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REVIEW

Biomaterials-enabled electrical stimulation for tissue healing and regeneration

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Abstract
The electrical microenvironment is considered a pivotal determinant in various pathophysiological processes, including tissue homeostasis and wound healing. Consequently, extensive research endeavors have been directed toward applying electricity to cells and tissues through external force devices or biomaterial-based platforms. In addition to in situ electroconductive matrices, a new class of electroactive biomaterials responsive to stimuli has emerged as a focal point of interest. These electroactive materials, in response to intrinsic biochemical (e.g., glucose) or external physical stimuli (e.g., light, magnetism, stress), hold significant potential for cell stimulation and tissue regeneration. In this communication, we underscore this distinct category of electroactive biomaterials, discussing the currently developed biomaterial platforms and their biological roles in stimulating cells and tissues during the healing and regeneration process. We also critically evaluate the inherent limitations and challenges of these biomaterials while offering forward-looking insights into their promise for future clinical translations.

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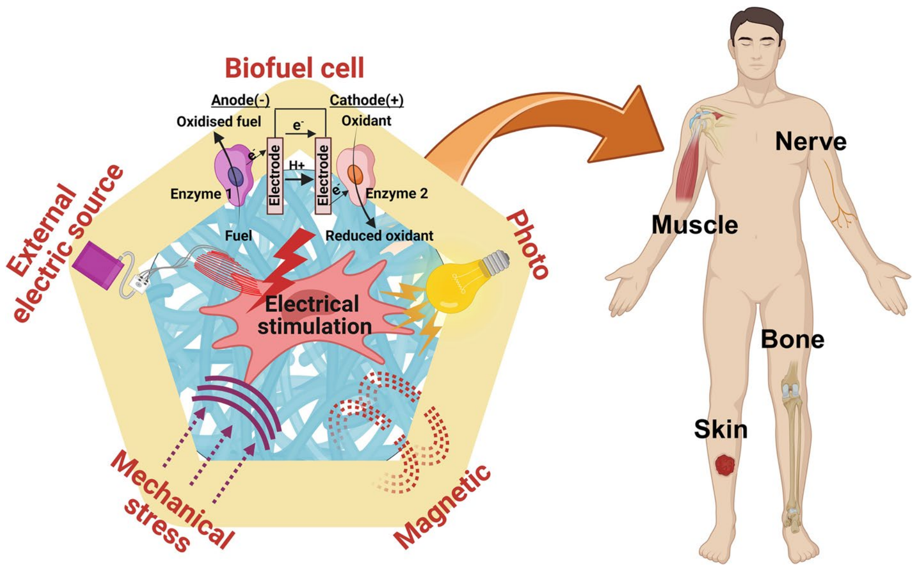
Graphical Abstract



Keywords Electricity · Mechano-electroactive materials · Physical stimuli · Cell stimulation · Tissue regeneration

Introduction

Cells encounter a diverse array of in vivo tissue microenvironments [1, 2]. The dynamic interaction of cells with physical and chemical cues of extracellular matrix (ECM) determines cellular behaviors, including anchorage, motility, differentiation, and survival [2–4]. Among the cues, electrical stimulation has emerged as a prominent determinant in modulating cellular functions. The electrically active milieu exerts discernible effects on diverse cell responses, such as alignment, proliferation, and differentiation, which often synergize with biochemical signals, thereby fostering tissue healing and regeneration [5–8].

Electrical stimulation has been demonstrated to exert diverse in vivo effects, including pain relief, improved blood circulation, reduced tension in vascular and skeletal muscles, and reabsorption of edema and joint fluid [9]. It also has a profound influence on cell behaviors in vitro. For instance, pulsed single-phase current significantly alters the shape, viability, structure, and adhesion of mouse myocytes, while dynamic electric field conditions favorably regulate osteoblast proliferation and differentiation [10, 11]. Specific electrical parameters can enhance neural cell growth and control neural stem cell differentiation [12, 13]. Moreover, electrical stimulation activates ion channels (e.g., Ca^{2+}, Na^{+}, K^{+}, Cl^{-}), leading to ion flow and cytoskeletal changes that directly influence cell migration [14–16]. While the exact mechanisms underlying the electrically activated biological events remain unclear, diverse signaling pathways, such as Wnt/GSK3β, PI3K/AKT, MEK/ERK, and TGF1/ERK/NF-BB, may contribute to those effects [17–19]. Consequently, electrical signals emerge as facile biophysical cues to regulate cellular functions, particularly in the tissue healing and regeneration process. In fact, biophysical cues encompass various modalities, including surface topography, matrix stiffness, ultrasound, light, magnetism, and electricity [2]. Among these biophysical cues, electricity has played unique roles in modulating diverse cellular behaviors and tissue functions, such as stimulating cell motility, proliferation, and differentiation as well as wound healing, pain relief, and tissue regeneration.

As such, recent scientific attention has centered on the development of biomaterials with appropriate electrical conductivity, thereby establishing electrical microenvironments for the transmission of biophysical signals to cells [20–29]. The electrical microenvironments are crucial for various biological processes, encompassing cellular metabolism, ion transport for maintaining homeostasis, and tissue repair. Electrical fields guide cell migration, directing them to get involved in acute wound repairing process. For instance, Zhao et al. reported that endogenous electrical field serves as a primary directional cue for cell migration during wound healing [30]. Also, Liang et al. created an electrical microenvironment to investigate the impact on epidermal cells during wound healing, where

100 mV/mm electrical field applied could accelerated wound healing [31]. Additionally, electrical signals were observed to promote angiogenesis, facilitating the formation of new blood vessels and enhancing nutrient supply to the healing site of tissues [32].

As such, the biomaterials with appropriate electrical conductivity can serve as implantable materials and devices to augment defective and degenerative tissues, regulating cell–matrix interactions and ultimately improving tissue regeneration [4, 22, 33–38]. Furthermore, more recently, advanced platforms that can function through external energy, such as light, magnetism, and stress (e.g., employing piezoelectric materials) as well as via biochemical reactions (e.g., glucose) have also been explored to provide electrical signals and promote tissue healing [39–42].

With these in mind, this review underscores the significance of electro-stimulating biomaterials, including conductive materials and various stimulus-responsive biomaterials, designed to facilitate efficient electrical conduction. We investigate stimulation parameters that can optimally induce cellular activation and explore the mechanisms underpinning the electrically stimulated events. We further highlight the potential limitations and challenges of existing approaches and offer forward-looking perspectives for the clinical applicability of optimally designed electrical stimulation systems in the future.

Strategies for biomaterial-enabled electrical stimulation

Electroactive biomaterials possessing high electrical conductivity facilitate the efficient transfer of electrical stimulation. These materials often feature π bond-based backbones characterized by extended chains of loosely bound electrons. Upon reduction or oxidation through dopant molecules, they exhibit enhanced electron mobility. Such materials often comprise a composite of inorganic substances, including carbon nanotubes (CNT) [43–45], graphene oxide (GO) [46–48], black phosphorus (BP) [49, 50], Mxene [51, 52], with polymers such as polypyrrole (PPy) [28, 48] and polyaniline (PANI) [53, 54]. After being processed into conduits or scaffolds by mold casting or 3D printing, these composites provide high electrical conductivity, enabling efficient electrical stimulation to cells.

Beyond external power sources for electrical stimulation, active research is ongoing concerning materials capable of self-electricity generation in response to internal and external body environments. Building on the effective and stable electron transfer facilitated by these conductive materials, significant emphasis is placed on the development of biofuel cells. These devices harness organic fuels present in body fluid, predominantly employing enzymes such as glucose oxidase (GOx), lactate oxidase (LOx), and glucose dehydrogenase (GDH) for anions [55, 56], and enzymes like bilirubin oxidase (BOD), platinum (Pt), and laccase for cations, to produce electricity through their interactions [56–58].

Furthermore, materials responsive to external stimuli have recently been highlighted to be electrically active. These materials are often semiconductor-based. Some representative examples are the composites with poly(3-hexylthiophene) (P3HT) nanoparticles [59], thin-film Si mesh structure [60, 61], and titania nanowire arrays deposited with Au nanoparticles [61, 62]. For example, when exposed to light, these materials undergo structural changes, affecting their conductivity. Additionally, photoconductive nanomaterials, like graphene or semiconducting nanoparticles, can experience changes in charge carrier mobility or concentration when illuminated. Specific light-sensitive proteins are utilized to modulate the electrical activity of cells, which can trigger conformational changes in these proteins. Moreover, researchers have pioneered electroactive materials leveraging magnetic fields, namely the effects of electromagnetic fields (EMF). When a conductive biomaterial, such as a magnetic nanoparticle-loaded material, is exposed to an external magnetic field, magnetic nanoparticles tend to align along the field. This alignment changes the spatial distribution of charges, leading to generating an electric field within the biomaterial. Similarly, when an external stress or force is applied to the piezoelectric biomaterial, it distorts the crystalline lattice structure. The mechanical deformation leads to the displacement of positive and negative charges within the crystal lattice, resulting in the development of electric potential across the material. Such piezoelectric materials have been developed with inorganic materials such as ZnO, $BaTiO_3$, and Whitlockite [63–65], or polymers like polyvinylidene fluoride (PVDF) and poly-L-lactic acid (PLLA) [39, 66–69]. These piezoelectric materials were formulated into scaffolds or hydrogels for a diverse range of cell and tissue stimulations.

Many studies have reported that the voltage ranges for cell stimulation and tissue healing typically span from millivolts (mV) to volts (V), where the selection of a specific voltage depends on the intended applications, target tissues, and experimental parameters. This spectrum encompasses very low voltages, sometimes below the mV threshold, which are often harnessed to investigate in vitro activation of cells, such as intracellular ion influx and related signalings [70]. Alternatively, higher voltages, ranging from hundreds of mV to several V, find utility in the in vivo tissue activation, such as cardiac pacing, muscle stimulation, and brain stimulation [71]. The corresponding current stimuli typically fall within the range of approximately 1 μA down to several nA [72, 73].

In summary, electrical stimulation approaches leverage the in situ electrical conductivity of materials or the

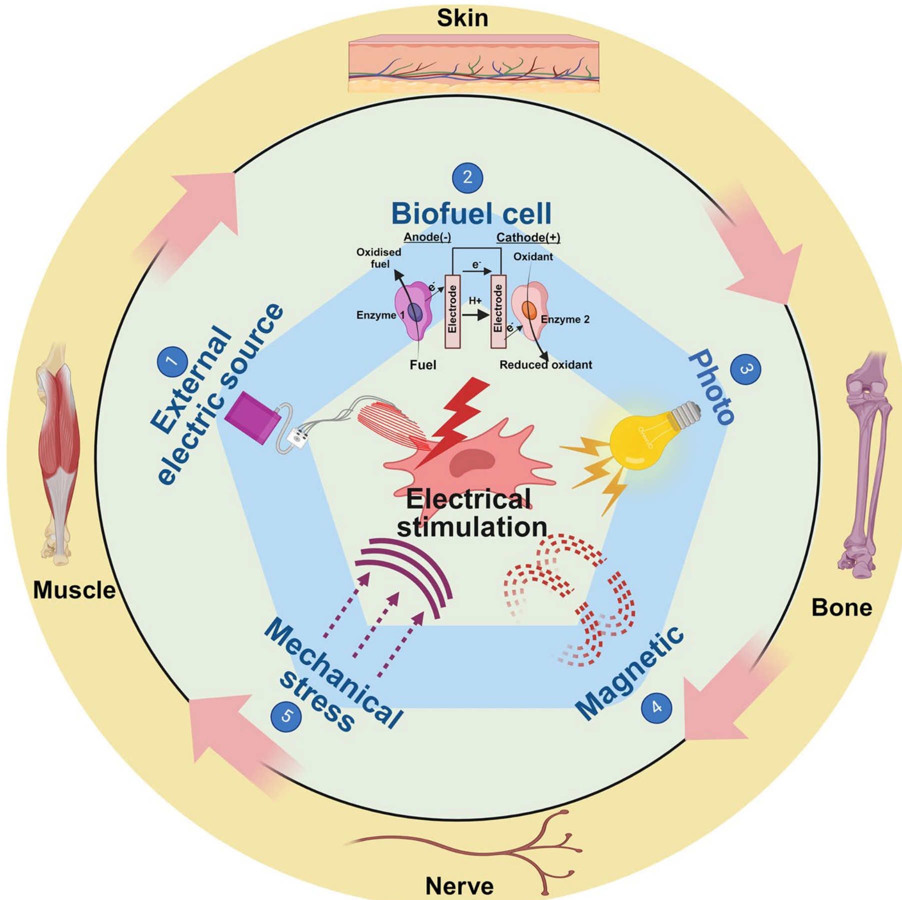


Fig. 1 Illustration depicting various electrical stimulation approaches utilizing biomaterials: in situ electroconductive materials linked to external electric sources, environmentally electroactive methods like enzymatic biofuel cells, and materials responsive to external stimuli (light, magnetic, stress). The generated electricity activates various cells and tissues (nerve, muscle, skin, and bone), contributing to the healing and regeneration process

stimuli-responsiveness of semiconducting, magnetism, and piezoelectric materials, which can generate appropriate electricity for the activation of cells and tissues (e.g., nerve, muscle, bone, and skin). This contributes significantly to the healing and regeneration process, as illustrated in Fig. 1.

Electrical stimulation based on in situ conductive biomaterials

The effectiveness of materials exhibiting electrical conductivity akin to native tissue has been extensively validated, underscoring their potential to serve as a viable electrical stimulation source in specific environments to promote cell proliferation, motility, and differentiation. These conductive materials possess a unique combination of electrical conductivity and biocompatibility, enabling biomedical usages for diverse tissues [2, 3, 74–76]. Specifically, they provide electrical stimulation for tissue regeneration, serve as electrodes in bioelectrochemical systems and implantable devices, and contribute to the development of biosensors for sensing and diagnostics. A diverse array of materials that possess intrinsic electrical conductivity, spanning polymers, carbon nanomaterials, and metal nanomaterials, have thus been potentially employed [75–78], as discussed in this section.

Providing microcurrent with electroconductive biomaterials

Conductive biomaterials, typically composed of hydrophilic polymer matrix with conductive polymer or inorganic fillers [50, 76, 77], have been developed into hydrogels or tissue scaffolds that exhibit tunable electrical and mechanical properties. The incorporation of conductive elements empowers a diverse range of conductivity, closely mirroring tissue-specific electrical conductivity, while the polymeric matrix allows shape formability to satisfy the mechanical properties. Table 1 lists the conductive biomaterials developed to provide microcurrent for the repair and regeneration of diverse tissues, including skin, bone, muscle, and nerve.

For skin regeneration, various conductive materials have been developed. For instance, PPy-combined gelatin methacryloyl (GelMA) hydrogels could accelerate skin tissue regeneration [19]. The conductive hydrogels modulate intracellular Ca^{2+} concentrations, stimulating protein phosphorylation in PI3K/AKT and MEK/ERK pathways,

Table 1 Summary of representative studies on electrically conductive biomaterials, including their electrical properties, biocompatibility, mechanical properties, and the applications, with or without the external electrical field

Ref	Conductive materials	Conductivity/current/voltage range	Applied electrical field	Cytotoxicity	Mechanical properties	Applications
[19]	oxidized chondroitin sulfate	0.312 ± 0.03 S m^{-1}	Not applied	Biocompatible	-	Neurovascular regeneration
[79]	polypyrrole	3.75×10^{-2} S m^{-1}	Not applied	< 9.7 µg/mL	64 MPa (flexible)	Spinal cord injury
[80]	polyaniline	1.18 S m^{-1}	Not applied	< 10 µg/mL	38.2 ± 2.2 MPa (Elastic)	Myogenic differentiation
[53]	Graphene oxide	0.87 ± 1.6 S m^{-1}	Not applied	< 20 µg/mL	18.64–24.59 MPa (Highly stretchable)	Peripheral nerve regeneration
[81]	Silver nanowire (AgNW)	1.54×10^{5} S m^{-1}	Not applied	< 1 µg/mL	~ 2.6×10^{3} MPa (Flexible/ stretchable)	Accelerated wound healing
[82]	Mxene	4×10^{-2} S m^{-1}	0.35 V	10-400 µg/mL	436 MPa (Weak mechanical flexibility)	Osteogenic differentiation
[83]	Polypyrrole	$5.62 \pm 0.38 \times 10^{-2}$ Sm^{-1}	4–8 × 10^{-3} V	-	-	Myocardium infarction (MI)
[38]	Polydopamine, GO	5×10^{-1} S m^{-1}	0.1 V	Up to 250 µg/mL	~ $200 \pm 180.32 \times 10^{-3}$ MPa (Stretchable)	Accelerated wound healing
[84]	Polydopamine, GO	1.6×10^{2} S m^{-1}	0.3 V	-	-	Periodontal bone tissues
[85]	Titanium disc	7.4×10^{5} S m^{-1}	0.2 V	Up to 10 µg/mL	~ 130 MPa (very flexible)	Osteogenic differentiation
[86]	Bacterial cellulose (BC)-PPy	10^{-6} -1 S m^{-1}	-	~ 100 µg/mL	(flexible)	Cardiomyocyte differentiation
[87]	PPy	5–18 S m^{-1}	-	-	-	Spinal cord injury repair
[88]	PCL-CNT	15.69–178.63 S m^{-1}	-	0.8–10 µg/mL (CNT)	~ 25×10^{3} Mpa (CNT), 38.7 Mpa (PCL) (Highly flexible)	Nerve regeneration
[89]	PPy-Silk fibroin (SF)	-	5 V	Biocompatible	70 ± 6 MPa (SF)	Cardiac tissue Engineering
[90]	PPy	-	~ 2.5 A	-	-	Neurite outgrowth
[91]	Cellulose /PPy	8 S m^{-1}	-	-	25×10^{3} MPa (Cellulose)	Nerve regeneration
[92]	PPy-Polyurethane (PU)	2.3×10^{-4} S m^{-1}	-	Biocompatible	30–150 × 10^{3} MPa (Polyurethane, elastic& flexible)	Myoblast differentiation
[93]	Polypyrrole (PPy)	-	10^{-5} A	-	-	Neurite outgrowth
[94]	PCL/Cellulose	-	0.5 V	Biocompatible	-	Nerve regeneration
[95]	PPy/PLLA	-	~ 50–200 V	< 9.7 µg/mL	~ 80 MPa (PLLA, low ductility)	Wound healing
[96]	PLLA/PANi	-	100 V	-	-	Nerve regeneration
[97]	PPy	-	5×10^{-5} A	-	-	Muscle regeneration
[98]	$Mg(OH)_2$/GO/HA	-	0.1 A, 120 V	~ 10 µg/mL (HA)	~ 174 MPa (HA, highly stretchable)	Bone regeneration

ultimately assisting in the recovery of full-thickness diabetic skin wounds (Fig. 2a,b). In addition, conductive silver nanowires were combined with alginate-based gels [47] to provide a flexible and formable electrode, considered to be alternative to conventional metal electrodes, which could promote wound healing by improving re-epithelialization, vascular formation, immune control, and infection prevention in skin wounds (Fig. 2c). Furthermore, when PPy was made into a nanofiber form with silk fibroin or cellulose the conductive nanofiber scaffolds were effective in cardiac tissue regeneration [86, 89]. Likewise, PANI nanofiber with poly(ε-caprolactone-gelatin (PCL-Gelatin) [99] supported effective cardiac tissue regeneration, and the PANI hydrogel with hyaluronic acid [53] also demonstrated potential

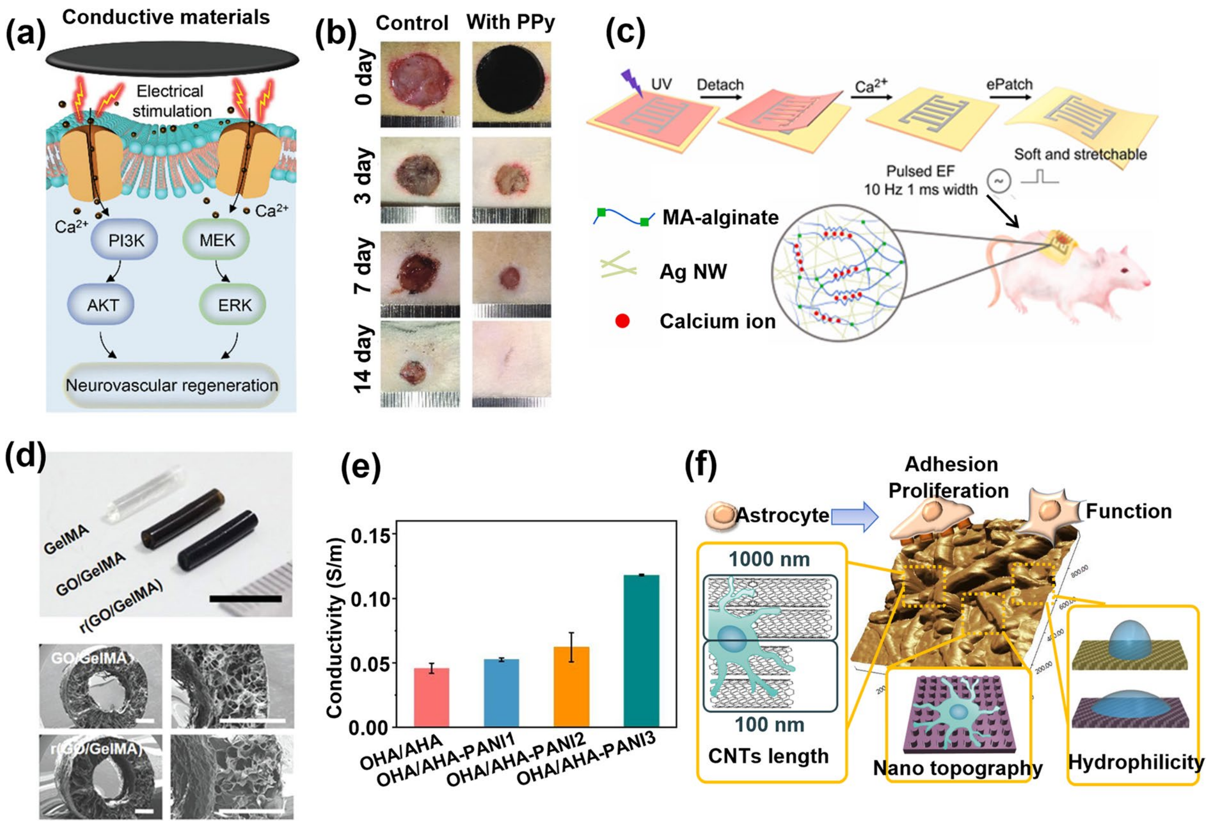


Fig. 2 **a** Illustration detailing the mechanism by which conductive hydrogel enhances neurovascular regeneration in vivo. The conductive hydrogels modulate intracellular Ca^{2+} concentrations, stimulating protein phosphorylation in PI3K/AKT and MEK/ERK pathways. (**b**) Photographs showing PI3K/AKT and MEK/ERK pathways assisting in the recovery of full-thickness diabetic skin wounds. Adapted with permission from [19], copyright 2022, John Wiley & Sons. (**c**) Diagram illustrating the fabrication of epatch and the double-crosslinked network of AgNW-MA-Alginate-based gel to provide a flexible electrode for wound healing Adapted with permission from [81], copyright 2022, Elsevier. (**d**) Scanning electron microscope (SEM) images displaying the morphology of synthesized GelMA, GO/GelMA, and r(GO/GelMA) conduits (scale bar: 500 μm) meant for neural repair Adapted with permission from [80], copyright 2020, John Wiley & Sons. (**e**) Bar graph depicting the conductivity of hydrogels made from conductive polymers. Adapted with permission from [53], copyright 2023, Elsevier. (**f**) Schematic image and characteristics of the carbon nanotube (CNT) platform designed for interaction with astrocytes. Adapted with permission from [101], copyright 2022, Springer nature

for skeletal muscle regeneration. Furthermore, bone bioactive materials were combined with conductive materials for bone regeneration. For the sample, hydroxyapatite-GO composites with biopolymers were effective in enhancing bone regeneration through the effects of electrical conductivity and ionic release from the inorganic elements [98, 100].

The most widely studied area of conductive biomaterials is neural repair, such as spinal cord [79] and peripheral nerve injuries [80] (Fig. 2d). These nerve conduits incorporate various conductive materials, such as CNT, graphene (oxide), and conductive polymers, facilitating remarkable electrical conductivity (Fig. 2e). The conductive mechanisms are also proven to be diverse, including electrode integration, ion migration, and the piezoelectric effect, which effectively deliver electrical signals to damaged nerves enabling axonal growth and functional recovery. Various conductive substrates, including length-specific MWCNT [101, 102], super-aligned CNT sheets [55, 103], and composite scaffolds consisting of reduced graphene oxide and PANI have shown promise in enhancing neural function and promoting nerve regeneration (Fig. 2f). These materials exert the effects by influencing astrocyte function, facilitating spiral ganglion neuron growth, and improving microstructural properties. The use of these conductive substances has the potential to impact nerve survival, adhesion, neurological development, and synaptic formation. This opens up exciting possibilities for therapeutic interventions in the field of neurological diseases and nerve regeneration.

While the electrically conductive biomaterials have demonstrated remarkable repair capacity of diverse tissues by offering microcurrents to cellular environments, connecting external electrical sources can potentially enhance the transfer of electricity, thereby intensifying the stimulation of cells and tissues induced by electrical currents [4, 104, 105].

Polypyrrole has been a superior choice due to its high electrical conductivity, good biocompatibility with a cytotoxicity limit of up to 9.7 μg/mL, and versatile synthesis methods enabling diverse structures. Nevertheless, it is prone to oxidative degradation over time. Polyaniline shares similar properties but lacks long-term stability in smart devices. On the other hand, carbon-based materials, specifically carbon nanotubes (CNTs) and graphene oxide (GO), exhibit outstanding electrical conductivity and provide a large surface area for cell attachment and growth [106]. Their long-term electrochemical stability is typically superior to metal-based materials like silver nanowires (AgNW) because silver nanowires can corrode and degrade with a cytotoxicity limit of < 1 μg/mL, particularly in corrosive environments or under repeated mechanical stress [107, 108]. This distinction underscores the preference for carbon-based materials in applications where long-term stability is critical. However, there are cytotoxicity concerns with these materials at higher concentrations. Therefore, the selection of materials for electrical stimulation applications should carefully consider various factors, including long-term stability, biocompatibility, and electrical conductivity.

Connecting electric field to electroconductive materials

Electrical stimulation can be enhanced by applying externally induced impulses to the electroconductive materials, ultimately accelerating tissue recovery [109]. External electric field applications amplify the electrical current output of the electrically conductive materials.

Various methods exist for electrical stimulation by applying external electrical circuits, including direct, capacitive, and inductive coupling. Direct coupling represents a commonly used approach. One notable application was observed in transcutaneous electrical nerve stimulation. In this approach, conductive electrodes establish direct physical contact with the target tissue. For instance, neurite outgrowth could elongate when cultured on scaffolds made of electrospun PLLA/PANI fibers [110] or gold nanoparticle

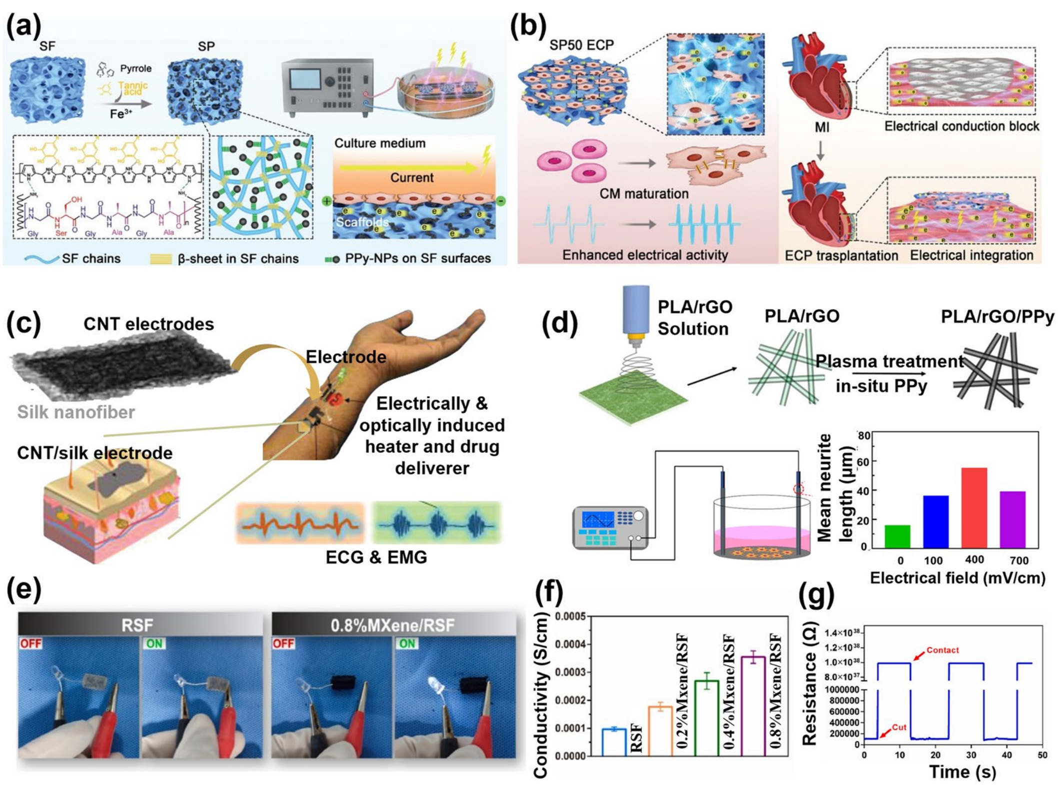


Fig. 3 **a** Schematic image showing fabrication of SP(silk fibroin and polypyrrole) and its response to external ES, (**b**) application of electroactive cardiac patch SP50 ECP showing improved electrical integration of host heart under external ES of 5 V/cm to myocardial cells, Adapted with permission from [83], copyright 2022, John Wiley & Sons. (**c**) illustrative image of SNF/CNT based E-tattoo, based on silk nanofibers and MWCNT Adapted with permission from [118], copyright 2021, John Wiley & Sons (**d**) schematic illustrating preparation of PLA/rGO and PLA/rGO/PPy, with cellulose for improved neurite outgrowth. Adapted with permission from [119], copyright 2021, Elsevier (**e**) electrically conductive pathways created by RSF and Mxene/RSF double-crosslinked network nanocomposite hydrogel that incorporates horseradish peroxidase and hydrogen peroxide to illuminate an LED, which under an applied voltage to promote bone regeneration. (**f**) electrical conductivities of various concentrations of Mxene, (**g**) real-time resistance response measurement tested for Mxene/RSF hydrogel using the cut-contact method. Adapted with permission from [82], copyright 2023, Elsevier

composites [111] through direct coupling. Capacitive coupling is another method involving capacitors to transmit electrical energy to a target tissue or device. Capacitors, capable of storing and releasing electrical energy upon voltage fluctuations, facilitate the delivery of stimulating signals via one capacitor plate while positioning the other in proximity to the target tissue. This system obviates the need for a conductive scaffold. Gonzalez and colleagues, for instance, employed capacitive coupling to administer a 4 mV/cm electrical stimulation to chondrocytes, resulting in significant augmentation of cell proliferation [112]. On the other hand, inductive coupling harnesses a tunable electromagnetic field generated by a conductive coil encompassing the cell culture system, commonly referred to as pulse electromagnetic field stimulation.

Conductive materials, when subjected to an applied electrical field, have demonstrated remarkable potential for tissue regeneration. For instance, in the context of wound healing, PPy integrated with PLLA was utilized with external electric fields ranging from 50 to 200 mV/mm [95]. Regenerated bacterial cellulose/MXene hydrogels, under electric fields of 0–400 mV/mm, also enhanced skin wound healing [113]. In addition, Li et al. employed a controlled electrical stimulation technique using an approximate DC voltage of 10 V for wound healing [114]. In comparison, Brown et al. applied higher voltage pulse stimulation (30–60 V) to induce a high rate of wound closure in rabbits and guinea pigs [115].

For skeletal muscle regeneration, PPy-based electrically conductive scaffolds, upon stimulation with an external electrical current of 50 μA, showed higher expression of contractile proteins [97]. Furthermore, conductive scaffolds were instrumental in producing functional heart tissue and promoting tissue reconstruction for the treatment of heart attacks [83] (Fig. 3a). By applying an electrical stimulation of 5 V/cm to myocardial cells upon these scaffolds, engineered cardiac patches with precise thickness and electrical activity could be created (Fig. 3b). This direct electrical stimulation has resulted in the expression of crucial cardiac markers, improved resistance to shrinkage, and enhanced electrical coupling performance. In vivo studies demonstrated their effectiveness in enhancing left ventricular remodeling, restoring cardiac function, and improving the propagation of electrical signals. Carbon-based conductive materials such as MWCNT and GO have also been used for muscle regeneration. For instance, the integration of MWCNT with PPy could promote myoblast differentiation [116] under electrical stimulation of 0.125 mA/cm^2. Recently, an electronic tattoo (E-tattoo, Fig. 3c) based on silk nanofibers and MWCNT (SNF/MWCNT) was developed for therapeutic purposes, which could be activated by the low level of electrical signals (3.5 nA to 0.3 μA) [117]. MWCNT-doped gelatin-cellulose scaffolds were also demonstrated to be effective for skeletal muscle tissue upon external electrical activation [118].

For nerve regeneration, scaffolds were also used in combination with electrical stimulation [96]. For instance, PANI-based scaffolds, often hydrogels, have proven effective in enhancing nerve regeneration by stimulating neuron proliferation and neurite growth, primarily through efficient electrical delivery [120, 121]. Scaffolds based on PPy were also employed to enhance neurite outgrowth. For instance, Shi et al. developed nano-porous scaffolds by incorporating DBSA-doped PPy with cellulose, resulting in improved neurite outgrowth [91]. Conductive composite fibers that incorporate GO also demonstrated the ability to enhance cell proliferation and promote neurite growth, as observed in PC12 cells incorporating DBSA-doped PPy-cellulose as nano-porous scaffolds [122] (Fig. 3d). These studies underscore the versatility of electrically conductive polymeric scaffolds, in combination with external electrical stimulus, for the regeneration of neural tissues.

For bone regeneration, various types of conductive composites were used. For instance, Chao et al. developed Mxene nanosheet/silk fibroin double-crosslinked network nanocomposite hydrogel that incorporates horseradish peroxidase and hydrogen peroxide to enhance bone repair [82] (Fig. 3e). This conductive scaffold, under an applied voltage ~ 100 mV/mm, was proven to promote bone regeneration with concurrent electrical activity, fostering electrophysiological microenvironment assessment in vitro, such as evaluations of cell suitability, electrical conductivity, bone inductivity, bone immunomodulatory capability, and angiogenesis (Fig. 3f, g). In vivo studies also showed bone regeneration and neovascularization treatment using a critical-sized longitudinal bone defect model. In addition to the inherent electrical signals found within bones, external electrical stimulation has been shown to exert various osteogenic responses, including enhanced ion mobility and bone growth [119, 123–125].

Some of the representative studies on electrically conductive biomaterials, including their electrical properties and applications, with or without the external electrical field, are outlined in Table 1. Direct electrical stimulation can significantly boost cell activity and regeneration, enhancing regeneration efficiency. However, it carries risks such as apoptosis and the release of toxic substances (e.g., COx, NOx, SOx) when applied at higher-than-optimal energy levels [126–128].

In clinical contexts, rigorous testing and standardization are essential to validate the reliability and reproducibility of these materials. Biocompatibility stands out as a supreme concern, thus the conductive biomaterials need to be carefully evaluated for their biocompatibility with the physiological environment, ensuring minimal inflammation, immune response, or rejection [129]. Furthermore,

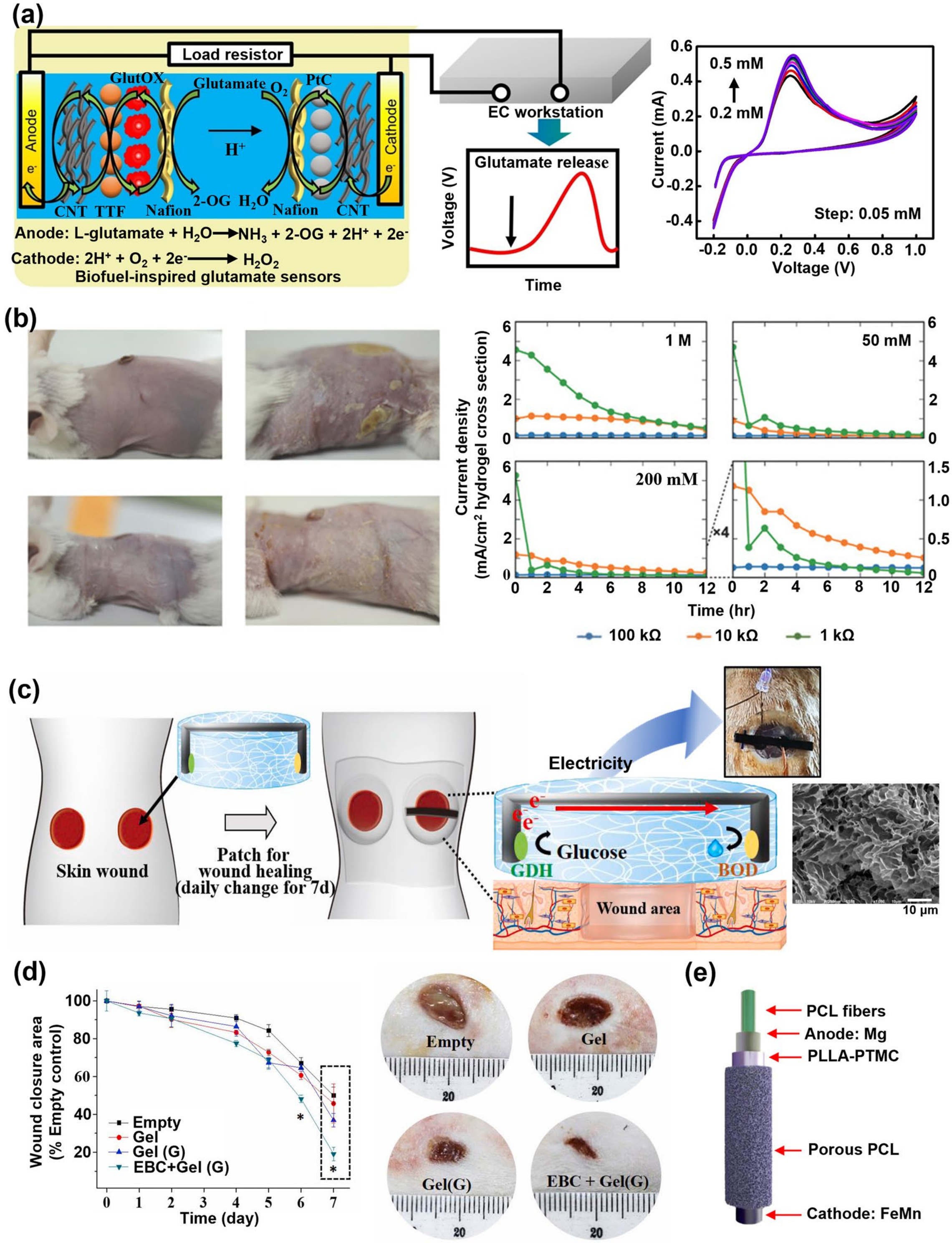


Fig. 4 Representative examples of electroactive materials in response to intrinsic microenvironmental cues: (**a**) Illustration showing the electricity-generation working principle of flexible, miniaturized biofuel-inspired glutamate sensor that can monitor glutamate release in the nervous system within the cerebral spinal fluid and cyclic voltammetry performed from 0.2 mM to 0.5 mM, Adapted with permission from [135], copyright 2023, John Wiley & Sons (**b**) current density change of bioelectrical plaster with different concentrations from actual mouse skin images after 7 days of hydrogel application, Adapted with permission from [136], copyright 2017, John Wiley & Sons (**c**) electricity self-generating enzymatic-biofuel-cell (EBC) skin patch for wound healing, consisting of anodic enzyme and cathodic counterpart, which is developed into a hydrogel form of polyacrylamide (PAA) containing glucose and EBC, (**d**) the in vivo wound healing efficacy, Adapted with permission from [133], copyright 2021, Elsevier and (**e**) design of self-electrified miniaturized conduit device incorporating dissolvable galvanic cells that generates open circuit voltage. Adapted with permission from [138], copyright 2020, Science Advances, AAAS

the long-term stability of these materials is a critical factor, especially when considering their integration into chronic medical interventions. Degradation over time can compromise the effectiveness of the biomaterial and pose risks to patient health. Additionally, the integration of these technologies with existing medical practices necessitates particular efforts, such as consideration of long-term stability in the electrical connections. Also, practical limitations, including power sources and wiring constraints, can reduce the feasibility of direct electrical connections [130, 131], which warrants further developments.

Electroactive materials in response to intrinsic microenvironmental cues

Enzymatic biofuel cells (EBC) harness biological fuels such as glucose and oxygen to efficiently convert chemical energy into electrical energy, resulting in the generation of electricity. Mainly utilizing microorganisms or enzymes to facilitate chemical reactions, these biofuel cells enable the conversion of electrons in these reactions into electric current as they traverse from positive to negative poles in external circuits. Some recent works have highlighted the potential of these biofuel cell principles as tissue regeneration devices through in situ electrical stimulation of cells and tissues.

The development of self-powered, autogenerating electrical devices has opened up possibilities for establishing localized electrical microenvironments within tissues, with potential applications in tissue repair and wound healing. These devices can take various forms, including the glucose-responsive EBC skin patch [132] and miniaturized galvanic cell-based devices seamlessly integrated into biodegradable scaffolds, as demonstrated in recent biofuel cell studies [133].

The functional glucose-responsive EBC can serve as a biocompatible tool that converts glucose in the body into electrical energy, finding biomedical applications like implantable artificial organs and drug delivery biosensors. For instance, Prasad et al. [134] developed a millimeter-sized biofuel cell (Fig. 4a) to monitor glutamate release in the nervous system within the cerebral spinal fluid (CSF). Inspired by this, Kai et al. [135] generated ionic current along the skin surface through an EBC that is firmly attached to the skin (Fig. 4b). These biocompatible materials act as wearable power sources, maintaining flexibility, excellent skin contact, biocompatibility, and long-term current stability, contributing to wound closure. Furthermore, Lee et al. [136] demonstrated the potential of EBC as a promising power source for in vivo implantable biomedical devices because the device possesses an intrinsic ability to generate electrical stimulation, enhancing proliferation, migration, and differentiation of muscle precursor cells. The glucose oxidase-based EBC was also proven to stimulate neural cells [137].

One recent study by Kim et al. [132] has further developed the EBC system for in vivo skin patches and demonstrated the biological electroactive mechanisms (Fig. 4c). The EBC system could be powered by enzymes such as GDH and BOD, generating an in situ electrical current. Electricity generated by EBC was shown to activate the mechanosensitive ion channel Piezo1, inducing calcium influx in endothelial cells and fibroblasts, thereby stimulating cell motility and migration ability. This study highlights the critical role of self-generating electricity in the tissue regenerative process, specifically for skin wound healing (Fig. 4d), by stimulating cell viability and mobility in vivo while supporting vascular formation, collagen deposition, and re-epithelialization. While the EBCs have shown great promise in activating cells and repairing diverse tissues in the form of electricity-autogenerating implantable devices, there is a need for further improvements in materials and device designs to optimize their effectiveness, such as electrical lifetime and degradability. Addressing one of these challenges, Liu et al. [139] introduced biodegradable, self-electrified, ultra-miniaturized conduit devices that incorporate dissolvable galvanic cells (Fig. 4e). These recent works on EBC systems demonstrate well the in situ responsiveness to tissue microenvironmental cues, such as glucose and glutamate, thereby self-generating electricity, offering the possible uses as wireless innovative biomedical materials and devices for wound healing and recovery of damaged tissues.

In discussing the three approaches to ES generation, the effectiveness depends on specific application requirements. The efficacy of using in situ conductive biomaterials is contingent upon the particular biomaterial utilized. For instance, materials like PPy, exhibiting a conductivity range of 5–8 Sm^{-1}, can enhance neurite outgrowth when coupled with an external current of 10^{-5}A. While diverse designs of conductive materials lead to varied applications, their enhanced conductance generally synergizes with electrical stimulation [2, 138]. The EBC system introduces a novel means of applying in situ electricity without external wires, promising more patient-friendly medical devices. However, its power outputs are typically low and short-term, necessitating improvements in materials. Conversely, external connections offer higher electrical efficiency and greater controllability with desired stimulation parameters. Therefore, choosing between these approaches requires considering factors such as power needs, stimulation duration, biocompatibility, and practicality in the intended biological environment.

On-demand electrical stimulation through external stimuli-responsive biomaterials

Previously, many studies aimed to address the constraints associated with materials requiring direct electrical connections. Prominent among the active investigations are employing materials capable of generating electricity in response to external stimuli, such as light, magnetic field, and mechanical stress. This strategy enables the controlled delivery of microcurrents to enhance cellular activity without direct electrical contacts, instead functioning 'on demand' control over the electricity [107, 140–142]. These on-demand stimuli-responsive biomaterials are designed to exhibit tailored responses to diverse cues, effectively converting them into electrical signals [68, 107, 142]. This innovative approach has brought a paradigm shift to traditional electrical stimulation methods by eliminating the need for direct physical connections, rather enabling wireless and remote-controlled electrical stimulation, possibly offering minimally invasive applications.

One such category of biomaterials is optoelectric materials, which are capable of converting light into electrical signals. By incorporating light-responsive components like photoactive molecules or semiconductor nanoparticles into the matrix, these materials can generate electrical stimulation when exposed to specific wavelengths of light [54, 59, 60]. This allows targeted and controlled stimulation of cells and tissues, opening promising avenues for therapy and interfaces with electronic devices. The molecular-level mechanism of action for light-induced responses can vary based on the specific properties of the materials. Photoexcited molecules generate electron–hole pairs by promoting electrons to higher energy levels [143]. These charge carriers can contribute to increased electrical conductivity. Biomaterials with conjugated systems, such as pi-bonded systems and aromatic rings can undergo electron delocalization upon light absorption which can increase materials conductivity. Moreover, light energy can be transferred between molecules within the biomaterials. Excitons (bound electron–hole pairs) form as a result of this energy transfer, affecting the electronic state and conductivity of materials.

Similarly, magneto-responsive biomaterials harness magnetic fields to generate electrical signals. These materials can convert applied magnetic fields into electrical stimulation by incorporating magnetic nanoparticles or other magnetically responsive components [144–147]. At the molecular level, magnetic moments in nanoparticles align in the direction of the external magnetic field, influencing the overall properties of the biomaterials. This alignment can modulate conductivity through changes in electron transport or structural rearrangements, providing a basis for responsive behavior at the atomic level [148]. This wireless and remote-controlled stimulation approach offers non-invasive and versatile interfaces, making them valuable for various applications from tissue engineering to human–machine interaction.

Another notable category is piezoelectric biomaterials, which generate electrical signals in response to mechanical deformation or pressure. These materials possess intrinsic piezoelectric properties, allowing them to convert mechanical energy into electrical energy [63–69]. When an external mechanical stress is applied, the basic structural arrangement deforms, producing a net dipole, i.e., the separation of the molecular positive and negative centers. As a result, the electrons within the materials re-equilibrate, and fixed charges emerge on opposing surfaces of the materials, with the materials becoming electrically polarized, producing electric current [16, 107].

These biomaterials can generate electrical stimulation that can find diverse applications, including tissue regeneration, biosensing, and neural interfaces, by applying external mechanical forces or vibrations. This section highlights the potential of these externally induced electrical stimulation using responsive biomaterials, offering promising avenues for advanced biomedical applications.

Photoreactive biomaterials for electrical stimulation

The photoelectric effect, an intriguing phenomenon extensively applied in various technologies like photodetectors and solar cells, harnesses both inorganic semiconductor materials, such as silicon and titanium, and organic semiconductor polymers, like poly(3-hexylthiophene) (P3HT). When these materials absorb light at specific frequencies, their electrons become excited, forming electron–hole pairs. These electrons are subsequently segregated into the conduction band, while the holes occupy the valence band, ultimately generating an electrical current (Fig. 5a) [142]. Ongoing research endeavors are focused on developing materials that can maximize the efficiency of this electrical stimulation process. The evolution of wireless and remote light stimulation represents significant advances from traditional wired electrical stimulation methods. It offers minimally invasive, enduring interfaces, holding considerable promise for addressing tissue damage and degenerative disorders [149].

In this context, semiconductor polymer nanoparticles, particularly p-type polymer nanoparticles utilizing P3HT, have gained substantial attention. These high-performance conjugated polymers exhibit exceptional photoelectric properties and desirable solubility in organic solvents. Notably, scaffolds based on P3HT have demonstrated the ability to promote neuronal maturation upon exposure to green light.

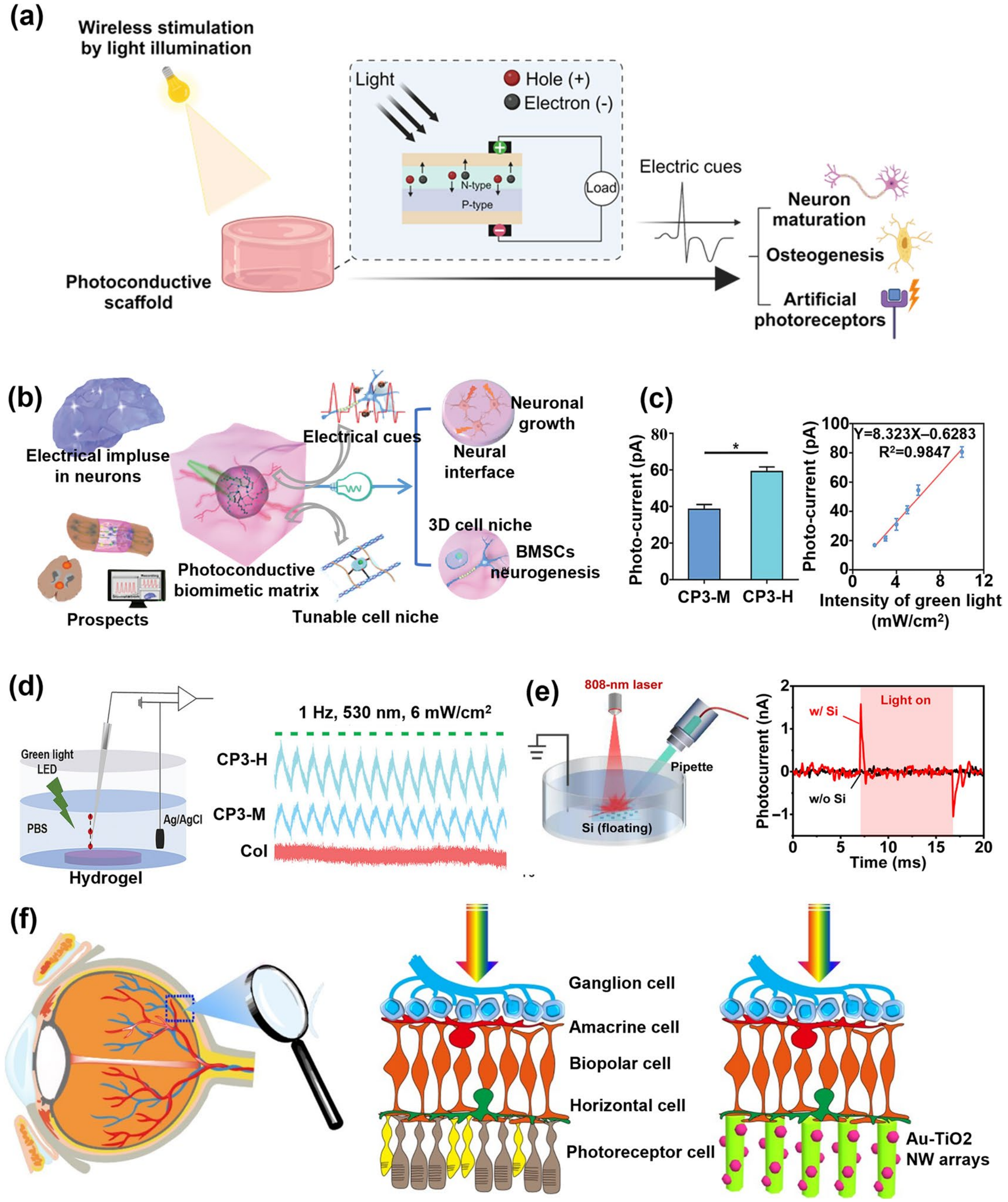


Fig. 5 Representative studies on electrical stimulation by light-responsive materials: (**a**) Schematic illustration showing mechanism when a photoconductive scaffold is illuminated by light, (**b**) schematic illustration depicting electrical impulses in neurons influencing the treatment of nerve injuries and neurodegenerative diseases and creating a bioactive platform for remote and wireless optoelectrical stimulation through the integration of photoconductive P3HT NPs into the biomimetic hydrogel, (**c**) mean photocurrents produced by hydrogels on green light illumination, (**d**) illustrative image showing green light irradiation on hydrogel patch and its photocurrent response, Adapted with permission from [59], copyright 2022, John Wiley & Sons (**e**) schematic of 3D Si-based hybrid scaffold for photocurrent measurement and photocurrent response for 3D Si-based scaffolds, Adapted with permission from [60], copyright 2023, Science Advances, AAAS. (**f**) schematic illustration comparing a blind retina, which lacks natural photoreceptors, and its interface with a retina featuring nanowire (NW) arrays. The blind retina's necrotic photoreceptor layer (rod and cone cells) is substituted with an Au-TiO2 NW array serving as artificial photoreceptors. Adapted with permission from [61], copyright 2018, Springer Nature

However, due to their high reactivity in the presence of moisture, it is anticipated to degrade soon, which is a significant drawback. A novel approach was implemented by Wu et al. [59], who integrated hydrophilic P3HT nanoparticles into a biomimetic hydrogel matrix for neuronal maturation. The composition of the hydrogel matrix and cross-linking degree were adjusted to meet various applications. P3HT nanoparticles within the hydrogels efficiently converted

Table 2 Summary of representative studies that report electrical properties, biocompatibility, mechanical properties, and the range of generated currents of tissue regeneration materials that generate microcurrents in response to light or magnetic fields

Ref	Responsive materials	External sources (optimal conditions)	Generated current or voltage range	Cytotoxicity	Mechanical properties	Applications
[59]	P3HT	500–550 nm of green light	~6.0×10^{-11} A	~0.4 μg/mL	Flexible	Neurogenesis
[60]	Silicon	~808 nm of near-infrared light	No mention	~10 μg/mL	120 MPa (High elasticity)	Bone regeneration
[61]	Silicon	200–550 nm of UV, green–blue light	UV- 1.45×10^{-9} A Blue-1.08×10^{-10} A Green- 8.7×10^{-11} A	Biocompatible	-	Artificial retinal prosthesis
[154]	3-(4,5-dimethoxy-2-nitrophenyl)-2-butyl ester (DMNPB)	350–365 nm of light	No mention	-	-	Cell adhesion, inflammation, vascularization
[155]	Neodymium boron (NdFeB)	Magnetism	10.5×10^{-3} V	100 μg/mL	850–1050 MPa (Elastic)	Conversion of fibroblasts into neurons
[156]	$CoFe_2O_4$, $BaTiO_3$	Magnetism	10 V	0.630 μg/mL (Co^{2+} ion)	1.5–125 MPa ($CoFe_2O_4$)	Cell proliferation, differentiation, upregulated gene expression
[144]	$CoFe_2O_4$, $BaTiO_3$, PVDF-TrFE	Magnetism	8–10 V	-	-	Bone repair, osteogenesis

light signals into electrical signals under pulsed green light exposure, generating tens of picoamperes of photocurrent (Fig. 5b-d). This phenomenon promoted the growth of cortical neurons surrounded by the hydrogels and stimulated neuronal differentiation of bone marrow MSCs encapsulated in the hydrogels. This study emphasized the potential for developing future neural electrodes and scaffolds that respond to external stimuli beyond traditional electrical stimulation.

A similar concept of 3D biomimetic optoelectronic scaffolds responsive to external infrared light was explored by Wang et al. (Fig. 5e) [60]. The Si-based 3D biomimetic scaffolds not only provided a 3D hierarchical structure for directing cell growth but also modulated cell activity through photo-induced electrical impulses. The scaffolds, remotely controlled by infrared light, could electrically alter the membrane potential and intracellular calcium dynamics of stem cells, effectively promoting cell proliferation and differentiation. The Si-integrated scaffolds demonstrated improved osteogenesis in a mouse model upon light stimulation. The wirelessly powered optoelectronic scaffolds eliminated the need for tethered electrical implants and degraded completely in a biological environment. Integrating topographical and optoelectronic cues in Si-based 3D scaffolds is considered to offer more effective biological modulation with broad biomedical applications.

In another study by Jing et al. [61], artificial photoreceptors were created based on gold nanoparticle-decorated titania nanowire arrays for restoring visual responses in blind mice with degenerated photoreceptors. These photoreceptors showed spatial resolution of more than 100 μm and exhibited green, blue, and near UV light responses in retinal ganglion cells (RGCs) (Fig. 5f). The functional preservation of the rest of the retinal circuit was indicated by the blockage of ON responses in RGCs using glutamatergic antagonists. Furthermore, neurons in the primary visual brain responded to light following nanowire array subretinal implantation, as demonstrated by the improvement in pupillary light reflex, indicating behavioral recovery of light sensitivity. These findings highlight a new optoelectronic tool kit for retinal lower prosthetic devices, demonstrating significant potential for vision recovery in visually impaired patients.

Table 2 presents the biomaterials systems that generate electricity upon optimal external light sources. The technology of generating electrical currents within light-responsive materials constitutes an active research area, which frequently faces several challenges. First, operational voltages are notably low, yielding the generation of exceedingly modest electrical currents, and operating parameters remain constrained [150]. In this context, recent studies demonstrate the ability of hair regeneration by body movement and its applicability in wearable epidermal areas through integrating light and external electrical energy. Despite the apparent benefits of generating electricity from light, the system still relies on additional external electrical energy to generate voltages ranging from several hundred mV to 10 V [6, 117]. Moreover, optoelectric systems show high sensitivity to environmental perturbations within biological environments, including variances in pH levels and fluctuations in the presence of diverse biochemical agents [151], which often exert a detrimental influence on electrical performance. Furthermore, sustaining consistent electrical output over prolonged durations within the complex and dynamic environment of

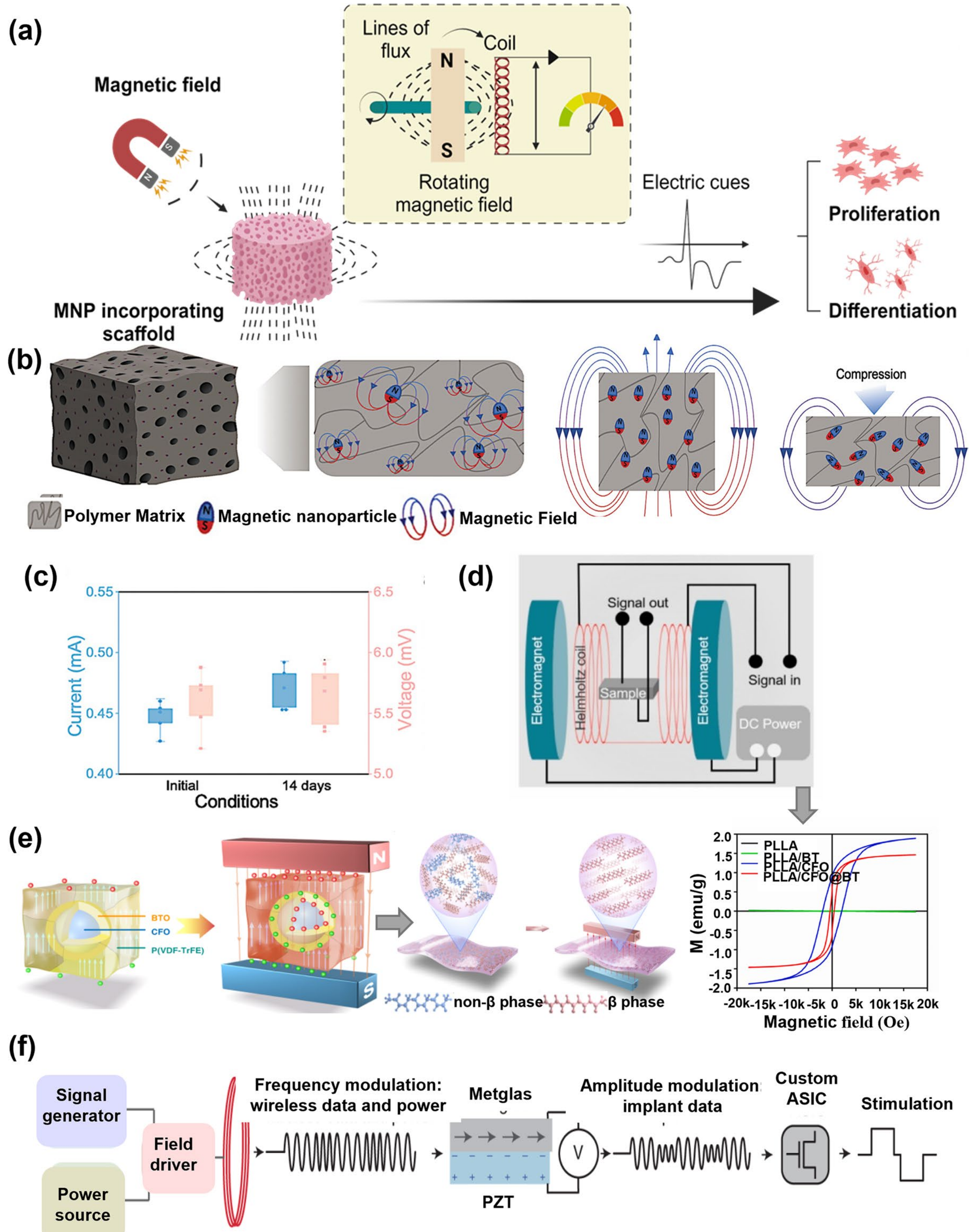


Fig. 6 Representative studies on electrical stimulation by magnetic-responsive materials: (**a**) Schematic of magnetic responsive platforms illustrating the mechanism of magnetic field effect on magnetic nanoparticles (MNP) containing scaffolds, (**b**) image showing magnetic nanoparticles dispersed in the polymeric matrix and magnetic dipole alignment changing magnetic flux density and its compressed state, (**c**) current and voltage outputs under initial and final days from magnetoelastic generator, Adapted with permission from [156], copyright 2022, John Wiley & Sons (**d**) diagram showing magnetoelectric coefficient test system and magnetization hysteresis loop where CFO nanoparticles undergo deformation, Adapted with permission from [157], copyright 2022, Elsevier (**e**) interface polarization due to applied magnetic field and transition of PVDF from α to β phase. Adapted with permission from [145], copyright 2023, Springer Nature. (**f**) The process of the ME-BIT implant receives power and converts the magnetic field to an electric field by the magnetoelectric film, transfers strain to the piezoelectric layer, PZT, and induces a voltage. Adapted with permission from [161], copyright 2022, Springer Nature

the human body remains a significant challenge [152]. In instances where these technologies are intended for in vivo applications, internal light transmission is also limited, which is further compounded by the barrier posed by the multi-layered human epidermis [153]. Therefore, overcoming these multifaceted hurdles can satisfy the electrical performance of optoelectric biomaterials under a spectrum of physiological conditions encountered within the human body. Consequently, extensive research endeavors are underway to address these intricate and pressing concerns.

Electricity generation by biomaterials in response to magnetic field

The generation of electromagnetic energy relies on the fundamental principle of electromagnetic induction, as elucidated by Faraday's law. This principle postulates that when a conductor is subjected to the influence of a magnetic field, mainly when there is relative motion or variation in the magnetic field strength, it induces an electromotive force within the conductor. This induced force, in turn, facilitates the flow of electric current through the conductor, thereby generating electrical energy [157]. Magnetic responsive platforms have thus been developed in biomedical applications to harness this principle effectively (Fig. 6a). In these platforms, the materials or devices experience alterations in their electromagnetic environment, thereby inducing electromotive force and consequent electrical signals. These signals can be employed for various applications, including electrical stimulation within biological systems [158–160].

Some recent studies have utilized the giant magnetoelastic effect in soft systems [155, 162–167] to create scalable electrical stimulation platforms. The magnetoelastic effect originates from the alignment of magnetic dipoles within soft systems, showcasing a more powerful magneto-mechanical coupling compared to traditional rigid metal alloys. Libanori et al. [155] invented a magnetoelastic generator (MEG) by dispersing magnetic nanoparticles like neodymium boron (NdFeB) within liquid silicon rubber and applying gentle air pressure (Fig. 6b). The magnetoelastic generator could convert disturbances into significant electrical currents and voltages (Fig. 6c). This electrical stimulation platform demonstrated a remarkable increase in fibroblast conversion into neurons (104%) and enhancement in neuronal maturation (251%), showing potential for organ-on-a-chip systems and future neural engineering applications.

Another intriguing approach, as explored by Fangwei et al. [156], demonstrated magnetic-electrical coupling effects to generate electrical stimulation remotely. This method involves the creation of a core–shell structure by growing a piezoelectric platform (PLLA) just above self-constrained $CoFe_2O_4$ (CFO) nanoparticles. The CFO core undergoes deformation when exposed to an external magnetic field (Fig. 6d) resulting from the movement and rotation of magnetic domains. This strain is transmitted through the $BaTiO_3$-bound region within the interface. Recent experiments conducted by Wenwen et al. [144] integrated polarized $CoFe_2O_4$@$BaTiO_3$/polyvinylidene fluoride trifluoroethylene (PVDF-TrFE) core–shell particles into these approaches (Fig. 6e). The efficiency of converting magnetic and electrical energy was significantly enhanced, leading to activated bone regeneration. Furthermore, in vivo experiments demonstrated that the complex membrane could create an electrically conductive environment promoting bone regeneration, even in inflammatory conditions.

The work by Joshua et al. [168] further highlighted the magneto-electrics with wireless technology for data and power transfer, offering high power density, tolerance for misalignment, and deep tissue operation (Fig. 6f). The miniature MagnetoElectric-powered Bio ImplanT (ME-BIT) delivered stimulation using a bioelectronic implant of millimeter-size. The ME-BITs maintained functional power levels over a broader range of misalignment compared to ultrasound-powered devices and did not require ultrasound gels or foams for energy coupling. These miniature ME-BITs demonstrated sufficient power density to stimulate large animal models within a blood vessel, surpassing other wireless power technologies for bioelectronic implants.

The biomaterial systems generating micro-electrical energy under a magnetic field are summarized in Table 2. The materials that utilize magnetic fields to generate minute electrical currents and provide electrical stimulation typically encounter limitations in biocompatibility, necessitating consideration for potential biotoxicity concerns [2]. Furthermore, the generated electrical power is often constrained, and the efficiency of microcurrent generation through magnetic fields tends to be relatively low, limiting the overall efficacy [161]. External factors such as environmental conditions and magnetic interference can also significantly influence electrical output [169]. Moreover, within the biological environment, these materials can experience performance degradation due to chemical oxidation, leading to diminished long-term stability [170]. Consequently, designing materials for microcurrent generation using a magnetic field necessitates stable and consistent electrical production [171]. For clinical applications, consistent performance within the biological environment without showing degradation and toxicity is necessary [172–174], warranting future studies.

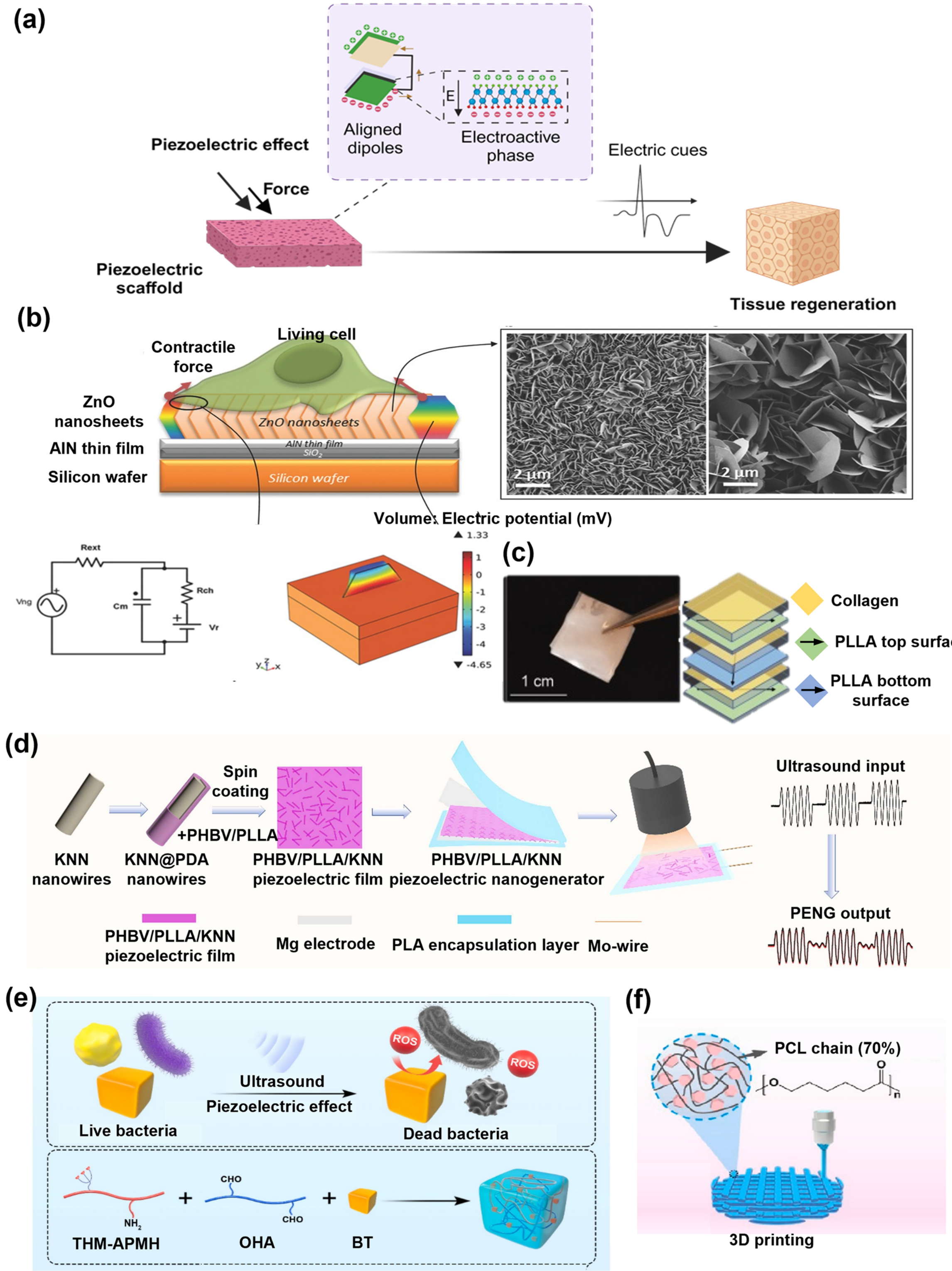


Fig. 7 Representative studies on electrical stimulation by piezoelectric materials: (**a**) Schematic illustration showing mechanism of piezoelectric effect, (**b**) inherent cell forces acting on ZnO nanosheets based piezoelectric nanogenerators and SEM images of NGs, Adapted with permission from [63], copyright 2017, John Wiley & Sons (**c**) image showing the construction of piezoelectric PLLA nanofiber scaffold which acts as an electrical stimulator under mechanical stress, Adapted with permission from [67], copyright 2022, AAAS (**d**) mechanism showing ultrasound-driven ES enhancing peripheral nerve repair by implantable PHBV/PLLA/KNN nanogenerator film and the in vivo delivery, Adapted with permission from [66], copyright 2022, Elsevier (**e**) schematic of US-triggered photocatalytic therapy involving BT-OHA/THM-APMH hydrogel which exhibits self-healing and adhesion properties for wound healing, Adapted with permission from [64], copyright 2023, Elsevier and (**f**) PWH-PCL composite scaffold using 3-D printing technology designed to establish an endogenous electric field at bone defect sites facilitating Mg^{2+} release to increase bone bioactivity. Adapted with permission from [65], copyright 2023, Elsevier

Piezoelectric biomaterials generating stress-responsive electricity

The operational principle of piezoelectric materials for generating delicate electrical stimulation involves shifts in the distances between molecules or atoms, typically achieved through changes in applied pressure [175]. Consequently, these alterations result in variations in the internal charge distribution and electrical imbalance, ultimately generating an electrical field (Fig. 7a).

Piezoelectric materials hold promise for addressing challenges related to invasive electrical signal delivery in regenerative therapy. They exhibit electromechanical coupling and flexibility, allowing them to serve as self-powered stimulators that harness mechanical force from organisms and external stimuli without wired connections [176, 177]. Recent advancements in nanostructured piezoelectric energy harvesters, such as piezoelectric nanogenerators, have enabled active sensing, electrical stimulation therapy, and the passive harvesting of biomechanical energy to power on-body devices from external sources [178]. Moreover, the use of wireless electrical cues via electrospun piezoelectric polymeric nanofibers presents a non-invasive and cellular-level approach to generate localized electrical stimulation [179, 180]. The emergence of piezoelectric nanogenerators represents significant advancements in intelligent regenerative therapy. Over the past decade, these devices have made rapid progress and are positioned to play a fundamental role in future state-of-the-art personalized healthcare [181]. Due to their highly efficient conversion of mechanical energy to electrical energy, ease of implementation, and capacity for self-powering, these nanogenerators facilitate a broad spectrum of potential healthcare applications.

Recent exploration of piezoelectric materials for self-powered, miniaturized applications has witnessed significant growth since their discovery. Zinc oxide has become a central focus due to its compatibility with low-temperature nano-structuring, contrasted with several ferroelectric materials that demand high-temperature processing. However, specific synthesis methods for ZnO nanostructures have limitations, including their low quantity and physical stability. Moreover, materials like lead zirconate titanate (PZT) and barium titanate, known for their high piezoelectric coefficients, have gained considerable interest. Recent research, mainly focused on PZT-based studies, seeks to develop high-performance PZT stretchable piezoelectric nanogenerators.

Gonzalo and colleagues [63] have demonstrated that interactions between living cells and 2D ZnO nanosheets in piezoelectric nanogenerators establish a local electric field (Fig. 7b). This electric field arises from the unique properties of ZnO nanosheets characterized by the reduced thickness (<20 nm) and high aspect ratio (>100), enabling bending in response to cellular forces. Consequently, charge separation within the crystalline structure of ZnO generates an electric field via the piezoelectric effect. This self-stimulating mechanism effectively regulates cell activity without external stimuli, enhancing macrophage movement and ion channel activation in osteoblast-like cells. Noteworthy attributes of these nanoscale voltage generators include their small size (smaller than a cell), voltage output comparable to typical cell membrane potential, and instant electric power utilization for cell stimulation, eliminating the need for energy storage [39]. While significant progress has been made with piezoelectric nanogenerators, recent attention has shifted towards remotely induced ultrasound activation of these generators. Self-powered piezoelectric nanogenerators incorporating ZnO have considerable potential in advancing motor recovery and neural function. This was substantiated by Yun et al. [182] through the creation of ZnO-loaded PCL nanogenerator scaffolds designed to address peripheral nerve injuries (PNIs).

Barium titanate ($BaTiO_3$, BTO) is a compound with exceptional dielectric and ferroelectric properties that have shown promise in promoting bone regeneration with piezoelectric properties. For instance, Wu et al. [183] have demonstrated that coating piezoelectric scaffolds with BTO stimulates osteogenic differentiation in MSCs and angiogenesis in endothelial cells. Similarly, BTO-coated scaffolds were also developed to enhance osteogenesis and vascularization in vitro. Additionally, multifunctional hydrogels embedded with BTO nanoparticles were developed [64]. The BTO nanoparticles respond to ultrasound, generating reactive oxygen species (ROS) and thus effectively eliminating bacteria, while the hydrogels exhibit self-healing and adhesion properties, demonstrating therapeutic efficacy for wound healing (Fig. 7e).

While in vivo transcutaneous devices have faced significant challenges through conventional approaches, a recent study by Wu et al. [66] addressed this issue. They proposed in vivo electrical stimulation utilizing ultrasound-driven biodegradable piezoelectric nanogenerators made of biodegradable PLLA, potassium sodium niobate (KNN), nanowires, and poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV) (Fig. 7d). The inclusion of biodegradable encapsulation layers and electrodes further enhances the safety. By harnessing ultrasound as an energy source, these implantable nanogenerators provide flexible electrical stimulation to peripheral nerves, promoting nerve regeneration and tissue repair.

As such, PLLA platforms have been actively used for piezoelectric nanogenerators. Zhu et al. [184] engineered a PENG (Piezoelectric Nanogenerator) device using PLLA electrospun nanofibers, which yielded a voltage output of 0.55 V and a current of 230 pA. Also, Smith et al. [185] proposed PLLA nanowires as nanogenerators, harnessing shear piezoelectricity where the material generates current in response to shear stress. A fully biodegradable triboelectric

Table 3 Summary of representative studies on piezoelectric biomaterials that can generate electricity upon applied external stress, including the type of materials, range of electricity generated, biocompatibility, mechanical properties, and application areas

Ref	Materials	Generated current/voltage range for ES	Cytotoxicity	Mechanical properties	Applications
[66]	PHBV/PLLA/KNN	0.6×10^{-6} A	-	-	Nerve tissue repair
[67]	PLLA nanofiber	3.6 V	Biocompatible	-	Cartilage, subchondral bone regeneration
[65]	Whitlockite (PWH)	0.7–2.3 pC/N	~100 µg/mL	~0.306 ± 0.039 MPa	Cell proliferation, migration, and differentiation in bone tissue
[110]	PVDF nanofiber, Carbonized polydopamine (CPDA)	6.0×10^{-8} A	Biocompatible	70–100 MPa (PVDF, low strength &stretchability)	Wound healing
[112]	PVA-PVDF	2.82 V, 248.16×10^{-9} A	Biocompatible	3–6 MPa (PVA)	Diabetic wound repair
[191]	ZnO-PCL	0.04–0.12 V	Up to 100 µg/ml (ZnO)	30–38 MPa Highly tensile	Peripheral nerve regeneration
[192]	PCL-PVDF	~0.4 V	Biocompatible	38.7 MPa (PCL) (Highly flexible)	Peripheral nerve regeneration
[193]	PVDF/ZIF-8	(60–90) 10^{-9}A	Up to 30 µg/ml (ZIF-8)	100 MPa (ZIF-8)	Angiogenesis, osteogenesis
[194]	PVDF-GO	1.36–2.64 V			Nerve tissue engineering
[195]	$BaTiO_3$	$(0.07–0.19)\times10^{-3}$ V	Up to 50 µg/ml	486 ± 75 MPa	Neuronal Stimulation
[196]	P(VDF-TrFE)/$BaTiO_3$	$\sim2\times10^{-3}$ V	-	-	Neuroblastoma cells differentiation
[197]	ZnO/PDMS	0.3–0.9 V	-	-	Enhanced cell migration, metabolic activity, and differentiation
[198]	Poly(vinylidene fluoride–trifluoroethylene)/PCL	0.011–0.026 V	-	-	Promoted cardiomyocyte attachment, proliferation, and alignment
[186]	PLLA nanofiber	45 V, 9×10^{-6}A	-	-	Green energy harvesting machine
[183]	$BaTiO_3$ coated Ti6Al4V scaffold	$10.8\times10^{-6}\pm0.97$ A	-	-	Bone repair

nanogenerator (TENG) comprising aligned PLLA fibers and chitosan, gelatin, and polyhydroxybutyrate (PHB) was also devised as an energy harvesting machine [186]. These aligned PLLA fibers outperformed random PLLA fibers, achieving approximately 5.5 times higher voltage and 2 times higher current. In another work, Deokjae et al. have devised a self-enhanced electrostatic discharge TENG (SED-TENG) capable of producing around 2200 V peak voltage and 7 A peak current, transferring 50 µC of charge per cycle. The SED-TENG holds significant capability as an ultrahigh output energy harvesting tile for practical applications [187]. Furthermore, Liu et al. [67] discovered that a biodegradable piezoelectric scaffold made of PLLA can act as an electrical stimulator when subjected to mechanical force or joint stress (Fig. 7c). Piezoelectric charge of the scaffold facilitated protein adsorption, cell migration, and the release of endogenous TGF-β, aiding in tissue regeneration. In vivo testing on rabbits undergoing exercise treatment yielded promising results, suggesting potential applications in osteoarthritis treatment and tissue repair.

Similarly, PVDF, characterized by piezoelectricity, was developed into nanofiber scaffolds for tissue repair. PVDF combines high piezoelectric attributes with exceptional mechanical strength, high thermal stability, desirable flexibility, and biocompatibility. It exhibits a significant piezoelectric coefficient, with $d_{33} = 49.6$ pm/V, and a dielectric constant ranging from 6 to 12, surpassing many other organic polymers [188]. Of note was the increase in β-phase crystalline structure during electrospinning, significantly increasing the piezoelectric effect [110, 189]. A recent study demonstrated that electrospun PVDF-based fibers could enhance the osteogenic differentiation of human MSCs into osteoblast cells and promote early matrix mineralization, primarily due to the presence of a higher piezoelectric β-phase [190]. While electrospun PVDF fiber shows limitations due to its inherent hydrophobic nature, which is not ideal for tissue engineering, the hydrophilicity can be enhanced through simple modifications using co-polymers or surface functionalization. Along with polymers, Whitlockite was another material shown to be piezoelectric. Recently, Wang et al. [65] developed composite 3D printed scaffolds made of piezoelectric Whitlockite and PCL (Fig. 7f). This scaffold was designed to establish an endogenous electric field at bone defect sites while facilitating Mg^{2+} release to increase bone bioactivity. The scaffolds showed inhibition of osteoclasts while promoting MSC differentiation into neurogenic, angiogenic, and osteogenic lineages. The scaffolds facilitated neo-bone formation in a rat calvarial defect model, highlighting its potential for regenerating neuro-vascularized bone tissue. In Table 3, the piezoelectric biomaterials that can generate electricity upon applied external stress are listed, including the type of materials, the range of electricity generated, and the application areas.

While holding great promise, these piezoelectric materials present notable limitations that require attention. First, their biocompatibility remains a critical concern, necessitating further research and development to make these materials more suitable for in vivo applications [199]. Second, the electrical energy generated by external stimuli is limited, and the efficiency of the piezoelectric effect is currently relatively low, restricting potential applications for medical devices [68]. Future research efforts should focus on overcoming these drawbacks to achieve higher power generation and improved efficiency. Moreover, piezoelectric materials are susceptible to environmental factors, making the preservation of their long-term stability and consistent performance challenging. Research into material design and stability is crucial to address these issues effectively [200]. Furthermore, the physical stress induced by the piezoelectric effect can impact cells and tissues, especially under high-loading conditions. Minimizing such physical stress and developing safe designs and applications for cells and tissues is thus imperative. Addressing these is vital to maximize the potential of piezoelectric materials and facilitate future clinical applications.

Implementing technologies for clinical electrical stimulation with external stimuli (light, magnetism, piezoelectric force) may face challenges like precision in targeting, biocompatibility, safety assessment, regulatory approval, patient variability, treatment integration, long-term stability, and ethical considerations—these must be finely adjusted to achieve precise and targeted electrical stimulation without unintended consequences. The need for standardized testing becomes even more pronounced to validate the reliability and reproducibility of these external stimuli across diverse clinical scenarios. Interdisciplinary collaboration between materials scientists, engineers, and medical professionals is essential to address these challenges effectively.

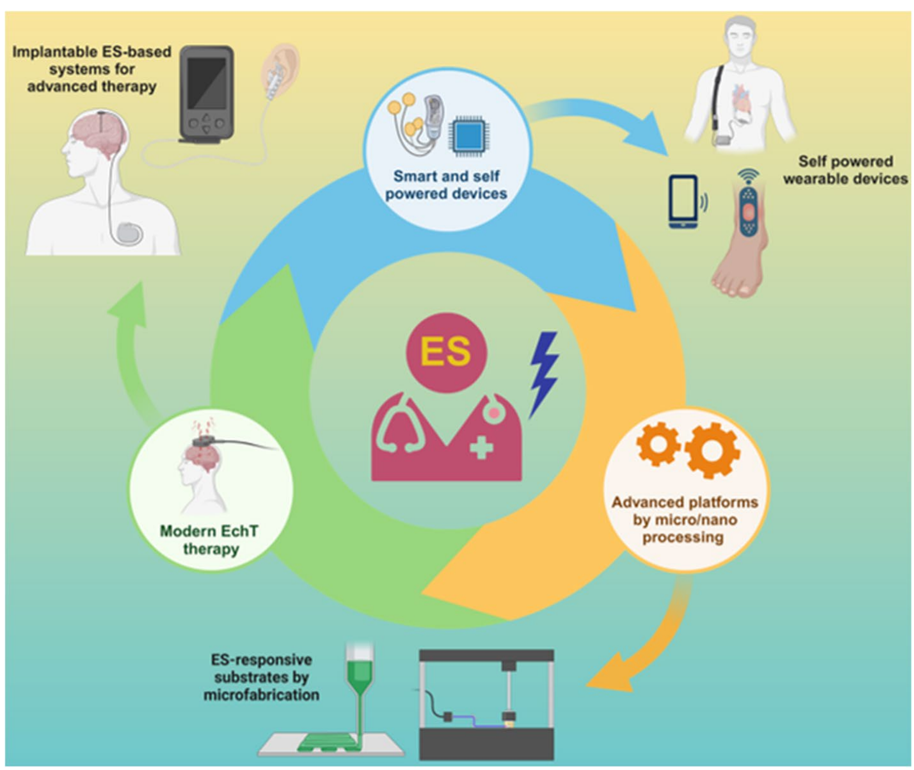


Fig. 8 Schematic illustrating the current developments and future trends in biomaterials-enabled ES systems, including advanced ES therapies like electrochemical therapy (EchT), implantable ES-based systems for advanced therapy, smart and self-powered devices for noninvasive ES production, and smart devices employing novel electroactive nanomaterials

Conclusion and perspectives

As witnessed, biomaterials-based electrical stimulation has played significant roles in healing damaged and diseased tissue, harnessing the distinctive attributes of conductivity and responsiveness of materials. These biomaterials, whether facilitating direct electrical connectivity or auto-generating micro-electric fields in response to various stimuli, hold immense promise for medical applications.

In principle, two primary strategies have been developed to allow electrical stimulation through biomaterials. The first entails in-situ electroconductive biomaterials, wherein conductive elements are integrated into tissue scaffolds to facilitate intercellular electrical signal propagation and stimulation. However, ensuring clinically applicable conditions necessitates careful consideration of external power sources. Therefore, an effort was made to explore a wireless system that generates electrical power within the in vivo milieu, such as biofuel cells.

The second strategy centres on external stimulus-responsive biomaterials endowed with the remarkable capability to self-generate electricity in response to diverse external cues, such as light, magnetic fields, or mechanical stress. The future of this field is continuously evolving with the development of more biocompatible materials that can efficiently convert various stimuli, even in combination. This is expected to enhance the efficiency of electricity generation. Notable examples include thermoelectric conversion via body heat sources, electric conversion triggered by pH changes, and the integration of multiple stimuli. Employment of in situ electroconductive biomaterials can be more effective compared to a second strategy in specific applications. In situ stimulation with conductive materials allows for targeted and localized delivery of electrical impulses directly to the desired area, minimizing energy loss and improving efficiency. External stimuli sources may encounter impedance and dispersion issues, potentially reducing their effectiveness.

Recent strides in biomaterials for ES have opened new avenues for tissue healing and regeneration. Future trends suggest a deeper integration of smart materials with sensors to monitor real-time physiological responses, allowing adaptive and personalized ES [201]. With the continuous development of material science, nanotechnology, micro/nano processing techniques, novel electroactive nanomaterials, and delicately designed devices, the possibilities to realize innovative ES therapies have significantly increased. For instance, the emergence of new technologies like nanogenerators has broken the limitations of traditional technologies. Of note, fine-tuning electrical stimulation parameters, optimizing bioactive factors, and developing non-invasive, implantable electrical stimulation devices with precise control and monitoring capability can expand the applications. It is also imperative to underscore that transitioning from these cutting-edge materials to clinical practice necessitates a rigorous evaluation of biocompatibility and specific functions, mainly through relevant animal models.

From a clinical perspective, advanced ES therapies have captured considerable attention in cancer treatment, encompassing direct methodologies like irreversible electroporation and electrochemical therapy (EchT), as well as indirect approaches involving self-powered devices [202] (Fig. 8). Moreover, self-powered neurostimulation via biomaterials and bioelectronics has become a promising approach to exploring, repairing, and modulating neural systems [203, 204]. Specific conductive polymers have been employed to facilitate electrical communication with neurons, showing promise in restoring damaged neural pathways. The clinical severity of spinal cord injuries (SCIs) varies from AISA grade A (most severe, with complete motor and sensory loss) to grade E (typical motor and sensory function). Ongoing trials explore combined therapies, such as a collagen scaffold with EES (Electrical Epidural Stimulation), umbilical cord blood mononuclear cells with lithium carbonate, and locomotor training [205, 206]. Although in vivo studies are limited [207], they reveal enhanced motor recovery in rats with a combination of NT-3 loaded PCLEEP scaffold and rehabilitation, surpassing results from the scaffold alone. Furthermore, for cardiac applications, conductive scaffolds have enhanced electrical signal propagation in cardiac tissue engineering. These case studies not only highlight the versatility of conductive biomaterials but also provide valuable insights into their safety, efficacy, and feasibility in clinical scenarios, thereby contributing to the ongoing evolution of bioelectronic therapies. Through continued efforts, biomaterials-enabled ES systems will open new horizons in the field of tissue healing and regeneration.

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Declarations

Competing interests Kim HW is an Associate Editor for Med-X. The paper was handled by another Editor and has undergone a rigorous peer review process. Kim HW was not involved in the journal's peer review or decisions related to this manuscript.

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