and a loose matrix of type I collagen, glycoproteins, fibronectin, and hyaluronic acid [120–122]. Chronic wounds, specifically nonhealing ulcers, disrupt the regulation of the epidermal stem cell environment [123]. A small cell population and persistent inflammation caused by an infection, a lack of oxygen, reduced blood flow, and/or excessive fluid discharge characterize this disruption [124]. Extensive research is continuously being conducted to utilize stem cells for nonhealing wounds. Stem cells significantly impact various stages of wound healing, including the reduction of inflammation, movement of cells, growth, and specialization. However, their exact roles are still incompletely understood [124–126].

Remodelling in the healing and scarring of skin wounds

The remodelling phase of wound healing ends with the formation of a scar. During normal adult wound healing, the wound is closed, and the original tissue is replaced with a collagen scar. Embryonic wounds may heal without scars during gestation [127, 128]. The epidermis and dermis of scarless foetal lesions are completely restored, accompanied by reticular collagen matrix formation. Prenatal wound healing in sheep involves skin regeneration before the second trimester, whereas embryonic wound healing in humans causes early scarring [129]. This difference may be explained by the unique way that foetal fibroblasts respond to the profibrotic substance TGF-β [130]. Wound healing processes in children and adults result in scars, with cutaneous scars having a distinct collagen pattern and a lack of epidermal appendages. Wound healing relies heavily on myofibroblasts, which are important in wound contraction. Dermal fibroblasts activated after injury become protomyofibroblasts, which emerge ~4 days after injury and are present in both normal connective tissue and early granulation tissue [131]. The activation of TGF-β [132] and the splice variant ectodysplasin A (EDA) fibronectin cause protofibroblasts to transform into myofibroblasts that express α-smooth muscle actin [133]. Focal adhesions between the ECM and the intracellular cytoskeleton enable myofibroblasts to produce contractile forces. Wound contraction and contracture are clinical terms for tissue shortening or distortion, resulting in reduced mobility and function. Scar remodelling takes months to years and typically results in an initial red appearance due to dense capillaries. Scars can develop hyperpigmentation in individuals with darker skin tones and those with excessive sun exposure. Wounds gain strength over time, and the molecular pathways responsible for excessive repair are being investigated. The skin tissue of burn patients shows reduced collagenase activity and increased levels of profibrotic cytokines [134]. Apoptosis, or programmed cell death, does not occur during repair, and fibroblasts still release ECM components [135]. Clinical variables and molecular regulation influence scar development. Incisions should be made along natural skin tension lines to minimize the appearance of the scar and reduce tension. Wounds with well-defined edges heal with minimal scarring. The second phase of healing causes increased scar development. Hyperpigmentation and hypopigmentation intensify scar differentiation, enhancing visibility. Wounds should be protected from light to prevent blackness. Hypertrophic scars and keloids occur in humans and are rare in animals [136]. Hypertrophic scars are elevated, reddish, and pruritic and often develop due to severe stretching forces on wounds. They are most common in extremities intersecting joint surfaces and can be minimized through physical therapy. These scars eventually diminish and become level with the surrounding skin. Early identification and prompt therapy are crucial for addressing severe scarring and preventing infection [137]. Sun protection must be used to minimize the occurrence of scar hyperpigmentation. Patients more likely to experience significant scarring may find it helpful to take preventative steps such as using ointments or silicone gel sheeting and concurrently administering intralesional steroid injections with hypoallergenic microporous tape [137, 138]. Silicone gel sheeting is the only treatment for hypertrophic scars with strong evidence of effectiveness [139]. Silicone gel sheeting has a history spanning >20 years and has been supported by multiple randomized controlled trials that have demonstrated its safety and effectiveness [138, 140]. Research has focused on reducing scars through hydration, temperature, and mechanical tension. Anti-TGF-β treatments were initially studied in foetuses, but the complex process of scar development and remodelling remains unresolved [141]. Further research is needed to investigate the redundancy of actions among growth factors. Most likely, TGF-β alone is not the sole growth factor that decreases scar formation and fibrosis in humans and should be addressed. Recently, the mechanics of tissues, the healing process of wounds, and the strength of the inflammatory response (Figure 3) have received attention to address the issue of excessive scarring. Novel medications are now being used to treat fibrotic diseases in clinical phase II and III trials [142]. Efforts are being made to investigate the effects of antibodies against TGF-β, integrin $\alpha v\beta 6$, interleukin-13, connective tissue growth factor (CTGF)/CCN2, and other molecules on liver and lung fibrosis and keloids. The use of leukotriene receptor antagonists, angiotensin-converting enzymes, calcium antagonists, and statins as whole-body treatments for asthma, high blood pressure, and high cholesterol has been shown to reduce scarring [143]. These unintended consequences have been partially replicated in animal models [144].

Angiogenesis in the healing of skin wounds

Angiogenesis, the process of developing a functional blood vessel network, is crucial for wound healing, restoring blood flow, providing nutrition and oxygen exchange, and eliminating metabolic waste [145]. Wound healing depends heavily on neovascularization, which influences the entire process from the initial skin injury to final healing [146, 147]. The microvasculature is crucial for clotting, minimizing bleeding, and forming a temporary wound structure. The wound microenvironment supports new blood vessels and regeneration, providing nutrients and eliminating waste. The neovascularization process is disorganized, with functional and defective capillaries shrinking or disappearing naturally [148]. Several factors contribute to chronic, nonhealing wounds, forming an unfavourable environment that prevents skin healing. Hyperglycaemia, chronic inflammation, and deficits in growth factors and cytokines hinder the recruitment of stem cells needed for adequate angiogenesis [146]. Stem cells positively affect skin wound healing, particularly blood vessel regeneration [146]. This process appears to be aided by stem cells or progenitor cells via a variety of paracrine actions, including increased levels of proangiogenic substances such as vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), basic fibroblast growth factor (bFGF), EGF, TGF-β, and IGF-1 [149–152]. Researchers have reported that stem cells can heal chronic wounds in rats with diabetes injury [150, 151, 153, 154]. Recent studies have focused increasing attention on the role of pericytes in wound healing [155]. Pericytes play crucial roles in vascular formation, endothelial stabilization, the blood-brain barrier (BBB), fibrosis regulation, and immune responses. They express adhesion molecules such as VCAM-1 and E-selectin, triggering neutrophil movement and tissue migration [156–159]. Pericytes exert their anti-inflammatory effects by preventing the activation of chemokine-recruited T cells in response to specific antigens [160]. Pericytes, which undergo dedifferentiation and transform into activated fibroblasts that produce collagen, can exhibit profibrotic activity [161]. The growth of scar tissue

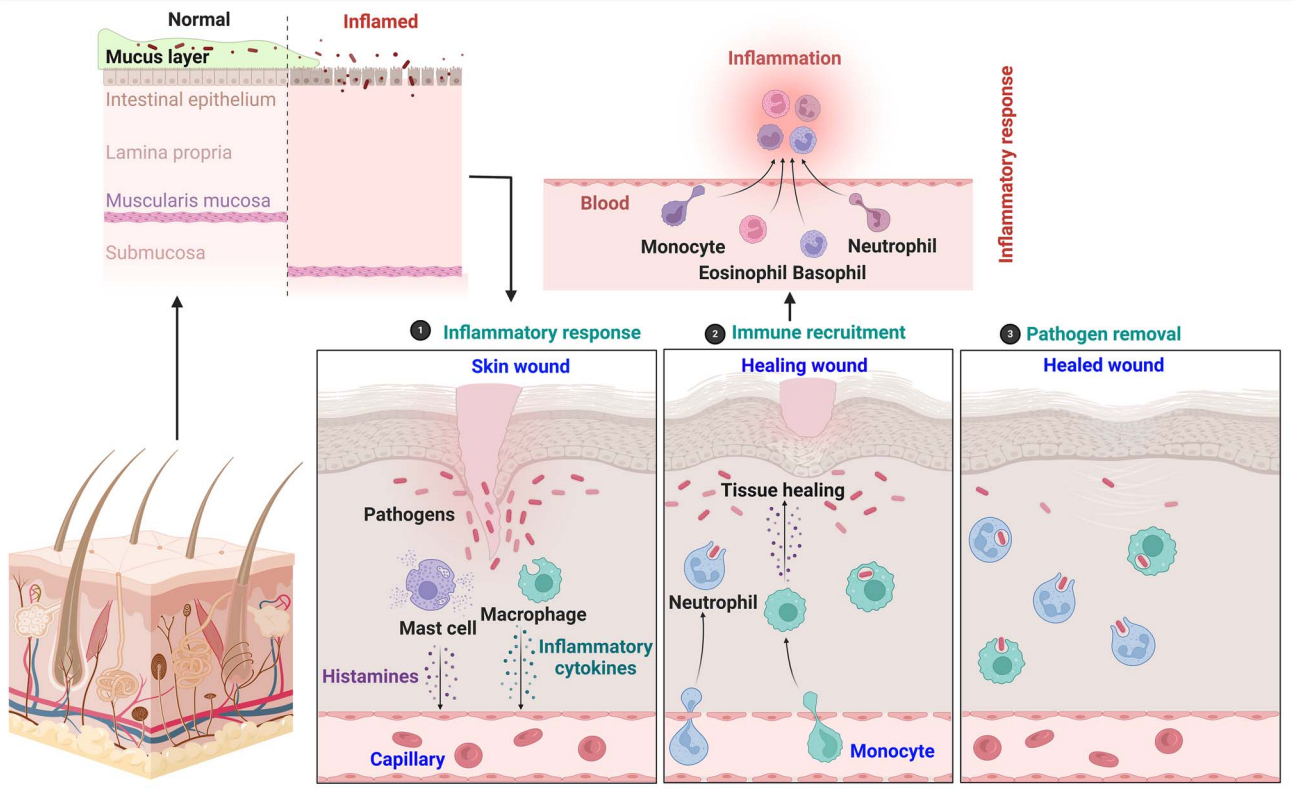


Figure 3. The inflammatory response is an important defence mechanism triggered by damaged tissues. The inflammatory response in the skin involves immune cells releasing cytokines, blood vessel dilatation, and phagocyte engulfment of pathogens. Acute inflammation is protective, whereas chronic inflammation can promote skin diseases

during hypertrophic scarring may occur because pericytes or transdifferentiated myofibroblasts are more sensitive to low oxygen levels, which blocks or partially blocks small blood vessels [155, 162]. Studies have indicated that normal wound healing can occur despite decreased blood vessel growth and capillary bursts [163, 164]. This observation is attributed to the fact that despite having less blood vessel creation than adult skin, lesions to foetal skin and the oral mucosa heal without leaving scars [163, 165]. The reduced creation of scars in foetal skin and the oral mucosa may be attributed to a weaker inflammatory response and the accelerated development of newly formed capillary networks [163]. Anti-angiogenic medications have been proposed as potential therapeutics for hypertrophic scars and keloids [163, 166, 167]. A study suggests that inhibiting angiogenesis during skin wound healing is potentially counterintuitive. Normal skin regeneration can still occur despite a decreased number of capillaries if tissues receive sufficient nutrients [163]. Prompt treatment of skin lesions remains challenging because of the lack of efficient wound-healing techniques. Stem cell-based therapies, particularly the use of mesenchymal stem cells (MSCs) extracted from adult and foetal tissues, have been popular for treating acute and chronic skin lesions. Stem cells can stimulate angiogenesis, promote neovascularization and accelerate wound healing [168].

Sympathetic neurotransmitters: sources from neurons and paracrine signalling

Skin cells: neurotransmitter synthesis

Recent studies have examined the factors influencing the relationship between psychological stress and skin diseases. Stress triggers an active skin response involving hormones, neurotransmitters, and skin immune cells, controlling inflammation and triggering corticosteroid secretion [169]. Resident skin cells release signalling molecules through paracrine signalling to preserve normal tissue features. In addition to having unique cell surface receptors, they also synthesize neuropeptides and catecholamines. Norepinephrine (NE)- and acetylcholine (ACh)-synthesizing enzymes and a range of these neurotransmitter receptors are present in keratinocytes in all epidermal layers [170, 171]. Enzymes such as phenylethanolamine-N-methyl transferase (PNMT) and tyrosine hydroxylase, which aid in the production of norepinephrine, are found in keratinocyte vesicles. NE was detected in the culture medium of isolated keratinocytes [74]. Basal keratinocytes in the skin produce more norepinephrine, enabling calcium entry and cell maturation. Beta-adrenoreceptors are abundant in various skin areas and in fibroblasts. Epidermal layers have a high β2-adrenoceptor density, with β2-AR prominent in sweat glands [172]. Atopic dermatitis and psoriasis cause keratinocyte dysfunction and reduce norepinephrine levels by inhibiting the development of keratinocytes in the native epidermis [173]. ACh is produced in all human cells, and the ratio of acetylcholinesterase (AChE) synthesis to AChE breakdown indicates its activity. Keratinocytes have equal capacities for synthesis and release, with AChE activity detected in the basal layer. The epidermis expresses multiple ACh receptors in a pattern that is unevenly distributed among keratinocytes [174].

Normal skin sympathetic regulation

The dermis contains the autonomic nerves situated close to dermal appendages, blood vessels, and lymphatic vessels. These nerves are only sympathetic nerves, except for those

in the face and skin. Cuticle vasoconstrictors, piloerectors, and sudomotor neurons are related to these fibres [175]. Both types possess unmyelinated axons of the C-type and are situated in the paravertebral ganglia [176]. Microneurography studies have shown that a single sympathetic unit provides innervation to an area of skin ranging from 24 to 350 mm^2 [177]. The differentiation of cholinergic sympathetic fibres near eccrine sweat glands and apocrine sweat glands from noradrenergic sympathetic fibres near arterioles or erector pili muscles was made more accessible by immunolabelling histological studies of glands [178]. These fibres are located at different depths in the dermis. Sensory fibres pass immediately through the basal membrane, whereas sympathetic fibres pass gradually [179]. Vasoconstrictor nerve endings innervate skin arterioles, altering EC integrity near capillaries. Adrenergic fibres stimulate piloerection and control hair follicle activity. Sudomotor fibres promote heat waste and increase sweating during stress reactions. Adrenergic nerve terminals release NPY, epinephrine, and protein O-mannose kinase (POMK)-generated peptides [180]. Sympathetic fibres aid in wound healing, affecting superficial muscles and subcutaneous adipose tissue. Deep soft tissue trauma affects these tissues, with the sympathetic nervous system regulating heat storage and release [181, 182]. Sympathetic fibres that innervate blood vessels are found only in skeletal muscles, yet new research indicates that they may also regulate the force of muscular contractions [183, 184].

Sympathetic control during typical wound healing

Keratinocytes

The phenotype of keratinocytes depends on the keratin expression profile after a lesion. Basal keratinocytes proliferate and replace lost corneocytes, whereas mature keratinocytes transition to become activated or contractile. Contractile keratinocytes reduce the wound area, increasing susceptibility to infection or chronic conditions [94, 185]. Intact epidermal cells can produce NE, which allows them to influence one another and inhibit the process of inflammatory activation. Activation of the β2-adrenergic receptor *in vitro* inhibits the movement of keratinocytes [186, 187]. Epinephrine is a more potent keratinocyte migration inhibitor than norepinephrine [188]. Several cellular processes occur after β2-AR is activated in keratinocytes. These processes include the dephosphorylation of extracellular signal-related kinase (ERK), the induction of the promigratory signalling cascades, and the serine/threonine phosphatase PP2A [189]. The β2-AR agonist isoproterenol also inhibits the growth of keratinocytes [190]. In contrast to immune cells, keratinocytes contribute to the proinflammatory cellular response through β2-AR. Epinephrine increases the generation of interleukins, and the interaction between β2-AR and TLRs greatly enhances the inflammatory response [191]. The epidermis is constantly exposed to pathogens and the environment, which contribute to the immune response in the skin. The inhibition of kupffer cells (KCs) by 2-AR may be counterbalanced by the release of cytokines [192]. Wounding in cultured keratinocytes results in the rapid release of norepinephrine and a long-lasting reduction in the expression of the β2-AR protein and genes responsible for synthesizing catecholamines [193]. Scratch wounds in cultured keratinocytes reduce β-adrenoceptor gene expression, suppress β2-adrenoceptor activity, and reduce norepinephrine production. ICI-118551, an antagonist of β2-adrenergic receptors, reduces these effects [194]. β2-AR can exert harmful effects after exposure to epinephrine, leading to keratinocyte blockage *in vitro* [194]. α2-Adrenoceptors (α2-ARs) located on the presynaptic membrane decrease the release of catecholamines. Thus, the external activation of NE-stimulated neurons can enhance wound healing by suppressing NE release [195]. A2-ARs enhance the movement of keratinocytes. NE stress leads to the dominance of ap2ARs over ap2 adrenoceptors, resulting in fast migration [196]. Activating α-adrenoceptors prevents KCs from transitioning from a basal or mature state to an active state. ACh is also present in large quantities in the epidermis and can directly influence keratinocytes through cellular receptors. Keratinocytes and melanocytes express five molecular subtypes of muscarinic and nicotinic receptors [170]. ACh receptor activity can be blocked concurrently in the laboratory, leading to the inhibition of the growth and proliferation of organotypic skin cultures. The inhibition of nAChR receptors results in less significant alterations than the inhibition of mAChR receptors in terms of culture thickness and the expression of maturation marker genes [197, 198]. ACh is important for enhancing keratinocyte cohesiveness [199, 200]. Similar to NE, ACh also increases the production of cytokines in keratinocytes. Cytokine activation can balance the effects of direct inhibition [201]. The activation of M3 mAChR inhibits the movement of KCs, whereas the activation of M4 mAChR promotes their movement [202]. Experiments conducted in a controlled laboratory environment demonstrated that the a9 nAChR receptor is crucial for initiating cell migration. In the absence of this receptor, the KCs remain firmly adhered to the surface. Several receptors with contrasting actions inhibit the efficacy of targeting the cholinergic system in wound healing [203, 204]. The interactions between neuropeptides and KCs have received limited attention. VIP promotes the movement and growth of keratinocytes [205–207]. The presence of the NPY receptors Y1 and Y4 was observed in every layer of human skin in a previous study [208]. Notably, CGRP and VIP stimulate cAMP production in cultured keratinocytes, resulting in increased cell proliferation. Conversely, NPY reduces cAMP levels, leading to the opposite effects. NPY blockers may have beneficial effects [209].

Immune cells and inflammation

Acute inflammation in the initial stages of injury impacts the healing process. It affects blood vessels, attracting granulocytes and facilitating white blood cell movement. Sympathetic fibres regulate inflammation through neurotransmitters. Trauma can cause a surge in catecholamine levels, enhancing skin arteriole constriction and redirecting blood towards essential organs. This process can impede leukocyte movement and prevent severe haemorrhaging [210, 211]. Subsequent studies refuted this discovery. Capillary permeability increases in diabetic skin because of decreased vascular constriction without sympathetic activity [212, 213]. Catecholamines act as antagonists of other cytokines and inflammatory mediators by preventing the increase in capillary permeability at the wound site. Several studies have shown that catecholamines can influence the activity of leukocytes [214]. β2-Adrenergic receptors, which are the most prevalent, have been discovered on all types of leukocytes with varying densities [215]. Adrenergic receptors

exist in various types and have different characteristics in different types of animals and cells. In terms of quantity, $\beta 2$ receptors are followed by $\alpha 1$, $\alpha 2$, and $\beta 1$ receptors [216]. $\beta 2$-ARs control immunological responses by inhibiting the release of cytokines such as TNF-α, preventing leukocyte migration and chemotactic signals [217]. The concentration of IL-10 increases quickly upon $\beta 2$-AR activation, resulting in either immunosuppression or localized inflammation [218]. Possible processes involve the inhibition of NF-κB through protein kinase A (PKA) and the production of the β-arrestin 2 protein [218, 219]. Norepinephrine significantly reduces the phagocytic activity of both neutrophils and macrophages in wounds on rats, inhibiting macrophages at physiological and pharmacological levels [220–222]. Insufficient data exist concerning the involvement of α-adrenoceptors in the process of soft tissue wound healing. They typically exhibit proinflammatory properties. α-Adrenergic agonists stimulate the synthesis of proinflammatory cytokines, the proliferation of immune progenitors, and the formation of ROS [223, 224]. During various instances of inflammation, the activation of α-adrenoceptors leads to an increase in numerous pathogenic responses. Systemic inflammation leads to increased consumption of TLR-driven cytokines by macrophages [225]. Furthermore, α-1B receptors have the capacity to establish heterodimeric complexes with chemokine receptors and govern their function [226, 227]. In summary, the sudden release of catecholamines decreases inflammation by interacting with $\beta 2$-adrenergic receptors. This observation is interesting since the natural healing process of wounds depends heavily on inflammation [228, 229]. Even with extensive research, the danger of inflammation or taking anti-inflammatory medications still cannot be predicted. In several situations, glucocorticoids can impede the healing process of wounds or even cause them to form [230, 231]. However, glucocorticoids have been shown to promote wound healing in some species [232]. Furthermore, medicines that impact β-AR exhibit significant variability across various inflammation models and disorders [233–236]. In a simple wound model, a beta-blocker was shown to increase the rate of cell division, the migration of neutrophils and MCs, the density of myofibroblasts, and the density of blood vessels. However, it also caused an overall delay in healing [237]. The wound area was reduced in the propranolol group of rats with the streptozotocin-induced diabetes 7 and 14 days after the injury. Additionally, reductions in the number of inflammatory cells and the level of MMP-9 were observed [238]. $\beta 2$-AR is crucial for preventing inflammation and tissue damage in the sympathetic nervous system. β-Adrenergic receptors have less affinity for binding NE, leading to the release of IL-10. α-Adrenergic receptors bind to more mediators, and TNF-α release is more dominant. Undamaged sympathetic fibres reduce inflammatory reactions at wound edges and intensify closer to the lesion's core [174]. The immune system depends on the proinflammatory molecule acetylcholine, which is released by sudomotor sympathetic neurons and can cause cholinergic reactions that maintain the balance of inflammation [239, 240]. Leukocytes express various types of cholinergic receptors: the M1-M5 muscarinic receptors and the a3, a5, a7, a9, and a10 nAChR subunits [240, 241]. Both types of cholinergic receptor suppress the release of cytokines from leukocytes, although mAChR has been more extensively studied [242–244]. Furthermore, releasing acetylcholine can potentially reduce inflammation near lesions. In contrast to catecholamines, acetylcholine (ACh) induces vasodilation, enhancing leukocyte extravasation [199, 245]. Cholinergic neurons, particularly sympathetic sudomotor neurons, are characterized by the presence of VIP. VIP increases the development of blood vessels in wounds and exerts anti-inflammatory effects by increasing the number of Treg cells and decreasing the release of TNF-α and IL-6 [246–248]. Vasomotor sympathetic nerve terminals in the skin largely synthesize NPY. The precise mechanism by which NPY contributes to the healing of soft tissue wounds is not fully understood. NPY is a proinflammatory factor in various diseases [249–252]. NPY stimulates the generation of cytokines in leukocytes by interacting with the Y1 and Y5 receptors. However, the functions of other types of NPY receptors and their involvement in cytokine production have been poorly documented [250, 253]. NPY, a neurotransmitter in the skin, promotes inflammation without suppressing the immune system during wound healing. It requires immune cells to resist sympathetic nerve fibres [254]. Diabetic patients with Charcot foot have highly concentrated semaphorin 3C, resulting in fewer sympathetic fibres [255]. A study investigated the presence of cytokines and hormones in inflamed tissue. TNF-α attracts nerve fibres, whereas 17β-oestradiol repels them [256]. Sepsis induces nerve repulsion in primary immune organs, leading to systemic inflammatory responses. Individuals with sepsis have 16% sympathetic fibres, affecting immunological modulation and reducing inflammation specificity [257].

Cells of blood vessels

Blood circulation must eventually be improved to ensure rapid and efficient recovery. All neurotransmitters and neuropeptides with sympathetic properties influence angiogenesis [258–260]. By activating $\beta 2$-AR in both mouse wound models and human skin wounds, phospho-ERK-mediated cytoskeletal remodelling is inhibited, which slows wound re-epithelialization and healing [261]. Notably, similar effects were observed on cultured vascular smooth muscle cells [262, 263]. In addition, the activation of $\beta 2$-AR inhibits the movement of ECs and the process of angiogenesis, which is the construction of new blood vessels in a process dependent on cAMP [264]. The overexpression of the $\alpha 1$-AR gene in vascular cells may cause changes in circulatory dynamics. These modifications could indirectly lead to dysfunctional keloid scars with elevated levels of $\alpha 1$-AR production [265]. NPY levels remain high during the active phase of the sympathetic nervous system (SNS). This neuropeptide causes a long-term increase in vascular tone, similar to arterial hypertension. Reduced neuropeptide Y (NPY) synthesis in the skin is frequently associated with diabetes mellitus [80]. Sympathetic nerve fibres release NPY, which promotes the proliferation and migration of ECs [79, 266]. Ablation of NPY Y2 receptors in mice delays wound healing by blocking angiogenesis [80].

Fibroblasts

Fibroblasts play a critical role in wound healing throughout advanced stages. Inflammation is halted when scarring and functionality are restored in part by growth factors [267, 268]. Fibroblasts produce adrenergic and cholinergic receptors of almost every type. $\beta 2$ receptors are more effective during the proliferation phase. $\beta 2$-AR agonists have been found to hinder contraction and fibrosis, diminish the scar area,

and enhance scar quality in zebrafish and pig skin wound models [269]. cAMP inhibits extracellular matrix contraction and makes fibroblasts move faster [270, 271]. The inhibition of beta-adrenoceptors delays wound contraction and epidermal healing. Furthermore, the neoepidermal thickness, collagen density, and hydroxyproline levels are all decreased, as reported in other investigations [237]. Propranolol reduces the wound size in rats with streptozotocin-induced diabetes at 7 and 14 days after injury. Furthermore, MMP-9 is downregulated, whereas nitric oxide levels, collagen deposition, the MC count, cell proliferation, and blood vessel density are all elevated [238]. β2-AR antagonism leads to increases in angiogenesis, fibroblast activity, and re-epithelialization [272]. Agonists increase inflammation, immune cell division, and ROS and TGF-β production [223, 224]. Different types of acetylcholine receptors are expressed by dermal fibroblasts. These receptors include α-3β2, a5, a7, a9 nAChRs, M2, M4, and M5 mAChRs [199, 200]. The cellular effects have rarely been investigated; however, activation of the cholinergic receptor stimulates the development or alteration of the matrix [273].

Angiogenesis and the sympathetic nervous system

Several neurotransmitters, such as dopamine, play important roles in regulating blood vessel growth through the sympathetic nervous system. Angiogenesis is a crucial process that depends on dopamine, highlighting the relationship between the neural and vascular systems (Figure 4).

Angiogenesis and sympathetic neurotransmitters

Studies have indicated that norepinephrine (NE) contributes to the growth and development of cancers [274]. NE promotes the growth of new blood vessels in tumours from mice with ovarian cancer by upregulating the expression of VEGF [275]. Moreover, it increases the expression of VEGF in melanoma, oral cancer, ovarian cancer, and nasopharyngeal cancer, which promotes the formation of new blood vessels and the spread of tumours into neighbouring tissues [276]. Hypoxia-inducible factor-1 production often decreases in response to hypoxia. 1-AR and -AR are essential for this process. Moreover, this process involves the cAMP/PKA/Akt/p70S6K pathway [277]. NE also promotes the growth of new blood vessels and the invasion of adjacent tissues by upregulating the expression of interleukin (IL)-8 and IL-6 in human melanoma cell lines [278]. The mechanism of action of NE appears to involve the activation of ARs in malignant cells, which leads to a significant increase in the synthesis and release of the angiogenic mediators VEGF, IL-6, and IL-8 [279]. NE elicits intricate biological responses under typical circumstances. NE stimulates the growth of uterine arterial ECs (P-UAECs) from pregnant sheep [280]. This process is mediated by 2-ARs and 3-ARs [280]. NE activates the AR/cAMP/PKA pathway, which induces VEGF mRNA production in HUVECs. This effect may be due to NE stimulation activating 1-ARs and extracellular protein kinases [281]. NE induces programmed cell death in the hearts of newborn rats by stimulating 2-ARs. This caspase-2-dependent pathway is activated by decreased Bcl-2 expression [282, 283]. Therefore, the contrasting effects of NE on ECs derived from various sources in laboratory settings should be considered. In addition, NE increases VEGF production, which leads to a significant increase in the number of capillaries in the gastrocnemius muscle of ischaemic mice [284]. Researchers have shown that mice lacking NE have higher rates of angiogenesis and formation of new blood vessels than normal mice. This increase in angiogenesis could be due to NE-induced death of ECs [188]. NE stimulates the migration of endothelial progenitor cells (EPCs) in a mouse model of hindlimb ischaemia [188]. Hence, the function of NE in angiogenesis may vary under different circumstances. [285] NPY, a potent angiogenic factor, stimulates many stages of angiogenesis both *in vivo* and *in vitro* [286]. One study suggested that neuropeptide Y (NPY) and its associated receptors are present in HUVECs. The autocrine NPY pathway acts through HUVECs as both the source and the site of action [287]. In addition to promoting the formation, migration, and attachment of HUVECs to the extracellular matrix, NPY also promotes the formation of tube-like structures on collagen or Matrigel™ that resemble capillaries [286]. The lack of blood and oxygen supplies to tissues leads to increased production of NPY and its receptors, which triggers angiogenesis, a process mediated by NPY and the Y2 receptor [288]. NPY is as effective as VEGF and bFGF at promoting angiogenesis [286, 287].

Angiogenesis and sympathetic adrenergic receptors

2-ARs are essential for wound healing and angiogenesis in skin and soft tissues. 2-ARs cause blood vessels to be less permeable, resulting in increased blood vessel growth. Stress-induced activation enhances new blood vessel formation in tumours. 2-AR agonists increase VEGF levels [188]. The overexpression of 2-ARs can promote the growth of new blood vessels in heart disease-affected animals, such as rats with high blood pressure, and increase VEGF levels [289]. Several retinal disorders cause pathologic angiogenesis that relies on 2-AR activity to some extent. In animals with hypoxia-inducible retinopathy, blocking the 2-AR decreases the amount of substances that help blood vessels grow and the number of abnormal blood vessels that form in the retina. This treatment leads to the successful control of retinal blood vessel growth [290]. However, studies have shown that the activation of AR (mostly 2-AR) causes programmed death of heart ECs in neonatal rats [282]. Research has demonstrated that activating 2-AR in living organisms decreases the formation of new blood vessels in wounds. In contrast, blocking 2-AR promotes the growth of blood vessels in mouse wounds. Therefore, the impact of 2-ARs on angiogenesis remains uncertain, as whether their activation leads to an increase or decrease in angiogenesis remains unclear [188]. The effects of 2-ARs on angiogenesis are contingent upon multiple circumstances. Activation of the 3-AR receptor on human retinal ECs increases their proliferation and migration [291]. Isoproterenol, a nonselective alpha-adrenergic receptor agonist, has been shown to prevent human dermal microvascular ECs (HDMECs) from migrating and forming tubes. After the administration of isoproterenol, angiogenesis is reduced in mice with full-thickness skin abnormalities on their backs [263]. However, multiple investigations have indicated that isoproterenol promotes the growth of ECs in infant haemangiomas (IHECs) [290, 292, 293]. Tumour vascularization in animal models of lung cancer and breast cancer is considerably increased after AR activation, leading to a subsequent decrease in blood vessel density. Furthermore, AR activation results in the release of angiogenic factors, such as VEGF, IL-8, and IL-6, in many tumour cells. This process leads to a significant acceleration of tumour development [279]. In contrast, the

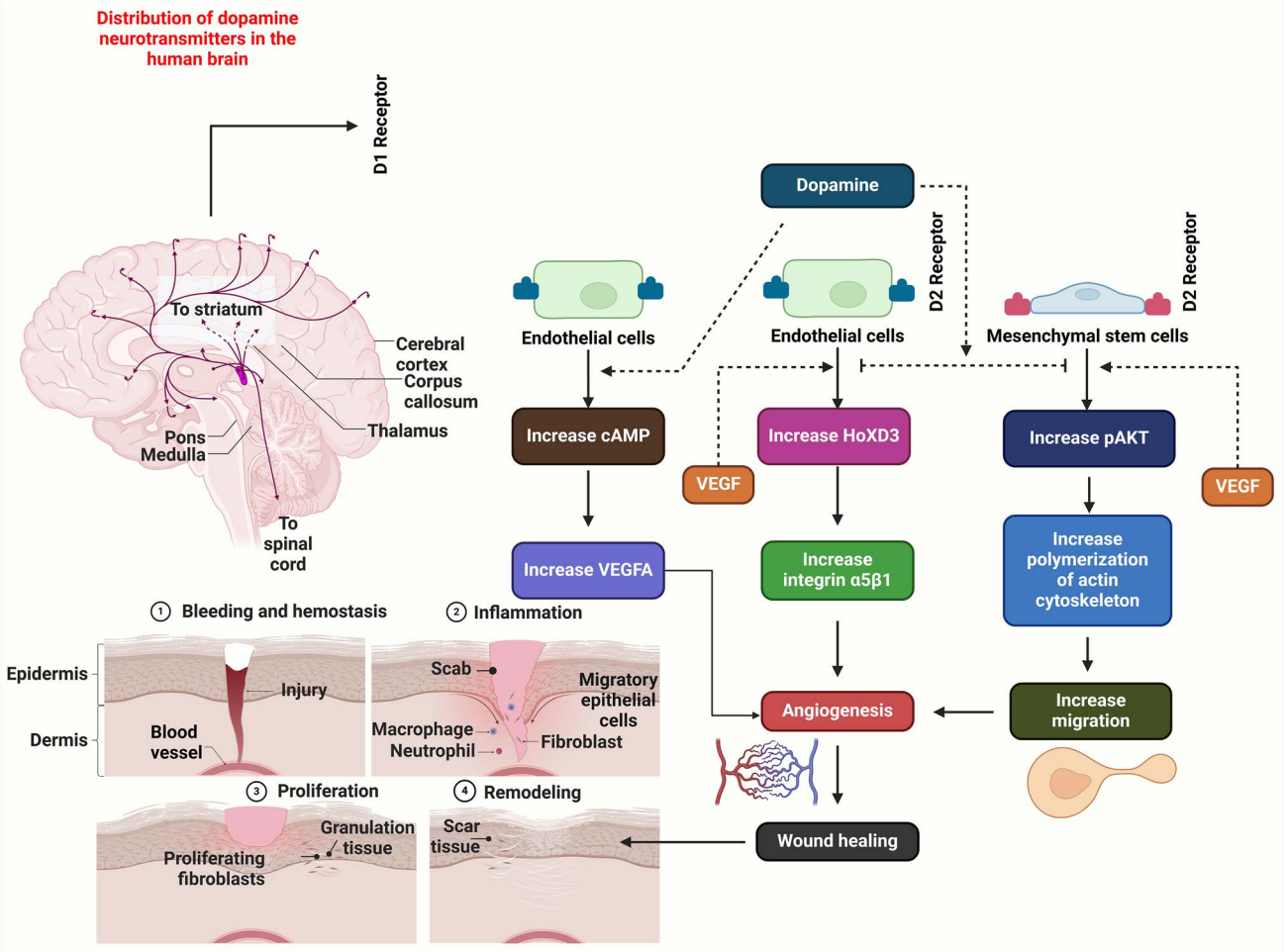


Figure 4. Dopamine plays an important role in modulating angiogenesis during wound healing. cAMP, cyclic adenosine 3′,5′-monophosphate; D1 receptor, dopamine D1 receptor; D2 receptor, dopamine D2 receptor; HoxD3, homeobox D3; pAKT, phospho-AKT; VEGF, vascular endothelial growth factor

activity of AR is inhibited by propranolol, which inhibits the growth and movement of HUVECs. It also prevents tube formation by HDMECs and human brain microvascular ECs, resulting in decreased angiogenesis [294]. Propranolol induces apoptosis and hinders the growth of IHECs [295]. In addition to reducing the expression of VEGF, propranolol inhibits the angiogenesis of haemangiomas by suppressing bFGF expression [296]. Propranolol inhibits the growth of the human placenta and retina pericytes in the laboratory and in infant haemangiomas (IHs) [297]. The treatment of IHs has been made possible because of its use. The oral administration of propranolol leads to an increase in the blood vessel density in the granulation tissue of rats. Both rats with normal blood glucose levels and rats with streptozotocin-induced diabetes mellitus [238, 298] exhibited this effect. However, the impact of propranolol on wound healing outcomes differed between the two groups. In rats with normal blood glucose levels, propranolol delayed wound healing, whereas in rats with streptozotocin-induced diabetes, it facilitated wound healing. These contrasting effects can be attributed to the different blood glucose levels in the two groups. The proangiogenic effects of propranolol on living organisms can be attributed to an increase in the quantity and movement of MCs. The release of histamine and heparin from MCs promotes the growth and migration of ECs. Additionally, propranolol increases the production of nitric oxide, which increases the amount of VEGF and macrophages [238, 298]. A study conducted on severely burned rats with third-degree burns covering 10% of their total body surface area revealed that administering propranolol orally at a dosage of 6 mg/kg led to increases in the secretion of matrix metalloproteinase-2, cell proliferation, collagen deposition, myofibroblast density, and re-epithelialization in wounds. However, the capillary density was lower in the experimental group than in the control group [299]. Hence, the functions of propranolol in angiogenesis are intricate. The activation of AR in tumours potentially stimulates angiogenesis, whereas the inhibition of AR reduces angiogenesis. During wound healing, the activation of AR inhibits the formation of new blood vessels (angiogenesis) but AR inhibition indirectly increases it. However, this effect is reversed if a low dose of an AR antagonist is administered orally. The impact of ARs on angiogenesis varies depending on the clinical conditions, and their activation or inhibition in normal ECs decreases angiogenesis. In a proliferation experiment, ARs stimulated cell division without AR involvement [280]. A study has indicated that specifically blocking ARs does not have any effect on the density of blood vessels or the healing process in the skin wounds of rats [298]. The AR agonist phenylepinephrine has been shown to enhance HUVEC growth and capillary formation [279].

Sympathetic nerves and vascular smooth muscle cells

Pathogens associated with hypertension induce NE release and excessive sympathetic activity. Rather than the media of arteries, the adventitia is innervated by sympathetic fibres. One study investigated the role of NE in controlling the release of extracellular vesicles from adventitial fibroblasts (AFs) and the proliferation of vascular smooth muscle cells (VSMCs) in subjects with hypertension [300]. This study revealed the role of the sympathetic nervous system (SNS) in developing VSMCs, which are linked to cardiovascular diseases, including hypertension and atherosclerosis. Researchers have used an *in vitro* coculture technique to assess the effects of sympathetic neurons on VSMCs. They reported that sympathetic innervation sustains the functional phenotype of VSMCs and stimulates the expression of contractile genes, suggesting that sympathetic innervation is crucial for VSMC differentiation [301]. Blood vessels that contain VSMCs also grow in the injured areas of soft tissues. These cells play a vital role in forming new blood vessels by interacting with nearby ECs [302]. Therefore, sympathetic nerve activity, neurotransmitters, and adrenergic receptors may affect angiogenesis. ARs have been observed in VSMCs, where they regulate cell constriction [303]. Rat aortic SMCs express all three subtypes of 2-AR, which activate VSMC contraction, relaxation, mitogen-activated protein kinase activity, and cell migration. Activation decreases the F-actin labelling intensity but does not induce cell proliferation [304]. NPY has potent mitogenic effects on VSMCs. NPY increases the number of VSMCs through the Y1 and Y2 receptors, showing a two-sided effect at different doses. This mechanism likely plays a role in capillary angiogenesis and collateral development [305]. The D4 receptor is also expressed in VSMCs, and when it is activated, it stops VSMCs from growing and moving through pathways mediated by insulin and angiotensin II. Additionally, activating D1-like or D3 receptors inhibits the growth of VSMCs triggered by insulin [306].

Physiology of the skin and wound healing

Skin wound healing involves the formation of an extracellular matrix, growth factors, cytokines, and cell migration and proliferation mechanisms [307]. The sympathetic nervous system is primarily responsible for innervating the skin. It constantly releases neurotransmitters and neuropeptides to control sudomotor, pilomotor, and vasomotor functions to maintain homeostasis. Among other substances, ACh, NE, CGRP, NPY, and vasoactive intestinal polypeptide regulate these actions. Studies have demonstrated that keratinocyte survival depends on acetylcholine [308]. The somatic sensory system serves as both an afferent and local efferent system. Nociceptive C-fibres secrete SP, CGRP, and neurokinin A. This system influences blood vessel widening, plasma leakage, pain regulation through neural modulation, and nerve activity–induced inflammation [309, 310]. Keratinocytes contain SP and CGRP receptors [311]. Research indicates that wound cells and nerve terminals produce neuropeptides, which are crucial in the inflammation process. CGRP induces the release of granules from neutrophils [312] and acts as a chemotactic agent for T lymphocytes [313], attracting fibroblasts. Sphingosine phosphate has been shown to impact many stages of inflammation. Serine proteases directly increase the expression of intercellular adhesion molecule 1 on ECs, which increases the migration and accumulation of leukocytes [314]. Additionally, SP stimulates TNF-α synthesis in MCs [315, 316] and activates macrophages [317]. NGF is a neurotrophic factor that is thought to play a crucial role in the process of wound healing in the PNS, muscle, eye, and skin. NGF attracts polymorphonuclear leukocytes through chemotaxis [318]. It is secreted by macrophages [319], keratinocytes, and fibroblasts [320], which facilitate the growth of nerves during wound healing. The trophic impact of NGF on nerves stimulates neuropeptide secretion, enhancing wound healing. Neuropeptides are released from nerve endings due to injury and inflammation, and MCs contribute to this process [321]. When inflamed, keratinocytes produce NGF, which also triggers MCs to release their granules. SP and CGRP production are aided by the enzyme tryptase, which is secreted by degranulated MCs [16]. Bradykinin and prostanoids induce the release of neuropeptides from nerve endings, even though they are associated with abnormal inflammatory conditions [322]. After injury, the wound undergoes immediate vascularization and remodelling. The proliferative phase is characterized by increased activity, providing oxygen and nutrients for cell migration, proliferation, and the production of extracellular matrix components. The release of mediators such as VEGF and angiopoietins stimulates the growth of ECs and vascular system reorganization at the wound site [323].

Clinical application

Neuropeptides promote wound healing in diabetic mice, but their practical use is uncertain because of the complex healing processes. Supranormal amounts of neuropeptides, such as SP, CGRP, and VIP, may cause harmful effects [324]. The stimulation of fibroblasts by SP may be responsible for the development of keloids [325]. Furthermore, studies have demonstrated that CGRP promotes the replication of keratinocytes by increasing DNA synthesis. The excessive production of CGRP is believed to contribute to psoriasis, a condition characterized by the excessive growth of keratinocytes [326]. The vasodilatory properties of SP have been linked with its role in rosacea [327]. Elevated levels of SP and NGF are believed to be associated with atopic dermatitis [328]. Higher doses of NGF used to treat peripheral neuropathy result in heightened pain, complicating its use [329]. A study assessing the impact of NGF on foot ulcer healing provided limited information on the use of neuropeptides and neurotrophins in topical applications [330]. Researchers have discovered that NGF positively impacts wound healing without any negative consequences. Additionally, they reported no negative effects when leg and foot ulcers were treated in three diabetes patients [331]. The treatment led to rapid and total healing of all the wounds, with minimal negative side effects. The fundamental mechanism of vacuum-assisted closure, a commonly used treatment, may be related to promoting nerve regeneration and enhancing wound neuropeptides. One study [332] measured the extent of nerve development and levels of neuropeptides in wounds formed in genetically diabetic mice that were treated with vacuum-assisted closure. Cyclical therapy in mice results in increased wound healing, increased nerve fibre density, and faster wound healing due to increased neuropeptide synthesis and growth factor release. Prevention is currently the most effective treatment for ulcers in diabetic and paraplegic patients, as nerve decompression decreases neuropathy, reducing foot ulcers and amputation [333]. The primary therapy for pressure ulcers involves local flaps and

behaviour modification. Treatment was performed by using sensate tensor fascia lata flaps in one group of patients [334] and using sural or sciatic nerve grafts to connect intercostal nerves above the spinal cord injury to the myocutaneous flap covering the defect in two other patients [335, 336]. The sympathetic skin response refers to the transient alteration in the electrical potential of the skin. This response can occur spontaneously or be triggered by various internal or external events that cause arousal. A noninvasive method for studying sympathetic system function involves suprasegmental structures [337]. The scientific and medical communities widely recognize neuropeptides and neurotrophic factors as essential components in healing. The development of therapies utilizing this concept is slowing, indicating the potential for advancements in wound-healing technologies, particularly for patients with diabetes [338]. Severe injuries restrict peripheral nerve regeneration, leading to impaired motor function and long-term impairment. Current treatments fail to optimize nerve cell viability and development. Gene and cell therapy–based medications can promote nerve growth by increasing essential regulators such as neurotrophic factors and extracellular matrix proteins in the targeted area. Growth factors play a unique role in promoting blood vessel expansion or supporting the growth and development of nerve cells. Growth factors have been extensively studied for their ability to accelerate nerve regeneration, with synergistic interactions crucial for angiogenesis and neurogenesis processes. Fibroblast growth factor 2 and VEGF are known for their roles in promoting the formation of new blood vessels. Fibroblast growth factor 2 and VEGF encourage brain cell proliferation, impacting neurodegenerative diseases and promoting regeneration through their neurotrophic and angiogenic capabilities [339]. Severe trauma to the CNS leads to the formation of a scar during wound healing. Scar tissue contains molecular structures similar to those of basement membranes and comprises primarily type IV collagen, glycoproteins, and proteoglycans. The inhibition of collagen scar formation allows the regeneration of cut axons in the brain and spinal cord, allowing them to extend into unaffected CNS tissue [340].

Conclusions

In summary, recent advancements in recognizing the complex role of neuroregulation in the healing of skin wounds represent a fundamental change in our comprehension of the healing process. The complex interaction between the nervous system and the cellular environment of the skin has become a central focus of investigation, providing a detailed understanding of the mechanisms that control tissue healing. Neuroregulation plays a crucial role in wound healing, and recent advances have shown the therapeutic implications for bioelectronic devices and targeted interventions. Understanding neurotrophic factors and neuromodulation techniques can lead to personalized approaches. The understanding of the neuroregulation of wound healing is rapidly advancing with advanced technologies such as artificial intelligence and bioinformatics, which are promising for identifying and understanding neuroimmune interactions. Neurostimulation devices and wearable technologies could revolutionize clinical applications with personalized neuromodulation strategies. The synergy between neuroscience and regenerative medicine is deepening, providing innovative solutions for tissue engineering. Future research will explore the role of neuroregulatory substances in wound healing stages, including inflammation, proliferation, and remodelling, and develop personalized treatments for complex wounds, particularly those in patients with chronic conditions. More research is needed to understand the molecular mechanisms by which the nervous system impacts wound healing. This research involves studying the roles of specific neuropeptides and neurotransmitters and their interactions with keratinocytes, fibroblasts, and immune cells during the healing process. Further research on the interplay between the immunological and neurological systems is crucial for wound healing, as inflammation plays a vital role. Researchers may investigate the impacts of neuroregulatory factors on the activation and resolution of inflammation by immune cells. Neuroregulatory mechanism–based biomarkers can be developed for the early identification of chronic wounds or complications in wound healing, potentially improving patient outcomes. Furthermore, research-based clinical treatments, such as nerve-targeted or neuropeptide-based therapies, could provide new treatments for wounds that are difficult to cure. Technological advancements in imaging, genomics, and proteomics may provide a deeper understanding of the neuroregulatory mechanisms underlying wound healing. These technologies can aid in the development of personalized medical techniques and the discovery of new therapeutic targets. Future research can optimize neuroregulation for skin wound healing, leading to more effective treatment methods and improved patient care.

Ethical approval and consent to participate

Not applicable.

Consent for publication

All the authors agree to publish this review.

Author contributions

Abdullah Al Mamun (Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Resources, Software, Validation, Visualization [equal]), Chuxiao Shao (Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Software, Supervision, Validation, Visualization [equal]), Peiwu Geng (Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Resources, Software, Validation, Visualization [equal]), Shuanghu Wang (Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Supervision, Validation, Visualization [lead]), and Jian Xiao (Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Resources, Supervision, Validation, Visualization [lead], Methodology, Project Administration [equal]).

Conflict of interest

None declared.

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Data availability

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References

1. Sen CK, Gordillo GM, Roy S, Kirsner R, Lambert L, Hunt TK. *et al*. Human skin wounds: a major and snowballing threat to public health and the economy. *Wound Repair Regen*. 2009;**17**:763–71. https://doi.org/10.1111/j.1524-475X.2009.00543.x.
2. Sullivan JV, Myers S. Skin structure and function, wound healing and scarring. In: *Plastic Surgery-Principles and Practice*. Elsevier. 2022, 1–14. https://doi.org/10.1016/B978-0-323-65381-7.00001-0.
3. Gupta D, Kaushik D, Mohan V. Role of neurotransmitters in the regulation of cutaneous wound healing. *Exp Brain Res*. 2022;**240**:1649–59. https://doi.org/10.1007/s00221-022-06372-0.
4. Das S, Baker AB. Biomaterials and nanotherapeutics for enhancing skin wound healing. *Front Bioeng Biotechnol*. 2016;**4**:82. https://doi.org/10.3389/fbioe.2016.00082.
5. Borena BM, Martens A, Broeckx SY, Meyer E, Chiers K, Duchateau L. *et al*. Regenerative skin wound healing in mammals: state-of-the-art on growth factor and stem cell based treatments. *Cell Physiol Biochem*. 2015;**36**:1–23. https://doi.org/10.1159/000374049.
6. Schiavon M, Francescon M, Drigo D, Salloum G, Baraziol R, Tesei J. *et al*. The use of Integra dermal regeneration template versus flaps for reconstruction of full-thickness scalp defects involving the calvaria: a cost–benefit analysis. *Aesth Plast Surg*. 2016;**40**:901–7. doi.org/10.1007/s00266-016-0703-0.
7. Boyce ST, Lalley AL. Tissue engineering of skin and regenerative medicine for wound care. *Burns Trauma*. 2018;**6**:4. https://doi.org/10.1186/s41038-017-0103-y.
8. Tottoli EM, Dorati R, Genta I, Chiesa E, Pisani S, Conti B. Skin wound healing process and new emerging technologies for skin wound care and regeneration. *Pharmaceutics*. 2020;**12**:735. https://doi.org/10.3390/pharmaceutics12080735.
9. Chouhan D, Dey N, Bhardwaj N, Mandal BB. Emerging and innovative approaches for wound healing and skin regeneration: current status and advances. *Biomaterials*. 2019;**216**:119267. https://doi.org/10.1016/j.biomaterials.2019.119267.
10. Ashrafi M, Baguneid M, Bayat A. The role of neuromediators and innervation in cutaneous wound healing. *Acta Derm Venereol*. 2016;**96**:587–94. https://doi.org/10.2340/00015555-2321.
11. Khalil Z, Merhi M. Effects of aging on neurogenic vasodilator responses evoked by transcutaneous electrical nerve stimulation: relevance to wound healing. *J Gerontol Ser A Biol Med Sci*. 2000;**55**:B257–63. https://doi.org/10.1093/gerona/55.6.B257.
12. Sa G, DiPietro LA. Factors affecting wound healing. *J Dent Res*. 2010;**89**:219–29. https://doi.org/10.1177/0022034509359125.
13. Sorg H, Tilkorn DJ, Hager S, Hauser J, Mirastschijski U. Skin wound healing: an update on the current knowledge and concepts. *Eur Surg Res*. 2017;**58**:81–94. https://doi.org/10.1159/000454919.
14. Darsow U, Ring J. Neuroimmune interactions in the skin. *Curr Opin Allergy Clin Immunol*. 2001;**1**:435–9. https://doi.org/10.1097/00130832-200110000-00009.
15. Cevikbas F, Steinhoff A, Homey B, Steinhoff M. Neuroimmune interactions in allergic skin diseases. *Curr Opin Allergy Clin Immunol*. 2007;**7**:365–73. https://doi.org/10.1097/ACI.0b013e3282a644d2.
16. Roosterman D, Goerge T, Schneider SW, Bunnett NW, Steinhoff M. Neuronal control of skin function: the skin as a neuroimmunoendocrine organ. *Physiol Rev*. 2006;**86**:1309–79. https://doi.org/10.1152/physrev.00026.2005.
17. Khalil Z, Helme R. Sensory peptides as neuromodulators of wound healing in aged rats. *J Gerontol Ser A Biol Med Sci*. 1996;**51**:B354–61. https://doi.org/10.1093/gerona/51A.5.B354.
18. Del Conde I, Shrimpton CN, Thiagarajan P, López JA. Tissue-factor–bearing microvesicles arise from lipid rafts and fuse with activated platelets to initiate coagulation. *Blood*. 2005;**106**:1604–11. https://doi.org/10.1182/blood-2004-03-1095.
19. Lee JH, Jung H, Song J, Choi ES, You G, Mok H. Activated platelet-derived vesicles for efficient hemostatic activity. *Macromol Biosci*. 2020;**20**:e1900338. https://doi.org/10.1002/mabi.201900338.
20. Kim JY, Song S-H, Kim KL, Ko J-J, Im J-E, Yie SW. *et al*. Human cord blood-derived endothelial progenitor cells and their conditioned media exhibit therapeutic equivalence for diabetic wound healing. *Cell Transplant*. 2010;**19**:1635–44. https://doi.org/10.3727/096368910X516637.
21. Huang P, Bi J, Owen GR, Chen W, Rokka A, Koivisto L. *et al*. Keratinocyte microvesicles regulate the expression of multiple genes in dermal fibroblasts. *J Invest Dermatol*. 2015;**135**:3051–9. https://doi.org/10.1038/jid.2015.320.
22. Arif S, Larochelle S, Moulin VJ. PLGF-1 contained in normal wound myofibroblast-derived microvesicles stimulated collagen production by dermal fibroblasts. *J Cell Commun Signal*. 2020;**14**:427–38. https://doi.org/10.1007/s12079-020-00572-5.
23. Evers LH, Bhavsar D, Mailänder P. The biology of burn injury. *Exp Dermatol*. 2010;**19**:777–83. https://doi.org/10.1111/j.1600-0625.2010.01105.x.
24. Szpaderska AM, Egozi EI, Gamelli RL, DiPietro LA. The effect of thrombocytopenia on dermal wound healing. *J Invest Dermatol*. 2003;**120**:1130–7. https://doi.org/10.1016/S0022-202X(18)32320-0.
25. Daley JM, Reichner JS, Mahoney EJ, Manfield L, Henry WL, Mastrofrancesco B. *et al*. Modulation of macrophage phenotype by soluble product (s) released from neutrophils. *J Immunol*. 2005;**174**:2265–72. https://doi.org/10.4049/jimmunol.174.4.2265.
26. Tziotzios C, Profyris C, Sterling J. Cutaneous scarring: pathophysiology, molecular mechanisms, and scar reduction therapeutics: part II. Strategies to reduce scar formation after dermatologic procedures. *J Am Acad Dermatol*. 2012;**66**:13–24. https://doi.org/10.1016/j.jaad.2011.08.035.
27. Profyris C, Tziotzios C, Do VI. Cutaneous scarring: pathophysiology, molecular mechanisms, and scar reduction therapeutics: part I. The molecular basis of scar formation. *J Am Acad Dermatol*. 2012;**66**:1–10. https://doi.org/10.1016/j.jaad.2011.05.055.
28. Frank S, Kämpfer H, Wetzler C, Stallmeyer B, Pfeilschifter J. Large induction of the chemotactic cytokine RANTES during cutaneous wound repair: a regulatory role for nitric oxide in keratinocyte-derived RANTES expression. *Biochem J*. 2000;**347**:265–73. https://doi.org/10.1042/bj3470265.
29. Werner S, Grose R. Regulation of wound healing by growth factors and cytokines. *Physiol Rev*. 2003;**83**:835–70. https://doi.org/10.1152/physrev.2003.83.3.835.
30. Schäffer M, Beiter T, Becker HD, Hunt TK. Neuropeptides: mediators of inflammation and tissue repair? *Arch Surg*. 1998;**133**:1107–16. https://doi.org/10.1001/archsurg.133.10.1107.
31. Ralevic V, Milner P, Hudlicka O, Kristek F, Burnstock G. Substance P is released from the endothelium of normal and capsaicin-treated rat hind-limb vasculature, in vivo, by increased flow. *Circ Res*. 1990;**66**:1178–83. https://doi.org/10.1161/01.RES.66.5.1178.
32. Liu JY, Hu JH, Zhu QG, Li FQ, Sun HJ. Substance P receptor expression in human skin keratinocytes and fibroblasts. *Br J Dermatol*. 2006;**155**:657–62. https://doi.org/10.1111/j.1365-2133.2006.07408.x.
33. Emanueli C, Salis MB, Pinna A, Graiani G, Manni L, Madeddu P. Nerve growth factor promotes angiogenesis and arteriogenesis in ischemic hindlimbs. *Circulation*. 2002;**106**:2257–62. https://doi.org/10.1161/01.CIR.0000033971.56802.C5.

34. Frank S, Kämpfer H, Wetzler C, Pfeilschifter J. Nitric oxide drives skin repair: novel functions of an established mediator. *Kidney Int*. 2002;**61**:882–8. https://doi.org/10.1046/j.1523-1755.2002.00237.x.
35. Baraniuk JN, Kowalski ML, Kaliner MA. Relationships between permeable vessels, nerves, and mast cells in rat cutaneous neurogenic inflammation. *J Appl Physiol*. 1990;**68**:2305–11. https://doi.org/10.1152/jappl.1990.68.6.2305.
36. Lindsey KQ, Caughman SW, Olerud JE, Bunnett NW, Armstrong CA, Ansel JC. Neural regulation of endothelial cell-mediated inflammation. *J Investig Dermatol Symp Proc*. 2000;**5**Elsevier: 74–8. https://doi.org/10.1046/j.1087-0024.2000.00013.x.
37. Helme R, Eglezos A, Hosking C. Substance P induces chemotaxis of neutrophils in normal and capsaicin-treated rats. *Immunol Cell Biol*. 1987;**65**:267–9. https://doi.org/10.1038/icb.1987.30.
38. Lambert R, Granstein R. Neuropeptides and Langerhans cells. *Exp Dermatol*. 1998;**7**:73–80. https://doi.org/10.1111/j.1600-0625.1998.tb00306.x.
39. Luger T, Lotti T. Neuropeptides: role in inflammatory skin diseases. *J Eur Acad Dermatol Venereol*. 1998;**10**:207–11. https://doi.org/10.1111/j.1468-3083.1998.tb00736.x.
40. Okamoto A, Lovett M, Payan D, Bunnett N. Interactions between neutral endopeptidase (EC 3.4. 24.11) and the substance P (NK1) receptor expressed in mammalian cells. *Biochem J*. 1994;**299**: 683–93. https://doi.org/10.1042/bj2990683.
41. Ansel JC, Kaynard AH, Armstrong CA, Olerud J, Bunnett N, Payan D. Skin-nervous system interactions. *J Invest Dermatol*. 1996;**106**:198–204. https://doi.org/10.1111/1523-1747.ep12330326.
42. Slominski A, Wortsman J. Neuroendocrinology of the skin. *Endocr Rev*. 2000;**21**:457–87. https://doi.org/10.1210/edrv.21.5.0410.
43. Arbiser JL, Karalis K, Viswanathan A, Koike C, Anand-Apte B, Flynn E. *et al*. Corticotropin-releasing hormone stimulates angiogenesis and epithelial tumor growth in the skin. *J Invest Dermatol*. 1999;**113**:838–42. https://doi.org/10.1046/j.1523-1747.1999.00760.x.
44. Gamse R, Saria A. Potentiation of tachykinin-induced plasma protein extravasation by calcitonin gene-related peptide. *Eur J Pharmacol*. 1985;**114**:61–6. https://doi.org/10.1016/0014-2999(85)90520-5.
45. Cruwys S, Kidd B, Mapp P, Walsh D, Blake D. The effects of calcitonin gene-related peptide on formation of intra-articular oedema by inflammatory mediators. *Br J Pharmacol*. 1992;**107**: 116–9. https://doi.org/10.1111/j.1476-5381.1992.tb14472.x.
46. Cruise BA, Xu P, Hall AK. Wounds increase activin in skin and a vasoactive neuropeptide in sensory ganglia. *Dev Biol*. 2004;**271**: 1–10. https://doi.org/10.1016/j.ydbio.2004.04.003.
47. Bowles WR, Harding-Rose C, Hargreaves KM. Chronic nerve growth factor administration increases the peripheral exocytotic activity of capsaicin-sensitive cutaneous neurons. *Neurosci Lett*. 2006;**403**:305–8. https://doi.org/10.1016/j.neulet.2006.05.020.
48. Kim LR, Pomeranz B. The sympathomimetic agent, 6-hydroxydopamine, accelerates cutaneous wound healing. *Eur J Pharmacol*. 1999;**376**:257–64. https://doi.org/10.1016/S0014-2999(99)00391-X.
49. Drummond PD, Drummond ES, Dawson LF, Mitchell V, Finch PM, Vaughan CW. *et al*. Upregulation of α1-adrenoceptors on cutaneous nerve fibres after partial sciatic nerve ligation and in complex regional pain syndrome type II. *Pain*. 2014;**155**:606–16. https://doi.org/10.1016/j.pain.2013.12.021.
50. Hong Y-K, Chang Y-H, Lin Y-C, Chen B, Guevara BEK, Hsu C-K. Inflammation in wound healing and pathological scarring. *Adv Wound Care*. 2023;**12**:288–300. https://doi.org/10.1089/wound.2021.0161.
51. Huang C, Dong L, Zhao B, Lu Y, Huang S, Yuan Z. *et al*. Anti-inflammatory hydrogel dressings and skin wound healing. *Clin Transl Med*. 2022;**12**:e1094. https://doi.org/10.1002/ctm2.1094.
52. Landén NX, Li D, Ståhle M. Transition from inflammation to proliferation: a critical step during wound healing. *Cell Mol Life Sci*. 2016;**73**:3861–85. https://doi.org/10.1007/s00018-016-2268-0.
53. Kähler CM, Herold M, Reinisch N, Wiedermann CJ. Interaction of substance P with epidermal growth factor and fibroblast growth factor in cyclooxygenase-dependent proliferation of human skin fibroblasts. *J Cell Physiol*. 1996;**166**:601–8. https://doi.org/10.1002/(SICI)1097-4652(199603)166:3<601::AID-JCP15>3.0.CO;2-9.
54. Tanaka T, Danno K, Ikai K, Imamura S. Effects of substance P and substance K on the growth of cultured keratinocytes. *J Invest Dermatol*. 1988;**90**:399–401. https://doi.org/10.1111/1523-1747.ep12456487.
55. Ziche M, Morbidelli L, Pacini M, Dolara P, Maggi CA. NK1-receptors mediate the proliferative response of human fibroblasts to tachykinins. *Br J Pharmacol*. 1990;**100**:11–4. https://doi.org/10.1111/j.1476-5381.1990.tb12043.x.
56. Lai X, Wang Z, Wei L, Wang L. Effect of substance P released from peripheral nerve ending on endogenous expression of epidermal growth factor and its receptor in wound healing. *Chin J Traumatol*. 2002;**5**:176–9.
57. Aloe L, Tirassa P, Laudiero L. Nerve growth factor in neurological and non-neurological diseases: basic findings and emerging pharmacological prospectives. *Curr Pharm Des*. 2001;**7**:113–23. https://doi.org/10.2174/1381612013398383.
58. Sofroniew MV, Howe CL, Mobley WC. Nerve growth factor signaling, neuroprotection, and neural repair. *Annu Rev Neurosci*. 2001;**24**:1217–81. https://doi.org/10.1146/annurev.neuro.24.1.1217.
59. Banks BE, Vernon C, Warner JA. Nerve growth factor has anti-inflammatory activity in the rat hindpaw oedema test. *Neurosci Lett*. 1984;**47**:41–5. https://doi.org/10.1016/0304-3940(84)90383-5.
60. Aloe L. Nerve growth factor, human skin ulcers and vascularization. Our experience. *Prog Brain Research*. 2004;**146**:515–22. https://doi.org/10.1016/S0079-6123(03)46032-9.
61. Burbach GJ, Kim KH, Zivony AS, Kim A, Aranda J, Wright S. *et al*. The neurosensory tachykinins substance P and neurokinin A directly induce keratinocyte nerve growth factor. *J Invest Dermatol*. 2001;**117**:1075–82. https://doi.org/10.1046/j.0022-202x.2001.01498.x.
62. Baroni A, Perfetto B, Canozo N, Braca A, Farina E, Melito A. *et al*. Bombesin: a possible role in wound repair. *Peptides*. 2008;**29**: 1157–66. https://doi.org/10.1016/j.peptides.2008.03.006.
63. Seike M, Ikeda M, Morimoto A, Matsumoto M, Kodama H. Increased synthesis of calcitonin gene-related peptide stimulates keratinocyte proliferation in murine UVB-irradiated skin. *J Dermatol Sci*. 2002;**28**:135–43. https://doi.org/10.1016/S0923-1811(01)00155-4.
64. El-Salhy M, Tjomsland V, Theodorsson E. Effects of triple treatment with octreotide, galanin and serotonin on a human pancreas cancer cell line in xenografts. *Histol Histopathol*. 2005;**20**:745–52. https://doi.org/10.3892/or.13.1.45.
65. Dallos A, Kiss M, Polyánka H, Dobozy A, Kemény L, Husz S. Effects of the neuropeptides substance P, calcitonin gene-related peptide, vasoactive intestinal polypeptide and galanin on the production of nerve growth factor and inflammatory cytokines in cultured human keratinocytes. *Neuropeptides*. 2006;**40**:251–63. https://doi.org/10.1016/j.npep.2006.06.002.
66. Wollina U, Knöll B, Prüfer K. Vasoactive intestinal peptide (VIP) supports migration and growth of human keratinocytes on polyurethane foils. *J Dermatol Sci*. 1993;**6**:55. https://doi.org/10.1016/0923-1811(93)91028-S.
67. González C, Barroso C, Martín C, Gulbenkian S, Estrada C. Neuronal nitric oxide synthase activation by vasoactive intestinal peptide in bovine cerebral arteries. *J Cereb Blood Flow Metab*. 1997;**17**:977–84. https://doi.org/10.1097/00004647-199709000-00007.

68. Rayan G, Johnson C, Pitha J, Cahill S, Said S. Vasoactive intestinal peptide and nerve growth factor effects on nerve regeneration. *J Okla State Med Assoc*. 1995;**88**:337–41.
69. Moller K, Zhang Y-Z, Håkanson R, Luts A, Sjölund B, Uddman R. *et al*. Pituitary adenylate cyclase activating peptide is a sensory neuropeptide: immunocytochemical and immunochemical evidence. *Neuroscience*. 1993;**57**:725–32. https://doi.org/10.1016/0306-4522(93)90018-B.
70. Warren J, Larkin S, Coughlan M, Kajekar R, Williams T. Pituitary adenylate cyclase activating polypeptide is a potent vasodilator and oedema potentiator in rabbit skin in vivo. *Br J Pharmacol*. 1992;**106**:331–4. https://doi.org/10.1111/j.1476-5381.1992.tb14336.x.
71. Granoth R, Fridkin M, Gozes I. VIP and the potent analog, stearyl-Nle17-VIP, induce proliferation of keratinocytes. *FEBS Lett*. 2000;**475**:78–83. https://doi.org/10.1016/S0014-5793(00)01628-8.
72. Piascik MT, Perez DM. α1-adrenergic receptors: new insights and directions. *J Pharmacol Exp Ther*. 2001;**298**:403–10.
73. Gonzalez-Cabrera PJ, Shi T, Yun J, McCune DF, Rorabaugh BR, Perez DM. Differential regulation of the cell cycle by α1-adrenergic receptor subtypes. *Endocrinology*. 2004;**145**:5157–67. https://doi.org/10.1210/en.2004-0728.
74. Pullar CE, Rizzo A, Isseroff RR. β-Adrenergic receptor antagonists accelerate skin wound healing: evidence for a catecholamine synthesis network in the epidermis. *J Biol Chem*. 2006;**281**:21225–35. https://doi.org/10.1074/jbc.M601007200.
75. Makrantonaki E, Vogel K, Fimmel S, Oeff M, Seltmann H, Zouboulis CC. Interplay of IGF-I and 17β-estradiol at age-specific levels in human sebocytes and fibroblasts in vitro. *Exp Gerontol*. 2008;**43**:939–46. https://doi.org/10.1016/j.exger.2008.07.005.
76. Clark RA. Biology of dermal wound repair. *Dermatol Clin*. 1993;**11**:647–66. https://doi.org/10.1016/S0733-8635(18)30218-3.
77. Freinkel RK, Woodley DT. *The biology of the skin*. CRC Press, 2001.
78. Liao M-H, Liu S-S, Peng I-C, Tsai F-J, Huang HH. The stimulatory effects of alpha1-adrenergic receptors on TGF-beta1, IGF-1 and hyaluronan production in human skin fibroblasts. *Cell Tissue Res*. 2014;**357**:681–93. https://doi.org/10.1007/s00441-014-1893-x.
79. Polak J, Bloom S. Regulatory peptides—the distribution of two newly discovered peptides: PHI and NPY. *Peptides*. 1984;**5**:79–89. https://doi.org/10.1016/0196-9781(84)90267-5.
80. Ekstrand AJ, Cao R, Björndahl M, Nyström S, Jönsson-Rylander A-C, Hassani H. *et al*. Deletion of neuropeptide Y (NPY) 2 receptor in mice results in blockage of NPY-induced angiogenesis and delayed wound healing. *Proc Natl Acad Sci*. 2003;**100**:6033–8. https://doi.org/10.1073/pnas.1135965100.
81. Jain M, LoGerfo FW, Guthrie P, Pradhan L. Effect of hyperglycemia and neuropeptides on interleukin-8 expression and angiogenesis in dermal microvascular endothelial cells. *J Vasc Surg*. 2011;**53**:1654–1660.e2. https://doi.org/10.1016/j.jvs.2011.02.019.
82. Karimi K, Odhav A, Kollipara R, Fike J, Stanford C, Hall JC. Acute cutaneous necrosis: a guide to early diagnosis and treatment. *J Cutan Med Surg*. 2017;**21**:425–37. https://doi.org/10.1177/1203475417708164.
83. Lazarus GS, Cooper DM, Knighton DR, Margolis DJ, Percoraro RE, Rodeheaver G. *et al*. Definitions and guidelines for assessment of wounds and evaluation of healing. *Wound Repair Regen*. 1994;**2**:165–70. https://doi.org/10.1046/j.1524-475X.1994.20305.x.
84. Ward J, Holden J, Grob M, Soldin M. Management of wounds in the community: five principles. *Br J Community Nurs*. 2019;**24**:S20–3. https://doi.org/10.12968/bjcn.2019.24.Sup6.S20.
85. Wallace LA, Gwynne L, Jenkins T. Challenges and opportunities of pH in chronic wounds. *Ther Deliv*. 2019;**10**:719–35. https://doi.org/10.4155/tde-2019-0066.
86. El Ayadi A, Jay JW, Prasai A. Current approaches targeting the wound healing phases to attenuate fibrosis and scarring. *Int J Mol Sci*. 2020;**21**:1105. https://doi.org/10.3390/ijms21031105.
87. Bielefeld KA, Amini-Nik S, Alman BA. Cutaneous wound healing: recruiting developmental pathways for regeneration. *Cell Mol Life Sci*. 2013;**70**:2059–81. https://doi.org/10.1007/s00018-012-1152-9.
88. George Broughton I, Janis JE, Attinger CE. The basic science of wound healing. *Plast Reconstr Surg*. 2006;**117**:12S–34. https://doi.org/10.1097/01.prs.0000225430.42531.c2.
89. Erickson JR, Echeverri K. Learning from regeneration research organisms: the circuitous road to scar free wound healing. *Dev Biol*. 2018;**433**:144–54. https://doi.org/10.1016/j.ydbio.2017.09.025.
90. Gethin G. Understanding the inflammatory process in wound healing. *Br J Community Nurs*. 2012;**17**:S17–22. https://doi.org/10.12968/bjcn.2012.17.Sup3.S17.
91. Velnar T, Bailey T, Smrkolj V. The wound healing process: an overview of the cellular and molecular mechanisms. *J Int Med Res*. 2009;**37**:1528–42. https://doi.org/10.1177/147323000903700531.
92. Kim HS, Sun X, Lee J-H, Kim H-W, Fu X, Leong KW. Advanced drug delivery systems and artificial skin grafts for skin wound healing. *Adv Drug Deliv Rev*. 2019;**146**:209–39. https://doi.org/10.1016/j.addr.2018.12.014.
93. Diller RB, Tabor AJ. The role of the extracellular matrix (ECM) in wound healing: a review. *Biomimetics*. 2022;**7**:87. https://doi.org/10.3390/biomimetics7030087.
94. Usui ML, Underwood RA, Mansbridge JN, Muffley LA, Carter WG, Olerud JE. Morphological evidence for the role of suprabasal keratinocytes in wound reepithelialization. *Wound Repair Regen*. 2005;**13**:468–79. https://doi.org/10.1111/j.1067-1927.2005.00067.x.
95. Enoch S, Leaper DJ. Basic science of wound healing. *Surgery (Oxford)*. 2008;**26**:31–7. https://doi.org/10.1016/j.mpsur.2007.11.005.
96. Raziyeva K, Kim Y, Zharkinbekov Z, Kassymbek K, Jimi S, Saparov A. Immunology of acute and chronic wound healing. *Biomol Ther*. 2021;**11**:700. https://doi.org/10.3390/biom11050700.
97. Lindholm C, Searle R. Wound management for the 21st century: combining effectiveness and efficiency. *Int Wound J*. 2016;**13**:5–15. https://doi.org/10.1111/iwj.12623.
98. Mustoe T. Understanding chronic wounds: a unifying hypothesis on their pathogenesis and implications for therapy. *Am J Surg*. 2004;**187**:S65–70. https://doi.org/10.1016/S0002-9610(03)00306-4.
99. Chen J, Ye P, Gu R, Zhu H, He W, Mu X. *et al*. Neuropeptide substance P: a promising regulator of wound healing in diabetic foot ulcers. *Biochem Pharmacol*. 2023;**215**:115736. https://doi.org/10.1016/j.bcp.2023.115736.
100. Zhao G, Usui ML, Lippman SI, James GA, Stewart PS, Fleckman P. *et al*. Biofilms and inflammation in chronic wounds. *Adv Wound Care*. 2013;**2**:389–99. https://doi.org/10.1089/wound.2012.0381.
101. McCarty SM, Percival SL. Proteases and delayed wound healing. *Adv Wound Care*. 2013;**2**:438–47. https://doi.org/10.1089/wound.2012.0370.
102. Ben-Porath I, Weinberg RA. The signals and pathways activating cellular senescence. *Int J Biochem Cell Biol*. 2005;**37**:961–76. https://doi.org/10.1016/j.biocel.2004.10.013.
103. Schultz GS, Sibbald RG, Falanga V, Ayello EA, Dowsett C, Harding K. *et al*. Wound bed preparation: a systematic approach to wound management. *Wound Repair Regen*. 2003;**11**:S1–28. https://doi.org/10.1046/j.1524-475X.11.s2.1.x.

104. Loots MA, Lamme EN, Zeegelaar J, Mekkes JR, Bos JD, Middelkoop E. Differences in cellular infiltrate and extracellular matrix of chronic diabetic and venous ulcers versus acute wounds. *J Invest Dermatol*. 1998;**111**:850–7. https://doi.org/10.1046/j.1523-1747.1998.00381.x.
105. Kuo P-C, Kao C-H, Chen J-K. Glycated type 1 collagen induces endothelial dysfunction in culture. *In Vitro Cell Dev Biol A*. 2007;**43**:338–43. https://doi.org/10.1007/s11626-007-9058-9.
106. Xiao T, Yan Z, Xiao S, Xia Y. Proinflammatory cytokines regulate epidermal stem cells in wound epithelialization. *Stem Cell Res Ther*. 2020;**11**:232. https://doi.org/10.1186/s13287-020-01755-y.
107. Volk SW, Bohling MW. Comparative wound healing—are the small animal veterinarian's clinical patients an improved translational model for human wound healing research? *Wound Repair Regen*. 2013;**21**:372–81. https://doi.org/10.1111/wrr.12049.
108. Knobloch K, Vogt P. Die rekonstruktive Sequenz des 21. Jahrhunderts. *Chirurg*. 2010;**81**:441–6. https://doi.org/10.1007/s00104-010-1917-3.
109. Rittié L. Cellular mechanisms of skin repair in humans and other mammals. *J Cell Commun Signal*. 2016;**10**:103–20. https://doi.org/10.1007/s12079-016-0330-1.
110. Rittié L, Sachs DL, Orringer JS, Voorhees JJ, Fisher GJ. Eccrine sweat glands are major contributors to reepithelialization of human wounds. *Am J Pathol*. 2013;**182**:163–71. https://doi.org/10.1016/j.ajpath.2012.09.019.
111. Rittie L, Farr EA, Orringer JS, Voorhees JJ, Fisher GJ. Reduced cell cohesiveness of outgrowths from eccrine sweat glands delays wound closure in elderly skin. *Aging Cell*. 2016;**15**:842–52. https://doi.org/10.1111/acel.12493.
112. Krawczyk WS. A pattern of epidermal cell migration during wound healing. *J Cell Biol*. 1971;**49**:247–63. https://doi.org/10.1083/jcb.49.2.247.
113. Lambert WC, Cohen PJ, Lambert MW. Role of the epidermis and other epithelia in wound healing: selected concepts. *Clin Dermatol*. 1984;**2**:24–33. https://doi.org/10.1016/0738-081X(84)90024-5.
114. Gov NS. Collective cell migration patterns: follow the leader. *Proc Natl Acad Sci*. 2007;**104**:15970–1. https://doi.org/10.1073/pnas.0708037104.
115. Omelchenko T, Vasiliev JM, Gelfand I, Feder H, Bonder E. Rho-dependent formation of epithelial "leader" cells during wound healing. *Proc Natl Acad Sci*. 2003;**100**:10788–93. https://doi.org/10.1073/pnas.1834401100.
116. Farooqui R, Fenteany G. Multiple rows of cells behind an epithelial wound edge extend cryptic lamellipodia to collectively drive cell-sheet movement. *J Cell Sci*. 2005;**118**:51–63. https://doi.org/10.1242/jcs.01577.
117. Jacinto A, Martinez-Arias A, Martin P. Mechanisms of epithelial fusion and repair. *Nat Cell Biol*. 2001;**3**:E117–23. https://doi.org/10.1038/35074643.
118. Stone RC, Pastar I, Ojeh N, Chen V, Liu S, Garzon KI. *et al.* Epithelial-mesenchymal transition in tissue repair and fibrosis. *Cell Tissue Res*. 2016;**365**:495–506. https://doi.org/10.1007/s00441-016-2464-0.
119. Santoro MM, Gaudino G. Cellular and molecular facets of keratinocyte reepithelization during wound healing. *Exp Cell Res*. 2005;**304**:274–86. https://doi.org/10.1016/j.yexcr.2004.10.033.
120. Blanpain C, Fuchs E. Plasticity of epithelial stem cells in tissue regeneration. *Science*. 2014;**344**:1242281. https://doi.org/10.1126/science.1242281.
121. Donati G, Watt FM. Stem cell heterogeneity and plasticity in epithelia. *Cell Stem Cell*. 2015;**16**:465–76. https://doi.org/10.1016/j.stem.2015.04.014.
122. Pastar I, Stojadinovic O, Yin NC, Ramirez H, Nusbaum AG, Sawaya A. *et al.* Epithelialization in wound healing: a comprehensive review. *Adv Wound Care*. 2014;**3**:445–64. https://doi.org/10.1089/wound.2013.0473.
123. Stojadinovic O, Pastar I, Nusbaum AG, Vukelic S, Krzyzanowska A, Tomic-Canic M. Deregulation of epidermal stem cell niche contributes to pathogenesis of nonhealing venous ulcers. *Wound Repair Regen*. 2014;**22**:220–7. https://doi.org/10.1111/wrr.12142.
124. Chen D, Hao H, Fu X, Han W. Insight into reepithelialization: how do mesenchymal stem cells perform? *Stem Cells Int*. 2016;**2016**:6120173. https://doi.org/10.1155/2016/6120173.
125. Yang M, Li Q, Sheng L, Li H, Weng R, Zan T. Bone marrow–derived mesenchymal stem cells transplantation accelerates tissue expansion by promoting skin regeneration during expansion. *Ann Surg*. 2011;**253**:202–9. https://doi.org/10.1097/SLA.0b013e3181f9ba1ah.
126. Tenenhaus M, Rennekampff H-O. Current concepts in tissue engineering: skin and wound. *Plast Reconstr Surg*. 2016;**138**:42S–50. https://doi.org/10.1097/PRS.0000000000002685.
127. Buchanan EP, Longaker MT, Lorenz HP. Fetal skin wound healing. *Adv Clin Chem*. 2009;**48**:137–61. https://doi.org/10.1016/S0065-2423(09)48006-5.
128. Lorenz HP, Whitby DJ, Longaker MT, Adzick NS, Fetal wound healing. The ontogeny of scar formation in the non-human primate. *Ann Surg*. 1993;**217**:391–6. https://doi.org/10.1097/00000658-199304000-00011.
129. Walraven M. *Cellular and molecular mechanisms involved in scarless wound healing in the fetal skin*. Vrije universiteit amsterdam, 2016.
130. Walraven M, Gouverneur M, Middelkoop E, Beelen RH, Ulrich MM. Altered TGF-β signaling in fetal fibroblasts: what is known about the underlying mechanisms? *Wound Repair Regen*. 2014;**22**:3–13. https://doi.org/10.1111/wrr.12098.
131. Tomasek JJ, Gabbiani G, Hinz B, Chaponnier C, Brown RA. Myofibroblasts and mechano-regulation of connective tissue remodelling. *Nat Rev Mol Cell Biol*. 2002;**3**:349–63. https://doi.org/10.1038/nrm809.
132. Mirastschijski U, Schnabel R, Claes J, Schneider W, Ågren MS, Haaksma C. *et al.* Matrix metalloproteinase inhibition delays wound healing and blocks the latent transforming growth factor-β1-promoted myofibroblast formation and function. *Wound Repair Regen*. 2010;**18**:223–34. https://doi.org/10.1111/j.1524-475X.2010.00574.x.
133. Hinz B, Mastrangelo D, Iselin CE, Chaponnier C, Gabbiani G. Mechanical tension controls granulation tissue contractile activity and myofibroblast differentiation. *Am J Pathol*. 2001;**159**:1009–20. https://doi.org/10.1016/S0002-9440(10)61776-2.
134. Armour A, Scott PG, Tredget EE. Cellular and molecular pathology of HTS: basis for treatment. *Wound Repair Regen*. 2007;**15**:S6–17. https://doi.org/10.1111/j.1524-475X.2007.00219.x.
135. Wassermann R, Polo M, Smith P, Wang X, Ko F, Robson M. Differential production of apoptosis-modulating proteins in patients with hypertrophic burn scar. *J Surg Res*. 1998;**75**:74–80. https://doi.org/10.1006/jsre.1998.5267.
136. Ud-Din S, Volk SW, Bayat A. Regenerative healing, scar-free healing and scar formation across the species: current concepts and future perspectives. *Exp Dermatol*. 2014;**23**:615–9. https://doi.org/10.1111/exd.12457.
137. Mustoe TA, Cooter RD, Gold MH, Hobbs FR, Ramelet A-A, Shakespeare PG. *et al.* International clinical recommendations on scar management. *Plast Reconstr Surg*. 2002;**110**:560–71. https://doi.org/10.1097/00006534-200208000-00031.
138. Monstrey S, Middelkoop E, Vranckx JJ, Bassetto F, Ziegler UE, Meaume S. *et al.* Updated scar management practical guidelines: non-invasive and invasive measures. *J Plast Reconstr Aesthet Surg*. 2014;**67**:1017–25. https://doi.org/10.1016/j.bjps.2014.04.011.
139. O'Brien L, Jones DJ, Cochrane Wounds Group. Silicone gel sheeting for preventing and treating hypertrophic and keloid scars.

Cochrane Database Syst Rev. 2013;**2013**:CD003826. https://doi.org/10.1002/14651858.CD003826.pub3.
140. Van den Kerckhove E, Stappaerts K, Fieuws S, Laperre J, Massage P, Flour M. *et al*. The assessment of erythema and thickness on burn related scars during pressure garment therapy as a preventive measure for hypertrophic scarring. *Burns*. 2005;**31**:696–702. https://doi.org/10.1016/j.burns.2005.04.014.
141. Occleston NL, O'Kane S, Goldspink N, Ferguson MW. New therapeutics for the prevention and reduction of scarring. *Drug Discov Today*. 2008;**13**:973–81. https://doi.org/10.1016/j.drudis.2008.08.009.
142. Hinz B. Targeting the myofibroblast to improve wound healing. In: *Wound Healing Biomaterials*. Elsevier. 2016, 69–100. https://doi.org/10.1016/B978-1-78242-455-0.00003-3.
143. Iannello S, Milazzo P, Bordonaro F, Belfiore F. Low-dose enalapril in the treatment of surgical cutaneous hypertrophic scar and keloid-two case reports and literature review. *Medscape Gen Med*. 2006;**8**:60.
144. Ko JH, Kim PS, Zhao Y, Hong SJ, Mustoe TA. HMG-CoA reductase inhibitors (statins) reduce hypertrophic scar formation in a rabbit ear wounding model. *Plast Reconstr Surg*. 2012;**129**:252e–61. https://doi.org/10.1097/PRS.0b013e31823aea10.
145. Guerra A, Belinha J, Jorge RN. Modelling skin wound healing angiogenesis: a review. *J Theor Biol*. 2018;**459**:1–17. https://doi.org/10.1016/j.jtbi.2018.09.020.
146. Demidova-Rice TN, Durham JT, Herman IM. Wound healing angiogenesis: innovations and challenges in acute and chronic wound healing. *Adv Wound Care*. 2012;**1**:17–22. https://doi.org/10.1089/wound.2011.0308.
147. Dulmovits BM, Herman IM. Microvascular remodeling and wound healing: a role for pericytes. *Int J Biochem Cell Biol*. 2012;**44**:1800–12. https://doi.org/10.1016/j.biocel.2012.06.031.
148. Sorg H, Krueger C, Vollmar B. Intravital insights in skin wound healing using the mouse dorsal skin fold chamber. *J Anat*. 2007;**211**:810–8. https://doi.org/10.1111/j.1469-7580.2007.00822.x.
149. Kusindarta DL, Wihadmadyatami H, Fibrianto YH, Nugroho WS, Susetya H, Musana DK. *et al*. Human umbilical mesenchymal stem cells conditioned medium promote primary wound healing regeneration. *Vet World*. 2016;**9**:605–10. https://doi.org/10.14202/vetworld.2016.605-610.
150. Milan PB, Lotfibakhshaiesh N, Joghataie M, Ai J, Pazouki A, Kaplan D. *et al*. Accelerated wound healing in a diabetic rat model using decellularized dermal matrix and human umbilical cord perivascular cells. *Acta Biomater*. 2016;**45**:234–46. https://doi.org/10.1016/j.actbio.2016.08.053.
151. Kong P, Xie X, Li F, Liu Y, Lu Y. Placenta mesenchymal stem cell accelerates wound healing by enhancing angiogenesis in diabetic Goto-Kakizaki (GK) rats. *Biochem Biophys Res Commun*. 2013;**438**:410–9. https://doi.org/10.1016/j.bbrc.2013.07.088.
152. Bodnar RJ. Chemokine regulation of angiogenesis during wound healing. *Adv Wound Care*. 2015;**4**:641–50. https://doi.org/10.1089/wound.2014.0594.
153. Barcelos LS, Duplaa C, Kränkel N, Graiani G, Invernici G, Katare R. *et al*. Human CD133+ progenitor cells promote the healing of diabetic ischemic ulcers by paracrine stimulation of angiogenesis and activation of Wnt signaling. *Circ Res*. 2009;**104**:1095–102. https://doi.org/10.1161/CIRCRESAHA.108.192138.
154. Lee KB, Choi J, Cho SB, Chung JY, Moon ES, Kim NS. *et al*. Topical embryonic stem cells enhance wound healing in diabetic rats. *J Orthop Res*. 2011;**29**:1554–62. https://doi.org/10.1002/jor.21385.
155. Bodnar RJ, Satish L, Yates CC, Wells A. Pericytes: a newly recognized player in wound healing. *Wound Repair Regen*. 2016;**24**:204–14. https://doi.org/10.1111/wrr.12415.
156. Vestweber D. How leukocytes cross the vascular endothelium. *Nat Rev Immunol*. 2015;**15**:692–704. https://doi.org/10.1038/nri3908.
157. Proebstl D, Voisin M-B, Woodfin A, Whiteford J, D'Acquisto F, Jones GE. *et al*. Pericytes support neutrophil subendothelial cell crawling and breaching of venular walls in vivo. *J Exp Med*. 2012;**209**:1219–34. https://doi.org/10.1084/jem.20111622.
158. Voisin M-B, Nourshargh S. Neutrophil transmigration: emergence of an adhesive cascade within venular walls. *J Innate Immun*. 2013;**5**:336–47. https://doi.org/10.1159/000346659.
159. Ayres-Sander CE, Lauridsen H, Maier CL, Sava P, Pober JS, Gonzalez AL. Transendothelial migration enables subsequent transmigration of neutrophils through underlying pericytes. *PLoS One*. 2013;**8**:e60025. https://doi.org/10.1371/journal.pone.0060025.
160. Pober JS, Tellides G. Participation of blood vessel cells in human adaptive immune responses. *Trends Immunol*. 2012;**33**:49–57. https://doi.org/10.1016/j.it.2011.09.006.
161. Humphreys BD, Lin S-L, Kobayashi A, Hudson TE, Nowlin BT, Bonventre JV. *et al*. Fate tracing reveals the pericyte and not epithelial origin of myofibroblasts in kidney fibrosis. *Am J Pathol*. 2010;**176**:85–97. https://doi.org/10.2353/ajpath.2010.090517.
162. Yemisci M, Gursoy-Ozdemir Y, Vural A, Can A, Topalkara K, Dalkara T. Pericyte contraction induced by oxidative-nitrative stress impairs capillary reflow despite successful opening of an occluded cerebral artery. *Nat Med*. 2009;**15**:1031–7. https://doi.org/10.1038/nm.2022.
163. DiPietro LA. Angiogenesis and wound repair: when enough is enough. *J Leukoc Biol*. 2016;**100**:979–84. https://doi.org/10.1189/jlb.4MR0316-102R.
164. Wietecha MS, Król MJ, Michalczyk ER, Chen L, Gettins PG, DiPietro LA. Pigment epithelium-derived factor as a multifunctional regulator of wound healing. *Am J Phys Heart Circ Phys*. 2015;**309**:H812–26. https://doi.org/10.1152/ajpheart.00153.2015.
165. Szpaderska A, Walsh C, Steinberg M, DiPietro L. Distinct patterns of angiogenesis in oral and skin wounds. *J Dent Res*. 2005;**84**:309–14. https://doi.org/10.1177/154405910508400403.
166. Mogili NS, Krishnaswamy VR, Jayaraman M, Rajaram R, Venkataraman A, Korrapati PS. Altered angiogenic balance in keloids: a key to therapeutic intervention. *Transl Res*. 2012;**159**:182–9. https://doi.org/10.1016/j.trsl.2011.10.002.
167. Diao J-S, Xia W-S, Guo S-Z. Bevacizumab: a potential agent for prevention and treatment of hypertrophic scar. *Burns J Int Soc Burn Inj*. 2010;**36**:1136–7. https://doi.org/10.1016/j.burns.2010.01.014.
168. Azari Z, Nazarnezhad S, Webster TJ, Hoseini SJ, Brouki Milan P, Baino F. *et al*. Stem cell-mediated angiogenesis in skin tissue engineering and wound healing. *Wound Repair Regen*. 2022;**30**:421–35. https://doi.org/10.1111/wrr.13033.
169. Pondeljak N, Lugović-Mihić L. Stress-induced interaction of skin immune cells, hormones, and neurotransmitters. *Clin Ther*. 2020;**42**:757–70. https://doi.org/10.1016/j.clinthera.2020.03.008.
170. Grando SA, Pittelkow MR, Schallreuter KU. Adrenergic and cholinergic control in the biology of epidermis: physiological and clinical significance. *J Invest Dermatol*. 2006;**126**:1948–65. https://doi.org/10.1038/sj.jid.5700151.
171. Grando SA. Cholinergic control of epidermal cohesion. *Exp Dermatol*. 2006;**15**:265–82. https://doi.org/10.1111/j.0906-6705.2006.00410.x.
172. Steinkraus V, Mak JC, Pichlmeier U, Mensing H, Ring J, Barnes PJ. Autoradiographic mapping of beta-adrenoceptors in human skin. *Arch Dermatol Res*. 1996;**288**:549–53. https://doi.org/10.1007/BF02505253.
173. Sivamani RK, Lam ST, Isseroff RR. Beta adrenergic receptors in keratinocytes. *Dermatol Clin*. 2007;**25**:643–53. https://doi.org/10.1016/j.det.2007.06.012.
174. Pongratz G, Straub RH. The sympathetic nervous response in inflammation. *Arthritis Res Ther*. 2014;**16**:504–12. https://doi.org/10.1186/s13075-014-0504-2.
175. Anderson C, Bergner A, Murphy S. How many types of cholinergic sympathetic neuron are there in the rat stellate ganglion?

Neuroscience. 2006;**140**:567–76. https://doi.org/10.1016/j.neuroscience.2006.02.021.
176. Macefield VG. Sympathetic microneurography. *Handb Clin Neurol*. 2013;**117**:353–64. https://doi.org/10.1016/B978-0-444-53491-0.00028-6.
177. Schmelz M, Schmidt R, Bickel A, Torebjork H, Handwerker H. Innervation territories of single sympathetic C fibers in human skin. *J Neurophysiol*. 1998;**79**:1653–60. https://doi.org/10.1152/jn.1998.79.4.1653.
178. Donadio V, Incensi A, Vacchiano V, Infante R, Magnani M, Liguori R. The autonomic innervation of hairy skin in humans: an in vivo confocal study. *Sci Rep*. 2019;**9**:16982. https://doi.org/10.1038/s41598-019-53684-3.
179. von Düring M, Fricke B. Organization of peripheral nerves in skin, musculoskeletal system and viscera. *Neuronal Activity in Tumor Tissue*. 2007;**39**:30–44. https://doi.org/10.1159/000100043.
180. Benarroch EE. Neuropeptides in the sympathetic system: presence, plasticity, modulation, and implications. *Ann Neurol*. 1994;**36**:6–13. https://doi.org/10.1002/ana.410360105.
181. Li X, Mao Z, Yang L, Sun K. Co-staining blood vessels and nerve fibers in adipose tissue. *J Vis Exp*. 2019;**144**:e59266. https://doi.org/10.3791/59266.
182. Bartness T, Ryu V. Neural control of white, beige and brown adipocytes. *Int J Obes Suppl*. 2015;**5**:S35–9. https://doi.org/10.1038/ijosup.2015.9.
183. Katayama K, Dominelli PB, Foster GE, Kipp S, Leahy MG, Ishida K. *et al*. Respiratory modulation of sympathetic vasomotor outflow during graded leg cycling. *J Appl Physiol*. 2021;**131**:858–67. https://doi.org/10.1152/japplphysiol.00118.2021.
184. Di Bona A, Vita V, Costantini I, Zaglia T. Towards a clearer view of sympathetic innervation of cardiac and skeletal muscles. *Prog Biophys Mol Biol*. 2020;**154**:80–93. https://doi.org/10.1016/j.pbiomolbio.2019.07.003.
185. Galkowska H, Wojewodzka U, Olszewski WL. Chemokines, cytokines, and growth factors in keratinocytes and dermal endothelial cells in the margin of chronic diabetic foot ulcers. *Wound Repair Regen*. 2006;**14**:558–65. https://doi.org/10.1111/j.1743-6109.2006.00155.x.
186. Chen J, Hoffman BB, Isseroff RR. β-Adrenergic receptor activation inhibits keratinocyte migration via a cyclic adenosine monophosphate-independent mechanism. *J Invest Dermatol*. 2002;**119**:1261–8. https://doi.org/10.1046/j.1523-1747.2002.19611.x.
187. Lee YB, Byun EJ, Kim HS. Potential role of the microbiome in acne: a comprehensive review. *J Clin Med*. 2019;**8**:987. https://doi.org/10.3390/jcm8070987.
188. Pullar CE, Manabat-Hidalgo CG, Bolaji RS, Isseroff RR. β-Adrenergic receptor modulation of wound repair. *Pharmacol Res*. 2008;**58**:158–64. https://doi.org/10.1016/j.phrs.2008.07.012.
189. Donaldson DJ, Mahan JT. Influence of catecholamines on epidermal cell migration during wound closure in adult newts. *Comp Biochem Physiol C Comp Pharmacol*. 1984;**78**:267–70. https://doi.org/10.1016/0742-8413(84)90081-1.
190. Pullar CE, Chen J, Isseroff RR. PP2A activation by β2-adrenergic receptor agonists: novel regulatory mechanism of keratinocyte migration. *J Biol Chem*. 2003;**278**:22555–62. https://doi.org/10.1074/jbc.M300205200.
191. Wu C-S, Tsao D-A, Chang H-R. Beta2-adrenergic receptor agonist inhibits keratinocyte proliferation by mechanisms involving nitric oxide. *Postępy Dermatol Alergol*. 2021;**38**:396–403. https://doi.org/10.5114/ada.2020.92918.
192. Dasu MR, Ramirez SR, La TD, Gorouhi F, Nguyen C, Lin BR. *et al*. Crosstalk between adrenergic and toll-like receptors in human mesenchymal stem cells and keratinocytes: a recipe for impaired wound healing. *Stem Cells Transl Med*. 2014;**3**:745–59. https://academic.oup.com/stcltm/article/3/6/745/6389830. https://doi.org/10.5966/sctm.2013-0200.
193. Parrado AC, Canellada A, Gentile T, Rey-Roldán EB. Dopamine agonists upregulate IL-6 and IL-8 production in human keratinocytes. *Neuroimmunomodulation*. 2012;**19**:359–66. https://doi.org/10.1159/000342140.
194. Sivamani RK, Shi B, Griffiths E, Vu SM, Lev-Tov HA, Dahle S. *et al*. Acute wounding alters the beta2-adrenergic signaling and catecholamine synthetic pathways in keratinocytes. *J Invest Dermatol*. 2014;**134**:2258–66. https://doi.org/10.1038/jid.2014.137.
195. Romana-Souza B, Nascimento AP, Brum PC, Monte-Alto-Costa A. Deletion of the α2 a/α2 C-adrenoceptors accelerates cutaneous wound healing in mice. *Int J Exp Pathol*. 2014;**95**:330–41. https://doi.org/10.1111/iep.12093.
196. Ivanov E, Akhmetshina M, Erdiakov A, Gavrilova S. Sympathetic system in wound healing: multistage control in normal and diabetic skin. *Int J Mol Sci*. 2023;**24**:2045. https://doi.org/10.3390/ijms24032045.
197. Kurzen H, Berger H, Jäger C, Hartschuh W, Maas-Szabowski N. Alpha 9 acetylcholine receptors are essential for epidermal differentiation. *Exp Dermatol*. 2005;**14**:155–5. https://doi.org/10.1111/j.0906-6705.2005.0266i.x.
198. Nguyen VT, Chernyavsky AI, Arredondo J, Bercovich D, Orr-Urtreger A, Vetter DE. *et al*. Synergistic control of keratinocyte adhesion through muscarinic and nicotinic acetylcholine receptor subtypes. *Exp Cell Res*. 2004;**294**:534–49. https://doi.org/10.1016/j.yexcr.2003.12.010.
199. Kurzen H, Wessler I, Kirkpatrick C, Kawashima K, Grando S. The non-neuronal cholinergic system of human skin. *Horm Metab Res*. 2007;**39**:125–35. https://doi.org/10.1055/s-2007-961816.
200. Buchli R, Ndoye A, Rodriguez JG, Zia S, Webber RJ, Grando SA. Human skin fibroblasts express m2, m4, and m5 subtypes of muscarinic acetylcholine receptors. *J Cell Biochem*. 1999;**74**:264–77. https://doi.org/10.1002/(SICI)1097-4644(19990801)74:2<264::AID-JCB11>3.0.CO;2-Z.
201. Kishibe M, Griffin TM, Radek KA. Keratinocyte nicotinic acetylcholine receptor activation modulates early TLR2-mediated wound healing responses. *Int Immunopharmacol*. 2015;**29**:63–70. https://doi.org/10.1016/j.intimp.2015.05.047.
202. Raja KS, Garcia MS, Isseroff RR. Wound re-epithelialization: modulating keratinocyte migration in wound healing. *Front Biosci (Landmark Ed)*. 2007;**12**:2849–68. https://doi.org/10.2741/2277.
203. Kurzen H, Schallreuter KU. Novel aspects in cutaneous biology of acetylcholine synthesis and acetylcholine receptors. *Exp Dermatol*. 2004;**13**:27–30. https://doi.org/10.1111/j.1600-0625.2004.00258.x.
204. Ndoye A, Buchli R, Greenberg B, Nguyen VT, Zia S, Lawry MA. *et al*. Identification and mapping of keratinocyte muscarinic acetylcholine receptor subtypes in human epidermis. *J Invest Dermatol*. 1998;**111**:410–6. https://doi.org/10.1046/j.1523-1747.1998.00299.x.
205. Wollina U, Huschenbeck J, Knöll B, Sternberg B, Hipler U-C. Vasoactive intestinal peptide supports induced migration of human keratinocytes and their colonization of an artificial polyurethane matrix. *Regul Pept*. 1997;**70**:29–36. https://doi.org/10.1016/S0167-0115(97)00011-6.
206. Haegerstrand A, Jonzon B, Dalsgaard C, Nilsson J. Vasoactive intestinal polypeptide stimulates cell proliferation and adenylate cyclase activity of cultured human keratinocytes. *Proc Natl Acad Sci*. 1989;**86**:5993–6. https://doi.org/10.1073/pnas.86.15.5993.
207. Bennett LAT, Johnson JM, Stephens DP, Saad AR, Kellogg DL, Jr. Evidence for a role for vasoactive intestinal peptide in active vasodilatation in the cutaneous vasculature of humans. *J Physiol*. 2003;**552**:223–32. https://doi.org/10.1113/jphysiol.2003.042135.
208. Dumont Y, Bastianetto S, Duranton A, Breton L, Quirion R. Immunohistochemical distribution of neuropeptide Y, peptide YY, pancreatic polypeptide-like immunoreactivity and their receptors in the epidermal skin of healthy women. *Peptides*. 2015;**70**:7–16. https://doi.org/10.1016/j.peptides.2015.05.002.

209. Takahashi K, Nakanishi S, Imamura S. Direct effects of cutaneous neuropeptides on adenylyl cyclase activity and proliferation in a keratinocyte cell line: stimulation of cyclic AMP formation by CGRP and VIP/PHM, and inhibition by NPY through G protein-coupled receptors. *J Invest Dermatol*. 1993;**101**:646–51. https://doi.org/10.1111/1523-1747.ep12371670.
210. Engel D. The influence of the sympathetic nervous system on capillary permeability. *J Physiol*. 1941;**99**:161–81. https://doi.org/10.1113/jphysiol.1941.sp003891.
211. Coderre TJ, Basbaum AI, Levine JD. Neural control of vascular permeability: interactions between primary afferents, mast cells, and sympathetic efferents. *J Neurophysiol*. 1989;**62**:48–58. https://doi.org/10.1152/jn.1989.62.1.48.
212. Lefrandt J, Bosma E, Oomen P, Van Der Hoeven J, Van Roon A, Smit A. *et al.* Sympathetic mediated vasomotion and skin capillary permeability in diabetic patients with peripheral neuropathy. *Diabetologia*. 2003;**46**:40–7. https://doi.org/10.1007/s00125-002-1004-5.
213. Sulakvelidze I, Baluk P, McDonald DM. Plasma extravasation induced in rat trachea by 6-OHDA is mediated by sensory nerves, not by sympathetic nerves. *J Appl Physiol*. 1994;**76**:701–7. https://doi.org/10.1152/jappl.1994.76.2.701.
214. Rough J, Engdahl R, Opperman K, Yerrum S, Monroy MA, Daly JM. β2 Adrenoreceptor blockade attenuates the hyperinflammatory response induced by traumatic injury. *Surgery*. 2009;**145**:235–42. https://doi.org/10.1016/j.surg.2008.09.013.
215. Landmann R. Beta-adrenergic receptors in human leukocyte subpopulations. *Eur J Clin Investig*. 1992;**22 Suppl 1**:30–6.
216. Scanzano A, Cosentino M. Adrenergic regulation of innate immunity: a review. *Front Pharmacol*. 2015;**6**:171. https://doi.org/10.3389/fphar.2015.00171.
217. Galvan DL, Danesh FR. β2-adrenergic receptors in inflammation and vascular complications of diabetes. *Kidney Int*. 2017;**92**:14–6. https://doi.org/10.1016/j.kint.2017.03.024.
218. Ağaç D, Estrada LD, Maples R, Hooper LV, Farrar JD. The β2-adrenergic receptor controls inflammation by driving rapid IL-10 secretion. *Brain Behav Immun*. 2018;**74**:176–85. https://doi.org/10.1016/j.bbi.2018.09.004.
219. Kolmus K, Tavernier J, Gerlo S. β2-adrenergic receptors in immunity and inflammation: stressing NF-κB. *Brain Behav Immun*. 2015;**45**:297–310. https://doi.org/10.1016/j.bbi.2014.10.007.
220. Gosain A, Gamelli RL, DiPietro LA. Norepinephrine-mediated suppression of phagocytosis by wound neutrophils. *J Surg Res*. 2009;**152**:311–8. https://doi.org/10.1016/j.jss.2008.05.001.
221. Gosain A, Muthu K, Gamelli RL, DiPietro LA. Norepinephrine suppresses wound macrophage phagocytic efficiency through alpha-and beta-adrenoreceptor dependent pathways. *Surgery*. 2007;**142**:170–9. https://doi.org/10.1016/j.surg.2007.04.015.
222. Lu Y-Z, Nayer B, Singh SK, Alshoubaki YK, Yuan E, Park AJ. *et al.* CGRP sensory neurons promote tissue healing via neutrophils and macrophages. *Nature*. 2024;**628**:604–11. https://doi.org/10.1038/s41586-024-07237-y.
223. Miksa M, Das P, Zhou M, Wu R, Dong W, Ji Y. *et al.* Pivotal role of the α2A-adrenoceptor in producing inflammation and organ injury in a rat model of sepsis. *PLoS One*. 2009;**4**:e5504. https://doi.org/10.1371/journal.pone.0005504.
224. Shaker MS, Bernstein JA. Neuroimmunology as the next frontier. *Ann Allergy Asthma Immunol*. 2023;**131**:535–6. https://doi.org/110.1016/j.anai.2023.08.596.
225. Grisanti LA, Woster AP, Dahlman J, Sauter ER, Combs CK, Porter JE. α1-adrenergic receptors positively regulate toll-like receptor cytokine production from human monocytes and macrophages. *J Pharmacol Exp Ther*. 2011;**338**:648–57. https://doi.org/10.1124/jpet.110.178012.
226. Enten GA, Gao X, Strzelinski HR, Weche M, Liggett SB, Majetschak M. α1B/D-adrenoceptors regulate chemokine receptor–mediated leukocyte migration via formation of heteromeric receptor complexes. *Proc Natl Acad Sci*. 2022;**119**:e2123511119. https://doi.org/10.1073/pnas.2123511119.
227. Gao X, Albee LJ, Volkman BF, Gaponenko V, Majetschak M. Asymmetrical ligand-induced cross-regulation of chemokine (CXC motif) receptor 4 by α1-adrenergic receptors at the heteromeric receptor complex. *Sci Rep*. 2018;**8**:2730. https://doi.org/10.1038/s41598-018-21096-4.
228. Hübner G, Brauchle M, Smola H, Madlener M, Fässler R, Werner S. Differential regulation of pro-inflammatory cytokines during wound healing in normal and glucocorticoid-treated mice. *Cytokine*. 1996;**8**:548–56. https://doi.org/10.1006/cyto.1996.0074.
229. Valls MD, Cronstein BN, Montesinos MC. Adenosine receptor agonists for promotion of dermal wound healing. *Biochem Pharmacol*. 2009;**77**:1117–24. https://doi.org/10.1016/j.bcp.2008.11.002.
230. de Almeida TF, de Castro PT, Monte-Alto-Costa A. Blockade of glucocorticoid receptors improves cutaneous wound healing in stressed mice. *Exp Biol Med*. 2016;**241**:353–8. https://doi.org/10.1177/1535370215612940.
231. Nguyen VT, Ngo QT, Ramirez RP, Nakamura T, Farman N, Aractingi S. *et al.* The myeloid mineralocorticoid receptor regulates dermal angiogenesis and inflammation in glucocorticoid-induced impaired wound healing. *Br J Pharmacol*. 2022;**179**:5222–32. https://doi.org/10.1111/bph.15932.
232. Tu H, Zhang D, Barksdale AN, Wadman MC, Muelleman RL, Li Y-L. Dexamethasone improves wound healing by decreased inflammation and increased vasculogenesis in mouse skin frostbite model. *Wilderness Environ Med*. 2020;**31**:407–17. https://doi.org/10.1016/j.wem.2020.07.003.
233. Durand M, Hagimont E, Louis H, Asfar P, Frippiat J-P, Singer M. *et al.* The β1-adrenergic receptor contributes to sepsis-induced immunosuppression through modulation of regulatory T-cell inhibitory function. *Crit Care Med*. 2022;**50**:e707–18. https://doi.org/10.1097/CCM.0000000000005503.
234. Lira A, Pinsky MR. *Should β-blockers be used in septic shock?*: Springer, 2014, **18**, 304. https://doi.org/10.1186/cc13878.
235. Nguyen LP, Omoluabi O, Parra S, Frieske JM, Clement C, Ammar-Aouchiche Z. *et al.* Chronic exposure to beta-blockers attenuates inflammation and mucin content in a murine asthma model. *Am J Respir Cell Mol Biol*. 2008;**38**:256–62. https://doi.org/10.1165/rcmb.2007-0279RC.
236. Henriquez AR, Snow SJ, Schladweiler MC, Miller CN, Dye JA, Ledbetter AD. *et al.* Adrenergic and glucocorticoid receptor antagonists reduce ozone-induced lung injury and inflammation. *Toxicol Appl Pharmacol*. 2018;**339**:161–71. https://doi.org/10.1016/j.taap.2017.12.006.
237. Souza BR, Santos JS, Costa AM. Blockade of β1-and β2-adrenoceptors delays wound contraction and re-epithelialization in rats. *Clin Exp Pharmacol Physiol*. 2006;**33**:421–30. https://doi.org/10.1111/j.1440-1681.2006.04383.x.
238. Romana-Souza B, Nascimento AP, Monte-Alto-Costa A. Propranolol improves cutaneous wound healing in streptozotocin-induced diabetic rats. *Eur J Pharmacol*. 2009;**611**:77–84. https://doi.org/10.1016/j.ejphar.2009.03.053.
239. Pavlov VA, Wang H, Czura CJ, Friedman SG, Tracey KJ. The cholinergic anti-inflammatory pathway: a missing link in neuroimmunomodulation. *Mol Med*. 2003;**9**:125–34. https://doi.org/10.1007/BF03402177.
240. Sato E, Koyama S, Okubo Y, Kubo K, Sekiguchi M. Acetylcholine stimulates alveolar macrophages to release inflammatory cell chemotactic activity. *Am J Phys Lung Cell Mol Phys*. 1998;**274**:L970–9. https://doi.org/10.1152/ajplung.1998.274.6.L970.
241. Koarai A, Traves SL, Fenwick PS, Brown SM, Chana KK, Russell RE. *et al.* Expression of muscarinic receptors by human macrophages. *Eur Respir J*. 2012;**39**:698–704. https://doi.org/10.1183/09031936.00136710.
242. Kawashima K, Fujii T, Moriwaki Y, Misawa H. Critical roles of acetylcholine and the muscarinic and nicotinic acetylcholine

receptors in the regulation of immune function. *Life Sci*. 2012;**91**: 1027–32. https://doi.org/10.1016/j.lfs.2012.05.006.
243. St-Pierre S, Jiang W, Roy P, Champigny C, LeBlanc É, Morley BJ. *et al.* Nicotinic acetylcholine receptors modulate bone marrow-derived pro-inflammatory monocyte production and survival. *PLoS One*. 2016;**11**:e0150230. https://doi.org/10.1371/journal.pone.0150230.
244. Lu J, Wu W. Cholinergic modulation of the immune system–a novel therapeutic target for myocardial inflammation. *Int Immunopharmacol*. 2021;**93**:107391. https://doi.org/10.1016/j.intimp.2021.107391.
245. Razani-Boroujerdi S, Singh SP, Knall C, Hahn FF, Peña-Philippides JC, Kalra R. *et al.* Chronic nicotine inhibits inflammation and promotes influenza infection. *Cell Immunol*. 2004;**230**: 1–9. https://doi.org/10.1016/j.cellimm.2004.07.007.
246. Delgado M, Pozo D, Ganea D. The significance of vasoactive intestinal peptide in immunomodulation. *Pharmacol Rev*. 2004;**56**:249–90. https://doi.org/10.1124/pr.56.2.7.
247. Gonzalez-Rey E, Chorny A, Fernandez-Martin A, Ganea D, Delgado M. Vasoactive intestinal peptide generates human tolerogenic dendritic cells that induce CD4 and CD8 regulatory T cells. *Blood*. 2006;**107**:3632–8. https://doi.org/10.1182/blood-2005-11-4497.
248. Delgado M, Chorny A, Gonzalez-Rey E, Ganea D. Vasoactive intestinal peptide generates CD4+ CD25+ regulatory T cells in vivo. *J Leukoc Biol*. 2005;**78**:1327–38. https://doi.org/10.1189/jlb.0605299.
249. Dimitrijević M, Stanojević S. The intriguing mission of neuropeptide Y in the immune system. *Amino Acids*. 2013;**45**:41–53. https://doi.org/10.1007/s00726-011-1185-7.
250. Chandrasekharan B, Nezami BG, Srinivasan S. Emerging neuropeptide targets in inflammation: NPY and VIP. American journal of physiology-gastrointestinal and liver. *Physiology*. 2013;**304**:G949–57. https://doi.org/10.1152/ajpgi.00493.2012.
251. Wheway J, Herzog H, Mackay F. NPY and receptors in immune and inflammatory diseases. *Curr Top Med Chem*. 2007;**7**: 1743–52. https://doi.org/10.2174/156802607782341046.
252. El-Salhy M, Hausken T. The role of the neuropeptide Y (NPY) family in the pathophysiology of inflammatory bowel disease (IBD). *Neuropeptides*. 2016;**55**:137–44. https://doi.org/10.1016/j.npep.2015.09.005.
253. Makinde TO, Steininger R, Agrawal DK. NPY and NPY receptors in airway structural and inflammatory cells in allergic asthma. *Exp Mol Pathol*. 2013;**94**:45–50. https://doi.org/10.1016/j.yexmp.2012.05.009.
254. Kunath J, Delaroque N, Szardenings M, Neundorf I, Straub RH. Sympathetic nerve repulsion inhibited by designer molecules in vitro and role in experimental arthritis. *Life Sci*. 2017;**168**:47–53. https://doi.org/10.1016/j.lfs.2016.11.009.
255. Koeck FX, Bobrik V, Fassold A, Grifka J, Kessler S, Straub RH. Marked loss of sympathetic nerve fibers in chronic Charcot foot of diabetic origin compared to ankle joint osteoarthritis. *J Orthop Res*. 2009;**27**:736–41. https://doi.org/10.1002/jor.20807.
256. Klatt S, Fassold A, Straub RH. Sympathetic nerve fiber repulsion: testing norepinephrine, dopamine, and 17β-estradiol in a primary murine sympathetic neurite outgrowth assay. *Ann N Y Acad Sci*. 2012;**1261**:26–33. https://doi.org/10.1111/j.1749-6632.2012.06628.x.
257. Hoover DB, Brown TC, Miller MK, Schweitzer JB, Williams DL. Loss of sympathetic nerves in spleens from patients with end stage sepsis. *Front Immunol*. 2017;**8**:1712. https://doi.org/10.3389/fimmu.2017.01712.
258. Okonkwo UA, DiPietro LA. Diabetes and wound angiogenesis. *Int J Mol Sci*. 2017;**18**:1419. https://doi.org/10.3390/ijms18071419.
259. Shome S, Rana T, Ganguly S, Basu B, Chaki Choudhury S, Sarkar C. *et al.* Dopamine regulates angiogenesis in normal dermal wound tissues. *PLoS One*. 2011;**6**:e25215. https://doi.org/10.1371/journal.pone.0025215.
260. Chakroborty D, Goswami S, Basu S, Sarkar C. Catecholamines in the regulation of angiogenesis in cutaneous wound healing. *FASEB J*. 2020;**34**:14093–102. https://doi.org/10.1096/fj.202001701R.
261. Pullar CE, Grahn JC, Liu W, Isseroff RR. β2-adrenergic receptor activation delays wound healing. *FASEB J*. 2006;**20**:76–86. https://doi.org/10.1096/fj.05-4188com.
262. Johnson R, Webb JG, Newman WH, Wang Z. Regulation of human vascular smooth muscle cell migration by β-adrenergic receptors. *Am Surg*. 2006;**72**:51–4. https://doi.org/10.1177/000313480607200112.
263. O'Leary AP, Fox JM, Pullar CE. Beta-adrenoceptor activation reduces both dermal microvascular endothelial cell migration via a camp-dependent mechanism and wound angiogenesis. *J Cell Physiol*. 2015;**230**:356–65. https://doi.org/10.1002/jcp.24716.
264. Drummond PD, Dawson LF, Wood FM, Fear MW. Up-regulation of α1-adrenoceptors in burn and keloid scars. *Burns*. 2018;**44**: 582–8. https://doi.org/10.1016/j.burns.2017.09.010.
265. Pradhan L, Cai X, Wu S, Andersen ND, Martin M, Malek J. *et al.* Gene expression of pro-inflammatory cytokines and neuropeptides in diabetic wound healing. *J Surg Res*. 2011;**167**:336–42. https://doi.org/10.1016/j.jss.2009.09.012.
266. Ranne J, Kalimo H, Pyykkö K, Scheinin M, Aaltonen V, Niinikoski J. *et al.* Wound healing in denervated rat groin skin flap. *Eur Surg Res*. 2000;**32**:197–202. https://doi.org/10.1159/000008763.
267. Jiang C-K, Tomic-Canic M, Lucas D, Simon M, Blumenberg M. TGFβ promotes the basal phenotype of epidermal keratinocytes: transcriptional induction of K# 5 and K# 14 keratin genes. *Growth Factors*. 1995;**12**:87–97. https://doi.org/10.3109/08977199509028955.
268. Hameedaldeen A, Liu J, Batres A, Graves GS, Graves DT. FOXO1, TGF-β regulation and wound healing. *Int J Mol Sci*. 2014;**15**: 16257–69. https://doi.org/10.3390/ijms150916257.
269. Le Provost GS, Pullar CE. β2-adrenoceptor activation modulates skin wound healing processes to reduce scarring. *J Invest Dermatol*. 2015;**135**:279–88. https://doi.org/10.1038/jid.2014.312.
270. Pullar CE, Isseroff RR. ß2-adrenergic receptor activation delays dermal fibroblast-mediated contraction of collagen gels via a cAMP-dependent mechanism. *Wound Repair Regen*. 2005;**13**: 405–11. https://doi.org/10.1111/j.1067-1927.2005.130408.x.
271. Pullar CE, Isseroff RR. The β2-adrenergic receptor activates pro-migratory and pro-proliferative pathways in dermal fibroblasts via divergent mechanisms. *J Cell Sci*. 2006;**119**:592–602. https://doi.org/10.1242/jcs.02772.
272. Pullar CE, Le Provost GS, O'leary AP, Evans SE, Baier BS, Isseroff RR. β2AR antagonists and β2AR gene deletion both promote skin wound repair processes. *J Invest Dermatol*. 2012;**132**: 2076–84. https://doi.org/10.1038/jid.2012.108.
273. Arredondo J, Nguyen VT, Chernyavsky AI, Bercovich D, Orr-Urtreger A, Vetter DE. *et al.* Functional role of α7 nicotinic receptor in physiological control of cutaneous homeostasis. *Life Sci*. 2003;**72**:2063–7. https://doi.org/10.1016/S0024-3205(03)00084-5.
274. Weston PJ, James MA, Panerai RB, McNally PG, Potter JF, Thurston H. Evidence of defective cardiovascular regulation in insulin-dependent diabetic patients without clinical autonomic dysfunction. *Diabetes Res Clin Pract*. 1998;**42**:141–8. https://doi.org/10.1016/S0168-8227(98)00094-1.
275. Moreno-Smith M, Lee SJ, Lu C, Nagaraja AS, He G, Rupaimoole R. *et al.* Biologic effects of dopamine on tumor vasculature in ovarian carcinoma. *Neoplasia*. 2013;**15**:502–IN15. https://doi.org/10.1593/neo.121412.
276. Tang J, Li Z, Lu L, Cho CH. β-Adrenergic system, a backstage manipulator regulating tumour progression and drug target in cancer therapy. *Semin Cancer Biol*. Elsevier, 2013;**23**:533–42. https://doi.org/10.1016/j.semcancer.2013.08.009.
277. Park SY, Kang JH, Jeong KJ, Lee J, Han JW, Choi WS. *et al.* Retracted: norepinephrine induces VEGF expression

and angiogenesis by a hypoxia-inducible factor-1α protein-dependent mechanism. *Int J Cancer*. 2011;**128**:2306–16. https://doi.org/10.1002/ijc.25589.
278. Yang EV, Kim S-J, Donovan EL, Chen M, Gross AC, Marketon JIW. *et al.* Norepinephrine upregulates VEGF, IL-8, and IL-6 expression in human melanoma tumor cell lines: implications for stress-related enhancement of tumor progression. *Brain Behav Immun*. 2009;**23**:267–75. https://doi.org/10.1016/j.bbi.2008.10.005.
279. Tilan J, Kitlinska J. Sympathetic neurotransmitters and tumor angiogenesis—link between stress and cancer progression. *J Oncol*. 2010;**2010**:1–6. https://doi.org/10.1155/2010/539706.
280. Jobe SO, Fling SN, Ramadoss J, Magness RR. A novel role for an endothelial adrenergic receptor system in mediating catecholestradiol-induced proliferation of uterine artery endothelial cells. *Hypertension*. 2011;**58**:874–81. https://doi.org/10.1161/HYPERTENSIONAHA.111.178046.
281. Seya Y, Fukuda T, Isobe K, Kawakami Y, Takekoshi K. Effect of norepinephrine on RhoA, MAP kinase, proliferation and VEGF expression in human umbilical vein endothelial cells. *Eur J Pharmacol*. 2006;**553**:54–60. https://doi.org/10.1016/j.ejphar.2006.09.048.
282. Fu Y-C, Chi C-S, Yin S-C, Hwang B, Chiu Y-T, Hsu S-L. Norepinephrine induces apoptosis in neonatal rat endothelial cells via down-regulation of Bcl-2 and activation of β-adrenergic and caspase-2 pathways. *Cardiovasc Res*. 2004;**61**:143–51. https://doi.org/10.1016/j.cardiores.2003.10.014.
283. Fu Y-C, Yin S-C, Chi C-S, Hwang B, Hsu S-L. Norepinephrine induces apoptosis in neonatal rat endothelial cells via a ROS-dependent JNK activation pathway. *Apoptosis*. 2006;**11**:2053–63. https://doi.org/10.1007/s10495-006-0192-8.
284. Jiang Q, Ding S, Wu J, Liu X, Wu Z. Norepinephrine stimulates mobilization of endothelial progenitor cells after limb ischemia. *PLoS One*. 2014;**9**:e101774. https://doi.org/10.1371/journal.pone.0101774.
285. Chakroborty D, Sarkar C, Yu H, Wang J, Liu Z, Dasgupta PS. *et al.* Dopamine stabilizes tumor blood vessels by up-regulating angiopoietin 1 expression in pericytes and Krüppel-like factor-2 expression in tumor endothelial cells. *Proc Natl Acad Sci*. 2011;**108**:20730–5. https://doi.org/10.1073/pnas.1108696108.
286. Zukowska Z. Atherosclerosis and angiogenesis: what do nerves have to do with it? *Pharmacol Rep*. 2005;**57**:229.
287. Zukowska-Grojec Z, Karwatowska-Prokopczuk E, Rose W, Rone J, Movafagh S, Ji H. *et al.* Neuropeptide Y: a novel angiogenic factor from the sympathetic nerves and endothelium. *Circ Res*. 1998;**83**:187–95. https://doi.org/10.1161/01.RES.83.2.187.
288. Lee EW, Michalkiewicz M, Kitlinska J, Kalezic I, Switalska H, Yoo P. *et al.* Neuropeptide Y induces ischemic angiogenesis and restores function of ischemic skeletal muscles. *J Clin Invest*. 2003;**111**:1853–62. https://doi.org/10.1172/JCI16929.
289. Ciccarelli M, Sorriento D, Cipolletta E, Santulli G, Fusco A, Zhou RH. *et al.* Impaired neoangiogenesis in β2–adrenoceptor gene-deficient mice: restoration by intravascular human β2–adrenoceptor gene transfer and role of NFκB and CREB transcription factors. *Br J Pharmacol*. 2011;**162**:712–21. https://doi.org/10.1111/j.1476-5381.2010.01078.x.
290. Martini D, Monte MD, Ristori C, Cupisti E, Mei S, Fiorini P. *et al.* Antiangiogenic effects of β2-adrenergic receptor blockade in a mouse model of oxygen-induced retinopathy. *J Neurochem*. 2011;**119**:1317–29. https://doi.org/10.1111/j.1471-4159.2011.07530.x.
291. Steinle JJ, Booz GW, Meininger CJ, Day JN, Granger HJ. β3-adrenergic receptors regulate retinal endothelial cell migration and proliferation. *J Biol Chem*. 2003;**278**:20681–6. https://doi.org/10.1074/jbc.M300368200.
292. Ji Y, Chen S, Li K, Xiao X, Zheng S, Xu T. The role of β-adrenergic receptor signaling in the proliferation of hemangioma-derived endothelial cells. *Cell Div*. 2013;**8**:1–11. https://doi.org/10.1186/1747-1028-8-1.
293. Orimo A, Gupta PB, Sgroi DC, Arenzana-Seisdedos F, Delaunay T, Naeem R. *et al.* Stromal fibroblasts present in invasive human breast carcinomas promote tumor growth and angiogenesis through elevated SDF-1/CXCL12 secretion. *Cell*. 2005;**121**:335–48. https://doi.org/10.1016/j.cell.2005.02.034.
294. Lamy S, Lachambre M-P, Lord-Dufour S, Béliveau R. Propranolol suppresses angiogenesis in vitro: inhibition of proliferation, migration, and differentiation of endothelial cells. *Vasc Pharmacol*. 2010;**53**:200–8. https://doi.org/10.1016/j.vph.2010.08.002.
295. Ji Y, Li K, Xiao X, Zheng S, Xu T, Chen S. Effects of propranolol on the proliferation and apoptosis of hemangioma-derived endothelial cells. *J Pediatr Surg*. 2012;**47**:2216–23. https://doi.org/10.1016/j.jpedsurg.2012.09.008.
296. Zhang L, Mai H-M, Zheng J, Zheng J-W, Wang Y-A, Qin Z-P. *et al.* Propranolol inhibits angiogenesis via down-regulating the expression of vascular endothelial growth factor in hemangioma derived stem cell. *Int J Clin Exp Pathol*. 2014;**7**:48–55.
297. Lee D, Boscolo E, Durham J, Mulliken J, Herman I, Bischoff J. Propranolol targets the contractility of infantile haemangioma-derived pericytes. *Br J Dermatol*. 2014;**171**:1129–37. https://doi.org/10.1111/bjd.13048.
298. Romana-Souza B, Santos JS, Monte-Alto-Costa A. β-1 and β-2, but not α-1 and α-2, adrenoceptor blockade delays rat cutaneous wound healing. *Wound Repair Regen*. 2009;**17**:230–9. https://doi.org/10.1111/j.1524-475X.2008.00453.x.
299. Romana-Souza B, Nascimento AP, Monte-Alto-Costa A. Low-dose propranolol improves cutaneous wound healing of burn-injured rats. *Plast Reconstr Surg*. 2008;**122**:1690–9. https://doi.org/10.1097/PRS.0b013e31818cbf67.
300. Ye C, Zheng F, Xu T, Wu N, Tong Y, Xiong X-Q. *et al.* Norepinephrine acting on adventitial fibroblasts stimulates vascular smooth muscle cell proliferation via promoting small extracellular vesicle release. *Theranostics*. 2022;**12**:4718–33. https://doi.org/10.7150/thno.70974.
301. Jafarkhani S, Khakbiz M, Amoabediny G, Mohammadi J, Tahmasebipour M, Rabbani H. *et al.* A novel co-culture assay to evaluate the effects of sympathetic innervation on vascular smooth muscle differentiation. *Bioorg Chem*. 2023;**133**:106233. https://doi.org/10.1016/j.bioorg.2022.106233.
302. Lee S, Yu L-H, Lim L-R, Lim H-J, Si J-E, Ko Y-G. *et al.* Down regulation of Jag-1 in VSMCs contributes to impaired angiogenesis under high glucose condition: experimental study using aortic rings of rats. *Clin Hemorheol Microcirc*. 2015;**61**:497–511. https://doi.org/10.3233/CH-141915.
303. Billaud M, Chiu Y-H, Lohman AW, Parpaite T, Butcher JT, Mutchler SM. *et al.* A molecular signature in the pannexin1 intracellular loop confers channel activation by the α1 adrenoreceptor in smooth muscle cells. *Sci Signal*. 2015;**8**:ra17-ra17. https://doi.org/10.1126/scisignal.2005824.
304. Richman JG, Regan JW. α2-adrenergic receptors increase cell migration and decrease F-actin labeling in rat aortic smooth muscle cells. *Am J Phys Cell Phys*. 1998;**274**:C654–62. https://doi.org/10.1152/ajpcell.1998.274.3.C654.
305. Zukowska Z, Grant DS, Lee EW. Neuropeptide Y: a novel mechanism for ischemic angiogenesis. *Trends Cardiovasc Med*. 2003;**13**:86–92. https://doi.org/10.1016/S1050-1738(02)00232-3.
306. Yu C, Wang Z, Han Y, Liu Y, Wang WE, Chen C. *et al.* Dopamine D4 receptors inhibit proliferation and migration of vascular smooth muscle cells induced by insulin via down-regulation of insulin receptor expression. *Cardiovasc Diabetol*. 2014;**13**:1–11. https://doi.org/10.1186/1475-2840-13-97.
307. Rodrigues M, Kosaric N, Bonham CA, Gurtner GC. Wound healing: a cellular perspective. *Physiol Rev*. 2019;**99**:665–706. https://doi.org/10.1152/physrev.00067.2017.
308. Grando SA, Crosby AM, Zelickson BD, Dahl MV. Agarose gel keratinocyte outgrowth system as a model of skin re-epithelization: requirement of endogenous acetylcholine for outgrowth initiation. *J Invest Dermatol*. 1993;**101**:804–10. https://doi.org/10.1111/1523-1747.ep12371699.

309. Grando SA. Biological functions of keratinocyte cholinergic receptors. *J Investig Dermatol Symp Proc*. 1997Elsevier;**2**:41–8. https://doi.org/10.1038/jidsymp.1997.10.
310. Sann H, Pierau F. Efferent functions of C-fiber nociceptors. *Z Rheumatol*. 1998;**57**:S8–13. https://doi.org/10.1007/s003930050226.
311. Richards A, Floyd D, Terenghi G, McGrouther D. Cellular changes in denervated tissue during wound healing in a rat model. *Br J Dermatol*. 1999;**140**:1093–9. https://doi.org/10.1046/j.1365-2133.1999.02908.x.
312. Richter J, Andersson R, Edvinsson L, Gullberg U. Calcitonin gene-related peptide (CGRP) activates human neutrophils–inhibition by chemotactic peptide antagonist BOC-MLP. *Immunology*. 1992;**77**:416.
313. Foster CA, Mandak B, Kromer E, Rot A. Calcitonin gene-related peptide is chemotactic for human T lymphocytes. *Ann N Y Acad Sci*. 1992;**657**:397–404. https://doi.org/10.1111/j.1749-6632.1992.tb22785.x.
314. Quinlan KL, Song I-S, Bunnett NW, Letran E, Steinhoff M, Harten B. *et al*. Neuropeptide regulation of human dermal microvascular endothelial cell ICAM-1 expression and function. *Am J Phys Cell Phys*. 1998;**275**:C1580–90. https://doi.org/10.1152/ajpcell.1998.275.6.C1580.
315. Wiedermann C, Wiedermann F, Apperl A, Kieselbach G, Konwalinka G, Braunsteiner H. In vitro human polymorphonuclear leukocyte chemokinesis and human monocyte chemotaxis are different activities of aminoterminal and carboxyterminal substance P. *Naunyn Schmiedeberg's Arch Pharmacol*. 1989;**340**:185–90. https://doi.org/10.1007/BF00168967.
316. Ansel JC, Brown JR, Payan DG, Brown MA. Substance P selectively activates TNF-alpha gene expression in murine mast cells. *J Immunol*. 1993;**150**:4478–85. https://doi.org/10.4049/jimmunol.150.10.4478.
317. Hartung HP, Toyka KV. Activation of macrophages by substance P: induction of oxidative burst and thromboxane release. *Eur J Pharmacol*. 1983;**89**:301–5. https://doi.org/10.1016/0014-2999(83)90511-3.
318. Gee AP, Boyle M, Munger KL, Lawman M, Young M. Nerve growth factor: stimulation of polymorphonuclear leukocyte chemotaxis in vitro. *Proc Natl Acad Sci*. 1983;**80**:7215–8. https://doi.org/10.1073/pnas.80.23.7215.
319. Kawamoto K, Matsuda H. Nerve growth factor and wound healing. *Prog Brain Res*. 2004;**146**:369–84. https://doi.org/10.1016/S0079-6123(03)46023-8.
320. Anand P, Foley P, Navsaria H, Sinicropi D, Williams-Chestnut R, Leigh I. Nerve growth factor levels in cultured human skin cells: effect of gestation and viral transformation. *Neurosci Lett*. 1995;**184**:157–60. https://doi.org/10.1016/0304-3940(94)11195-O.
321. Weller K, Foitzik K, Paus R, Syska W, Maurer M, Weller K. *et al*. Mast cells are required for normal healing of skin wounds in mice. *FASEB J*. 2006;**20**:2366–8. https://doi.org/10.1096/fj.06-5837fje.
322. Geppetti P. Sensory neuropeptide release by bradykinin: mechanisms and pathophysiological implications. *Regul Pept*. 1993;**47**:1–23. https://doi.org/10.1016/0167-0115(93)90268-D.
323. Veith AP, Henderson K, Spencer A, Sligar AD, Baker AB. Therapeutic strategies for enhancing angiogenesis in wound healing. *Adv Drug Deliv Rev*. 2019;**146**:97–125. https://doi.org/10.1016/j.addr.2018.09.010.
324. Crowe R, Parkhouse N, McGrouther D, Burnstock G. Neuropeptide-containing nerves in painful hypertrophic human scar tissue. *Br J Dermatol*. 1994;**130**:444–52. https://doi.org/10.1111/j.1365-2133.1994.tb03376.x.
325. Jing C, Jia-Han W, Hong-Xing Z. Double-edged effects of neuropeptide substance P on repair of cutaneous trauma. *Wound Repair Regen*. 2010;**18**:319–24. https://doi.org/10.1111/j.1524-475X.2010.00589.x.
326. Yu X-J, Li C-Y, Xu Y-H, Chen L-M, Zhou C-L. Calcitonin gene-related peptide increases proliferation of human HaCaT keratinocytes by activation of MAP kinases. *Cell Biol Int*. 2009;**33**:1144–8. https://doi.org/10.1016/j.cellbi.2009.07.003.
327. Lonne-Rahm S, Nordlind K, Edström DW, Ros A-M, Berg M. Laser treatment of rosacea: a pathoetiological study. *Arch Dermatol*. 2004;**140**:1345–9. https://doi.org/10.1001/archderm.140.11.1345.
328. Kim HO, Lee CH, Ahn HK, Park CW. Effects of tacrolimus ointment on the expression of substance P, nerve growth factor, and neurotrophin-3 in atopic dermatitis. *Int J Dermatol*. 2009;**48**:431–8. https://doi.org/10.1111/j.1365-4632.2009.03968.x.
329. Apfel SC. Nerve growth factor for the treatment of diabetic neuropathy: what went wrong, what went right, and what does the future hold? *Int Rev Neurobiol*. 2002;**50**:393–413. https://doi.org/10.1016/S0074-7742(02)50083-0.
330. Landi F, Aloe L, Russo A, Cesari M, Onder G, Bonini S. *et al*. Topical treatment of pressure ulcers with nerve growth factor: a randomized clinical trial. *Ann Intern Med*. 2003;**139**:635–41. https://doi.org/10.7326/0003-4819-139-8-200310210-00006.
331. Generini S, Tuveri M, Cerinic MM, Mastinu F, Manni L, Aloe L. Topical application of nerve growth factor in human diabetic foot ulcers. A study of three cases. *Exp Clin Endocrinol Diabetes*. 2004;**112**:542–4. https://doi.org/10.1055/s-2004-821313.
332. Younan G, Ogawa R, Ramirez M, Helm D, Dastouri P, Orgill DP. Analysis of nerve and neuropeptide patterns in vacuum-assisted closure–treated diabetic murine wounds. *Plast Reconstr Surg*. 2010;**126**:87–96. https://doi.org/10.1097/PRS.0b013e3181da86d0.
333. Aszmann O, Tassler PL, Dellon AL. Changing the natural history of diabetic neuropathy: incidence of ulcer/amputation in the contralateral limb of patients with a unilateral nerve decompression procedure. *Ann Plast Surg*. 2004;**53**:517–22. https://doi.org/10.1097/01.sap.0000143605.60384.4e.
334. Lüscher N, De Roche R, Krupp S, Kuhn W, Zäch G. The sensory tensor fasciae latae flap: a 9-year follow-up. *Ann Plast Surg*. 1991;**26**:306–11. https://doi.org/10.1097/00000637-199104000-00004.
335. Viterbo F, Ripari WT. Nerve grafts prevent paraplegic pressure ulcers. *J Reconstr Microsurg*. 2008;**24**:251–3. https://doi.org/10.1055/s-2008-1078692.
336. Jones JW. Reinnervated medial gastrocnemius free flap for closure of a recurrent ischial pressure sore: case report. *J Reconstr Microsurg*. 2002;**18**:397–400. https://doi.org/10.1055/s-2002-33023.
337. Vetrugno R, Liguori R, Cortelli P, Montagna P. Sympathetic skin response: basic mechanisms and clinical applications. *Clin Auton Res*. 2003;**13**:256–70. https://doi.org/10.1007/s10286-003-0107-5.
338. Hanna KR, Katz AJ. An update on wound healing and the nervous system. *Ann Plast Surg*. 2011;**67**:49–52. https://doi.org/10.1097/SAP.0b013e31822284de.
339. Idrisova KF, Zeinalova AK, Masgutova GA, Bogov AA, Jr, Allegrucci C, Syromiatnikova VY. *et al*. Application of neurotrophic and proangiogenic factors as therapy after peripheral nervous system injury. *Neural Regen Res*. 2022;**17**:1240–7. https://doi.org/10.4103/1673-5374.327329.
340. Hermanns S, Klapka N, Gasis M, Müller HW. The collagenous wound healing scar in the injured central nervous system inhibits axonal regeneration. *Brain Repair*. 2006;**557**:177–90. https://doi.org/10.1007/0-387-30128-3_11.

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