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Perspective

Self-powered electrical stimulation assisted skin wound therapy

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Skin wounds are one of the most common and major global public health problems. As the human body's largest organ, the skin is extremely vulnerable to invasion and damage by various physical, chemical, or biological factors [1]. Disruption of skin integrity means loss of its barrier function, which may lead to damage to the deeper tissues or disturbance of the internal microenvironment. It is estimated that 1%–2% of the world's population will experience chronic trauma during their lifetime, especially in recent years, the rising incidence has led to increased socioeconomic burden, making skin trauma an increasingly important clinical problem [2].

With the in-depth understanding of the causes and healing mechanisms of various wounds, as well as the continuous development of artificial intelligence drug design and biotherapy technology, many new prevention, diagnosis, and treatment strategies have emerged. However, the physiopathological impact of the physical properties of the wound itself, especially its electrical properties, is often overlooked. Numerous studies have demonstrated that the epithelial layer of intact skin maintains a potential difference due to the heterogeneous distribution of ion channels in skin epithelial cells [3]. Because of the higher cation concentration at the top of the epithelium, which has a higher potential compared to the bottom of the epithelium, ions can actively cross the cell membrane along this electrochemical gradient. At the same time, to maintain the electrochemical balance, some cations flow back to the top of the epithelium through the paracellular pathway, resulting in a stable transepithelial potential (TEP) in the epithelial layer. Once the wound is formed, the TEP is disrupted and the wound edge is short-circuited, thereby generating the endogenous electric field of the wound, with sodium, potassium, chloride, and calcium ions being the major contributors to the generation of the electric field [4]. From the perspective of tissue structure, the stratum corneum, epidermis, dermis, and subcutaneous tissue of the skin have different electrical properties, which may be related to the connection mode and composition of the cells [5]. The stratum corneum, composed of keratinized epithelial cells, determines the electrical impedance of the skin because it has very low water content and acts as an insulating layer. The dermis and subcutaneous tissue have a high cellular content and are the least electrical resistive of the skin layers. The epithelial cells of the epidermis are connected by tight junctions, which is why the epidermis is more resistive than the dermis.

Exogenous electrical stimulation, by modulating the electrical properties of the skin and wounds, has become a new type of physical therapy with positive effects on the inflammatory, proliferative, and remodeling phases of wound healing [6]. In the past few decades, electrical stimulation therapy has been used by clinical scientists to explore the potential of treating chronic wounds such as diabetic wounds, infected wounds, and burn wounds. However, in an overview of these studies, there are many unresolved issues with electrical stimulation wound therapy. (1) Although many studies have shown that exogenous electrical stimulation can affect the behavior of key cells in wound healing, there is still a lack of in-depth understanding of its molecular mechanism. (2) Few studies have taken a physical perspective to investigate whether exogenous electrical stimuli interfere with endogenous electric fields. (3) The electrical stimulation equipment commonly used in clinical practice is bulky and expensive, and therefore does not meet the need for miniaturization and portability of treatment devices. (4) Most importantly, the majority of these studies used electrical stimulation alone, however, whether electrical stimulation can replace the traditional gold standard of physical and pharmacotherapy and form a new treatment paradigm needs to be further investigated.

Until recently, the design of medical devices based on triboelectric nanogenerators (TENG) broke through the limitations of conventional electrostimulation therapy devices, due to their biosafety output performance, easy-to-integrate device structure, portability, and passive output characteristics [7,8]. On this basis, we put forward a new idea of electrical stimulation therapy that is more in line with the concept of translational medicine, that is, electrical stimulation is not a substitute for the "gold standard" treatment strategy, but is used in conjunction with pharmacotherapy and physical therapy as an "adjuvant" to eliminate the potential side effects of classical therapies in wound healing, which can better meet the requirements of surgical treatment and is easier to be accepted by physicians and patients.

Electrical stimulation synergizes with physical therapy strategies for wounds. Self-powered technology based electrical stimulation can combine with negative pressure wound therapy (NPWT) to treat acute and chronic large-area skin injuries, such as diabetic

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wounds, deep second-degree burns and scalds, and infectious wounds [9]. In the face of these acute/chronic wounds with unstable microenvironment, NPWT is one of the "gold standards" for clinical treatment [10]. However, clinicopathological evidence shows that although NPWT can promote wound healing by improving the wound microenvironment, the anti-infection ability of NPWT cannot be further translated into the clinical benefit of subsequent re-epithelialization. We found that a substantial decrease in wound potential occurred after NPWT treatment, and drainage fluid testing showed that the drained wound exudate contained a large number of ions. Therefore, it can be speculated that the difficulty of wound re-epithelialization may be due to the attenuation of endogenous electric field caused by NPWT-induced wound ion loss. To promote re-epithelialization of NPWT wounds, exogenous electrical stimulation provided by TENG serves as an "electrical adjuvant" to counteract the decrease in wound potential caused by NPWT. By combining a TENG with NPWT, an electroactive dressing (EGD, size: 15 cm $\times$ 10 cm $\times$ 5 cm, weight: $\sim$20 g) was designed to generate a safe unidirectional pulsed electric field while the negative pressure control device was operating. EGD reshaped the endogenous electric field of the wound, thereby triggering the strong electrotaxis response of epithelial cells and accelerating the re-epithelialization of the wound; at the same time, it also promoted the M2 polarization of macrophages, shortening the transition time from the inflammatory phase to the proliferative phase of the wound. In addition to good anti-inflammatory properties, EGD can also inhibit the formation of skin scarring by reconstructing mature epithelial microstructure and ordered extracellular matrix. NPWT combined with electrical stimulation non-invasively controlled all important wound repair stages, and the regenerated skin tissue was similar to the normal dermis in histology, chemical composition, and micro/nano structure, with higher quality and strength to resist secondary damage.

Electrical stimulation enhances the pharmacodynamics of wound treatment drugs. In addition to assisting physical therapy, we also demonstrated that self-powered technology based electrical stimulation can improve pharmacodynamics [11]. For small-area skin wounds that are inevitably encountered in daily life, the conventional treatment method is to directly smear medication, such as epidermal growth factor (EGF), on the wound [12]. However, the use of EGF usually encounters the following pharmacodynamic challenges: (1) macromolecular drugs have poor transdermal properties, making it difficult for them to penetrate the stratum corneum and be absorbed by the dermis; (2) there are a large number of reducing substances in the skin, such as reduced glutathione, which leads to the reduction and inactivation of drugs; (3) a high-concentration EGF environment can trigger receptor desensitization, making it difficult for drugs to exert their efficacy. The above issues can be well addressed by the microneedles-based self-powered transcutaneous electrical stimulation system (mn-STESS, size: 2 cm $\times$ 5 cm, weight: $\sim$5 g), a composite structure of TENG and two-stage microneedles. The microneedle structure of mn-STESS could not only puncture the stratum corneum and continuously deliver EGF to the dermal tissue, but also apply high-efficiency electrical stimulation to the skin in a low-resistance manner. Simply sliding one's finger over the surface of the mn-STESS can trigger the built-in TENG to produce electrical stimulation. The generated electrical stimulation increased the intermolecular distance by changing the molecular motion behavior of GSH and EGF, thereby inhibiting the reduction of EGF by GSH. More importantly, the electrical signal completely reversed the receptor desensitization caused by EGF, increased the efficacy of EGF by up-regulating the expression of EGFR, and ultimately promoted cell proliferation and migration by activating the EGF/EGFR pathway to achieve wound re-epithelialization. In view of the synergistic effect of electrical stimulation and drugs, it was named as "self-powered electrical adjuvant", which provides a potential solution for overcoming the resistance of classical drugs.

Perspectives and challenges. Taken together, self-powered technology based electrical stimulation can effectively address many of the challenges faced by traditional wound healing strategies. Compared with traditional electrical stimulation devices (direct current power supplies, signal generators, etc.), self-powered electrical stimulation devices have better shape plasticity, biosafety due to low currents, and a broader choice of materials. In terms of physical properties of the tissue, exogenous electrical stimulation therapy can significantly enhance the endogenous electric field of the wound, thereby reducing scars. In terms of cellular behavior and function, electrical stimulation therapy not only promotes the proliferation and migration of key cells for wound healing, but also affects the distribution of cell receptors and the polarization of macrophages (Fig. 1). However, as a novel combination therapy, electrical stimulation still has several challenges to be solved before its wide clinical application. (1) Self-powered technologies mainly include TENG, piezoelectric nanogenerator (PENG), biofuel cell, photovoltaic devices, and pyroelectric device [13,14]; however, combined therapeutic strategies based on self-powered electrical stimulation have been rarely reported. It is foreseeable that the new model of adjuvant therapy based on self-powered electrical stimulation technology and the innovation of related devices design are still a very important direction. (2) Although cell electrotaxis, cell receptors redistribution, and immune cell polarization have been observed in the presence of self-powered electrical stimulation, the signaling pathways leading to these phenomena remain unclear. It will be of great interest to explore the molecular mechanisms of cell electrotaxis triggered by self-powered electrical stimulation and to realize broader applications in the field of bioregulation. (3) Self-powered electrical stimulation has been shown to have positive effects in the treatment of acute wounds, infectious wounds, and burn wounds by regulating the behavior of epidermal cells and macrophages. However, numerous cells involved in wound healing have not been studied, such as fibroblasts, adipocytes, neutrophils, lymphocytes. How self-powered electrical stimulation can assist these cells to play an active role in wound healing remains to be further investigated. (4) The response to electrical stimulation varies among populations and cell types, so the development of standardized treatment protocols relies on the generalization and summary of results from a large number of experiments.

In summary, electrical stimulation is emerging as an extremely promising adjunct strategy for wound repair. The synergistic therapy of electrical stimulation and traditional treatment strategies (ELEC + X) may lead to a paradigm shift in medical devices for wound repair. "ELEC + X" is expected to be further extended to the treatment of diabetic skin diseases, high altitude frostbite, and other large or chronic wounds. More importantly, compared with the traditional treatment strategy, "ELEC + X" adds only limited cost to conventional treatments. Compared with expensive biopharmaceuticals and new medical devices, "ELEC + X" enable patients to achieve greater benefit at an affordable expenditure. With the continuous iteration of electrical stimulation devices and the expansion of their application range, the next generation of self-powered electrical stimulation devices is bound to bring revolutionary innovations to the biomedical field.

Conflict of interest

The authors declare that they have no conflict of interest.

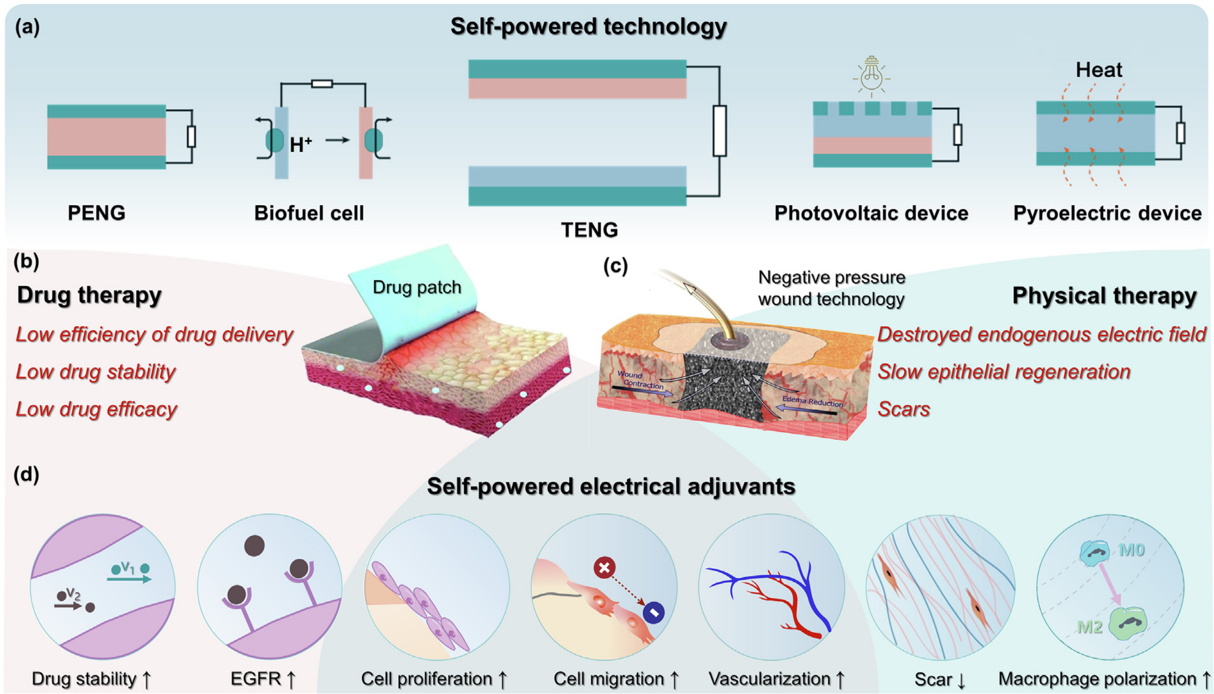

Fig. 1. Electrical stimulation based on the self-powered technology can be used as a self-powered electrical adjuvant in combination with traditional simple-a methods for wound repair. Self-powered electrical stimulation can complement the shortcomings of traditional medicine and physical therapy, and have a significant effect on each key behavior of wound healing while retaining the advantages of traditional physical therapy [9–12]. (a) Classification of self-powered technology. (b) Electrical stimulation enhances the pharmacodynamics of wound treatment drugs. (c) Electrical stimulation synergizes with physical therapy strategies for wounds. (d) Biological effects of self-powered electrical adjuvants in skin wound healing. Copyright © 2011, 2013, 2023 John Wiley and Sons; Copyright © 2022 Springer Nature.

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