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Electroactive polymers for tissue regeneration: Developments and perspectives

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Abstract

Human body motion can generate a biological electric field and a current, creating a voltage gradient of −10 to −90 mV across cell membranes. In turn, this gradient triggers cells to transmit signals that alter cell proliferation and differentiation. Several cell types, counting osteoblasts, neurons and cardiomyocytes, are relatively sensitive to electrical signal stimulation. Employment of electrical signals in modulating cell proliferation and differentiation inspires us to use the electroactive polymers to achieve electrical stimulation for repairing impaired tissues. Electroactive polymers have found numerous applications in biomedicine due to their capability in effectively delivering electrical signals to the seeded cells, such as biosensing, tissue regeneration, drug delivery, and biomedical implants. Here we will summarize the electrical characteristics of electroactive polymers, which enables them to electrically influence cellular function and behavior, including conducting polymers, piezoelectric polymers, and polyelectrolyte gels. We will also discuss the biological response to these electroactive polymers under electrical stimulation. In particular, we focus this review on their applications in regenerating different tissues, including bone, nerve, heart muscle, cartilage and skin. Additionally, we discuss the challenges in tissue regeneration applications of electroactive polymers. We conclude that electroactive polymers have a great potential as regenerative biomaterials, due to their ability to stimulate desirable outcomes in various electrically responsive cells.

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Keywords

Electroactive Polymers; Conducting Polymers; Piezoelectric Polymers; Polyelectrolyte Gels; Tissue Regeneration

1. Introduction

The biological electric field that the human body generates plays a pivotal role in wound healing due to the steady, direct current and electric field, which drives cells to migrate to the point of injury [1]. Moreover, a voltage gradient, called “action potential”, of −10 to −90 mV can trigger different cell types to change proliferation and differentiation by signaling across cell membranes [1,2]. The potential for harnessing the electric fields in cells to enhance growth and differentiation in biological systems has gained the attention of researchers. As is known, regeneration of damaged tissue begins with the growth and proliferation of cells [1,3]. Thus, to stimulate and enhance this regenerative process and thereby promote rapid healing of the damaged tissue, electroactive biomaterials are often considered for use as a tissue regeneration scaffold.

Electroactive materials provide a direct method for various forms of electrical stimulation to reach cells [3]. The electroactive materials include inorganic electroactive materials, metals and organic electroactive polymers. Recently, it is shown that specific amounts of electrical stimulation via electroactive materials could enhance the regeneration of cardiac [4], nerve [5,6] and bone through directing cell adhesion [7], growth, migration, apoptosis [8] and differentiation [9]. Thus, electroactive materials have the potential to evolve tissue healing and engineering treatments (e.g., bone [10,11] and nerve [12] regeneration). Particularly, electroactive polymers (EAPs) have received increasing attention (Figures 1 and 2) because the human body contains many electro-sensitive tissues such as bone, skin, nerve, heart and vessels [13]. In particularly, they have seen varied and extensive employment in tissue engineering (Table 1) because there are some advantages, such as the possibility of being constructed into varying shapes with attractive morphological features and a large selection of physical and chemical properties. To date, there are many reviews about the medical application of conducting polymers [5,14–16] and the tissue engineering application of piezoelectric materials [17,18]. However, there are few reviews for the application of electroactive polymers, including conducting polymers (CPs), piezoelectric polymers and polyelectrolyte gels, in tissue regeneration. This report will attempt to fill this gap.

2. Electroactive polymers

Under a stimulus, EAPs convert one form of energy into a more desirable electrical state, thus affording tremendous promise in emerging technologies for responsive prosthetics [69–71]. A typical characteristic property of EAPs is that they will undergo a large amount of deformation while under the pressure or being stretched. When electric charges are on the top of a polymer, a redistribution of charges within the polymer is observed; this is dependent on the polymer’s ability of being responsively mobile [69]. The observed response of the polymer to an electric field is divided into two distinct categories. One is dielectric properties (dielectric constants and dielectric relaxation). Another is conductive

properties (conductivity and dielectric strength) [70]. EAPs produce additional novel electrical properties, such as ferroelectric, photoconductive, piezoelectric, triboelectric, or pyroelectric characteristics [71]. Over the last ten years, EAP materials have garnered increasing attention as they are developed for different prospects in biomedicine such as tissue engineering scaffolds, drug delivery, biosensors, artificial muscles, actuators, power generators and various medical instruments and auxiliaries (Figure 1) [72–74]. So, the interest in EAPs is increased because these “smart materials” have the ability to be responsive under varied external stimuli [75]. EAPs are unique in the biomedical field because they can convert different types of signals, such as mechanical, thermal, and magnetic, into electrical ones. This provides the opportunity to use EAPs in scaffolds for the stimulation of cell growth in tissue regeneration [8, 76].

EAP history starts in 1880 with the discovery of electromechanical coupling effects from the experiment where the rubber fixed at one end changed from charged to discharged [77]. Sacerdote [78] then conducted the same experiment and revealed the relationship between strain and electric field. In 1925 a piezoelectric polymer was identified [78]. Despite a lack of further work being explored, EAPs have become known for their reaction to electrical stimulation and the promise of practical and convenient applications. EAPs are readily categorized into two groups (electronic and ionic, Table 2) on the basis of the differing activation principles [79]. Electronic EAPs function by using the electrostatic forces of two electrodes to cause actuation to contract a polymer; this includes materials such as piezoelectric, electrostrictive, and ferroelectric. Ionic EAPs, on the other hand, function by displacing the ions contained in the polymer to cause actuation [80]. Examples of the ionic EAPs include polyelectrolyte gels, conducting polymers, and polymer-metal composites [72,79].

The most common applications of EAPs are in actuators and sensors. In recent years, the tissue regeneration applications of some EAPs have been increasingly developed. For example, piezoelectric polymers function by delivering electrical stimulus with limited control, despite not having an external power supply [81]. CPs are biocompatible, with high conductivity/weight ratio and good optical properties. They are also capable of controlling electrical stimulation precisely. However, they need an externally powered electric field [5]. Additionally, conductive polymers allow fine-tuning of chemical, electrical, and physical properties to fit the needs of the biological moieties in which they are employed [3]. In this review, CPs, including Polypyrrole (PPy), Polyaniline (PANI), and Poly(3,4-ethylenedioxythiophene) (PEDOT), piezoelectric polymers, including Polyvinylidene fluoride (PVDF), Polyhydroxybutyrate (PHB), and Poly(L-lactic acid) (PLLA), as well as polyelectrolyte gels, will be discussed regarding their properties and applications in tissue regeneration.

2.1. Conducting polymers

The interest in the potential biomedical capabilities of CPs has driven researchers to develop novel techniques in order to harness CPs capabilities. CPs are unique in that they offer easy synthesis methods and exhibit desirable elecrical and optical properties that closely resemble those of metals and semiconductors [82–84]. Initially, polyacetylene was observed to be

conductive after being oxidized by iodine vapor, intriguing the interest of scientists [85,86]. However, polyacetylene is unstable in air and difficutlt to synthesize [87,88]. Now PPy, PANi, PTh and, PEDOT are the most extesnively studied CPs [88,89] (Figure 3).

CP synthesis can be done chemically or electrochemically. Chemical methods allow for customization of possible synthesis routes and scales, providing many variant CPs [90]. Despite the benefits of chemical synthesis, electrochemical synthesis provides an easier method. Therefore, it is the common procedure for making CPs [91]. Ease of synthesis and the ability to simultaneously dope and encase molecules are advantages to synthesizing CPs via electrochemical methods. However, in the electrochemical methods, challenge in covalent modification after synthesis of CPs and difficulty in removing films from electrodes are disadvantageous. Another limiting factor of electrochemical synthesis is its inability to function outside of a system where monomers are oxidized after applying potential, forming reactive radical ion intermediates allowing for polymerization. Despite the complexity of chemical synthesis, wider varieties of covalent modifications to the CP backbone and postsynthesis colvalent modifications are made possible with this method [92]. The chemical polymerization methods produce powders or exceptionally thick CP films; conversely electrochemical synthesis produces very thin CP films (20 nm), marking a major difference between the two. Several unique CPs are only synthesized while using chemcial methods but more known CPs (e.g. PPy, PANi, PTh (Polythiophene), PEDOT) are developed by utilizing chemical and electrochemical methods [14].

2.1.1. Polypyrrole—PPy is easy to be synthesized and modified on the surface and has a high electrical conductivity, so it is the most studied conjugated polymer [93]. PPy exhibits a high stability in environmental settings and stimuli-responsive properties. It helps cell attachment and proliferation, suggesting its possible use as a “smart” biomaterial [94]. Primarily, PPy is biocompatible [95,96], and chemically stable and conductive in physiological conditions [97]. PPy has easy and variable synthesis processes, allowing for large quantity synthesis at room temperature with multiple solvents [98,99]. PPy has the ability to be made usable in biomedicine by combining it with bioactive molecules [100,101]. Unfortunately, PPy is challenging to manipulate further after synthesis [102]. It also has a non-thermoplastic structure [99] after synthesis that is found to be insoluble, mechanically rigid, and brittle [102]. PPy today is used in fuel cells [103], corrosion protection [104], biosensors [105], drug delivery systems [106], biomaterials for neural tissue engineering [106], neural probes [48], and nerve guidance channels [107].

Despite the attractive processing properties of PPy, long term toxicity studies have yet to be evaluated *in vivo*. Additionally, the insoluble, rigid, and brittle composition of PPy limits post synthesis processing capabilities. This makes unmodified PPy a poor choice for many biomedical applications. In order to apply PPy as a biomaterial, further *in vivo* testing is needed due to its insoluble and rigid nature.

2.1.2 Polyaniline—Polyaniline (PANi) or aniline black, much like PPy, has been heavily studied [108]. PANi has three forms of existence, i.e., pernigraniline base (fully oxidized), emeraldine base (half-oxidized) and leucoemeraldine base (completely reduced) [108]. Additionally, PANi emeraldine provides the highest level of conductivity and stability [108].

PANi is cheap, environmentally stable, and easy to synthesize. It also has the capability to alternate between conductive and resistive states electrically [109]. Unfortunately, PANi lacks plasticity, is non-biodegradable and shows low cellular compatibility. Furthermore, once implanted chronic inflammation has been documented [86,110]. PANi is currently being tested for applications in biomedicine such as biosensors [111,112], neural prostheses, drug delivery and release system [113,114], and tissue engineering [60,115].

2.1.3. Polythiophene (PTh) derivative—PEDOT, a PTh derivative, is the third very interesting conjugated polymer [52]. PEDOT is synthesized by the polymerization of the bicyclic monomer 3,4-ethylenedioxythiophene (EDOT). Compared to PTh, PEDOT has improved properties in lowered band gap and its reduction and oxidation potential [116]. These properties provide PEDOT with a valuable electrical, chemical and environmental stability. When compared to PPy, PEDOT is more thermally established and conductive [117]. Investigations on PEDOTs capabilities and characteristics are fairly young when compared to PPy and PANI studies. Despite the fairly recent development of these investigations, PEDOT's biocompatibility is already well established. Today PEDOT is used in biosensing and tissue engineering [84], neural electrodes [51,118] and heart muscle patches [89].

2.1.4. Conducting polymer composites—CP's most attractive qualities are good stability, high electrical conductivity, and the capability to dispense biomolecules. CP's electrical, chemical, physical, and biocompatibility properties can also be modified to aid the applications. Despite the positive qualities, CPs is limited in biomedical applications because it is difficult to handle and brittle, while larger dopants can make these conditions worse. In order to bypass these technical challenges, CPs are blended or composited together with another polymer, which allows exploitation of positive aspects from both materials. By using CP composites, higher solubility and improved mechanical properties are obtainable for employment in biomedical applications while avoiding significant compromises to other properties, such as conductivity [14,119].

Effectively, researchers have managed to develop CP composites by combining CPs with other polymers for desired properties. For example, researchers have paired PPy and PANi as conducting fillers with natural polymers in an attempt to increase the processing ability of CPs, which can also improve the conductivity of insulating polymers [120,121]. CP composites have better mechanical properties resulting from doping with large molecules. These alternative processes aren't a perfect fix; the use of insulating molecules can produce electron conjugation interference within the CPs.

A lot of studies have been done on the *in vitro* capabilities of the CP composite materials. While this is important, there is a lack of animal studies, which must be done in order to move to human clinical trials in the future. CPs show promise in fulfilling a role for use as medical implant materials, specifically for neural stimulation and sensing. These materials also show promise in regenerating tissues that need electrical conductivity to assist with cell growth.

2.2. Piezoelectric polymers

Piezoelectric polymeric materials have no energy or power supply requirements to promote transient surface charge. Inspired from the piezoelectric character of the bone [122], the idea of using piezoelectric materials to correct bone defects emerged in the 1970s [123] because they have been shown to actively stimulate tissue by electrically and mechanically solicited responses. Piezoelectric materials have been studied by *in vivo* tests, and they have been shown to accelerate bone regeneration. Of the varying types of piezoelectric materials, piezoelectric polymers have shown to exhibit simple processing, flexibility and physical properties, making it an option for various applications. PLLA, PHB, PVDF and their co-polymers are the EAPs with the largest piezo, pyro, and ferroelectricity responses (Figure 4) [7,9]. To date, the most common piezoelectric polymers are PVDF, collagen, PHB and their composites.

2.2.1. Polyvinylidene fluoride—Piezoelectric properties are displayed by a small number of synthetic polymers, such as PVDF, PLA and PHB [81]. PVDF and its copolymers showed the highest piezoelectric constant among this group. Thus, they are the best applicable polymer of the piezoelectric response materials for specific applications [124]. PVDF exhibits impressive polymorphism. It has at least 4 crystalline phases, including α, β, γ and δ [125]. β-phase PVDF is considered the most appropriate for electrical response applications because it bears the best piezoelectric coefficients [126].

PVDF has significant electroactive properties for a biocompatible material [7]. The piezoelectric effect exhibits an electrical potential brought on by the induction of mechanical stress. The positive or negative surface charge carried by PVDF films is known to influence hydrophobicity of the specimens, developing a diversity in absorbed extracellular matrix protein conformation. This eventually leads to the control of stem cell adhesion and induced osteogenic differentiation. Studies have shown that osteoblast attachment and growth is heavily dependent on the surface charge [127], indicating that PVDF has the ability to be used as an osteogenic material when the surface charge of the substrates is needed to increase functionality [128].

2.2.2. Polyhydroxyalkanoates—Polyhydroxyalkanoates (PHAs), a unique biodegradable polymer, is a natural byproduct of bacteria as a carbon/energy complex [129,130]. This group of biopolymers, whether naturally occurring or engineered polyesters, exhibits a wide range of physical properties [129]. PHAs generally exhibit multi-lamellar structures that have aggregated into lamellar crystals that have varying orientations when in plane, or other bulky forms like films [130]. When PHA chains crystalize following melting of bulk materials, spherulites generally form; these crystals form in twisted radial lamellar structures. The polymers formed in this way exhibit piezoelectric and optical activity. These polymers are insoluble in water. They are also inert, non-toxic and highly stable in air. PHAs are usually broken up into two groups. Short chain PHAs have 3–5 carbon atoms in monomeric units whereas alternately medium chain length PHAs have a 6–18 carbon atoms in monomeric units. Poly(3-hydroxybutyrate) (P3HB) as well as poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (P(3HB-co-3HV)) are the most abundant PHAs [23,131].

2.2.3. Poly (L-Lactic acid)—Poly (lactic acid) (PLA) is a frequently used biomaterial. Primary characteristics include low density and processing power, as well as corrosion resistance, elastomeric behavior, and multi-purpose construction [72]. Due to its bio-resorption, low toxicity, degradation, biocompatibility and useful mechanical performance, its presence in the medical field continues to grow. PLA can exist as linear polyester stereoisomer forms, including (poly(L-lactic acid) (PLLA), poly(D-lactic acid) (PDLA) and poly(D,L-lactic acid) (PDLLA) [72,132]. PLLA has optical activity characteristics and PDLA exists as its optical isomer. Piezoelectric effects of drawn PLLA and PDLA have been studied in the past using rods and films [133,134]. It was shown that shear piezoelectric constant d_{14} increased with the draw ratio, obtaining values of approximately 10 pC/N. This happens because there is a noticeable increase of PLA polymers chain alignment caused by stretching [135,136]. PLLA is the most common form of PLA and is mainly used in biomedical applications [137]. PLLA shows promise as a biomaterial for applications in bone regeneration and growth as well as neural recovery because it can display the electro-response induced by stress.

2.2.4. Piezoelectric polymer composites—Despite the positive qualities of PVDF and other piezoelectric materials, their ability for external stimulation control is restricted. Piezoelectric polymers are blended or composited together with another material, which allows the resultant composite materials to integrate beneficial properties from both materials. By using piezoelectric polymer composites, higher stability and improved piezoelectricity can be achieved, enabling their biomedical applications. In general, piezoelectric polymer composites can be formed by blending piezoelectric polymers with other piezoelectric materials. PVDF and piezoelectric ceramics are mostly used to form piezoelectric polymer composites [138,139]. Thus, piezoelectric polymer composites exhibit the advantages of both piezoelectric polymers and ceramics, such as good flexibility, processability and biocompatibility as well as high piezoelectric constant. Moreover, compared to either piezoelectric ceramics or polymers alone, the piezoelectric polymer composites have improved mechanical stability [140], further favoring potential tissue regeneration applications.

2.3. Polyelectrolyte gel

Polyelectrolyte gel is a kind of polymer with ionized groups. It can be ionized in water or polar solvents to produce charges along the polymer chain [67,141,142]. Polyelectrolytes differ from neutral polymers due to the presence of ionic groups which are covalently attached [141]. Polyelectrolytes, like the well-known bio-polyelectrolyte DNA that has charged groups, carry both charged or chargeable groups. A polyelectrolyte multilayer can be made with a layer by layer (LbL) technique [67]. Polyelectrolyte gels share properties with both their macromolecules and electrolytes. Polyelectrolyte gels can induce charge movement or volume change in response to temperature, pH value, and environmental factors such as electric field or magnetic field changes. Thus, they can convert external stimuli into electrical and mechanical signals. They can be employed in biology due to their biocompatibility and extensive charge density [67]. A diverse set of polyelectrolytes can be used for biological tissues, such as polysaccharides, proteins, heparin, chitosan, and hyaluronic acid. Particularly, drug delivery and tissue engineering can be facilitated with

polysaccharide polyelectrolytes. Heparin, chitosan, and hyaluronic acid are biomedical polyelectrolytes that bear sulfate, amino, and carboxylate groups, respectively [142].

3. The biological response to electric stimulation

3.1. Protein behavior under electric stimulation

In many cases of biotechnological applications and biological phenomena, protein absorption is naturally occurring [143]. It is generally accepted that proteins take on a prominent role in guiding biological signaling and functions [144]. The first step of integration for surrounding cells and tissues with biomaterials is initiated by protein absorption [117]. Understanding cell-substrate interactions is critical when judging the biological reaction caused by implanted biomaterials. From the biological view point of the cells, proteins first coat implanted materials from blood and interstitial fluids before the cell adhesion occurs [145]. Protein adhesion generally mediates the cell adhesion, cell growth, and differentiation. However, interfacial protein absorption is found to be nonspecific, which can damage the usefulness of the biomaterial [117]. Therefore, biocompatibility and consequently the success of implants depend on the interfacial interactions between proteins and the synthetic materials [144].

A better understanding of the process starts with the knowledge about the polarization effect on the adsorption of proteins at the early stages of material implantation. This first stage is decisive because it will mediate the cells' attachment and subsequent tissue growth. Indeed, the nature, quantity, density, and conformation of adsorbed proteins all depend markedly on the biomaterial surface characteristics. In fact, the behavior of protein absorption is dependent on internal properties (e.g., protein, surface and solvent) and external stimuli (e.g., electric field, thermal, light, and magnetic field) [143]. Over the years, many studies have been done on protein absorption, concentrating on internal factors to control protein behavior on the surface [146,147]. However, when discerning which way is more favorable to control protein behavior, external factors prove to be both more convenient and flexible. In this case, it is possible to apply external stimuli to the system without modifying the properties of the component materials. With this method the external stimuli can be tuned to the desired direction and/or strength in order to optimize the system for various specific applications. Additionally the use of external stimuli can assist with interfacial property control [148], allowing for protein behavior control to happen indirectly at the interfaces. When considering external factors, a possible point of control of the spatial homogeneity is offered with the application of an electrical field; this method provides the same possible control for the growth and direction of protein monolayers [143]. Zhou et al elucidated that absorption of lysozymes was increased when surfaces were negatively charged, conversely, it was dampened by positive electric fields [143]. Primarily, proteins migrate and orient under an electrical potential gradient due to the overall net charge and permanent dipole. Electrical stimulation has the ability to electrically drive changes in the polymer's redox state in order to actively and precisely control protein interactions.

3.2. The cellular response to electric stimulation

Cellular response to electrical stimulation on a biochemical and physical level is extremely complicated and is still primarily a mystery. The cell membrane is the primary environmental contact and the surface of the membrane carries negatively charged chemical groups such as carboxylates and phosphates. Concentrations of soluble ions inside the variant ion pumps, transporters, and channels are the primary sources of regulation for cell activity. These various sources generally regulate membrane proteins that are sensitive to externally induced electrical stimuli, among other stimuli [149]. Certain regulatory membrane proteins as well as enzymes are considered voltage sensing proteins. These molecules sense and also use external electric fields as the mechanism of regulation. Once a cell is attached to a surface, it uses these ion channels and receptors built into the membrane to evaluate the environment. The cell then evaluates the chemical and physical signals being presented by the environment before integrins are used as a way to associate with proteins that link to the cytoskeleton intracellularly. This develops focal adhesions by binding the cluster integrin receptor and ligands of the extracellular matrix (ECM) [145].

Some studies [53,117] investigated electrical control with PEDOT substrates on extracellular matrix proteins, including cellular material interaction moderators like fibronectin (Fn). The goal of these investigations was to arrive at a possible electric control that works through changing cellular redox properties to assist in applications for culturing cells *in vitro* (e.g., to enhance cell proliferation). While electrical control is being applied, it can induce the change of the conformational states of the ECM protein, which causes shifts in cellular responses like migration or adhesion. Fn on oxidized PEDOT has possible applications in a specific conformation that exhibits motifs for cellular binding (i.e., RGD domain), which can assist in cell attachment and proliferation (Figure 5). Heparin doped oxidized PEDOT has mediated commanded release of fibroblast growth factors anchored to the surface to upregulate stem cell differentiation recently. This shows a correlation between electrochemical switches and accurate sequential mediation of stem cell states.

Our research group has found that PPy nano arrays on a titanium surface could be switched by redox potential [150,151]. We further studied a potential switchable PPy nanotubes doped with taurocholic acid (TCA). Such nanotubes showed reversible surface wettability, which further led to possible adsorption preference switching between three model proteins with different isoelectric points. The protein adsorption control further directed the adhesion and spreading of MC3T3-E1 osteoblasts (Figure 6A) [152]. Additionally, our group showed that β-Naphthalene sulphonic acid (NSA) doped PPy nanocone arrays controlled protein adsorption and bacterial adhesion as the surface potential and wettability were regulated by applying a redox potential [153]. Such control enabled the controlled cell adhesion to or detachment from the surface (Figure 6) [154]. The potential-switchable surface chemistry may provide clues for designing biointerfaces in biomaterials, and offer guidance for studying the dynamic cell behaviors. It would also shed light into intelligent drug delivery and release systems as well as controlling biological activities on the biomedical implants.

It has been reported that endogenous electric fields are 40 to 500 mV/mm in living tissue [155]. Transportation of macromolecules and ionic species connected with such fields is important in treating neurological injuries and wound healing [156,157]. Intra- and extra-

cellular ionic concentrations present a variation that results in a potential across the membrane of 10 to 90 mV in various cell types. Such shifts of potential have been indicative of a change in cell proliferation and differentiation [158]; When the excitable cells have been excited after being in a resting state, they show rapid spreading in response to an action potential [159].

Application of electrical stimuli is possible through either the medium or substrate [160]. Current application through CPs like PPy and PANI provide indirect routes for electrical stimulation [161]. CPs have shown a positive trend for cell proliferation and extension when they are used as a substrate even without the addition of electrical current, when compared to samples that did not have a CP based substrate [162,163]. Fn adsorption increased heavily when a 10 μA current was applied onto the surface directly, this was observed especially when Fn had high concentrations at early exposure stages. PC-12 cells seeded on the films of this nature had up to 50% longer neurite growth when compared to films that went unstimulated [164]. Schmidt et al [165] applied an electrical field at 100 mV/mm to a PPy-coated electrospun scaffold. Then they found the lengths and number of neurite-bearing cells significantly increased. This demonstrated that there is a tissue regeneration application potential with electrical stimulation through electroactive polymers [166].

4. Electroactive polymers for tissue regeneration applications

Non-electroactive polymers, such as polydimethylsiloxane (PDMS) [167–169] and poly (lactic-co-glycolic acid) (PLGA) [170,171] have been widely used in tissue engineering. Although they bear good biocompatibility and can be easily processed, they are not “smart” in that they do not respond to electrical stimuli. However, EAPs, while still having biocompatibility and easy processibility, can respond to electrical/mechanical stimuli, enabling them to influence the fate of cells or tissues electrically or mechanically. This unique feature allows them to serve as a unique “smart” candidate for developing the scaffolds capable of directing cell fate and promoting tissue regeneration.

4.1. Conducting polymers

CPs as a novel organic material originally began production in the mid-1970s [172]. CPs continue to attract a lot of attention as do their composites for two reasons. One is due to their interesting electrical and optical characteristics that are akin to inorganic semiconductors and metals. Another is because CPs also have classic polymer characteristics, like easy synthesis and processing flexibility [173]. The fact that electrical stimuli of CPs generate tissue response makes CPs increasingly interesting for a large diversity of biomedical applications including biosensors, modified neural electrodes, tissue engineering[174] as well as drug delivery [173,175,176]. In tissue engineering areas, the primarily used CPs include PPy [93], PANI [177], PEDOT [117].

4.1.1. Polypyrrole—PPy is generally the most studied CP for applications in biomedicine because of its good conductivity, environmental stability, facile preparation, redox and excellent biocompatibility [178,179]. A number of studies have shown PPy is compatible with various cells, including nerve cells, endothelial cells, myocardial cells, osteoblasts and mesenchymal stem cells (MSCs) [29,43]. With the development of biomedical material

technology, PPy has been shown increasingly promising in repairs and regeneration of damaged tissue.

Neural cells communicate via electric pulse as their membrane has voltage gated ion channels. These channels are triggered by variations occurring in electrical potential near them. An extensive amount of research has been done on the electric stimulation of neuron growth as it mimics neuron-neuron communication. Examination of PPy, both as neural probes [12] and as scaffolds, was implemented for nerve conduit since axon was elongated through electric stimulation. For example, Yow et al [180] fabricated a collagen-based 3D fibrous scaffold containing PPy and showed that human MSCs (hMSCs) grown on PPy fibers expressed characteristic markers denoting a neural lineage. They also demonstrated that cellular function could be influenced by external electric field utilization and that when stimulation was extended over a long period, it could be detrimental to the culture system [181].

Currently it is believed that Schwann cell (SC) migration precedes and enhances axonal repair in the peripheral nervous system [47]. Schmidt et al [43] have explored the SC behavior on PPy by utilizing electrical stimulation and the effect of SC behavior on the neural regeneration. Their study revealed average displacement of the SCs increased with the electrical stimulation, which had an overall net anodic migration effect. Additionally, protein adsorption had indirect effects after oxidation of the films due to electrical stimuli causing an extensive effect on the speed of migration but less so on the directionality. SCs would directly migrate from the proximal to the distal end of the injury induced by electrical stimulation through a conduit. The increase in SC migration to the distal end would result in a higher degree of neural regeneration and possibly an increase in functional recovery. Huang et al [47] provided evidence that the conductive PPy/chitosan films heightened the viability, adhesion as well as spreading of SCs with or without electrical stimuli (Figure 7). Interestingly, the electrical stimuli applied through the PPy/chitosan composites caused an extreme increase in the production of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) in comparison with cells that were not exposed to electrical stimuli [182]. These interesting results proved PPy to be invaluable in nerve repair.

Cardiovascular diseases are the primary cause for death compared to other illnesses [183]. Recently, attention has been paid to generating cardiac patches [58] and heart valves as “spare parts”, and developing functional myocardial stents for cardiac repair [184]. Electrical conductivity of the PPy scaffolds has the possibility to be a critical part of cardiac and neural tissue engineering. Electrical stimulation producing a reaction is a pivotal characteristic of neuron and myocyte differentiation and function [27,28,58] (Figure 8). Recently, cardiac differentiation has been promoted by using porous and fibrous scaffolds or 2D substrates incorporated with PPy or PANi [59–62,185].

Cardiac cells need to develop the right intracellular networks and matrix architectures, enabling the transmission of electrical impulses at a normal speed in the correct direction [186]. Cardiac muscle contraction, which forces the natural mechanical stretch of the heart, is triggered by waves of electrical impulses. Due to this fact, any hindrance in the electrical

signal conducting pathway develops into cardiovascular disease [187]. It is at this point that CP scaffold based methods have the chance to be applied to cardiac tissue regeneration.

For instance, PPy and heparin composites were found to be a positive substrate for endothelial cell proliferation [188] and vascularization was also promoted by PPy-hyaluronic acid composites [189]. In addition, the blood Rhesus factor, an antigen present on the surface of red blood cells, could be detected with erythrocytes doped PPy because Rhesus factor antigens were on the surface of cells. ELISA test confirmed that undoped PPy bound less antibodies than the erythrocytes doped PPy [25].

Bone is sensitive to electrical stimulation because of its piezoelectricity. Therefore, many experiments have been executed to modulate osteogenesis through implants transmitting electrical stimulation to cells. CPs are suitable materials as implants due to their responsivity of electrical signal. Thus, PPy also holds promise in bone tissue regeneration. In recent years, our team has constructed various biomolecules doped PPy nanostructures [190] and verified their biocompatibility suitable for bone repair. We have electrochemically constructed different kinds of PPy nanostructures doped with chondroitin sulphate (CS) [191], polydopamine (PDA) [192], taurine (Tau) [193] or citric acid [194]. We found that the surface wettability was reversibly switched under the redox potential [195,196] and that biomolecule doped PPy improved osteogenic differentiation. These works are important in driving the development of nanostructured PPy application in bone tissue regeneration.

4.1.2. Polyaniline—PPy has negative mechanical properties and poor processibility, limiting its possible applications. This disadvantage of PPy makes PANi a plausible alternative and a highly studied CP because PANi is cheap while having better processibility and good environmental stability [114,197]. Hence, many of PANi characteristics are known, including many structural forms, low cost production, good processibility, environmental stability, and the capacity to transport charges via the “doping/dedpoing” process [198]. Despite the possible benefits, PPy has been more studied than PANi for tissue engineering applications [173,175,199]. PANi was later proven to be biocompatible *in vitro* and *in vivo* [200]. Bidez et al. found that PANi and its variants could support the adhesion and proliferation of H9c2 cardiac myoblasts [201,202]. PANi and gelatin blends could be electrospun to form nanofibers for favoring H9c2 cell adhesion and growth [181]. These studies indicated the potential application of electroactive PANi in cardiac and nerve tissue regeneration.

The nervous system is a close network of neurons, cells that are excitable by electric signaling that transmit signals at an accelerated pace. Earlier many methods were proposed to repair and regenerate damage to the central and peripheral nervous systems, using several different non-conductive scaffolds [203]. With the development of CPs, scaffolds based on CPs have been exploited in the neural regeneration since neuronal function can be triggered by electrical stimuli. Several theories have evolved to explain how electrical stimulation positively regulates neurite growth and nerve regeneration [204,205]. CPs like PPy and PANi have provided a new way to accommodate and increase growth and regeneration of nerve tissue without growth factors, when constructed into scaffolds and stimulated by electrical signals [5, 206].

4.1.3. Poly(3,4-ethylenedioxythiophene)—PEDOT has a lot of potential as a regenerative material because successful application of PEDOT has led to the development of a neurotransmitter delivery system made of electronic ion pumps in animal models [207]. PEDOT is also used for synthesizing organic electrochemical transistors that can be applied to biosensing [208]. Richardson et al [209] studied relationships between neural cells and PEDOT in order to construct biomaterials that possessed an electric conductivity and could form functional interface with electrically active tissues (e.g. heart and skeletal muscle or the nervous system). They also developed microelectrodes and CP-live cell electrodes by using PEDOT to coat neural cells [5].

Implantable electrodes with PEDOT can be employed to induce nerve impulses electrically or record neuron signals [210]. For example, Green et al [211] prepared platinum electrodes coated with laminin peptides doped PEDOT. They then investigated the bioactivity of the peptides and the vitality and proliferation of PC12 cells on the electrodes. The results provide evidence that dopants of large peptides generate softer PEDOT films. Outgrowth of longer neurites was shown on the PEDOT films doped with laminin peptides than on those without being doped. Peramo et al [212] studied a process for in situ chemical polymerization of PEDOT in acellular muscle tissue constructs. These experiments showed in situ polymerization happened all through the tissue; this altered the substrate from a non-antigenic substrate to a substrate with extensive acellular properties, a pivotal alteration in order to test nerve repair and artificial prosthesis.

When neural cells were first seeded onto electrodes, direct electrochemical polymerization of PEDOT formed CP matrixes around adhered cells [25,213]. It was found that there is an intimate relationship between PEDOT surfaces and the neuronal membrane, causing the exhibition of an unusual polymer-electrode interface when the surface was coated by fragile filopodia and neurites [213]. Yu et al [214] have constructed CPs that have several interesting properties when they’re designed to mimic cell membranes, displaying elevated nonspecific enzyme/cell binding resistance as well as targeted cell recognition used for electrical communications persisting an extensive length of time. They determined that these membrane mimics were able to promote neural cellular behavior by incorporating biochemical and electrical stimuli. Neurite extension was highly impacted and increased on the CPs (Figure 9). Additionally, Schwan cells have the ability to secrete proteins due to electrical stimulation. These biomimetic PEDOTs display elevated electrical/ionic conductivities, making electrical communication possible and efficient at the cell-material interfaces. This method has far reaching opportunities for employment. CPs of this nature can be used to target ligand-receptor interactions as well as cell-electronic interfaces. Polymers such as these are attractive and necessary for *in vivo* testing of bioeletronic devices.

4.1.4. Conducting polymer composites—Allowing CPs to form composites with other materials is an alternative strategy for developing novel CP materials for tissue regeneration applications. For example, fiber materials coated with PPy doped dodecylbenzenesulfonate (DBS) were studied to mimic the ECM, providing a 3D microenvironment for cardiac progenitor cells (CPCs). Cell types with increasing sensitivity to these scaffolds were presented [215]. Petrov et al [216] have fabricated novel

nanocomposite cryogels made of electrically conductive 2-hydroxyethylcellulose/polyaniline (HEC/PANi). It showed positive response to cell growth and survival. Moreover, cell morphology was altered by electrical stimulation and cell arrangement was found to be parallel to the applied electrical field. PPy functionalized graphene (PPy-G) was originally synthesized by a simple but effective mall milling method [217]. PPy-G based aligned nanofibers were then designed to provide electrical stimulation and guide the growth of retinal ganglion cells (RGCs). Once electrical stimulation was applied to RGCs, their viability, neurite elongation, and antiaging properties showed significant enhancement. This result suggests applications for optic nerve regeneration with the same method is possible. Guo et al [218] have synthesized the CP composites made of polylactide and adjustable components of the aniline oligomer. The MC3T3-E1 cells and BMSCs cultured on the resultant CP composites exhibited cytocompatibility and a significant increase of cellular propagation [15]. Osteogenic differentiation of BMSCs was promoted by the CP composites. If such composites elicit the desired cellular response, they might be useful for modifying neural, cardiac and bone tissue implants.

4.2. Piezoelectric polymers

Piezoelectric materials, capable of generating electrical charges when exposed to a mechanical pressure, are the materials of choice for all the applications in which electro-mechanical transduction is needed. They represent one of the most valuable biomedical materials. Many studies confirmed that mechanical forces play a role in increasing osteogenic differentiation and morphogenetic maintenance [219]. Osteoclasts, osteoblasts, osteocytes and MSCs are sensitive to force stimulation *in vivo*, and have the unique capability to respond to it, because they are exposed to a dynamic and balanced mechanical environment. This environment, including tension, shear, stress, fluid strain and flow-potential, is the mechanical environment in nature. Due to the complexity of the bone, it is unlikely that the specific effects will ever be separated, but it is understood that multiple factors have the capability to independently regulate cell response and drive remodeling events within bone [220].

Bone bears piezoelectricity as a result of its constituent piezoelectric collagen fibers. Both dielectric and piezoelectric properties of bone are dependent on the frequency, direction, and intensity of the stimuli, as well as the humidity of bone. Piezoelectric coefficients of human bone have been recently measured up to 0.7 pC/N [221]. The recognition of the piezoelectric character of the bone inspired the idea emerging in the 1970s of using piezoelectric materials to correct bone defects. The suitability of a few piezoelectric materials (ceramics of barium titanate (BTO), PVDF, collagen, PLLA, and their composites) for bone substitution has been studied by *in vivo* tests. These tests have been shown to accelerate bone regeneration [222–225].

4.2.1. Polyvinylidene fluoride—PVDF and its copolymers are piezoelectric materials most suitable for biomedical application due to their highest piezoelectric properties [226]. The biocompatibility of PVDF has been investigated [227]. Studies have indicated that poled PVDF films controlled MSCs adhesion and activated osteogenic differentiation [7] due to

the variations of the surface charges. Therefore, PVDF may find applications where surface charge may influence the interaction between material's interface and tissue [228].

Piezoelectric nerve guidance channels made of PVDF have been tested *in vivo* on mice with transected sciatic nerve [229]. After four and twelve weeks of implantation, poled and unpoled PVDF channels were compared, and nerve regeneration was evaluated. In every tested animal, when comparing nerve regeneration, larger amounts of myelinated axons were found in piezoelectric channels than nerves that were regenerated under non-piezoelectric channels. These results were achieved without any external stimulus, only exploiting the positive effect of the presence of a piezoelectric material. Young et al [230] designed membranes of microporous PVDF immobilized with the lysine component in order to assist nerve tissue regeneration. PC-12 cells cultured on these membranes exhibited good cell attachment and propagation, supporting the possible applications for designing strategies that promote nerve tissue regrowth and regeneration. It was found that neurite extension was greatly increased on the piezoelectric materials such as PVDF [203]. PVDF nerve conduits with piezoelectricity were constructed and then the effect on a sciatic mouse nerve model was assessed [229]. It was found that piezoelectric nerve conduits increased peripheral nerve regeneration, allowing for further investigations into how electrical activity could manipulate nerve regeneration. Fine et al [231] fabricated nerve guidance channel by use of a vinylidenefluoride–trifluoroethylene copolymer and found that the resultant piezoelectric copolymer tubes greatly increased the nerve regeneration. Increased neurite elongation was identified due to the presence of surface and transient charges [230,232]. The advantages related to using piezoelectric materials for neural tissue regeneration are not only dependent on the enhanced neural cell function and tissue regeneration on such materials, but they are also related, in some cases, to a decreased glial cell adhesion and proliferation. Figure 10 showed the typical neurite tracing for a cell grown on the stimulated piezoelectric PVDF (S-PZ) [55].

Piezoelectric materials are well suited for employment in bone tissue engineering because bone has piezoelectric properties [233–235]. Varying morphologies or surface charges of PVDF materials could cause unusual behavior of bone cells [236]. Unlike characteristics exhibited by muscle cells, MC3T3-E1 cells presented better adhesion and propagation on positively poled piezoelectric PVDF membranes [38,237]. Different mechanical methods were used in varying conditions to test electrical response of cell types on the piezoelectric materials. Mechanical stimulus in this case is used as a mimic for the natural environment needed for cell development, as bone is generally constructed under these conditions. Mechanical stimulus can be varied to achieve higher cell proliferation rates [38]. Differentiation can also be established under multiple conditions in poled β-PVDF samples unlike under static conditions [238]. Non-poled β-PVDF samples did not exhibit this response due to a differing surface charge; this effect along with the addition of topography can enhance osteoblast cell differentiation and growth. These studies all indicated that poled β-PVDF samples improved cell behaviors. Our team recently has prepared a PVDF film on the Ti substrate (PVDF-Ti) as an electroactive implant to mimic the electrical microenvironment of bone [239]. Our cell assays showed that polarized PVDF-Ti induced the osteogenesis behavior of MSCs by altering its surface charge. Hence, PVDF can be used as a scaffold for bone regeneration.

Myocardium is an electroactive tissue. Because of the unusual characteristics of piezoelectric scaffolds, PVDF is a desirable material for cardiovascular tissue engineering. Lee et al [240] studied the vitality and function of cardiomyocytes (CM) taken from mouse embryonic stem cells (mES-CM) and endothelial cells (mES-EC) on the piezoelectric PVDF scaffolds. They have found that mES-CM and mES-EC both exhibited high viability and good adhesion on PVDF (Figure 11). Furthermore, mES-CM and mES-EC showed cardiac markers when cultured on the piezoelectric PVDF scaffolds. The piezoelectric scaffolds deliver the electrical stimuli needed for specific cell lines, facilitating new tissue engineering applications. Hence, there is a need for bioreactors that mimic various stimuli occurring in human body, so as to promote tissue regeneration using EAPs [18,241].

4.2.2. Polyhydroxybutyrate—PHAs are a kind of polymer produced by bacterial metabolism. Such polyesters produced by bacterial fermentation is one material with possible biomedical uses due to their natural, renewable, biodegradable, and biocompatible thermoplastic properties. These compounds can promote cell adhesion and proliferation; piezoelectric polymers PHB and poly (β-hydroxy butyric acid ester and β-hydroxy valeric acid) copolymers (PHBV) belong to this family. Their piezoelectric properties have allowed them to play a large role in health care and disease treatment.

To further develop possible repair techniques for peripheral nerve faults, synthetic neural conduits have been designed. PHAs are altered in various aspects to maintain proper neural prosthesis. For neural regeneration to be successful, the inner and outer microenvironments of the prosthesis must be in communication. Therefore, polymers that are porous are a viable choice for neural regeneration application and fibrous polymer tubes are a possible choice to improve regeneration because SCs can use them to align and trigger axonal elongation [242].

As another example, Bian et al [243] designed neuronal conduits out of PHB using various techniques. They found that PHB conduits did not perform as well as autologous nerve grafts in rate or amount of regeneration, but they did provide positive axonal regeneration with minimal inflammatory infiltration. When Fn and alginate were covered on the PHB fibers, it was found that such fibers could repair the spinal cord injury [244]. Similar success was found by other groups as well [245].

Studies of PHBV as a possible tissue engineering substrate are now increasing quickly. Rivard et al [246] showed that PHBV supported fibroblast growth rates comparable to those seen when collagen sponges were used for over one month. PHBV materials were stable throughout the culturing period even after four weeks of culturing. Conversely, collagen foams were found to contract. This result suggests that PHBV is a better choice than collagen as a polymeric substrate used for cell culturing. These piezoelectric polymer substrates are considered as transducers that can convert the mechanical energy of bone deformation into electrical stimuli and eventually control bone growth.

4.2.3. Poly(L-lactic acid)—PLLA is a slow crystallizing, semi-crystalline polymer. It has the ability to degrade into L-lactic acid, a substance that is non-toxic to humans. PLLA has been tested for 3D cell culture and dental transplantation for years, because of its

biocompatibility, non-toxic degradation products and easy processability [247]. PLLA is now employed in various biomedical applications as scaffolds, sutures, and drug carriers. PLLA has recently been employed as a tissue engineering material. For instance, Chang et al [248] showed that PLLA/chitosan electro-spun composite membrane minimized undesirable effects from fibroblasts and guided periodontal tissue regeneration. PLLA/PCL/hydroxyapatite nanofibrous scaffolds were also found to be a biocomposite for supporting the proliferation, differentiation and mineralization of osteoblasts, favoring their use in bone tissue regeneration [249].

Previous study showed that ECM-mimicking nanofibrous PLLA scaffolds facilitated adhesion, elongation and propagation of cardiovascular progenitor cells (CPCs) [250]. *In vivo* experiments showed that the scaffolds were in favor of cardiac tissue regeneration from CPCs. Park et al fabricated human fibroblast-derived matrix (hFDM) coated PLGA/PLLA fiber scaffolds [251]. They demonstrated that the hFDM-coated microfiber scaffolds could support the attachment and migration of human umbilical cord blood-derived mesenchymal stem cells (UCB-MSCs), and promoted the chondrogenic differentiation *in vitro*. Ma et al [252] successfully synthesized the electroactive polylactide (PLA)/aniline trimer (AT) shape memory polymers networks (SMP) with well-developed biodegradablity. It is evident that electroactive ESMP has a high level of biocompatibility and significantly increases the proliferation of C2C12 cells. SMPs are biocompatible and electroactive. They have intense mechanical characteristics and adjustable degradability. Hence, when electrically active, they are promising bone tissue engineering candidates.

4.2.4. Piezoelectric polymer composites—In order to advance osseointegration, osteogenesis and ossification in animal models, composites based on piezoelectric polymers have been employed. For instance, Deng et al [253] fabricated a nanocomposite membrane with polydopamine@$BaTiO_3$ nanoparticles (Dopa@BTO NPs) in P(VDF-PTrFE) to mimic the endogenous electric potential for bone defect repair. It was found that these membranes sustain the electric microenvironment, improving osteogenic differentiation of BMSCs and even rapid bone regeneration. They also presented the conceptual proof on the use of piezoelectric polymer-based composite membranes for bone defect repair (Figure 12). This study revealed that piezoelectricity is a critical parameter for designing biomaterials in tissue engineering.

4.3. Polyelectrolyte gel

Polyelectrolyte gel can absorb enormous amounts of water and swell. Polyelectrolyte gel is unusual in their reaction to environmental stimuli. For example, the induction of chemo-mechanical contraction electrically produces a biological response, unlike classic hydrogels that show no alteration in equilibrium swelling when the surrounding environment changes [254–256]. Additionally, polyelectrolytes like polysaccharides and charged filamentous proteins are found in biological tissues [257]. Because of these characteristics, polyelectrolyte gels show promise in employment as model systems for biological tissues, allowing them to serve as biomaterials that replace tissue damage [258]. The capacity of polyelectrolyte gels to be used in regenerative medicine should not be overlooked because they bear desired functions such as supporting cell adhesion, tunable chemistry, structural

integrity, biodegradability, and biocompatibility [259,260]. For example, cartilage-like structures in rabbits were formed due to the negative charge of the alginate gels after implantation for 4–6 months [261]. Further, negatively charged alginate microgels within hyaluronic acid hydrogels were found to promote cartilage regeneration [67,262].

5. Challenges in electroactive polymers for tissue regeneration

Electrostimulation, also commonly referred to as electro-therapy, is inspired by the fact that the torpedo fish produced a series of electric shocks to reduce and control the painful area of the body [263]. In fact, some cells such as nerve cells, myocardial cells and osteocytes, are sensitive to electrical stimulations. With the possibility to achieve an indirect or direct stimulation inside cells, electroactive materials are therefore extremely exciting and open a wide spectrum of applications in the tissue regeneration. For examples, conductive and piezoelectric EAPs were found to promote cardiac [264] and neural [265] regeneration compared to their non-electroactive counterparts.

However, the introduction of electroactive materials in biomedical research is often followed by a huge debate about their biological adaptation with living matter. The complexity of regenerating tissue (including bone, nerve, cardiac and cartilage) necessitates vigilant attention to structure, physicochemical property, biological performance, vascularization, neurotization, infection probability, and external stimulation competently matching human biology. Nevertheless, it is difficult to maintain all of these requirements for tissue regeneration simultaneously since they are often conflicting factors. Therefore, the major challenges of electroactive materials for tissue regeneration applications include the following aspects: 1) Improving biocompatibility, histocompatibility and antibacterial property of EAP; 2) Achieving rapid regeneration induced by EAP under stimuli; 3) Adaptation of the electrical/mechanical stimuli to tissue environments at a valid range; 4) Triggering multi-tissues regeneration by EAPs under stimuli.

When EAP based scaffolds are implanted *in vivo* for tissue regeneration purpose, they should be biocompatible, histocompatible and antibacterial. While much attention has been paid to the biocompatibility and histocompatibility in the past, the antibacterial property of EAPs has received less attention. We believe more work should be done to modify the EAPs to increase their antibacterial capability. Recently it was found that piezoelectric material exhibited an antibacterial property by producing reactive oxygen species (ROS) after polarization [266]. It was also found that doping CPs with antibacterial polypeptides could improve their antibiotic property and biocompatibility [267]. These successes suggest that EAPs can be made biocompatible, histocompatible and antibacterial by their own electroactive property or modification with bioactive (e.g. antibacterial) agents.

Rapid regeneration is important for the ease of pain. Currently, studies on the electroactive materials mainly focus on improving the differentiation of cells and verifying the biocompatibility of electroactive materials with tissues. However, some more long-term *in vivo* experiments need to be studied. In particular, some attempts should be implemented about modifying the electroactive materials for rapid tissue regeneration.

Bone, nerve, cardiac and cartilage cells and tissues are sensitive to electrical/mechanical stimulation. Electroactive materials can transmit the signals to these cells or tissues and improve cell function or tissue regeneration since the substrates provide the stimulatory cues for cells. However, the adaptation of electroactive materials to cells/tissues is challenging. The valid range of electrical stimulation to cells is now uncertain. Some more efforts should be made to determine the electrical stimulation range on the cells/tissues. Fundamental studies should be done to find how cells or tissues respond to different electrical/mechanical signals *in vitro* and *in vivo*.

Finally, it is challenging to incorporate a signal on electroactive materials to simultaneously trigger the regeneration of multiple tissues such as bone and blood vessels. To overcome such challenge, the scaffolds made of individual or multiple EAPs should be developed and implanted into the defects to exam their capability in inducing or promoting the multi-tissue regeneration *in vivo* under a single or multiple stimuli. Experiments *in vivo* with large animal models are necessary for further developing and improving electroactive scaffolds mimicking living tissue.

6. Conclusions and outlook

The development of EAPs is far from perfect, which leaves some issues to be studied. Electricity is well known to be present in living tissues, caused by resting potentials, action potentials and stress generated potentials. Extensive work has been conducted to elucidate whether mimicking these biologically active electric fields can increase the rate of growth and repair. These efforts of producing medically acceptable treatments have paid off in the form of approved treatments and clinical trials. EAP implants could generate charge and potential *in vivo* by body movement and physiological stress, which encourages nerve repair, bone formation and wound healing. They could also promote cellular adhesion, differentiation and migration under the mechanical or electrical stimulation. Hence, EAP scaffolds have the potential to be applied for the next level of tissue regeneration. However, most pure EAPs scaffolds are not proper for tissue regeneration because they need external power source or additional surface electrodes for conducting electrical stimulation. Therefore, their modifications such as composite formation are needed. Chemists should seek more modification methods to improve the adaptability of EAPs to tissue regeneration applications. Combining the advantage of different EAPs, for example piezoelectric and conducting, in physiological environments, by forming a composite of piezoelectric and conductive polymers may find further potential application in tissue regeneration. In addition, the use of EAPs as biomimetic membranes, ion channels and skin dressings are also worth further studying by biologists due to their capability of stimuli responsivity.

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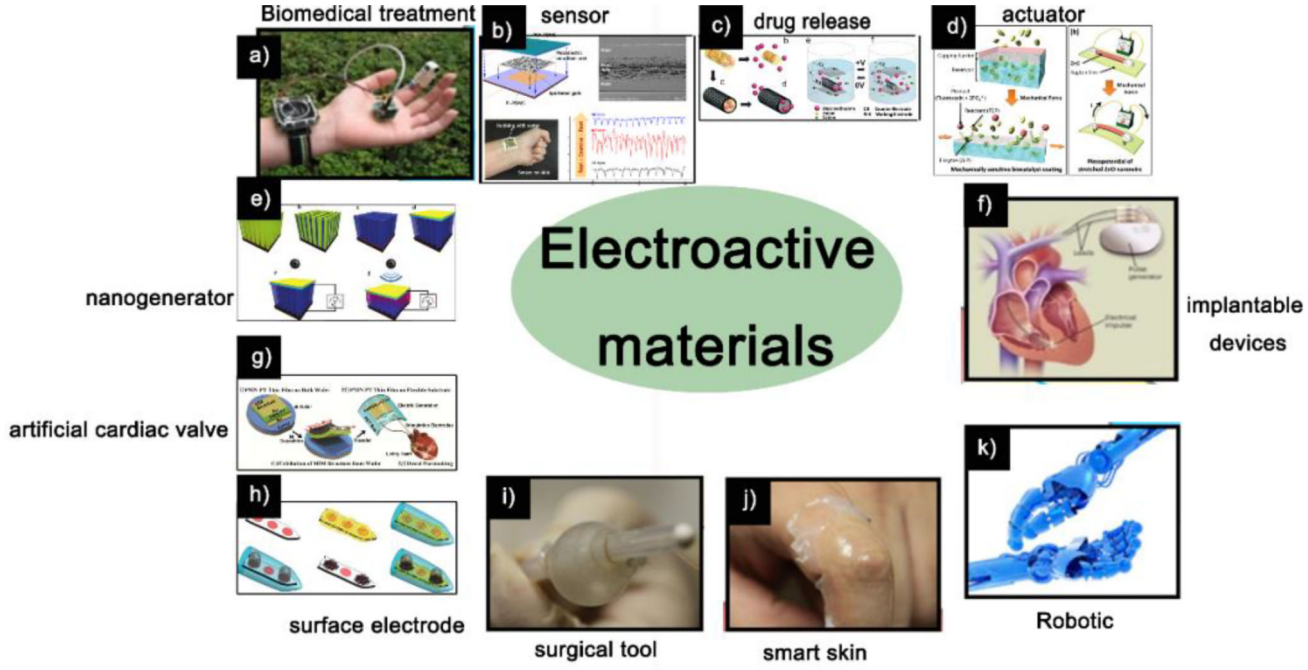

Figure 1.

The applications of electroactive materials. a) Piezoelectric materials used for biomedical treatment application; b) Piezoelectric sensor; c) Drug release from the PEDOT nanotubes was achieved through the contraction or expansion of the PEDOT nanotubes under external electrical stimulation; d) ZnO nanowire actuator resulted in mechanical stretching, which activate the enzymes; e) Potential of PVDF piezoelectric nanogenerator generated by sonic wave; f) Using piezoelectric materials in implantable devices; g) Use of piezoelectric materials in artificial cardiac valves; h) Conducting polymers on neural microelectrodes; i) Piezoelectric materials as surgical tools; j) Piezoelectric materials as smart skins; k) Piezoelectric materials as Robotics.

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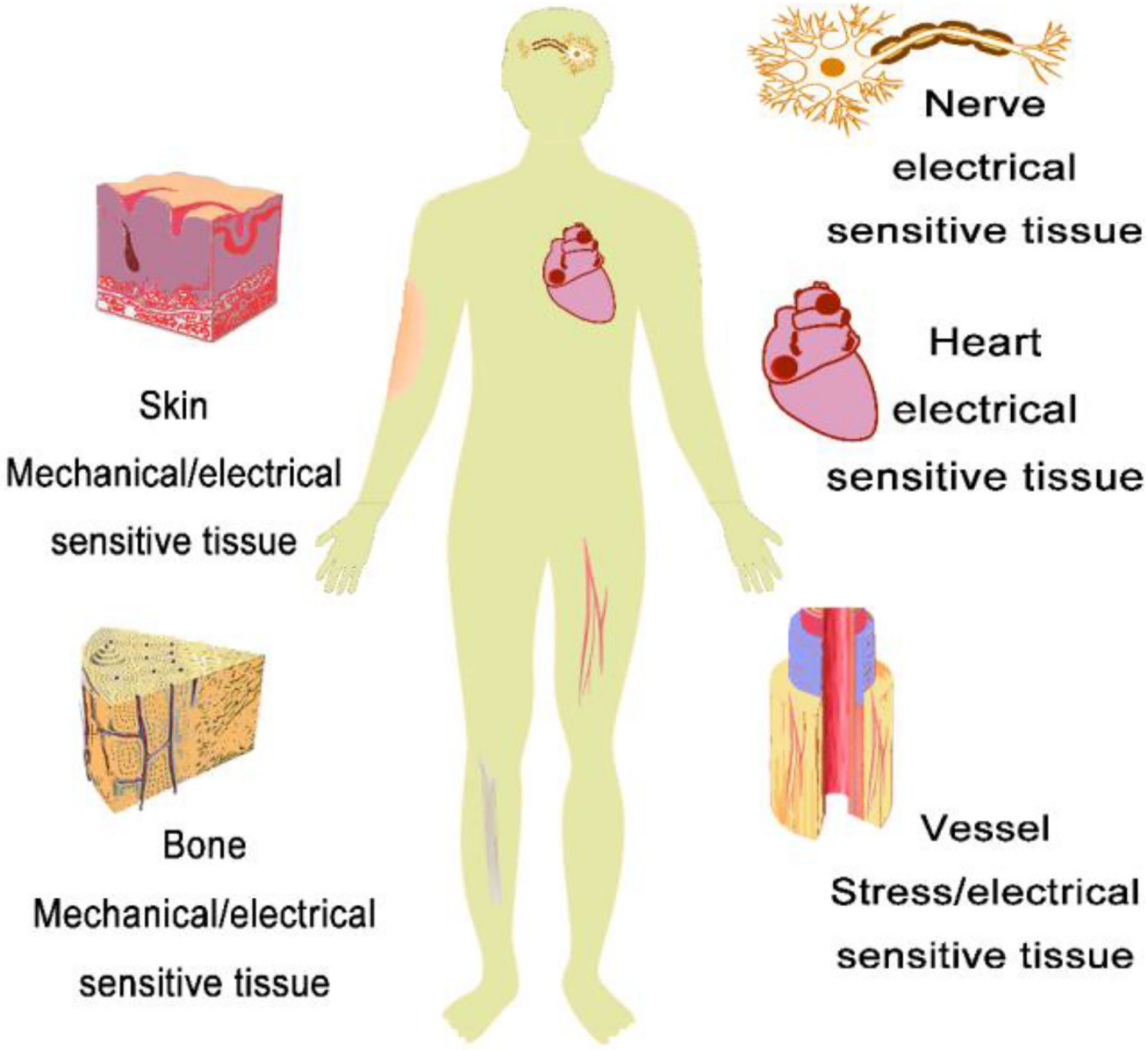

Figure 2.
Tissues in the human body are mechanically and/or electrically sensitive to specific environment, indicating that the electroactive materials have potential applications in tissue regeneration.

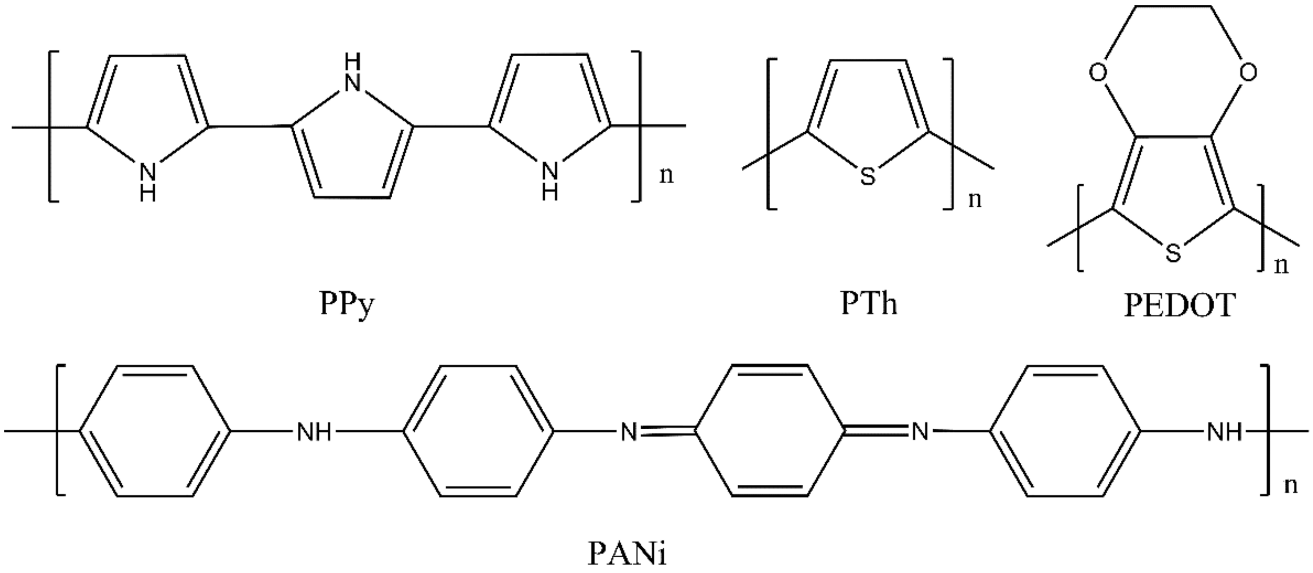

Figure 3.
Structures of some representative biomedical CPs.

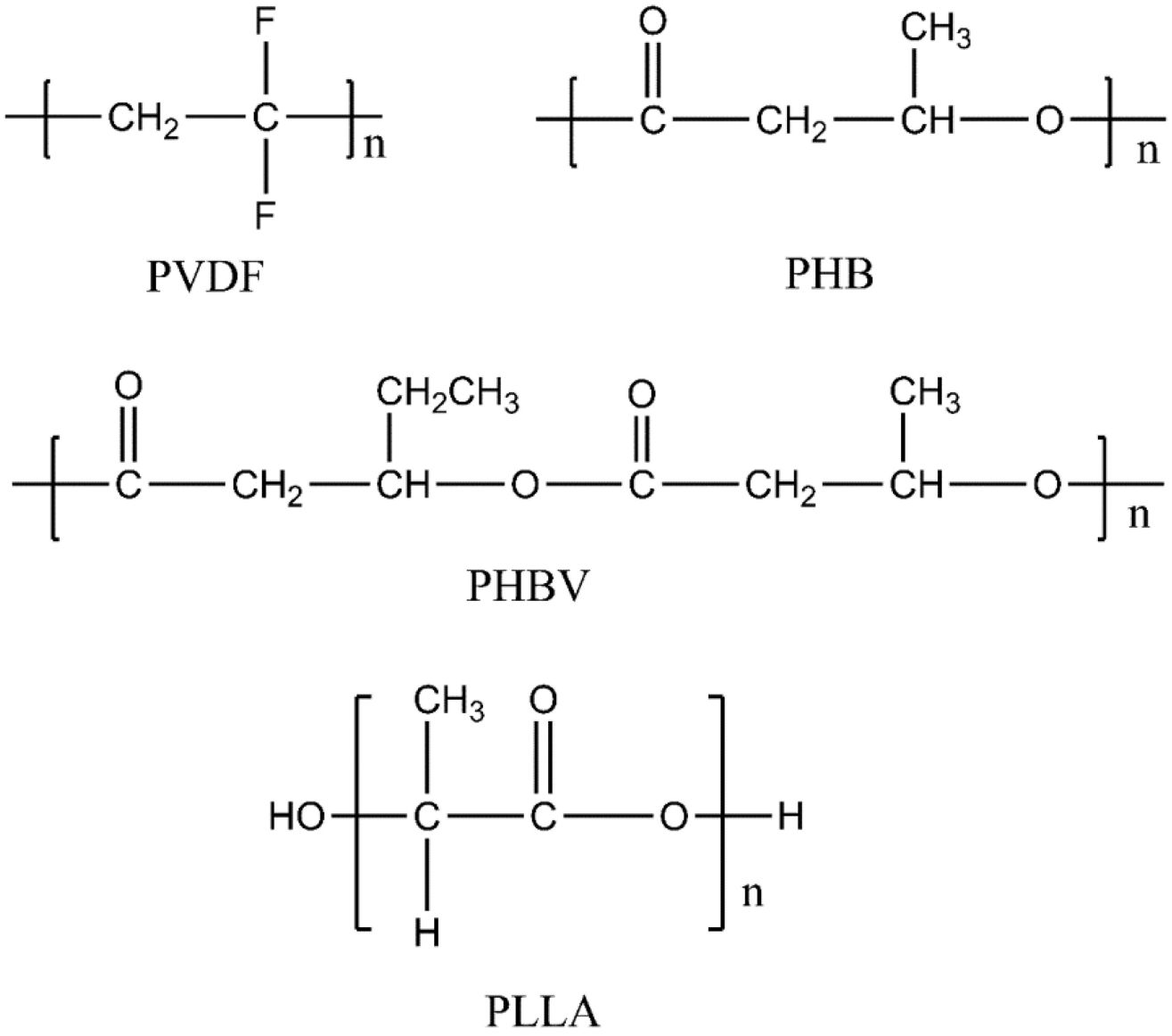

Figure 4.
Representative structures of some biomedical piezoelectric polymers.

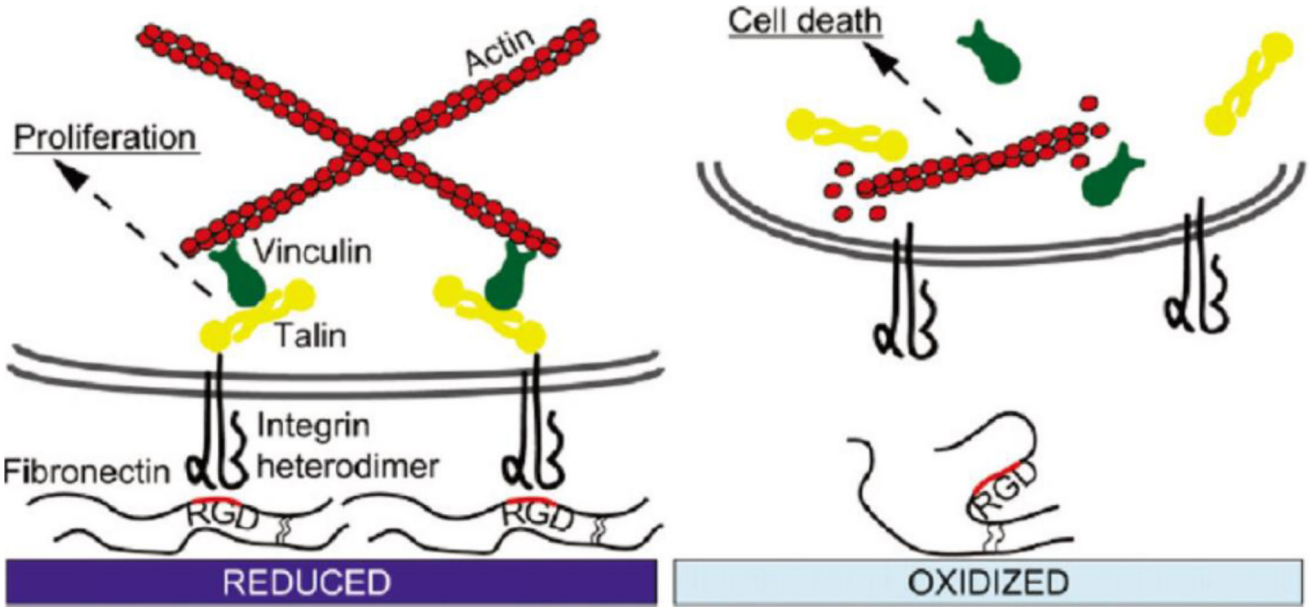

Figure 5.

Possible mechanism of cell interactions with reduced and oxidized PEDOT. When the cells grew on the reduced films, fibronectin was extended to present RGD sites for controlling cell adhesion. When the cells grew on the oxidized films, fibronectin became more compacted to hide RGD sites, preventing cell adhesion. [117], Copyright 2012, reproduced with permission from the American Chemical Society.

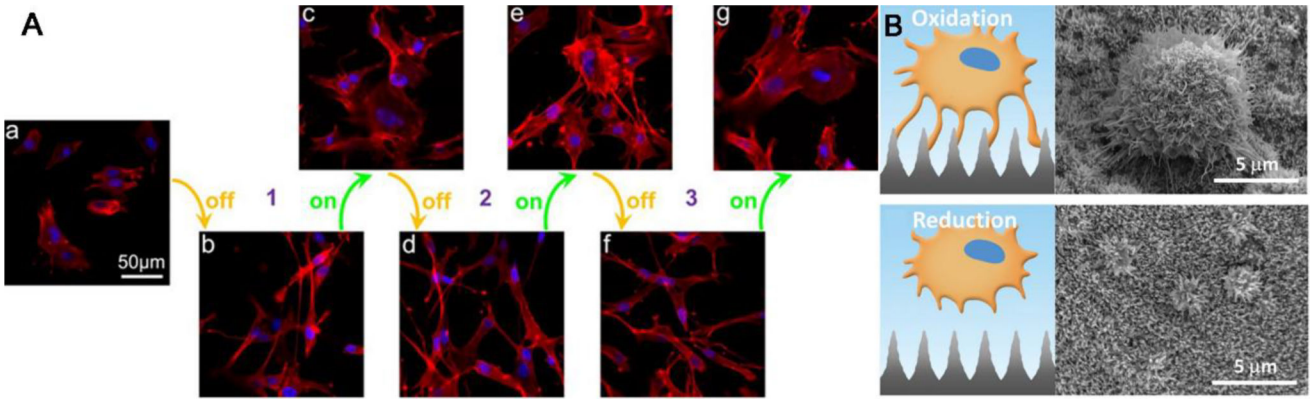

Figure 6.

Cell fate on different nanostructured conducting polymer PPy substrates. (A) Immunofluorescence stained bone forming cells after the cells were cultured on TCA-doped PPy nanotubes in their original state (a), potential-off states (b, d and f) and potential-on states (c, e and g); (B) Schematic and SEM image of cells on an oxidized and reduced PPy nanoarrays. The cells on oxidized PPy nanoarrays presented more and longer filopodia. They began to detach from the nanoarrays when the nanoarrays were reduced. Sources: (A) [152], Copyright 2014, reproduced with permission from the John Wiley and Sons; (B) [154], Copyright 2016, reproduced with permission from the John Wiley and Sons.

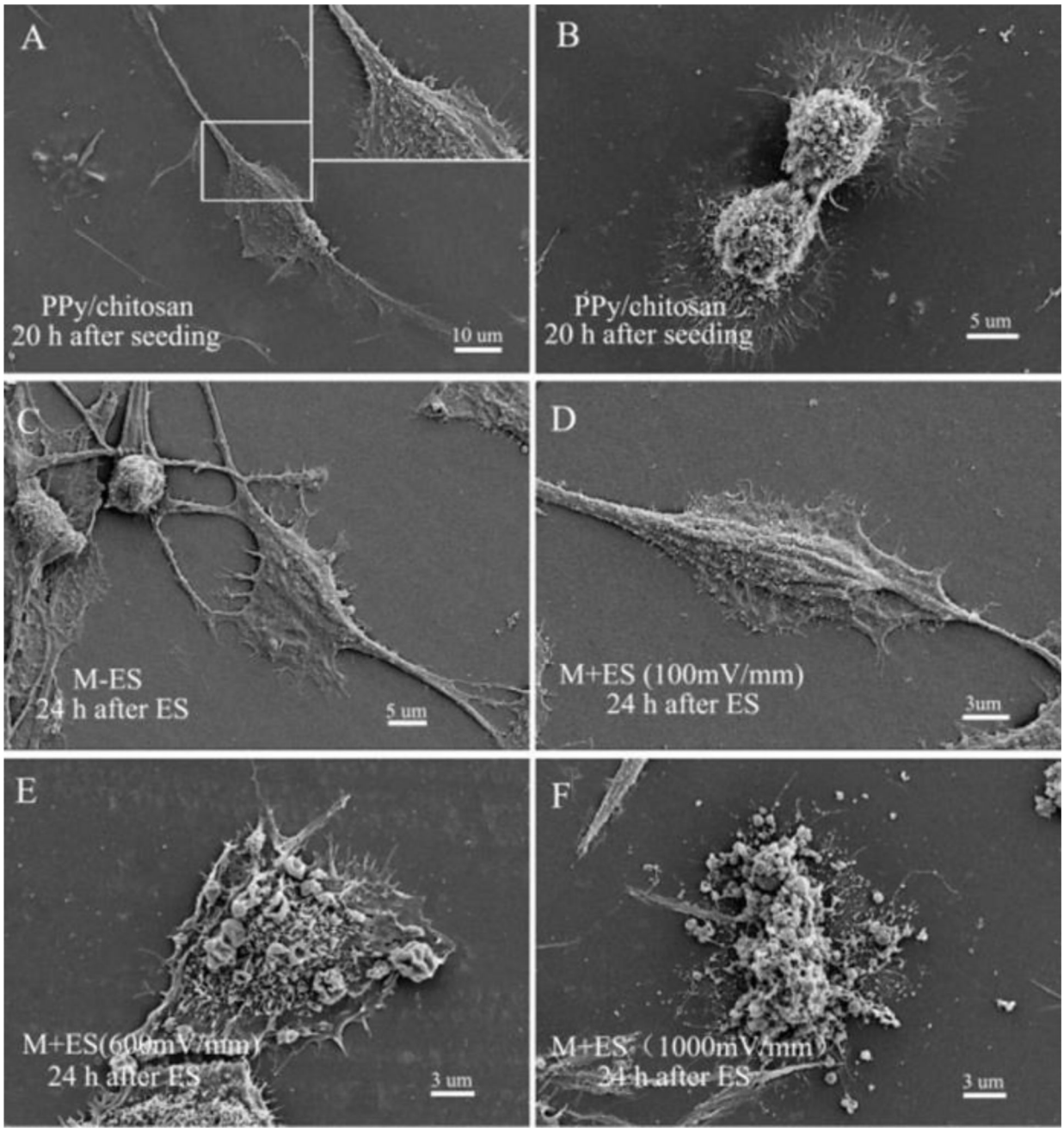

Figure 7.

SEM images of SCs cultured on PPy/chitosan films. Twenty hours later, SCs were spindle shaped (A) and in the division stage on PPy/chitosan membranes (B). SCs are shown from the conductive films without ES (M−ES) group (C) and conductive films with ES (M+ES) group: (D) 100 mV/mm, (E) 600 mV/mm, and (F) 1000 mV/mm. [47], Copyright 2009, reproduced with permission from the John Wiley and Sons.

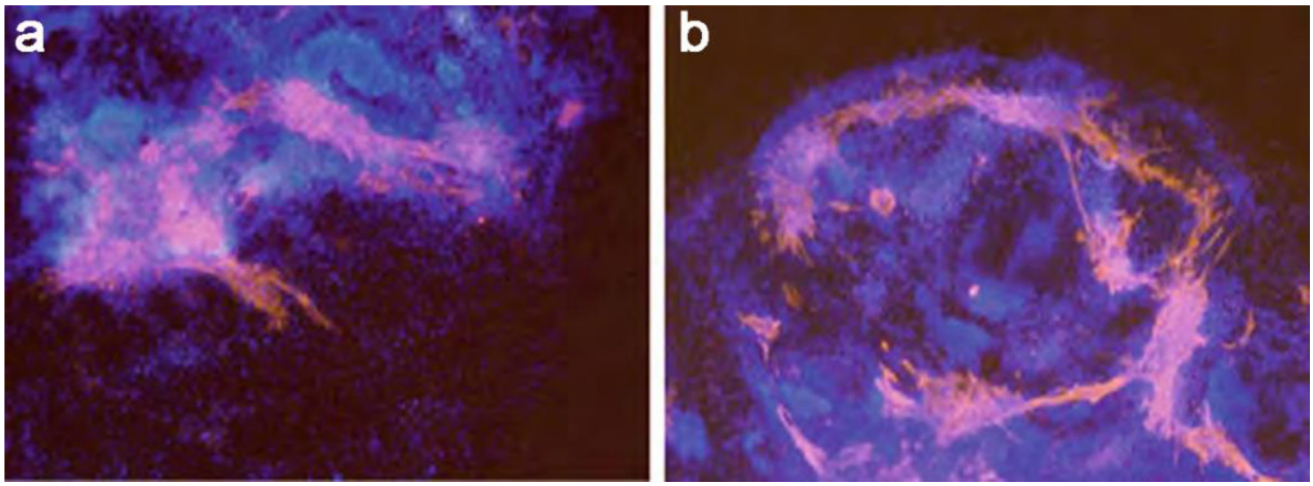

Figure 8.

Cardiac differentiation on day 14 from embryonic stem cells. (a–b) Typical images of unstimulated (a) and stimulated EBs (b). Red: areas where cardiac/ventricular differentiation occurred. Blue: nuclear DNA. It should be noted that red areas are corresponding to spontaneously contractile regions. [58], Copyright 2011, reproduced with permission from the Elsevier.

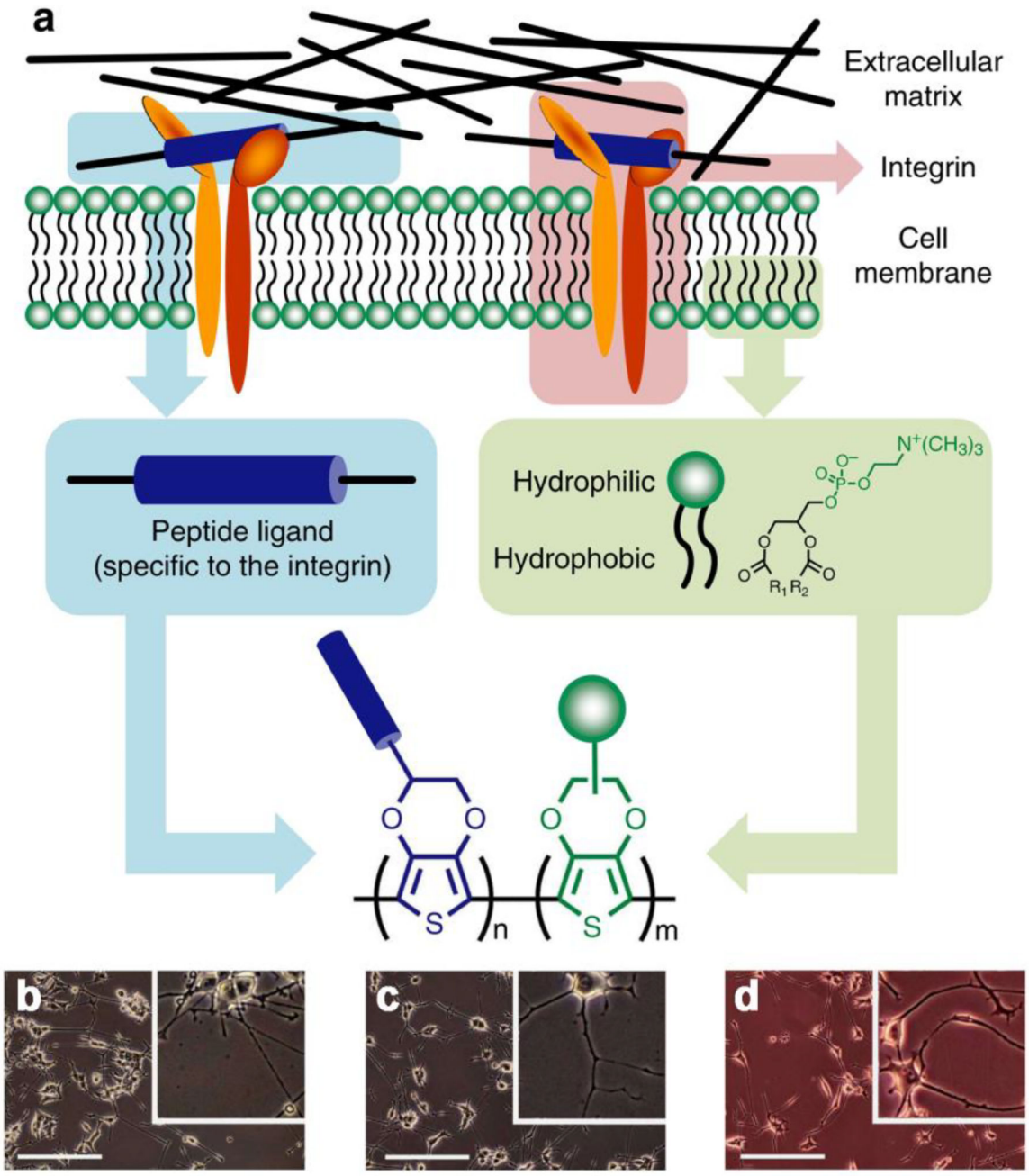

Figure 9.

The design and synthesis of conducting polymers to mimic cell membranes. (a) General idea of the biomimetic design so that interactions between cells and ECM can be mimicked. (b–d) Morphologies of differentiated PC12 cells that were cultured in NGF-supplemented medium for five days on different substrates, including (b) a PEDOT film, (c) a biomimetic PEDOT film, and (d) the biomimetic PEDOT film under electrical stimulation. The insets are magnified images. Scale bars=200 μm. [214], Copyright 2014, reproduced with permission from the Nature Publishing Group.

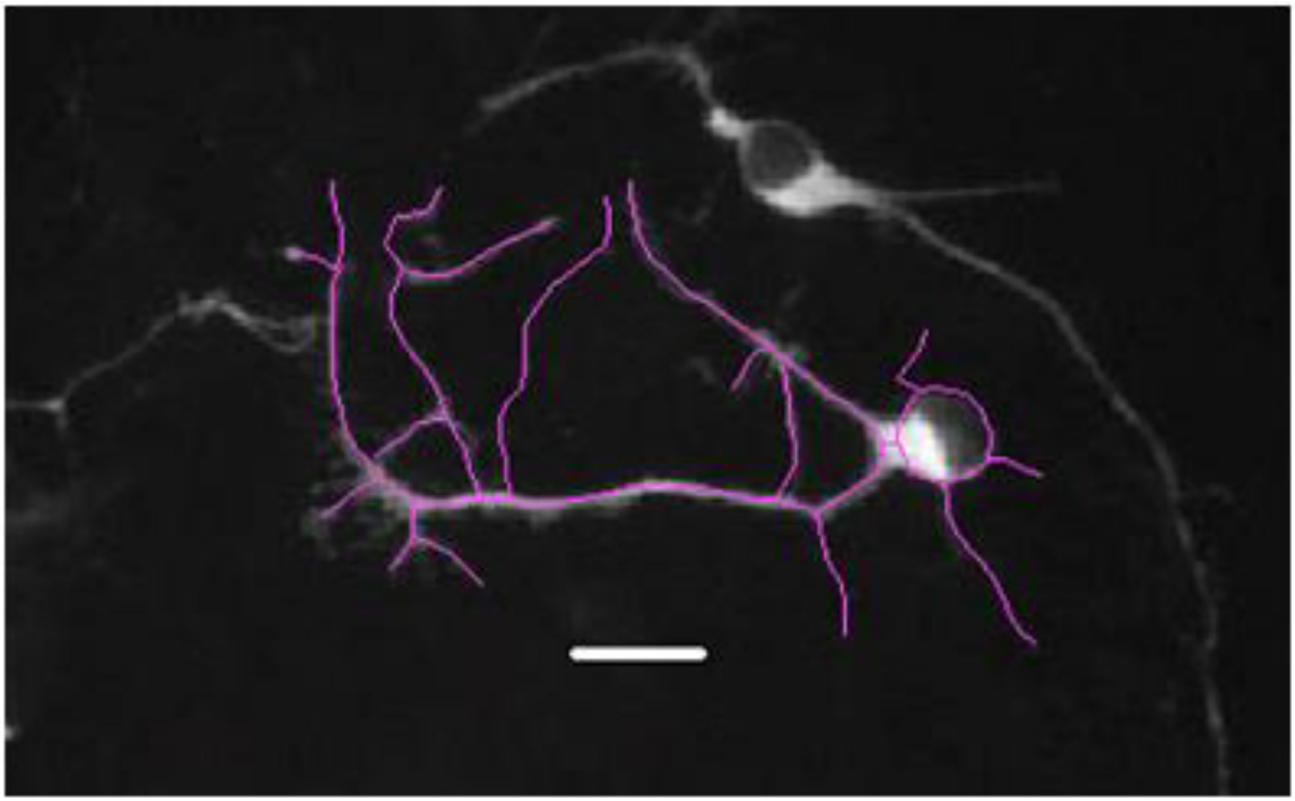

Figure 10.
Spinal cord neurons immunostained with a mouse anti-MAP2 antibody on stimulated piezoelectric PVDF after 5 days *in vitro*. Scale bar =15 μm. [55], Copyright 2012, reproduced with permission from the Springer.

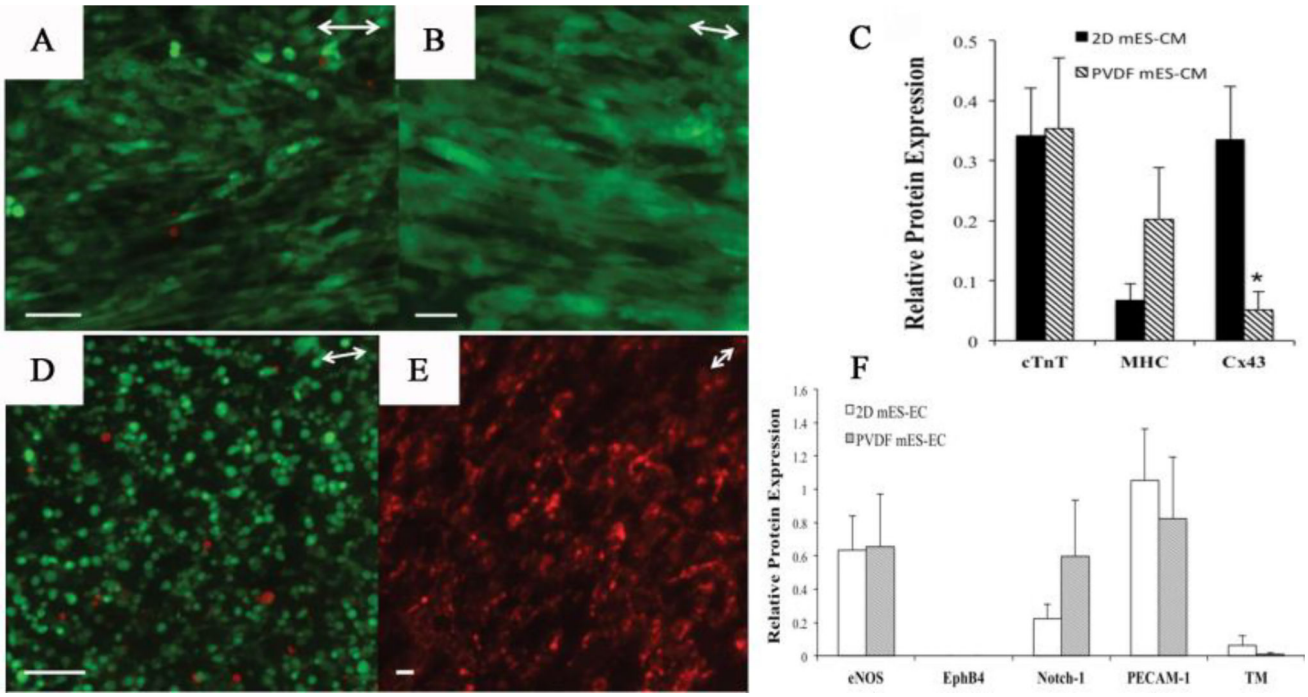

Figure 11.

Characterization of mES-CM and mES-EC cells grown on PVDF scaffolds for 6 days. (A) mES-CM stained by a live/dead assay, Scale bar=50 μm. (B) Strong cTnT-eGFP expression, Scale bar=20 μm. (C) Protein expression of in mES-CM grown in 2D substrates or on PVDF scaffolds. (D) mES-EC stained by a live/dead assay, Scale bar=50 μm. (E) Uptake of LDL (red) by mES-EC grown on PVDF scaffolds, Scale bar=50 μm. (F) Protein expression in mES-EC. Arrows represent principle fiber axis. [240], Copyright 2016, reproduced with permission from the John Wiley and Sons.

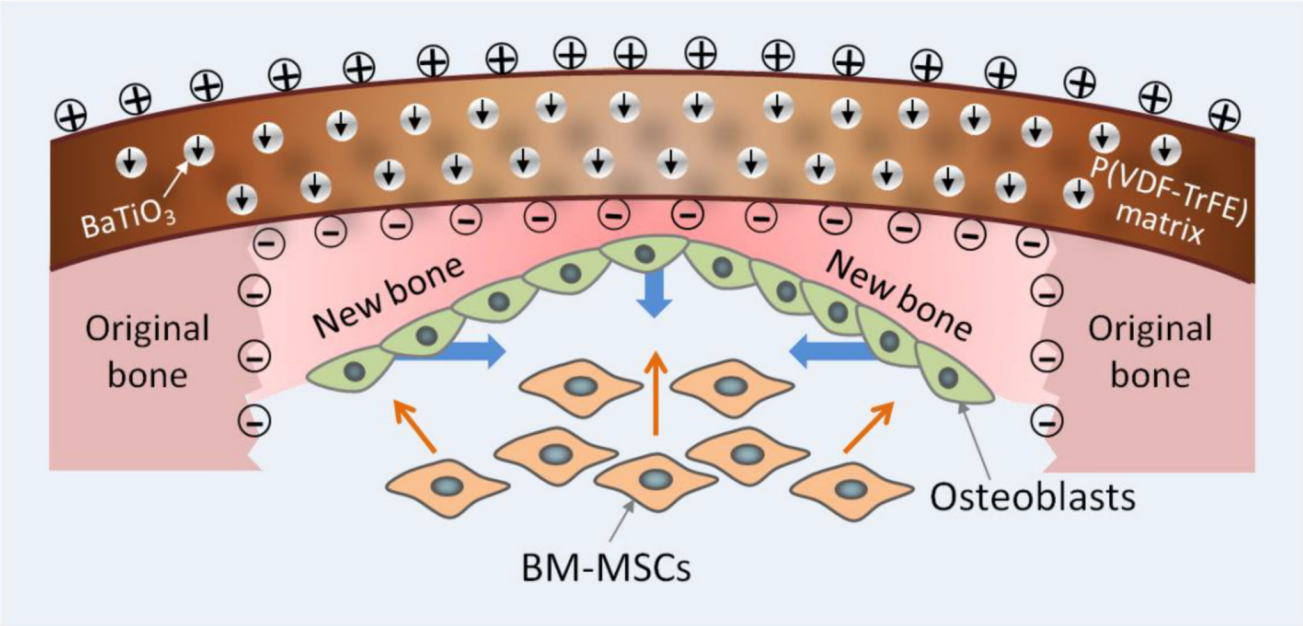

Figure 12.

Illustration of biomimetic electric microenvironment created by BTO NP/P(VDF-TrFE) composite membranes encouraging bone defect repair. Electrical dipoles of BTO NPs are reoriented in the direction of poling electric field after corona poling treatment, and consequently induced charges on the membrane. When the composite membranes are implanted like native periosteum covering the bone defect, endogenous BMSCs can be recruited by galvanotaxis and induced to differentiate into osteoblasts. Consequently, the electric microenvironment in the membrane resulted in swift bone regeneration and mature bone formation. The short black arrows denote the direction of electrical dipole in BTO NPs. The blue thick arrows denote the direction of new bone growth. The orange thin arrows denote the recruitment and osteogenic differentiation of BMSCs. [253], Copyright 2016, reproduced with permission from the American Chemical Society.

Table 1

Electroactive polymers in tissue regeneration application

Tissue regeneration application	Advantages	Limitations	Currently explored electroactive polymers
Bone tissue regeneration	Good biocompatibility and electroactivity, conducive to cell differentiation	Lack of biodegradability, hydrophobicity, needing external power source	PPy and derivatives [9,26–30] PPy/PDLLA [31] PCL-PPy [32] chitosan/PPy [33] PANi [34,35] PEDOT [36] PVDF [7,8,37,38] PHB [39,40] Polyelectrolyte [41]
Neural regeneration	Good biocompatibility, conductivity, stability. high specific surface area, Easy processing, conducive to cell differentiation	Decreased electrical contact at interface	PPy [42–48] PANi [49,50] PEDOT [51–54] PVDF [55] PHB [56, 57]
Myocardial regeneration	Being electroactive, biocompatible, porous, fibrous, conducive to cell differentiation	Hydrophobicity, not biodegradable, needing external power source	PPy [16,58,59] PANi [60–62] Conductive polymer composites [63] PEDOT [64] PVDF [24, 65] PU [66]
Cartilage regeneration	Being biocompatible, flexible, electroactive, conducive to cell differentiation	Poor biodegradability, needing external power source	Polyelectrolyte gels [67,68]

Abbreviations: Polypyrrole (PPy); Polypyrrole/Poly-Dl-Lactic Acid (PPy/PDLLA); Polycaprolactone-Polypyrrole (PCL-PPy); chitosan/polypyrrole (CS/PPy); Polyaniline (PANi); Poly(3,4-ethylenedioxythiophene) (PEDOT); Polyvinylidene Fluoride (PVDF); Polyhydroxybutyrate (PHB); polyurethane (PU)

Table 2

The advantages and disadvantages of two types of EAP

EAP type	Advantages	Disadvantages
Electronic	Can operate in air with no major constraints, generate deformation displacement under a DC voltage; Provide a greater mechanical energy density	Activation; requires high voltages
Ionic	Mostly induce bending displacement; Require low voltages	Maintain wetness; Do not hold strain under DC voltage