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Electroactive Biomaterials and Systems for Cell Fate Determination and Tissue Regeneration: Design and Applications

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During natural tissue regeneration, tissue microenvironment and stem cell niche including cell–cell interaction, soluble factors, and extracellular matrix (ECM) provide a train of biochemical and biophysical cues for modulation of cell behaviors and tissue functions. Design of functional biomaterials to mimic the tissue/cell microenvironment have great potentials for tissue regeneration applications. Recently, electroactive biomaterials have drawn increasing attentions not only as scaffolds for cell adhesion and structural support, but also as modulators to regulate cell/tissue behaviors and function, especially for electrically excitable cells and tissues. More importantly, electrostimulation can further modulate a myriad of biological processes, from cell cycle, migration, proliferation and differentiation to neural conduction, muscle contraction, embryogenesis, and tissue regeneration. In this review, endogenous bioelectricity and piezoelectricity are introduced. Then, design rationale of electroactive biomaterials is discussed for imitating dynamic cell microenvironment, as well as their mediated electrostimulation and the applying pathways. Recent advances in electroactive biomaterials are systematically overviewed for modulation of stem cell fate and tissue regeneration, mainly including nerve regeneration, bone tissue engineering, and cardiac tissue engineering. Finally, the significance for simulating the native tissue microenvironment is emphasized and the open challenges and future perspectives of electroactive biomaterials are concluded.

1. Introduction

Tissue engineering aims to regenerate damaged tissues as alternative of cell replacement therapy, autografts, and organ transplantation. It is a comprehensive discipline that incorporates multiple considerations, including design and fabrication of suitable biomaterial scaffolds, their compatibility with native tissue microenvironment, and the delivered biochemical and biophysical cues that might influence the host or laden cells.[1] That is to say, smart biomaterials act not only as inert structural support for damaged area, but also as active modulators for endogenous cell adhesion and functions. Additionally, they could provide biochemical and biophysical cues to trigger cell differentiation into tissue-specific cell lineages.[2] Physicochemical characteristics of biomaterials including chemical composition, structural feature, stiffness/elasticity, porosity, and adhesion-ligand density might provide appropriate biophysical cues for guiding stem cell differentiation into specific lineages and tissue regeneration.[3] Some preliminary review papers on tissue engineering biomaterials have summarized the effect of biomaterials' morphology, composition, and mechanical properties on stem cell differentiation.[3b,4]

In human body, bioelectricity is an integral part of organism. At the cell level, cell membrane potential plays an important role in the regulation of cell cycle, migration, proliferation and differentiation. And action potential determines cellular excitability especially for neurons and cardiomyocytes.[5] Bioelectricity is a ground base of the functions of electroactive organs/tissues, including central and peripheral nervous systems, muscles, heart and inner ear sensory epithelium. Specifically, it modulates a myriad of biological processes, such as functional and structural refinement of synapses/neuronal networks, neural conduction, synchronous contraction of cardiomyocytes, as well as muscle contraction.[6] Disruption of the steady-state electrical milieu of embryos might cause serious developmental defects, such as lack of cranium, misshapen head, abnormal or absent brachial development, and incomplete closure of neural folds in focused areas.[7] In addition, endogenous piezoelectricity widely exists in low-symmetry biomacromolecules and biomolecular assemblies, which is considered to be closely associated with tissue growth and remodeling, especially for bone regeneration.[8]

Recently, a range of electroactive biomaterials, including conductive and piezoelectric biomaterials, and their mediated electrostimulation have been developed to mimic the nature bioelectricity as a biophysical cue for modulation of stem cell

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fate and regenerative medicine.[9] Electroactive biomaterials are considered to be a new generation of smart biomaterials that allow directly deliver electrostimulation to target cells/tissues, or adjust their own characteristics under electrostimulation to adapt to the cell microenvironment. Electroactive biomaterials have the potentials to integrate the topological, chemical, mechanical cues, as well as electrical properties to meet the specific biological application requirements. Specifically, conductive materials enable charge transport at the cellular membrane interface, and regulate the interactions at cell–cell or cell/tissue–biomaterial interfaces.[10] Additionally, electrostimulation delivered through conductive and piezoelectric materials can further modulate cell and tissue behavior.[5,11] More importantly, electroresponsive biomaterials under electrostimulation could adjust their own characteristics, such as redox state,[12] hydrophobic/hydrophilic property,[13] conformation of surface ligand[14] and mechanical property.[15] The adjustable characteristics are beneficial to build a dynamic cells/tissues microenvironment at different developing periods, in collaboration with other factors (e.g., growth factor, mechanical stimulation, and surface structure).

The reviews of electroactive biomaterials have appreciated in recent years,[9] which summarize electroactive biomaterials for tissue regeneration, and provide an overview on the current progresses of the electroactive biomaterials for drug delivery and regenerative medicine. For tissue engineering application, an in-depth understanding of how the cell microenvironment evolves over time is critical for development of smart tissue engineering biomaterials. Another important aspect that should be paid attention is the pathways that might be used to impose electricity on cells/tissues via those conductive biomaterials. Currently, convenient and safe delivery of electrostimulation is an urgent requirement for tissue regeneration, especially for transforming basic researches into clinical applications. This review outlines recent developments of electroactive biomaterials for cell fate determination and tissue regeneration. First, we unveil the intrinsic nature of endogenous bioelectricity and piezoelectricity, as well as their crucial roles in tissues/organs development and regeneration. Then, the design rationale of electroactive biomaterials via imitating the natural bioelectricity in bodies is discussed. Based on this understanding, we mainly focus on conductive and piezoelectric biomaterials, and their applicable electrostimulation pathways especially with recently developed implantable energy harvesters (IEHs). In this paper, the system that integrates both electroactive biomaterials and electrostimulation devices or pathways is named as electroactive system. Instead of just summarizing recent progresses in electroactive biomaterials, our review also reveals the mechanism of electrostimulation in modulating cell activity via cell signaling and downstream biochemical responses and tissue regeneration, according to the dynamic microenvironment of respective cells and tissues. We also discuss the concurrent effect of electrostimulation with other biophysical cues of the biomaterials (i.e., stiffness, topology, and mechanical stimulation) and electricity-reinforced biochemical cues. Then, the applications of electroactive biomaterials in tissue regeneration, particularly for electrically sensitive tissues (nerve system, bone tissue, cardiac tissue, and others) are presented. We finally summarize the prospects of electroactive biomaterials for modulation of cell fate and tissue regeneration, and highlight the challenges that might be faced in future especially for clinical translation.

2. Endogenous Bioelectricity and Piezoelectricity

In human body, bioelectricity is an integral part of organism. At the nanoscale and molecular level, electrical signal generated from piezoelectric biomacromolecules under mechanical stress acts as a stimulus for controlling the precipitation of bone apatite for calcification, thereby promoting bone growth and remodeling.[16] At the cellular level, cell action potential determines cellular excitability especially for neurons and cardiomyocytes, thus modulating a myriad of tissue function, such as functional and structural refinement of synapses/neuronal networks, neural conduction, cardiomyocytes contraction, as well as muscle contraction.[6] At the tissue level, steady endogenous electric fields within embryos provide an overall template for tissue development during ontogeny.[17] In addition, it can mediate cell communication, and regulating important electrophysiological processes, such as synaptic plasticity and synchronization, myocardial contraction and rate, as well as tissue repairing and wound healing.[18]

2.1. Endogenous Bioelectricity

2.1.1. Membrane Potential and Action Potential

Almost all mammalian cells have a long-term, steady-state voltage potential (ca. -10 to -90 mV for different cell types) across the plasma membrane, called membrane potential (V_m) (**Figure 1**). The V_m arises from the presence of different transmembrane ion channels, pumps, and gap junction complexes, which help for the transport of specific ions and molecules across the cytomembrane.[19] Generally, terminally differentiated cells tend to be hyperpolarized (strongly polarized with more negative V_m), whereas developing cells including embryonic, stem, and tumor cells tend to be depolarized.

Electrically excitable cells such as neurons and myocytes can rapidly depolarize away from resting membrane potential, namely excitability. It results in millisecond propagated action potentials (AP) mediated by the change in V_m. In neural system, the AP propagation shapes neuronal circuit via neural transmission, and also induces functional and structural refinement of synapses/neuronal networks.[6a] In 1970s, exogenous electric field (EF) was first found to be able to stimulate neuron survival, migration,[20] and increase neurite outgrowth.[21] Although the mechanism is not fully understood up to now, rearrangement of cell membrane receptors/channels and intracellular cytoskeletal proteins are involved in the process.[22] In clinic, electrostimulation has been applied to manipulate central nervous system (CNS) as early as 1750s. Now, electrostimulation has been used in clinic to treat a wide range of neurological diseases, disorders, and injuries, including essential tremor, Parkinson's disease (PD), epilepsy, and spinal cord injuries.[23] For cardiomyocytes (CMs), their APs regulated by

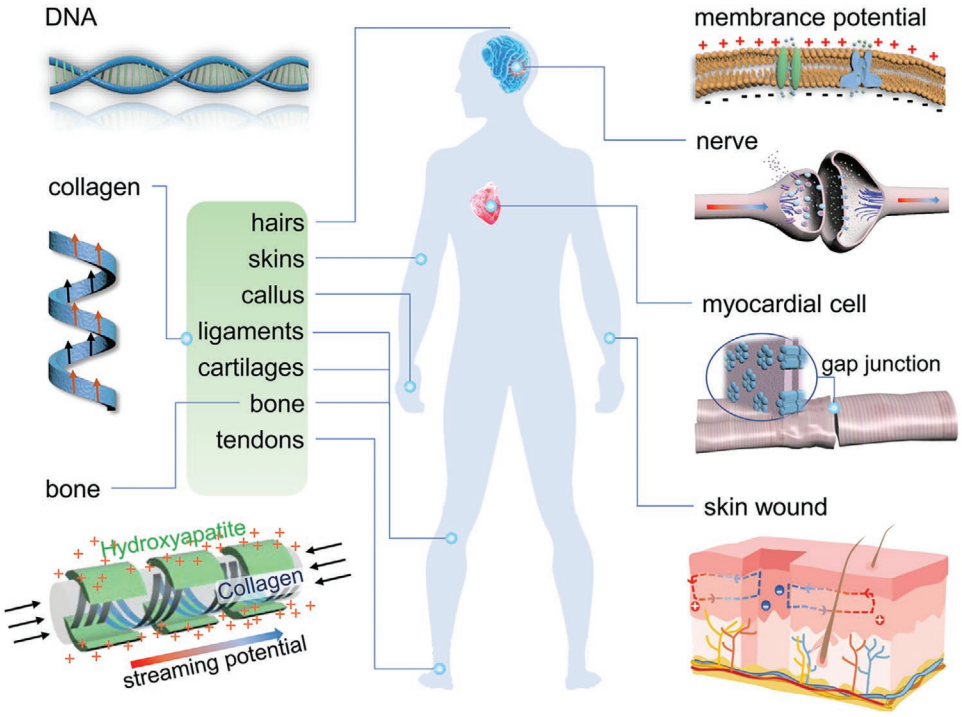

Figure 1. Endogenous bioelectricity (right) and piezoelectricity (left).

ion channels and gap junctions contribute to the spontaneous beating of the cells. The rhythmic AP continuously propagates in multicellular cardiac tissues, and traverses to the myocardium via Purkinje fibers to induce myocardial contractility.[6b] Thus, electrostimulation has been applied for heart failure therapy and myocardium rebuilding.[24]

Beyond electrically excitable cells, it is exciting that V_m as a cell-autonomous bioelectric regulator is also important in non-excitable cells for modulating a train of cellular activities such as cell cycle and proliferation.[25] It is also found V_m fluctuation, an outcome of combined activities of various ion channels and transporters, can functionally regulate tumorigenesis, cancer progression and metastasis.[19] Generally, cancer cells are in a depolarized state, and the membrane depolarization might be importance for stemness maintenance of cancer stem cells.

In addition to their roles as a maker of cell differentiation and maturation state, V_m and related signals also play instructive roles in the differentiation process and linage commitment of stem cells.[26] Hyperpolarization is an instructive trigger for accelerating stem cell differentiation. Conversely, V_m depolarization maintains stem cells in an undifferentiated state.[27] Accordingly, the expression and function of transmembrane ion channels may influence the stem cell differentiation. Induction of cells with a more negative V_m, namely hyperpolarization, is considered to be a promising therapeutic pathway. With the intrinsic cellular excitability especially for neurons and CMs, electrostimulation has been used for guiding maturation of these cells. Additionally, electrostimulation has also been applied to induce differentiation of stem cells into neuron,[28] CMs,[29] and nonexcitable osteoblasts (OBs)[30] from multipotent/pluripotent stem cells,[29a] progenitors,[28b] bone-marrow-derived mesenchymal stem cells (MSCs)[31] and induced pluripotent stem cells (iPSCs).[29b] It is expected that rational exogenous regulation of V_m might provide significant opportunities for therapeutic purpose including regenerative medicine.[19]

2.1.2. Endogenous Electric Field in Tissues

When we shift from a single cell to multicellular collections and tissues, striking parallel is found. Cells are regulated not only by their own V_m, but also V_m of their neighboring cells via gap junctions.[32] More importantly, endogenous electric fields (EFs) have been found for more than a half century. During embryogenesis, there is an endogenous electric current with a voltage gradient from 40 to 140 mV mm^{-1},[33] which plays a key role in regulating cell behaviors and tissue development, such as asymmetric left-right organs.[34] It has been reported that disruption of normal electrical milieu of embryos would cause serious developmental defects such as lack of cranium, loss of eyes, misshapen head, abnormal or absent brachial development, and incomplete closure of neural folds in focused areas.[7] Steady voltage gradients within embryos provide an overall template for tissue development during ontogeny.[17] In addition, endogenous EFs mediate the communication of electrically excitable cells, thereby regulating important physiological processes, such as synaptic plasticity and synchronization, as well as myocardial contraction and rate.[18]

Endogenous EFs also play important roles in tissue repairing and wound healing for a wide range of wounded and regenerated tissues/organs, including limbs, bone fractures, corneal, and skin wounds.[35] Taken skin wound as an example, a cross transepithelial potential ranging from 15 to 60 mV would be formed mainly due to the polarized

distribution of ion channels in the epithelial cells. A wound would disrupt ion flux across leaky cell membranes and epithelial barrier, and also short-circuit the transepithelial potentials for generating a lateral EF, or called leakage current (Figure 1). The magnitude of this lateral EF ranges between 40 and 200 mV mm^{-1} in mammalian wounds.[36] It acts as a directional cue for directing cell migration into the wound location for wound healing, called galvanotaxis.[37] Many kinds of cells including epithelial cells, embryonic cells, and fibroblasts have be found to have the ability to sense external EFs at physiological strength and migrate along the field gradients, most of them towards the negative pole.[38] This phenomenon of galvanotaxis may be related the redistribution of membrane components, intracellular organelles and activated intracellular signaling pathways.[39] The electrical currents present in the body after injury are responsible for various biological processes mediated by non-excitable cells, for early responses to wound healing and tissue regeneration.[40] In addition, since the function of resident stem cells is often determined by their in vivo location within tissues, the targeting of stem cells toward injury would be a crucial key for tissue regeneration. Beyond biochemical cues, bioelectricity guides the homing of stem cells. Under the physiological EF gradients, cells could migrate to wounds and recreate the necessary tissues by the coordination of cell secretion, proliferation, and differentiation.[41] Based on these notions, exogenous simulated bioelectrical EF has been applied for promoting would healing[42] and tissue regeneration for bone, limb, muscle, and nerve system in clinical studies.[43]

2.2. Endogenous Piezoelectricity

2.2.1. Piezoelectric Biomacromolecules

Piezoelectricity means electricity resulted from mechanical pressure. In detail, a certain material (nanocrystals, ceramics, and biological matters) generates and accumulates electric charges with opposite symbols on the surface when it is subjected to a mechanical stress or strain.[44] The generated electric charges are proportional to the applied stress according to the linear theory of piezoelectricity:[45]

$$P_{pe} = d \times T \tag{1}$$

where P_{pe}, d, and T are the generated polarization vector, piezoelectric strain coefficient, and the mechanical stress, respectively. Vice versa, the exposure to an electrical bias induces a deformation of the material, namely inverse piezoelectric effect:

$$S_{pe} = d \times E \tag{2}$$

where S_{pe} and E are the induced mechanical deformation of the material and the applied external EF strength, respectively.

Piezoelectricity in biosystems was first observed from a bundle of wool in 1940s.[46] The main component of hairs, wools, and horns is keratin in the form of right-handed α-helices, and its piezoelectricity is due to natural polarization and ordered arrangement of the α-helix.[8b,47] At nanoscale and molecular level, many biomacromolecules possess high structural order with intrinsic helical or chiral asymmetry, which cause low symmetry inherent polarization and piezoelectricity. For instance, a single collagen fibril with polar hexagonal crystalline unit and spiral structure has been proven to have piezoelectric effect by piezoforce microscopy (PFM).[48] Collagen molecules in the form of a spiral triple helix self-assemble through the hydrogen bonding of amine and carbonyl functional groups and pack into a quasi-hexagonal (C6) lattice of crystal fibrils. When a mechanical stress is applied, the displacement of hydrogen bonds redistributes dipole moments to the longitudinal axis of the collagen molecules, causing permanent polarization (Figure 1).[9c] The piezoelectric heterogeneity within collagen fibrils correlates with the periodic variation of their overlap and gap regions. Other biomolecules and bioassemblies including proteins/peptides,[49] deoxyribonucleic acids (DNA),[50] and virus[51] have also been found to have piezoelectric effect. Generally, the piezoelectric coefficients of natural biomacromolecules are relatively low, typically in the range of 0.1–10 pm V^{-1},[52] but the piezoelectric effect might play a vital role in tissue regeneration and physiological processes.

2.2.2. Piezoelectricity in Tissues

Within body, the electrical, mechanical, and chemical activities are inevitably coupled with each other. At the macroscale and tissue level, piezoelectric effect has been found in a number of plant and animal tissues. Collagen as an ECM protein contributes to the piezoelectric effect of many animal tissues, including bones, hairs, tendons, ligaments, skins, callus and cartilages.[8a,b,53] Elastin as another ECM protein contributes to the piezoelectricity in blood vessels.[49b,54] The function of natural piezoelectricity remains elusive, but it is generally considered to be closely associated with many physiological processes, tissue growth and remodeling.

Taking bone as an example (Figure 1), it could be considered as a natural piezoelectric composite, in which the non-centrosymmetric collagenous matrix (≈22 wt%) is densely fibrillar packed and embedded in hydroxyapatite (HAp) crystals (≈69 wt%).[55] Due to the structural anisotropy, bone shows an anisotropic piezoelectric response. The highest piezoelectric coefficient (d_{14}) of the femur could reach 0.7 pC N^{-1} in a shear mode.[56] Bone deformation causes a spontaneous polarization and electric potential, mainly contributed from the piezoelectricity of collagen (along with HAp) and streaming potential.[57] It is generally believed that piezoelectricity is the cause of dry bone stress evoked potential, while the mechanism responsible for wet bone is streaming potential. The theory of streaming potential indicates that the potential generated by stress in wet bone is mainly due to the flow of ion containing interstitial fluid through bone caused by pressure.[58] According to the Wolff's law, electrical signal generated from mechanical stress acts as a stimuli for promoting bone growth and remodeling.[16a] The switchable surface potential of bone under physiological deformation controls the precipitation of bone apatite for calcification.[16b] Furthermore, OBs and osteoclasts that are responsible for bone formation and reabsorption, respectively, can response to piezoelectricity that acts as a signal of cell

mechanotransduction and mechanosensation.[8c] Based on the endogenous piezoelectric effect, exogenous electrostimulation has been used to induce a positive effect on bone regeneration and enhancement of osteogenic activity.[59]

3. Electroactive Biomaterials and Electrostimulation

Not very long after the discovery of natural bioelectricity and biopiezoelectricity, development of biomaterials that could guide cell behavior and tissue regeneration have attracted growing interest as an interdiscipline of molecular chemistry and physics, engineering material, biology and medicine. Great endeavors have been devoted to the design and fabrication of biomaterial scaffolds from electroactive biomaterials, including biocompatible conductive and piezoelectric materials. It is more challenging and comprehensive for delivery of efficient electrostimulation via these biomaterials, according to different requirements of respective tissues and lineage commitment of stem cells.

3.1. Conductive Biomaterials

For tissue engineering involving electrically excitable cells/tissues, electrically conductive materials enable charge transportation at the cell–substrate interface and regulate the interactions at the cell–substrate or cell-cell interfaces.[10b,c] Cell behaviors including adhesion, proliferation, self-renewal or differentiation, and cellular signaling could be modulated on these conductive biomaterials.[60] Recent studies have reported the fabrication of conductive biomaterial scaffolds with proper biophysical properties (e.g., micro-/nanostructures, stiffness, and conductivity) for mimicking natural tissue microenvironment and stem cell niche. In some researches, simple culture of stem cells on conductive biomaterials without electrical stimulation could regulate the cell self-renewal or differentiation and ECM regeneration. The references of electrically conductive biomaterials for cell regulation are outlined in **Table 1**. They are divided into three categories: carbon-based biomaterials, metal/metal oxide, and conductive polymers (**Figure 2**).

Carbon-based biomaterials have aroused considerable research interests in biomedical science, from 3D graphite, 2D graphene, 1D carbon nanotubes (CNTs), to 0D carbon dots (C-dots), fullerene and nanodiamonds.[61] Although these carbon-based materials are all mainly composed of carbon element, the carbon allotropic forms, sizes, mechanical properties, and surface chemistry endow them with diverse properties.[10a,62] Among them, graphene and CNTs based materials are most widely employed in tissue engineering, due to their inimitable mechanical features, chemical stability, large specific surface area, and high electrical conductivity. For tissue engineering application, carbon-based biomaterials are commonly used as reinforcing agents to increase the mechanical performance and conductivity of polymer matrix.[62,63] In addition, their large surface area and abundant functional groups facilitate the loading and releasing of bioactive species, including chemical drugs, growth factors, genes and proteins.[61a]

Traditionally, bulk metals including titanium (Ti), magnesium, and stainless steel have been employed as bone repair implants due to their high mechanical properties, fatigue resistance, and conductivity.[64] Porous metals scaffolds were also designed to increase stress conduction, load therapeutic drugs, and increase vascularization in the scaffolds.[65] Recently, metal-based biomaterials with micro-/nanostructures, especially Au nanomaterials (AuNMs) have been developed for biomedical applications.[66] AuNMs (such as Au nanoparticles, Au nanorods, Au nanowires)[67] with good biocompatibility are considered to be an appropriate reinforcing material that can improve electrical conductivity and stiffness of tissue engineered scaffolds by adjusting AuNMs concentrations.[1b,67a,68] In addition, their advantages of high surface areas and facile surface modification via gold-thiol chemistry are beneficial to convenient drug loading. Besides Au nanostructures, other metal/metal oxide, such as nanostructured Ag, Zn, Ti, B, Sr, Mg, Cu, Pt, and MoS_2 have also been employed in tissue engineering, especially for bone repair.[69]

Compared with carbon-based materials and metals, conductive polymers not only have electrically conductive properties, but also possess attractive properties as common polymers, especially flexibility and low stiffness. Thus, they have striking advances in the area of biomedical applications. The conductivity of conductive polymers (oxidized and reduced states) is in the range of 10^{-7} to 10^{3} S cm^{-1}.[70] Their electrical conductivity origins from the conjugated double bond throughout the polymer matrix.[71] Figure 2 lists the typical conducting polymers commonly used in biomedical field, including polypyrrole (PPy), polyaniline (PANi), polythiophene (PTh), poly(3,4-ethylenedioxythiophene) (PEDOT), etc. Size, functional groups, and charge distribution of dopants (counterions) have great influence on the conductivity and performance of conducting polymers. Besides, some emerging conductive materials, such as MXene quantum dots,[72] nanosheets,[73] and composite scaffolds[74] are also employed to promote tissue regeneration.

Composite conductive biomaterials can integrate the advantages of multiple materials. In addition to adjusting the conductivity to match the target tissue, the stiffness of the composite biomaterial could also be tuned to be comparable to ECM of specific tissues/organs, from soft brain tissue (≈1 kPa) and myocardial tissue (≈10 kPa) to stiff bone tissue (25-50 kPa).[75,76] The integrated functions of adjustable surface topography, surface energy, drug release, and electricity-driven actuation are being exploited to coregulate cell/tissue behaviors and function.[77] Although there are various conductive biomaterials, as well as many processing techniques, the challenge of designing a biocompatible and conductive microenvironment for tissue regeneration is still open. Inorganic conductive additives (e.g., CNTs, rGO, and AuNMs) exhibit excellent conductivity even at low concentrations, while their poor dispersion in polymer matrix reduces the uniformity of the composite biomaterials and limits large-scale fabrication. In addition, due to the unmatched mechanical properties between the inorganic additives and polymer matrix, tension and bending induced deformation of the composite biomaterials would affect their conductivity.

Generally, rationally designed conductive biomaterials have good biocompatibility.[78] However, long-term biosafety and biodistribution should not be ignored. It is reported that toxicity

Table 1. Stem/progenitor cells differentiation and cell function modulation on electrically conductive biomaterials.

Conductive biomaterials	Conductive scaffolds	Electrostimulation	Stem/progenitor cells	Outcome cell line	Refs.
Graphene and derivatives	Graphene film/3D scaffold	/	NSCs/MSCs	Neurons	[197f,199h–j,197l,m,202]
	Graphene	0.1–0.5 V, 1 ms, 1–5 Hz, 1–3 d	hBMSCs	Neurons/OBs	[301]
	Graphene	0.1 V, 50 Hz, 10 min/d for 15 d	rMSCs	SCs	[302]
	Graphene–polyelectrolyte multilayer	/	Neural progenitor cells (NPCs)	Neurons	[196c]
	Graphene–NP film	/	NSCs	Neurons	[197g]
	PDA/RGD–graphene–PCL	/	SCs	Neuron/astrocyte	[10b]
	Graphene/silk fibroin films	/	miPSCs	Neuron/astrocyte	[303]
	Graphene/PEDOT	Biphasic, 30 μA, 1 Hz, 3000 pulses/day for 21 d	rMSCs	Neurons	[119b]
	Graphene substrate	/	NSCs/MSCs/hiPSC	CMs	[280–281,304]
	Collagen/graphene	Monophasic, 2.5 V cm^{-1}, 1 Hz, 48 h	Alignment and maturation of the ESC-CMs		[286]
	Graphene hydrogel		Differentiation of the new bone from the host bone		[243b]
	Graphene/poly(trimethylene carbonate) (PTMC)	Biphasic, 0.01 mA, 2.5 ms, 100 Hz, 4 h/d for 7 d	MSCs	OBs	[305]
	GO coated nanofiber	/	NSCs	Oligodendrocytes	[203]
	GO/methacryloyl-substituted tropoelastin	<15 V, 50 ms, 0.5–3 Hz	CM growth and maturation		[306]
	GO/alginate	/	hMSC	OBs	[241d]
	GO/chitosan	/	hADSCs	OBs	[241c]
	rGO sheet	/	NSCs	Neurons	[197k]
	rGO/collagen	/	MSCs	Neurons	[197n]
	rGO/PCL		PC12	Neurons	[307]
	rGO/GelMA	Biphasic, 3–6 V cm^{-1}, 50 ms, 0.5, 1, 2, and 3 Hz	Synchronous contraction of cardiac tissue constructs		[282]
	rGO/PAAm (polyacrylamide)	5 V, 10 ms, 1 Hz, 4 h/d for 3–7 d	C2C12	Myotubes	[294a]
	rGO/poly (citric acid-octanediol-polyethylene glycol) (PCE)	/	C2C12	Myotubes	[294b]
CNTs	Thin film or substrate	/	NSCs	Neurons	[197a,b,216,197c,217b]
	MWCNTs/chondroitin sulphate	/	NPCs	Neurons	[198]
	MWCNTs/PET fibrous matrices	/	ESC	Neurons	[199]
	CNTs/collagen	/	MSCs	Neurons	[197e]
	MWCNTs/PEGDA	Biphasic, 0.1–1 mA, 100 ms, 100 Hz, 4 d	mNSCs	Neuron/astrocyte	[308]
	CNTs	3 V cm^{-1}, 10 ms, 1 Hz, 2 d	mESCs	CMs	[309]
	CNTs hybrid hydrogel	3 V cm^{-1}, 10 ms, 1 Hz, 2 d	mMSCs	CMs	[310]
	CNTs/PCL/silk fibroin	/	Aligned, elongated, maturation of CMs		[278b]
	CNT-GelMA/Au/PEG	Square waveform, 50 ms, 0.5–6 V, 0.5, 1.0, and 2.0 Hz	Control the beating behavior of the pseudo-3D cardiac tissue construct		[15a]
	CNTs-GelMA	/	CMs maturation		[285]
	MWCNTs/PLLA	1.5 V, 1.5 h per d for 7 d	rBMSCs	OBs	[311]
	CNT/collagen	0.5–0.6 mA, 20 min	hMSCs	OBs	[312]
	MWCNT/PEDOT	Sine wave, 60–80 V, 10 ms, 0.5–8 Hz	C2C12	Myotube	[296a]
	Pyrolysed 3D carbon	/	NSCs	Neurons	[198]
	Silk fibroin/carbon nanofiber	/	MSC	OBs	[313]
PEDOT	PEDOT:PEG film	/	NSCs	Neurons	[209a]
	PEDOT/chitosan/gelatin	/	rNSCs	Neuron/astrocyte	[314]
	PEDOT-HA/Cs/gel	/	rNSCs	Neuron/astrocyte	[315]

Table 1. Continued.

Conductive biomaterials	Conductive scaffolds	Electrostimulation	Stem/progenitor cells	Outcome cell line	Refs.
	Polyurethane (PU)/PEDOT:PSS/liquid crystal GO	Biphasic, 0.25 mA cm^{-2}, 100 ms, 250 Hz, 8 h per d for 3 d	NSC	Neurons	[316]
	Collagen/alginate/PEDOT:PSS	/	Maturation and beating of hiPSC-CMs		[60a]
	PEDOT:PSS	/	MC3T3-E1	OBs	[246]
	PEDOT–COOH	/	C2C12	Myotube	[317]
PPy	PPy (DBS) film	/	NSCs	Neurons	[208a]
	Laminin/PPy	/	ESCs, NSCs	Neurons	[208b]
	Polyphenol/TA/PPy	/	NSCs	Neurons	[60b]
	PPy/poly (L-lactic acid-co-ε-caprolactone) (PLCL)	0.1 V cm^{-1}, 4 h per d for 7 d	PC12	Neurons	[318]
	PPy/PLA	Rectangular wave, 0.04 V, 30 min	PC12	Neurons	[319]
	DOPA/PPy/PGA Springs	/	Maturation and synchronous contraction of CMs		[277]
	HPAE-Py/Geln	/	Reconstruction of cardiac function, revascularization of the infarct myocardium		[275]
	PPy	2 V, 4 h/2 d for 12 d	MSCs	OBs	[250c]
	PPy	Biphasic, 15/500/1200 mV, 10 ms, 1 Hz, 1 h per d for 2 d	MC3T3-E1	OBs	[320]
	PPy/PCL	0.2 mA, 4 h per d for 21 d	MSCs	OBs	[321]
	PPy/chitosan	0.2 mA, 4 h per d for 21 d	MSCs	OBs	[10a]
	PPy-PDA-HAp	300 mV	BMSCs	OBs	[322]
	PPy/PTMC	Biphasic, 50 μA, 0.25–1 ms, 10 Hz, 4 h per d for 14 d	Adipose stem cells (ASCs)	Smooth muscle cells (SMCs)	[323]
PANi	PANi/collagen/HA	/	Longer contraction time, higher contractile amplitude, and lower beating rates		[10c]
	PANi/PLA	/	rbBMSCs	OBs	[248]
	ANi/chitosan/HAp	2 V, 100 Hz, 2 h per d for 14 d	hbBMSCs	OBs	[324]
	PANi/gelatin	Square wave, 6 V, 1 ms, 1 Hz, 1 d	C2C12	Myotube	[295]
Gold	Gold NPs/PCL/gelatin	/	PC12	Neurons	[204]
	PDA-gold/PCL	/	BMSCs/SCs	Neurons	[205]
	Gold nanorod/gelatin	/	Rhythmic contraction of the CMs		[320]
	Gold nanorod/GelMA	2–10 V, 2 ms, 1–3 Hz	Synchronous tissue-level beating of CMs		130
	Au/PCL-gelatin	3V, 50 ms, 1 and 2 Hz	Synchronized contraction of CMs		[271]
Si NWs	Si NWs	3.75 V cm^{-1}, 1 Hz, 9 d	hiPSC	CMs	[325]

of carbon-based biomaterials depends on their size, doses/concentrations, and surface oxygen contents.[79] The possible mechanism involved in their cytotoxicity include induction of protein aggregation through abnormally strong interactions with proteins, and destruction of cell membrane structures.[80] In vivo animal experiments showed that CNTs can induce reactive oxygen species (ROS)-mediated inflammation, epithelioid granulomas and fibrosis that lead to lung malfunction.[81] And carbon-based materials, especially C-dots, could accumulate in multiple organs, including liver, spleen, stomach, kidney, brain, and heart,[82] and cause neurotoxicity, neuronal behavioral deficits and damages, heart and dopaminergic alterations and affect neuronal gene expression.[83] While some studies have shown carbon-based materials could specifically distribute in vivo and rapidly excrete from the body through kidney.[84] For metallic implants, although some studies have shown that the released metal ions could promote osteogenesis by serving as structural components of bone forming enzymes and proteins,[69b,85] there are still concerns about the potential toxicity of those metal ions and nanoparticles. For instance, the metal ions can produce hydroperoxide radicals and cause cytotoxicity.[86] Au nanostructures have high chemical stability and been considered to have good biocompatibility, but their long-term metabolism also needs further evaluation due to its inactivity to biodegrade. The biological toxicity of conductive polymers mainly originates from low-molecular-weight toxic impurities generated during the synthesis process and degradation products,[87] which may produce oxidative stress and change the intracellular mitochondrial membrane potential (MMP).[88] Thus, it is urgent to evaluate the biocompatibility, cytotoxicity, and biometabolic physiology of conductive biomaterials after different administration pathways to ensure the biosafety.

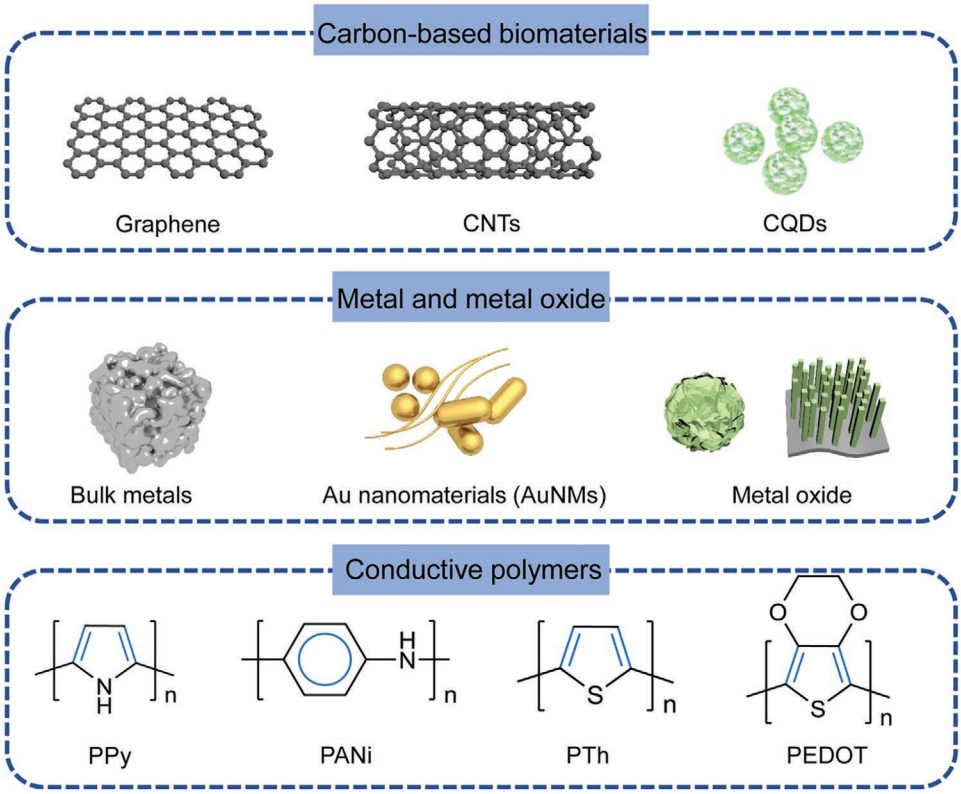

Figure 2. Typical conductive biomaterials used in the field of tissue engineering.

3.2. Conductive Biomaterial-Based Electrostimulation

For a long history, exogenous electrostimulation was directly applied to cell culture media or local tissues including deep brain stimulation, activation of neurons and CMs, modulation of stem cell differentiation, and activation of tissue repairing. However, these plate electrodes have many limitations. First, it lacks selectivity and spatial resolution. The presupposed non-target cells/tissues might be greatly influenced. Second, the cell culture media or surrounding tissues would weaken the voltage that is ultimately applied to the target cells/tissues.[89] Conductive biomaterials with micro-/nanostructure could not only deliver extra electrostimulation according to physiological needs, but also act as biological scaffolds on which cells adhere tightly,[90] thus reducing the voltage loss caused by the surrounding media. And reasonable morphology, chemical, mechanical properties of conductive biomaterial can synergistically directing cell adhesion, proliferation, and differentiation. Thus, conductive biomaterial-based electrical stimulation can provide a diverse platform for regulating cell behavior and stem cell fate in tissue engineering.

3.2.1. Direct Electrostimulation for Tissue Regeneration

Enlightened by the bioelectricity in human bodies, biomimetic electrostimulation has become a spotlight of research for the modulation of a myriad of biological processes, such as stem cell differentiation, neural conduction, muscle contraction, embryogenesis, and tissue regeneration.[5a] The external electrostimulation not only provides a tool to regulate cell therapeutic response, but also accelerates to reveal the underlying mechanism of endogenous bioelectricity.

Electrostimulation can be delivered to cells/tissues through DC or alternating current (AC) (**Figure 3**a). DC stimulation is the most basic electrostimulation method. The amplitude of voltage, current, and stimulus duration can be adjusted. It is widely applied in biomedical field probably because it can be easily generated by batteries.[91] It was found that DC stimulation (30–250 mV mm^{-1}) can promote migration of neural stem/progenitor cell toward the cathode.[92] In another report, both strong DC EFs (10–15 V cm^{-1}) and weak DC EFs (≤5 V cm^{-1}) were able to cause intracellular calcium elevation, promote cell elongation, and guide motility of osteoblast-like cells.[93] DC electrostimulation has some disadvantages, such as the formation of capacitive bilayer near the electrodes. In addition, pH alteration and by-products from electrolysis might also cause biological toxicity. For AC stimulation, in addition to voltage and stimuli duration, waveform (monophase or biphase; square wave, sine wave, triangle wave, and pulse wave, etc.), frequency and pulse width can also be varied (Figure 3a). Among them, biphasic electrostimulation can maintain a charge balance, thereby minimizing cell damage.[94] AC stimulation with low frequencies (<1 Hz) can regulate behavior of neuron that derived from ESCs and iPSCs[95] and evoke network maturation in the cortical neuron.[96] The contraction and maturation of CMs derived from human ESCs, iPSCs, and cardiac progenitor cells were also modulated by endogenous AC electrical

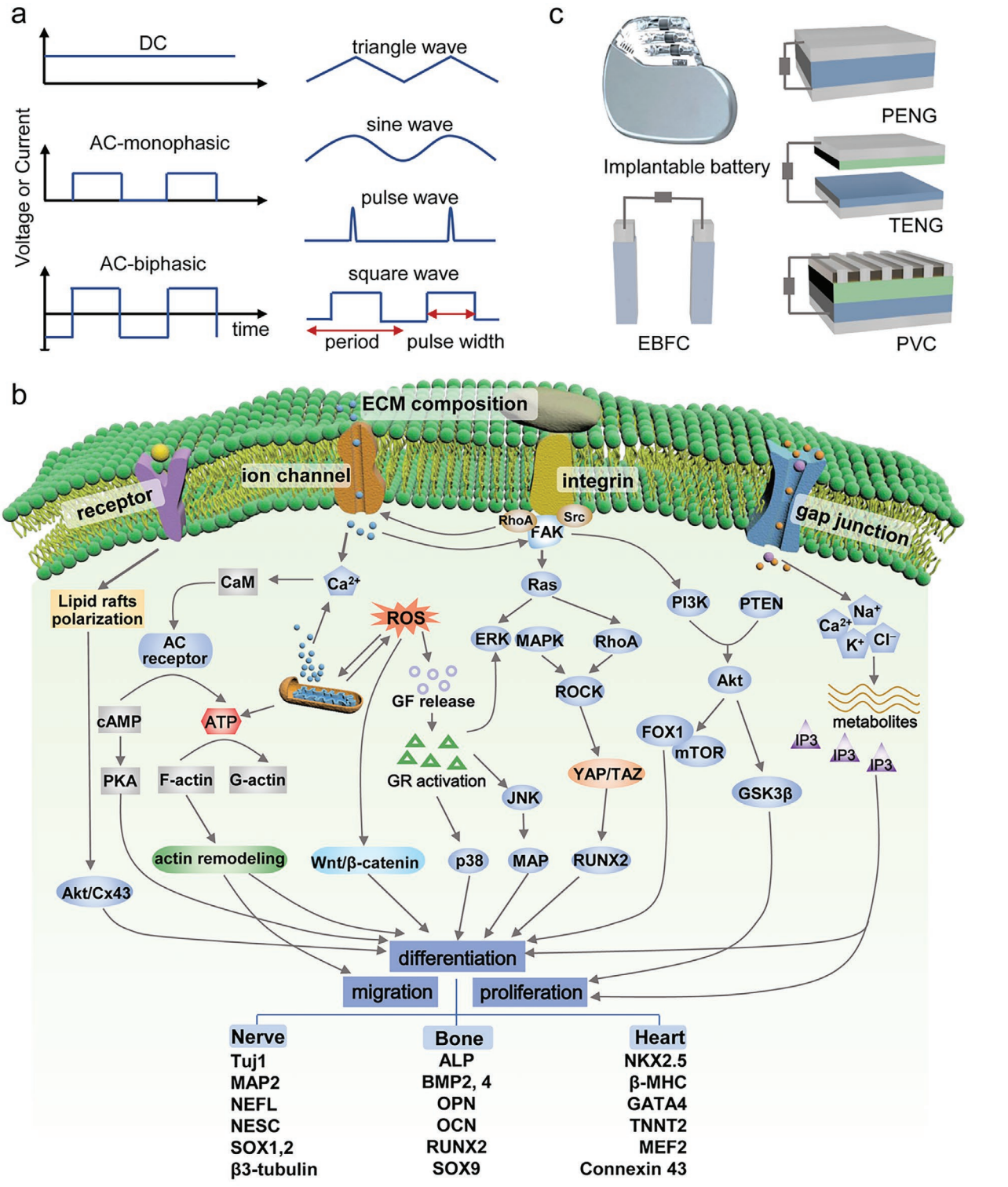

Figure 3. a) Electrostimulation waveforms for tissue regeneration. b) Possible pathways involved in the biological response to electrostimulation. Electrostimulation could act through intracellular calcium ions, membrane receptors, ATP, ROS, gap junctions and ECM compositions. Subsequently, the essential signaling pathways are triggered to modulate cell proliferation, migration, and differentiation. GF, growth factor; GR, growth receptor; CaM, calmodulin; AC, adenylyl cyclase; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; ERK, extracellular signal regulated kinase; FAK, focal adhesion kinase; JNK, c-jun N-terminal kinase; MAPK, mitogen activated protein kinase; PI3K, phosphatidylinositol-3 kinase; PTEN, phosphate and tensin homolog; Src, steroid receptor coactivator; YAP, yes-associated protein; TAZ, transcriptional coactivator with PDZ-binding motif; ROCK, Rho-associated protein kinase; MAP, microtubules-associated protein; mTOR, mammalian target of rapamycin; FOX1: forkhead box protein 1; GSK3β, glycogen synthase kinase-3. c) Devices to apply direct electrostimulation.

fields (1–10 Hz).[18b,97] Moreover, AC stimulation can significantly promote osteogenic differentiation even in the absence of exogenous drugs and/or growth factors.[98] Although most of works apply electrostimulation with fixed voltage or electrical field, current is also a key parameter that cannot be ignored. It is found that current above the threshold might cause cell death,[99] such as 20 mA in case of treating nonunions.[100]

Electrostimulation has been proven to play an important role in modulating cell activity both in vitro and in vivo, while the exact mechanisms of these electrical-induced biochemical responses are still obscure. The electrical activity of cells and conductive materials is based on ionic processes and electron flow or transfer, respectively. It is vital to clarify the electrical interaction between materials and cells. The cell membrane potential is regulated by the inflow and outflow of ions, which can be simulated by an equivalent circuit using a voltage source, a capacitor, and a resistor.[89] In which, the voltage source represents the cellular resting membrane potential; the capacitor represents the intracellular and extracellular charge separated by the nonconductive cell membrane; and the variable resistors represent ion channels. An external electrical stimulation generated by piezoelectric or conductive materials can be modeled by another voltage source. Thus, external electrostimulation would affect cell membrane potential, membrane receptors, ion channels, gap junctions, etc. There are several pathways that might be potentially involved (Figure 3b): 1) Intracellular calcium ions and calcium signaling: Electrostimulation is able to locally change the V_m and activate the voltage-gated calcium channels (VGCC), allowing an influx of extracellular Ca^{2+} into cytoplasm. In addition, electrostimulation can induce recombination of membrane proteins via phospholipase C, subsequently causing Ca^{2+} release from intracellular calcium reservoirs.[89,101] The Ca^{2+} transients in both cases would activate the cytoskeletal calmodulin, and further accelerate cell proliferation and change growth factors expression.[9c,99a,102] 2) Membrane receptors: Electrostimulation can induce asymmetric assembly and disassembly of F-actin filaments, and regulate the distribution, expression or conformation of transmembrane receptors (e.g., growth factor receptors, integrin-β molecules, and adenosine A_{2A} receptors),[103] thereby influencing related intracellular signaling pathways in cell migration or differentiation via ligand-receptor binding. 3) Adenosine triphosphate (ATP): Electrostimulation may promote cell metabolism and accelerate ATP depletion, thus altering membrane related behaviors, such as endocytosis and exocytosis, adhesion, and migration.[104] However, some reports suggested that DC electrostimulation ranging from 10 to 1000 μA promoted membrane-bound ATP synthesis,[105] and then these ATP would be consumed for conversion of monomeric G-actin to polymeric F-actin for reorganization of actin cytoskeleton.[106] 4) ROS: Electrostimulation controlled ROS generation at a physiologic level can trigger essential signaling pathways related to cell proliferation and differentiation, including MAPK pathways and subsequent ErK1,2, JNK, and p38 signaling cascades.[107] It has been reported that a mild rise in hypoxia-induced ROS enhancement can promote proliferation and differentiation of MSC.[107a,108] 5) Gap junctions: Gap junctions not only enable adjacent cells to exchange small molecules, but also form electrical coupling and metabolic coupling between those cells. Electrostimulation can change the cell gap junctions, affect exchange of signaling molecules such as calcium, potassium, cyclic nucleotides and inositol phosphates, and promote the development and communication of electroactive cells.[109] 6) ECM compositions: Electrostimulation can alter ECM compositions by affecting proteins, soluble ions or charged groups, which could be perceived by cells through integrins.[110]

Subsequently, the original biophysical electrostimulation can be converted into biochemical cues for cells to read through intracellular signaling cascades, which matters in regulating cell behaviors including cell lineage commitment. Protein activation via phosphorylation nearly runs through the whole signaling pathways. Typically, phosphorylation of FAK, a linker bridging integrins and cytoskeleton, can be passively turned on by electrostimulation. Then it can further stimulate actin remodeling together with downstream mechano-signaling like MAPK pathways and ERK1/2 that are closely related to cell proliferation and differentiation, and JNK required for subsequent MAP activation and neurogenesis.[111] Studies also reveal that electrically induced intracellular calcium concentration increase reinforces the activation of unique calcium/calmodulin pathway in cardiomyogenic differentiation.[112] Additionally, pulsed electrical fields can promote the secretion of growth factors and further get involved in p38 signaling transduction to induce myogenic lineage choice.[113] Moreover, other associated pathways that collectively constitute the intricate signaling networks to synergistically mediate cell regulation have been extended to Wnt signaling pathway for osteogenesis, PI3K/PTEN signaling and its downstream Ark for cell survival and apoptosis. All of these are responsible for the expression of proliferative and differentiative genes.[112,114]

3.2.2. Devices to Apply Direct Electrostimulation

There are several different pathways to impose electrostimulation on cells/tissues, including direct stimulation, capacitive stimulation, inductive stimulation, and combined stimulation.[5b] For capacitive stimulation and inductive stimulation, cells indirectly perceive electric field or electromagnetic field, and do not directly contact with biomaterial electrodes. Thus, we mainly focus on direct electrostimulation via conductive biomaterials in this section. Commercial electrical stimulators are mostly applied for direct electrostimulation, especially for in vitro cell experiments.[94] Their electrical parameters (voltage, current, waveform, frequency, and stimulation time) can be fine-tuned, helpful to screen out the most suitable electrostimulation conditions for different cells/tissues. For in vivo applications, they are bulky and require wire connections between stimulators and electrodes. It is inconvenient, and might increase potential safety risks after implantation. Implantable batteries have been successfully used in implantable medical electronic devices, such as cardiac pacemakers, deep brain stimulators, and cochlear implants.[115] Combined with the corresponding electrodes, they have produced positive therapeutic effects in clinical application. Unfortunately, regular replacement of battery is needed due to limited battery capacity (e.g., lifetime of cardiac pacemakers = 7–10 years),[116] which not only increases financial burden of patients, but also increases the risk of postoperative infection.

Recently, implantable energy harvesters (IEHs) have been proposed, which can harvest power from organisms or surrounding environment, such as human mechanical energy, in vivo redox reaction, endocochlear potential and ambient light and temperature.[117] Therefore, a series of self-powered electrostimulation devices has been developed (Figure 3c), including piezoelectric nanogenerators (PENGs),[118] triboelectric nanogenerators (TENGs),[119] mass imbalance oscillation generator (MIOG),[120] enzymatic biofuel cells (EBFCs),[121] untracochlear potential (EP) collector,[122] photovoltaic cell (PVC),[123] and pyroelectric nanogenerators (PYENGs).[124]

Human mechanical motions in daily life, such as limb movement, heartbeat, and respiration, could produce abundant kinetic energy. PENGs convert mechanical energy into electricity based on piezoelectric materials, which have been designed as an energy harvester to generate electricity and applied to the electrodes. In 2006, Wang and Song first designed a ZnO nanowire-based PENG to harvest tiny vibrational energy.[125] Recently, the output performance has been improved up to 20 V/1 μA for implantable PENG,[126] and 130 V/800 nA for wearable PENG.[127] TENG could convert mechanical energy into electricity based on the coupling effects of triboelectrification and electrostatic induction, which was first proposed by Wang and co-workers in 2012.[128] In order to be applied in different scenarios, TENGs with four fundamental working modes have been developed, including vertical contact-separation mode, lateral sliding mode, single electrode mode, and freestanding triboelectric-layer mode.[129] Generally, humidity seriously affects output of the TENG due to its nature of electrostatic induction. Thus, encapsulation is a necessary step for stable output of implantable TENG.[130] Driven by cardiac motion of a pig, the open-circuit voltage and short-circuit current of an implantable TENG reached up to 65.2 V and 0.5 μA, respectively.[130] Hinchet et al. designed a thin vibrating TENG that can harvest external mechanical energy delivered by an ultrasound. The output generated by the ultrasound ex vivo reached 2.4 V and 156 μA under the porcine tissue.[131] MIOG is another mechanical energy harvester based on the conventional automatic watch mechanism.[132] By affixing MIOG to a sheep heart for 1 h, the generator produced 330 impulses with a mean power of 16.7 μW that was translated into 11.1 μJ per heartbeat.[120]

EBFCs are hybrid systems that combine the electrochemical energy conversion with biocatalysis.[121a] They can utilize redox reaction in the body, such as glucose, to generate low-intensity direct current (DC) for electrostimulation or powering bioelectric devices.[121b,133] The advantages of mild operating conditions and simple device structure promote EBFCs to be a desirable implantable power source. A modified biocatalytic buckypaper electrode with millimeter-scale size of $2 \times 3 \times 2$ mm^3 generated electrical power of 2–10 μW when implanted in a living gray garden slug.[134] As another electrochemical energy in body, EP arises from the electrochemical gradient between endolymph and perilymph, which is the largest positive DC electrochemical potential in mammals (70–100 mV).[122] This potential has been utilized to power implanted devices. For example, Mercier et al.[122] designed a chip to extract a minimum of 1.12 nW from the EP of a guinea pig to power a wireless radio. Under the premise of not interfering with normal cochlea function, the low EP voltage and extractable power are two major challenges for harvesting net positive energy.

In addition to harvesting mechanical and electrochemical energy in body, researchers also utilize energy in environment, such as light and heat. Thus PVC and PYENGs are employed to generate electricity for in vivo electrostimulation.[135] Due to its nature of photoelectricity, most PVCs are used in eyes or under the skin where light is easily transmitted.[136] And PYENGs generally need to artificially create a temperature gradient to meet the temperature difference required to generate electricity.[124]

In general, researchers have developed a variety of electrostimulation devices that could be applied for in vitro and in vivo electrostimulation. Their practical application is determined by the specific tissue microenvironment. Mechanical energy harvesters (PENG, TENG, and MIOG) are more suitable for the application in heart and bone tissue, due to the regular mechanical heartbeats and joints movement in bodies. High compatibility with corresponding tissues is the foundation requirement for the implantable devices. Thus, biocompatible materials are used directly to fabricate or encapsulate IEHs. High energy conversion efficiency and stable output also need to be further optimized. For harsh stimulation conditions, it is necessary to charge the generated electricity from IEHs into the battery and then control the electrical output when needed. In addition, high flexibility, and suitable size, mechanical strength, and elastic modulus are also important for easy adhesion to different biological tissues, reducing interference with surrounding tissues.

3.3. Piezoelectric Biomaterials and Electrostimulation

Piezoelectric biomaterials can generate piezopotential to regulate the behaviors and fate of stem cells. It is generally believed that its electrostimulation mechanism is similar to that of electrical stimulation via a conductive material, which mainly focuses on the membrane potential, ion channels, membrane receptors, and ECM compositions.[14b,89] Micro-/nano-structured scaffolds from piezoelectric materials are independently discussed because of the special physiochemical and electromechanical coupling properties of piezoelectric materials different from conductive materials. Piezoelectric materials are characterized by two opposite effects: direct piezoelectric effect (generation of electricity under an applied pressure), and reverse piezoelectric effect (deformation of material in response to an applied EF). Responsive to respective physical stimuli, both effects can act as determinant cue for regeneration of different tissues.

3.3.1. Piezoelectricity and Piezopotential

Piezoelectricity origins from the noncentrosymmetric nature of material, including noncentrosymmetric crystal structure in inorganic piezoelectric materials and noncentrosymmetric molecular structure and orientation in organic piezoelectric materials.[137] Due to the special electromechanical coupling properties, electricity is generated when the piezoelectric

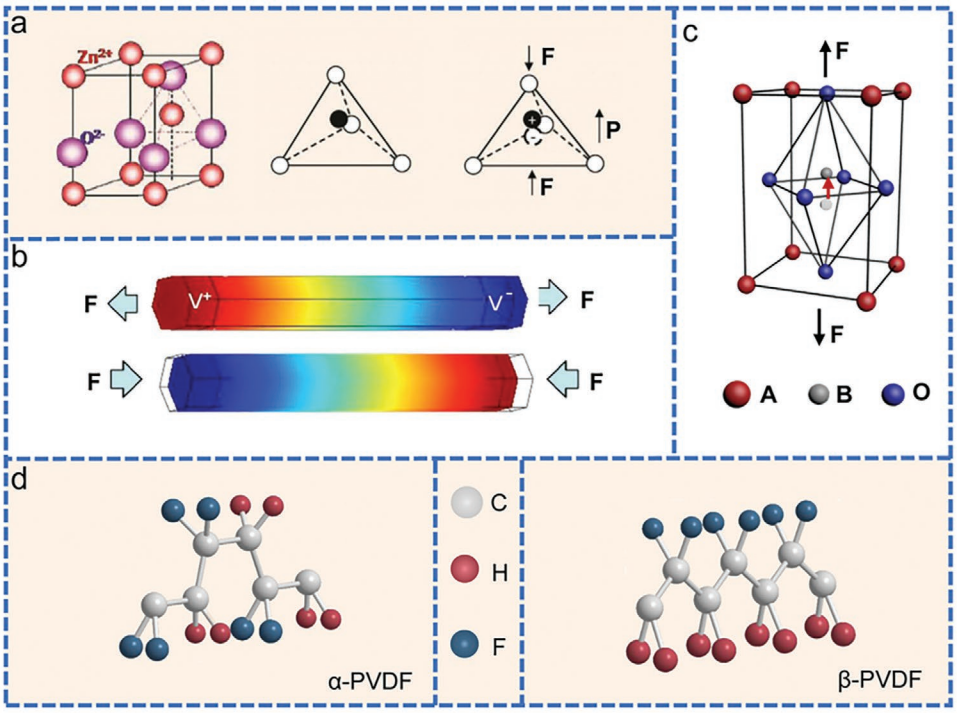

Figure 4. a) Atomic model of the wurtzite-structured ZnO, and schematic illustrations of stress induced electric dipole moment. Reproduced with permission.[140] Copyright 2012, Wiley-VCH. b) Numerical piezopotential distribution along a ZnO NW under axial stretch or compress. Reproduced with permission.[143a] Copyright 2009, American Institute of Physics. c) Atomic model of the perovskite structured ceramics (ABO_3). d) Molecular structure of α- and β-phase PVDF.

material is deformed and vice versa, which is piezoelectric effect and converse piezoelectric effect, respectively. Piezoelectric effect is a molecular phenomenon that induces a macroscopic potential through continuous overlay of the dipole polarization, which is the piezoelectric potential (piezopotential).[125,138]

Piezoelectricity in inorganic materials arises from the non-centrosymmetric crystal structure. When the crystal is under a mechanical stress, the displacement of positive and negative ions inside the crystal produces a dipole moment. It could not be cancelled out by other dipoles.[139] **Figure 4**a depicts piezoelectric effect of wurtzite-structured ZnO semiconductor.[140] In an unstrained hexagonal ZnO crystal structure, positive Zn^{2+} and negative O^{2-} are tetrahedrally coordinated and the centers of anions and cations overlap with each other, so there is no polarization. When a stretched or compressive stress is applied, the relative displacement of Zn and O atoms causes the transfer of positive and negative charges centers to the opposite directions, resulting in a dipole moment in the unit cell. Hence, there appears a macroscopic piezopotential in the ZnO crystal due to the continuous overlay of dipole moments (Figure 4b).[141] For perovskite structured ferroelectric ceramics (ABO_3), it has a nonzero net charge in the unit cells even if no mechanical stress is applied. And an external stress can further shift the relative position of the B site inside the unit cell and change its electrical polarity (Figure 4c).

Piezoelectricity in organic materials origins from the orientation and arrangement of molecular dipoles. Taking PVDF [$(CH_2{-}CF_2)_n$] as an example, it has five crystal phases with three chain conformations: *trans*–gauche–*trans*–gauche conformation (TGTG′) for α and δ phases, all trans (TTTTT) for β phase, and T3GT3G′ for γ and ε phases.[142] Among them, α and β phases are predominant (Figure 4d). The dielectric property of PVDF derives from the different electronegativity of F and H atoms, generating a dipole moment along the F→H direction.[9c] The α phase exhibits no piezoelectricity, because the chains are packed in the unit cell resulting in a net cancellation of dipole moments. The β phase has the highest piezoelectricity due to the parallel orientation of dipole moments causing the highest net electric dipole moment.[137,143]

3.3.2. Pathways for Generating Piezopotential

Ferroelectric materials can produce permanent polarized potential even without strain. For other piezoelectric materials, mechanical deformation (elongation, twisting, bending, or compression) is an indispensable requirement for the generation of piezopotential. Piezopotential have been widely employed to regulate carrier transmission in transistors,[144] photocatalysis,[145] solar cells,[146] and light-emitting diodes (LED).[147] Different methods, such as speed-controlled motor, ultrasound wave, mechanical brushing/sliding, internal strain of crystal by thermal stress and water flow have been developed to induce mechanical deformation to generate piezopotential. And intriguing helical structure was designed to amplified the deformation.[139] For tissue engineering applications, pathways for exerting mechanical stress are more limited. It is necessary to take into account cell viability and adhesion during

deformation of the piezoelectric biomaterials. As well, for in vivo application, the availability and biosafety of the pathway should be considered.

Recently, to control the material deformation accurately, a custom vibrating platform with selectable frequency and amplitude was employed to generate vibration, and a sensor attached to the culture plate bottom was used to quantify the vibration amplitude.[148] Dynamic bioreactor was also designed to apply cyclic compression.[149] A speaker was attached on the bottom of the bioflex culture plate, and the frequency and intensity of vibration were controlled by function generator and power amplifier.[150]

Ultrasonic wave is sound wave with a frequency higher than 20 000 Hz. Due to its high tissue penetration and good directionality, it has been used for diagnostic imaging, promotion of drug delivery, and sonodynamic therapy.[151] When using ultrasound as a mechanical force source, both acoustic pressure and ultrasonic cavitation effect play major roles in driving deformation of the piezoelectric materials. Sound pressure causes tiny bubble nuclei expansion and closure rapidly to generate shock waves. And ultrasonic cavitation is a dynamic process including expansion, closure and oscillation.[153b] Furthermore, ultrasonic power, frequency and periodically turn on/off can be adjusted precisely by ultrasonic transducers.[152]

Interestingly, magneto-electric (ME) materials have been designed to induce piezopotential of piezoelectric materials by a magnetic field. A magnetic stimulus causes strain of magnetic material, and the strain is further transferred to intimately connected piezoelectric material to produce an electrical response. This is the magnetoelectric coupling in two-phase ME materials.[153] Magnetic field has been widely applied for magnetic resonance imaging, magnetic hyperthermia, and targeted drug delivery. It has a deep tissue penetration and high precision in controlling the motion of magnetic materials.[154] $CoFe_2O_4$@$BaTiO_3$ (CFO@BTO) core–shell ME nanoparticles,[155] ME nanowires, and nanoeels[156] have been prepared to trigger the ME effect electric dipole by applying a AC magnetic field. The nanoeel consisted of a flexible piezoelectric tail (PVDF-based copolymer), linked to a nickel rings decorated PPy nanowire for magnetic actuation.[156c] By changing the external magnetic field, the nanoeel can be switched from a tumbling motion to a wobbling motion (**Figure 5**a). And the actuation of nanoeel deformed the soft PVDF-based tail, which induced its electric polarization changes and realized controlled drug release based on electrostatic repulsion (Figure 5b).

In nature tissues, the mechanical force generated by cell activity is continuously applied to ECM. Nanowire-based platforms have been employed as force sensors to monitor cell traction forces through quantitatively analyzing the bending of the nanowires (Figure 5c).[157] It was found cell traction-mediated soft fibers realignment and gel contraction,[158] as well as cellular contraction caused breakage of the fiber cross-links, allowing the cells to recruit more fibers (Figure 5d).[159] Although the materials mentioned above are not piezoelectric, these studies suggested cell activities (i.e., cell spreading, migration, contraction, and CMs beating) and corresponding cell traction forces can induce deformation of piezoelectric biomaterials with special structure or suitable hardness. Inspired by this, our group has fabricated piezoelectric PVDF films with nanostripe array structures, which could generate a surface piezopotential about +3.4 mV according to finite element simulation by cell traction (10 nN), which was over 3500 times compared with the flat PVDF film. This high surface piezopotential could efficiently promote neuron-like differentiation of rbMSCs (Figure 5e,f).[160]

In addition, some tissue activities or human body movements can also be utilized to generate piezopotential for in vivo tissue repair, such as heartbeats for cardiac tissue engineering and joint activities for bone tissue engineering.[157a,161] Reasonable design of morphology and structure of piezoelectric biomaterial enables it to more efficiently utilize biomechanical energy in cells, tissues and organs, generating a feedback electrostimulation on corresponding matters.

3.3.3. Piezoelectric Biomaterials for Tissue Regeneration

In this section, piezoelectric biomaterials are introduced with categories of i) inorganic piezoelectric materials, ii) organic piezoelectric materials (including natural and synthetic biopolymers), and iii) piezocomposites. Their biomedical applications in stem cell determination and tissue regeneration is highlighted in the next section.

The first piezoelectric material with single crystal α-quartz was observed by the Curie brothers in 1880, whereas its application was limited to acoustic devices due to low piezoelectric coefficient and inefficient signal transduction. Perovskite structured ceramics (ABO_3), such as BTO, $SrTiO_3$, $LiTaO_3$ and $LiNbO_3$, exhibit high electromechanical coupling and good biocompatibility.[9c] For example, BTO nanoparticles have a low cytotoxicity even at high concentrations.[162] Lead-containing piezoceramics such as PZT has high piezoelectricity. The piezoelectric constant of ternary solid solutions of perovskites such as $Pb(Zn_{1/3}Nb_{2/3})O_3$ (PZN) and $PbTiO_3$ (PZN-PT) could reach as high as 2000 pC N^{-1}, but potential toxicity of lead limits their biomedical application.[9c] To reduce cytotoxicity of lead-based piezoceramics, researchers have encapsulated biocompatible materials on them, such as Ti,[163] but the leakage of Pb^{2+} ions still cannot be ignored.

Recently, the third-generation semiconductors, most of which have wurtzite structure, such as ZnO, AlN, BN, and GaN, have been proven to have semiconductor properties and piezoelectric effect, simultaneously.[141b] Although their piezoelectric coefficients are always lower than the above-mentioned piezoelectric ceramics, they can generate piezopotential comparable to cell membrane potentials, which is enough to regulate cell behavior.[137,164] Besides, 2D odd-layered MX_2 (M = Mo, W, etc.; X = S, Se, or Te), MX (M = Ga, In, Sn or Ge; X = Se or S), GaP, GaAs, GaSb and black phosphorus also have piezoelectric effect.[165]

Compared with piezoceramics, although piezopolymers have relatively low piezoelectric coefficients, their advantages of high flexibility and relatively low stiffness meet the requirements of tissue engineering biomaterials, especially for soft tissue applications. A variety of structures including microspheres, nanofibers, films, and hydrogels have been fabricated through different preparation technics, such as electrospinning, spin coating, and template method.[52b] PVDF and P(VDF-TrFE)

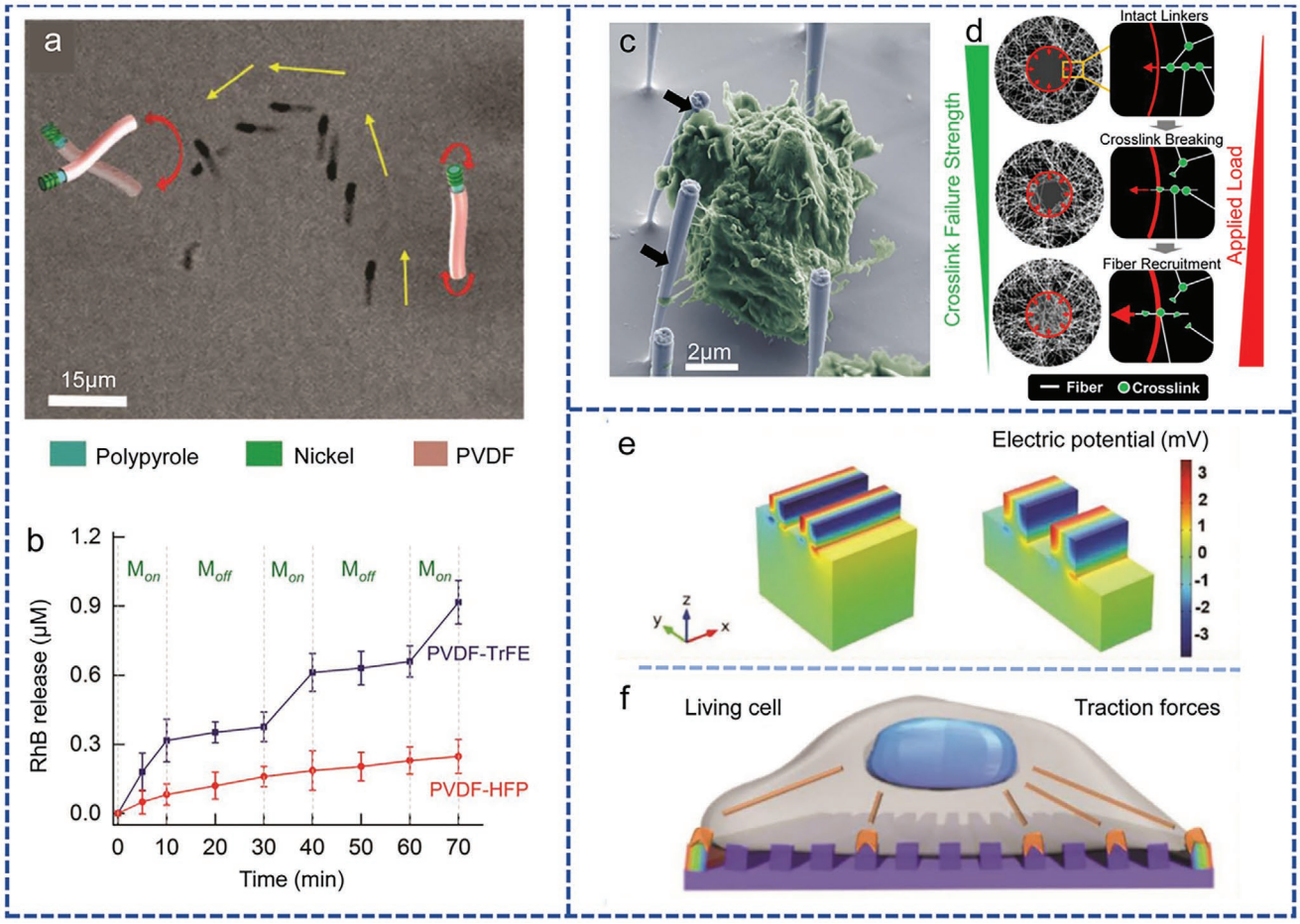

Figure 5. a) Time-lapse image showing a single hybrid nanoeel transition from a surface-walking swimming mode to a wobbling motion upon changing the parameters of magnetic fields. b) The corresponding pulsatile release of rhodamine (RhB) with (M_{on}) and without (M_{off}) a magnetic field. Reproduced with permission,[158c] Copyright 2019, Wiley-VCH; c) Cell migration-induced nanowire deflections. Reproduced with permission.[157c] Copyright 2018, American Chemical Society. d) Tensile forces generated by cellular contraction lead to breakage of the fiber cross-links, which allowed the cells to recruit more fibers. Reproduced with permission,[159] Copyright 2017, National Academy of Sciences. e) The electric potential generated on the nanostriped PVDF when strained by a tangential force of 10 nN. f) Inherent cell forces of living cells grown on the surface of PVDF with nanoscaled stripe arrays. Reproduced with permission.[160] Copyright 2019, Wiley-VCH.

($d_{33} = -38$ pC N^{-1})[166] are widely investigated due to their high piezoelectric response and good mechanical properties. Among the five crystal phases of PVDF, the β phase exhibits the highest piezoelectricity ($d_{33} = -33$ pC N^{-1}; $d_{31} = 23$ pC N^{-1}).[137] As mentioned above, piezoelectricity of PVDF origins from orientation and arrangement of the F→H dipoles. To increase piezoelectricity, the materials could be processed via poling at a high electrical field, annealing, mechanical stretching, melt-recrystallization and incorporation of graphene.[47,167] Electrospinning is the most common method for fabricating piezoelectric PVDF. Both high applied voltage and high-speed rotating collector cause micro-/nanofibers stretching, conducive to increase polarity. In addition, to reduce its hydrophobicity for better cell adhesion and tissue affinity, PVDF has been modified by incorporation of inorganic nanomaterials, mixing with hydrophilic polymers, or treated with oxygen plasma.[160,168] Poly (L-lactic acid) (PLLA), a biodegradable and bioabsorbable piezopolymer, shows promise as a functional biomaterial in tissue engineering applications. Mechanical stretching is effective to improve the crystallinity and piezoelectricity of PLLA, and its shear piezoelectric constant d_{14} can reach ≈10 pC N^{-1} with the draw ratio increases.[169] Polyhydroxyalkanoate (PHA) is another commonly used biodegradable piezopolymer, including poly(3-hydroxybutyrate) (PHB) and poly(3-hydroxybutyrate-3-hydroxyvalerate) (PHBV).[170] It is a bacterial synthetic polyester as a carbon source and energy storage substance in the organism. PHA has twisted radial lamellar structure and exhibits different orientations when aggregated to films,[9b] thus possessing piezoelectricity (1.6–2.0 pC N^{-1}).[52b,171] Although the piezoelectric coefficient of PHA is relatively low, its unique biodegradable, biocompatible, and mechanical properties allow it to be used to fabricate scaffold and biosensor.

Natural piezopolymers attract more attention in tissue engineering due to their low toxicity and biodegradability. In general, many biomacromolecules have piezoelectricity, as we have introduced in the section of endogenous piezoelectricity. In addition to collagen and other proteins, cellulose, chitin, and chitosan are also widely investigated as natural piezopolymers.

Cellulose is a linear homopolymer of glucose with a low piezoelectric coefficient of ≈0.1 pC N^{-1}.[172] Chitin is a natural polysaccharide with a piezoelectric coefficient of ≈0.2–1.5 pC N^{-1}.[173] It is widely existed in shells of crustaceans, mollusks, insects, and cell wall of fungus. Since its hydrophilicity, chitin is benefit to promoting cell adhesion and spreading.[47] Chitosan is a biodegradable linear polysaccharide by partial deacetylation of chitin, and its solubility is greatly improved. Due to their low toxicity, good biocompatibility, biodegradability and flexibility, natural piezopolymers have been used in nerve and cartilage tissue engineering for stem cells adhesion, proliferation, differentiation, and functional cell growth.[174] More recently, researchers have synthesized biomimetic piezoelectric supramolecules and micro-/nanostructures especially with polypeptides and peptide crystals.[175] Recently, a higher piezoelectric coefficient over 200 pm V^{-1} has been realized.[176] With good biocompatibility and low immunogenicity, we vision that these piezoelectric molecules would open up a wide avenue for the development of new generations of biomimetic piezoelectric materials.

Moreover, piezocomposites integrate the advantages of piezoceramics and piezopolymers, thus exhibiting high piezoelectric coefficient, good flexibility, biocompatibility, and improved mechanical stability. A common compounding method is to disperse the piezoceramic nanostructures into polymer matrix to fabricate polymer matrices-based composites, such as microspheres, fibers, films, and hydrogels.[48,52b] The improved performance of piezocomposites further promotes the application of piezoelectric biomaterials in tissue engineering field.

3.4. Electroresponsive Biomaterials

Triggered by environmental variations (e.g., temperature, pH, electricity, light, and magnetic field), stimuli-responsive biomaterials exhibit specific changes of their own characteristics, which have attracted considerable interest due to their bionic nature and widespread biomedical application potentials.[177] Among them, electrostimulation has several attractive advantages, including noninvasiveness, high spatiotemporal controllability, and rapid and reversible induction.[178] For tissue engineering, a spectrum of functional biomolecules (e.g., growth factors, therapeutic drugs, genes, and proteins) could play important roles in regulating cell behaviors, cell fate determination, and tissue regeneration. Electroresponsive biomaterials can release therapeutic agents on-demand with predetermined magnitude and time schedule, when actuated by an appropriate electrical stimulus. Most of current electroresponsive drug delivery systems are based on electrically induced redox reaction of conducting polymers. Taking PPy as an example (**Figure 6**a), its oxidized form has abundant positive charge along the carbon backbone, serving as active sites for complexing negatively charged drugs by electrostatic and hydrophobic interactions.[12a] When PPy is electro-reduced to neutral, the loaded drugs are expelled from the PPy matrix, thereby triggering drug release. Electroresponsive drug-release systems are commonly designed in the form of thin films or hydrogels, in which drugs are directly incorporated.[179] This drug loading and release is limited by the chargeability of the loaded drugs. To overcome this restriction, conducting polymers films are employed as nanoswitches to gate nonelectroactive materials as the drug container.[180] For example, a thin PPy layer (≈1.5 μm) was covered on nanoporous anodized aluminum oxide membrane (Figure 6b).[12b] The ON/OFF release of model protein drug was realized by shrank of PPy chains in the oxidation state (0.1 V, the expulsion of hydrated sodium ions) and expanded to cover the pores in the reduced state (–1.1 V). To improve the drug loading and release rate, nanoscaled dispersed/colloidal systems, such as nanoparticles, micelles, and vesicular structures are also developed.[181] Electrostimulation can also indirectly control drug release from pH-responsive scaffolds via electro-induced pH changes.[182]

Electroresponsive interfaces can control cell adhesion, release, migration, as well as stem cell differentiation via electrically induced conformational changes of RGD.[14a,183] RGD as a tripeptide sequence (Arg-Gly-Asp) generally exists in ECM proteins that mediates integrin-mediated cell adhesion. Lashkor et al.[184] directly exposed (open circuit conditions) or concealed (–0.4 V) RGD by folding and stretching the RGD-grafted charged backbone of oligopeptide. Another research[14a] indirectly exposed or concealed RGD by electrostatic attraction and repulsion of negatively charged sulfonate moiety without RGD modification (Figure 6c). In addition, surface electrical potential generated by piezoelectric materials is also used to in situ induce conformational change of the adsorbed proteins to fit different physiological needs. According to molecular dynamics simulation (Figure 6d), a higher RGD exposure was observed on the material surface with a 53 mV electrostatic potential, which was more conducive to cell adhesion. When the surface potential was 88 mV, the height of RGD decreased, and the distance between RGD and synergy domain of fibronectin decreased from 41 to 33 Å. Under this dynamic modulation, a fast cell proliferation was observed.[14b]

Furthermore, electrically induced mechanical forces or motion of electroresponsive biomaterials have been used to regulate cells/tissues behavior. Polyelectrolyte hydrogels generate deformation by repeatedly swelling and deswelling under an EF. It is due to osmotic pressure changes inside and outside of the hydrogel caused by charged ion transferring to the anode or cathode sides.[185] A biocompatible and electroresponsive hydrogel-based smart scaffold composed of acrylic acid and fibrin was developed to mechanically stimulate cells. The pulsatile electrostimulation (± 0.06 V mm^{-1}) induced dynamic alternation of the scaffold and significantly enhanced cell growth-in and alignment.[186] Electrically driven biorobots have been widely studied as engineering biohybrid tissue actuators, especially for regulating the motion of cardiac tissue and skeletal muscle.[15,187] For example, a biohybrid valveless pump-bot was proposed, which was consisted of a soft hydrogel tube with both ends connected to a stiffer polydimethylsiloxane (PDMS), and a skeletal muscle ring wraps around the soft tube (Figure 6e).[188] Triggered by spontaneous muscle contraction or electrostimulation (9 V; 4 Hz), this pump-bot established a net unidirectional fluid flow up to 22.5 μL min^{-1} (Figure 6f,g).

In general, electroresponsive scaffolds are composed of a class of electroactive biomaterials that can adjust their own biochemical and biophysical properties or environmental conditions through external electrostimulation to adapt cells and

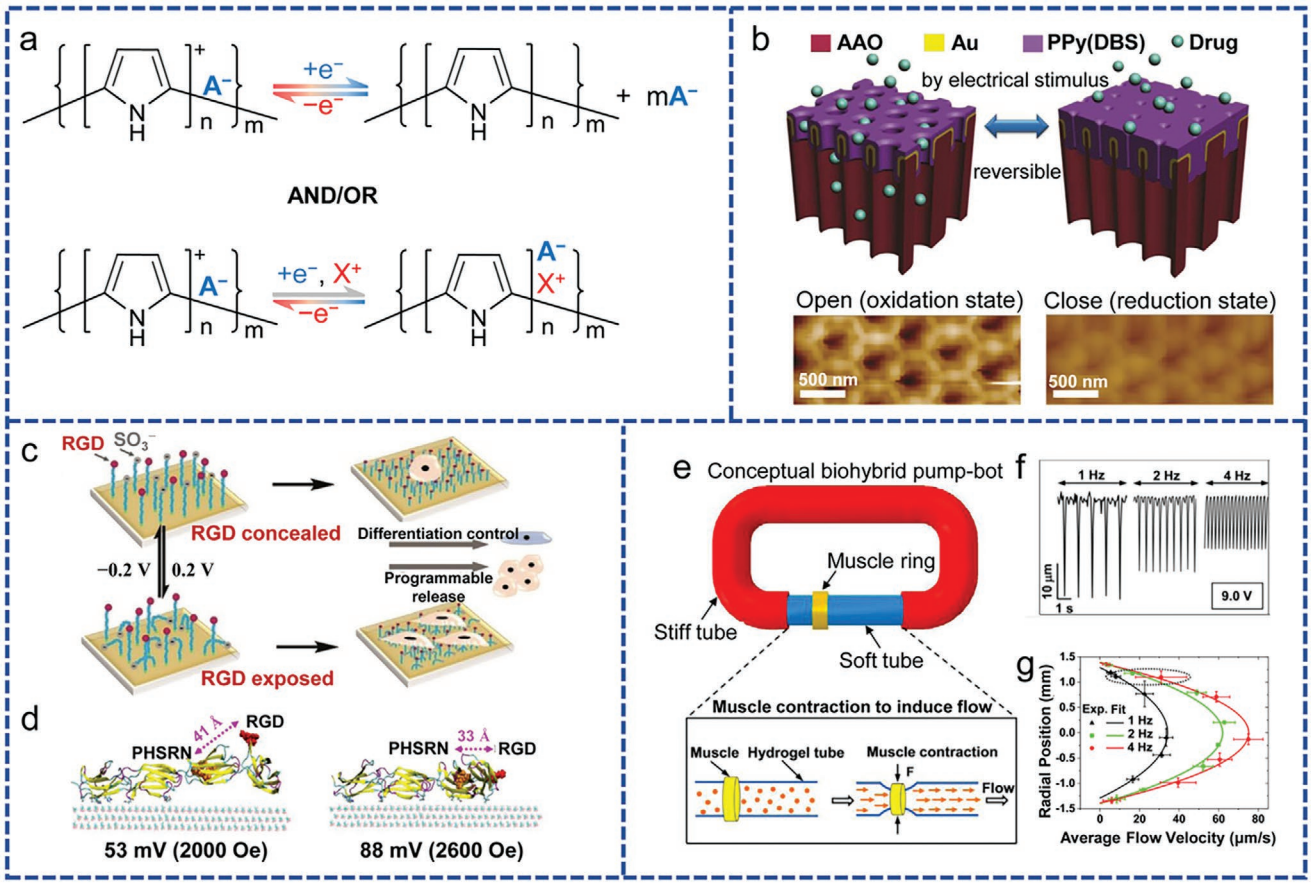

Figure 6. a) The electrodynamic character of PPy. b) Electrically responsive nanoporous PPy membrane: Reversible change of pore size between oxidation/reduction states, and in situ AFM height images corresponding to the oxidation and the reduction states. Reproduced with permission.[12b] Copyright 2011, American Chemical Society. c) Potential-responsive surfaces for the dynamic manipulation of cell behavior. Reproduced with permission.[14a] Copyright 2019, Wiley-VCH. d) Molecular dynamics simulation for conformation of FN-III7–10 on the CFO/P(VDF-TrFE) composite film with 53 and 88 mV. Reproduced with permission.[14b] Copyright 2018, American Chemical Society. e) Schematic illustration of the biohybrid pump-bot. Muscle contraction along the circumferential direction compresses the hydrogel tube in the radial direction which drives a unidirectional flow. f) Time-varying deformation of hydrogel tube induced by muscle rings at electrical stimulation frequencies with a voltage of 9 V. g) Flow patterns along cross-section of the hydrogel tube in the middle at an electrical stimulation voltage of 9 V. Reproduced with permission.[188] Copyright 2019, National Academy of Sciences.

tissues at different periods. Therefore, electrostimulation acts on cells indirectly, and it is mainly from the effect of the adjustable properties of the material (mechanical property, redox state, hydrophobic/hydrophilic property, and conformation of surface ligand) on cells, including membrane deformation, ion channels activation, integrin-mediated cytoskeleton remodeling, and nucleartransduction, etc.[189] They are appealing candidates in transforming basic researches into clinical applications.

4. Application in Tissue Regeneration

Electroactive biomaterial-mediated stem cell differentiation/trans-differentiation into specific cell lineages is of great significance for tissue regeneration. Although the underlying molecular events and mechanism of electroactivation are not completely clear, there are some general guidelines for the design of smart biomaterials. Besides that morphology and mechanical properties of biomaterials should match tissue microenvironment, it is important to imitate tissue electrophysiological environment. In mature nervous system, neurons form synapses to transmit electrical signals and integrate into neuronal circuits. After axonal injury, neurons switch from an active electrical transmission state back to an electrically silent and growth-competent state.[190] Similarly, native myocardium is an electrically excitable tissue with a conductivity from 1.6×10^{-3} to 5×10^{-5} S cm^{-1}.[191] After myocardial infarction (MI), beating CMs are replaced by a fibrotic scar with higher stiffness and electric resistivity,[75] thus hindering the synchronous contraction of myocardial tissue and inhibiting ventricular function. As for bone tissue, it could be considered as a natural piezoelectric composite, and its highest piezoelectric coefficient (d_{14}) could reach 0.7 pC N^{-1}.[56] The endogenous bioelectric potential in bone defect walls range from −52 to −87 mV.[192] For tissue regeneration, determination of favorable changes in natural tissue repair, and biomimetic construction of matched microenvironment along with biochemical/biophysical cues are important for long-term tissue regeneration. In this section, we mainly focus on the applications of electroactive biomaterials in stem cell determination and tissue regeneration, particularly in

Table 2. Stem/progenitor cells differentiation and cell function modulation on piezoelectric biomaterials.

Piezoelectric biomaterial	Piezoelectric scaffold	Electrical features	Deformation	Stem/progenitor cells	Outcome cell line	Refs.
PVDF	PVDF	/	/	NSC	Neuron/astrocyte	[326]
	PVDF	$d_{33} = -30 \pm 2$ pC N^{-1}	Ultrasound	PC12	Neurons	[327]
	PVDF	/	Cell traction	rbMSCs	Neuron-like cells	[160]
	PVDF/PCL	$d_{33} = 13.2$ pm V^{-1}	/	SCs	Neurons	[227a]
	P(VDF-TrFE)	/	/	SCs neurite extension and myelination		[328]
	P(VDF-TrFE)/BTO	$d_{31} = 53.5$ pm V^{-1} $g_{31} = 0.24$ mV N^{-1}	Ultrasound	SH-SY5Y	Neurons	[225]
	P(VDF-TrFE)/CFO	/	Ultrasound	PC12	Neuron-like cells	[156a]
	P(VDF-TrFE)	/	/	mESC	CMs/endothelial cells	[291]
	P(VDF-TrFE)	/	Cardiac contractile	hiPSC	CMs	[161a]
	PVDF/Ti	$d_{33} = -28$ pC N^{-1}	/	BMSCs	OBs	[329]
	PVDF	/	/	hBMSCs	OBs	[330]
	PVDF	/	Cell adhesion forces	Calcium transients of OBs		[168]
	PVDF	$d_{33} = -32$ pC N^{-1}	/	C2C12	Myotube	[296b]
	P(VDF-TrFE)	/	Bioreactors	MSCs	OBs/chondrocytes	[149]
	P(VDF-TrFE)	$d_{33} = 10$ pC N^{-1}, surface potential = −53 mV	/	BM-MSCs	OBs	[107c]
	P(VDF-TrFE)/BTO	/	/	MSCs	OBs	[331]
	PVDF/CFO	/	Magnetic fields	Proliferation of preosteoblasts		[262]
	P(VDF-TrFE)/Dopa@BTO	Surface potential = −76.8 mV	/	BM-MSCs	OBs	[259]
$BaTiO_3$(BTO)	BTO NPs	/	Ultrasound	Neural stimulation		[183]
	PLGA/BTO	/	/	H9C2	Myotubes	[290]
	S. platensis@Fe_3O_4@ BTO	/	Ultrasound	PC12	Neurons	[228]
	BTO/PHBV	$d_{33} = 1.4 \pm 0.03$ pC N^{-1}	/	Cartilage regeneration		[332]
$BiFeO_3$ (BFO)	BFO	Surface potential = +75 mV	/	MSCs	Osteoblast	[263]
	CFO@BFO/GelMA	/	Magnetic fields	SHSY5Y	Neuron-like cells	[11]
ZnO	ZnO/PDMS	/	Cyclic bending / stretching	hMSCs	CMs	[293]
KNN	KNN	220.2 pm V^{-1}	/	BMSCs	Osteoblast	[263]
PHB	PHB-PANi	/	Ultrasound	hBMSCs	Osteoblast	[251]
Nylon-11	Nylon-11 NPs	/	Ultrasound	Dental pulp stem cells	Osteoblast	[333]

electrically sensitive tissues. Detailed conductive biomaterials and electrostimulation parameters, as well as corresponding cell responses are listed in Table 1. Piezoelectric biomaterials and their mediated cell modulation are listed in **Table 2**.

4.1. Nerve Regeneration

During neuronal development, the growth ability of axons gradually decreases. Neurons in an active electrically transmitting state would form synapses to transmit information and integrate them into functional neuronal circuits.[193] In adult tissue microenvironment of CNS, the inherent poor regenerative ability of neurons and the existence of inhibitory factors are the main obstacles to axons regeneration and functional reconstruction. For the individuals suffering from spinal cord injury or stroke, it might lead to a permanent disability.[193a,194] For peripheral nervous system (PNS), although its self-repairing ability is relatively stronger, permanent neurological deficits are still usual accompanied by failure of nerve regeneration and development of chronic pain.[190] For neural regeneration, it is a challenge for repairing large lesions in both CNS and PNS that cannot be directly reconnected by end-to-end surgery. It is helpful to committed differentiation of stem cells into functional neurons, guidance of neural cell growth, promotion of axonal elongation, and signal propagation.[9a,195] Since nerves are electrogenic cells, electroactive biomaterials and nerve guidance channels (NGCs) are explored for this purpose.

Conductive graphitic-based materials[196] are found to be capable to support neuron survival, neurite outgrowth, and cellular electrical signaling. Their good conductivity is favorable for synaptic connection and signal transmission. CNTs[196c,197] have been used to fabricate electrically conductive biomaterials for promoting neural differentiation from NSCs,[199a,d,f–k,198] ESCs,[197o,199] MSCs,[197e,199l–n] and iPSC.[197b] A varieties of techniques including layer-by-layer method,[196c,197a]

electrospinning,[197b] self-assembly,[197e,198] chemical vapor deposition,[197i] pyrolysis,[198] and 3D printing[197m] have been used to fabricate carbon-based conductive scaffolds for neural differentiation and nerve regeneration. The conductive scaffolds with 3D porous structure[199m,n,198] are advantageous for cell growth-in, providing cells with a mimic tissue microenvironment. It is interesting that without addition of any exogenous biochemical factors, hMSCs could be differentiated into neuron-like cells on graphene (3DG) composite scaffold by 3D printing with a high graphene content (60 vol%),[197m] although the mechanism is still not clear. An graphene loaded polycaprolactone (PCL) nanostructured scaffold was fabricated for peripheral nerve restoration, with polydopamine (PDA) and RGD coating to improve cell adhesion. This conductive 3D graphene scaffold can significantly enhance neural-related proteins and neurotrophic factors expression, promote axonal regrowth and remyelination after peripheral nerve injury.[10b]

Currently, some contradictory conclusions still exist from different studies. Yang and co-workers found multiwalled carbon nanotubes (MWCNTs) in polyethylene terephthalate (PET) matrix could promote neural differentiation of ESCs.[199] However, another study by Le and co-workers found only GO had the promotion effect, whereas graphene and CNTs had not.[197o] Along with conductivity, the complicated physicochemical factors of scaffolds including surface chemical property,[200] stiffness,[201] alignment,[202] and micro-/nanoscaled topography may have combined influence on cell fate. In addition to induced differentiation into neuron, GO coated nanofibers were also used for guiding NSCs into oligodendrocytes, a kind of myelinating cells in CNS.[203]

Other conducting inorganic nanomaterials are also used to increase the conductivity of scaffolds. AuNPs were decorated onto the surface of electrospun nanofibers for promoting axonal elongation of neurons.[204] A PDA-coated gold/PCL nanostructured scaffold was fabricated via multilayer molding, and the fabricated conductive NGCs exhibited satisfactory recovery of sciatic nerves and angiogenesis.[205] Interestingly, electromagnetized AuNPs along with reprograming factor can facilitate an efficient direct lineage conversion to induced dopaminergic (iDA) neurons under specific electromagnetic field (EMF) conditions (**Figure 7**a).[206] AuNPs were modified with thiol-containing ligands to induce magnetic polarization by the "Fermi hole effect." After in vivo treatment, PD mice exhibited a remarkable restoration of movement in an open-field, including increased total travel distance and a higher probability of activity in the center zone of the open field. Additionally, dopamine (DA) levels and electrophysiological properties were significantly enhanced compared with the untreated PD mice (Figure 7b), indicating the formation of synapses with neurons of the host brain. Eight weeks after the treatment, EMF/AuNP exposure along with reprograming factor converted astrocytes into iDA neurons in the brain.

Li and co-workers fabricated a porous film assembled from MoS_2 nanoflakes. The film has a high conductivity of 2.5×10^{-4} S cm^{-2}. With the electrical conductivity and nanoporous structure, the film efficiently increased cell proliferation and attachment of NSCs. After 15 d differentiation, cells on the MoS_2 conductive film have a 1.85-fold neurite outgrowth compared with that on cell culture plate.[207]

Compared with conductive inorganic materials, 3D scaffolds made of electrically conductive polymers have the advantages of flexibility and low stiffness with low Young's modulus, thus more suitable for soft nervous systems. Scaffolds composed of CPs including PPy,[62b,210] PEDOT,[209] and PANi[210] have been used to fabricate neural scaffolds. Due to the versatility for synthesis of conductive polymers, a range of bioactive surface was designed. Zhu et al. reported a cell membrane-mimicking conducting polymer capable of electrically interfacing with neurons selectively and efficiently. It can promote neurite outgrowth while minimizing immune recognition, thereby avoiding immunogenic scar formation.[94] PEDOT-carbon microfibers modified with PLL/heparin/bFGF/fibronectin also showed good integration, establishing contraction with neuronal somas, axons, dendrites and glial cells, with little even no scarring response.[211] Zhou et al. designed a soft conducting polymer hydrogel based on a plant-derived polyphenol, tannic acid (TA), cross-linking and doping conducting PPy chains, which significantly promoted new endogenous neurogenesis in a hemisection model of spinal cord injury.[60b]

In addition, integration of conductive polymers with other softer polymers can further improve the flexibility, biodegradability and processability.[212] For example, incorporation of temperature-sensitive hydrogels can fabricate injectable conductive 3D scaffolds.[213] Aligned micro-/nanofibers can enhance cell anisotropy and neurite length.[214] It should be noted that topographical features, surface hydrophobicity–hydrophilicity, mechanical strength, protein adsorption, and biomolecules incorporation[215] of the scaffolds may also play concurrent key roles.[197c,i,216,217] For instance, embryonic hippocampal neurons cultured on patterned PPy microchannels (1 and 2 μm wide) polarized faster, with a twofold increase in the number of cells with axons compared to the cells cultured on the unpatterned PPy film.[218]

Although the biomaterials with good electrical conductivity have a positive effect on neurite outgrowth and neural differentiation, those effects related therapeutic outcome is still limited. Furthermore, in most of cases, the promotion effect on cell differentiation could not be orientated into the specific cell linages. Biological and chemical differentiation-inducing agents are generally required, concurrently, in the differentiation process.

Given the tremendous roles of the endogenous bioelectric signals, electrostimulation, matched to the tissue electrophysiological environment and delivered from conductive biomaterials to cells/tissues, has been developed for neural regeneration, treatment of neurological disease by promotion of neurite extension[219] and neural differentiation of stem cells. It has been reported that even without addition of any differentiation-inducing agents, those effects could be realized.[28a] Sun et al.[220] reported that PPy-coated nanofibers scaffold can enhance proliferation of Schwann cells (SCs), while not induce differentiation of PC12 cells. Importantly, electrostimulation (100 mV cm^{-1}; 1 h per day) could further induce SCs differentiation without neural growth factor, and the neurite length was increased with increasing PPy content in the scaffold. Based on these results, they designed a PPy-coated NGC, which showed a similar performance of nerve regeneration to an autograft.[221] Indispensability of electrostimulation in neural differentiation was also verified.[222]

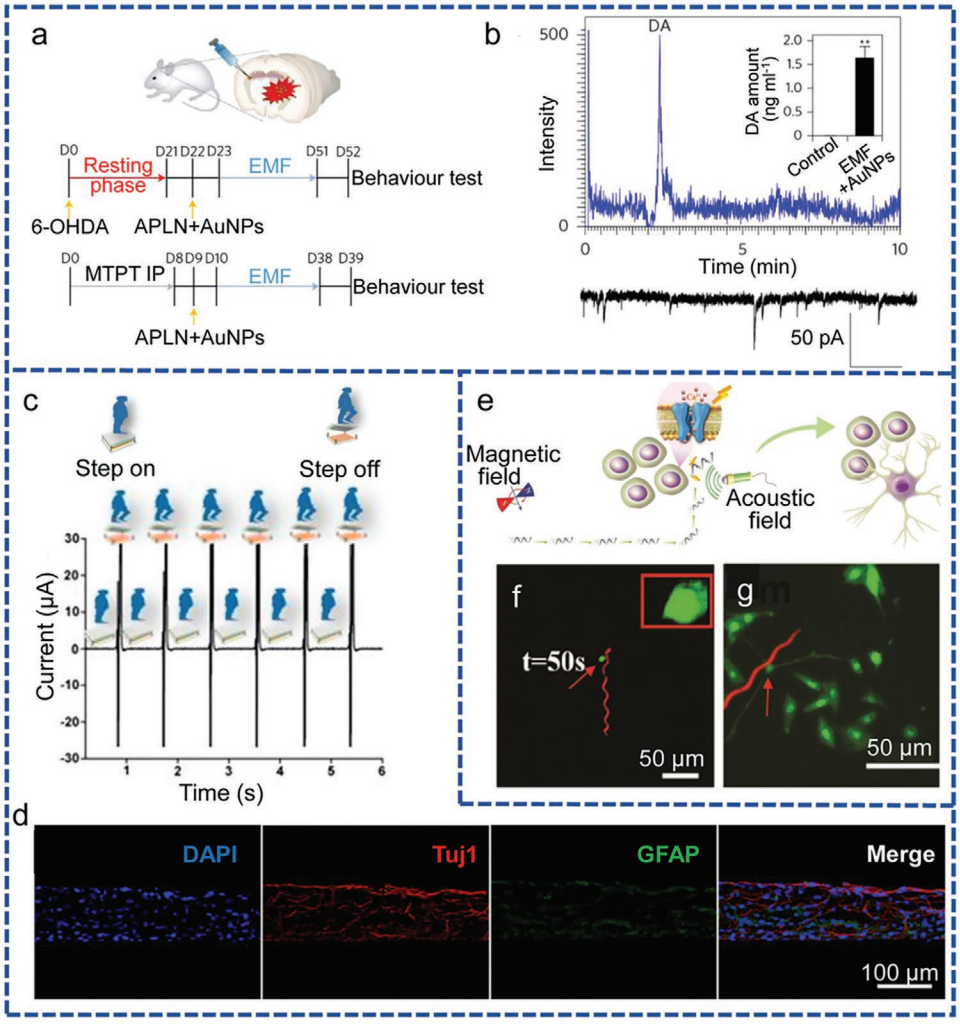

Figure 7. Rescue of Parkinsonian phenotypes in MPTP- and 6-OHDA-induced PD mouse models by in vivo direct lineage reprogramming using the EMF-induced magnetized AuNPs system. a) A schematic diagram of in vivo experiment. b) DA measurement of iDA neurons in the striatum of 6-OHDA-lesioned mice and EMF-AuNPs-treated 6-OHDA-lesioned (top). Spontaneous postsynaptic currents of GFP+ in vivo converted iDA neurons after EMF-treating (bottom). Reproduced with permission.[206] Copyright 2017, Springer Nature. c) The current of TENG driven by human walking steps. d) The nucleus (blue) and neural-specific antibodies Tuj1 (red) and GFAP (green) of cells with TENG electrostimulation for 21 d on the rGO–PEDOT microfiber. Reproduced with permission.[119b] Copyright 2016, American Chemical Society. e) Schematic illustration of a micromotor to induce the differentiation of the targeted neural stem-like cell. f) Ca^{2+} imaging of target PC12 cell stimulated by the *S. platensis*@Fe_3O_4@tBTO with ultrasound for 50 s. g) Fluorescence image of differentiated PC12 cells stimulated by *S. platensis*@Fe_3O_4@tBTO under ultrasound (target cell in red arrow). Reproduced with permission.[228] Copyright 2020, Wiley-VCH.

With rational designed scaffolds to support cells and rebuild tissue structures, safe and convenient approach of electrostimulation is equally crucial for potential clinical translation. Our group designed a self-powered wearable TENG that can generate a stable output of 30 μA driven by human walking steps for electrostimulation (Figure 7c).[119b] Delivery of this electrical signal through rGO-PEDOT hybrid microfibers can induce MSCs differentiation into neuron-like cells (Figure 7d).

Specifically, piezoelectric biomaterials can be employed as both scaffold and electrical stimulation source, realizing noninvasive neuronal stimulation without requiring additional wires and electrodes.[9c,223] Several kinds of piezoelectric biomaterials have been used for neuronal differentiation and nerve regeneration, such as PVDF and its copolymer (P(VDF-TrFE)),[148,224] BTO nanoparticles,[183,225] and boron nitride nanotubes (BNNTs).[226] Under ultrasound stimulation, the generated piezopotential from both BTO nanoparticles on cytomembrane and piezoelectric polymer scaffolds attached to cells can stimulate neuron-like cells or promote neuronal differentiation of stem cells in vitro.[183,225] For in vivo applications, soft and flexible piezoelectric polymer (e.g., 3D PVDF-based scaffolds) as NGCs exhibited significant electrophysiological, morphological and functional nerve restoration through electromechanical interactions under cell traction.[227] In addition, ME composite materials, such as P(VDF-TrFE)/CFO,[156a] GelMA/CFO@ BTO,[11] *Streptomyces platensis*@Fe_3O_4@BTO,[228] were designed for precise neural stem-like cell stimulation and neuronal differentiation. ME materials can generate electricity by manipulation

of magnetic field based on magnetostriction/magnetomotion and piezoelectric effect. For example, Liu et al.[228] sequentially coated Fe_3O_4 and BTO nanoparticles onto *S. platensis* to obtain a helical-shaped biohybrid micromotor. Owing to the magnetism of Fe_3O_4, this micromotor can autonomously move to a target PC12 cell under the guidance of a low-intensity rotating magnetic field. Then, in situ piezopotential of BTO was generated by an ultrasound stimulation to induce intracellular Ca^{2+} transients and neuronal differentiation of the target cells (Figure 7e–g). Then, the cells were treated with different inhibitors to investigate the potential mechanisms, and found that the activation of Ca^{2+} channels may play a crucial role in the piezoelectricity-dependent differentiation of neural stem-like cells. Dong et al.[11] fabricated helical microswimmers of GelMA hydrogel modified with CFO@BTO core–shell ME nanoparticles, and utilized magnetic fields for both actuating the microswimmer and triggering piezopotential of BTO. The rotating magnetic fields actuated microswimmers rotating around their long axis, and generating a translational motion. Also, alternating magnetic fields caused magnetostriction of CFO core, which was then exerted on the BFO shell to induce transient change of its surface charges, thus promoting cell differentiation. Without additional mechanical energy input, mechanical stress from cell traction could direct impose on and induce surface piezopotential of PVDF.[162,224a] With combination of aligned nanoscaled stripe array structure, it could manipulate neuron-like differentiation of rbMSCs.

4.2. Bone Tissue Engineering

Since primary bone cells are not electrically excitable,[5a] the design of electroactive biomaterials for bone tissue engineering is mainly inspired by the piezoelectric features of bone tissues.[229] As aforementioned, bone could be considered as a natural piezoelectric composite, mainly composed of piezoelectric collagen matrix and HAp crystals. Streaming potential is the primary drive for strain-generated potential in wet bone.[230] Surface electric potential caused by mechanical bone strain can accumulate charged macromolecules, inducing conformational changes of adsorbed proteins[231] and facilitating apatite deposition from Ca^{2+} and PO_4^{3-} ions,[232] thereby promoting bone growth and remodeling. Both OBs and osteoclasts play an irreplaceable role in bone repair process. OBs are responsible for the formation and organization of bone ECM and subsequent mineralization.[233] A proportion of OBs are trapped as osteocytes in the lacunae of the bone matrix, which are mainly responsible for intercellular communication.[234] Osteoclasts are polarized cells with a ruffled border region of cell membrane. Osteoclastic bone resorption involves mineral dissolution and followed degradation of the organic phase.[235] In bone regeneration, electric signal is considered as an important cue for promoting osteoblast proliferation[236] and osteodifferentiation of stem cells.[237] Thus, conductive bone grafts are desired for promoting bone regeneration. In addition, biodegradability, high mechanical strength and osteointegration are beneficial for bone graft materials.[238]

Graphene containing micro-/nanostructured scaffolds including film,[239] 3D foam,[240] hydrogel,[241] have been reported to be able to promote osteogenic differentiation and osteogenesis. Especially, graphene was compounded with calcium phosphates (e.g., HAp and β-tricalcium phosphate), integrating good conductive of the former and osteoconductivity of the later.[242] The possible reasons for promotion of osteogenic differentiation are the π–π stacking interactions between the basal plane of graphene-based materials and aromatic rings in the osteogenic inducer molecules,[241c] thus increasing the concentration of osteogenic inducer at the scaffold surface. Additionally, the abundant functional groups in GO facilitate the adsorption and hydrogen bonding of proteins[243] and calcium deposition/biomineralization.[241d]

Currently, the results for CNTs in bone regeneration is controversial. In one study, CNTs promoted osteogenic differentiation of MSCs and ectopic bone formation in vivo.[217a] However, it has also been reported that carboxylated CNTs had no significant effect on adipogenesis, osteogenesis and chondrogenesis of human MSC.[244] And a contradictory result was reported that carboxylated CNT inhibited proliferation, osteogenic differentiation, and adipogenic differentiation of mouse MSCs.[245] It is deduced that their difference in size, concentrations, and surface oxygen contents and stem cell source may responsible for the discrepant results.

Conductive polymers show great potential in bone regeneration due to their responsivity of electrical signal.[9b] Several studies demonstrated that conductive polymers, including porous PEDOT:PSS,[246] PEDOT/PCL,[247] PANi/PLA nanofibrous scaffolds,[248] and PHB-PANi,[249] could induce osteogenic differentiation of stem cells and bone regeneration, sometimes with an external electrical stimulation.[10a,242d,250] Notably, postoperative inflammation might lead to high ROS level for 1–2 weeks,[251] which not only is harmful to cells, but also inhibits osteogenesis.[252] The ability of conductive polymers to scavenge and control ROS[253] also promotes bone regeneration during inflammation in the initial stage of bone regeneration.

Scaffolds and growth factors are two critical factors affecting bone regeneration in bone tissue engineering, while wide application of growth factors is limited by their poor stability.[254] Cui et al.[255] constructed a nonviral plasmid vector (phBMP-4) that can control expression of human bone morphogenetic protein-4 (hBMP-4) under the trigger of doxycycline (Dox) (**Figure 8**a). This vector was controlled released from an electroactive triblock copolymer of PLA-block-aniline pentamer-block-PLA (PLA-AP) with poly(lactic-*co*-glycolic acid) (PLGA)/HA. Electrostimulation (500 mV, 100 Hz, and 50% duty cycle) caused movement and release of the charged gene carrier complex and thus resulting in an acceleration of phBMP-4 release (Figure 8b). This multifunctional scaffold enhanced cell proliferation and osteogenesis differentiation in vitro, and as well as accelerated bone repair of rabbit radial defect in vivo.

Inspired by the bone piezoelectric features, design of piezoelectric biomaterials is a promising biomimetic strategy for bone regeneration. Piezoelectric biomaterials, such as PVDF,[168,256] P(VDF-TrFE),[107c,149] BN nanotube/P(VDF-TrFE),[257] PLLA,[258] PDA@ BTO/P(VDF-TrFE),[259] HA/PLLA,[260] BTO/HAp,[261] $BiFeO_3/SrTiO_3$,[192] PVDF/CFO,[262] $K_{0.5}Na_{0.5}NbO_3$ (KNN)[263] have been used for promoting cell proliferation, osteogenic differentiation, HAp deposition, and bone formation. Ultrasound,[264] magnetism-driven magnetostriction,[262] and cell traction forces[168] have been employed to

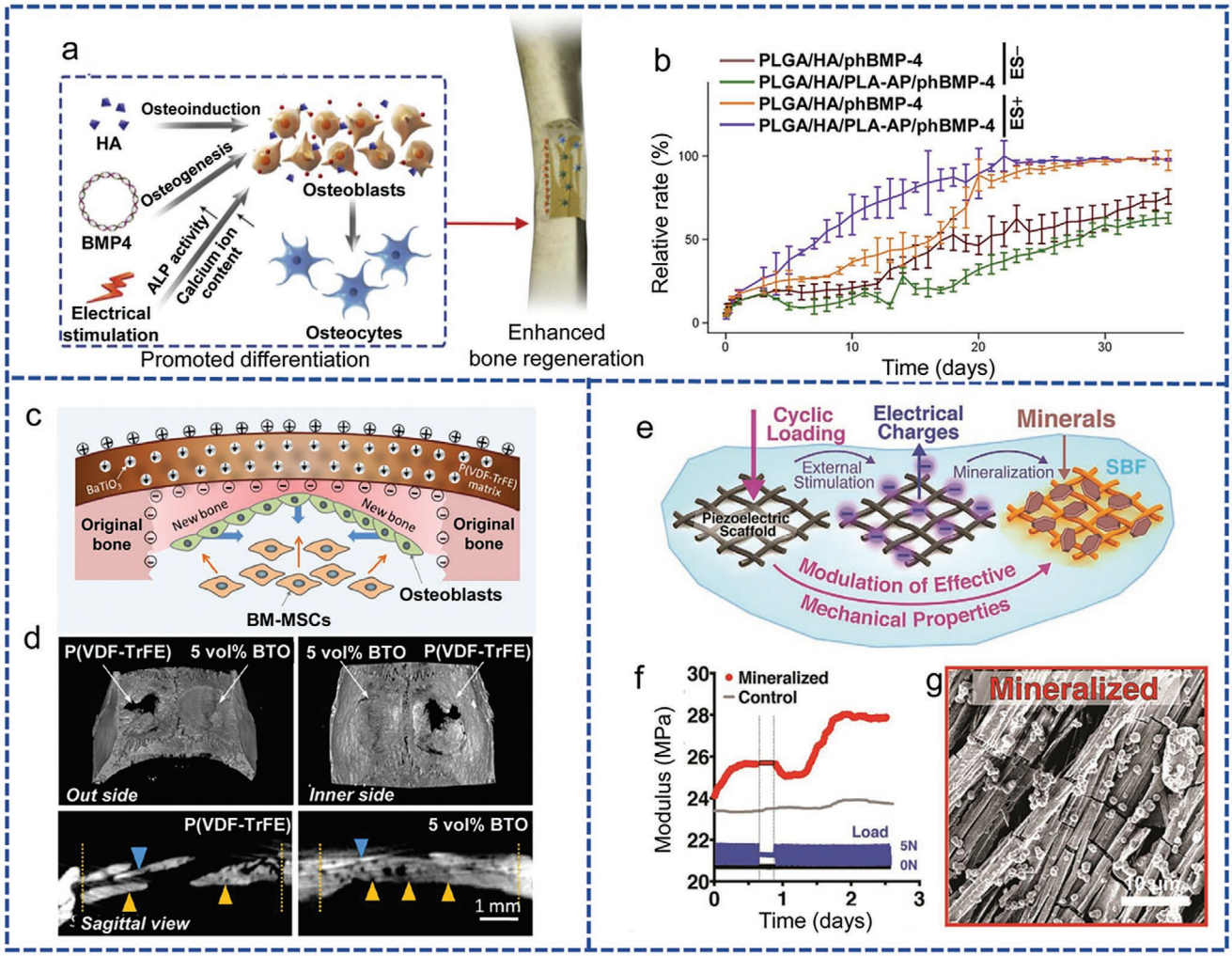

Figure 8. a) A smart electroactive tissue engineering scaffold for efficient bone repair. b) Gene release profiles from different scaffolds with or without electrostimulation (ES). Reproduced with permission.[255] Copyright 2020, Elsevier Ltd. c) Illustration of biomimetic electric microenvironment created by BTO NP/P(VDF-TrFE) composite membranes for bone defect repair. d) Representative micro-CT images and sagittal view images of critical-sized rat calvarial full-thickness defects at 12 weeks postimplantation. Blue arrows denote the residual membrane materials. Yellow arrows denote the regenerated new bone. Yellow dotted lines denote the boundary between nascent bone and host bone. Reproduced with permission.[259] Copyright 2016, American Chemical Society. e) Schematic diagram of the formation process of minerals on the PVDF scaffold. f) The material showed a self-adapting mechanical property by increasing modulus under dynamic loading. g) Images of the PVDF scaffold after submerged in SBF showing the formation of minerals, scale bar is 10 µm. Reproduced with permission.[265] Copyright 2020, Wiley-VCH.

trigger the deformation of piezoelectric biomaterials for generation of surface piezopotential, while some reports did not clearly indicate the mechanical force source that caused their deformation.[107c,263] For example, after corona polarization treatment of 5 vol % PDA@BTO incorporated P(VDF-TrFE), the polarized film had a surface potential of –76.8 mV, which was in the range of natural endogenous biopotential.[259] This film was more conducive to promoting osteogenic differentiation in vitro than the P(VDF-TrFE) with a surface potential of –42 mV, and achieved a rapid repair of bone defects because of sustainable maintenance of the electric microenvironment in vivo (Figure 8c,d). Oppositely, An electropositive $BiFeO_3$ nanofilm (BFO+, +75 mV) was designed, which can establish a built-in EF between the BFO+ nanofilm and electronegative bone defect walls (–52 to –87 mV).[192] The attraction between the positive and negative charges caused more electronegative fibronectin (isoelectric point of pH 4.8–6.4) to cluster on the nanofilm. Thus, there are more cellular binding sites to facilitate cell adhesion and migration, thereby triggering implant osseointegration and bone healing. Both of the two opposite electric potentials could promote bone repair, which might be related to the different structures of the bone defect in animals. Moreover, the negative potential film utilized galvanotaxis of MSCs to recruit cells; while the positive potential film attracted electronegative fibronectin to promote cell adhesion.

Inspired by the natural bone mineralization process, a piezoelectric material that can respond to external mechanical stimulation was designed to induce mineral deposition (Figure 8e).[265] After immersing PVDF films ($d_{31} \approx 23$ pC N^{-1}) in a simulated body fluid (SBF) for one week, HAp minerals

were preferentially deposited onto the negatively charged surface, which was consistent with the natural endogenous biological potential. This phenomenon indicates that the biomimetic electrical signals are more conducive to tissue repair. And an external mechanical loading can induce higher electrical charges, thereby enhancing mineral growth rate. Because further biomineralization of the scaffold could increase its mechanical property, this system can dynamically adjust its own mechanical stiffness depending on the external loading (Figure 8f,g). This process facilitated the development of smart coatings on bone implants to alleviate problems brought by mechanical mismatch.

Besides osteogenic differentiation, PVDF,[266] P(VDF-TrFE),[149] and BTO/PHBV[267] have also been used to promote cartilage regeneration. Damaraju et al. reported that the fate of MSC was determined by piezoelectricity of the scaffold, where P(VDF-TrFE) with streaming potential of 25.2 ± 2.5 μV promoted chondrogenesis and annealed P(VDF-TrFE) (61.1 ± 1.5 μV) promoted osteogenesis.[149]

Interestingly, converse piezoelectric effect of piezoelectric materials is also utilized to induces bone formation in vivo. A Li-battery powered piezoelectric PVDF actuator was designed to mechanically stimulate bone.[268] After implanting actuators in sheep femur and tibia osteotomy cuts for one-month, the rates of bone deposition and new bone generation were significantly higher under a sinusoidal AC stimulation (5 V, at 1 Hz and 3 Hz for 15 min) compared to the static controls. These progresses suggest that both piezoelectric effect and converse piezoelectric effect of piezoelectric biomaterials could be used to effectively promote bone growth and remodeling.

4.3. Cardiac Tissue Engineering and Others

Native myocardium is an electroactive tissue (1.6×10^{-3} S cm^{-1} (longitudinally) to 5×10^{-5} S cm^{-1} (transversally)) capable of transferring electrical signals and allowing heart to beat.[191] For global heart function restore, it is necessary to restore the impulse propagation. Electrical connection of the isolated CMs to an intact tissue could synchronize contraction and restore ventricular function. In cardiac tissue engineering especially for repairing myocardial tissues in MI, electrically conductive biomaterials have positive contribution in electrical signal propagation, enhancement in cardiomyocyte function, increase of cell-cell interaction for coordinating the beatings of the CMs, and cardiomyocyte commitment of stem cells. The underling molecular mechanism mainly includes the stimulation of gap junction protein Connexin 43 expression[269] and Ca^{2+} signal conduction.[270] In addition to fundamental requirement of biocompatibility and biodegradability, morphology, electrical conductivity, and elasticity matching with cardiac tissue (≈10 kPa) are favorable for the cardiac scaffolds or patches to mimic the native ECM.[75,270] For instance, gold nanowires incorporated in alginate scaffold bridged the electrically resistant pore walls of alginate and improved electrical communication between adjacent cardiac cells.[67b] AuNPs impregnated thiol-2-hydroxyethyl methacrylate have tunable conductivity and elasticity, facilitating cardiomyocyte function.[269b] In vitro assessment of the engineered-tissue performance and control of their function after implantation is indispensable for cardiac tissue engineering. Feiner et al.[271] integrated gold electrode-based device with electrospun fibers as hybrid cardiac patches for online monitoring electrical activities of cardiac tissues. Besides, according to physiological needs, the system can manipulate and reverse tissue contraction and release soluble biofactors by electrostimulation for regulation of cardiac function (**Figure 9**a).

Conductive polymer containing scaffolds have been fabricated to deliver electrical pulses to increase synchronized beating of CMs, enhancing cell–cell communication[272] and cardiomyogenic differentiation,[273] such as PANi/PLGA nanofibrous meshes,[269a] collagen/hyaluronic acid/PANi,[10c] PPy film,[274] hyperbranched poly(amino ester) (HPAE)–Py/gelatin hydrogels,[275] PPy-chitosan hydrogel,[270] poly(thiophene-3-acetic acid) (PTAA)/ethacrylated aminated gelatin hybrid hydrogel network,[273] and collagen/alginate/PEDOT:PSS.[60a] In a composite DA/methacrylated-gelatin/poly(ethylene glycol) diacrylate (PEGDA) cryogel incorporating PPy NPs, the PPy NPs can be transferred from donor patch to the infarcted tissue, stimulating the immigration of neomyocardium to the infarcted area and eventually yield an improvement in cardiac function.[276] Recently, injectable biomaterials have shown great potential in cardiac tissue engineering by preventing ventricular dilation, improving conduction velocity, and enhancing angiogenesis. Song et al.[277] developed an injectable DA-coated PPy/poly(glycolic acid) (PGA) spring (Figure 9b). After injection, tangled coils formed an elastically conductive 3D network, which can not only modulate cardiac function, but also measure the contractile force of CMs (Figure 9c–e).

CNT-incorporated hydrogels as scaffolds can promote cardiac cell adhesion and maturation, and improve cell electrical coupling.[278] SWCNTs incorporated injectable thermosensitive hydrogel was applied for cardiac tissue engineering with the ability of promoting cardiomyogenic differentiation of brown ADSCs.[279] Shin et al. constructed a batoid-fish-shaped pseudo-3D cardiac tissue,[15a] which consisted of two micropatterned hydrogel layers: a PEG hydrogel substrate as a mechanically stable structure and a GelMA layer embedded with CNTs as a cell attachment substrate (Figure 9f). This biomimetic scaffold facilitated high myofiber organization and self-actuating motions aligned with the cell contraction (Figure 9g). In addition, applying electrostimulation (0.5–6 V, 0.5–2.0 Hz) through the embedded Au microelectrodes can further control the beating behavior of this pseudo-3D cardiac tissue (Figure 9h,i). Graphene was reported to be able to promote cardiomyogenic differentiation of ESCs[280] and MSCs.[281] CMs showed stronger contractility and faster spontaneous beating rate on rGO-incorporated GelMA.[282] Interestingly, graphene flake was incorporated into a stem cell spheroid for improving cardiac function[283] and cardiomyogenic differentiation.[284] Lee et al.[285] reported that compared to low conductive GO-GelMA, electrically conductive CNT- and rGO- GelMA scaffolds were more conducive to promote desirable morphology of CMs and elevated expression of functional cardiac markers. More importantly, the biohybrids of collagen and pristine graphene with stiffness and electrical conductivity matching the native cardiac tissue significantly increased metabolic activity of CMs and cross-striated sarcomeric structures. And electrostimulation

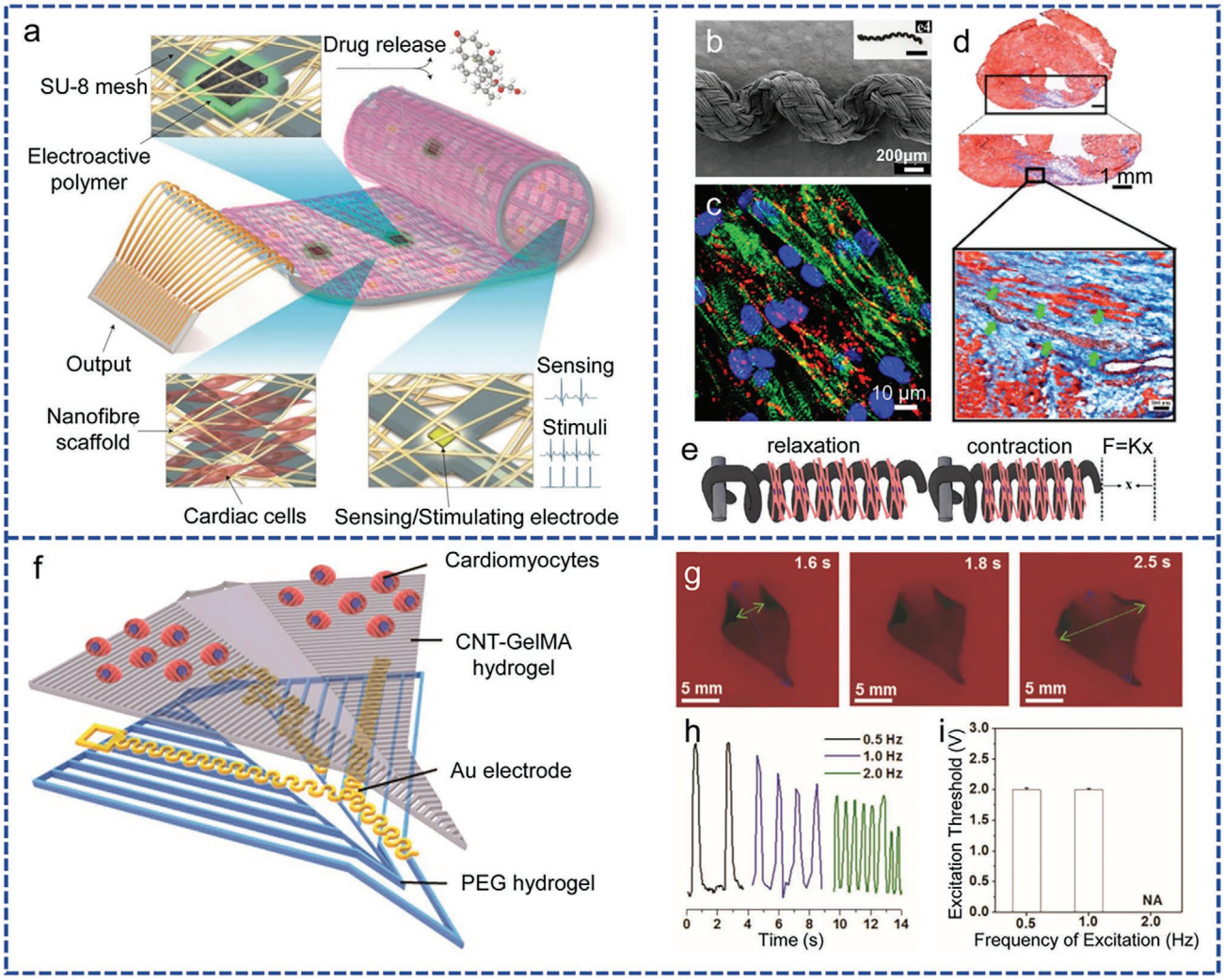

Figure 9. a) Schematics of the microelectronic cardiac patch integrated with sensor of tissue electrical activity, electrical stimulation and controlled release of biomolecules within the tissue microenvironment. Reproduced with permission.[271] Copyright 2016, Springer Nature. b) SEM image and photograph of the DOPA-coated Ppy/PGA spring scaffold. Scale bars in a1: 0.5 cm. c) The α-actinin (green) and cx43 (red) protein levels in CMs on spring scaffold at day 7 detected by immunofluorescent staining. d) Myocardium (red) and fibrous tissues (blue) in heart sections after 4 weeks. The springs could be observed in the scar zone (green arrows). e) The mechanism interpretation of conductive spring for monitoring cell contractile force. Reproduced with permission.[277] Copyright 2019, American Chemical Society. f) Schematic illustration of the layer-by-layer structure of the construct. g) Photographs of the freestanding bioinspired soft robot cultured for 5 d taken at 1.6, 1.8, and 2.5 s. The blue and green line represents the longitudinal axis and transverse axis displacement, respectively. h) Beating response of the bioinspired soft robot when stimulated with an AC external electrical field at 1 V cm^{-1} and with various frequencies from 0.5 to 2.0 Hz. i) Excitation threshold voltage required at different frequencies (0.5, 1.0, and 2.0 Hz) when electrical stimulation was applied via the embedded Au microelectrodes. Reproduced with permission.[15a] Copyright 2018, Wiley-VCH.

that was consistent with the beating frequency of CMs (2.5 V cm^{-1} monophasic stimulation at 1 Hz) based on biohybrid collagen/graphene composite can enhance the alignment and maturation of ESC-derived CMs.[286]

In body, heartbeat is a spontaneous biomechanical force that has been collected by TENG or PENG to generate electrical energy as a pulse sensor[118,287] or power to drive implanted cardiac pacemaker.[130] Recently, Ouyang et al. designed a self-powered symbiotic pacemaker, which integrated energy harvesting (TENG) and storage as well as cardiac pacing together. The energy harvested from each cardiac motion cycle of pig reached 0.495 μJ, successfully correcting sinus arrhythmia and preventing deterioration.[130] Microscopically, the contraction of CMs also can be utilized to trigger the deformation of piezoelectric materials, thereby inducing piezopotential for in situ electrostimulation of the cells. Cardiomyocyte contraction force (20–140 nN)[288] was significantly higher than the cell traction force (1–10 nN).[160] Liu et al. demonstrated a contractile cardiomyocyte-driven PVDF piezoelectric nanofiber as a biogenerator, which generated an output of 200 mV (open-circuit voltage) and 45 nA (short-circuit current).[289] Piezoelectric PLGA/BTO,[290] electrospun P(VDF-TrFE),[161a,293] PCL/P(VDF-TrFE),[292] ZnO nanorods/PDMS[293] have also been explored for promoting CMs proliferation, alignment, contraction, cell-cell communication,

and myocardial differentiation. Not only that, piezoelectric scaffolds can also monitor contractile activity of CMs and heart based on the voltage transients, simultaneously.[161]

Similarly, electroactive biomaterials (both conductive and piezoelectric materials) have been employed in skeletal muscle tissue regeneration for promoting myogenic differentiation,[294] myotube formation, maturation,[295] and myotube fusion.[296] And extra AC electrostimulation can cause calcium transients and regulate myotube contraction.[295–297] For other applications, electroactive biomaterials were also used for the maintenance of undifferentiated state of multi-potent cells instead of using feeder cells or ECM,[298] as well as reprogramming of somatic cells into iPSCs.[299]

5. Conclusions and Outlook

Electroactive biomaterials and their delivered electrostimulation have made impressive progresses in regenerative medicine, from promoting cell migration, proliferation and differentiation, to modulating nerve conduction, muscle contraction, and tissue regeneration. Currently, there are still great challenges and broad space for optimal integration of biomaterials, donor cells and host microenvironment, finally translating the laboratory findings to clinic applications.

An in depth understanding of cell dynamic microenvironment is conducive to specifying the criteria of biomaterials design. Throughout human life, cell and tissue microenvironments change at different periods, especially during organ development and tissue repair. For tissue regeneration, determination of favorable changes in tissue repair, and biomimetic construction of those changing microenvironment is important for adapting long-term repair process. Stimuli-responsive biomaterials are considered as potential 4D tissue engineering scaffolds, which can exhibit specific characteristic changes when triggered by endogenous or exogenous environmental variations (such as temperature, pH, electrical potential, light, mechanical force or magnetic field). Moreover, it is worth noting that cells themselves are also dynamic. Changes in cell membrane potential, tissue electrophysiological environment, cell adhesion, migration and tissue mechanical activities are always existing. If the endogenous changes can be utilized to stimulate biomaterials and induce their favorable changes, it is possible to realize cell-regulated dynamic biomaterials to imitate cell microenvironment without any external stimuli. For electrostimulation, in this respect, cell/tissue traction activated piezoelectric effect from rational designed piezoelectric biomaterials is a good example.

The biocompatibility of biomaterials should be paid sufficient attention, especially the long-term biosafety and compatibility with the host tissues. Now, the results for some nanomaterials are still controversial (e.g., CNTs).[79d] To analyze the safety and biological effects of biomaterials, high-throughput assay is expected to realize a multifactorial evaluation and selection in parallel.[4a] The influence and metabolism of degradation products of electroactive materials should also be considered.

Excitatory transmission in nerve and heart system is a complex process, which can happen within a few ms (nerve) to 0.1 s (heart). It is of great significance to optimize electrostimulation conditions (including voltage, frequency, pulse width and stimulation time duration) that match the electrophysiological characteristics of target tissue. For specific cells, tissues or organs, although the adjustment range of electrostimulation parameter is relatively narrow, small changes might cause differential cell/tissue responses. Due to the complexity of the electrophysiological environment of cells and tissues, it is vital to clarify the interaction between the electron-based electrical stimulation of conductive/piezoelectric materials and the ion-based electrical activity of living organisms. And the available voltage reaching cell membrane is not only determined by the EF and electrodes, but also related to the conductivity of the biomaterials, the media and the electrical property of cytomembrane.[164] In addition, the interaction and feedback between cells/tissues and electroactive biomaterials, as well as exact mechanisms and intracellular signaling pathways are still obscure. It is urgent to reveal the interplay between cells/tissues and biomaterials, thereby identifying the universal design principles of electroactive biomaterials and electrostimulation at tissular, cellular, molecular, and genetic levels. Moreover, convenience and patient compliance for electrostimulation should be kept in mind for possible clinic translation. With rational design and full consideration of biocompatibility, wearable and implantable energy harvesters that can harvest power from organisms or surrounding environment has great potential to impose electrostimulation via electroactive biomaterials.

For both in vitro and in vivo applications, it is important to real-time feedback the cell activities and tissue recovery so as to optimize cell dynamic microenvironment and external stimulation. Electroactive materials have great potential in integration of electrostimulation and monitor of physiological signal. For example, conductive biomaterials could serve as both electrodes to realize the input of external electrostimulation and the output of electrical transients of electroactive cells and tissues, simultaneously.[271,300] Based on their electromechanical coupling properties, piezoelectric biomaterials also can be employed as sensors to monitor mechanical activity of motile cells/tissues, such as myocardial contraction and heartbeats.

In the design of biomaterial systems, coordination of electronic properties with other biophysical and biological cues are very important. Multifunctional integration (e.g., chemical composition, morphology, mechanical stiffness, biological factors, external stimuli, sensing and dynamic response) should be considered. In bodies, immune system has a crucial role in clean up damaged tissues and recruit endogenous cells for modulation of innate regeneration. It is attractive to design biomaterials with ability to regulate immune response toward tissue regeneration. It is still an unknown and open field that if electro-activity of biomaterials would interact with the immune system and influence immune response. Totally, with current progresses and huge space for development, electroactive biomaterials show tremendous potential for tissue regeneration.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

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