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Review

Piezoelectric electrospun fibers for tissue regeneration: synergizing microarchitecture and enhancement strategies

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ABSTRACT

Piezoelectric electrospun fibers, distinguished by their ability to be fabricated into highly flexible, ECM-mimicking architectures and tunable structures that enable efficient conversion of mechanical stimuli into bioelectrical signals, have emerged as promising piezoelectric scaffolds in tissue engineering. This review presents a novel and systematic analysis of integrated multidimensional approaches to enhance piezoelectric performance in electrospun fibers, with an emphasis on microarchitecture self-enhancement strategies, piezoelectric coupling, enhanced crystallinity, stress concentration, spatial confinement, and interface-anchored enhancement strategies. Additionally, various methods for generating electrical signals within these fibers are detailed, along with their diverse applications in tissue engineering. Finally, the challenges and future directions for piezoelectric electrospun fibers are discussed, aiming to provide valuable insights into the design of new high-performance piezoelectric scaffolds and next-generation tissue scaffolds.

1. Introduction

The core goal of tissue regenerative medicine is to repair or replace damaged tissues and organs by constructing functional biological scaffolds through the synergy of cells, scaffolds, and signaling molecules [1]. However, traditional tissue engineering scaffolds primarily focus on physicochemical properties such as biocompatibility, biodegradability, and pore structure [2], while lacking strategies that can dynamically respond to and actively regulate cell behavior [3,4]. Bioelectricity, as an inherent and dynamic physical signal within living organisms, plays a crucial role in cellular communication, tissue formation, physiological function maintenance, and even pathological repair processes [5]. Specifically, these electrical signals are generated by ionic gradients, cell membrane potentials, and transmembrane ionic currents, and undergo significant changes after tissue injury [6]. Such electrical signals are considered early indicators for tissue repair and can guide cell migration toward the injury site, while also regulating processes such as ion channel activity and intercellular communication [7]. For example, the piezoelectric effect in bone tissue can generate surface potential under stress and regulate osteoblast differentiation [8]; electrical stimulation (ES) can guide the directional growth of nerve axons [9]; and the endogenous electric fields can drive epithelial cell migration to promote wound healing [10]. Moreover, studies have shown that appropriate ES can effectively promote cell proliferation, migration, differentiation, and regulate gene expression and extracellular matrix (ECM) remodeling, thus affecting the regenerative process of tissues [11]. Therefore, precisely and continuously delivering electrical signals has become a key issue in tissue regeneration.

In exploring the role of ES in tissue repair, piezoelectric materials offer a novel paradigm for mimicking the electromechanical coupling properties of natural tissue, thereby enabling dynamic electrical regulation [12]. Compared to traditional ES devices, which are highly invasive and offer poor spatiotemporal control, piezoelectric scaffolds provide an alternative and innovative solution for wireless ES by converting mechanical energy into localized electrical energy [13]. In addition, the regeneration process necessitates scaffolds that provide an ideal living space for cell adhesion, proliferation, differentiation, and nutrient exchange [14,15]. Electrospun nanofiber scaffolds deliver a high specific surface area,

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interconnected pore structure, and tunable mechanical properties, which facilitate cell anchoring, migration, and growth [16]. In this context, piezoelectric electrospun fibers have emerged as promising scaffolds in tissue engineering, offering bionic topographical cues and mechanical support, as well as controllable conversion of mechanical stimuli into electrical signals spatiotemporally [17]. This multimodal signal integration can more comprehensively and efficiently simulate the complex microenvironment, providing more intelligent guidance for cell growth and differentiation [18]. Moreover, piezoelectric fibers can be combined with other active substances to construct multi-functional scaffolds [19]. This integrated strategy can further enhance the scaffold's ability to regulate cell function and tissue induction, providing a comprehensive approach to complex tissue repair.

For efficient tissue regeneration, the piezoelectric properties of these electrospun fibers must be precisely regulated to provide optimal ES [20]. In recent years, researchers have further developed strategies to modulate the piezoelectricity of fibers by adjusting their material components, structural design, spinning process, and post-treatment process [21]. Differing from traditional piezoelectric enhancement strategies, these emerging modulation strategies are instructive. Although some reviews are emerging on piezoelectric materials and piezoelectric nanogenerators [1,22], there is no relevant review summarizing the enhancement strategies of piezoelectric electrospun fibers, and the worth of their applications in tissue engineering and regenerative medicine is underestimated. More importantly, optimizing the piezoelectric properties of electrospun fibers to enhance tissue repair remains a challenge.

Based on this, this review presents an overview of the various types of piezoelectric fibers with emphasis on self-enhancement strategies brought about by their micromorphology and architecture (aligned, interlocking structures, core-shell, hollow, multilayer and three-dimensional structures), innovatively summarizes the effects enabled by filler incorporation, including piezoelectric effect coupling, crystallinity improvement, stress concentration, spatial confined effects, and interfacial anchoring enhancement strategy. In addition, different methods of generating electrical signals on piezoelectric fibers are summarized and presented for diverse biomedical applications (drug delivery, antibacterial and wound healing, nerve tissue engineering, cardiovascular tissue engineering, bone tissue engineering, cartilage tissue engineering, and other tissues) (Fig. 1). Finally, current challenges are discussed, and future directions are envisioned. It is hoped that such piezoelectric electrospun fiber scaffolds, which deeply integrate materials science, bioelectronics, and regenerative medicine, will offer valuable and forward-looking insights into the design of new high-performance piezoelectric scaffolds and next-generation tissue scaffolds.

2. Piezoelectric electrospun fibers

Creating novel biomedical scaffolds with properties such as biodegradability, biocompatibility, and mechanical properties matching those of tissues has long been an area of ongoing research [23]. Electrospinning technology is an advanced manufacturing method that uses a high-voltage electrostatic field to stretch polymer solutions or melts into micro- and nanoscale fibers [24–26]. Its advantages are mainly as follows: (1) Electrospun fibers have extremely high specific surface area and interconnected pore structure, which is conducive to cell adhesion, proliferation, and nutrient delivery, simulating the microenvironment of natural ECM [23,27]. (2) By adjusting the spinning parameters, fibers with different diameters, morphologies, and alignments can be prepared, thereby regulating cell orientation, migration, and differentiation and promoting regeneration of specific tissues [28]. (3) A wide range of materials can be processed, including natural polymers, synthetic polymers, and composite systems. This allows researchers to construct personalized and customized scaffolds by selecting appropriate materials tailored to the needs of different tissues [29]. (4) Electrospun fibers can be loaded with growth factors, drugs, or other bioactive molecules to achieve functionalization of the scaffold and to facilitate tissue regeneration [30–32].

Based on the biomimetic structural advantages of conventional electrospun fibers, researchers are working to endow them with active biological responses to dynamically regulate the cellular microenvironment, thereby addressing the bottleneck that limits the efficiency of tissue regeneration [33]. In this context, piezoelectric electrospun fibers enable the construction of biological interfaces with coupled mechanical-electrical signals by integrating piezoelectric effects into the fiber system [34]. While preserving

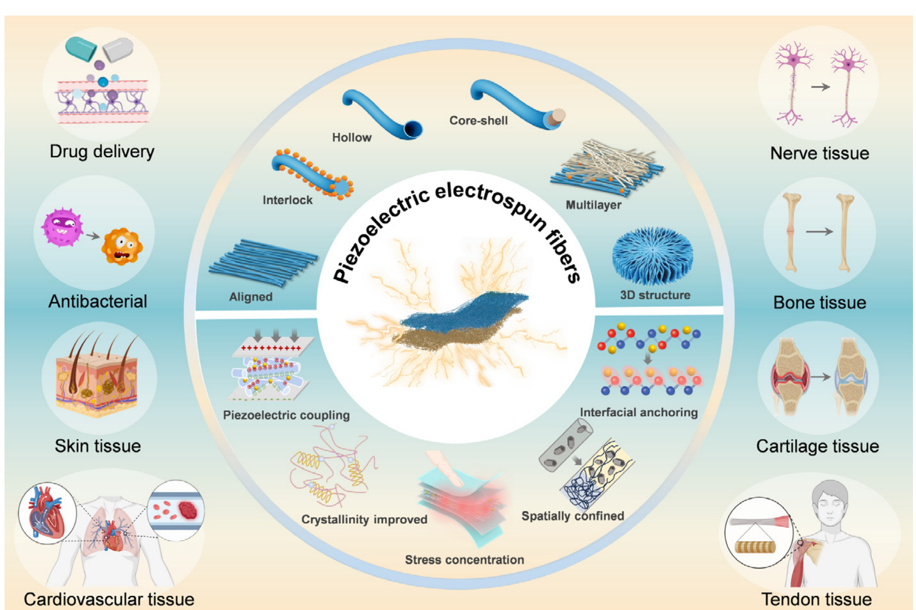

Fig. 1. Schematic illustration of microarchitecture/enhancement strategies on piezoelectric fibers and their application in tissue engineering.

the topological features of the original electrospun scaffolds, these fibers can generate electrical signals spontaneously under external mechanical stimulation, mimicking the electrical microenvironment of natural tissues [35]. To achieve this goal, an important point is the selection of the piezoelectric component. Current piezoelectric materials can be divided into three categories: inorganic piezoelectric materials (e.g., lead zirconate titanate (PZT) and barium titanate (BTO)), organic piezoelectric materials (e.g., polyvinylidene fluoride (PVDF) and its copolymers), and composite piezoelectric materials. Unlike the conventional fabrication of piezoelectric generator devices, piezoelectric fibers demand consideration of processing feasibility and mechanical requirements, such as flexibility. This restricts the source of components for piezoelectric fibers to polymers, and concerns over the toxicity of high inorganic ceramic content have driven research to seek alternative piezoelectric materials for biomedical applications [36]. Consequently, the current sources of piezoelectric fibers are mainly polymer systems, which can be classified as inorganic piezoelectric material-polymer fibers, natural polymer piezoelectric fibers, synthetic polymer piezoelectric fibers, and composite piezoelectric fibers. All piezoelectric fibers referred to in the remainder of this review are prepared via electrospinning.

2.1. Inorganic piezoelectric material-polymer fibers

Inorganic piezoelectric material-polymer fibers are relatively rare, since polymers are needed in the spinning process to provide viscosity and spinnability. In contrast, the piezoelectric effect is supplied by inorganic piezoelectric materials, which are dominated by BTO and zinc oxide (ZnO). For example, a polycaprolactone (PCL)/ZnO piezoelectric nerve conduit was developed by electrospinning. Where PCL is a biocompatible material, and ZnO can generate stable and desirable endogenous ES for better *in situ* nerve bridging [37]. Similarly, PCL/BTO nanofiber membrane and graphene oxide-doped hydrogel were integrated for the treatment of erectile dysfunction caused by peripheral nerve injury. This patch, which generates electrical signals with BTO, exhibits excellent piezoelectric properties and significantly promotes axonal growth [38]. It was also found that PZT/polyurethane fiber membranes can be used as flexible energy harvesters, harnessing energy from human movement while remaining flexible [39]. However, the fibers derived solely from inorganic piezoelectric components have limited piezoelectric properties and cannot guarantee idealized flexibility and biocompatibility.

2.2. Polymer piezoelectric fibers

Polymer systems are the most common piezoelectric fiber systems, encompassing both natural and synthetic polymer piezoelectric fibers. Since some reviews have been very concrete in classifying and describing piezoelectric substances, this review will focus on the polymer piezoelectric electrospun fibers.

It is well known that the piezoelectric effect has been observed in biomaterials that comprise many organs in the human body and nature. These natural piezoelectric materials can be categorized into amino acids, peptides, proteins, and polysaccharides [35]. The carboxyl and amino groups are aligned in the same direction in the periodic structure, thereby inducing a bulk piezoelectric response in the non-centrosymmetric amino acid crystals [40]. Among them, the most studied is glycine (Gly) with a very high shear piezoelectric coefficient of 195 pm/V [41]. Gly crystals were doped into PCL to prepare piezoelectric nanofibers with stable piezoelectric properties (19 pC/N), which can produce a high ultrasonic output of 334 kPa at 0.15 V when prepared for ultrasonic transducers [42]. Similar to amino acids, peptides are short chains with a similar structure, with phenylalanine dipeptide (FF) being the most studied system. For example, the nano-thresholding method was used to prepare FF crystal fibers exhibiting both flexible and piezoelectric properties (d_{33} = 10 pC/N) [43]. A fibrous membrane was prepared by embedding Boc-PP nanotubes within a polymer matrix, which can generate voltages up to 30 V under periodic mechanical force (1.5 N) [44]. Proteins, formed by amino acids linked by peptide bonds, also exhibit piezoelectric properties, e.g., collagen, keratin, and silk fibroin (SF) [45]. A single SF electrospun fiber has an apparent piezoelectric constant of 38 ± 2 pm/V [46]. Recent studies have revealed for the first time that silk sericin has a high longitudinal piezoelectric constant of 12 pC/N, enabling ES that can restart beating in blocked hearts [47]. Cellulose and chitin are examples of piezoelectric polysaccharides [48]. For example, aligned cellulose fiber (CNF) composites with piezoelectric charge constants of 14.5 pC/N were prepared by coating CNF suspensions on electrospun CNF/poly(vinyl alcohol) (PVA) fiber membranes [49]. The piezoelectric response of the aligned chitin nanofibers is also comparable to that of collagen fibers and much higher than that of gelatin fibers [50].

However, the piezoelectric coefficients of natural fibers are typically low, limiting their practical applications, so efforts have been made to investigate the piezoelectricity in synthetic polymers [45]. Among synthetic polymer fibers, the piezoelectric effect is mainly represented by PVDF and its copolymers, poly(L-lactic acid) (PLLA), polyamides, polyacrylonitrile (PAN), and some polyhydroxyalkanoates, such as poly(β-hydroxybutyrate) (PHB), poly(3-hydroxybu tyrate-co-3-hydroxyvalerate) (PHBV) [51]. For example, the introduction of shape memory polyurethane elastomers into PVDF not only imparts shape memory properties to the scaffolds but also provides mechanical stimulation to generate an electrical charge that promotes osteogenesis [52]. PLLA nanofibers are widely used in osteogenesis and nerve regeneration fields due to their biodegradability and ES properties [53]. Other, less commonly mentioned piezoelectric polymers, such as nylon-11, can generate open-circuit voltages as high as 17 V when subjected to an 8 N impact force [54]. More importantly, it has excellent heat resistance and maintains excellent piezoelectric output at high temperatures. A piezoelectric constant of 39.0 pm/V was achieved by reducing the fiber diameter of PAN to 40 nm through a size-limiting effect [55]. Related studies have also demonstrated that the piezoelectric PHBV scaffold exhibits superior calcium deposition compared to a non-piezoelectric PCL scaffold [56].

2.3. Composite piezoelectric fibers

To achieve more optimal piezoelectric properties, mixtures of two piezoelectric substances are often used, with the most common being an inorganic piezoelectric substance added as a filler to a piezoelectric polymer fiber substrate [57]. For instance, the optimized PVDF/BTO fiber exhibits a polar β-phase content of up to 82.39 % and achieves an open-circuit voltage of 19 V in the bending mode [58]. Compared to random PLLA fibers, the incorporation of ZnO into PLLA to prepare oriented fibers results in higher crystallinity and piezoelectric output [59]. Moreover, there are also piezoelectric polymers that combine the two to achieve better piezoelectric properties. When the piezoelectric nanofibers of nylon 11/Gly are fabricated using an optimized 8:2 combination ratio, they can generate open-circuit voltages and short-circuit currents of 11.2 V and 11.57 μA, respectively, which is a significant performance enhancement over pure nylon 11 [60]. More interestingly, the conjugated polymer nanofiber systems formed by conducting polymers and PVDF also all exhibit higher piezoelectric properties than pure PVDF fibers [61]. Table 1 lists some representative piezoelectric fibers. It is believed that with the researchers' in-depth investigation, novel fibers with higher piezoelectric coef-

Table 1
Representative types of piezoelectric electrospun fibers.

Type	Piezoelectric component	Piezoelectric coefficient	Fiber substrate	Output	Advantages/applications	References
Inorganic piezoelectric fibers	ZnO	d_{33} = 12–14 pC/N	PCL	V_{max} = 5 V	Biocompatible & stable ES	[37]
	BTO	d_{33} ~100 pC/N	PCL	V_{max} = 9.54 V	Promote axonal growth	[38]
Natural piezoelectric fibers	Gly	d_{16} = 178 pm/V; d_{33} = 19 pm/V	PCL	Charge = 360 pC	Degradable & drug delivery	[42]
	Boc-PP	d_{33} = 17.9 pm/V	PLLA/PCL	V_{max} = 30 V	Bio-energy sources	[44]
	SF	d_{33} = 38 pm/V	SF	V_{max} = 8 V	Implantable medical devices	[46]
	CNF	d_{33} = 19 pm/V	CNF/PVA	V_{max} = 78.5 mV	Energy harvesting	[49]
	Chitin	d_{33} = 3.98 pm/V	Chitin	V_{max} = 0.3 V	Renewable & antibacterial	[50]
Synthetic piezoelectric fibers	PLLA	d_{14} = 12–19 pC/N	PLLA	V_{max} = 2.4 V	Self-degrade & biocompatibility	[74]
	PAN	d_{33} = 39 pm/V	PAN	V_{max} = 3.8 V	Heat resistance	[55]
Composite piezoelectric fibers	BTO/PVDF	d_{33} ~20 pC/N (PVDF)	PVDF	V_{max} = 19 V	High piezoelectricity	[58]
	ZnO/PLLA	/	PLLA	V_{max} = 7.9 V	High flexibility & sensitivity	[59]
	Gly/nylon 11	d_{33} ~2 pC/N (nylon 11)	Nylon 11	V_{max} = 11.2 V	Mechanical superiority	[60]

ficients and multifunctional properties will further expand their applications in biomedicine.

2.4. Other technologies for preparing piezoelectric fibers

Beyond electrospinning, several other promising techniques for preparing nanofibers exist, including melt spinning, wet spinning, dry spinning, microfluidic spinning, and force-spinning [62]. Among these, force-spinning utilizes mechanical centrifugal force rather than an electrostatic field [63]. During the force-spinning process, the polymer solution or melt is stretched to the nozzle under centrifugal force. The thickness, uniformity, and surface morphology of the nanofibers depend on key parameters including fluid viscoelasticity, surface tension, nozzle aperture, jet velocity, and angle. This significantly increases fiber yield and simplifies the production process. More importantly, Mamidi et al. [64] reported that the single-nozzle fiber production rate can exceed 1 g/min, significantly surpassing the output of any laboratory-scale electrospinning setup. The absence of high-voltage configurations ensures safety during fiber preparation. Furthermore, compared to electrostatic forces, centrifugal forces can overcome higher viscosities and surface tensions, making them suitable for polymer solutions or melts.

Based on these advantages, force-spinning holds promise as a viable method for manufacturing high-performance wearable biosensors and devices [65]. For instance, PVDF-$BaTiO_3$ nanofibers produced using force-pinning technology achieved a maximum output of 35.8 V [66]. This is attributed to the shear forces generated during centrifugal stretching, which promote the oriented alignment of PVDF molecular chains and enhance the proportion of β crystalline phase. Similarly, the output voltage of graphene-coated PVDF/PANI fiber scaffolds fabricated via force-spinning reached 75 mV [67]. Overall, with its high yield, low cost, and material versatility, force-spinning demonstrates significant potential for the preparation of piezoelectric fibers, particularly for scenarios requiring large-scale production.

3. Piezoelectric enhancement strategies on electrospun fibers

Piezoelectric fibers are required to provide dynamic ES to modulate cellular behavior in tissue engineering [68]. However, most existing piezoelectric fibers suffer from insufficient piezoelectricity and limited bioactivity [69]. Enhancing the piezoelectric properties to optimize electro-mechanical coupling efficiency is a major challenge [70]. This section emphasizes strategies for modulating and enhancing the piezoelectric properties of electrospun fibers. From the spinning process to the common enhancement strategies (annealing and polarization, etc.), while highlighting how the micromorphology and architecture of piezoelectric fibers (aligned/interlocked structure/core-shell/hollow/multilayer and 3D structures) can be guided to achieve self-piezoelectric improvement, and multi-dimensional filler reinforcement strategies.

3.1. Regulation of electrospun parameters

The core electrospinning process involves a spinning solution of suitable concentration, under an appropriate electric field and propulsion rate, which then undergoes Taylor cone formation, charged jet extrusion, nanofiber bundles integration, and deposition on the collector [24,71]. Within this process, electrospun fibers with different piezoelectric properties can be obtained by manipulating the spinning process and parameters, such as solution composition, fiber diameter, fiber membrane thickness, and collector rotation speed [29].

For example, PLLA fibers with different diameters were prepared by varying the mass concentration, revealing that the piezoelectric properties are inversely proportional to the concentration [72]. By reducing the diameter of PAN nanofibers to 40 nm, a piezoelectric constant of 39.0 pm/V can be achieved [55]. This can be attributed to the smaller fibers altering molecular chain arrangement through space-limiting effects, thereby increasing the electroactive content. Apart from altering the spinning solution concentration and fiber diameter, longer needles can also enhance the piezoelectric properties of nanofibers, which is related to the laminar flow process of molecular chains inside the metal needles [73]. Compared with short needles, longer needles provide a more sufficient activation time for molecular chains under certain spatial motion confinement. Meanwhile, the collector's speed affects fiber orientation, and highly oriented fibers have better piezoelectricity [53,74]. In general, the high speed of the collector enables further stretching of the charged jets, inducing a more regular arrangement of the dipoles in the molecular chains [75].

3.2. Post-treatment process

Conventional post-processing methods for enhancing piezoelectricity include annealing and polarization. Fiber membranes with ferroelectric properties can exhibit improved piezoelectric performance through polarization treatment [76]. Investigating the piezoelectric properties of PLLA at different annealing temperatures shows that the piezoelectric coefficient is positively correlated with the annealing temperature [9]. This is related to the activation energy of molecular chain motion. Typically, the annealing temperature is several tens of degrees higher than the glass transition temperature of the polymer used for spinning, but lower than the thermal degradation temperature. Overall, the temperature, polarization, and pressure field are favorable for the ordered arrangement of molecular chains [77], and can also be combined to achieve optimal piezoelectric properties. Nevertheless, ferroelectric piezoelectric fibers are more suitable for polarization treatment, whereas non-ferroelectric but inherently semi-crystalline fibers are more amenable to annealing processes.

3.3. Self-reinforcing piezoelectric fiber construction strategies

To meet the quest for high piezoelectricity across various application requirements, researchers have begun exploring the modulation of piezoelectricity due to the flexibility in fiber fabrication. Electrospun fibers with different morphologies can be obtained via altering the spinning procedure and solution components [29], such as aligned, interlocked, hollow, core-shell, multilayer, and three-dimensional (3D) structures (Fig. 2). The microstructure and morphology brought about by these fibers can modulate piezoelectric properties and guide cell fate and tissue regeneration.

Topological design is widely known as a piezoelectric enhancement mechanism to improve the electromechanical responsiveness of electrospun fiber membranes [78]. Among these, the aligned structure is the most commonly employed [49]. As shown in Fig. 3a, MSCs inoculated on aligned piezoelectric nanofibers exhibited elongated morphology and higher intracellular calcium activity [79]. Moreover, the cells can adjust their morphology and adhesion force, thus affecting the real-time piezoelectric output. Some microstructures can also endow fiber membranes with high piezoelectricity and sensitivity, and most of these form interlocking structures on the fiber surface by *in situ* growth methods [80,81]. For example, the "dogwood-like" structure of ZnO NWs on TPU fiber membranes enables ultra-wide linear sensing range monitoring [82]. A similar effect is achieved when ZnO is combined with flexible PVDF [83], where the hierarchical interlocking structure of the ZnO nanorods creates a stronger piezoelectric potential when the PVDF/ZnO nanofibers are under stress (Fig. 3b). Apart from that, the core-shell structure is more effective than simple doping and bilayer structures in improving the piezoelectric properties of fiber membranes [84]. However, when a non-piezoelectric polymer is used as the core layer, the core-shell structure of the fibers also endows a stronger piezoelectric performance. As shown in Fig. 3c, incorporating a non-piezoelectric polymer core (polycarbonate, PC) increases the piezoelectric coefficient of PVDF-TrFE nanofibers by 110% [85]. This is essentially done by adjusting the thickness of the shell layer, and experiments have shown that the thinnest shell layer exhibits the best output performance [86]. This approach can also be used for piezoelectric fibers with hollow structures. The hollow PVDF nanofibers with high β-phase content and high porosity are obtained by modulating the ratio of water-soluble polymers [87]. The piezoelectric output increases with the incorporation of water-soluble polymerization, and the maximum output voltage is approximately three times that of normal PVDF nanofibers (Fig. 3d).

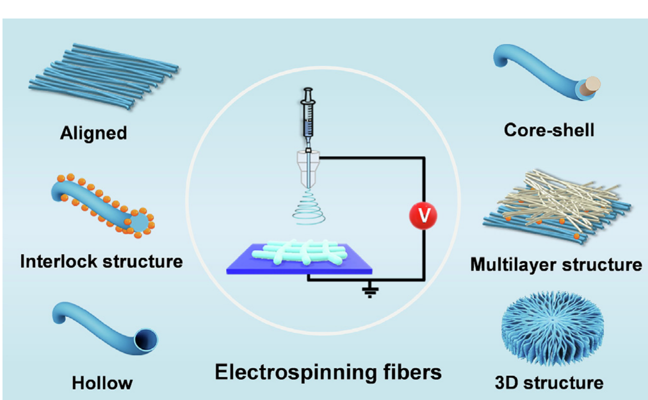

Fig. 2. Piezoelectric fiber scaffolds fabricated based on electrospinning technology.

Compared to directly co-spinning, it is more advantageous to construct multilayer fiber scaffolds that modulate stress perception and output magnitude between the layers. For example, samples with BTO sandwiched between PVDF-TrFE nanofibers showed higher piezoelectric output with a maximum enhancement of about 457% compared to samples with BTO uniformly dispersed in PVDF-TrFE fibers (Fig. 3e) [88]. Meanwhile, some 3D fiber scaffolds were prepared due to considerations of better piezoelectric/-conductive networks and supplying space for cells and tissues [89]. As shown in Fig. 3f, 3D fiber aerogel scaffolds exhibit effective electrical output under ultrasound (US) stimulation, with this output positively correlated with US power. These 3D fiber scaffolds not only effectively remodel the electrical microenvironment but also accelerate osteogenic differentiation [90]. This porous fiber structure also presents significant advantages in acoustic-electrical conversion and energy harvesting [91], and it is anticipated that deeper research into fiber construction processes will uncover more innovative fiber structures with great potential.

3.4. Fillers enhancement strategies

When a single piezoelectric component fails to meet the requirements, incorporating secondary or additional components (collectively termed fillers) is often employed to boost piezoelectricity. We summarize and redefine here the various enhancement strategies that have emerged based on multicomponent electrospun fibers (Fig. 4). Among them, the piezoelectric effect and mechanism brought by fillers can be categorized as follows: (1) piezoelectric effect coupling, (2) crystallinity improvement, (3) stress concentration amplifying the piezoelectric effect, (4) spatially confined effect, (5) interfacial anchoring enhancement strategy. Table 2 also lists some representative filler-reinforced piezoelectric strategies for electrospun fibers.

3.4.1. Piezoelectric effect coupling

The "1+1" strategy is the easiest way when faced with a piezoelectricity deficiency. This stems from the fact that the substrates commonly used for spinning are organic polymers, whose piezoelectric properties are not as satisfactory as those of inorganic piezoelectric substances. Therefore, the most common strategy for piezoelectric enhancement is to dope inorganic piezoelectric particles [92]. As shown in Fig. 5a, doping BTO NPs into PLLA increases the potential for multidirectional potential generation across the fiber membrane, thereby improving the piezoelectric output [76]. The d_{33} piezoelectric coefficient of the fiber membrane increases with increasing BTO doping ratio. Similarly, incorporating SiC and $FeCl_3$ into the PVDF fiber matrix synergistically improves the PVDF's piezoelectric properties [93]. Adding multiple reinforcements to amplify the synergistic piezoelectric enhancement effect is also possible [94]. Currently, the most common fillers are still based on BTO, ZnO, and carbon nanotubes as representative conductive additives.

3.4.2. Crystallinity improvement

Many piezoelectric polymers are semi-crystalline, so increasing their crystallinity is beneficial for improving piezoelectric properties. In the case of common PLLA and PVDF, the former's piezoelectricity is correlated with the degree of crystallinity, while the latter is related to the content of the β-phase. As shown in Fig. 5b, the therapeutic drug zoledronic acid (ZA) for the treatment of osteoporosis was cleverly used as a nucleating agent to enhance the

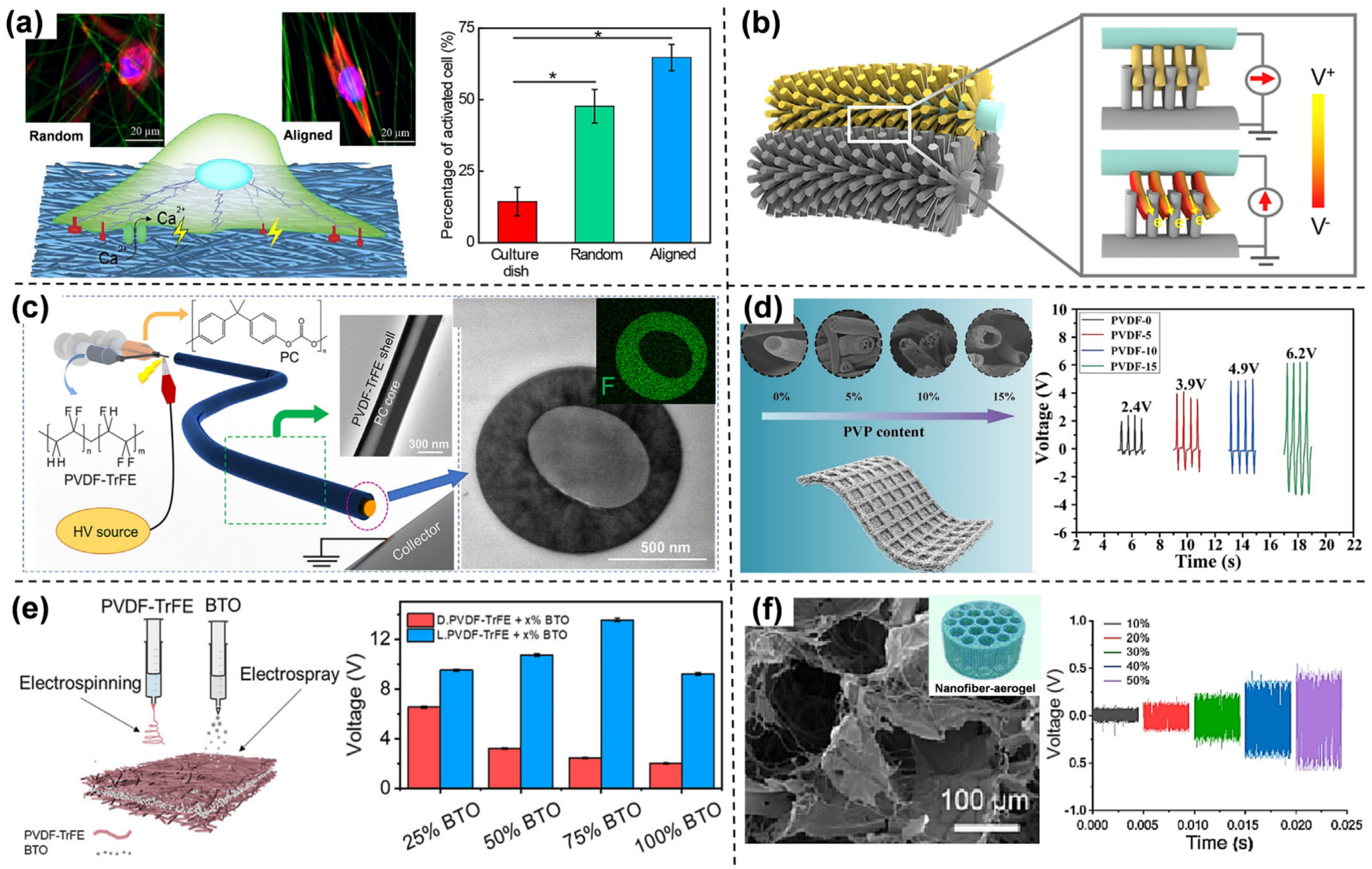

Fig. 3. Different morphologies and microarchitectures of self-enhanced piezoelectric electrospun fibers. (a) Effect of random/aligned fibers on cell morphology and activation state. Reproduced with permission from Ref. [79], Copyright 2021, Elsevier. (b) Schematic diagram of the piezoelectric potential generated on ZnO NRs grown on the fiber surface. Reproduced with permission from Ref. [83], Copyright 2020, Elsevier. (c) PVDF-TrFE nanofibers with a core-shell structure. Reproduced with permission from Ref. [85], Copyright 2023, American Chemical Society. (d) PVDF fibers with different degrees of hollowness and their piezoelectric properties. Reproduced with permission from Ref. [87], Copyright 2024, Elsevier. (e) Electrical output of PVDF-TrFE with different contents of BTO in the sandwich structure. Reproduced with permission from Ref. [88], Copyright 2023, American Chemical Society. (f) The morphology of 3D porous scaffolds and electrical output at different US frequencies. Reproduced with permission from Ref. [90], Copyright 2023, Elsevier.

piezoelectricity of PLLA [95], which effectively inhibited the osteolytic activity of osteoclasts along with the crystallization degree of PLLA, resulting in a desirable piezoelectricity coefficient of 8.02 pC/N. Similarly, by introducing $BaTi_2O_5$ nanorods (BT2) into PVDF nanofibers, the β-phase content of PVDF was greatly increased thanks to the high aspect ratio of BT2 arranged directionally in the PVDF fibers and stretched at high rotational speeds [96]. Related studies have shown that when carbon-coated zinc oxide (ZnO@C) nanoparticles are used as additives, a synergistic enhancement of the two effects of piezoelectric coupling and β-phase increase in PVDF nanofibers can be achieved to improve the piezoelectric output capability [97]. These approaches have inspired researchers to enhance piezoelectric properties by modulating crystallinity and crystal shape.

3.4.3. Stress concentration

Piezoelectric materials are essentially characterized by their ability to convert perceived forces into electrical signals. In addition to increasing the piezoelectric coefficient of the fiber itself, it is also possible to modulate the magnitude of the force perceived by the piezoelectric fiber. As shown in Fig. 5c, ZnO nanoparticles doped into PLLA fibers can induce stress concentration, and the results of simulation calculations show that the output voltage of PLLA/ZnO composite fibers is 2.5 times higher than that of PLLA fibers, and the energy density is 6.5 times higher than that of PLLA [59]. It is shown that the doping of fillers can induce stress concentration and amplification on the fibers, significantly enhancing piezoelectric properties. Similarly, BTO coating on PVDF surfaces can greatly amplify piezoelectric output through induced polarization and stress transfer mechanisms [98]. However, the bonding between the filler and the polymer matrix is not ideal. To solve this problem, Chen et al. [99] constructed a PDA-based interfacial linkage structure that improves contact and stress transfer ability between the inorganic filler and the organic matrix. According to the phase-field simulation of stress distribution (Fig. 5d), mechanical stresses on PDA-coated electrospun fibers can effectively reach the inorganic filler, forming a more uniform and denser stress distribution around the piezoelectric fibers, thereby enhancing electromechanical coupling efficiency.

3.4.4. Spatially confined effect

As mentioned before, when the polymer solution is confined to a very narrow channel and stretched by an electric field during the spinning process, it is easier to obtain an ordered structure. Similarly, some fillers can also provide a "spatial confinement" effect. When appropriately sized MXene nanosheets are added to the PVDF fibers, the composite system forms a spatially restricted structure. This structure traps the MXene nanosheets within the oriented nanofibers, resulting in a significantly higher interaction density compared to an unconfined structure (Fig. 5e) [100]. This spatial confinement enables optimal dipole alignment in PVDF, thereby enhancing the piezoelectric performance. This is also

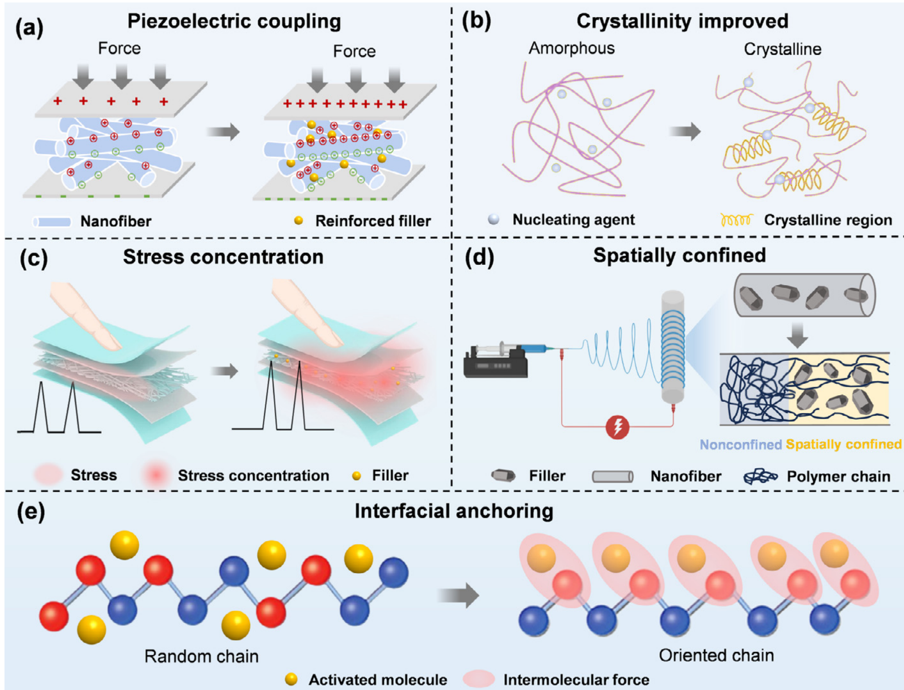

Fig. 4. Enhancement strategies for the piezoelectric property of electrospun fibers. (a) Piezoelectric effect coupling; (b) crystallinity improvement; (c) stress concentration amplifying the piezoelectric effect; (d) spatially confined effect; (e) interfacial anchoring enhancement strategy.

Table 2
Representative types of filler-reinforced piezoelectric strategies for electrospun fibers.

Strategies	Fillers	Fiber substrate	Piezoelectric property	Mechanisms	References
Piezoelectric effect coupling	BTO	PLLA	V = 1.8 V	Enhancement effect derived from two piezoelectric components	[76]
	BTO	PVDF	V = 19 V		[93]
Crystallinity improvement	ZA	PLLA	d_{14} = 8.02 pC/N	Improving piezoelectric properties by increasing crystallinity	[95]
	BT2	PVDF	V_{max} = 14 V		[96]
	ZnO@C	PVDF	V_{max} = 37 V		[97]
Stress concentration	ZnO	PLLA	V = 7.9 V	Fillers induce a more uniform stress distribution/stress concentration effect	[59]
	PDA@BTO	PVDF	V = 11 V		[99]
Spatially confined effect	MXene	PVDF	V = 3.1 V	Spatially confined and local anchoring enhance β-crystal phase formation	[100]
	MXene	PVDF	V_{max} = 4.2 V		[101]
Interfacial anchoring effect	Gly	PLLA	V = 1.2 V	Intermolecular forces of the filler induce an ordered arrangement of polymer chains	[102]
	DA	PVDF	V_{max} = 16.2 V		[104]

related to the abundance of functional groups in the MXene nanosheets, which interact with the PVDF chains at the interface, promoting an all-trans conformation via interfacial polarization effect [101]. With this coupling of interfacial polarization and spatially confined effect, the fibers exhibit a high-voltage electrical response.

3.4.5. Interfacial anchoring enhancement strategy

Unlike the non-reactive fillers mentioned above, some fillers can interact with fiber components, thereby promoting a more regular arrangement of the dipoles. This enhancement principle is referred to as the interfacial anchoring enhancement strategy [21].

As shown in Fig. 5f, PLLA/Gly nanofibers with core-shell-like structures were prepared by an interfacial anchoring strategy [102]. Molecular dynamics simulations confirmed that the –OH group on Gly and the C=O group on PLLA, and density functional theory further confirms that the system's total energy is minimized when the two bonds form preferentially. This approach promotes the crystallization of oriented PLLA polymer chains that exhibit significantly enhanced piezoelectric properties. The cations in the ionic liquid can also interact with C=O on the molecular chain to improve the piezoelectric properties of the composite fiber membrane [103]. Similarly, strong intermolecular interactions between the –NH_2 group on dopamine (DA) and the –CF_2 group on PVDF can align the PVDF molecular chain and promote its β-phase content [104]. In this case, controlling the additive content is crucial. The highest d_{33} value of the fiber membrane was achieved at a DA content of 1.0 wt%, yielding the highest output of 16.2 V. Considering the intermolecular interactions with the fiber substrate, adding a second component is a promising approach to improve the piezoelectric properties.

4. Different ways for generating electrical signals

Since piezoelectric materials can respond to subtle changes in mechanical forces and generate electrical signals. These mechanical forces can originate from a wide range of sources, from the smallest adhesion traction generated by cells on fibers to the largest biomechanics generated by human physiological activities [11]. In addition, external stimuli such as the US and the magnetic field can also induce changes in mechanical energy, thereby eliciting electrical signals [34]. Different ways for generating electrical

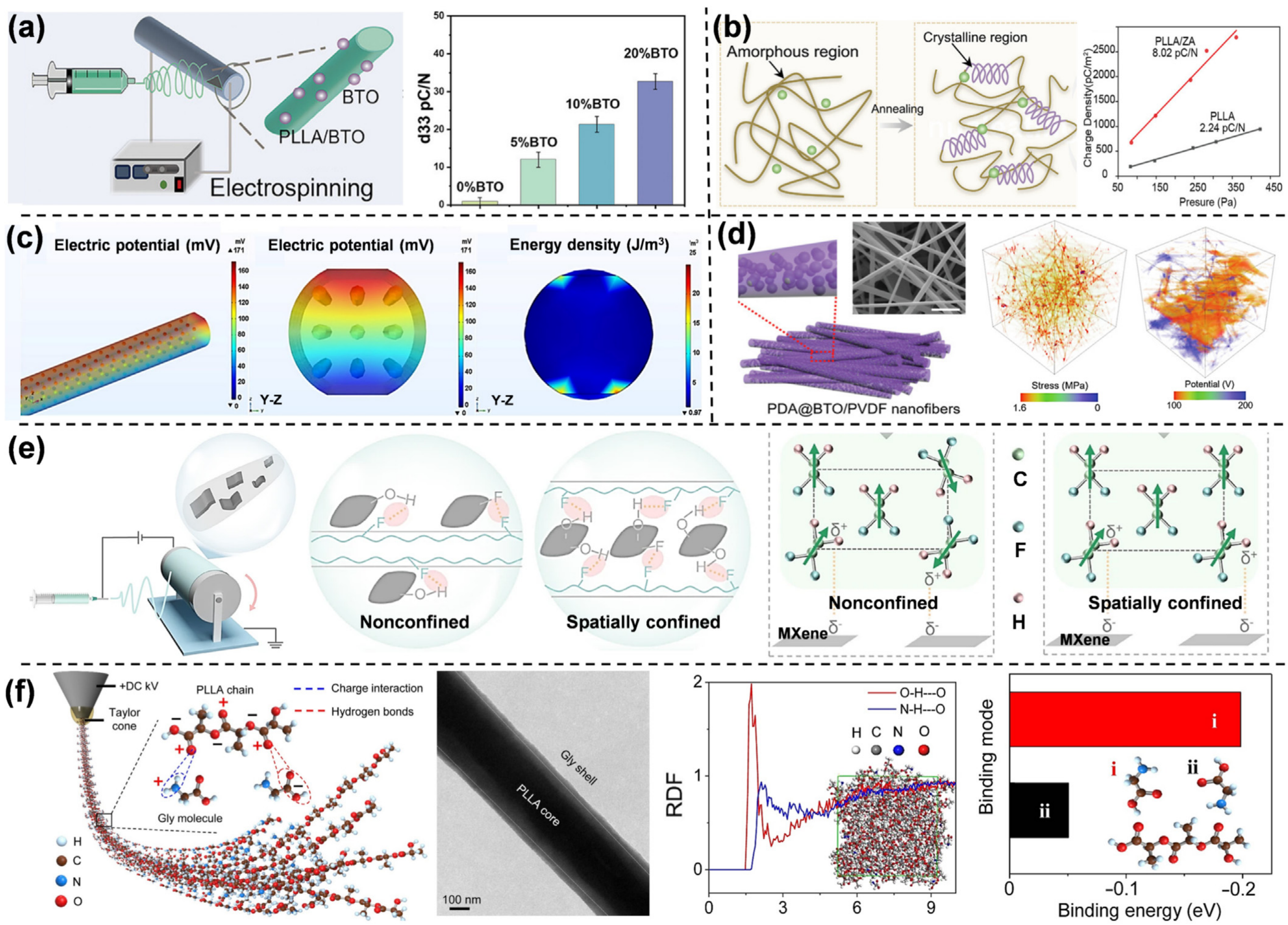

Fig. 5. Filler enhancement strategies. (a) Piezoelectric doping coefficient with different BTO contents on the fiber membrane. Reproduced with permission from Ref. [76], Copyright 2024, Wiley-VCH. (b) Diagram of PLLA fiber membrane crystallinity increase to enhance piezoelectric performance. Reproduced with permission from Ref. [95], Copyright 2024, Wiley-VCH. (c) Piezoelectric potential and energy density distribution of the fiber model. Reproduced with permission from Ref. [59], Copyright 2023, Elsevier. (d) Effect of PDA@BTO filler on stress and potential distribution of PVDF fibers. Reproduced with permission from Ref. [99], Copyright 2021, Wiley-VCH. (e) Spatial confinement effect of MXene in PVDF fibers and induction of molecular chain ordering. Reproduced with permission from Ref. [100], Copyright 2024, Springer Nature. (f) Schematic diagram of PLLA chain alignment induced by intermolecular interactions during electrospinning and molecular dynamics simulations. Reproduced with permission from Ref. [102], Copyright 2024, The American Association for the Advancement of Science.

signals on piezoelectric fibers can be categorized as follows: (I) cellular traction force, (II) body movement, (III) US-mediated, and (IV) other physical stimuli mediated (magnetic/sound field mediated, etc.) (Fig. 6).

4.1. Cellular traction force

The electric potential generated by cells adhering to the piezoelectric fibers can counteract the cells to deliver electrical stimuli, thus promoting tissue formation [105]. As illustrated in Fig. 7a, the COMSOL simulations reveal the generation of significant positive and negative potentials near the adhesion sites, and that the potentials of the piezoelectric fibers are positively correlated with both the number of adhesion sites and the strength of the applied force [106]. Relevant studies have shown that cell traction forces generated during cell growth and migration can deform piezoelectric fibers, thereby generating piezoelectric signals [95]. The piezoelectric signals generated during MSCs' growth and migration can accelerate their osteogenic differentiation and mineralization (Fig. 7b). Nevertheless, the specific magnitude of the traction and potential generated by the cells on the piezoelectric fibers warrants further clarification.

4.2. Body movement

The source of the electrical signal in the piezoelectric fibers can be the body's movement/exercise routine, particularly in the context of motor system treatments. For example, Zhu et al. [107] used a treadmill to motivate rats to exercise, thereby stimulating the implanted fiber scaffold to generate electrical signals for rotator cuff repair (Fig. 7c). Similarly, the healing performance of thigh skin wounds was observed by training the mice to exercise through a closed running wheel, and the pulling of the thigh muscles provided ES to the fibrous scaffolds to promote wound healing [108]. Compared with the control group, the exercise group exhibited greater neovascularization with a more complete lumen structure (Fig. 7d). This ES mediated by body movement can be well integrated with exercise rehabilitation training for better tissue regeneration.

4.3. US-mediated

In addition to the aforementioned cellular forces and body movements to perform force-electrical conversion, the controllable, portable, and non-invasive external stimuli-mediated ES

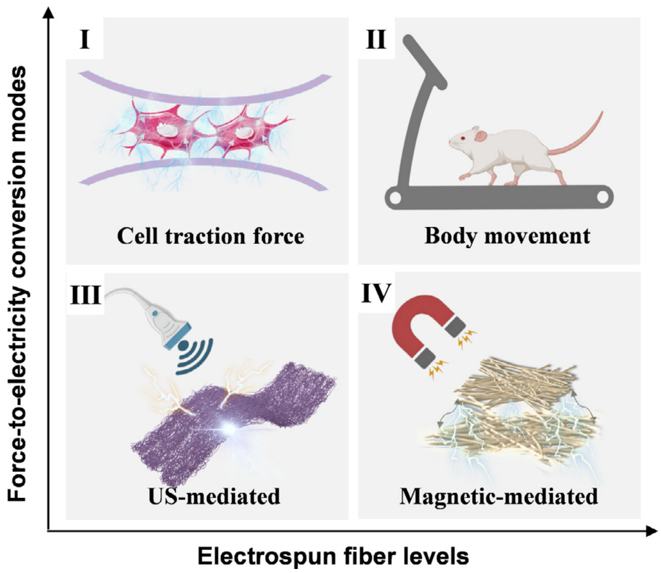

Fig. 6. Activating methods for piezoelectric stimulation based on electrospun fibers.

therapy has been widely investigated in recent years. Among them, US-mediated ES has made promising progress in the studies of stem cell differentiation [109], bone differentiation, and nerve regeneration [110]. As shown in Fig. 7e, intracellular calcium ion changes were monitored using the calcium fluorescent probe Fluo-4 AM. Following the US application, the fluorescence intensity within cells on the pcm-PLLA scaffolds increased markedly compared with the control group. These results suggest that the piezoelectric effect triggered by US can activate calcium channels on the cell membrane, thereby influencing osteogenic differentiation [111]. Under US activation, the prepared fiber scaffolds activated both membrane protein Piezo1 and calcium channels, elevating intracellular Ca^{2+} concentration and activating the downstream Ras/MAPK and PI3K/Akt signaling pathways (Fig. 7f) [9]. They ultimately promoted the neural differentiation of MSCs, as well as the secretion of neurotrophic factors and VEGF. More importantly, the low cost, high biosafety, and portability of US can be very convenient for sports medicine and home therapy [112]. As an external stimulation device, the thermal effects generated by US are unavoidable. It is necessary to control the frequency and monitor temperature in real time, ensuring that the US produces ES rather than other physical factors.

4.4. Other physical stimuli mediated

Apart from the commonly used US-mediated protocols, ES treatments mediated by other external stimuli based on piezoelectric fiber platforms are uncommon, primarily due to limitations in tissue penetration depth and portability [33]. However, similar to the US, the sound waves propagated by the horn can transmit electrical signals to cells, thus better regulating the execution of cellular behaviors and functions [108,113]. Recently, magneto-electric fiber scaffolds have attracted widespread attention under their unique magnetic-mechanical conduction-electrical induction cascade coupling [114]. Specifically, when subjected to an external magnetic field, the magnetic material will shift and rotate between magnetic domains, resulting in mechanical deformation. At the same time, adjacent piezoelectric fibers can generate a corresponding piezoelectric potential. As shown in Fig. 7g, by adjusting the loading of $CoFe_2O_4$ (CFO) nanoparticles, the PLLA/CFO fiber membrane can be endowed with excellent cascade control of mechanical deformation-piezoelectric response with the assistance of the magnetic field. The magnetoelectric synergistic effect could promote the sodium-potassium pump expression, which led to an increase in intracellular Ca^{2+} concentration (Fig. 7h) [115]. Future research needs to explore more precise and smarter methods of force-electrical switching activation to establish more effective personalized treatment protocols.

5. Piezoelectric electrospun fibers for tissue regeneration

Electrical signals play a central role in the physiological maintenance and development of electroactive tissues, including nerves, the heart, bones, skin, and skeletal muscles. For example, transmembrane potentials mediated by ion channels (resting potential ∼−70 mV, action potential ∼30 mV) guide axonal extension toward specific directions and synapse formation during neural development. The heart's rhythmic electrical impulses form precise excitation-contraction coupling, ensuring sequential contraction of the atria and ventricles to maintain effective cardiac output (resting potential ∼−90 mV, action potential ∼30 mV) [1]. Transepithelial potentials in skin tissue generate lateral electric field gradients of 40–200 mV/mm between injured and surrounding areas during tissue injury. These drives directed Na^+ and Cl^- ion flow, generating endogenous currents of 4–10 μA/cm^2. Studies also pointed out that the d_{14} in the dermis layer of skin tissue is 0.05–0.1 pC/N, while that in the epidermis layer is 0.01–0.03 pC/N [116]. In bone tissue, electrical activity originates from the non-centrosymmetric structure of collagen fibers, which alters axial polarization and generates piezoelectric effects [117]. Reports indicate the piezoelectric coefficient of the femur under shear stress is 0.7 pC/N, while the tibia exhibits higher values ranging from 7.66 to 8.48 pC/N [118]. Cartilage's piezoelectric response depends on collagen fiber deformation under shear forces, generally making electrical signals more pronounced in deeper cartilage layers.

Therefore, researchers can leverage the intrinsic piezoelectric properties/electrical signals within biological tissues to establish a piezoelectric theoretical foundation, thereby inspiring innovative therapeutic strategies. Piezoelectric electrospun fibers integrate the advantages of bioelectrical modulation and fibrous scaffolds, allowing the preparation of fibrous scaffolds with customized structures and electroactivity [119]. Such scaffolds not only provide physical support for cell growth but also generate electrical signals through the piezoelectric effect to better regulate cell behavior [120]. This multimodal integration of signals can more comprehensively and efficiently mimic the complex microenvironment *in vivo* [35]. It has been shown to have great potential in skin tissue, nerve tissue, cardiovascular tissue, bone tissue, cartilage tissue, and other tissue regeneration [23]. This section will describe and summarize the progress of various applications of piezoelectric electrospun fibers in tissue engineering, offering insights into the design of next-generation tissue engineering scaffolds from the perspective of piezoelectric properties.

5.1. Skin tissue engineering

The unique potential of piezoelectric fiber scaffolds in skin tissue engineering can be attributed to two aspects. On the one hand, the piezoelectric effect generates microcurrent and reactive oxygen species (ROS), which disrupt bacterial membranes, thereby conferring broad-spectrum antimicrobial activity [121]. Meanwhile, piezoelectric fiber scaffolds can also mimic endogenous electrical signals to activate fibroblast migration, angiogenesis, and growth factor secretion, accelerating wound tissue repair and regeneration [108]. Compared with traditional dressings, piezoelectric scaffolds do not require an external power supply

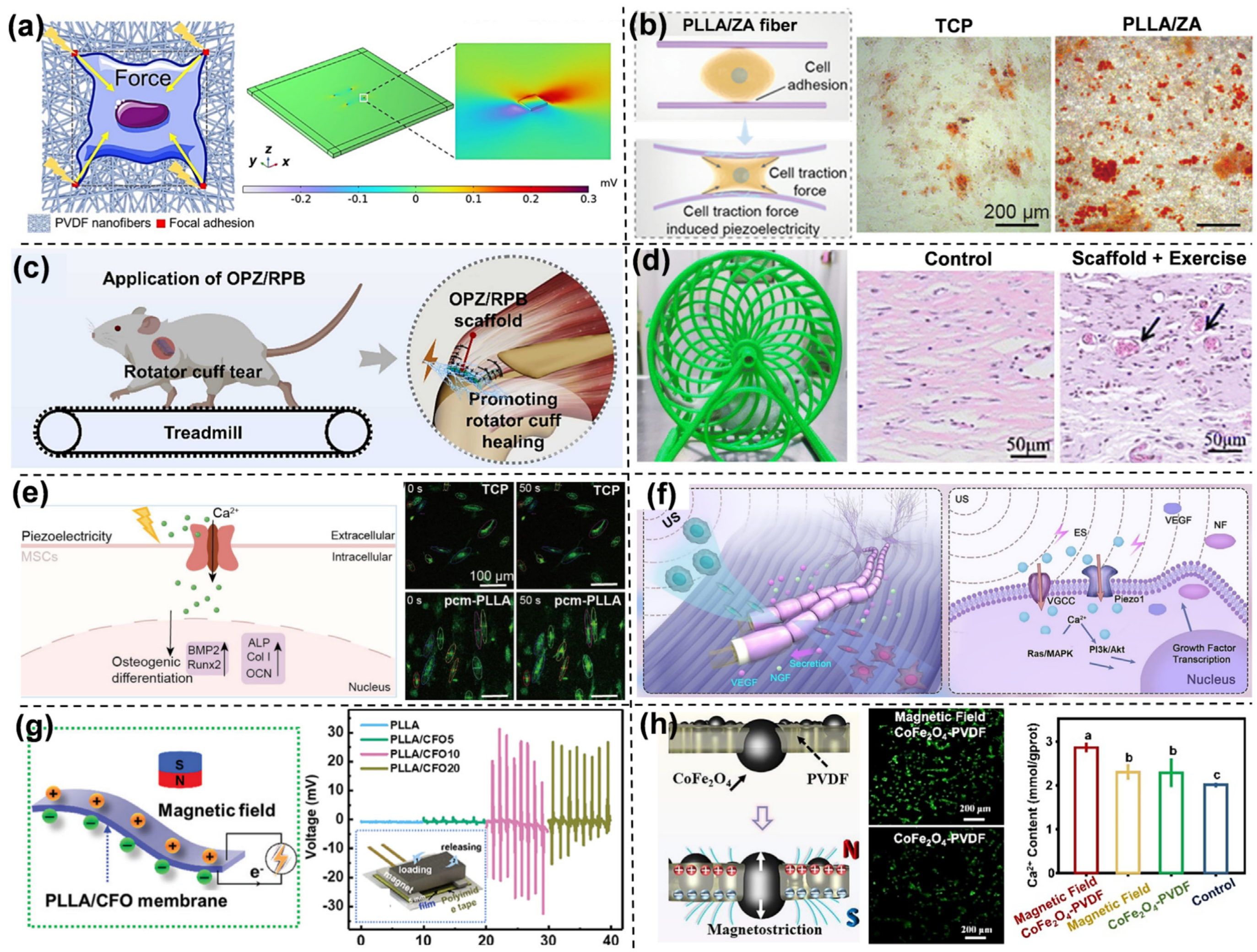

Fig. 7. Different ways for generating electrical signals on piezoelectric electrospun fibers. (a) Schematic of cell adhesion and piezoelectric potential distribution on PVDF nanofibers. Reproduced with permission from Ref. [106], Copyright 2024, Elsevier. (b) Cell force-mediated electrical stimulation promotes calcium deposition. Reproduced with permission from Ref. [95], Copyright 2024, Wiley-VCH. (c) Exercise-activated local electrical stimulation to promote tendon and bone healing. Reproduced with permission from Ref. [107], Copyright 2024, Elsevier. (d) The HE staining indicates that exercise promotes wound healing. Reproduced with permission from Ref. [108], Copyright 2023, The Royal Society of Chemistry. (e) Activation of cell membrane calcium channels and changes in calcium flow in response to piezoelectric signals. Reproduced with permission from Ref. [111], Copyright 2024, Elsevier. (f) A diagram of the electrical stimulation promotes paracrine secretion. Reproduced with permission from Ref. [9], Copyright 2025, Cell Press. (g) Magnetoelectric responsiveness and piezoelectric output of PLLA/CFO fibers. Reproduced with permission from Ref. [114], Copyright 2024, Wiley-VCH. (h) Magnetic fibers enhance intracellular Ca^{2+} concentration to regulate cardiomyocytes. Reproduced with permission from Ref. [115], Copyright 2024, Elsevier.

or antibiotics, reducing the risk of drug resistance. Their highly porous fibrous structure promotes cell infiltration and nutrient exchange, further optimizing the healing microenvironment [122].

As shown in Fig. 8a, the pulsed charge generated by the piezoelectric implant under US stimulation is transferred to the bacterial biofilm, effectively disrupting its macromolecular components, such as membrane proteins. This disruption further impairs the electron transport chain of the biofilm, inhibiting the proliferation of *E. coli* [123]. This piezoelectric implant also showed successful anti-infective efficacy in a rat cecum ligation and perforation model. When PVDF fibers and graded TiO_2 nanotubes (NTs) form a three-dimensional scaffold (3DMA), the bacteria reach the NT layer and are killed by the positive charge trap [124]. Compared to the pure titanium group (PT), 3DMA significantly inhibited *S. aureus* and *E. coli* colonization to 30.4 % and 61.9 %, respectively (Fig. 8b). While in response to LPS and IFN-γ stimulation, the 3DMA group suppressed the expression of iNOS (an inflammatory marker in M1 macrophages) and slightly increased the expression of CD206 (a marker highly expressed in M2 macrophages) (Fig. 8c). This can be attributed to the mechanical interaction between macrophages and PVDF fibers, generating an electric field to modulate the anti-inflammatory phenotype.

Combining piezoelectric fibers with external US to produce controlled ES can be used for wound healing and preventing bacterial infections. As shown in Fig. 8d, the group receiving the PLLA scaffold and US demonstrated the fastest rate of wound healing and new skin formation compared to all control groups [125]. Piezoelectric fibers can also be integrated with other therapies to promote tissue regeneration [126]. Under the combined effect of piezoelectric and photothermal effects, PLLA fibers confer antimicrobial properties by generating ROS through piezoelectric polarization. Meanwhile, oxidation products and ES enhance cell proliferation and migration, thereby accelerating wound healing [127]. And the photothermal effect upregulates the HSP90 expression to provide mild heat to accelerate wound regeneration (Fig. 8e). Overall, the multifunctional integration, biocompatibility,

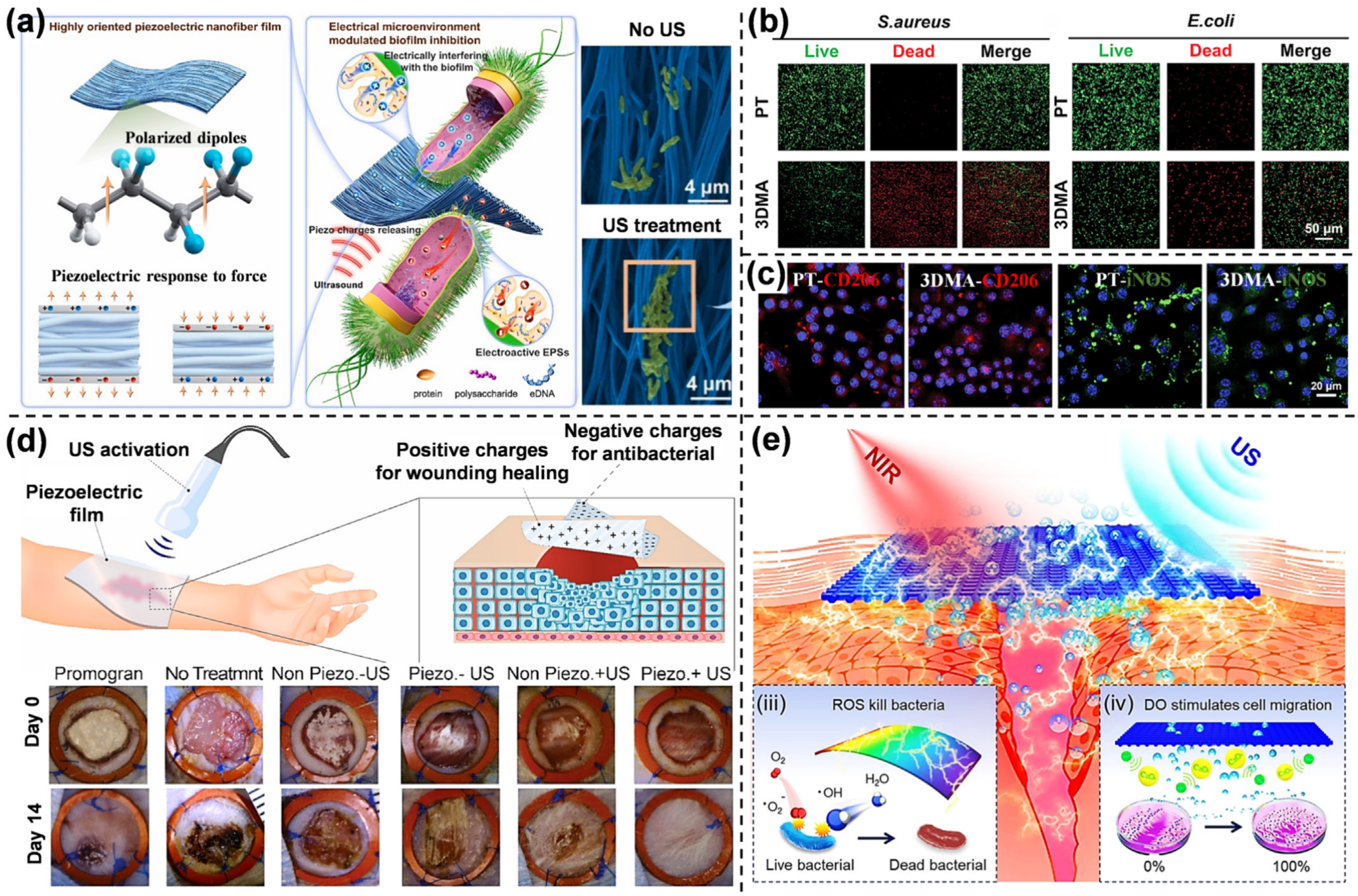

Fig. 8. Piezoelectric electrospun fiber-based platform for antibacterial and wound healing. (a) A schematic diagram for the inhibition of biofilms by polarized dipole-activated electrical effects in piezoelectric fibers. Reproduced with permission from Ref. [123], Copyright 2023, Elsevier. (b) Live/dead images of *S. aureus* and *E. coli* cultured in different groups, and (c) immunofluorescence images of macrophages in different groups. Reproduced with permission from Ref. [124], Copyright 2023, Wiley-VCH. (d) A schematic illustration of the wound healing promotion and antimicrobial effect of piezoelectric PLLA fibers, and representative images of wound healing in each group at different time points. Reproduced with permission from Ref. [125], Copyright 2023, Elsevier. (e) Synergy of piezoelectric and photothermal effects for the treatment of infected wounds. (iii) Under US applied, PLLA generates ROS due to its piezoelectric polarization properties, thereby conferring antibacterial activity. (iv) The dissolved oxygen (DO) generated promotes cell proliferation and migration, accelerating wound healing. Reproduced with permission from Ref. [127], Copyright 2023, Elsevier.

and intelligent potential of piezoelectric fibers provide an innovative solution for safe and efficient smart wound dressing design and infected wounds.

5.2. Cardiovascular tissue engineering

With their unique electromechanical coupling characteristics, piezoelectric fibers provide breakthrough solutions for cardiovascular tissue engineering, covering areas such as myocardial repair, cardiac pacing, vascular repair, and blood flow monitoring [128]. It is expected to facilitate the leap from static replacement to dynamic functional reconstruction in cardiovascular repair [129].

In myocardial repair, piezoelectric fibers can simulate the electrophysiological microenvironment of cardiomyocytes, promoting the regeneration of damaged tissues through electrical signaling. As shown in Fig. 9a, the incorporation of bilayer graphene nanoflakes (BGF) enhanced the electrical conductivity and piezoelectric properties of PVDF nanofibers. Immunofluorescence staining and quantitative analysis showed that H9c2 cells cultured and stimulated on BGF/SDF scaffolds exhibited greater differentiation and expressed higher levels of α-actin. This indicates that ES could promote higher expression of cardiac-specific markers by forming reinforced myonodal structures [130]. It was previously mentioned that $CoFe_2O_4$/PVDF fiber scaffold can synthesize sodium-potassium enzymes, increasing intracellular Ca^{2+} (Fig. 9b). This triggers cardiomyocyte contraction to overcome the non-conductivity of damaged cardiomyocytes [115].

It is worth mentioning that piezoelectric fiber-based devices are used in cardiac pacing, where their self-powered feature can reduce reliance on batteries in conventional pacemakers and enable more precise rhythm regulation. After implanting a piezoelectric nanogenerator (PNG) prepared from piezoelectric fibers into the lateral wall of the left ventricle, the PNG generated voltages synchronized with the heartbeat and the corresponding ECG [131]. The PNG implanted *in vivo* could successfully harvest energy from each heartbeat for pacing (Fig. 9c). In addition, vascular graft scaffolds constructed with piezoelectric fibers can optimize the endothelialization process through dynamic electrical response and provide real-time feedback of intravascular blood flow information. As shown in Fig. 9d, integrated pressurized vascular grafts (PVGs) can accurately assess the "unblocked-blocked-unblocked" status in artificial artery models. Stimulated by pulsatile blood flow, the PVG assessed pulse frequency in rabbits and demonstrated superior accuracy in hemodynamic monitoring compared to commercially available pressure sensors, supporting postoperative assessment [132]. This "battery-free" piezoelectric scaffold integrates tissue engineering and ES, providing a great promise for cardiovascular repair, dynamic monitoring, and personalized therapy, which are expected to drive the development of next-generation cardiovascular implantable devices.

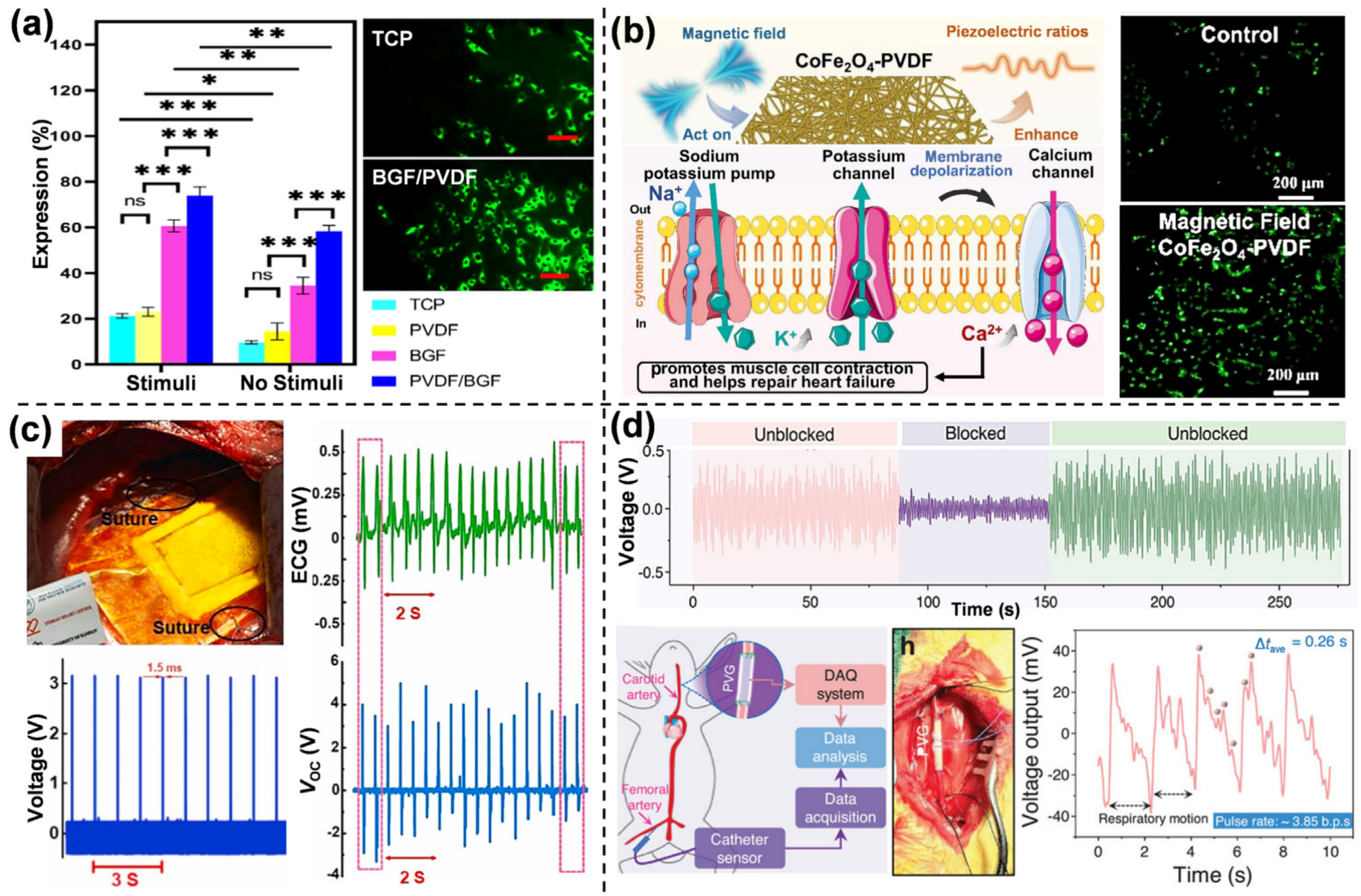

Fig. 9. Piezoelectric electrospun fibers for cardiovascular tissue engineering. (a) Immunofluorescence images and quantitative analysis of α-actinin in H9c2 cultured on different scaffolds. Reproduced with permission from Ref. [130], Copyright 2024, American Chemical Society. (b) A schematic diagram of the enhanced sodium-potassium enzyme and Ca^{2+} concentration in cardiomyocytes by magneto-electric fibers. Reproduced with permission from Ref. [115], Copyright 2024, Elsevier. (c) The open-circuit voltage of the piezoelectric fiber generator *in vivo*, and the corresponding ECG signal. Reproduced with permission from Ref. [131], Copyright 2021, Elsevier. (d) Voltage output changes in unobstructed and obstructed states after scaffold implantation, as well as the schematic of the *in vivo* implantation experiment and the actual measured outputs. Reproduced with permission from Ref. [132], Copyright 2024, Wiley-VCH. ns: no significance; *P < 0.05, **P < 0.01, ***P < 0.001.

5.3. Nerve tissue engineering

It is well known that the electrical signals generated by piezoelectric fibers can activate intracellular signaling pathways, mimic the electrophysiological microenvironment, and modulate neuronal membrane potential and calcium channel activity, thereby accelerating axonal extension and myelin formation [133]. The synergistic effect of this piezoelectric fiber topology and dynamic ES can support the regeneration and functional recovery of nerve tissues. For example, the growth rate and intracellular Ca^{2+} concentration of neuronal cells cultured on PLLA nanofibers were approximately twofold higher than those of normal cells [134]. ZnO-containing fibrous scaffolds can generate electrical signals for Schwann cell-mediated axon growth via force-electric conversion [135]. Piezoelectric nerve conduits prepared using PCL/ZnO nanofibers could generate endogenous piezoelectric stimulation, promoting sciatic nerve regeneration [37]. Immunostaining of the neurofilament markers NF 200 (green) and S100 (red) showed that nerve regeneration was considerably promoted, exhibiting superior sciatic nerve repair (Fig. 10a). In our recent work, inspired by the process of embryonic neural development, a neural conduit (ND-SENS) consisting of a piezoelectric fiber membrane with ordered micro-nanostructures and a hydrogel loaded with stem cells was developed to mimic the physical and chemical signals generated by embryonic development [9]. After placing DRGs in ND-SENS scaffolds for 10 d of co-culture, DRGs exhibited highly oriented axons, both in terms of maximum length and average length, and the highest percentage of Tuj1-positive cells in the ND-SENS w/o US group compared to the ND-SENS group (Fig. 10b). Compared with other experimental groups, the ND-SENS group had the highest level of axon diameter and regenerated myelin sheath regeneration, close to the level of the autograft group.

The electrical signals generated on the piezoelectric fibers can also synergistically enhance drug release and therapeutic mechanisms, thereby improving drug efficacy and tissue regeneration. As shown in Fig. 10c, the piezoelectric nanofiber-derived hydrogel catheter has a synergistic effect of US-triggered ES and drug release [19]. This means that it not only induces directional neurite extension and promotes axon growth via ES but also enables controlled nerve growth factor release via US triggering. In addition, the US-activated piezoelectric fibers have good tissue penetration, which endows non-invasive stimulation and effective delivery to deep tissues. As shown in Fig. 10d, US-activated piezoelectric fibers can be a biodegradable ultrasonic transducer that opens the blood-brain barrier and facilitates deep-brain drug delivery [74]. When FITC-labeled dextran was used in the drug model, significant levels of green fluorescent signals were found around microvessels in the mouse brain in the piezoelectric fiber-constructed US transducer and microbubble-treated group. This offers a promising approach for diagnosing and treating deep-seated neurological disorders in the brain.

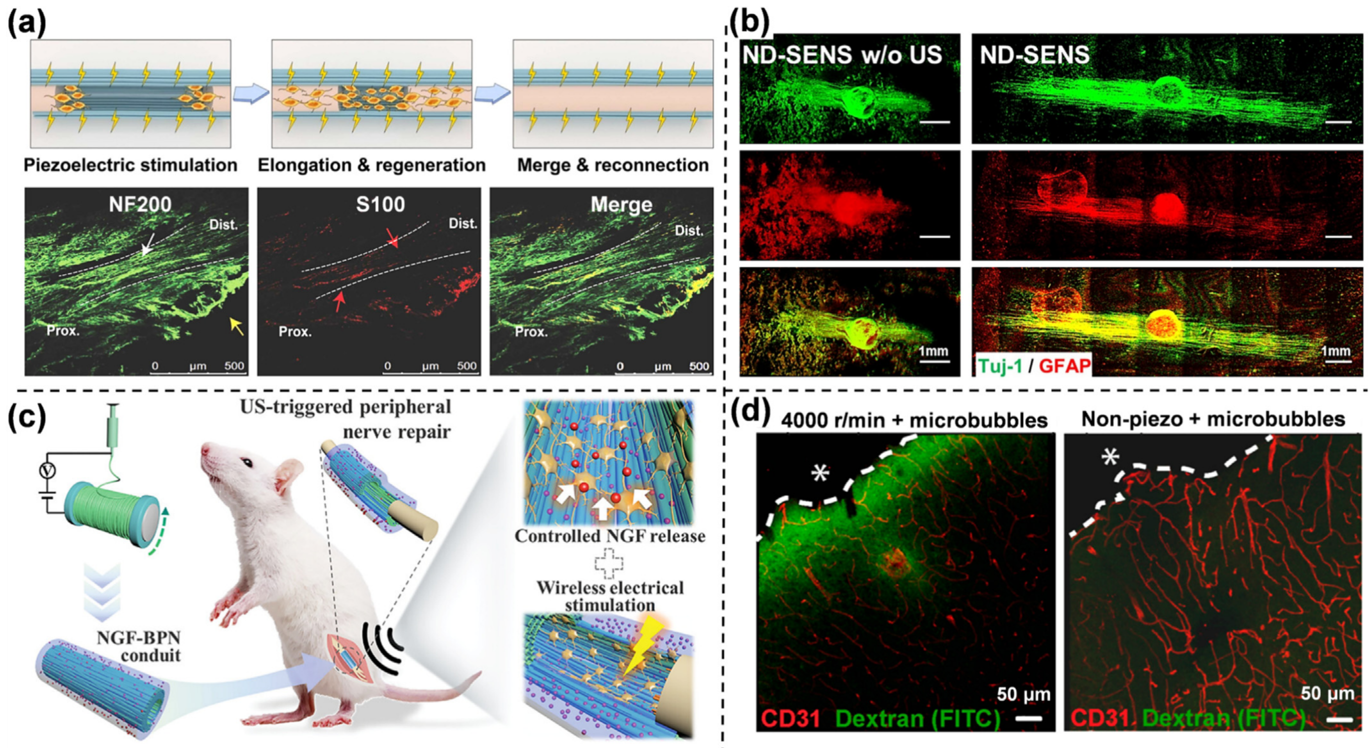

Fig. 10. Piezoelectric electrospun fibers for nerve tissue engineering. (a) A schematic diagram of piezoelectric stimulation to promote Schwann cell recruitment and regeneration of injured axons and post-implantation fluorescent staining labeling of NF200 and S100. Reproduced with permission from Ref. [37], Copyright 2022, Elsevier. (b) Images of DRG growth status in different groups, where green represents Tuj1 and red represents GFAP. Reproduced with permission from Ref. [9], Copyright 2025, Cell Press. (c) A schematic diagram of a piezoelectric nanofiber-derived hydrogel nerve conduit for peripheral nerves. Reproduced with permission from Ref. [19], Copyright 2024, Wiley-VCH. (d) Representative images show the signal of dextran (FITC) with different treatments. Reproduced with permission from Ref. [74], Copyright 2020, National Academy of Sciences.

Moreover, piezoelectric fiber scaffolds enable synergistic neurostimulation with US and electricity while treating diseases associated with nerve damage [38]. However, current research remains focused on sciatic nerve regeneration. It is hoped that more efficient piezoelectric fiber scaffolds can be developed in the future to explore the synergistic mechanism of multimodal stimulation, to advance their application in central nerve repair, neurodegenerative diseases, and pain management.

5.4. Bone tissue engineering

As a non-invasive physical therapy, ES is effective in promoting bone regeneration [136]. Studies have shown that ES can modulate the directed differentiation of MSCs and osteoblast activity [113,137]. This can be attributed to enhanced calcium ion influx and expression of osteogenesis-related proteins, which accelerate bone matrix deposition and remodeling [138]. Notably, bone itself has piezoelectric properties, and mechanical loading induces endogenous electrical signals in bone tissue [139]. Based on this, piezoelectric fiber scaffolds can mimic this physiological mechanism by converting mechanical energy into ES, providing a dynamic microenvironment for bone regeneration [119]. In addition, piezoelectric fibers are structurally bionic and mechanically adaptable, allowing the components to be adjusted to be both flexible and degradable to meet the needs of bone defects. As shown in Fig. 11a, a porous 3D scaffold was obtained by combining piezoelectric ZnO/PHB nanofibers and chitosan (CS) [90]. After filling the bone defect area, it can generate controlled ES under US stimulation, which in turn remodels the electrical microenvironment and enhances osteogenic activity through the activatable calmodulin (CaM)/calcineurin (CaN)/nuclear factor of activated T cells (NFAT) signaling pathway. The CT images in Fig. 11b show bone regeneration at 4 and 8 weeks. Compared with the control group, the CS/PHB@ZnO + US group demonstrated superior bone defect repair, which may be related to the unique 3D structure and the promoting effect of ES. After 8 weeks of implantation, the CS/PHB@ZnO + US group achieved a BV/TV ratio of 66 %, with regenerated bone tissue exhibiting a denser structure.

During the bone regeneration phase, it is important to consider the initial recruitment of stem cells and the subsequent regeneration of immune and vascular systems [140]. In our work, a biomimetic tissue-engineered scaffold (pcm-PLLA) for the bone microenvironment was developed, which can generate piezoelectric signals to activate cytosolic calcium channels and PI3K signaling pathways to promote osteogenic differentiation [111]. In addition, the scaffold can also promote macrophage M2 polarization and angiogenesis (Fig. 11c). At 12 weeks of implantation in the cranial defect area, the thickness of the new bone in the pcm-PLLA + US group was already almost the same as that of the original bone (BV/TV = 94.4 %), which was much greater than that in the PLLA group (BV/TV = 70.7 %). The coupling of electrical signals provided by the drug and the piezoelectric fibers can also promote the regeneration and remodeling of the neural, vascular, and immune microenvironments during the bone repair process [141].

Occasionally, it is also necessary to consider repairing the upper cartilage and treating bone infections or even bone tumors when regenerating bone tissue. As shown in Fig. 11d, the coupling of electrical and chemical signals (sustained release of bioactive Sr^{2+} and SiO_3^{2-} ions) was achieved by combining PLLA with bioceramics ($SrSiO_3$). The synergistic enhancement of cartilage formation and BMSC osteogenic activity can be achieved under low-intensity pulsed ultrasound (LIPUS) stimulation [142]. At 8 weeks,

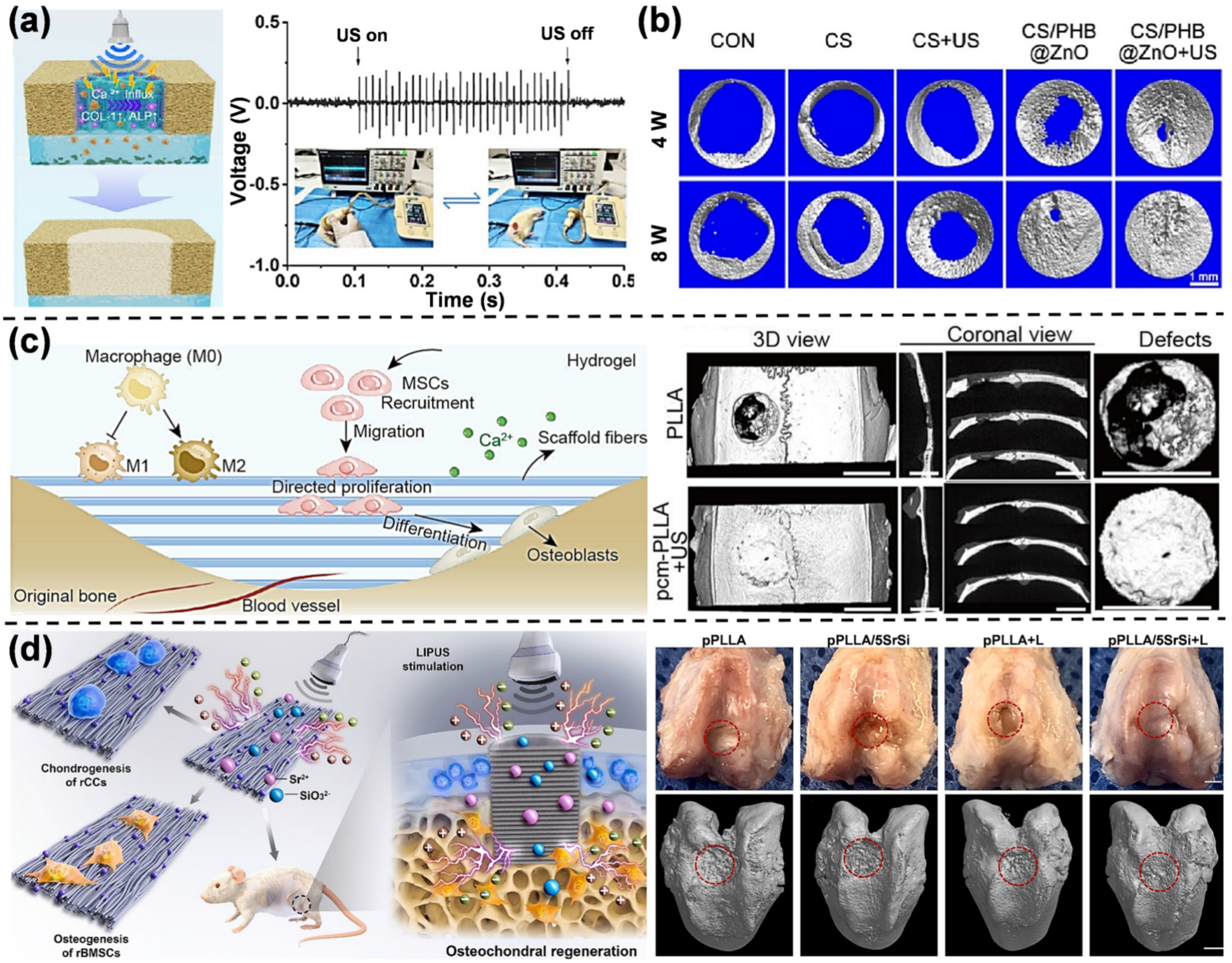

Fig. 11. Piezoelectric electrospun fibers for bone tissue engineering. (a) Schematic of bone regeneration of the scaffold and the generated piezoelectric output under US stimulation. (b) Micro CT images of new bone formation after 4 and 8 weeks of implantation of different scaffolds. Reproduced with permission from Ref. [90], Copyright 2023, Elsevier. (c) Schematic representation of the biological effects of the scaffold *in vivo* and the area of new bone after 12 weeks (scale bar = 5 mm). Reproduced with permission from Ref. [111], Copyright 2024, Elsevier. (d) The electrical signals generated by LIPUS stimulation and the sustained release of ions synergistically promote cartilage regeneration and subchondral bone reconstruction, as well as digital photographs and micro-CT images of the defect area at 8 weeks postoperatively in different groups. Reproduced with permission from Ref. [142], Copyright 2025, Elsevier.

compared to the limited repair in the other groups, the pPLLA/5SrSi + L group demonstrated cartilage-like organization similar to the natural cartilage. Micro-CT further characterized complete subchondral bone repair in the experimental group, enabling integrated cartilage and subchondral bone repair. Moreover, multiple stimulation coupling can be used to achieve bone regeneration along with the treatment of bone diseases [143]. For example, spatiotemporal modulation of osteosarcoma elimination and new bone regeneration can be accomplished by combining piezoelectric and photothermal effects [144]. In the future, more smart piezoelectric scaffolds should be developed in combination with other technologies to dynamically regulate the bone regeneration microenvironment [52], thus promoting the development of personalized bone repair treatment.

5.5. Cartilage tissue engineering

As a vascular-free tissue, cartilage possesses limited self-repair capacity. ES can influence chondrocyte proliferation, differentiation, and matrix synthesis, thus promoting cartilage repair [145]. Moreover, piezoelectric fibers can generate local bioelectric fields under mechanical loading, mimicking the piezoelectric microenvironment of natural cartilage [146], and can achieve synchronous regeneration that matches the mechanics of cartilage tissue.

As shown in Fig. 12a, an injectable hydrogel formed by embedding PLLA staple fibers into a collagen matrix can generate electrical signals on its own under US activation, thereby enhancing cell migration and inducing stem cells to secrete TGF-β1 to promote cartilage formation [147]. After injection into a critical size defect of osteochondral bone in rabbits for 2 months, the piezo hydrogel (Piezo + US), which received US activation, had an improved hyaline cartilage structure and good mechanical properties (Fig. 12b), which can be attributed to the fact that the electrical signals recruited cells and induced the cells to secrete TGF-β cytokines and to differentiate towards the chondrocytes, and finally to deposit the cartilaginous matrix [148]. Similarly, biodegradable piezoelectric scaffolds can be prepared by layer-by-layer stacking of collagen and PLLA fiber membranes. This scaffold can generate controllable piezoelectric signals under applied force or joint load-

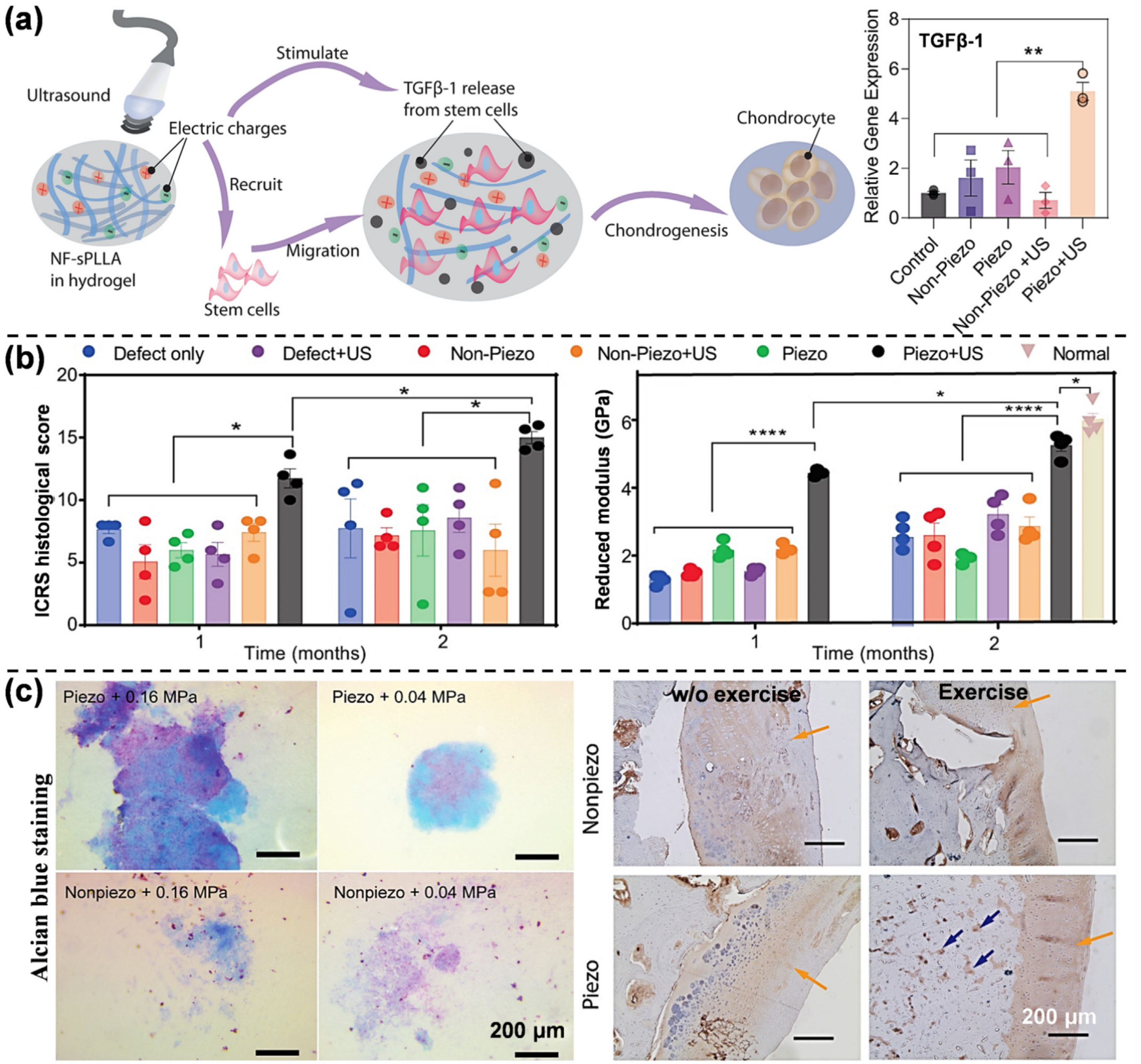

Fig. 12. Piezoelectric electrospun fibers for cartilage tissue engineering. (a) An illustration of the promotion of chondrogenesis by recruiting stem cells and inducing the generation of TGF-β1. (b) ICRS histologic assessment and evaluation of new cartilage modulus within the defects in different groups. Reproduced with permission from Ref. [147], Copyright 2023, Springer Nature. (c) Alcian blue staining after 14 d of incubation at different pressures and type II collagen staining after 1 month of scaffold implantation. Reproduced with permission from Ref. [149], Copyright 2022, The American Association for the Advancement of Science. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{****}P < 0.0001$.

ing, and promote cell migration or recruitment. It also induces endogenous TGF-β through the calcium signaling pathway and promotes cartilage formation [149]. Cultured adipose-derived stem cells (ADSCs) had more glycosaminoglycan production than ADSCs cultured on non-piezoelectric scaffolds when the external force was at 0.16 and 0.04 MPa (Fig. 12c). Immunohistochemical staining also demonstrated that chondrocytes within the regenerative defects in the group shown to have been given exercise exhibited increased expression of type II collagen, showing the great advantage of combining sports medicine and piezoelectric scaffolds. This combination of ES through physical therapy, such as exercise, can be used to treat not only cartilage-related diseases but also to regenerate other damaged tissues.

5.6. Other tissue engineering

In addition to the common clinical scenarios mentioned above, piezoelectric fibers are also employed in several applications, including skeletal muscle, tendon, and rotator cuff-related tissues [150]. For example, piezoelectric poly-3-hydroxybutyrate/poly-β-alanine aligned fiber scaffolds can mimic skeletal muscle tissue by virtue of their superior chemical, morphological, mechanical, and electroactive properties [151]. Tendon is an important weight-bearing tissue involved in the transmission of tension between muscle and bone [152]. Similar to bone and cartilage, compact, highly aligned piezoelectric collagen progenitor fibers are primarily responsible for mechanical transduction in tendon tissue. Culturing MSCs on PLLA fibers, the fibers not only directed the rearrangement of the actin cytoskeleton but also induced the differentiation of MSCs into tendon lineages [153]. It was also demonstrated that PCL fibers loaded with the piezoelectric tetragonal crystal system $SrTiO_3$ can mimic the endogenous electrical microenvironment of tendon tissue, upregulate the expression of tendon-associated genes through Wnt, MAPK, and PI3K-Akt signaling pathways, reduce inflammatory responses, and improve collagen deposition [154].

ES also has a positive regulatory role in achieving synchronized regeneration at the tendon-bone interface. The mechanical requirements for tendon-bone healing were met by preparing oriented PLLA/ZnO and randomly aligned PLLA/BTO bilayer fibrous membranes. The ZnO and BTO nanoparticles endowed the fibrous scaffolds with piezoelectric responsiveness, inducing tendonogenic and osteogenic differentiation, respectively [107]. The combination of piezoelectric scaffolds and appropriate exercise training was verified in a rat rotator cuff tear model to promote rotator cuff repair, providing new insights into the regeneration of other weight-bearing/motor function tissues. Moving forward, piezoelectric fibers are expected to play a role in more widespread tissue regeneration fields by modulating multiple cell behaviors and tissue microenvironments. For example, combining piezoelectric materials and growth factors enables the design of piezoelectric fiber scaffolds with specific electrical properties and bioactivity. Alternatively, coupling photothermal and drug delivery systems can achieve multimodal modulation, promoting the precise repair and functional reconstruction of multi-tissue interfaces and deep organs.

6. Conclusion and perspectives

In summary, Piezoelectric electrospun fibers have emerged as promising piezoelectric scaffolds in tissue engineering. These piezoelectric electrospun fibers hold the potential to revolutionize existing therapies and demonstrate promise in key areas of tissue engineering, including skin tissue, cardiovascular tissue, nerve tissue, bone tissue, cartilage tissue, and other tissue engineering applications. Among these, approaches such as microarchitecture self-enhancement strategies, piezoelectric coupling, enhanced crystallinity, stress concentration, spatial confinement, and interface-anchored enhancement strategies can improve the piezoelectric properties of electrospun fiber scaffolds. With the deepening integration and collaboration across multiple disciplines, piezoelectric electrospun fibers are poised to redefine the design paradigm of next-generation tissue engineering scaffolds, ushering in a new era of tissue remodeling regulation in regenerative medicine.

Despite the high potential of piezoelectric electrospun fibers in tissue engineering and biomedicine applications, several challenges and development opportunities remain, focusing mainly on optimizing the performance of piezoelectric fibers, the mechanism of interaction with cells and tissues, and clinical translation (Fig. 13).

6.1. Optimization of piezoelectric electrospun fibers

The development and performance optimization of piezoelectric electrospun fibers involve advancements in three key areas: novel material innovation, fiber structural design, and biodegradability and mechanical compatibility. First, the pursuit of novel piezoelectric fibers with high piezoelectric coefficients remains critical. This requires in-depth investigations into dipole alignment mechanisms and piezoelectric enhancement strategies to optimize existing fiber systems. Concurrently, integrating material genomics and machine learning enables accelerated discovery of high-performance piezoelectric materials. Artificial intelligence-driven tools can also analyze material properties, predict performance outcomes, and facilitate personalized tissue regeneration solutions [155]. Building upon this foundation, density functional theory, molecular dynamics, and other biomolecular simulations can provide theoretical insights for the development and performance optimization of fibers, such as determining spinning parameters and doping ratios, and investigating interfaces and interactions between different materials within piezoelectric composites [156]. As for structural design, advanced nanotechnology enables multiscale structural design to confer intelligent responsiveness. These endow fibers to dynamically adjust their properties to adapt to physiological environments, such as pH or temperature changes. Moreover, combining 3D printing technology or shape-memory functionality also allows precise reconstruction of complex tissue architectures [52]. For biodegradation and mechanical compatibility, developing degradable piezoelectric biomaterials represents an ideal solution for implantable scaffolds. These materials can minimize foreign body reactions and eliminate the need for secondary removal surgeries [41]. Concurrent optimization of mechanical properties to match target tissue requirements will further enhance therapeutic outcomes in tissue repair applications.

6.2. Biology and diagnostics

Although ES exhibits significant regulatory effects on various cells and tissues, the precise mechanisms underlying its cellular modulatory actions remain elusive. For example, quantitative relationships associating piezoelectric coefficients with cell growth, proliferation, and differentiation remain elusive. Establishing a "material structure-defined electrical signal-biological effect" platform provides a clear roadmap for next-generation personalized tissue engineering scaffolds. It is worth noting that a standardized protocol for evaluating the piezoelectric properties of fiber scaffolds is urgently needed (including loading conditions, applied frequency, and device composition). Future research should prioritize the mechanistic elucidation of piezoelectric fiber-cell/tissue interactions, establishing quantitative correlations among piezoelectric properties, structural parameters, and biological effects to enable precise modulation of cellular behaviors. Further development should explore "Electro-X" multimodal strategies by integrating drug delivery, bioactive factors, or combining photothermal therapy, chemo-dynamic therapy, etc., thereby achieving synergistic electro-chemo-mechanical regulation. Additionally, the combined therapeutic effects of ES, pharmacokinetics, and growth factors warrant further investigation. More interestingly, the incorporation of flexible electronics will advance the development of closed-loop therapeutic systems. These intelligent platforms can continuously monitor microenvironmental changes in damaged tissues while dynamically regulating piezoelectric fiber scaffolds via external devices, generating adaptive electrical outputs. Such integration establishes a full-cycle regulatory cascade encompassing lesion detection—electrical stimulation—tissue remodeling, ultimately propelling regenerative medicine toward intelligent feedback-driven paradigms.

6.3. Clinical translation

The ultimate goal of piezoelectric fiber development is clinical translation, which necessitates systematic solutions to post-implantation immune responses and comprehensive evaluations of long-term biocompatibility. For example, smaller nanoparticles of materials such as ZnO and BTO are more readily phagocytosed by macrophages, potentially triggering stronger inflammatory responses. The impact of their degradation products on macro-

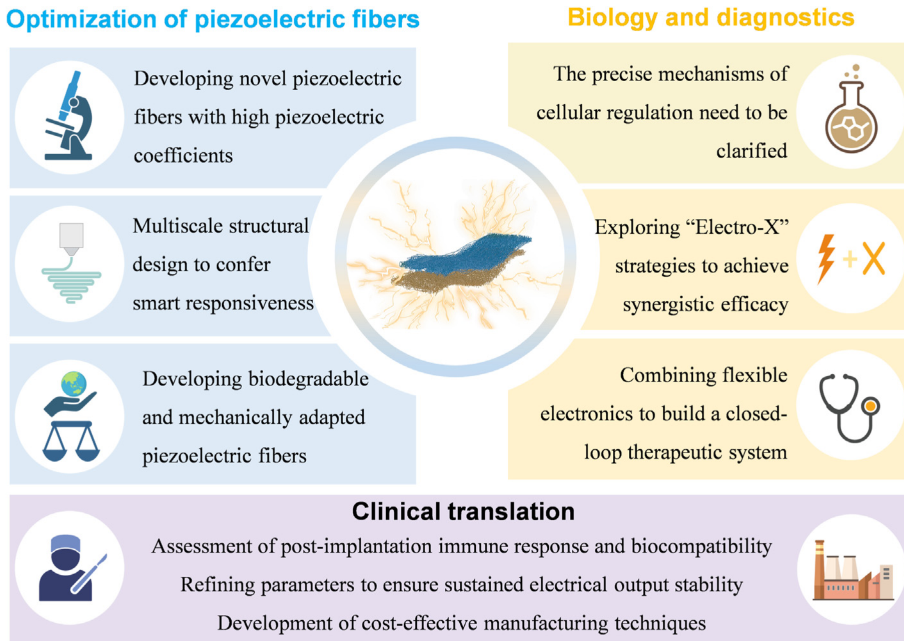

Fig. 13. Key considerations and development directions in piezoelectric fibers for tissue regeneration.

phage polarization should not be overlooked. Additionally, non-degradable or slowly degrading components like PVDF may persistently induce low-level chronic inflammation. Future research should further explore the potential genotoxic mechanisms associated with nanomaterials and evaluate long-term immune responses [157]. Within the complex biological environment inside the body, piezoelectric fibers inevitably interact with biomolecules and cells. Protein adsorption and biofouling may affect piezoelectric charge generation, altering the material's local stress distribution and piezoelectric response. Anti-protein adsorption coatings can be introduced to mitigate this effect. The long-term stability of piezoelectric fibers is also an important factor, which can be enhanced by introducing cross-linked structures and improving encapsulation techniques. Concurrently, establishing a degradation-output coupling model ensures the sustained electrical signal output throughout the expected service life.

Furthermore, methodological advancements in cost-effective fabrication techniques are critical. To achieve industrial-scale production, multi-nozzle arrays and conveyor-belt collection systems are required to enhance fiber output efficiency. Concurrently, optimizing and monitoring parameters such as jet voltage, flow rate, and environmental conditions ensures stability in fiber diameter, morphology, and piezoelectric properties. For developing complex structures, multi-coaxial nozzle technology and auxiliary collection techniques are required. Incorporating in-situ monitoring technology enables real-time feedback on fiber deposition status, which, combined with machine learning algorithms, to adjust process parameters. The addition of fillers should consider their dispersibility and stability during electrospinning, balancing functional performance with cost control. Furthermore, the entire production process should be designed to minimize energy consumption while maximizing raw material recovery and reuse.

Finally, a quantitative correlation model of piezoelectric properties and cellular signaling pathways was developed through multidisciplinary collaboration with clinicians and the use of intelligent tools. Meanwhile, considering the disparity between idealized laboratory mechanical stimulation and the complex dynamic loading environment in natural tissues, future research should employ finite element analysis combined with biomechanical models to ensure sustained electrical output stability in piezoelectric fibers. These coordinated efforts will ultimately facilitate widespread clinical implementation of piezoelectric fibers in regenerative medicine.

Conflict of interest

The authors declare that they have no conflict of interest.

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Author contributions

Longfei Li contributed to data collection, organized the framework, and writing of the original draft. Xi Cui and Ruizeng Luo participated in writing-review & editing, and Zhou Li performed conceptualization, supervision, and writing-reviewing.

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