

Accelerated Skin Wound Healing by Electrical Stimulation

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When the integrity of the skin got damaged, an endogenous electric field will be generated in the wound and a series of physiological reactions will be initiated to close the wound. The existence of the endogenous electric field of the wound has a promoting effect on all stages of wound healing. For wounds that cannot heal on their own, the exogenous electric field can assist the treatment. In this review, the effects of exogenous electrical stimulation on wound healing, such as the inflammation phase, blood flow, cell proliferation and migration, and the wound scarring is overviewed. This article also reviews the new electrical stimulation methods that have emerged in recent years, such as small power supplies, nanogenerators (NGs), and other physical, chemical or biological strategies. These new electrical stimulation methods and devices are safe, low-cost, stable, and small in size. The challenge and perspective are discussed for the future trends of the electrical stimulation treatment in accelerating skin wound healing.

may be caused by acute injury (e.g., surgical wounds, skin abrasions), or other chronic diseases (e.g., diabetic ulcers, venous ulcers).^[2] Most wounds can be repaired by themselves in about two weeks.^[3] The process of wound healing is mainly divided into four phases: the coagulation phase (Figure 1A), the inflammation phase (Figure 1B), the proliferation phase (Figure 1C), and the remodeling phase (Figure 1D). However, some wounds cannot heal timely and orderly.^[4] A variety of systemic or local factors may cause disturbances in the microenvironment and interfere with the repair process, thereby slowing down the process of wound healing, leading to chronic or even non-healing wounds.^[5] With the cost of treatments mounting each year, skin wounds affect millions of people around the world. As a

1. Introduction

Skin is the largest organ of the human body, which protects the internal tissues and organs from the invasion of harmful external factors. Skin wound refers to the break of normal anatomical structure and function on the skin. Besides, it would destroy the microenvironment of local tissue.^[1] The skin wounds

consequence, wound healing, returning the injured site to normal state, is extremely important and urgent.^[2,6] With the understanding of the healing process gradually growing, the focus on treatment for chronic wound has evolved from simple debridement and topical dressing treatment to more complex microenvironment therapy.^[7]

Ever since the German physiologist Emil Du-Bois Reymond first recorded the endogenous current in the wound,^[8] researchers have detected bioelectricity on the wounds of various animals.^[9] Thus, it raised an interesting question of whether bioelectricity has effect on wound healing. Afterward, some studies proved that the existence of bioelectricity can accelerate the process of wound healing by speeding up the migration of key cells.^[10] Based on it, researchers have lucubrated the influences of exogenous electrical stimulation on wound healing and achieved some good results. Although some researchers had reviewed the effects of electrical stimulation from the several directions, such as the phenomenon,^[11] types of current,^[12] a certain type of wounds or effects,^[13] hardly anyone have reviewed the relationship of wound healing and electrical stimulation from the each step of the wound healing process and introduced the exogenous electrical stimulation methods different from traditional electrical stimulation of power supply.

In this paper, we reviewed the effect of electrical stimulation on wound healing. First, we introduced the generation and features of endogenous electric field, as well as the characteristics of exogenous electrical stimulation. Then, we focused on the effects of electrical stimulation on skin wound healing, and describe them in detail. Particularly, we introduced the new exogenous electrical stimulation methods that have emerged in recent years for skin wound healing. In the end, the existing challenges and future trends of accelerating skin wound healing had been discussed.

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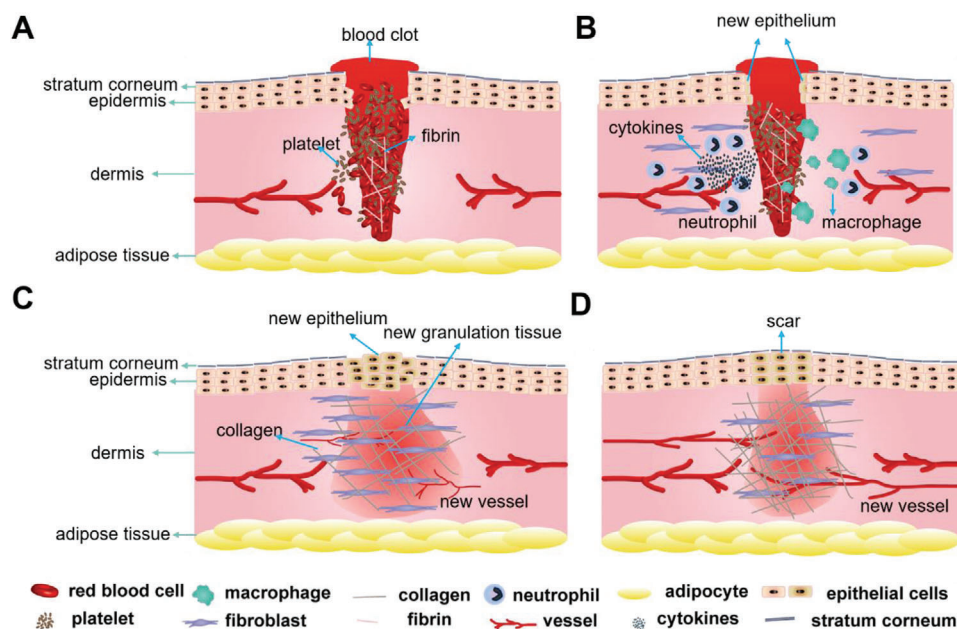


Figure 1. The process of skin wound healing. A) Coagulation phase. This phase is characterized by the formation of blood clots to protect the wound. The blood clot is mainly composed of red blood cells, platelets and a cross-linked fibrin network.^[2] B) Inflammation phase. The main characteristic of this phase is the inflammatory response. In this phase, macrophages, neutrophils and lymphocytes migrate to the wound and secrete cytokines.^[14] C) Proliferation phase. Tissue regeneration is the key feature of this phase. At this time, fibroblasts, epithelial cells, and endothelial cells migrate and proliferate, and form the new epithelium, granulation tissue and vessels.^[15] D) Remodeling phase. This phase involving wound contraction and remodeling may cause scars.^[16]

2. Endogenous Electric Field of Skin Wounds

Bioelectricity refers to the endogenous electrical signals generated by ion channels, pumps, and electrical synapses (gap junctions) on the plasma membrane.^[18] Decades ago, Barker et al. measured the voltage (10–60 mV) in hamster and human skin wounds by recording device (Figure 2), and first proposed the “skin battery” theory.^[17] They believed that the electric field intensity was negatively correlated with the distance from the edge of the wound. Ghadamali et al. found that the endogenous electric field of acute skin is connected with the size of the wound surface.^[19] Afterward, it has been found that the generation of endogenous electric field on skin wounds is related to the directional transport of ions by polarized epithelial cells.^[20] The Na^+ and Cl^- channels of epithelial cells are located in the apical plasma membrane, while the K^+ channel and Na^+/K^+ -ATPase are located in the basal plasma membrane (Figure 3A).^[21] This asymmetric distribution of ion channels produces the current across the cell. Meanwhile, the directional transport of ions by epithelial cells forms the trans-epithelial potentials (TEP) (Figure 3B). Studies have shown that the current of the wound is caused by short-circuiting TEP after epidermis damage (Figure 3C).^[20] Compared with the surrounding intact skin, the wound site is acted as a cathode.^[22] Due to the electric potential difference between the injured site and the normal skin around the wound, there would be low-intensity direct current flows from the normal skin to the wound.^[17,23] Cl^- and Na^+ are the main components of wound current, it means the essence of wound current is ion flow, so Cl^- and Na^+ pumps play a very important role in maintaining the electric potential of wound.^[10a,24]

To figure out the impact factors of the changes in wound potential to the wound healing process, researchers manipulated the ion transport of epithelial cells to change the intensity of wound potential. Activating ion transport through pharmacological effects or using genetic methods to change the number of ion pumps, they found that variation on wound potential intensity will affect the speed of wound healing.^[10a,20,25] Afterward, they proposed some possible mechanisms about the impact of wound potential in wound healing process: a) DNA and collagen synthesis increase; b) wound healing related cells migrate to the cathode or anode; c) Antibacterial effect in vitro and in vivo.^[13b,26]

3. Exogenous Electrical Stimulation for Skin Wound Healing

Exogenous electrical stimulation in wound treatment is mainly used for simulating or enhancing wound potential.^[12] In general, electrical stimulation treatment uses two electrodes located on different locations to transfer current to the wound tissues. Since 1960s, researchers have been studying the electrical stimulation treatment and its effect on wound healing.^[27]

According to the directionality of current (or voltage), electrical stimulation can be divided into two types: unidirectional current (or voltage) and bidirectional current (or voltage). The unidirectional current includes the direct current (DC) and unidirectional pulse current (PC). The unidirectional current is characterized by a unidirectional flow of charged particles which means it has a constant polarity (charge unbalanced) (Figure 4A). This feature enables the unidirectional current to simulate endogenous electric field. Therefore, the anode of electrical stimulation device is

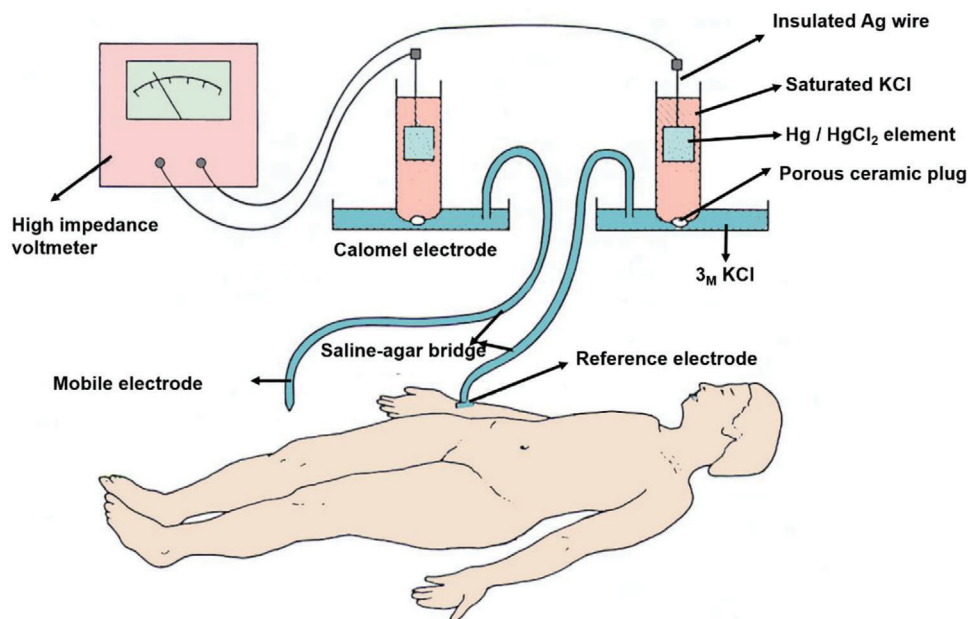


Figure 2. Schematic diagram of skin potential recording device. The subjects need to lie on their backs. The mobile electrode and reference electrode were connected to calomel electrodes immersed in 3 M KCl by the saline-agar bridge. Calomel electrode consisted of the insulated Ag wire, saturate KCl, Hg/HgCl₂ element and porous ceramic plug. Using the high impedance voltmeter could avoid measurement errors due to skin impedance. Added a drop of saline on the mobile electrode to ensure that the electrode is in contact with the stratum corneum. The reference electrode was placed on the volar aspect of the forearm. Removing the mobile electrode could measure the TEP in different locations of skin. Adapted with permission.^[17] Copyright 1983, British Association of Dermatologists. Published by John Wiley & Sons.

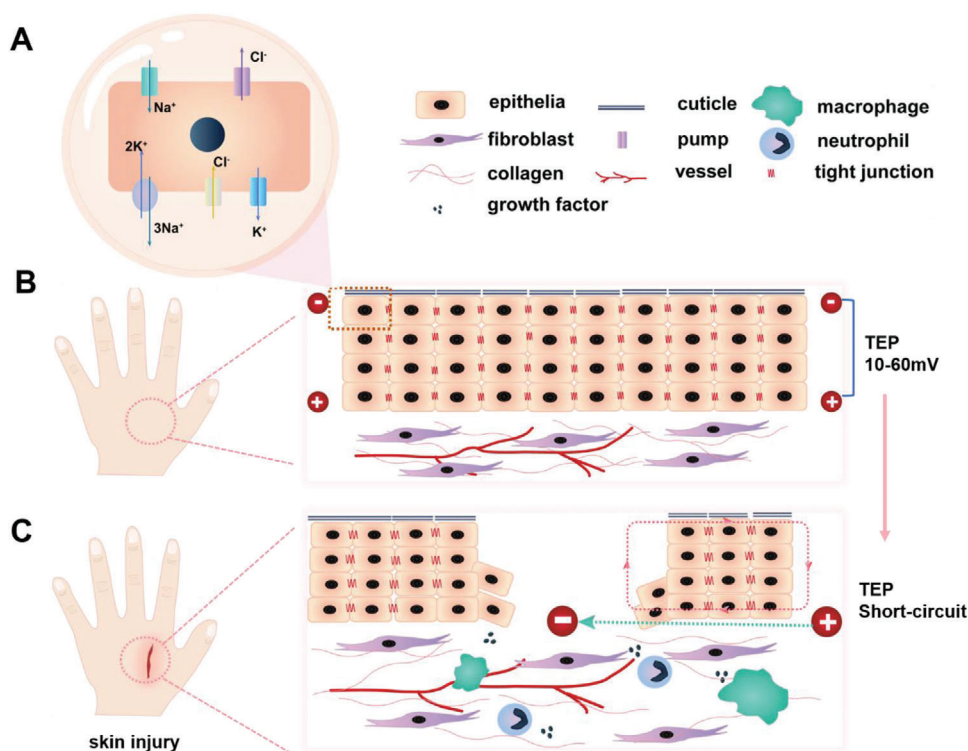


Figure 3. The generation of transepithelial potential (TEP) and endogenous electric field of skin wounds. A) Distribution of ion channels in epithelial cells. The Na⁺ and Cl⁻ channels of epithelial cells are located in the apical plasma membrane, while the K⁺ channel and Na⁺/K⁺-ATPase are located in the basal plasma membrane.^[21] B) TEP of the epidermis when skin is intact. The directional transport of ions by epithelial cells forms the TEP, and the electrical potential at the bottom of the epithelium is higher than at the top.^[11] C) Endogenous electric field of skin wound is caused by short-circuiting TEP when damaged. The electrical potential is directed to the wound and the positive pole is at the edge while the negative at the wound.^[20]

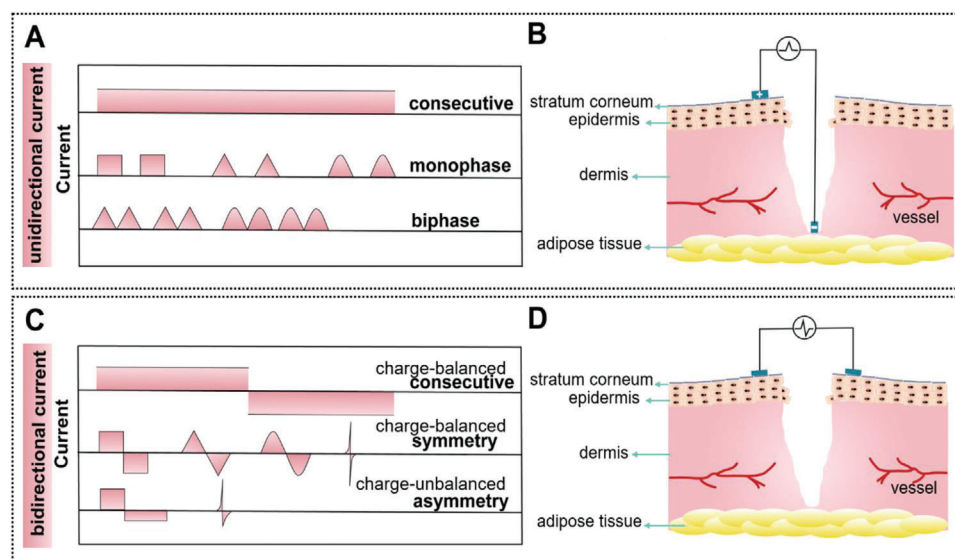


Figure 4. Waveform of electrical stimulation and the position of electrode. A) The common waveforms of unidirectional current (charge-unbalanced), such as consecutive constant current (DC), monophasic PC, and biphasic PC. B) When the electrical stimulation waveforms are unidirectional current, the positive electrode is usually placed on the normal skin and the negative electrode is placed in the wound. C) The common waveforms of bidirectional current, such as consecutive reverse current (charge-balanced), reverse symmetry PC (charge-balanced), and reverse asymmetry PC (charge-unbalanced). D) When the electrical stimulation waveforms are bidirectional current, both electrodes are usually on normal skin.

always fixed on the normal skin around the wound and the cathode to the center of wound (Figure 4B). However, if the unidirectional current stimulates the wound continuously for a long time, it will generate thermal effect and damage the skin.^[28] Bidirectional current is the current with reverse polarity (Figure 4C). When bidirectional current stimulates the wound, the charged particles in the area under the electrode will be alternately arranged. The two electrodes of electrical stimulation device are usually placed on the normal skin, which is on the either side of the wound (Figure 4D). When this current being applied on the wound, it can greatly reduce or even avoid the thermal effect.^[28b] Compared with unidirectional current, bidirectional current has fewer adverse reactions, and the electrodes are less invasive, so it might have broad prospects in clinical treatment.^[29] Regardless of the working modes, either unidirectional current or bidirectional current has the similar effects on wound healing (Figure 5).

4. The Effect of Electrical Stimulation on Skin Wound Healing

Here, we summarize and list a variety of electrical stimulation together with their impacts (Table 1), and introduced the effects on skin wound healing in detail.

4.1. The Effect on the Inflammation Phase

The immunological reaction involves a variety of immune cells, such as neutrophils, macrophages, mast cells, and lymphocytes. These cells can engulf the debris of cells and pathogens, release a series of growth factors and cytokines at the wound,

and amplify the wound signal released during the coagulation phase.^[3,30] Both neutrophils, macrophages, mast cells, and lymphocytes have response to the presence of electrical fields.

4.1.1. Recruitment of Immunocytes

For the early phase of inflammatory, accelerating the recruitment of immunocytes and cytokines have a certain role in promoting wound healing. For the entire inflammation phase, the acceleration of the recruitment is beneficial to speed up the wound healing process. Studies have shown that macrophages, lymphocytes, and neutrophils can migrate to the wound driven by endogenous electrical stimulation.^[31] Brandon et al. thought the electric response of macrophages, such as being recruited to the wound, is mainly mediated by voltage-gated potassium (K_V) channel.^[31a] Francis et al. found DC electric fields could control the migration of T lymphocytes in vivo and peripheral blood lymphocytes toward the cathode in vitro.^[31b] Valuably, Wang et al. found that the electrical stimulation has effect on the activation of signaling mediators during the inflammation phase.^[31c] They used PC electrical stimulation to recruit neutrophils into the polyvinyl alcohol (PVA) sponge implanted under the skin to monitor immune cells and molecules. The recruitment of neutrophils may be related to extracellular signal-regulated kinase (ERK) phosphorylation.

4.1.2. Resolution of Inflammation

The prolongation of the inflammatory response will seriously affect the speed of wound healing. For the late phase of inflammatory, electrical stimulation can reducing the number of immunocytes and cytokines, which has a certain role in the

Table 1. The summary of skin wound healing by electrical stimulation of traditional power supply.

Device ^{a)}	Type of current	Intensity/duration/frequency of electrical stimulation	Animal or cell model	Effect of skin wound healing	Ref.
Battery-powered unit	Unidirectional DC	Current: 600–800 μ A / Time: 2 h (2 times per day)	Human (ischemic skin ulcer)	Reduce the number of pathogens and reduce infection	[37]
Keithley 2400 Source Meter	Unidirectional PC	Current: 600 μ A (maximum) Voltage: 5 V(maximum)/ Time: 1 h / Frequency: <0.5 Hz	Mice (acute wound)	Recruitment of immunocytes and cytokines	[31c]
Stadyn Vara / Pulse Galvanic Stimulator	Unidirectional PC	Current: 35 mA / Time: 30 min (2 times per day) / Frequency: 128 Hz	Pigs (acute wound)	Reduce the number of mast cells and shorten the inflammation phase	[30]
AB-2100 electrical stimulation device	Unidirectional DC	Current: 300 μ A / Time: 30 min per day	Rats (acute wound)	Shorten the inflammation phase	[32]
	unidirectional DC	Voltage: 4.5 V Current: 40 mA / Time: 15 min / Frequency: 2 Hz	Rats (acute wound)	Decreased the expression levels of pro-inflammatory cytokines and inhibited the inflammatory phase	[36]
Portable 6 V battery operated pulsed galvanic stimulator	unidirectional PC	Current: 35 mA / Time: 30 min (2 times per day) / Frequency: 128 Hz	Human (chronic leg ulcers)	Reduce the number of mast cells and reduce scars	[33]
	unidirectional DC	Current: 300 μ A / Time: 300 min per day	Rats (acute wound)	Shorten the inflammation phase	[34]
BTL 5000 series device	unidirectional DC	Current: 600 μ A / Time: 1 h per day	Rats (acute wound)	Decreased the FGF-2 levels and shorten the inflammation phase	[35]
	unidirectional PC	Current: 2.5–3 mA / Time: 1 h per day / Frequency: 100 Hz			
Constant-current generator	unidirectional DC	Current: 1 mA / Time: 3 days	Rabbits (acute wound)	Had an antibacterial effect on the <i>Pseudomonas aeruginosa</i>	[38]
Leclanche P-70 battery	unidirectional DC	Current: 0–100 μ A	Human (no wound)	Had an antibacterial effect at the anode	[39]
Intelect model 500-Stimulator	unidirectional HVPC	Time: 3–5 min per time / Frequency: 120 Hz	Hamsters (acute wound)	Curbed macromolecular leakage from the microvessels and reduce oedema	[40]
Grass S48 stimulator	unidirectional PC	Voltage: 20 V / Time: 1 min per time / Frequency: 5 Hz	Rats (thermal burn)	Increased tissue blood flow	[41]
Challenge 8000A	bidirectional PC	Current: 20 mA / Time: 30 min (two times per day) / Frequency: 30 Hz	Human (chronic ulcer)	Improved the response of the wounds to electrical stimulation	[42]
Signal generator	Unidirectional PC	Electric field: 100 mV mm ⁻¹ / Time: continuous	Pigs (acute wound)	Promoted the migration of epithelial and formation of new epithelium	[43]
Signal generator	unidirectional PC	Electric field: 100 mV mm ⁻¹ / Time: continuous	Pigs (acute wound)	Promoted the migration and proliferation of epithelial and formation of new vessels	[44]
	unidirectional DC	Electric field: 200 mV mm ⁻¹	Primary keratinocytes	Directed cell migration through PI3K and PTEN signaling	[10a]
Generator	unidirectional DC	Current: 50–300 μ A	Pigs (acute wound)	Promoted the migration, proliferation of epithelial and secretion of collagen	[45]
Standard 9-V battery	unidirectional DC	Current: 20–100 μ A / Time: 30 min (2 times per day)	Pigs (acute wound)	Increased fibroblast ingrowth and collagen fiber arrangement	[46]

(Continued)

Table 1. Continued.

Device ^{a)}	Type of current	Intensity/duration/frequency of electrical stimulation	Animal or cell model	Effect of skin wound healing	Ref.
WMCS W200 device	unidirectional DC	Current: 2 μ A	Fibroblasts (NIH-3T3)	Promoted fibroblasts proliferation and migration in an ERK 1/2-or p38-dependent way via MAPK's phosphorylation	[47]
Signal generator DC power supply	bidirectional AC bidirectional BES (PC) unidirectional DC	Voltage: 180 mV / Time: 1 h (2 times per day) Voltage: 180 mV / Time: 1 h (2 times per day) / Frequency: 1.688 Hz Voltage: 180 mV / Time: 1 h (2 times per day) /Frequency: 1.688 Hz	Fibroblasts (NIH-3T3)	Promoted the proliferation of fibroblasts and the production of collagen and growth factors	[48]
EGS Model 100–2	unidirectional HVPC	Voltage: 0–300 V / Current: 50 μ A / Frequency: 120 Hz	Fibroblasts (IMR-90)	Induced DNA synthesis for fibroblast proliferation	[49]
	unidirectional DC	Electric field: 75–100 mV / mm	Endothelial cells (HUVEC)	Promoted endothelial cells migration and to release VEGF	[50]
BTL-5000 series	unidirectional DC unidirectional PC	Current: 600 μ A / Time: 1 h (1 time per 2 days) Current: 2.5 – 3.0 mA / Time: 1 h (1 time per 2 days) / Frequency: 100 Hz	Rats (acute wound)	Released VEGF	[51]
Constant current stimulator Direct current source	bidirectional AC unidirectional DC	Current: 0.7 mA / Time: 2 h (1 time per 5 days) /Frequency: 40 Hz Current: 0.7 mA / Time: 2 h (1 time per 5 days)	Pigs (acute wound)	Affected the hardness of scars	[52]
Portmax 300 electrical stimulation device	unidirectional PC	Voltage: 0 – 12.5 V / Time: 15 min (1 times per 2 days) /Frequency: 200 Hz	Mice (diabetic)	Affected the tensile strength of scars	[53]

^{a)} DC, direct current; AC, alternative current; PC, pulsed current; BES, biomimetic electrical stimulation; HVPC, high voltage pulsed current; FGF-2, fibroblast growth factor-2; PI3K, phosphatidylinositol-3-OH kinase-g; PTEN, phosphatase and tensin homolog; ERK 1 / 2, extracellular signal-regulated kinase 1 / 2; MAPK, mitogen-activated protein kinase; VEGF, vascular endothelial growth factor.

resolution of inflammation. Jonathan et al. discovered that PC electrical stimulation could reduce the number of mast cells.^[30] Demir et al.,^[32] Weiss et al.,^[33] Taskan et al.,^[34] and Mohammad et al.^[35] reported that electrical stimulation could cause the number of polymorphonuclear leukocyte (PNL) and mast cells reduced in the wound. In their works, compared with the control group, the duration of the inflammation phase in the electrical stimulation group was shortened. Seren et al. discovered the expression levels of pro-inflammatory cytokines in the skin decreased significantly by transcutaneous electrical nerve stimulation (TENS), such as tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1 β). It indicated that TENS can shorten the healing process by the resolution of inflammation.^[36]

4.1.3. Antibacterial

When the concentration of bacteria reaches a certain level, the inflammatory cells cannot kill these microorganisms. At this

time, the wound will be infected. Persistent wound infection is the main factor leading to delayed wound healing.^[54] Although antibiotics can be used to treat bacterial infections, long-term use of antibiotics may fail to control the chronic wounds, and lead to increased antibiotic resistance.^[55] Wolcott et al. pioneered the research of the effect of exogenous electrical stimulation on antibacterial property in vivo. They used negative polarity DC to treat chronic wounds colonized by *Pseudomonas* and *Proteus* species.^[37] They found that a few days later, the chronic wound was free of pathogens. Rowley et al. found negative polarity DC had an antibacterial effect on the *Pseudomonas aeruginosa* in the wound of rabbit.^[38] Bolton et al. noted that the DC electrical stimulation would cause a bactericidal effect at the anode, without effect at the cathode.^[39] They found that the antibacterial effect was positive correlation of the duration and current density of electrical stimulation. Using electrical stimulation alone may not achieve the perfect antibacterial effect. Some researchers have introduced antibacterial materials on the basis of electrical stimulation to improve the antibacterial effect. For example, Chu

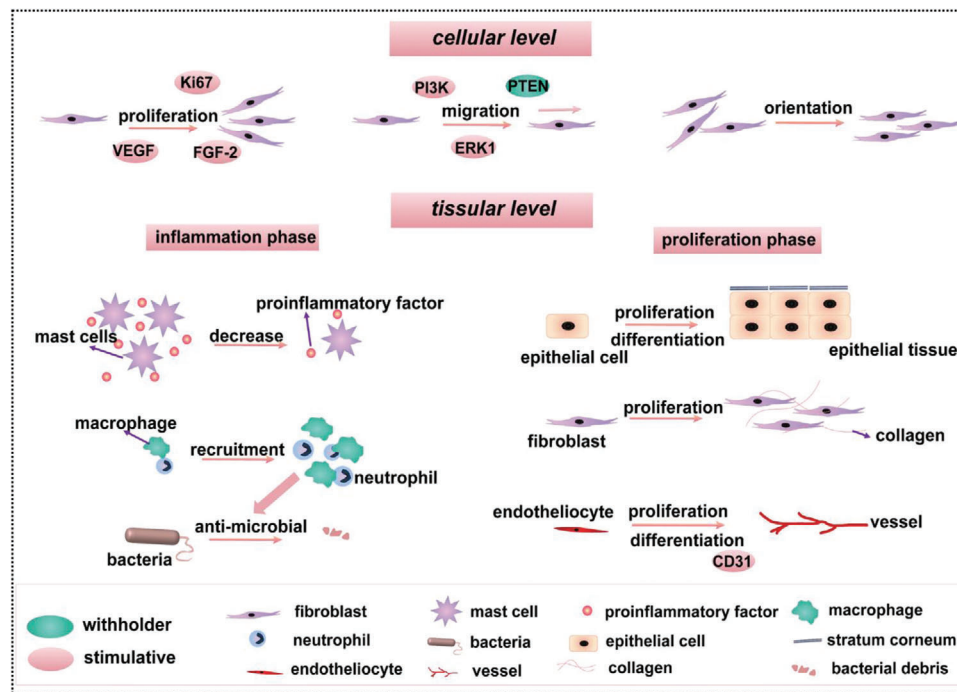


Figure 5. The effects of electrical stimulation on wound at the cellular and tissular level. At the cellular level, electrical stimulation could accelerate the proliferation of cells by increasing the expression of Ki67, VEGF and FGF-2. And electrical stimulation could promote the cell migration by promoting the secretion of PI3K and ERK1 and decreasing the expression of PTEN. Besides, the electrical stimulation also could guide the orientation of cells. At the tissular level, the electrical stimulation mainly has positive effects on inflammation phase and proliferation phase. In the inflammation phase, electrical stimulation could recruit the macrophages and neutrophils and promote inflammation to subside by decreasing the number of mast cells and proinflammatory factor. It also has the antibacterial effect may be caused by recruitment of immunocytes. At the proliferation phase, the epithelial cells, fibroblasts and endotheliocytes proliferation and differentiation could accelerate by electrical stimulation. The differentiation of endotheliocytes may be related to the expression of CD31.

et al. found that the silver nylon dressing enhanced the antibacterial effect under DC electrical stimulation.^[56] These studies have achieved positive results and showed guiding significance to the antibacterial treatment with electrical stimulation.

The mechanism of direct antibacterial activity by electrical stimulation still remains inconclusive, while there are some proofs about the indirect antibacterial effect. The electrical stimulation can recruit neutrophils and macrophages to indirectly realize the antibacterial effect.^[26] Whereas, some evidences have showed that bacteria in chronic wounds do not exist in a free state, but form highly antibiotic-resistant polymicrobial biofilms.^[54a,57] The electrical stimulation has been proved that can reduce the adhesion of bacteria, which may reduce the chance of biofilm formation.^[58] Considering the fragility of the human cells, whether the electrical stimulation have harmful influences on them still remains a problem. But, due to the existence of skin capacitance, the extracellular environment will be relatively stable at appropriate intensity of current to ensure the safety of the living environment of cells.^[59] For bacteria attached to the skin, they can be easily killed because of the rapid change of living environment (e.g., the change of pH).^[39,60] All of these studies about the antibacterial effects of electrical stimulation on wounds have shown that electrical stimulation can indirectly assist the wound healing by reducing the number of pathogens in the wound or reducing its motility, with less negative effect on cells.^[61]

4.2. Reduce Oedema

Oedema is caused by increased vessel blood pressure, which greatly reduces the patient's local blood circulation and tissue oxygenation.^[27b] In short, the presence of oedema may delay wound healing. As early as the 1980s, researchers have found that electrical stimulation could reduce oedema in animal models.^[62] Taylor et al. found that cathodic electrical stimulation treatment could reduce oedema.^[40] Young et al. used the same pulsed direct current to treat venous leg ulcers (VLUs), and found that the oedema level of the wound and surrounding tissues was significantly reduced after electrical stimulation.^[27b]

4.3. The Effect on Tissue Blood Flow (BF)

Electrical stimulation has been used as an auxiliary means to increase tissue blood flow and promote wound healing.^[37,63] The increase of blood flow helps the delivery of nutrients. Zeinab Khalil et al. used non-invasive TENS technology to treat wounds in aging rats and found that low-frequency electrical stimulation can improve the vascular response of aged rats.^[41] In addition, they also found that under low-frequency electrical stimulation, vascular responses around sensory nerves can be activated and accelerate wound healing in aging rats. There are some studies found that when the wound was treated with electrical stimulation in a

warm room (32 °C) for 4 weeks, the skin BF of chronic wounds increased significantly, and the rate of wound healing increased by 60%.^[64] Jin et al. found that enhanced vasodilation, which increasing the BF, may improve the response of the wounds to electrical stimulation.^[42] These studies have shown that electrical stimulation treatment is beneficial to the increase of tissue BF, and accelerate the wound healing process.

4.4. The Effect on the Migration and Proliferation of Cells

The proliferation phase mainly includes the formation of new granulation tissue and epithelium. This phase involved the fibroblasts, endothelial cells and epithelial cells, which have been found to be responsive to electrical signals in researches.^[10] The movement of these cells is related to the endogenous electric field generated in the injured tissue. Zhao et al. discovered that electrical signals control the cell directed migration through phosphatidylinositol-3-OH kinase-g (PI3K) and phosphatase and tensin homolog (PTEN).^[10a] An important aspect for electrical stimulation to accelerate wound healing is that the electric field can provide directional cues for the cells, and override directional cues such as chemokine gradients and pressures for cell migration. This is something that cannot be replaced by other treatments.^[10a,20] Abundant studies have proved that exogenous electrical stimulation also has a promoting effect on cell proliferation, and can accelerate the process of wound healing.^[10a,65]

4.4.1. Migration and Proliferation of Epithelial Cells

The epidermis, which mainly consists of epithelial cells, is the outermost tissue of the skin, and the speed of wound closure is closely related to its speed of repair. The migration and proliferation of epithelial cells correlates with the mechanism of basal skin potential.^[66] The main findings of researches showed that anode DC electrical stimulation can guide epithelial cells to accelerate wound closure by improving the recovery speed of the endogenous electric field.^[17,67] Alvarez et al. and Mertz et al. found that anodic DC and high voltage pulsed current (HVPC) electrical stimulation caused faster formation of epidermis.^[45,67] Some studies have found that applying a DC electric field as low as 10 mV mm⁻¹ is sufficient to induce the directional migration of keratinocytes.^[68] Moreover, the migration of keratinocytes has a dose effect, that is, within a certain range of DC field strength, keratinocytes will migrate faster under a higher field strength than lower. Liang et al. used a negative pressure device to hold the electrodes in place for continuous electrical stimulation (Figure 6A).^[43] They found that the electric fields (100 mV mm⁻¹) can speed up the migration of epidermal cells. In contrast, a reverse electric field (-100 mV mm⁻¹) inhibited wound healing.

4.4.2. Proliferation and Migration of Fibroblasts

The first effect that been noticed in the proliferation phase by researchers was the effect of exogenous electrical stimulation on fibroblasts. In 1988, Dunn et al. evaluated the effect of DC electrical stimulation on fibroblast growth using carbon fiber electrodes doped with collagen sponge matrix.^[46] Preliminary results

showed that DC electrical stimulation increased fibroblast in-growth and collagen fiber arrangement in collagen sponges. Fibroblasts also showed directional migration to the anode, which may be caused by activation of PI3K and Na⁺ / H⁺ exchange isomer 1 (NHE1).^[69] Unlike the last study, Konstantinos et al. observed that both the rates of scratch closure and proliferation increased significantly by electrical stimulation.^[47] They believed that microcurrents may accelerate the rate of cell migration and proliferation through the phosphorylation of mitogen-activated protein kinase (MAPK). So et al. used the extracellular matrix (ECM) to simulate the in vivo environment (Figure 6B).^[48] They found that AC, DC, and biomimetic electrical stimulation (BES) at the same electric field strength all promoted the proliferation of fibroblasts together with the production of collagen and growth factors. Besides, they found that BES has the best effect.

During the proliferation phase, the granulation tissue is mainly composed of fibroblasts and their secreted collagen. In the early phase of wound healing, elevated levels of collagen can help wounds heal properly.^[70] Studies have found that HVPC and DC electrical stimulation can induce DNA synthesis for fibroblast proliferation.^[49,71] Alvarez et al. and Canseven et al. discovered DC electrical stimulation increased the content of collagen, which synthesized by fibroblasts.^[45,72] In short, electrical stimulation can promote the proliferation of fibroblasts and the secretion of collagen by fibroblasts, thus promoting the formation of granulation tissue.

4.4.3. Migration of Endothelial Cells and Angiogenesis

Angiogenesis is a vital part in the proliferation phase, and also an important component of granulation tissue. The formation of new vessels can improve tissue oxygenation and nutrient delivery, also can provide a good microenvironment for wound healing.^[73] Vascular endothelial growth factor (VEGF) appears immediately after injury and induces endothelial cell migration, proliferation, and vascularization.^[74] Endogenous electric field can induce the release of VEGF to guide endothelial cells migration.^[50,75] Studies have proved that exogenous electrical stimulation could increase the expression of VEGF at the wound, which may be one possible mechanisms of vascularization under electrical stimulation.^[35,50,51,76] Zhao et al. found that endothelial cells migrated by the tissue cytoskeletal actin filaments—lamellipodia.^[50] These findings indicate that electrical stimulation can improve the healing rate of wounds by accelerating the migration and vascularization of endothelial cells.

4.5. Scars

In clinical treatment, the remodeling stage is the most concerned stage in the course of wound treatment.^[77] At this phase, a large amount of collagen is deposited, which is closely related to scar. The existence of scars not only affects the appearance, but may even affect the patient's daily life. Only a few researchers have paid attention to the effect of electrical stimulation on scars when exploring the effect of electrical stimulation on wound healing.

For the first time, Weiss et al. studied the relationship between electrical stimulation and scars. They found that electrical

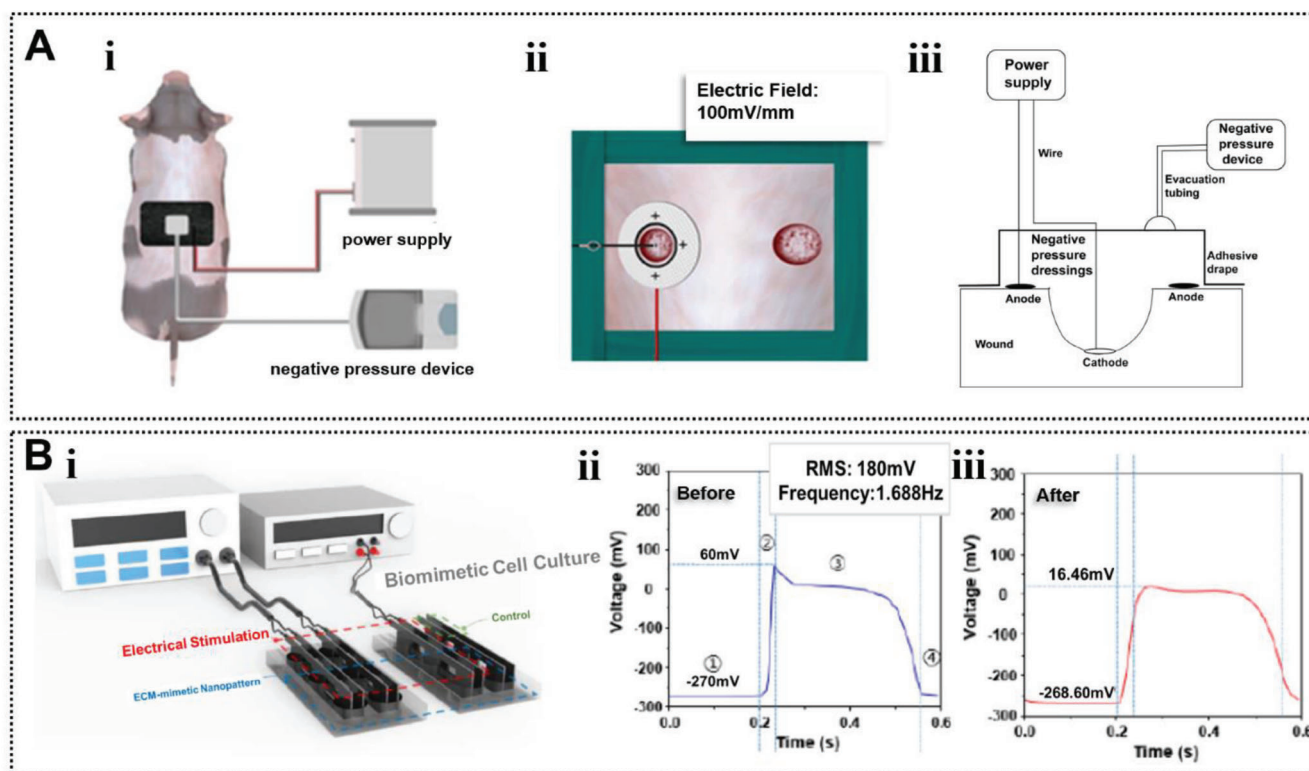


Figure 6. Traditional electrical stimulation devices for wound healing. A) Usage of low-frequency PC electrical stimulation in promoting wound closure. i) The unidirectional PC was generated by the power supply and the negative pressure device made the ring and needle electrodes fixed. ii) The ring electrode acted as an anode was fixed on the normal skin around the wound, and the needle electrode acted as a cathode was fixed on the center of wound. Under the negative pressure, a steady electric field (100 mV mm^{-1}) could be applied to the wound. iii) The conceptual diagram of wound treatment (longitudinal section). The negative pressure device could fix the electrodes. Reproduced with permission.^[43] Copyright 2020, Elsevier. B) Using bionic electrical stimulation to promote fibroblast proliferation and collagen synthesis. i) The signal generator (supplies the PC and BES) and DC power supply provided the electrical stimulation to cells. DC, AC, and BES were applied to three columns of six wells, and the last column was used as the control group. ii) The voltage waveform applied by an exogenous BES generator. iii) The voltage waveform actually applied to the cells. Reproduced with permission.^[48] Copyright 2020, Elsevier.

stimulation can change the thickness of scars.^[33] Kambic et al. found that AC and DC not only can promote wound healing, but also have a certain impact on the hardness of scars.^[52] Habiba et al. used low-voltage pulsed current (LVPC) electrical stimulation to study the potential mechanism of wound closure in diabetic mice.^[53] They found that the collagen deposition in deep scars was positive related to the strength of electrical stimulation. The results showed that electrical stimulation may have an effect on the tensile strength of scars.

5. Electrical Stimulation Treatment Devices and Methods for Skin Wound Healing

Exogenous electrical stimulation treatment is closely related to electrical stimulation devices. The electrical stimulation devices commonly used in clinical treatment are mostly traditional electrical stimulation devices. Traditional electrical stimulation devices are mainly power devices that can generate different types of currents, such as DC power supplies (output DC),^[38,48] signal generators (output AC and PC),^[43,44,52] etc. Although they have achieved good results when applied to wounds, the traditional electrical stimulation devices are relatively large and difficult to

carry around. In addition, patients can only be treated in the specific place like hospital, which causes huge medical expenditures.

With the improvement of medical standard, clinical applications put forward new requirements for electrical stimulation treatment equipment. In the current trend, they have become hot topics that developing personalized medical services and realizing the miniaturization, low-cost, portability, safety, and stability of electrical stimulation devices. Faced to these requirements, researchers have proposed many new strategies for improving the electrical stimulation treatment devices. Here, we list some examples in Table 2, such as miniaturization of power supplies,^[78] NGs,^[79] and methods that use physical, chemical or biological principles to simulate or enhance endogenous electric fields.^[80]

5.1. Miniaturization of Power Supply

The large and expensive characteristics of traditional power supplies have led researchers to consider small power supplies, such as dry batteries. Button cell are a common mobile power source, which has the characteristics of small size, low cost, and portability. However, the output of the button cell is small and unstable.

Table 2. The summary of skin wound healing by electrical stimulation of new-type power supply.

Device ^{a)}	Type of current	Intensity/duration/frequency of electrical stimulation	Animal or cell model	Effect of skin wound healing	Ref.
battery	unidirectional HVMPC	Voltage: 40 V / Time: 1 h (1 time per 2 days) /Frequency: 100 Hz	T2D rat (chronic wound)	Accelerating angiogenesis, enhancing epithelial formation and inhibiting scar formation	[78]
TENG	bidirectional PC	Open circuit voltage: 2 V / Time: 24 h /Frequency: 1 Hz	Fibroblasts (L929)	Promote the migration of fibroblasts	[79a]
TENG	bidirectional PC	Short circuit current: 10 – 100 μ A / Frequency: 120 – 280 Hz	Fibroblasts (L929)	Promote the migration and proliferation of fibroblasts	[79b]
TENG	bidirectional PC	Open circuit voltage: 0.2 – 2.2 V /Time: continuous Frequency: 0.5 – 1.83 Hz	Rats (acute wound) / Fibroblasts (NIH-3T3)	Promote the proliferation, migration and differentiation of fibroblasts	[79c]
TENG	bidirectional PC	Open circuit voltage: 10 V / Frequency: 0.5 – 2 Hz	Mice (acute wound) / Diabetes mellitus fibroblasts	Promote the migration, proliferation and secretion of angiogenic growth factors of dermal fibroblasts	[79d]
PENG	bidirectional PC	Open circuit voltage: 0.5 V / Frequency: 1 Hz	Mice (acute wound) / Fibroblasts (NIH-3T3)	Promote the proliferation and migration of fibroblasts	[79e]

^{a)}TENG, triboelectric nanogenerator; PENG, piezoelectric nanogenerator; PC, pulsed current.

Wang et al. designed a wound dressing using chitosan-Vaseline gauze (CVG) and a flexible electrical stimulation device.^[78] The electrical stimulation device of the dressing is composed of a battery, a circuit management module and electrodes. The circuit management module can convert the DC current output by the battery into a high-voltage monophasic pulsed current (HVMPC). The dressing can effectively promote the proliferation and migration of human umbilical vein endothelial cells (HUVEC) to accelerate vascularization, and have a positive effect on re-epithelialization and inhibiting scar in the treatment of diabetic wounds.

5.2. Nanogenerators (NGs)

NGs were proposed by Wang et al. in 2006, which were originally developed for self-powered systems based on piezoelectric effect and triboelectric effect.^[81] It is proved that the nanogenerator is the effective application of Maxwell's displacement current in energy harvesters and sensors.^[82] NGs can convert mechanical energy such as human motion, vibration energy or water energy into electrical energy.^[83] NGs can be typically divided into two categories, one is piezoelectric nanogenerator (PENG) and the other is triboelectric nanogenerator (TENG). PENG is composed of piezoelectric materials, flexible substrate, and electrodes.^[84] TENG was developed based on triboelectrification and electrostatic induction between two different materials. NGs are self-powered, portable, flexible, wearable, low-cost, and high-safety (high voltage but low current). The development of self-powered electrical stimulation devices based on NGs is undoubtedly a feasible strategy for the treatment of wounds.^[84,85]

Li et al. designed an implantable triboelectric nanogenerators (iTENGs) (Figure 7A).^[79a] iTENGs can collect energy from biological activities and convert it into electricity for electrical stim-

ulation. Similar to DC electrical stimulation, the iTENGs could promote the migration of fibroblasts with the same voltage intensity. Hu et al. designed a rotatory disc-shaped TENG (RD-TENG) when exploring new type of electrical stimulation device for wound treatment (Figure 7B).^[79b] Using different current outputs of the RD-TENG electrical stimulation system to explore the effects on behavior of fibroblasts, they found that the influence on migration and proliferation of fibroblasts are the most obvious with the current of 50 μ A.

Several researchers have investigated the effect of NG-based electrical stimulation treatment devices on wound closure in animals. Wang et al. designed an electric bandage based on TENG.^[79c] After the bandage is worn by the rat, the mechanical energy generated by the rat's breathing can be collected and converted into electric energy. This bandage provides an exogenous electric field for the wound to accelerate wound healing. Their experiments in vitro found that the electric field can promote the proliferation, migration and differentiation of fibroblasts. Recently, Jeong et al. designed a wearable ion triboelectric nanogenerator patch based on TENG and fully stretchable gel (Figure 8).^[79d] Studies have found that the electric field generated by ion TENG can accelerate the migration, proliferation of fibroblasts and promote the secreting of angiogenic growth factor to speed up wound healing. Du et al. designed an electrical stimulation skin patch based on PENG.^[79e] The patch is made of a mussel-inspired hydrogel matrix and polyvinylidene fluoride (PVDF) nanofibers, which can generate low-frequency pulse voltage (up to about 0.5 Vpp) at the wound. This voltage can not only promote the proliferation and migration of fibroblasts, but also effectively promote the deposition of collagen, angiogenesis, and re-epithelialization in the body by increasing the expression of the growth factors, and quickly close the wound.

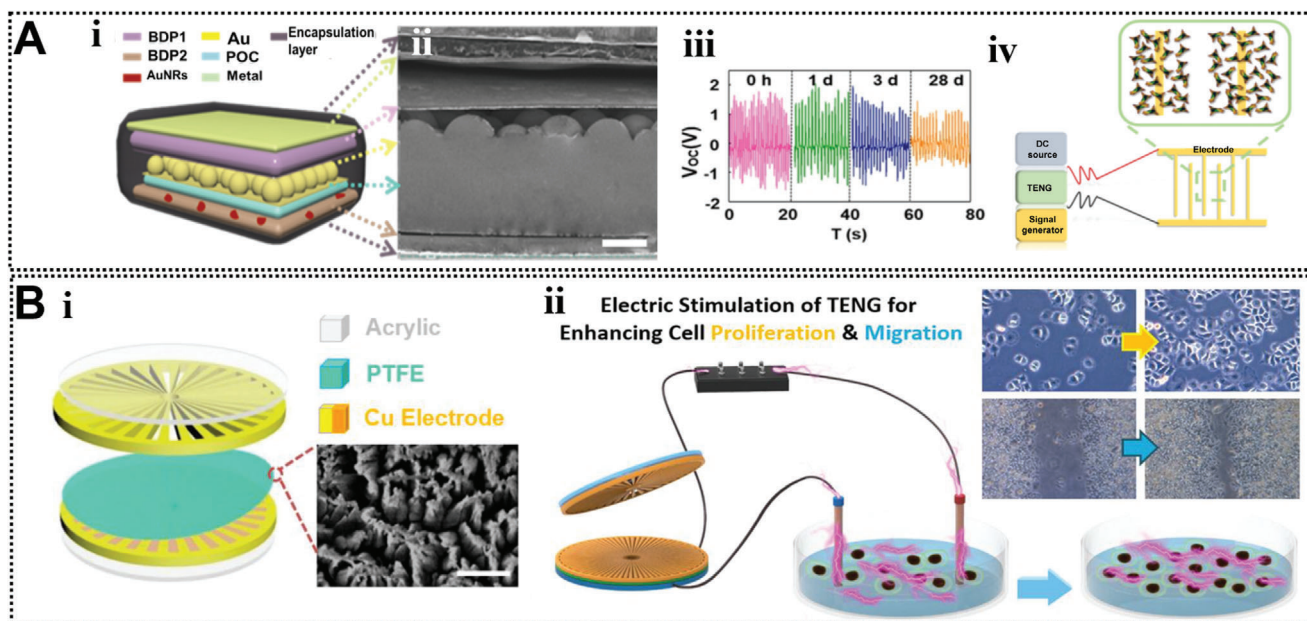


Figure 7. Nanogenerators (NGs) for wound healing in vitro. A) Degradable triboelectric nanogenerators (iTENGs) used to promote the migration of fibroblast. i) The structure of iTENG. The Au-deposited hemispheres-array-structured layer is both the triboelectric material and electrode. The other triboelectric layer is the Biodegradable Polymer 1 (BDP1) and its electrode is magnesium. ii) Section view of BD-iTENG (SEM, scale bar: 500 μm). iii) The open circuit voltage of iTENG in vivo is ≈ 2.0 V, and it persisted about 70% of the voltage on the 28th day. iv) Schematic diagram of the electrical stimulation for fibroblasts by BD-iTENG and other power sources using interdigital electrodes in vitro. Reproduced with permission.^[79a] Copyright 2018, Elsevier. B) Rotatory disc-shaped TENG (RD-TENG) used to promote the proliferation and migration of fibroblast. i) The RD-TENG is made up of acrylic (as a base), PTFE (as a triboelectric layer) and Cu electrode (as the other triboelectric layer). ii) Schematic illustration of electric stimulation system for fibroblasts proliferation and migration. The system consists of a RD-TENG, a rheostat and a cell culture dish which has two electrodes. The fibroblasts migration and proliferation could be increased by RD-TENG. Reproduced with permission.^[79b] Copyright 2019, Elsevier.

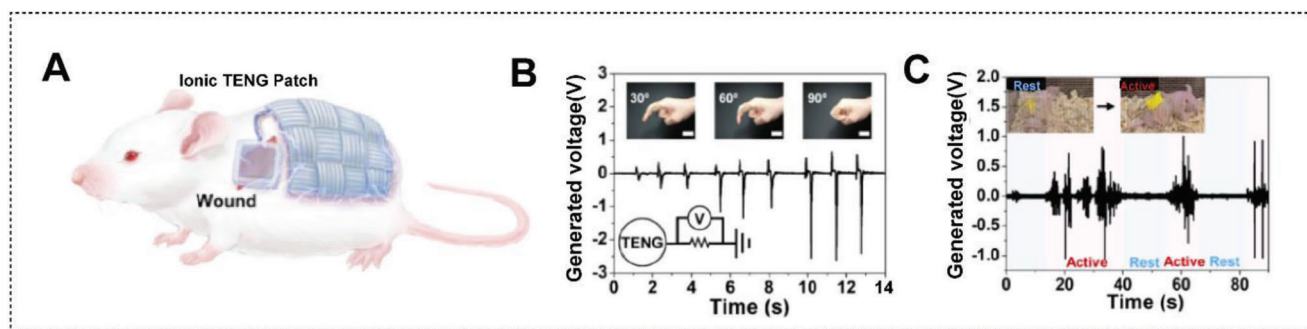


Figure 8. Wearable ion triboelectric nanogenerator patch based on TENG used for wound healing. A) Schematic illustration of the TENG patch for wound healing based on triboelectricity. The TENG is woven by the organogel and elastomeric microtubular structure. B) Voltage of patch generated by bending at 30°, 60°, and 90° (the maximum value is ≈ 3.3 V). C) Output of patch driven by the movement of mouse in the resting and active state (the maximum value is ≈ 2.2 V). Reproduced with permission.^[79d] Copyright 2021, Elsevier.

5.3. Other Methods to Enhance the Electric Field of Wound

Since the key cells of wound healing have response to the electric signals, some people have proposed other methods to create a charged environment. As early as 1992, Thomas et al. used particles with positive charge on the surface to create a locally charged environment.^[80a] They found that it promoted wound healing on the back of rats. In recent years, material science has developed rapidly, and researchers have begun to directly use materials to create a charged environment for wounds. For exam-

ple, Bhang et al. used the piezoelectric properties of zinc oxide nanowires to create a charged environment to wounds.^[80c] They designed a piezoelectric patch using unidirectionally arranged zinc oxide nanowires. The patch can undergo mechanical deformation when the animal moves, and generate an electric field on the wound. They found that induced electric field could promote the wound healing process through enhanced cell metabolism, migration and protein synthesis. Li et al. combined a photosensitive semiconductor polymer (SP) with an electrospun poly(ϵ -caprolactone) (PCL) nanofiber scaffold.^[80b] Under the excitation

of a red light-emitting diode (LED), this scaffold can generate a current to promote proliferation of the human dermal fibroblasts (HDF). Nishizawa et al. used flexible enzyme electrodes, stretchable hydrogels and enzymatic biofuel cell (EBFC) to prepare a stretchable bioelectric paste.^[86] Bioelectric Plaster was added for the electrical manipulation of biological functions, which acts as built-in enzymatic biofuel cell. The EBFC can produce an enzyme-catalyzed electrochemical reaction on the skin and generate ion current on the surface of the skin. The wound model of mouse showed that the ion current of the bioelectric cream can accelerate wound healing.

6. Discussion and Outlook

The skin is the first barrier to protect the human body. It is necessary to repair skin wounds in time. Electrical stimulation has been used in clinical treatment of wounds for many years to simulate and enhance the endogenous electric field. This review outlines the role of electrical stimulation in wound healing, focusing on each step of the wound healing process and summarizes the devices or methods enhancing or simulating the endogenous electric field. According to these cases, it is not difficult to find that most of the key cells in wound healing are electrically responsive, which makes electrical stimulation become an important method in wound treatment. Although many types of electrical stimulation have been proved effective in promoting wound healing, there are several crucial problems need to be solved.

6.1. Accuracy and Personalization

Individual differences put forward requirements to the strategy of electrical stimulation for wound treatment, such as the treatment of large/small and chronic/acute wounds. The causes and characteristics of different wounds are not completely the same. When using electrical stimulation treatment, the differences require the features of various individuals and their wounds need to be considered. Future research should focus on the improvement in type, intensity, frequency, and duration of electrical stimulation.

6.2. Combination of Treatments

Traditional treatment methods (e.g., dressings,^[87] hyperbaric oxygen therapy,^[88] negative pressure therapy^[89]) and new treatment methods (e.g., electrical stimulation, vibration, ultrasound^[90]) both have obvious effects in wound therapy. The unlike treatment methods have different effects and mechanisms on wound healing. The combination of multiple treatments may produce synergistic effects and bring better effects, such as combining the negative pressure and electrical stimulation.^[43] The effects and synergistic mechanisms of these combined treatments need to be lucubrated some time.

6.3. Integration and Multifunction

The common electrical stimulation treatment device only contains electrical stimulation source and electrodes nowadays. In

the future, electrical stimulation treatment devices should include the functions like stimulation, detection and monitoring in a time. Wang et al. used electrical stimulation to intervene in the inflammatory phase of the wound, with the electrical stimulation treatment device being already added the function of monitoring at the same time.^[31c] The progress of material science, structural design and manufacturing technology has created a broad development space for the electrical stimulation treatment devices. For clinical applications, we need more integrated and multifunctional devices to improve the efficiency of treatment.

6.4. Self-Powered Devices

NGs can convert the small/micro mechanical energy into electrical energy, especially the energy collected from human breathing,^[79c] heartbeat,^[91] and movement.^[92] Being widely used in wearable and implantable electronic devices, NGs can not only be used as power resources, but also sensors.^[93] It is even possible to prepare degradable NGs through rational use of materials.^[94] Except for NGs, there are many other types of self-powered devices available, such as photovoltaics and pyroelectricity,^[95] and these devices also provide inspirations and solutions for electrical stimulation treatment. How to ingeniously and reasonably design self-powered electrical stimulation equipment and apply it to clinical treatment of skin wounds is a matter that should be settled in the future. The research of self-powered electrical stimulation devices will become a hotspot in years to come.

Faced with these challenges, future researches about electrical stimulation could combine with the cutting-edge technologies in materials science, electronics, mechanical engineering, and tissue engineering to propose better treatment methods for wound healing. Apart from accelerating skin wound healing, the electrical stimulation is expected to reduce or even eliminate sequela including scars with more comfortable use feeling.

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Conflict of Interest

The authors declare no conflict of interest.

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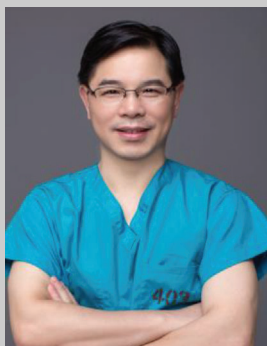
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