

REVIEW

# The potential application of electrical stimulation in tendon repair: a review

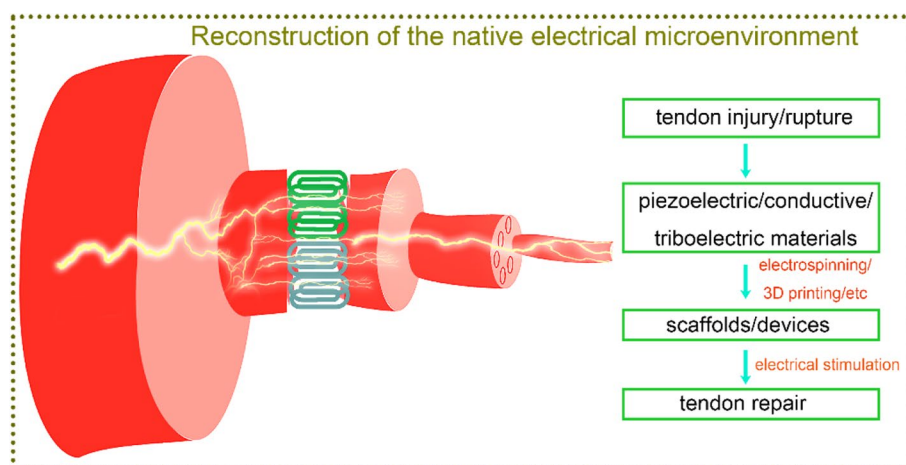
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## Abstract

Tendons are connective tissues with a regular three-dimensional structure containing collagen fibers, and the oriented collagen fibril gives tendons a piezoelectric effect. After tendon injury or rupture, the native electrical microenvironment in which it is located is disrupted, and the electrical signal pathway is blocked. Electrical stimulation (ES) can guide cell orientation, promote tissue differentiation, and enhance tendon repair. Therefore, bioactive materials that generate ES are ideal for repairing tendons by restoring the native electrical microenvironment. This review focuses on the application of piezoelectric materials, conductive materials, and triboelectric materials in tendon repair. They produce ES in different ways. Piezoelectric materials generate charges through deformation within the crystal under the action of force, which in turn causes the arranged dipole moments to deform, resulting in a net electric field. Conductive materials can generate a large number of freely moving charged particles under the action of an electric field and thus can conduct current. When two different triboelectric materials come into contact, opposite charges are formed on each surface, resulting in contact electrification. The materials are inextricably linked to each other, so the scaffold is developed that may be a single or multiple ES scaffold. For example, the mixed application of conductive material poly(3,4-ethylenedioxythiophene): poly(styrenesulfonate) (PEDOT: PSS) and piezoelectric material poly-L-lactic acid (PLLA), as well as the combined application of piezoelectric material polyvinylidene fluoride (PVDF) and triboelectric material nylon. More interestingly, PVDF is both a piezoelectric material and can generate charges under friction. Therefore, the development of high-performance cross-materials that can generate ES may be a better research direction in the future of tendon repair.

## Graphical Abstract



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## Highlights

- Tendon exhibits a piezoelectric effect due to the directional arrangement of the collagen fibril.
- Piezoelectric, conductive, and triboelectric biomaterials can generate electrical signals to repair tendon.
- Long-term self-powered, flexible, wearable devices that integrate therapeutic and monitoring functions will be needed for tendon repair.

**Keywords** Oriented collagen fibril · Native electrical microenvironment · Electrical stimulation · Tendon repair

## Introduction

Tendons are connective tissues composed of collagen, elastin, water, and proteoglycans, efficiently transmitting muscle forces to bones to enable joint movements [1, 2]. Tendons have an oriented three-dimensional internal structure of collagen fibers, consisting mainly of longitudinally aligned fibers but also transversely and horizontally oriented fibers, which gives healthy natural tendons a fibro-elastic structure and high resistance to mechanical loading [1, 3].

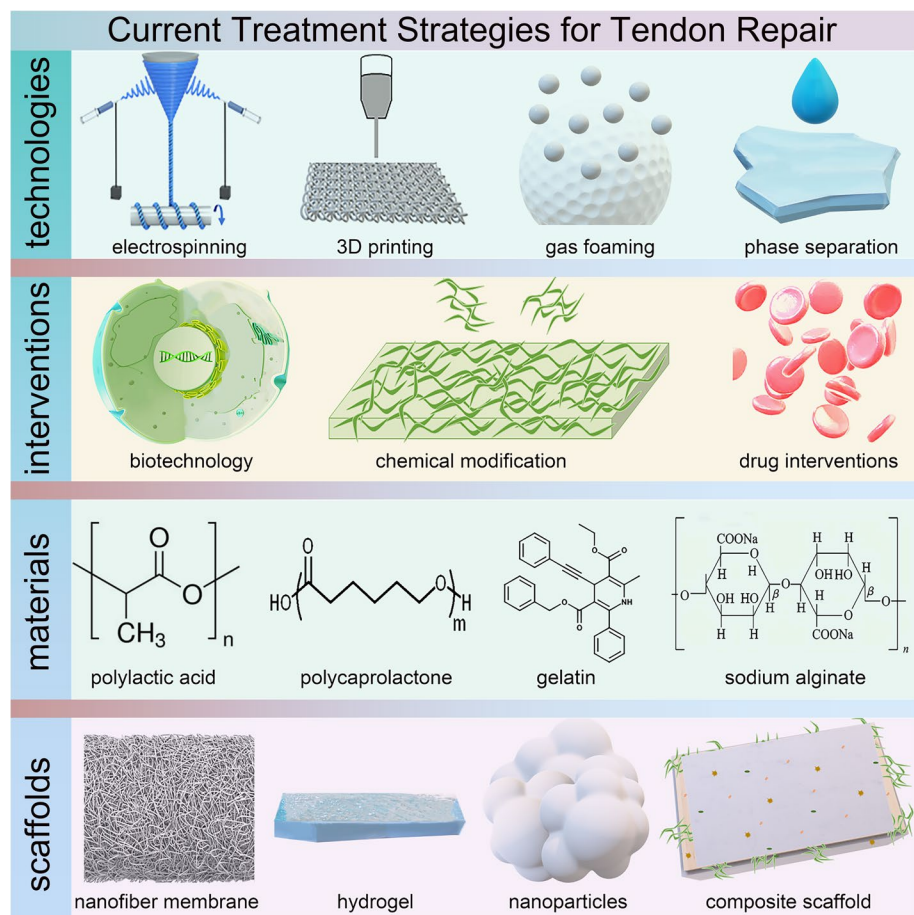
Tendinopathy is a growing health problem that affects an estimated 100 million or more people worldwide each year [4]. The characteristics of tendinopathy include collagen fiber deformation, increased capillary and arterial proliferation, increased inflammatory mediators, dysregulation of extracellular matrix (ECM) homeostasis, changes in pain perception, and impaired tendon mechanical properties [5]. Injuries to tendons, tendon-bone junctions, and associated tissues can be caused by trauma, chronic overuse, and age-related degeneration [6, 7]. From a pathological and physiological perspective, various risk factors such as mechanical abuse, internal and external variables can lead to the onset of tendinopathy, which can still be repaired at this time; the accumulation and growth of risk factors lead to tendon injury and degeneration; finally, insufficient tendon function and load-bearing capacity can lead to tendon lesions, resulting in tendon tears or ruptures [8]. These injuries can be divided into two subcategories: acute injuries (traumatic injuries to previously healthy tissue) and chronic (degenerative) injuries [9]. It also can be categorized according to the structure affected: rotator cuff tendinopathy, lateral epicondylitis and medial epicondylitis, patellar tendinopathy, gluteal tendinopathy, hamstring tendinopathy, quadriceps tendinopathy, Achilles tendinopathy, iliotibial band syndrome [10, 11]. Tendon injury is a common debilitating musculoskeletal disease in sports medicine, which can lead to loss of function, comfort, and even mobility, and the treatment cost is relatively high [12, 13].

The diagnosis of tendinopathy is primarily based on clinical symptoms and examination of the patient's pain and

stiffness after activity [14]. Tendon healing is a complex process that includes stages of inflammation, proliferation and remodeling [15]. Due to the slow, strain-dependent, and low cellular and vascular of the tendon repair, it leads to ECM disorder, making it difficult to treat after rupture [16, 17]. The natural healing ability of adult tendons is limited, and the current treatment methods mainly include conservative treatment with exercise, nonsteroidal anti-inflammatory drugs, and shock wave therapy in the early stage, as well as surgical treatment in the late stage [18, 19]. Currently, cell-free therapy in regenerative medicine is one of the main treatment methods for tendon injuries, with the most prominent source being the secretome of stem cell origin. The benefits of this therapy are multifaceted, including reducing immunogenic responses, maintaining post-storage activity, the ability to target characteristic tissues, and higher safety [20]. Chemical drugs are usually taken orally, while biological agents such as peptides, growth factors, or antibodies typically require parenteral administration [21]. Conservative treatments provide only temporary relief, and surgery can cause re-tearing and even harm that affects the patient's quality of life, these treatment options are limited and often lead to unsatisfactory clinical outcomes [19]. During the repair process, there may be complications such as tendon adhesions, local swelling and pain, wound infection, and limited movement [22, 23]. The structure and strength of the tendon are not fully restored after long-term repair, and patients rarely regain their pre-injury range of motion [24]. That is to say, the complete healthy repair of the tendon is a great challenge.

Currently, there are many strategies to enhance tendon repair through different technologies, interventions, and materials to create a variety of scaffolds (Fig. 1). They have been extensively studied in the field of tendon repair, either individually or in combination [25–28]. Biophysical cues present in biomaterials such as strain hardening, elasticity, porosity, cell adhesion ligands, mechanical loading, and fiber orientation are essential for adequate cell infiltration, cell differentiation, cell arrangement, matrix deposition, and cell migration [21]. Tu et al. [29] modified bioactive electrospinning fibers

**Fig. 1** Various scaffolds are made through different technologies, interventions, and materials and applied individually or in combination for tendon repair



with soluble tendon-derived ECM to promote mesenchymal tendon differentiation and rat Achilles tendon regeneration. Cai et al. [30] designed a self-healing hydrogel with macrophage regulatory and reactive gene silencing properties and found it to be highly effective in reducing inflammation and inhibiting tendon adhesion. Chae [31] proposed a gradient cell-loaded multi-tissue structural construct implant through three-dimensional cell printing technology, which promoted the effective recovery of shoulder motor function and accelerated the healing of the tendon-bone interface in vivo. The above methods are already very mature in the research of repairing tendons. Furthermore, tendon tissue engineering scaffolds that mimic the structure, composition, mechanical properties and induce tissue regeneration of tendons, which has shown great research value in this field.

Tendons can transmit electrical signals in the face of mechanical stress, distributing and controlling the force exerted by the muscle on the attaching tissues to produce movement [8]. However, once the tendon is ruptured, the electrical signal transmission pathway is blocked and the native microenvironment of the tendon is disrupted. During progressive wound healing, the rate of wound healing gradually slows down due to a decrease in bioelectricity released by the surrounding tissues [32]. It is equally important to

be able to mimic the native microenvironment of tendons in future studies. Therefore, electroactive biomaterials have emerged as a new generation of smart biomaterials capable of directly applying ES to target cells or tissues [33]. The family of electroactive biomaterials consists mainly of piezoelectric biomaterials, conductive biomaterials, triboelectric biomaterials, and other biomaterials that generate electrical signals under specific stimuli (e.g., pH, light, temperature) [33]. In the latest research, the piezoelectricity of tendons can be used for tendon repair. However, there are few strategic studies summarizing the restoration of the tendon's native electrical microenvironment through ES materials to promote repair. Thus, this review will make a brief introduction to the piezoelectric source of tendon, the application of ES materials, and the future development in tendon repair.

## Piezoelectricity of the tendons

### Bioelectricity

Bioelectricity refers to electric fields that are naturally applied or generated in living systems [34]. Bioelectricity

is an integral part of living systems, in which endogenous electric fields (EFs) play a crucial role in early embryonic development to tissue regeneration [35]. EFs are the basis of bioelectrical signal conduction and the priority signal of regeneration of damaged tissue [36]. At the cellular level, the difference in endogenous membrane potential within each cell leads to the generation of bioelectricity, which guides cell behavior including orientation, migration, adhesion, proliferation, and differentiation [37]. Physiological loads in asymmetric biological components such as skin, bones, dentin, tendons, muscles, hair, and many others can activate specific molecular cell signaling processes, triggering the generation of electrical potentials. This characteristic is called piezoelectricity [38, 39]. Due to the importance of bioelectricity, electrotherapy has evolved to accelerate wound healing, deep brain stimulation, tissue regeneration, improvement of musculoskeletal conditions, and fracture recovery [35].

### The structure of the tendon determines its piezoelectric properties

In tendons, type I collagen (COL I) is the main structural protein, accounting for approximately 90% of the total collagen content and 60% of the tendon dry mass [40]. The fibrous tissue of tendons is regular: the tropo-collagen constitutes fibril, the fibril and primary resident cells, tenoblasts, and tenocytes constitute fiber, the fiber constitutes fascicle, and fascicle constitutes the tendon matrix [41, 42]. The hexagonal stacking of collagen molecules in cross-section is thought to be the origin of collagen piezoelectricity, where collagen generates an electrical charge under strain, and thus the oriented collagen fibril makes tendons piezoelectric [43, 44]. In other words, when the tendon is strained by force, the collagen fibril will keep the tendon in its native electrical microenvironment (Fig. 2).

Different piezoelectric domains on tens of nanometers to micrometers scale were observed in human tendons

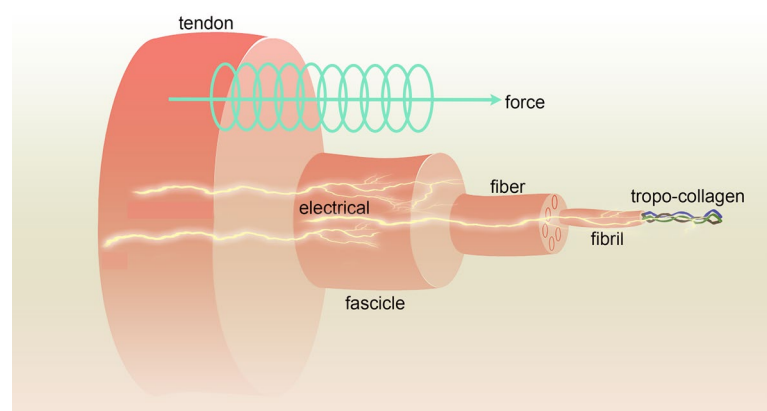
using piezoresponse force microscopy [45]. Moreover, at the nanoscale, it has been found that the longitudinal piezoelectric coefficient of a single collagen fibril is approximately one order of magnitude larger than the macroscopic measurement of tendons [46]. Studies have shown that collagen fibril exhibit unipolar axial polarization due to the redirection and magnitude changes of permanent dipoles of single charged and polar residues caused by mechanical stress, manifested as shear piezoelectric materials with a shear piezoelectric constant of  $d_{15} \sim 1 \text{ pm V}^{-1}$  [47, 48]. Majid [49] showed that individual collagen fibril of the bovine Achilles tendon consist of piezoelectrically inhomogeneous gaps and overlapping regions, with the overlapping regions having significant piezoelectricity and the gaps regions having lesser piezoelectricity. This piezoelectric heterogeneity is essentially related to the structural heterogeneity of the region under subfibrillar. At the same time, it has also been found that the resistance of current passing through collagen fibril was minimal by the bovine Achilles tendon is connected in series with a control resistor in a direct current (DC) circuit. That is to say, when an electric current passes through, the inherent electrical characteristics of the tendon will cause the current to preferentially respond along the direction of collagen fibril [50].

## Piezoelectric stimulation

### Piezoelectric materials

Piezoelectric materials can convert mechanical energy into electrical energy and are considered smart materials [51]. This phenomenon is caused by the transient deformation of the atomic structure of the material under mechanical stress, where the material loses its center of symmetry and forms a net dipole moment [52]. In this case, the distance between the positive and negative charge centers changes

**Fig. 2** The tendon composed of regular, oriented collagen fibril will strain under the action of force, which leads to the piezoelectric effect



and the surface free charge is partially released to generate piezoelectricity [53].

There are many applications of piezoelectric materials in tissue regeneration, including natural piezoelectric crystals, piezoelectric ceramics, piezoelectric polymers, and piezoelectric composite materials in bone, cartilage, nerve, skin, tendon, and cardiovascular tissue repair [54, 55]. Such as the scaffolds made from proteins, polysaccharides, PLLA, silk fibroin, etc. in tendon repair [56–58]. Due to their biocompatibility, biosafety and environmental sustainability, natural piezoelectric biomaterials are considered a promising candidate in this emerging field [59]. Meanwhile, piezoelectric polymers and their composite materials have become active scaffolds for tissue engineering applications due to their ability to enhance cellular function [60]. With the development of technology, piezoelectric composite materials will become mainstream, which retain the advantages and eliminate the disadvantages and has good flexibility, processability, high piezoelectric constant, and electromechanical coupling coefficient [61]. A wide range of piezoelectric nanomaterials has been explored by changing the material composition, crystallinity, nano to macroscale hierarchies, processing and post-processing conditions, which significantly affect their piezoelectric properties. The design of smart biomaterials capable of actively interacting with living systems by mimicking the properties of bio-piezoelectric structures is of great importance to the entire field of tissue engineering [62]. Scaffolds need to have excellent mechanical properties including stiffness, elasticity, and tensile strength to ensure functional integration and support physiological loads, which is particularly important in tissues subject to a dynamic mechanical environment [63]. Therefore, piezoelectric composite materials can provide high mechanical properties as well as continuously optimized piezoelectric properties to enhance the stability and functionality of tendon repair scaffolds in dynamic biological environments.

The electric fields exhibited by piezoelectric materials, whether strain-induced, temperature-induced, or spontaneously realized, have a dramatic effect on the electronic properties inside and outside the material [64]. Therefore, piezoelectric materials generate charges under physiological stress and body movement, and exhibit good effects in tissue regeneration and other aspects after implantation in the body [65]. As a tendon implant, it is very promising for tendon regeneration as it can use the body's kinetic energy to generate the electrical signals necessary for tendon growth and restore the native electrical microenvironment.

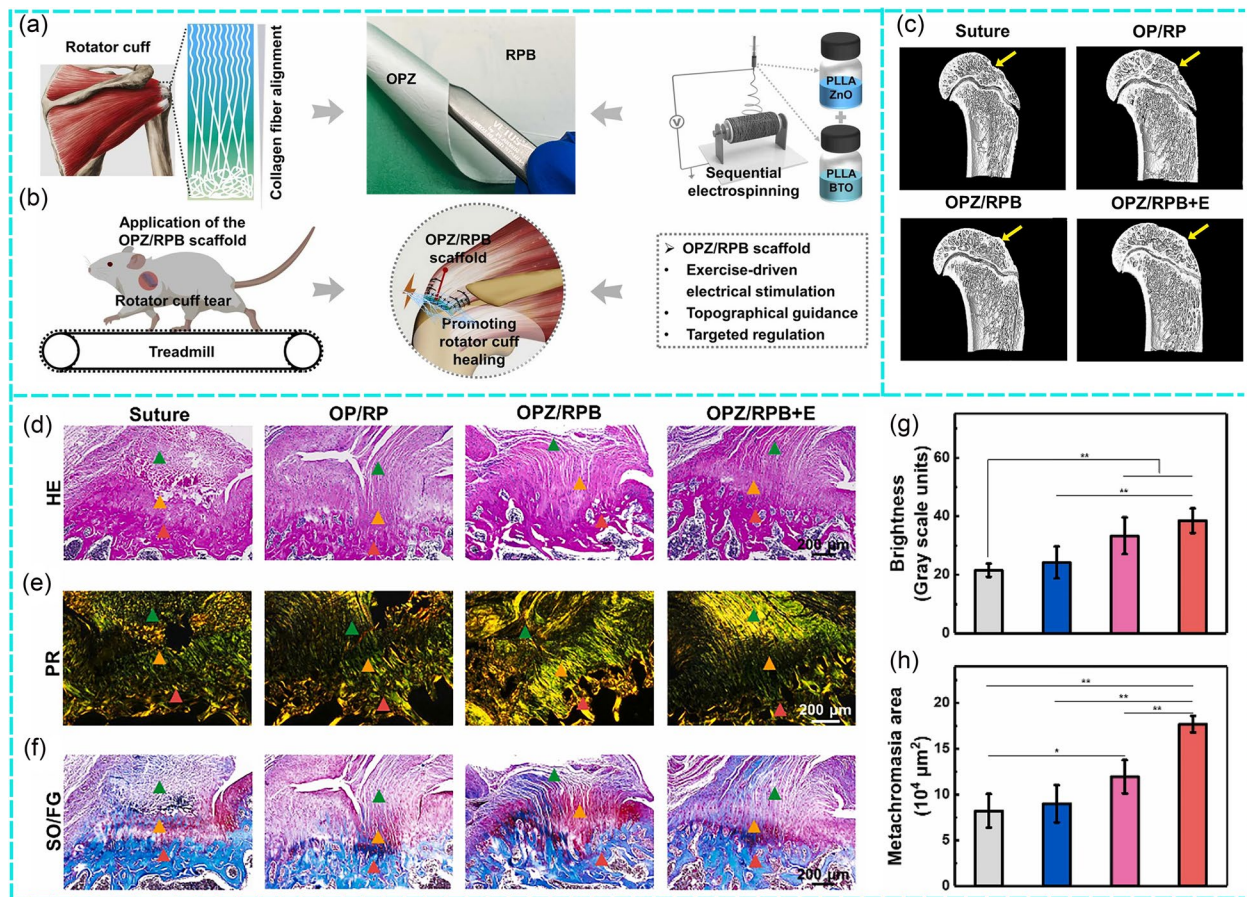
### Application of piezoelectric materials

Tenocytes have high mechanical sensitivity. Their unique sensory mechanisms include mechanosensitive ion channels

involved in repairing signaling pathways [66]. Mechanosensitive ion channels are a class of gated ion channels composed of membrane-integrated proteins that play an important role by converting mechanical forces into ionic currents across the cell membrane [67]. For example, PIEZO1 is a mechanically activated ion channel in tenocytes that promotes tendon function by inducing tendon-specific gene expression and structural changes, thereby enhancing motor function [68]. The piezoelectric-derived electric field generated during physiological movement may provide additional bioelectric signal clues to activate tendon-specific regeneration pathways [69]. Fernandez-Yague et al. [69] designed a self-powered piezoelectric-bioelectrical device to modulate tendon repair-related signaling pathways by modulating mechanosensitive ion channels to promote tendon-specific over non-tenogenic tissue repair processes. Ge et al. [70] developed a highly stretchable polyester-based piezoelectric elastomer with good biocompatibility, which promoted the regeneration of the Achilles tendon in a rat acute injury model, effectively improving its behavioral function and biomechanical properties.

Current research focuses on improving piezoelectricity by promoting dipole orientation such as blending with fillers [71]. Zhang [72] prepared Janus nanofiber scaffolds of PLLA/zinc oxide (PLLA/ZnO) and PLLA/barium titanate (PLLA/BTO) through electrospinning, and combined them with motion-driven ES and nano topological effects to promote tendon to bone healing (Fig. 3). Among them, PLLA is a common material used to make piezoelectric tissue engineering scaffolds, and the addition of both ZnO and BTO improved the piezoelectricity of the scaffolds, which stimulated the proliferation of tenocytes, induced tendon differentiation, and promoted the proliferation and differentiation of osteoblasts, thus promoting bone regeneration. It has been suggested that BTO naturally promotes tissue regeneration by using its piezoelectric properties to induce stable and repeatable electrical signals when subjected to mechanical stress. These electrical signals are transmitted simultaneously with mechanical forces to voltage-sensitive and mechanically-sensitive ion channels on the surface of the cell membrane, resulting in intracellular calcium ion inflow, which enhances cell regeneration [73]. Strontium (Sr) is the metal element with the highest content in tendon tissue. Tetragonal-SrTiO<sub>3</sub> (T-SrTiO<sub>3</sub>) is particularly interesting, showing obvious piezoelectric properties at low temperatures and changing into ferroelectric properties under environmental conditions. The addition of T-SrTiO<sub>3</sub> in the polymer can effectively create a favorable electrical microenvironment for tendon repair [74].

In addition, piezoelectric materials have other functions, such as inhibiting bacterial growth and colonization by inducing changes in charge distribution under stress. For example, ZnO can produce reactive oxygen species (ROS)



**Fig. 3** Schematic illustration of the fabrication of the Janus nanofibrous scaffolds (a). The possible synchronous healing mechanism of the tendon-bone interface stimulated by exercise-driven ES and topographical guidance (b). The representative micro-CT images (the yellow arrows pointed to the insertion site of the greater tuberosity) (c). Representative images of the reconstructed tissues at 4 weeks after surgery (red triangle: bone; orange triangular: cartilage; green triangular: tendon), Hematoxylin and eosin (H&E) staining (d), Picrosirius red (PR) staining (yellow: Col I; green: Col III) (e), and Safranin-O/Fast green (SO/FG) staining (f). Analysis of the collagen birefringence based on PR staining (g). Comparative analysis of total metachromasia area based on SO/FG staining (h). Reproduced with permission from [72]. Copyright © 2024 Elsevier Ltd

to effectively eliminate bacteria, demonstrating strong anti-bacterial activity [75]. Furthermore, the effective interfacial charge transfer caused by the piezoelectric effect makes the piezoelectric materials have good redox catalytic activity [76]. In addition, piezoelectric materials can mimic natural electrical currents in human cells [77]. For example, when piezoelectric devices are implanted in the body, they can collect the body's movement to self-power, thus avoiding the use of medical implants with toxic batteries [78].

### Piezoelectric devices

The piezoelectric phenomenon has been observed in many biological tissues and macromolecules, which has promoted the development of bio-intelligent devices. Piezoelectric devices usually refer to a type of electronic or optoelectronic device based on the piezoelectric effect, and their most basic

regulating unit is usually called a piezoelectric transistor. According to their structure and working mechanism, they can be broadly divided into two categories, namely field-effect transistors and piezoelectric transistors [79]. With the in-depth research in the field of piezoelectricity, many piezoelectric materials have been used to make piezoelectric crystal devices, such as aluminum nitride, lead zirconate titanate, ZnO, gallium nitride, barium titanate, PVDF-co-hexafluoropropylene [80, 81]. Piezoelectric devices have many advantages such as high electromechanical coupling effect, high power density, fast response time, compact structure, and so on, which make them used in the biomedical field [82].

Biological piezoelectricity has great potential for in vivo sensing, drug delivery, and tissue reconstruction, especially in biomaterials and systems where piezoelectric responses caused by strong supramolecular dipoles can be modulated

through molecular chemistry and packaging [83]. Furthermore, many electric devices are powered by batteries, and power supply for a long period cannot be guaranteed because of the loss of ordinary batteries, while piezoelectric materials can be realized to be self-powered in the body to meet practical needs. At the same time, computer modeling makes it possible to insert various requirements such as shape, size, thickness, type, energy supply, and load-bearing capacity. Moreover, the degradation rate and piezoelectric effect of the material can be precisely adjusted through computer-aided design and simulation technology, thus preventing the material from degrading too fast or too slow to ensure the stability of piezoelectricity [84]. The personalized customization of the piezoelectric biosensor is realized by optimizing the structure of the piezoelectric scaffold. Thus, in the new field of body computing in personalized healthcare, biosensors can extract physical and physiological signals in real-time and parse them into actionable health information using big data analytics and artificial intelligence to determine interventions and treatments based on sensor output [85]. It has led to substantial results in the research and development of piezoelectric and sensor devices made of functional piezoelectric materials, such as piezoelectric nanogenerators that convert mechanical energy into environmentally friendly, sustainable electrical energy via nanoscale piezoelectric materials [86]. Wearable sensors provide continuous, non-invasive monitoring of physiological signals, enabling real-time health tracking for early detection of disease and improved management practices [87]. Implantable medical electronic devices that can improve people's quality of life, such as cochlear implants, cardioverter defibrillators, artificial retinas, etc. [88]. These wearable or implantable piezoelectric devices facilitate the development of self-powered medical devices. Li [89] reported an amino acid-based piezoelectric bio-crystalline film with tissue-compatible all-round stretchability and non-destructive piezoelectricity, which is a key step towards tissue-compatible biomedical devices. Shu [90] proposed a wearable and stretchable bioelectronic patch for detecting tendon activity. It was composed of functional piezoelectric thin films containing PVDF, metal conductors, and dielectric materials, and had been systematically optimized in terms of structure and mechanics. In addition, by integrating the patch with the microcontroller unit, a real-time monitoring and healthcare system for tendons was established, which could process the collected data and provide feedback for motion assessment. Specifically, the patch on the ankle could be used to measure the maximum force exerted on the Achilles tendon during jumping. This work not only provided a simple strategy for monitoring changes in the Achilles tendon throughout the body, but also contributed to a deeper understanding of human activities (Fig. 4).

Currently, in the development of viable bio-piezoelectric materials and the realization of applications such as biosensors, electric motors, and energy harvesters, the biggest challenges are constrained modes, directional control, and polarization direction. To overcome these obstacles, researchers have recently experimented with bio-piezoelectric element recognition, screen printing, cloud computing, and electromagnetic field-induced configuration techniques [91]. Some defective devices may cause immune reactions when piezoelectric devices are implanted into the body. Therefore, a strict device safety evaluation system is required for biocompatibility assessment, toxicity assessment, degradation cycle research, and long-term monitoring [92]. Based on this, the demand for piezoelectric devices with high performance, small size, low power consumption, and flexibility is growing [93]. However, the large-scale synthesis and manufacturing of piezoelectric biological devices are still difficult to achieve practical applications at present. Many studies are still at the basic stage of research. Combining wearable piezoelectric collectors with high power density and wireless charging technology is a developmental driver for future implantable medical devices to increase their lifespan [94]. Piezoelectric materials are expected to be the next generation of tissue engineering scaffolds, so computational models of piezoelectric scaffolds will have significant potential in supporting structural design that promotes tendon repair.

## Direct electrical stimulation

### Common types and application

Extracorporeal shock waves, low-intensity pulsed ultrasound, mechanical stress, direct ES, combined magnetic fields and exercise therapy have been shown to have a beneficial effect on tendon healing [95]. It can be noted that direct ES can guide the development and regeneration of many tissues [96]. Direct ES may be a potential regulator that promotes cell proliferation, differentiation, and ultimately ECM synthesis *in vitro* [97]. Carla [98] found that micro-current stimulation could promote hyaline cartilage repair in immature male rats. Casagrande [99] found that low-frequency ES could increase collagen synthesis and promote the healing of rat Achilles tendon. Labanca et al. [100] proposed that ES was effective in improving the strength and function of the patient's hamstring tendon graft after reconstruction of the anterior cruciate ligament (ACL).

Currently, common ES devices include direct coupled (DCP) stimulation, capacitive coupled (CCP) stimulation, inductive coupled (ICP) stimulation, or a combination thereof. DCP requires placing a cathode at the site of injury and a complementary anode in the surrounding soft



**Fig. 4** Applications and an exploded view of the patch (a). The operating procedures of the system and demonstration of applying the patch for recoding the arm's bending (b). An optical image of the patch's fixation, using the bioelectronic system for gait analysis, and APP displays on a cellphone (c). Reproduced with permission from [90]. Copyright © 2021 Sheng Shu et al.

tissue to exert its effect [101]. Common applications of DC stimulation include transcranial DC stimulation, which is a non-invasive technique consisting primarily of a battery-powered current generator and a cathode and anode on the scalp [102]. Transcranial DC stimulation can establish a causal relationship between a limited area of the brain and

its potential perception, cognition, and motor functions. It has been tested to treat various mental and neurological disorders, including depression, stroke, and changes in consciousness [103]. In addition, DC stimulation can promote the secretion of prostaglandins, morphological factors, and growth factors by cells, thereby affecting them

[79]. DC electric fields can enhance the migration ability of anterior cruciate ligament fibroblasts and promote the expression of COL I, which can be used to promote ligament healing and repair [92].

CCP stimulation typically involves placing two skin electrodes on opposite sides of the target tissue. By applying low-frequency alternating current, the electric field can be generated at the defects [101]. The U.S. Food and Drug Administration has approved non-invasive bone growth stimulators that function through two methods: CCP and ICP [104]. It has also been shown that CCP electric fields are a non-invasive and cost-effective treatment modality that can potentially restore internal homeostasis in articular cartilage [105]. Lee et al. [106] constructed a wireless, chipless, immune-tolerant *in vivo* strain sensing suture system around an inductor connected to a capacitive fiber optic strain sensor, which could continuously monitor the mechanical stiffness changes of reconstructed Achilles tendon throughout the healing process.

ICP stimulation is applied through an electromagnetic coil. A pulsed magnetic field is generated by a wire coil that circulates current, and the pulsed magnetic field induces a secondary electric field that varies over time within the exposed tissue [107]. Pulsed current has many functional effects, such as attaching surface electrodes to painful areas and applying low-frequency pulse current (1–100 Hz) to suppress excessive pain [108]. In addition, because most portable or battery-powered stimulators can only provide pulsed current, it is more widely used in sports training and rehabilitation [109]. Pulsed electromagnetic fields regulate cellular processes by emitting pulsed, variable intensity and frequency electromagnetic fields [110]. Girolamo et al. [111] found that 1.5 mT- pulsed electromagnetic fields treatment was the most effective in terms of cell proliferation, up-regulation of tendon-specific gene expression, and release of anti-inflammatory cytokines and growth factors in healthy human tenocyte cultures *in vitro*. In a rat model of acute bilateral supraspinatus tear repair, a non-invasive pulsed electromagnetic field might promote early postoperative tendon-to-bone healing, improve biomechanical properties and COL I expression [112].

Direct ES plays multiple important roles in promoting tendon repair. In a recent study, it was noted that neuromuscular ES can induce the development of tissues such as bone, cartilage, and tendons, which are important components of motor organs and basic mechanisms of repair after injury [113]. Dohnert et al. [114] found that continuous high-frequency transcutaneous electrical nerve stimulation significantly reduced pain intensity and significantly improved knee mobility, muscle strength, and medication uptake after ACL reconstruction. A similar study found that neuromuscular ES of the adductor humerus muscle in patients with

rotator cuff tears improves shoulder-humerus distance and the ability to rotate the shoulder blades upward during arm lifts [115]. It has been shown that low-frequency ES promotes mitochondrial bioactivation [116]. Further studies have shown that electrical signals can affect the polarization of macrophages by improving mitochondrial function and promoting adenosine triphosphate synthesis [75]. This was similarly validated by Tu et al. [117], who suggested that ES of the sympathetic nerves can lead to a decrease in the concentration of the inflammation-related factors IL-6 and IL-1 $\beta$  and inhibit the inflammatory response around the tendon. In addition, ES also has the function of promoting vascular dilation, enhancing vascular permeability, and increasing local tissue blood flow [118].

## Conductive materials

Research showed that direct ES could modulate cellular components, such as ion channels and cytoskeletons, to regulate cell behavior and function [119]. The inherent conductivity of conductive scaffolds in tissue regeneration provides local ES at the implantation site, allowing for the transmission of ion signals based on cells during cellular processes, guiding cells to align in specific directions, and promoting their differentiation in various tissues, achieving the effect of repairing damaged target tissues [101]. Common conductive materials include platinum-gold alloy, magnesium alloy, polypyrrole, polyaniline, PEDOT, carbon nanotubes, graphene and other two-dimensional (2D) nanomaterials [120, 121].

PEDOT: PSS with high conductivity and water dispersibility is a favorite combination in bioelectronics [122]. An anisotropic, high strength, toughness, and conductivity hydrogel made from poly (vinyl alcohol), cellulose nanofiber, PEDOT: PSS as a tendon substitute has restored the motor function and contributed to the treatment and rehabilitation of dysfunctional tissues in SD rats [123]. PEDOT: PSS nanoparticles were coated on electrospun nanofibers of poly ( $\epsilon$ - caprolactone), which reduced the gap area between muscle fibers under the ES and enhanced muscle regeneration after rotator cuff repair [124]. The researchers further found that PEDOT: PSS matrix could inhibit fat accumulation and fibrosis, improve tendon morphology and tensile properties [125]. Yang [126] reported a bondable, stretchable, biocompatible, and gel-free TPP electrode based on tannic acid, PEDOT: PSS, and polyvinyl alcohol, and then a metal-polymer electrode array patch (MEAP) composed of liquid metal circuitry and TPP electrodes, which could continuously monitor tendon displacements and control tendon stretching within a safe range, thus reducing the risk of muscle or tendon injury (Fig. 5).

Carbon-based conductive materials can be used as load-bearing materials and are also capable of adsorbing proteins, and can be used to stimulate tissue growth by forming

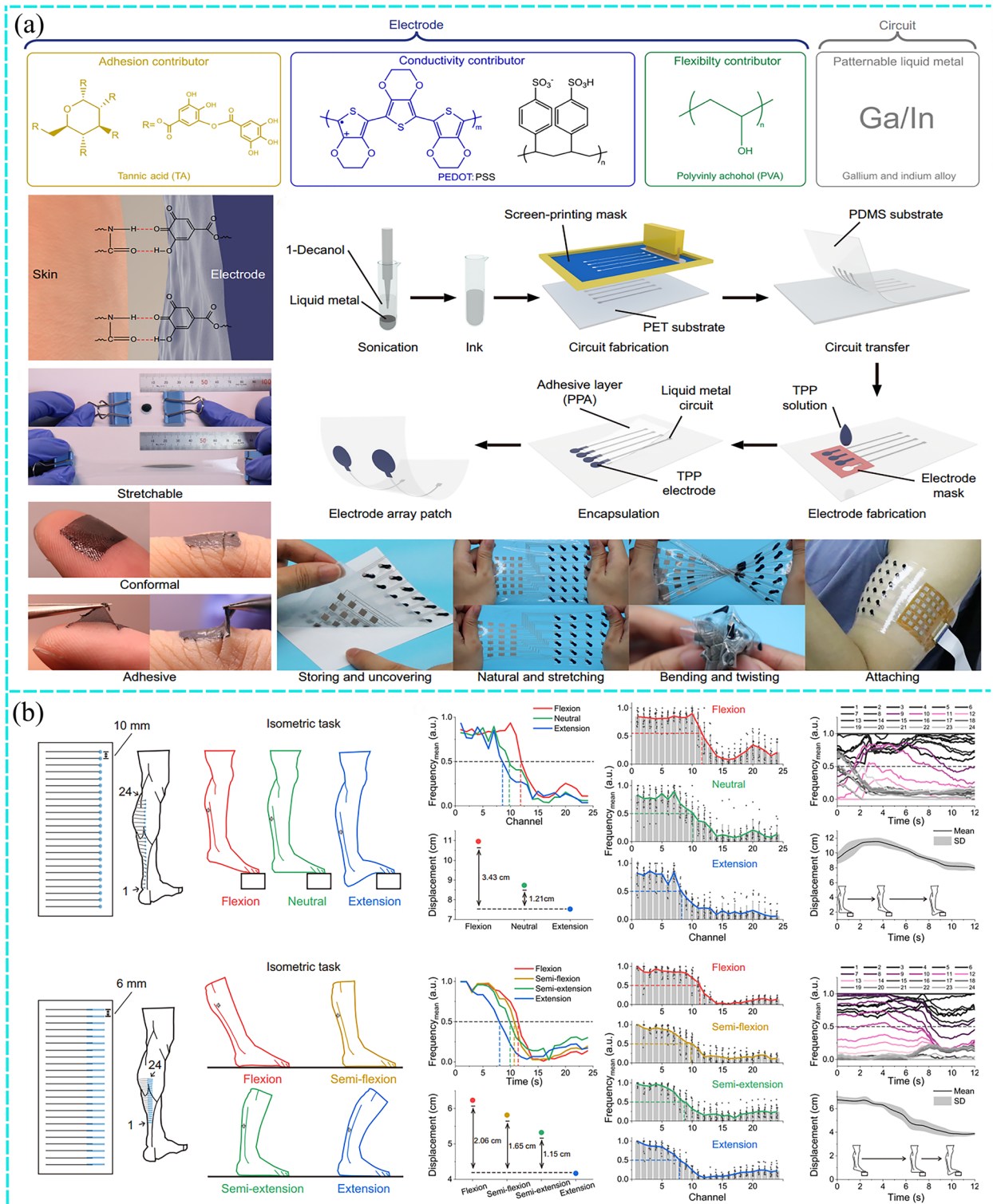
conductive microcircuits through exogenous ES [127, 128]. Carbon nanomaterials have good conductivity and can be used for electrophysiological signal transmission in muscle and nerve tissues, as well as for controlling cell fate [129]. Thus, various structures of carbon-based materials can be designed to mimic the spatial structure and surface morphology of tendon fibers, and epigenetic cues provided by the morphology and topography of the cellular microenvironment synergize with those derived from ECM stiffness to enhance overall regeneration [130]. Pan [131] made an electro-tendon by *Nephila pilipes* spider dragline silk, single-walled carbon nanotube, and PEDOT: PSS. This electro-tendon could be bent and stretched over 40,000 times without changing conductivity. When attached to a pressure sensor and mounted on the fingers of a humanoid robot, the robotic hand could grasp a variety of objects, such as balloons, needles, and aerosols, without crushing and damaging the objects (Fig. 6). Wang [132] designed hierarchical helical carbon nanotube fibers as a substitute for the bone-integrated anterior cruciate ligament. Due to the multi-scale channels of the fibers and carbon-driven osteogenesis, the rabbit and sheep models were able to run and jump normally after 13 weeks of implantation. Yu et al. [133] designed a carbon fiber-mediated electrospinning scaffold, which was almost filled with collagen fibers in a rabbit Achilles tendon defect repair model. The transcriptome sequencing results showed that the expression of fibronectin and tenomodulin was upregulated, and their related proteoglycans and glycosaminoglycan binding protein pathways were enhanced, which could regulate the TGF- $\beta$  signaling pathway, optimize ECM assembly, and promote tendon repair.

Compared with traditional materials, 2D materials such as the graphene family are widely used in tissue regeneration, such as tendon regeneration, due to their excellent mechanical properties, large surface area, good biocompatibility, optical transparency, biological function, and controllable electronic and electrochemical properties [134]. The gel of graphene oxide and platelet-rich plasma developed by Bao et al. [135] had good biocompatibility and could promote the proliferation of bone marrow mesenchymal stem cells and the differentiation of osteogenesis and cartilage. The structure of newly formed tendons was similar to natural tendons and had good biomechanical properties, which could effectively improve tendon-bone healing. In addition to graphene, other 2D nanomaterials such as transition metal dichalcogenides (TMDs), antimonene (AM), black phosphorus (BP), metal-organic frameworks (MOFs), 2D metal carbides and nitrides (MXenes) have emerged successively in biomedical applications [136]. Compared to one-dimensional or three-dimensional (3D) nanomaterials, 2D nanomaterials have the highest specific surface area, resulting in a greater number of surface atoms compared to volume atoms. The presence of a large number of surface atoms provides high surface energy

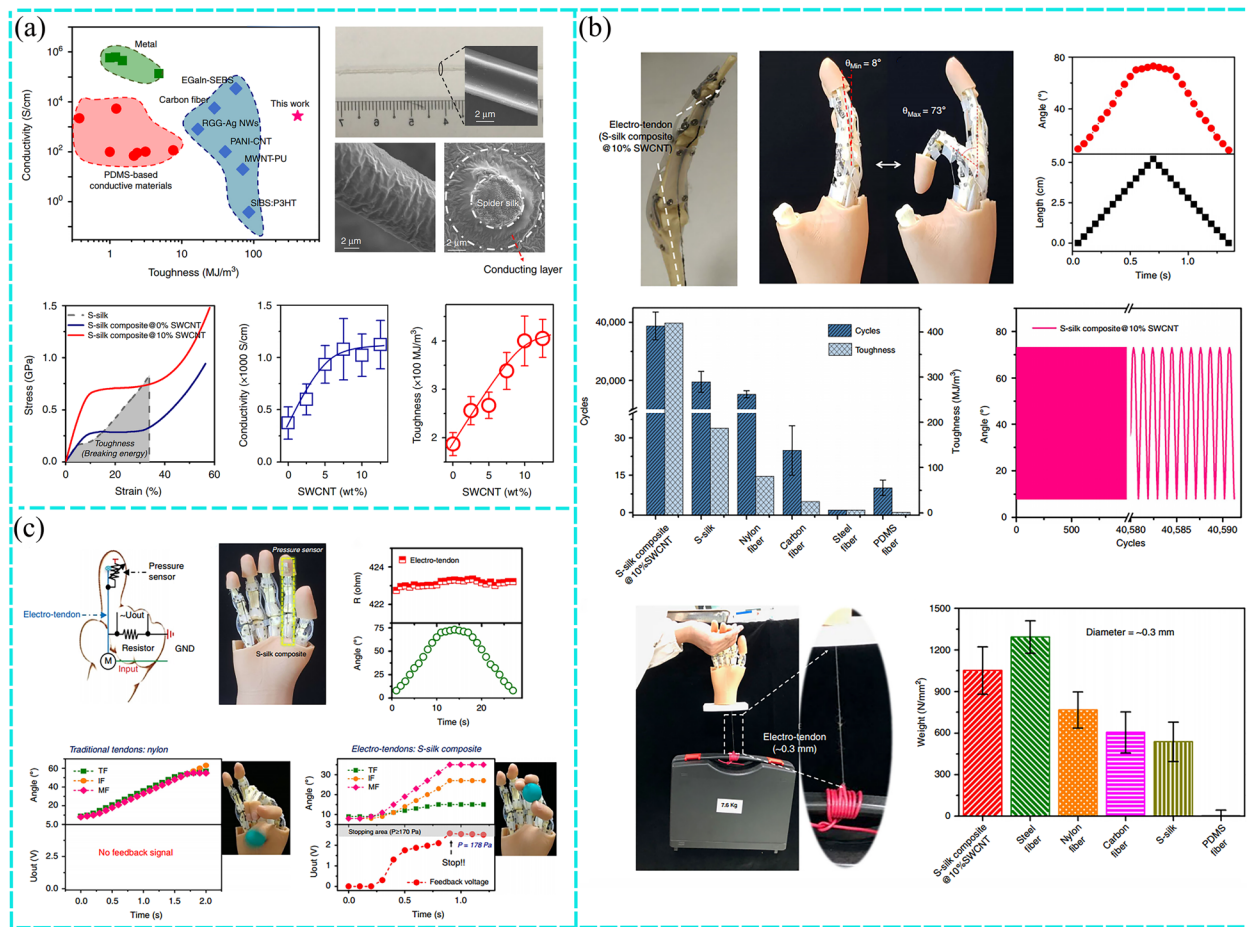
and can provide a large number of surface anchoring points. This unique characteristic enhances the interaction between 2D nanomaterials and biological components, including cells, cellular components, and biomolecules [137]. Chen et al. [138] designed a NO-loaded MOFs encapsulated in polycaprolactone/gelatin aligned coaxial scaffold, it could promote tendon regeneration in a shorter healing period with better biomechanical properties by angiogenesis. Garg et al. [139] proposed wearable MXene high-density surface electromyography arrays. In the context of biomechanical research and rehabilitation of joint and tendon pathology, this array could be used to identify and study pathological muscle activation patterns, provide precise rehabilitation treatment, and contribute to overall quality of life. These emerging materials are currently not widely used in tendon repair and are in the development stage. In the future, their potential for tendon regeneration can be further studied.

## Triboelectric stimulation

Currently, there are also triboelectric nanogenerator (TENG) mechanisms that can access human signals. The TENG is a device that uses the coupled effects of electrostatic induction and triboelectrification to convert mechanical energy in the surrounding environment into electrical energy [140]. In general, when two materials come into contact with each other, chemical bonds are formed between certain parts of the surface, and frictional charges are generated due to the transfer of charges from one surface to the other to balance the electrochemical potential [141]. When the frictional layer of TENG circulates between contact and separation caused by biomechanical motion, an alternating current is generated between the two electrodes, which can be used for biomedical applications [142]. Thus, the TENG itself can be used as a highly sensitive sensor or electrical simulator to enable self-powered biomedical technologies for human diagnosis and therapy [143]. TENG can work as a self-powered device, which is conducive to reducing the size and cost of the entire integrated system, thus improving portability and longevity. At the same time, it has significant features and performance such as flexibility, lightweight, high electrical output, and fast response to mechanical stimuli [144]. At present, many materials have been used as triboelectric materials to fabricate high-performance TENG due to their excellent charge transfer and capture ability during friction. For example, polytetrafluoroethylene (PTFE), fluorinated ethylene propylene (FEP), and PVDF have been used as the electron-withdrawing part of the TENG. In turn, polymer materials containing electron-donating groups, such as nylon, silk and wool, are often used as electrophobic parts of the TENG [145].



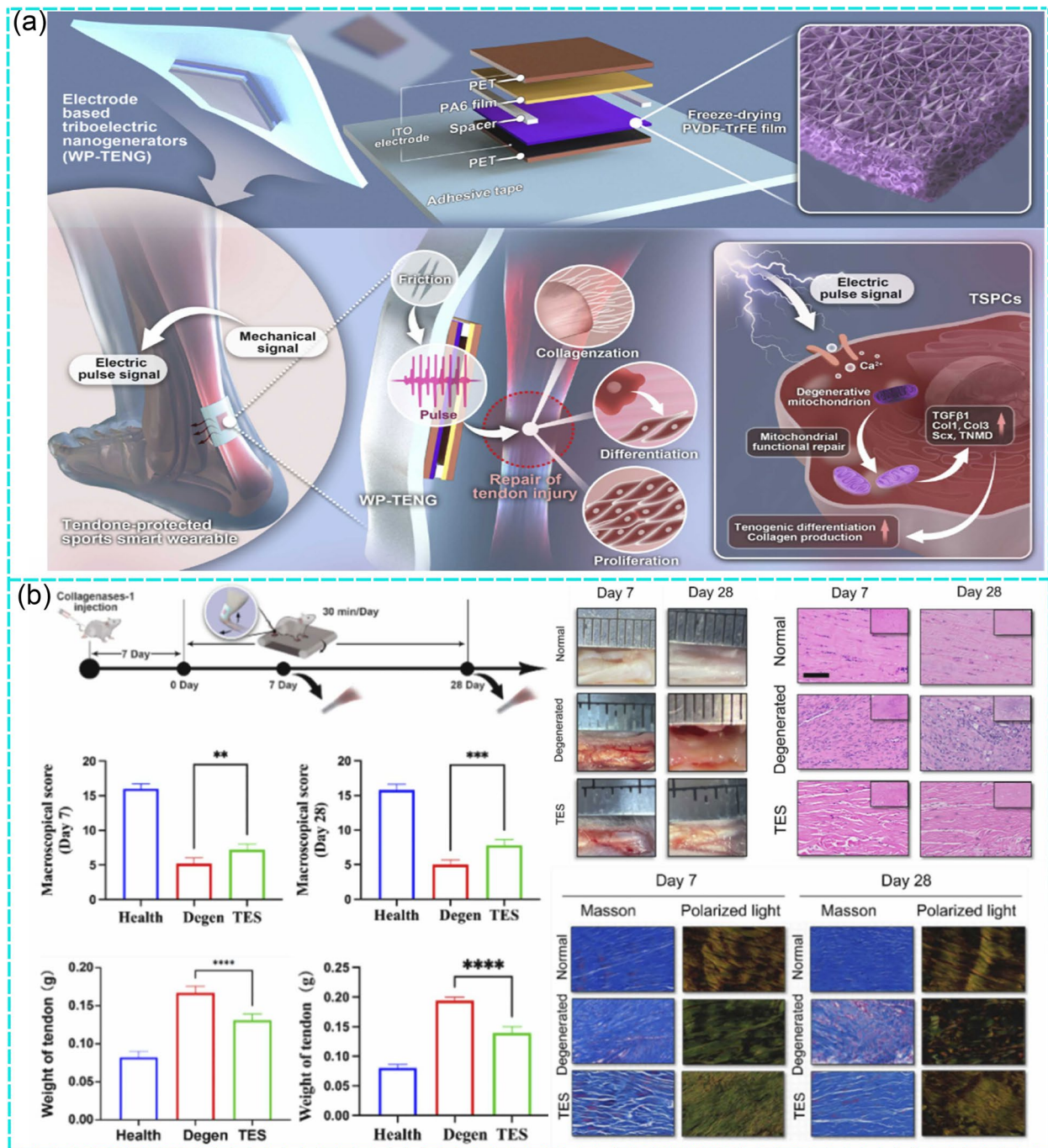
**Fig. 5** Schematic diagram of the composition and fabrication of MEAP (a). Schematic diagrams of MEAPs on the gastrocnemius and Achilles tendon, and normalised mean frequencies of the electromyography signals tests (b). Reproduced with permission from [126]. Copyright © 2023, The Author(s)



**Fig. 6** Toughness and conductivity of spider silk composites (a). Performance of humanoid robotic hands assembled with S-silk composite as electro-tendon (b). Feedback processes of the humanoid robotic hand when grasping objects (c). Reproduced with permission from [131]. Copyright © 2020, The Author(s)

The ability of living cells to generate electrical signals and respond to electrical stimuli is a key feature in the regulation of cell behavior and cell-microenvironment interactions [146]. Therefore, TENG can be applied to living organisms to collect energy and output electrical stimulation to act on cells and change their activities. Thus, it regulates cell function and interferes with cell fate, which is further developed into a new method for health care and disease intervention [147]. Hu et al. [148] designed a rotatory disc-shaped TENG (RD-TENG). The RD-TENG consists of a print circuit board (PCB) deposited with radial Cu as the rotator and another PCB-coated interdigital Cu electrodes and adhered with a PTFE film as the stator, providing a variable alternating signal in a wide range of voltages and currents. The test found that RD-TENG could promote fibroblast proliferation and migration through triboelectric stimulation. At the same time, other studies have found that triboelectric stimulation could restore the vitality of aging bone marrow mesenchymal stem cells [149]. These studies showed that

triboelectric stimulation could play a positive role in cell regulation. Wang et al. [150] developed a diode-amplified TENG that could amplify the triboelectric output, thereby effectively stimulating the muscle directly. Sharma [151] indicated that ES induced by piezoelectric-driven TENG and electroactive hydrogel composites accelerates the repair of diabetic foot ulcers. Wu et al. [152] prepared polyvinylidene fluoride-trifluoroethylene (PVDF-TrFE) films with high porosity. It was combined with polyamide (nylon 6, PA6) to form a flexible, high-performance TENG. Based on this, a self-powered wearable ES patch with an integrated TENG was proposed for tendinopathy treatment. The bionically designed ES patch is attached directly to the affected tendon. It underwent deformation and friction during movement and generated a pulsed electrical output, which was then converted into an electric field to treat the tendon lesion. The ES patch could significantly improve motor function, promote collagen regeneration, and reduce the degree of tissue inflammatory infiltration and recovery time in rats with tendinopathy (Fig. 7).



**Fig. 7** Schematic illustration of the wearable TENG and TES patch-mediated treatment of tendinopathy (a). In vivo tendinopathy treated using a collagenase 1 model using a self-powered TES patch (b). Reproduced with permission from [152]. Copyright © 2023 Elsevier Ltd

In addition, the TENG still has some critical issues that need to be addressed. For example, the output stability of TENG is threatened by a variety of external environmental conditions, including the temperature and humidity of the human body. TENG may be affected by corrosion, internal compression, or oxidation caused by humidity in body fluids

[143]. Therefore, the criteria for selecting TENG materials for higher efficiency and performance are generally: biocompatibility, mechanical properties, surface potential properties, flexibility, chemical stability, additional features consistent with the applications [153].

## Discussion and future outlook

Tendons are an important part of the musculoskeletal system, which holds muscle ends firmly to the bone and stores and transfers energy during movement. When tendon ruptures, it can cause pain, affect movement, and reduce quality of life. Minor tendon injuries will recover gradually with bed rest assisted by medication and functional exercises. For severe injuries that involve surgery, the subsequent repair time becomes longer, and there may be complications such as re-rupture and tendon adhesions during this process. Repairing a ruptured tendon, therefore, is not a matter to be taken lightly. Most of the artificial, non-biodegradable materials such as Gore-Tex polytetrafluoroethylene, polycarbonate, and polypropylene that are now commonly used in clinical have not been satisfactory over time [154, 155]. Currently, more and more researchers have developed a series of biodegradable scaffolds that mimic the structure and function of tendons to replace defective tendons. Such as 3D printing scaffolds, electrospinning scaffolds, hydrogels, microspheres, etc. It is worth noting that all living organisms have an intricate network of bioelectric signals. In the human body, endogenous bioelectric signals carried by ions and electrons mediate the regulation of patterns and behaviors at the cellular, tissue, and organ levels [156]. Bioelectricity plays an important role in physiological and pathological processes such as cell arrangement, adhesion, proliferation, differentiation, migration, and tissue regeneration. The biophysical clues provided by suitable biomaterials can simulate the function of tendons, affect cell expression, and affect the speed of tendon repair. Among them, electroactive biomaterials can help ruptured tendons restore their native electrical microenvironment, assist surrounding tissues in releasing bioelectricity, and accelerate wound healing. Therefore, the emergence of low-cost ES materials can be used to create scaffolds or devices that can reconstruct the tendon's electrical microenvironment for use in tendon surgery.

Materials exhibiting piezoelectric effects typically have asymmetric crystal structures, allowing ions within the material to rearrange during mechanical deformation, thereby generating charges on the two opposing surfaces of the material. When the material is subjected to an external electric field, the arrangement of these ions is further adjusted, causing the overall polarization of the material and enhancing its piezoelectric response [157]. The ability of tendons to maintain their homeostasis after dynamic loading and return to their original state after injury depends in part on the restoration of primitive multiscale strain transfer mechanisms. When forces are applied through the ECM, cellular deformation through the actin cytoskeleton induces nuclear strain, which in turn affects transcription and a range of cellular responses [158]. Further, piezoelectric materials

simulate the natural internal environment to regulate local immunity, promote cell proliferation and differentiation, and enhance ECM synthesis, thereby achieving the goal of tissue repair [157]. In the design of the scaffolds, it is necessary to fully consider their electrical characteristics to maintain stability under mechanical load. Therefore, in order to adapt to the deformation, flexible and scalable scaffolds were developed, which gave the scaffolds basic wavy structure and hierarchical buckling structures to bear better mechanical properties [159]. The design of percolated networks has also been used in conductive materials, which can form a continuous network and adapt to mechanical strain through hinging/sliding, such as carbon nanotubes, silver nanowires, and copper nanowires [160]. Metal-based biomaterials are commonly used as reinforcement materials, and the conductivity and mechanical strength of tissue engineering scaffolds can be improved through surface modification and mixed filling, such as gold nanomaterials [161].

However, the application of piezoelectric materials in biomedical fields also faces several problems: the fragility of some materials, low efficiency, toxicity, and environmental impact [162–164]. As a result, green and biodegradable piezoelectric materials such as organic biodegradable amino acids, peptides, proteins, polysaccharides, and synthetic polymers are increasingly being pursued [165]. These natural or synthetic materials can either be broken down into basic molecules such as water and carbon dioxide or reabsorbed under biologically benign or physiological conditions [166]. In the long-term repair of tendons, the above adverse conditions can be avoided and the healthy repair of tendons can be promoted. For example: chitosan is a linear polysaccharide consisting of two different  $\beta(1-4)$  structural units randomly bonded together, which is recognized as a piezoelectric material. It is biocompatible, biodegradable, non-toxic, and easy to form a film, so it has a wide range of applications in the field of medicine and other fields [167]. PLLA is a transparent and very flexible plant-derived piezoelectric polymer material suitable for use in mobile devices. In addition, the piezoelectric constant of PLLA films can be designed and improved by increasing the crystallinity and molecular orientation, giving it many applications in future biosensors [168]. PVDF is a semi-crystalline piezoelectric polymer with five different crystal phases, among which the  $\beta$  phase is the most important, with high polarizability and high high-voltage sensitivity [169]. Kim [170] proposed a tendon-inspired piezoelectric sensor based on PVDF. The sensor can resist tensile loads and slides, and has the advantages of being flexible, lightweight, and compatible.

Smart repair scaffolds are endowed with mechanical, and electrical responses, etc., so the healing process can be optimized through dynamic response to the physiological environment [63]. For example, piezoelectric materials under

mechanical response, conductive materials under electrical response, and TENG under electrostatic and frictional coupling response. Our somatosensory system relies on receptors to convert stimuli into action potentials and transmit signals through neurons that are ultimately received and analyzed by the brain in order to make timely decisions. So the ideal sensors made from smart repair materials should be endowed with intelligent feedback and real-time monitoring capabilities [171]. For instance, carbon-based nanomaterials, MXenes, and other materials have been made into flexible sensors. Interestingly, the electromechanical properties of piezoelectric materials make it possible to convert the strain generated by biological movements (such as muscle contractions, body movements, blood circulation, breathing, heartbeat, etc.) into electrical energy [172]. It can easily record affinity interactions without the need for any special reagents, and the required loading sensitivity can typically be in the microgram range [173]. Therefore, piezoelectricity is highly suitable for manufacturing physical sensors and biosensors. Especially in the development of intelligent repair scaffolds and biosensors related to tendons, the cellular level electrical stimulation has a regulatory effect on the response of mechanical signals, which can manipulate ion channel activity to promote tenocytes differentiation [174]. Furthermore, it can not only be used as an implantable medical device to achieve a long-term stable energy supply, but also as a real-time sensing device to monitor a variety of vital signs such as heart rate, breathing, and blood pressure [53]. The use of the electrical release characteristics of piezoelectric materials to achieve accurate, controllable, and minimally invasive catalytic treatment may bring breakthroughs for future precision medicine or smart therapy [76]. In this way, biosensing scaffolds (electrospinning fiber membrane, hydrogel, 3D printing scaffolds, etc.) made from piezoelectric materials in various ways can not only restore the electrical microenvironment of tendon loss, but also monitor the status of tendon repair in real-time and make timely adjustments according to the actual situation. This not only saves time and costs, but also accelerates the tendon repair process, which is beneficial for the repair of ruptured tendon defects in patients.

Direct ES provides a precise, non-pharmacological means to regulate and control biological processes. This method has the potential to restore or enhance physiological functions damaged by disease or injury by integrating complex electrical signals, device interfaces, and designs targeting specific biological mechanisms [175]. According to previous research reports, DC stimulation, alternating current stimulation, and low-frequency pulsed electromagnetic fields could promote the healing of tissues such as bone, cartilage, nerves, and tendons [176]. Meanwhile, many biomaterials have attracted attention due to their conductivity properties, such as carbon-based conductive materials,

metal-based conductive materials, ion-based conductive materials, conductive polymers, and conductive composite materials [177]. Traditional direct ES devices require additional external power sources, making them less portable and comfortable. In addition, the potential for clinical use of ES therapy has not been fully realized due to spasticity, muscle pain, skin irritation, and inconvenience to the patient. Although some preclinical studies have reported the use of ES in tendons, these have not been translated into clinical research. Therefore, the potential strategic mechanism of conductive materials as tendon-tissue engineering scaffolds remains to be explored to a large extent. Therefore, the development of self-powered, flexible ES devices and the implementation of integrated treatment scaffolds or equipment are of great significance [178]. This requires high sensitivity, self-healing ability, and good biocompatibility to be taken into account in material design and manufacturing [179]. The materials that can generate ES are often diverse in dynamic environments, such as piezoelectric PVDF can also produce triboelectricity under friction. Therefore, there are intricate relationships between piezoelectric materials, conductive materials, and triboelectric materials. Further, the scaffolds and devices that can generate ES through electrospinning, 3D printing, etc. are also diverse. Therefore, the cross-application of materials that generate ES to maximize its functionality may have great potential for the development of tendon repair.

However, these materials still face many challenges that need to be solved, and efforts to break through the bottlenecks to hope for early clinical applications, the main points are as follows:

- 1) The surface morphology and structure of generated ES can affect cell behavior and tissue repair time. At present, there is a great need for intelligent biomaterials that can simulate tendon orientation structures, transmit physiological signals, and restore the native electrical microenvironment.
- 2) In addition, the degradation of the material can affect ES effectiveness. Therefore, the key challenge is to determine the balance between the degradation rate of scaffolds and the kinetics of tissue repair. That is to say, materials with different degradation rates should be selected based on the duration of tissue repair, and in vivo degradation should be simulated in vitro to repeatedly verify whether the degraded materials at different time points can still generate ES. For tendon, sufficient voltage and lifespan during degradation to ensure continuous current output and play a long-term role in the body to be suitable for the repair of various major tendon diseases.
- 3) Furthermore, some materials can cause excessive immune responses after implantation and affect the

repair process, so various scaffolds need to have biocompatibility and non-toxic degradation. For example, some conductive materials can be toxic in excess, and some electrodes can precipitate toxic products due to excessive heat. Then the scaffolds should be treated reasonably well in advance of fabrication to ensure that they are not harmful to organisms while not affecting their performance.

- 4) Computer modeling can help optimize the structure of the scaffold to achieve personalized customization, and it is also important to be able to monitor the connection between the scaffold and the surrounding tissue after implantation. At the same time, it should be possible to monitor the recovery of electrical pathways in the damaged tissue. The scaffold is further endowed with the function of monitoring the recovery of key pathways related to tendon diseases, so as to improve the rehabilitation plan in real time.
- 5) Finally, the comfort of the scaffolds in vivo also needs to be taken into account. The search for non-foreign body sensing and the long-term function of scaffolds is not only needed for tendon tissue repair but also for other tissue regeneration. With the increasing demand for wearable and implantable electronics, matching energy conversion devices and storage devices have become a popular research topic. Tendon, as an important connector that transmits muscle power to the bone, is an indispensable part of energy conversion. It is also important to develop a wearable and implantable electronic device to replace the missing tendon and achieve energy transfer.

## Conclusions

Tendons have a piezoelectric effect due to their special tissue structure, i.e. the directional arrangement of collagen fibril. The reconstruction of the destroyed native electrical microenvironment after the tendon injury is crucial. Currently, the scaffolds made of piezoelectric biomaterials, conductive biomaterials, triboelectric biomaterials, and other biomaterials that generate ES are a key means to reconstruct the native electrical microenvironment of tendons. However, ES scaffolds are currently limited in development or clinical translation. In the future, the development of long-term self-powered, flexible, and therapeutically integrated scaffolds or ES devices would be a major advancement in the field of tendon repair.

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