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Review

# Conductive biomaterials for muscle tissue engineering

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ABSTRACT

Muscle tissues are soft tissues that are of great importance in force generation, body movements, postural support and internal organ function. Muscle tissue injuries would not only result in the physical and psychological pain and disability to the patient, but also become a severe social problem due to the heavy financial burden they laid on the governments. Current treatments for muscle tissue injuries all have their own severe limitations and muscle tissue engineering has been proposed as a promising therapeutic strategy to treat with this problem. Conductive biomaterials are good candidates as scaffolds in muscle tissue engineering due to their proper conductivity and their promotion on muscle tissue formation. However, a review of conductive biomaterials function in muscle tissue engineering, including the skeletal muscle tissue, cardiac muscle tissue and smooth muscle tissue regeneration is still lacking. Here we reviewed the recent progress of conductive biomaterials for muscle regeneration. The recent synthesis and fabrication methods of conductive scaffolds containing conductive polymers (mainly polyaniline, polypyrrole and poly(3,4-ethylenedioxythiophene), carbon-based nanomaterials (mainly graphene and carbon nanotube), and metal-based biomaterials were systematically discussed, and their application in a variety of forms (such as hydrogels, films, nanofibers, and porous scaffolds) for different kinds of muscle tissues formation (skeletal muscle, cardiac muscle and smooth muscle) were summarized. Furthermore, the mechanism of how the conductive biomaterials affect the muscle tissue formation was discussed and the future development directions were included.

## 1. Introduction

Muscle tissues play a vital role in human body, comprising more than 50% of body mass and controlling force generation, body locomotion and internal organs' function [1–3]. However, muscle tissues as soft tissues are very easy to get injured. Muscle tissue injury will lead to movement disorder and organ dysfunction, which results in not only the pain for the patients, but also a heavy financial burden on their family and governments. Skeletal muscle tissue could regenerate after a slight injury [4,5]. Unfortunately, for the severe injuries, whose mass loss is higher than 20%, the endogenic regeneration is helpless, and fibrosis and scarring will happen [6]. The situation to cardiac muscle injury is even worse: cardiac muscle tissue exhibits very limited regeneration capacity after injury [7–9]. When a cardiac muscle injury happens, fibroblasts will replace the loss of cardiomyocytes to form scar tissue, leading to arrhythmia and heart remodeling [10–12]. Nowadays, the most widely used treatment for severe muscle tissue injury is surgical reconstruction. Unfortunately, the low survival rate, morbidity of donor site and lack of donor source severely limited its application [6,13]. Therefore, a new therapeutic strategy with high efficiency to treat with muscle injuries is in urgent need.

Tissue engineering has been proposed to be a promising therapy for tissue repair by Vacanti and Langer [1,14]. It has been applied to repair a lot of tissues, such as the nerve tissue [15–18], bone tissue [19–23], and skin tissue [24–32], and achieved impressive results. Muscle tissue engineering, forming functional tissues by combination of scaffolds, cells and growth factors, has been thought of as a promising therapeutic method to treat with muscle injuries and has drawn much attention in recent decades [33–35]. Biomaterial, with the function of mimicking native extracellular matrix, is an essential factor in tissue engineering [36]. As a result, the development of biomaterials for muscle tissue engineering is of great importance. One of the unique behaviors of muscle tissues is their contracting activity, which is in response to the electrical signals [37]. This makes the capacity to conduct electrical

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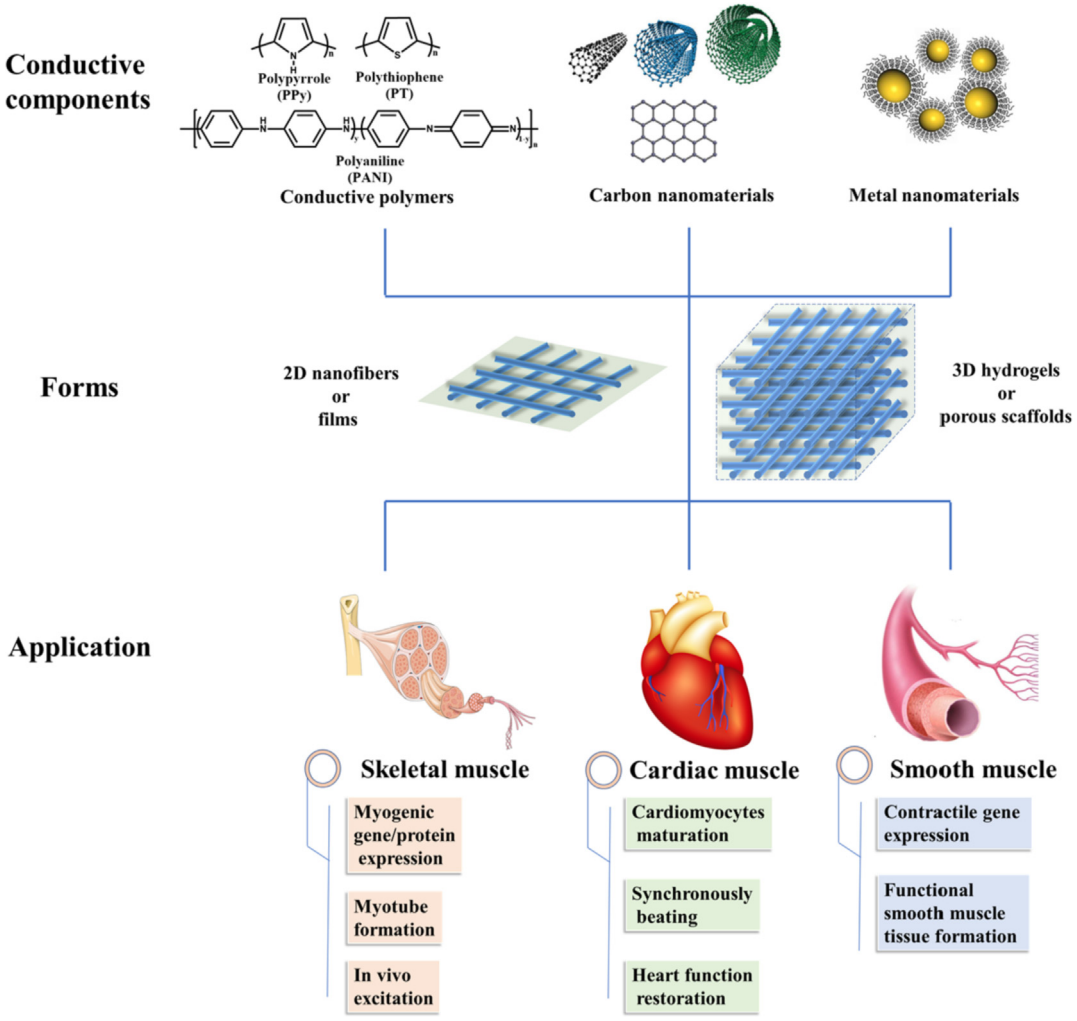


**Fig. 1.** Schematic illustration of conductive biomaterials' fabrication, forms and their application in muscle tissue repair.

signals very important for biomaterials used in muscle tissue engineering. Conductive biomaterials, with conductivity that is similar to native muscles, are promising candidates for muscle tissue engineering scaffolds. Conductive biomaterials have been demonstrated to promote the proliferation and differentiation behavior of electrical stimuli responsive cells, such as neuron cells [17,38,39], bone cells [40,41] and muscle cells [42–45]. Conductive polymers [46–49], carbon nanomaterials [50–52] and metal nanomaterials [53,54], as three main conductive biomaterials, have been widely investigated and their application in muscle tissue engineering has drawn much attention. Researchers have developed various types of conductive biomaterials, such as films [45,55], nanofibers [56,57], hydrogels [58–60] and 3 dimensional (3D) porous scaffolds [61,62], to facilitate the ex vivo or in vivo muscle tissue formation.

The fast development and promising results of conductive biomaterials for muscle tissue regeneration motivated the preparation of this review. In the first part, a brief overview of the synthesis and fabrication of different types of conductive biomaterials is provided, including new methods and interesting technologies (Fig. 1). The applications of those conductive biomaterials in different kinds of muscle tissue regeneration and the muscle repair outcomes are presented as well (Fig. 1). The mechanism on how conductive biomaterials promote the muscle tissue regeneration is also discussed. Furthermore, the future direction for conductive biomaterials development in muscle tissue engineering is proposed, hoping to provide new perspectives for researchers in conductive biomaterials area.

## 2. Fabrication of conductive biomaterials for muscle tissue repair

Different kinds of conductive materials shows different properties. Conductive polymers are easily conjugated to other polymers to form a conductive scaffold [63,64]. However, most of the conductive polymers are not water soluble and can not be degraded in vivo [65]. Oligomers of the conductive polymers such as the oligo-aniline overcomes the non-degradability but their conductivity is lower than that of the conductive polymers [66,67]. Carbon nanomaterials including carbon nanotubes, graphene and other carbon based nanomaterials have high conductivity but they can not be soluble in water and their dispersion in the solution is also an issue [64]. Metal nanomaterials, including gold nanoparticles and silver nanoparticles, also showed good conductivity, but they can not be degraded in vivo and may have a higher cytotoxicity than the other conductive materials [67,68]. All those conductive materials have their own advantages and drawbacks, and how to take advantage of them and reduce the unexpected drawbacks in the synthesis of conductive materials is a big challenge. Lots of conductive biomaterials researchers devote themselves to this area and a large number of those materials are applied in muscle tissue regeneration (Tables 1–3). Here, we listed some of the outstanding works in this area, hoping to pave a way for researchers in this area to find out a good direction.

### 2.1. Conductive polymers-based conductive biomaterials

Conductive polymers, with electrical and optical properties similar

**Table 1**
Conductive biomaterials used in skeletal muscle tissue engineering.

| Conductive component | | Electrical stimuli | Cell type | Animal model | Main effects | Reference |
|---|---|---|---|---|---|---|
| **Conductive polymer** | PANI | N/A | Mouse C2C12 myoblast | N/A | Promote cell growth, orientation and myotube formation | [90] |
| | PANI | Square pulses, 6 V, 1 Hz, 1 ms duration | Mouse C2C12 myoblast | N/A | Enhance myogenesis, myotube maturation, A-band formation, colocalization of the DHPR and RyR receptors and E-C coupling | [88] |
| | PANI | N/A | Human mesenchymal stem cells | N/A | Support cell growth, promote hMSCs differentiation into muscle-like cells (gene expression and immumocytochemistry) | [89] |
| | PANI | N/A | Mouse satellite cells | N/A | Inhibit proliferation but promote differentiation | [91] |
| | ACAT (amino group capped aniline trimer) | N/A | Mouse 3T3 fibroblast | N/A | Cell proliferation and spreading | [104] |
| | ACAT (amino group capped aniline trimer) | N/A | Mouse C2C12 myoblast | N/A | Promote cell proliferation, myotube formation (mRNA and protein level) | [55] |
| | AP (aniline pentamer) | N/A | Mouse C2C12 myoblast | N/A | Promote cell proliferation, myotube formation (mRNA and protein level) | [107] |
| | Graphene oxide (GO)/PANI | N/A | Mouse satellite cells | N/A | Promote proliferation and differentiation | [173] |
| | PANI | N/A | Mouse C2C12 myoblast, adipose-derived mesenchymal stem cells | N/A | Promote cell proliferation, antibacterial | [119] |
| | PANI | N/A | Mouse C2C12 myoblast | N/A | Promote cell growth, elongation and myotube formation. Direct nuclei and myotube orientation | [59] |
| | PASA(poly(aniline-*co*-N-(4-sulfophenyl) aniline) | N/A | Mouse C2C12 myoblast | N/A | Promote C2C12 cell proliferation and myogenic differentiation | [93] |
| | PPy | N/A | Mouse C2C12 myoblast | N/A | Support cell adhesion and spreading | [120] |
| | PEDOT/CNTs | N/A | Rat muscle cells | N/A | Good cytocompatibility | [174] |
| | PEDOT | N/A | NG108-15 neuron cells; mouse C2C12 myoblast | N/A | Support cell adhesion and spreading | [117] |
| **Carbon nanomaterials** | CNT | Voltage 8 V, frequency 1 Hz, and duration 10 ms | Mouse C2C12 myoblast | N/A | Aligned CNTs promote myotube orientation in the same direction and promote myotube formation and myogenic gene expression | [139] |
| **Carbon nanomaterials** | GO | Yes | Ex vivo muscle tissue excitation test | N/A | Low excitation threshold | [175] |
| | CNT | N/A | Mouse C2C12 myoblast | N/A | Nanoscale features control the myoblasts differentiating into myocytes, microscale alignment cues orchestrate fusion of multiple myocytes into multinucleated myotubes | [176] |
| **Metal** | $Pd_{42.5}Cu_{30}Ni_{7.5}P_{20}$ alloy | Voltage 4 V, frequency 1 Hz, and duration 10 ms for 2 continu-ous days | Mouse C2C12 myoblast | N/A | Effective in regulating attachment and spreading of the C2C12 myoblast, promote myotube formation, contraction and metabolic activity. | [162] |

**Table 2**
Conductive biomaterials used in cardiac muscle tissue engineering.

| Conductive component | | Electrical stimuli | Cell type | Animal model | Main effects | Reference |
|---|---|---|---|---|---|---|
| **Conductive polymer** | Aniline tetramer | N/A | Mouse C2C12 myoblast, ADMSC | In vivo cell retention | Enhance in vivo cell retention ratio, controlled cell release, antibacterial | [44] |
| | PPy | N/A | Endothelial progenitor cells and cardiac progenitor cells | N/A | CPC sensitive to high surface roughness of the PPy materials | [129] |
| | PPy | N/A | HL-1 atrial myocytes | N/A | Conductive film could promote formation of connexin-43 to enhance cell-cell communication, resulting in higher velocities for calcium wave propagation, and reducing calcium transient duration | [177] |
| | Aniline trimer (AT) | N/A | H9c2 cardiac myoblast and rat neonatal cardiomyo-cytes | Subcutan-eous implantation | Promote expression of marker protein of cardiomyocytes maturation, well-organized sarcomere formation and synchronic calcium transition. | [178] |
| | poly(thiophene-3-acetic acid) (PTAA) | 1.0 Hz, 1 V, and 2 ms pulses | Rat brown adipose derived stem cell | Subcutan-eous implantation | Improve cardiac differentiation efficiency of BADSCs and upregulate CX43 expression. | [179] |
| | PPy nanoparticles | N/A | Neonatal rat cardiomyo-cytes | Myocardial-infarction (MI) affected rat models | Enhance synchronous contraction and CX43 and α-actin gene expression. In vivo implantation elevated the fractional shortening and ejection fraction by ~50% and reduced the infarct size by 42.6% | [180] |
| | PANI | N/A | H9c2 cardiac myoblast and rat neonatal cardiomyo-cytes | N/A | Higher proliferation of H9c2 cell on the conductive sheets than on PLA sheets. Conductive sheets enhance the maturation and higher frequency of spontaneous beating of the CMs. | [56] |
| **Carbon nano-materials** | CNT | Frequency, 1 Hz; voltage, 3 V; duration, 10 ms | Mouse embryonic bodies | N/A | Significantly enhance EB differentiation into cardiomyocytes | [58] |
| | CNT | Biphasic square (frequency; 1 Hz, pulse duration; 2-ms) | Neonatal rat cardiomyo-cytes | N/A | Improve excitation threshold, promote maturation of cardiomyocytes | [140] |
| | CNT | Rectangular, 2 ms, 2 V $cm^{-1}$, 1 Hz | Neonatal rat cardiomyo-cytes | Excised rat heart to test the synchron-ous pacing enabled by the SA-CNT | Direct the alignment of CMs with the orientation of CNTs and the sarcomeric striations perpendicular to the CNT orientation. CX43 gene and protein upregulation. Achieve normal beating rhythm on artificial myocardium | [181] |
| | CNT | N/A | Neonatal rat cardiomyo-cytes | Sprague-Dawley (SD) rats with large myocardial infarct | Good to cardiac tissue contraction, upregulate gene expression of cTnT and CX43. Improve the effect of ECT's inhibition of pathological deterioration of myocardium | [175] |
| **Carbon nano-materials** | CNT | Frequency, 1 Hz; voltage, 3 V; duration, 10 ms) for two days | Embryonic bodies | N/A | CNTs enhance the mechanical integrity and electrical conductivity of embryonic bodies and reduce the proliferation of EB but enhance the differentiation rates of EBs into cardiomyocytes | [182] |
| | CNT | N/A | Neonatal rat cardiomyocytes in core and endothelial cells in shell | N/A | Conductive nanofibers promote cardiomyocytes orientation and maturation, endothelial cells in the shell helped the endothelialized myocardium formation. | [60] |
| | Carbon nanohorns | N/A | Neonatal rat ventricular myocytes (NRVM) and cardiac fibroblast | N/A | Electrically conductive carbon nanohorns substrates could enhance the adhesion and proliferation of NRVM but inhibit the proliferation of cardiac fibroblast | [183] |
| | Carbon nanofiber | N/A | Neonatal rat cardiomyo-cytes | N/A | Enhance cardiomyocytes metabolic activity and upregulate cardiomyocytes specific gene expression | [61] |
| **Metal** | Gold nano particle (GNP) | N/A | Messenchymal stem cells | N/A | Support MSCs' migration, active metabolism, and proliferation; enhance cardiac marker gene expression | [161] |
| | Gold nanowires | Rectangular, 2 ms, 5 V/cm, 1 Hz | Neonatal rat cardiomyo-cytes | N/A | Obtained thicker and more aligned tissue than on the pristine alginate scaffold and facilitate a synchronous beating of the CMs. Enhance the CX43 and α-sarcomeric actin protein expression | [184] |

**Table 3**
Conductive biomaterials used in smooth muscle tissue engineering.

| Conductive component | | Electrical stimuli | Cell type | Animal model | Main effects | Reference |
|---|---|---|---|---|---|---|
| **Conductive polymer** | PPy | 10 Hz, 50 μA, 1 ms pulse width; 10 Hz, 50 μA, 0.25 ms pulse width | Human adipose stem cells | N/A | PPy-coated scaffold enhanced ASC number and increased the smooth muscle protein expression comparing to the uncoated PTMC scaffold. Long duration electrical stimuli (1 ms) increased the ASC viability, while short duration electro stimuli (0.25 ms) decreased the ASC viability in comparison with non-stimuli group | [125] |
| | PPy | 50 μA sinusoidal electrical stimulation at 0.05, 5 and 500 Hz | Vescular smooth muscle cells and A7r5 cells | N/A | Promote VSMCs growth and direct their differentiation into a more contractile phenotype by giving a 5 Hz electrical stimuli | [185] |
| | PPy | N/A | Human umbilical vein endothelial cells (hECs) ; Human aortic vascular smooth muscle cells (hSMCs) | N/A | pMAS doped PPy support hEC and hSMCs adhesion and proliferation best among other dopant doped PPy substrates and heparin doped PPy supports proliferation of hECs but inhibits that of hMSCs | [186] |

to metal and inorganic semiconductor, were proposed in 1970s as a new kind of conductive materials. They were synthesized more easily and showed better processability in comparison with traditional conductive materials. Conductive polymers themselves could assemble into unique 2D morphologies. Liu et al. [69] developed a simple, general oxidative template assembly method to generate bulk quantities of conductive polymers with nano-clip like morphology. Conductive polymers with other morphologies, such as spindle-shaped [70], sand-glasses shape [71] and flower shape [72], were also developed. In 1997, the conductive polymer, polypyrrole (PPy), was used in tissue engineering as a substrate for cell culture [73]. Since then, the conductive polymers-based biomaterials have attracted more and more attention of the researchers. Although varieties of conductive polymers have been developed via different synthetic methods [74–78], their non-degradability and poor processability limited their application [79]. Thus, conductive polymer blending with natural or synthetic polymers have been widely investigated and used in the biomaterial area. Naturally derived polymers, such as collagen [80], chitosan [49,81,82] and gelatin [82,83], have a good capacity of supporting cell attachment. However, they also have drawbacks, such as the immunogenicity and complicated structural composition, which limited their in vivo application [36]. On the other hand, synthetic polymers [84] have more controllable structure and less immunological issues, but their biocompatibility could be a challenge [36,64]. Fortunately, researchers keep working on those conductive polymers-based biomaterials and try to find a balance of using naturally derived polymers and synthetic polymers.

Even though the first conductive polymer-based substrate was designed for nerve tissue regeneration [73], researchers found that the conductive polymers could also serve as suitable substrates for many other electrical signal excitable cells [17,85,86], such as the muscle cells [87]. More and more works on muscle tissue regeneration using conductive polymers have been reported in recent decades [44,88,89] and different kinds of biomaterials based on the conductive polymers has been proposed, such as hydrogels [42,49], films [90,91], and 3D scaffolds [92,93], etc.

#### *2.1.1. Conductive polymers-based 2-dimensional (2D) biomaterials*

A remarkable character of muscle tissue is their contraction behavior-skeletal muscles' contraction makes the body movement possible, the heart pumps the blood all over the body by cardiac muscle contraction, and smooth muscles contract to achieve the gastrointestinal motility.

Nanofibers have been shown to promote cell adhesion and used as substrates for many tissue engineering scaffold, such as bone [94–96], cartilage [92,97], blood vessel [98,99] and nerve [100–102]. In 2008, Jeong et al. [103] studied the electroactive elastic polyaniline/poly(L-lactide-*co*-epsilon-caprolactone) (PANI/PLCL) nanofiber's effects on cell adhesion. PLCL was blended with polyaniline doped with camphorsulfonic acid (CSA) to obtain the conductive polymers, and afterwards, the polymers were used to prepare uniform and smooth nanofibers by electrospinning. These nanofibers showed tunable breaking elongation ranging from 391.54 ± 9.20% to 207.85 ± 6.74% when changing the CSA-PANI concentration and the conductivity of the nanofibers increased significantly when CSA-PANI was incorporated. In Chen et al.'s study [90], nanofibers composted of polycaprolactone (PCL) or PCL/PANI were formed into random or aligned structure by conducting an external magnetic field in the collector region to study the topographical and electrical cues effects on skeletal muscle cells behavior (Fig. 2). By incorporating PANI into PCL fibers, the electrical conductivity of these nanofibers was increased from undetectable level to $6.36 \pm 0.66 \times 10^{-3}$ S/cm. Ostrovidov et al. [88] developed a gelatin-polyaniline composite conductive nanofiber to promote the myotubes maturation. Nanofibers were fabricated by electrospinning after PANI, gelatin and CSA dissolved in N, N-Dimethylformamide/Milli-Q water mixture. Introduction of PANI in these nanofibers increased the

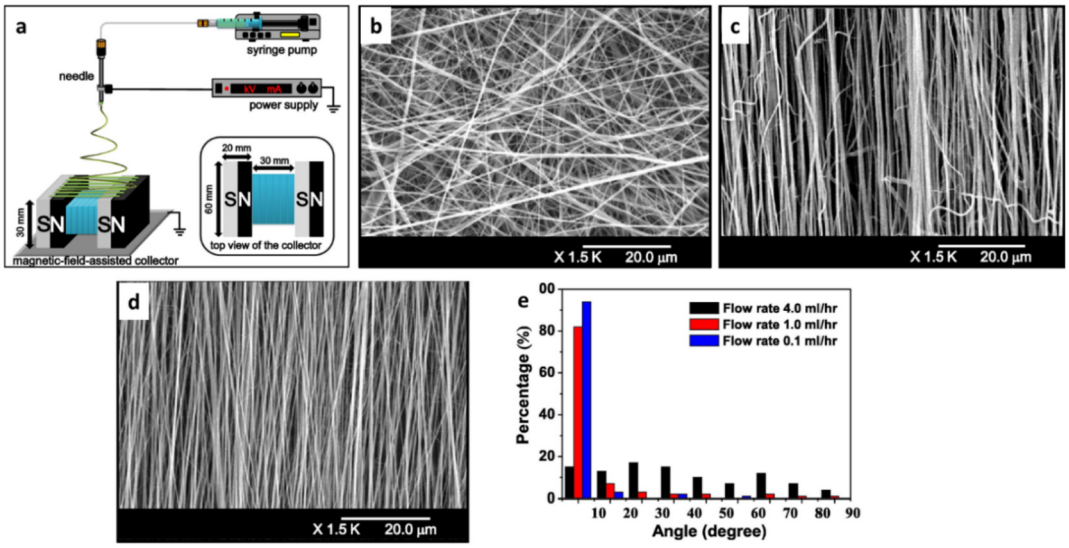


**Fig. 2.** (a) Fabrication of aligned nanofibers by magnetic field-assisted electrospinning (MFAES) method. SEM images of PCL/PANI-3 nanofibers fabricated at solution flow rate of (b) 4.0 ml/h, (c) 1.0 ml/h and (d) 0.1 ml/h. (e) The orientation distribution of these nanofibers. Reprinted from Ref. [67,90]. Copyright (2013), with permission from Elsevier.

conductivity of those nanofibers and the myotube formation on those composite nanofibers was significantly enhanced, as well as the myotube maturation. Mohamadali et al. [89] developed a polyaniline/polyacrylonitrile (PANI/PAN) copolymer nanofibrous scaffold by electrospinning, and in order to improve the cell attachment behavior, the scaffold was modified by non-thermal oxygen plasma. This nanofibrous scaffold showed great potential in muscle tissue engineering.

Another kind of 2D conductive substrates for muscle tissue formation is casted films. Xu et al. [104] formed a conductive polyurethane (CPU) elastomeric film by casting aniline trimer modified PCL to a Teflon dish. In their study, PCL was firstly modified with hexamethylene diisocyanate (HDI) in both end and subsequently reacted with amino group capped aniline trimer to obtain the CPU. To form the films, the CPU polymers dissolved in HFIP, doped with CSA, and casted into films. The CPU films with a conductivity ranged from $2.7 \pm 0.9 \times 10^{-10}$ to $4.4 \pm 0.6 \times 10^{-7}$ S/cm and tensile strength from 17.9 ± 2.0 to 3.1 ± 0.3 MPa showed great potential to be used as biomaterial in skeletal muscle tissue repair. Moreover, similar to electrical stimuli, mechanical stimuli could also promote the formation and maturation of the myotubes [105,106], which leads to the trend of developing conductive elastomers as biomaterials for muscle tissue regeneration. Chen et al. [55] developed a biodegradable polyurethane-urea (PUU) elastomer with conductivity (Fig. 3). Conductive amino-caped aniline trimer, poly(lactic acid) (PLA), and dimethyl propionic acid were linked together by HDI to achieve a conductive elastic PUU block copolymer. C2C12 myoblast cells were seeded on the films and their proliferation and differentiation results all indicated the positive effect of this kind of conductive PUU films on skeletal muscle tissue regeneration. Our group also designed a poly(ethylene glycol)-*co*-poly (glycerol sebacate) (PEGS) polymer based conductive elastomer by introducing aniline pentamer (AP) into PEGS [107]. HDI was used as a crosslinker and by changing poly(ethylene glycol) (PEG) and AP concentration in the polymer, the hydration properties, mechanical properties and conductivity of these elastic films can be adjusted.

### 2.1.2. Conductive polymers-based 3D biomaterials

2D conductive matrix showed a great promotion on myoblast proliferation and differentiation (Table 1). However, the human tissues are all more complicated structures than monolayer of cells and natural extracellular matrix are 3D environments for tissue formation. Meanwhile, 3D environments showed almost totally different effects on cell behavior (like cell migration [108], proliferation [109], and differentiation [109] et al.) from 2D environment [110]. To simulate the native extracellular matrix, 3D biomaterials were needed. To date, the most widely investigated 3D biomaterials forms are hydrogels [111,112] and porous scaffolds [113].

*2.1.2.1. Conductive polymers-based hydrogels.* Muscle tissues are soft tissues with a Young's modulus around 1–2 kPa [114], and substrate's modulus around 1–10 kPa has been demonstrated to promote the myogenesis of mesenchymal stem cells [115,116]. Therefore, hydrogels, with natural hydrated properties and tissue-like mechanical properties, are good candidates for muscle tissue engineering substrates. Conductive polymers/oligomers formed hydrogels not only showed good biocompatibility, but also possessed suitable electroconductivity. PANI, PPy, and polythiophene (PT) et al. have been widely used as conductive polymers whose conductivity is mainly because of their alternated single and double bond, and they can be both physically blended into polymer systems and conjugated onto polymer chains [65,67]. Sasaki et al. [117] developed a series of molecular permeable electronic devices to help to regenerate the muscle tissues. Poly(3,4-ethylenedioxythiophene) (PEDOT) and polyurethane (PU) were used to fabricate a double network hydrogel by a method combining chemical polymerization and electropolymerization. PEDOT acted as the conductive part and the electrical conductivity was up to 120 S/cm. This hydrogel also showed excellent stability and high stretchability. Another microfluidic system based on conductive hydrogel was developed by Hosseinzadeh and colleagues [118]. Poly(acrylic acid) (PAA) hydrogels were interpenetrated with PANI, which provided not only a microfluidic pattern but also formed a 3D nanofibrous environment for the tissue formation. Satellite cells were cultured in this microfluidic hydrogel system and their myogenesis differentiation was confirmed by the immunofluorescence staining. Zhao et al. [119] used PANI grafted quaternized chitosan (QCS) as the main body and crosslinked with oxidized dextran to obtain the conductive hydrogel. QCS endowed this hydrogel with antibacterial property and PANI responsible for the conductivity. C2C12 cells exhibited a higher proliferation behavior on this conductive hydrogel than on the QCS hydrogel, indicating their potential application in skeletal muscle tissue engineering. Gellan gum (GG) spongy-like hydrogel (SLH) modified with PPy was demonstrated to be a promising substrate for skeletal muscle tissue engineering by Berti et al. [120]. PPy distributed in or on the hydrogel through an in situ chemical oxidative polymerization to get the conductive PPy-GG-

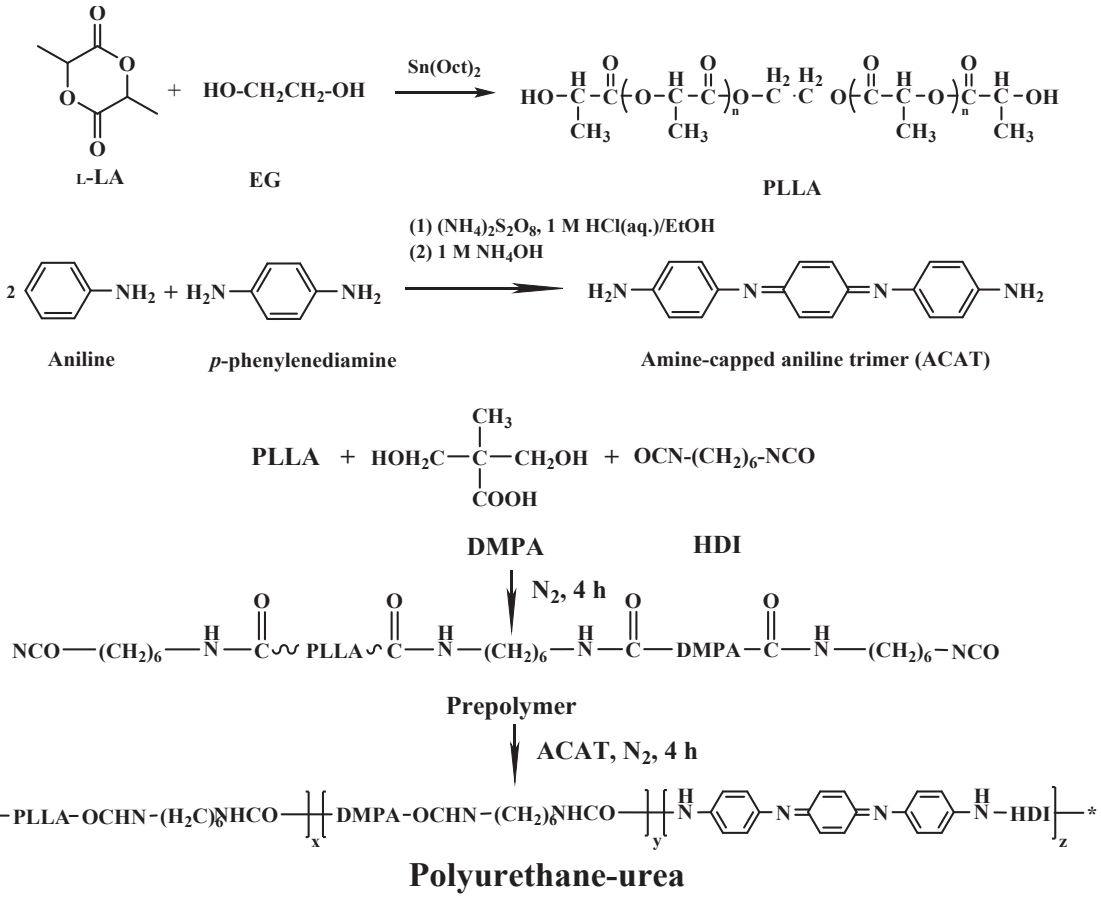


**Fig. 3.** Synthetic methods of PLLA, ACAT, and PUU copolymer. Reprinted from Ref. [55]. Copyright (2015), with permission from ACS Publication.

SLH. These PPy-GG-SLH could serve as a promising platform to help to investigate the electrical stimuli effects on skeletal muscle cells.

Conductive oligomers are another kind of conductive molecules with a better degradability in comparison with conductive polymers, and they have been extensively investigated in recent decades [79,121]. Wang et al. [122] used multi-armed tetraaniline-polyethylene glycol diacrylate (TA-PEG) as a crosslinker to react with thiolated hyaluronic acid (HA-SH) through an in situ Michael addition reaction to obtain a hydrogel with a conductivity similar to myocardium (Fig. 4). Because of the hydrophilic properties of PEG, the conductive TA-PEG could be dissolved in aqueous solution which enabled the hydrogel's encapsulation of the lipo/plasmid complex. Moreover, adipose derived stem cells were also encapsulated in the hydrogel for the in vivo injection to treat with myocardial infarction (MI). Our group has developed a conductive self-healing antibacterial hydrogel for cardiac cell delivery [44]. Chitosan was grafted with conductive aniline tetramer and crosslinked with aldehyde group modified PEG. This hydrogel not only showed a fast and repeatable self-healing behavior, but also exhibited many other excellent properties that are beneficial for in vivo utilization, such as the linear cell release behavior, anti-bacteria property and tissue adhesive behavior. Meanwhile, in vivo injection results suggested this hydrogel could enhance the cell retention ratio by 5 times in comparison with direct injection of cell suspension.

*2.1.2.2. Conductive polymers-based 3D porous scaffolds.* Scaffolds with porous structure could serve as 3D substrates for cell attachment and migration. Suitable pore size is beneficial for cells exchanging nutrition and metabolic waste. Conductive scaffold could not only provide enough space for cells to form tissues, but also be good for cell-cell interaction. For cardiomyocytes, conductive matrix could help cells to achieve synchronous rhythm [123] and increase expression of connexin 43 [124]. In recent years, various conductive scaffolds for muscle tissue repair have emerged, among which conductive polymers-based scaffold is one of the most popular ones.

A silk fibroin (SF) based conductive scaffold for skeletal muscle tissue regeneration is developed by Zhang et al. [93]. In this work, a water-soluble conductive polymer-poly(aniline-*co*-N-(4-sulfophenyl) aniline) (PASA) was used to endow the scaffold with conductivity (Fig. 5). The scaffold was formed via a self-assembly and bulk phase separation method. By votexing at a speed of 2800 rpm, the globules were aligned into fibrillar structure and the protein was intertwisted and assembled into scaffolds, subsequently. PASA was embedded in the abundant β-sheets and helical entanglements of the silk fibroin network in the scaffolds. Silk fibroin gave the scaffold a good biocompatibility and C2C12 cells on this scaffold showed a high viability, as well as the good proliferation and myogenic differentiation behavior. Björninen et al. [125] used poly(trimethylene carbonate) (PTMC) to form a porous scaffold and coated it with PPy in thickness of 2–5 μm. PPy coating roughed the surface of PTMC scaffold by forming micro- and nanoscale topography. Higher level of all the smooth muscle cell (SMC) markers were shown when adipose stem cells (ASCs) were cultured on the PPy coated scaffolds compared with that cultured on uncoated PTMC scaffolds.

*2.1.3. Dopant on the property of the conductive biomaterials*

An important parameter in the conductive polymers-based biomaterials is the dopant. Dopant is essential for conductive polymers and have vital influence on not only conductivity, but also material morphology and cell behavior. Yang et al. [126], using trypan blue (TB) as both dopant and crosslinker, developed a 3D nanostructured polypyrrole conductive hydrogel. When doped with TB, the polypyrrole formed a regularly oriented nanofiber structure rather than the

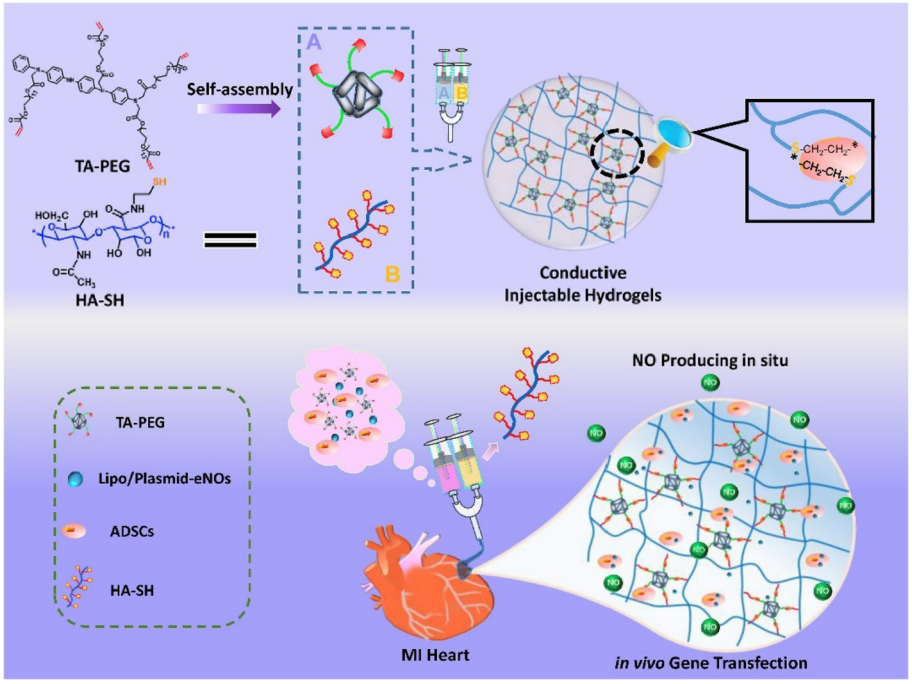


**Fig. 4.** Schematic sketch showing how to construct the conductive injectable hydrogel. TA-PEG is soluble in water and the hydrogel can form in aqueous solution. DNA-eNOs nanoparticles and ADSCs are encapsulated inside this hydrogel to treat myocardial infarction. Reprinted from Ref. [122]. Copyright (2018), with permission from Elsevier.

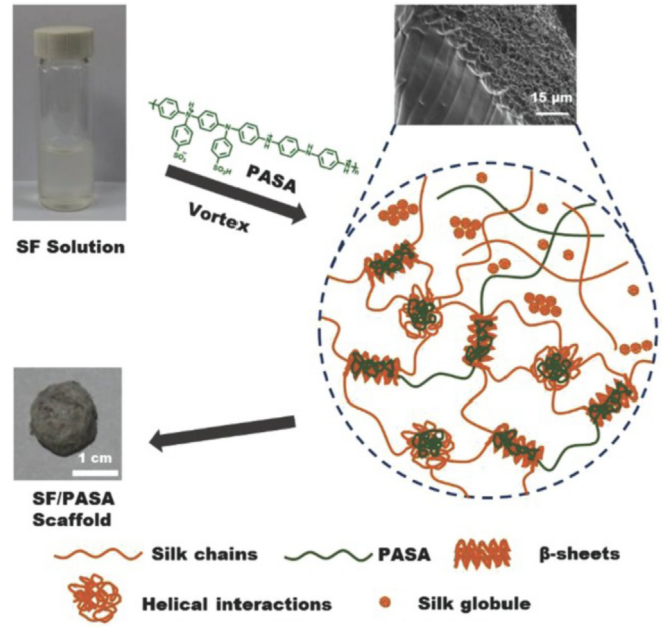


**Fig. 5.** The SF/PASA scaffolds' fabrication. Silk fibroin assembles into beads following by forming networks enriching in β-sheets after vortex. Reprinted from Ref. [93]. Copyright (2017), with permission from Wiley.

granular particles as pure polypyrrole appearing. Runge et al. [127] showed that when doped with proper dopants, the cell proliferation and cell body extension of the nerve cells could be promoted. However, different dopant has different effect on neurite extension. Thompson et al. [128] further studied different dopant's effect on nerve growth. Sodium salts of para-toluene sulfonate (pTS), dodecylbenzene sulfonate (DBS), poly(4-styrenesulfonate) (PSS), hyaluronic acid (HA) and chondroitin sulfate (CS) and the ammonium salt of poly (2-methoxyaniline-5-sulfonic acid) (PMAS) were the six dopants that involved in the PPy synthesis in this study. They revealed that the dopant could affect both the conductivity and the roughness of the PPy films and further affect their biocompatibility. Smallest dopants (pTS and DBS) are found to have the best biocompatibility for neural cell culture. In muscle tissue engineering, conductive polymers are always used after doping. Gelmi et al. [129] studied the impact of dopants' and PPy materials' surface properties on the endothelial progenitor cells (EPCs) and cardiac progenitor cell's (CPCs) behavior. Different kinds of dopants, including inorganic molecules, polyelectrolytes, and biomolecules, were involved in this study and they found that different dopants could lead to different surface properties of the PPy materials, such as the water contact angle and the roughness. When using perchlorate ($LiClO_4$) and hyaluronic acid (HA) as dopants, the material had higher surface roughness compared to other molecules doped PPy material and on these high-surface-roughness materials, the CPCs showed low density and live cell number, indicating that the CPCs were sensitive to high surface roughness. However, a systematic study of how dopants affect muscle cell behavior is still need to be investigated.

### 2.2. Carbon nanomaterials-based conductive biomaterials

Carbon nanomaterial, with diverse of allotropes and variety of forms, is also one of the conductive sources for biomaterials to achieve conductivity. Carbon nanotubes and graphene are two of the most widely used carbon nanomaterials in the biomedical field. These organic nanomaterials could be conjugated [130–132] or dispersed [133–136] into other polymers or just as a coating layer [137,138] for traditional matrix to endow them with conductivity.

#### 2.2.1. Carbon nanotube based conductive biomaterials

In most of the carbon nanotubes-based conductive materials study, carbon nanotubes (CNTs) were used as addictive via dispersing into other polymers, and the dispersing method also varied. Ahadian et al. developed a series of hybrid hydrogels containing CNTs for muscle tissue formation. In 2013, they used the dielectrophoresis method to align the CNTs into the gelatin methacrylate (GelMA) hydrogel and showed higher maturation of muscle myofibers [139]. They further applied the CNT-GelMA hydrogel into the study of the differentiation from embryonic bodies toward cardiomyocytes [58]. CNTs also aligned within the GelMA hydrogel via dielectrophoresis approach. And they fabricated microwells on the hydrogels to encapsulate mouse embryonic bodies (EBs). After two-continuous-day application of electrical

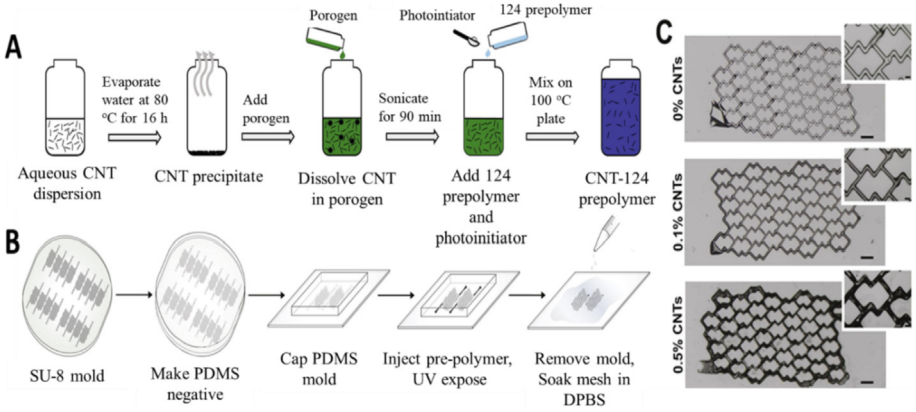


**Fig. 6.** Preparation and characterization of scaffold. (A) Process of 124 polymer-CNT prepolymer preparation. (B) Preparation of a patch scaffolds by molding of the polymers. (C) Bright field images showing the mesh-structured polymer materials with 0, 0.1%, and 0.5% CNTs concentration in 124 polymer (Scale bars: 400 μm (left) and 100 μm (top right)). Reprinted from Ref. [140]. Copyright (2017), with permission from Elsevier.

pulse stimulation, the cardiac differentiation of the EBs was significantly enhanced. In 2017, they developed a polyester-CNTs scaffold by dispersing CNTs into poly(octamethylene maleate (anhydride) 1, 2, 4-butanetricarboxylate) (124 polymer) [140]. CNTs were mixed with poly (ethylene glycol) dimethyl ether (PEGDM) to get an evenly dispersed solution, then this solution was added into the 124 polymer solution, mixed well, poured to a mold and crosslinked by UV light (Fig. 6). The final crosslinked structure exhibited high elasticity and good conductivity. Increase of CNTs concentration could enhance the surface moduli but reduce the bulk moduli. Cardiac tissue showed higher maturity on the 0.5% CNT content substrates than that on the 0% and 0.1% CNT substrates.

Carbon nanomaterials can be dispersed not only into the synthetic polymer, but also into the natural polymers, such as chitosan [141–143] and collagen [144–146]. Martins and colleagues [61] dispersed the carbon nanofibers into the chitosan and formed a conductive scaffold using a precipitation method. In comparison with pure chitosan scaffold, the chitosan/carbon scaffold showed a better promotion on cardiomyocytes metabolic activity. Meanwhile, cardiomyocytes on the conductive scaffold showed a higher cardiac related gene expression level than that on the chitosan scaffold.

### 2.2.2. Graphene-based conductive biomaterials

Graphene is 2D sheet with a thickness of single-atom that has attracted much attention of the researchers from chemistry, biotechnology and materials physics area. The first kind of graphene, few-layers graphene (FLG), was isolated by peeling from the 3D graphite [147]. And nowadays, a lot of graphene-related materials were developed, such as graphene nanosheets, graphene oxide (GO), and reduced GO (rGO). Because of its unique structure and the strong C–C bonding, graphene exhibited high electrical conductivity. The defect-free monolayer graphene showed an electrical conductivity of $10^4$ S/cm [148]. The composites' conductivity could be significantly increased after using graphene as a filler. However, graphene is easy to aggregate, leading to their uneven dispersion in the composites. Many groups have tried hard to solve this issue. The most widely used method is sonication. In this way, graphene is usually dissolved into an aqueous solution and sonicated for 30–70 min to get a homogeneous solution [149,150]. Zhou et al. [151] developed an injectable oligo(poly(ethylene glycol) fumarate) (OPF)/graphene oxide (GO) hydrogel by dispersing GO into the OPF solution with a 45 min incubation. This hydrogel showed semiconductive properties. Hydrogels with different GO concentrations (0.3 mg/mL, 0.6 mg/mL and 1.0 mg/mL GO/OPF) were generated to investigate the GO concentration's effects on materials properties and cardiac regeneration. Introduction of GO in the hydrogel could increase the roughness of the hydrogel (Fig. 7a). The conductivity of the hydrogel was also enhanced greatly by incorporation of GO and 1.0 mg/mL GO concentration hydrogel showed the highest conductivity ($4.235 \times 10^{-3}$ S/cm, Fig. 7b). They also built an ex vivo setup to test the excitation threshold of muscle tissues (Fig. 7c). OPF hydrogels with/without GO were injected in the gap of muscle tissues and acted as a bridge for the connection of two pieces of muscle tissues. Electrical stimuli were applied to one side of the muscle piece and the beating and contraction behavior of the other piece of muscles were checked. OPF/GO (1.0 mg/mL) hydrogel showed lower threshold in comparison with the pure OPF hydrogels (Fig. 7d). Kaur and colleagues [152] fabricated a graphene/polyurethane composites using different method to investigate the processing method's effect on the composites' conductivity. They used the solution mixing, melt processing and in situ polymerization method and found that solution mixing method is the most promising method to prepare the graphene/polyurethane composite among all these three methods. Liang et al. [153] used the filtration method to fabricate a graphene silk composite film. In their study, silk fiber was cut into short segments and dispersed with graphene in an aqueous solution, ultrasonicating to get a homogeneous suspension. The suspension was filtered under vacuum and dried to obtain the film, following with reduction. A double-faced graphene/silk film was obtained with a porous and hierarchical top layer.

The introduction of graphene not only can increase the electrical conductivity of the materials, but also improve their mechanical properties. Sayyar et al. [154] showed that after adding graphene into the poly(trimethylene carbonate) to form a scaffold, the tensile strength increased by more than 100% and the conductivity also showed orders of magnitude improvement. Pristine graphene was also reported to improve the stiffness and electrical conductivity of the biohybrides of collagen and pristine graphene [155].

## 2.3. Metal-based conductive biomaterial

Metals as conductive biomaterials are always in the forms of nanomaterials, such as nano-Au, nano-Ag and nano-Cu. They can be prepared into various types such as nanoparticles, nanowires, nanotubes, and nanofibers. In nanoscale, these metals exhibited large surface area, porosity, orientation and remarkable conductivity. Meanwhile, they also showed good biocompatibility [156,157] and their high surface free energy leading to the easy modification on the surface [158,159], as well as the easy loading of drugs [68,160]. Baei et al. [161] developed a thermosensitive conductive hydrogel as a substrate for cardiac tissue regeneration. In their study, they prepared a kind of chitosan-stabilized gold nanoparticles (CS-GNPs) via mixing tetrachloroauric acid with chitosan solution, as well as adding sodium citrate. The hydrogel was obtained by crosslinking these CS-GNPs using β-glycerophosphate disodium salt solution (β-GP) (Fig. 8). This hydrogel showed a good electrical conductivity of 0.13 S/m, which is similar to the native myocardium. Meanwhile, the hydrogel exhibited thermosensitive behavior that it would be a fluidic state when in 23 °C but would gelate at 37 °C, which would be beneficial for in vivo application. Ahadian and colleagues [162] formed a hybrid GelMA-

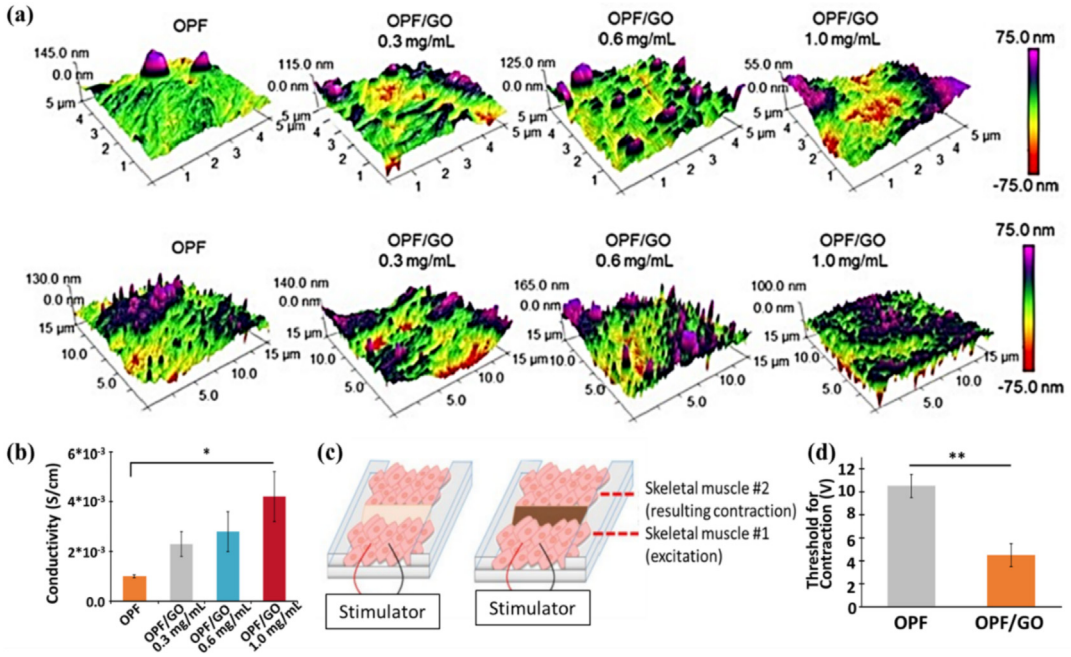


**Fig. 7.** (a) Roughness of the OPF hydrogels with different GO concentration. (b) Conductivity of OPF hydrogels with different GO concentration. (c) Scheme of the ex vivo setup for the test of excitation threshold of muscle tissues and (d) the results of excitation threshold of muscle tissues. Reprinted from Ref. [151]. Copyright (2018), with permission from Ivyspring International Publisher.

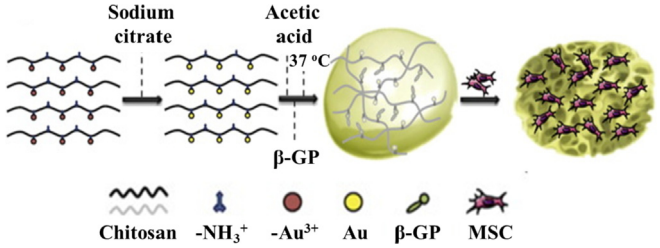


**Fig. 8.** Schematic sketch of fabrication and in vitro cell seeding on scaffolds. Reprinted from Ref. [161]. Copyright (2016), with permission from Elsevier.

palladium-based metallic glass sub-micron wires (PdMGSMWs) hydrogel for skeletal muscle tissue regeneration. They used the $Pd_{42.5}Cu_{30}Ni_{7.5}P_{20}$ alloy to form the PdMGSMWs and deposit this kind of sub-micron wires in the GelMA prepolymer substantially crosslinking with UV light to form the conductive hydrogel. This hydrogel also showed good conductivity as well as mechanical properties, which thanks to the metallic glass sub-micron wire. Similarly, a UV-crosslinkable gold nanorod (GNR) - incorporated GelMA hybrid hydrogel were formed by Navaei and colleagues [163]. Gold nanorods were obtained through a seed-mediated-growth method. Afterwards, the GNRs were embedded into the GelMA hydrogel to achieve an electrical conductive hydrogel for engineering cardiac tissue constructs.

## 3. Application of conductive biomaterials in muscle tissue repair

In the regeneration process of muscles, there is a very important stage, the inflammatory phase, which could facilitate the following stage of repair [164]. Taken skeletal muscle as an example, in the injured muscle, rupture of the myofibers always could be found, accompanied with necrosis [3]. Mononuclear inflammatory cells are the first ones who sense the factor secreted by the disrupted myofibers and they further recruit other circulating inflammatory cells to the injury site by releasing chemotactic signals [165]. Many cytokines and growth factors, such as tumor necrosis factor-α (TNF-α), fibroblast growth factor (FGF), insulin like growth factor (IGF) and IL-6, have been reported that they could regulate the behavior of satellite cells in the repair and remodeling process [3]. Within 2 h of injury, the neutrophils invade the muscle, and macrophages are coming subsequently [166]. When macrophages arrive the battle field, phagocytosis and removal occur, which trigger the repair phase. In this phase, macrophages show two different types, the pro-inflammatory macrophage (M1), who helps to clean up disrupted cells and recruit the muscle progenitor cells, and the anti-inflammatory macrophage (M2), which contributes to the regeneration process [167].

Muscle progenitor cells recruited by the M1 cells proliferate and differentiate into functional myotubes facilitated by the M2 cells. These newly formed myotubes need to be reorganized and fused with the existing myofibers, which is the character of the third stage, remodeling. In this stage, the remodeling of the scar tissue and the regaining function of myotubes happen. However, if the injury is severe, due to the limited proliferation capacity of the myoblast, the myotube formation rate is slower than that of the scar tissue formation, which finally leads to the thick scar tissue and prevents the fusion of myofibers [3].

According to all that information about the regenerative process of muscle tissues, how to inhibit the scar tissue formation and facilitate more muscle tissue formation (including proliferation of progenitor cells and their differentiation) are two main issues. Conductive materials have been demonstrated to promote electrical-responsive cells proliferation [32,49] and enhance the myotube formation by abundant studies [55,89,91]. Meanwhile, some conductive materials also demonstrated to reduce the cardiac fibroblast proliferation, which will reduce the scar tissue formation. Electrical stimuli can also induce the Spp1 gene expression in macrophages, which is related to the macrophage maturation, inflammation and also a characteristic of the M2c subtype of the M2 macrophages [168]. Therefore, conductive materials have been widely used in the muscle tissue regeneration area and here we are going to further discuss their application in different types of muscle tissue regeneration.

A vast amount of 3D conductive polymers-based conductive biomaterials was developed during the past few decades and was applied to different areas, such as the energy storage [126], drug delivery [169–171] and tissue engineering. In tissue engineering studies, a large

number of electroactive conducting hydrogels were applied into neural regeneration [66,81,82]. Manouchehri et al. [172] developed chitosan-oligoaniline hydrogel as a coating layer for neural interfaces and it turns out to promote the PC12 cell activities. Almost at the same time, Bagher et al. [83] also found that chitosan-aniline pentamer/gelatin/agarose hydrogel could promote the olfactory ecto-messenchymal stem cells differentiation into the motor neuron-like cells. Another main application area of conductive hydrogels in tissue engineering is the muscle tissue engineering field (Tables 1–3).

Muscle tissues can be separated into three different types, skeletal muscle tissues, cardiac muscle tissues and smooth muscle tissues. Skeletal muscles are in charge of movement and force generation in the body, and they request for the high elasticity and stretchability of the scaffolds. Cardiac muscles are more sensitive to electrical signals and their structures are more complicated, resulting in the ingenious design of the conductive biomaterials. Smooth muscles are distributed in the vascular and digestive system, and they are also sensitive to electrical stimuli. However, the application of conductive biomaterials on smooth muscle tissue repair is lack of investigation.

### 3.1. Conductive biomaterials in skeletal muscle tissue engineering

#### 3.1.1. 2D conductive biomaterials in skeletal muscle tissue engineering

Conductive biomaterials showed great potential to help muscle tissue repair due to their good biocompatibility and other promotion effect on cell attachment, proliferation and myogenic differentiation (see Tables 1 and 4). Jeong et al. [103] found that cells (human dermal fibroblasts, NIH-3T3 fibroblasts, and C2C12 myoblasts) on the conductive PANI/PCL nanofibers showed better adhesion behavior than that on the PCL nanofibers. Furthermore, to explore the conductivity and orientation's effects on the skeletal muscle tissue formation, C2C12 myoblast cells were seeded on the random and oriented PANI/PCL nanofibers in Chen et al.'s work [90] (Fig. 2). And they found that C2C12 cells seeded on the aligned conductive PCL/PANI nanofibers showed the best myotube formation and myotube maturation. What's more interesting is that the aligned nanofibers could promote myotube formation, on the other hand, the conductivity of the nanofibers showed more effects on inducing myotube maturation. Cell attachment and spreading behavior also related to the elastomer's hydration properties. Mckeon-Fischer et al. [174] developed a PEDOT nanoparticle and PCL electrospun conductive composite scaffold to help skeletal muscle regeneration. Multi-wall CNTs were also induced into the scaffold and enhanced the elastic modulus and yield stress. Rat muscle cells were seeded on this scaffold, indicating good cytocompatibility of this scaffold and their potential in neuromuscular junction regeneration. Hosseinzadeh et al. [91] used the PAN-PANI electrospun nanofibrous scaffolds as the substrates for satellite cells adhesion and differentiation. And they found that the PAN-PANI scaffolds could promote satellite cells proliferation and differentiation. With conductivity and high Young's modulus, the PAN-PANI nanofibrous scaffold could enhance the maturation of satellite cells, and with the increase of the scaffold stiffness, the cell proliferation would be inhibited but the differentiation would be promoted. In our work [107], the elastic conductive poly(ethylene glycol)-co-poly(glycerol sebacate)-aniline pentamer (PEGS-AP) films were developed and the conductive segment, AP, could not only endow the biomaterials with good electrical conductivity, but also adjust films' hydrophilicity. C2C12 myoblast cells showed different adhesion and proliferation behavior on films with different AP concentration. Films with 9% AP content showed the most adhesive cells after 4 h seeding and the cell number on 9% AP films was 4 times higher than that on 0% AP film when C2C12 cells were cultured for 3 days. Meanwhile, in comparison with non-conductive PEGS elastomer, our conductive PEGS-AP elastomer promoted the myogenic differentiation of C2C12 myoblasts by increasing the MyoG and TnnT gene expression by 67 and 46 times compared to PEGS films. Mahmoudifard et al. [173] developed a series of composite nanofibers based on graphene (G)/GO nanosheets and polyacrylonitrile (PAN)/PANI nanofibers via electrospinning. Muscular satellite cells were seeded on these nanosheets and cells on the PAN/PANI-CSA/G nanofibers showed the best proliferation and differentiation behavior among all these groups due to the higher stiffness and enhanced conductivity value of the nanofibers.

#### 3.1.2. 3D conductive biomaterials in skeletal muscle tissue engineering

3D environments are of great importance to generate functional and matured muscle tissues owing to their similarity to the extracellular matrix and beneficial for 3D complicated tissue formation. Hydrogels with conductive component have been demonstrated to be a good candidate as 3D biomaterials for skeletal muscle tissue engineering. In 2014, Sasaki et al. [117] developed a double network electroconductive hydrogel hybrid which showed potential to be used in muscle tissue engineering. In their work, C2C12 myoblast cells were seeded on the conductive double network hydrogel based on PEDOT and PU. Cells seeded on this conductive hydrogel showed better adhesion behavior and viability in comparison with cells on the non-conductive double network hydrogels. GelMA hydrogel incorporated with (PdMGSMWs) glass sub-micron wires was demonstrated to regulate C2C12 myoblast adhesion and spreading more efficiently [162]. When electrical stimulation was applied, the myotube formation, contraction behavior and metabolic activity were enhanced. Aligned conductive nanofibers together with photocurable hydrogel was used to fabricate a core-shell composite substrate to mimic the structure of native skeletal muscle by Wang et al. [59]. C2C12 myoblast were seeded on the nanofiber yarns which was embedded in the hydrogel. These nanofiber yarns provided space for C2C12 cells growth, and directed their elongation and promoted the myotube formation (Fig. 9a, b and c). The nuclei also showed anisotropic properties (higher nuclear aspect ratio in comparison with cells seeded on 2D environment) when cells were seeded on nanofiber

**Table 4**
Gene and protein expressed in skeletal and cardiac muscle with/without electrical stimuli.

| | Skeletal muscle | | Cardiac muscle | |
|---|---|---|---|---|
| | Gene | Protein | Gene | Protein |
| Without electrical stimuli | Myosin [89,91]<br>Troponin-T1 [55,93,107]<br>Myogenin [55,89,93,107]<br>α-actinin [89,91]<br>MyoD [91,93] | Myosin heavy chain (MHC) [55,59,93,107] | Cx-43 [177] | Sarcomere actin [56,178,180,187]<br>Cx-43 [56,175,177,178,180,187]<br>N-cadherin [187]<br>Desmo-somes [187]<br>cTnT [175] |
| With electrical stimuli | Sarcomeric actin [139,162]<br>MRF4 [139,162]<br>Myogenin [88,139,162]<br>MHCHd/x [139,162]<br>α-actinin [139,162]<br>Vinculin [162] | Myosin heavy chain (MHC) [88,139,162] | Nkx2.5 [58]<br>Troponin T2 [58]<br>Actc1 [58] | CX-43 [181,184]<br>Troponin I [184]<br>Sarcomere actin [140]<br>Troponin T [58] |

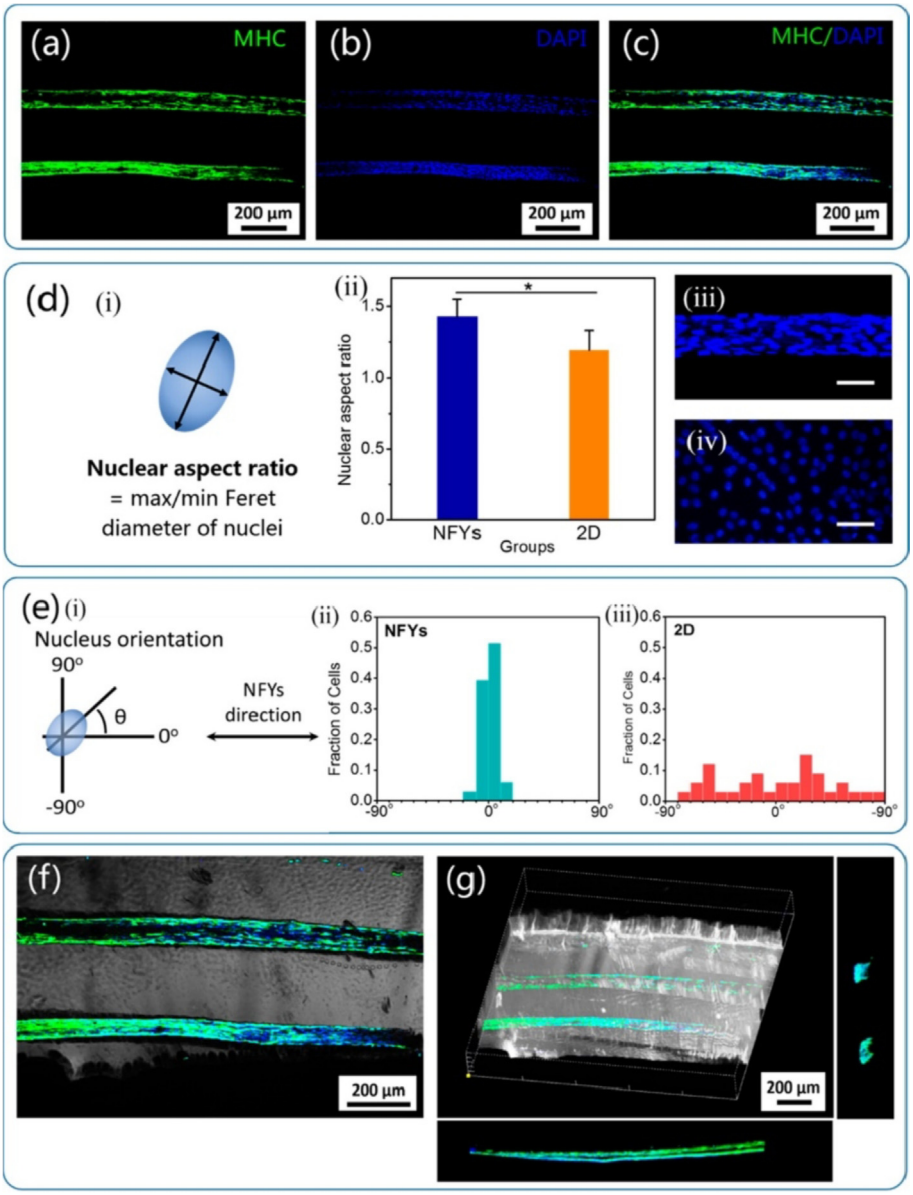


**Fig. 9.** Immunofluorescence staining of C2C12 cells seeded on the nanofiber yarns and embedded in hydrogel: (a) myosin heavy chains (stained with green), (b) nucleus (stained with blue) and (c) the merged image of MHC and nucleus. (d) Definition of nuclear aspect ratio (i), statistical analysis of nuclear aspect ratio in different culture conditions (ii) and the images of nuclei of cells cultured within the core-shell scaffolds (iii) and 2D TCP (iv). Scale bars = 50 μm. (e) The angle between the long axis of the nuclei and the direction of aligned NFYs indicating the myotubes alignment (i), and the histograms of the relative alignment of myotubes within the scaffolds (ii) and on 2D TCP (iii). (f) Merged image of aligned NFY cores with myotubes inside. (g) Three-dimensional side view of highly organized myotubes inside the core-shell scaffolds. Reprinted from Ref. [59]. Copyright (2015), with permission from ACS publications.

yarns (Fig. 9d). They also measured the angle between nuclei orientation and nanofiber's direction, which indicated that the long axis of the nuclei were mostly coincident with the direction of nanofiber yarns (Fig. 9e). Myotubes were also aligned in the same direction of nanofiber yarns, suggesting that this core-shell scaffold showed great ability to induce 3D cellular alignment and elongation, as well as the ability of promotion on elongated myotube formation (Fig. 9f and g).

3D conductive scaffolds with porous structure are also a good candidate in helping skeletal muscle tissue regeneration. Patel et al. [176] developed carbon-based hierarchical scaffolds to help myoblast differentiation. The scaffolds have both micro- and nanoscale architectures. Two different types of scaffolds, interconnected microporous carbon foam and aligned carbon-fiber-built mats, were fabricated. CNTs were grafted on these two kinds of scaffolds to obtain the nanoscale structure. C2C12 myoblast cells on these two different kinds of scaffolds showed similar adhesion and proliferation behavior. However, only the aligned fibrous scaffold could facilitate the fusion of myocytes into myotubes, even though both of these two kinds of scaffolds have nanofibrous architecture. Furthermore, the demonstrated nanoscale architecture could change the surface properties of the scaffolds, such as the nano-roughness and wettability, subsequently affect the adhesion and growth of the myoblast. But for the myogenesis differentiation and myotube formation, it depends on the synergy of both nanoscale architecture and the micro-/macroscale structure of the substrates.

### 3.2. Conductive biomaterials in cardiac muscle tissue engineering

#### 3.2.1. 2D conductive biomaterials in cardiac muscle tissue engineering

Biomaterials in cardiac tissue engineering are requested for suitable conductivity that could mimic the native cardiac extracellular matrix and induce the synchronous beating of the newly generated cardiac tissues. Conductive cardiac patches were investigated widely in recent years to facilitate the new cardiac tissue formation and recovery of the myocardial function after myocardial infarction. Gelmi et al. [129] had conducted a fundamental research to explore the conductive polymers effect on cardiac progenitor cells' viability. The results showed that the conductive polymer materials could serve as a feasible support matrix for endothelial and cardiac progenitor cells and cardiac progenitor cells are sensitive to the high surface roughness. Conductive materials also have effects on electrophysiological developments of cardiomyocytes. Spearman and colleagues [177] fabricated conductive interpenetrating networks of PPy and PCL and investigated their effects on

electrophysiological development of cardiac cells. In their study, HL-1 cardiomyocytes were used, and cells showed good attachment behavior on PCL and PPy-PCL films. The CX43 proteins were peripheral localized in HL-1 cells on PPy-PCL films in comparison to that on PCL films. The cardiomyocytes monolayers' calcium wave propagation was faster, and the calcium transient duration was shorter on the PPy-PCL films than that on the PCL films, indicating the promotion of cardiac muscle function. Our group recently developed a series of electroactive biodegradable films with different size of micropatterns based on poly (sebacate acid) (PGS) and aniline trimer (AT) [178]. Concentration of AT in the films was demonstrated could affect not only the proliferation of H9c2 cardiac cells, but also the cardiac specific marker (α-actinin and CX43) expression of primary cardiomyocytes. When AT was 10 wt % in the polymer, the promotion effects of this films on cardiac cell proliferation and differentiation are the best. And we further studied the micropatterns' effect on cardiomyocytes morphology, distribution and functionalization. Micropatterned films with different ratios of groove to ridge (50/50 μm, 100/50 μm) were obtained by casting PGS-AT solution on pre-designed mold and crosslinking with HDI. Primary CMs seeded on films with micropatterns aligned along the groove/ridge but that on the flat films grew randomly. Meanwhile, on 50/50 μm micropatterned films, the CMs showed the highest aspect ratio (~8) which was only around 3 when on the flat films. The amplitude of $Ca^{2+}$ transient of CMs on films with 50/50 μm micropatterns are the highest, which could further lead to the synchronized and strong beating of CMs.

CNT itself has been demonstrated to promote electrophysiological homogeneity of the artificial cardiac tissues [181]. In this study, Ren and colleagues formed a super aligned carbon-nanotube sheets for cardiomyocytes culture to mimic the native cardiac extracellular matrix. This super aligned (SA) structure directed the alignment of the cardiomyocytes seeded on this sheet and led to the appearance of massive sarcomeric striations that were perpendicular to the oriented direction. CX43 protein and gene expression were higher in cells on the SA-CNT matrix than that on the cover glasses, which, together with the sarcomeric striation formation, indicated that the SA-CNT sheets could promote cardiomyocytes formation (Fig. 10a–e, h). This SA-CNT sheet also allowed the electrical signal transmission which is beneficial for the artificial myocardium achieving normal beating rhythm. With electrical stimuli (E-SA-CNT), the CX43 protein showed a higher expression level no matter in comparison with that cultured on SA-CNT or on cover glass (Fig. 10 f, g). Wu et al. [183] incorporated carbon nanohorns (CNHs) into the collagen to obtain a biocompatible substrate for cardiac tissue formation. They evaluated the effects of CNHs on the neonatal rat ventricular myocytes (NRVMs) and the results showed that the substrates with CNHs promoted the NRVMs adhesion and proliferation. Besides, the addition of CNHs could inhibit the cardiac fibroblasts proliferation and enhance the mechanical and electrical genes expression and maturation of the NRVMs. Ahadian et al. [182] embedded CNTs in EBs to induce their differentiation toward cardiac tissues. CNTs could increase the integrity and conductivity of EBs, as well as their Young's modulus. EBs' differentiation towards cardiomyocytes was significantly enhanced when embedded with CNTs, while the proliferation rate was decreased.

#### 3.2.2. 3D conductive biomaterials in cardiac muscle tissue engineering

Utilization of 3D conductive biomaterials in cardiac tissue engineering has drawn much attention in recent years. The most basic method to fabricate 3D conductive matrix is incorporating nanoscale conductive materials in biocompatible hydrogels or scaffolds. Dvir et al. [184] developed a nanowired 3D hydrogel as cardiac patches to support cardiac tissue formation. The gold nanowires in the alginate hydrogel promoted the electrical communication between cardiac cells in different pores of scaffolds, which resulted in a thicker and better aligned tissue formation on the nanowired hydrogel than that on the pristine alginate. The gold nanowire also made electrical stimuli possible and the electrical stimuli led to synchronous cell contraction. In another study, single walled carbon nanotubes (SWNTs) were incorporated into gelatin hydrogels and served as conductive scaffolds for engineered cardiac tissue formation [175]. In vitro study showed that the SWNTs could facilitate the cardiac contraction and were beneficial for expression of electrochemical associated proteins. After in vivo implantation, the functional measurement was carried out, and the results indicated the critical role of SWNTs in improving engineered cardiac tissue's performance in inhibiting myocardial pathological deterioration. Wang et al. [180] developed a conductive cryogel to serve as cardiac tissue patch based on PPy conductive nanoparticles. PPy nanoparticles in the hydrogel could increase the expression of α-actin and CX43, leading to the synchronous contraction of cardiomyocytes. Implantation of this cardiac tissue patch in rat acute myocardial infarction (AMI) model resulted in the improvement of cardiac function and reduction of infract size. Cardiac tissues have specific anisotropic structure and it is important for the scaffolds in cardiac tissue engineering to guide 3D cellular orientation. Wu et al. [60] presented an interwoven aligned conductive hybrid scaffold to mimic the anisotropic cardiac structure. Rat neonatal cardiomyocytes were seeded on the nanofiber yarn and encapsulated in the photocurable hydrogels to co-culture with endothelia cells. This complicated structure scaffold could induce cellular orientation, promote cardiomyocytes maturation, and enhance endothelialization, which led to their potential application in engineering 3D cardiac anisotropy (Fig. 11). Wang et al. [56] generated PLA/PANI conductive scaffold by electrospinning. The maturation, spontaneous beating and cell-cell interaction of rat primary cardiomyocytes on this kind of scaffolds were enhanced even without electrical stimuli, which is an inspired sign that the conductive polymer itself may have some effects on the maturation and spontaneous rhythm of the cardiomyocytes. 3D conductive substrates could also promote the differentiation of stem cells into cardiomyocytes. Yang et al. [179] developed a series of electrically conductive double-network hydrogel (HEDN) to act as cardiac tissue engineering scaffold. The HEDN were fabricated based on conductive chemically crosslinked poly(thiophene-3-acetic acid) (PTAA) and photo-crosslinking methacrylated aminated gelatin (MAAG). Brown adipose-derived stem cells (BADSCs) seeded on these hydrogels showed good viability and proliferation behavior. Meanwhile, these conductive hydrogels can also promote the cardiogenic differentiation of BADSCs. Around 30% of BADSCs on the HEDN1 hydrogel (pure PTAA hydrogel) expressed cTnT protein, the specific marker for cardiomyocytes. Additionally, with the conductive component PTAA decreased from 100% to 0%, the numbers of $cTnT^+$ cells were decreased from ~30% to ~15%. Electrical stimuli were also applied to promote cardiogenic differentiation. An increase of $cTnT^+$ cells' percentage from 31.8% ± 1.34%–42.6% ± 1.64% at day 7 ($p < 0.01$) could be seen after application of electrical stimuli.

### 3.3. Conductive biomaterials in smooth muscle tissue engineering

The contractile phenotype of smooth muscle cells could be directed by electrical stimuli, and several conductive biomaterials has been investigated to serve as smooth muscle tissue engineering substrates in recent years [125,185]. In 2008, Rowlands and Cooper-White [185] first demonstrated the conductive substrates could promote smooth muscle cells proliferation and contractile protein expression. Collagen IV and Matrigel coated conducting PPy substrates doped with hyaluronic acid were used for vascular smooth muscle cells culturing. With sinusoidal electrical stimuli, the proliferation and contractile proteins expression were increased. Stewart et al. [186] investigated PPy with different dopants' effects on the adhesion and proliferation of smooth muscle cells. According to their results, PPy doped with poly(2-methoxyaniline-5-sulfonic acid) (PMAS) are beneficial for smooth muscle cell attachment and proliferation, but with heparin as dopant, the proliferation of smooth muscle cells was inhibited. Bjorninen et al. [125] used PPy-coated scaffolds to investigate the impact of electrical

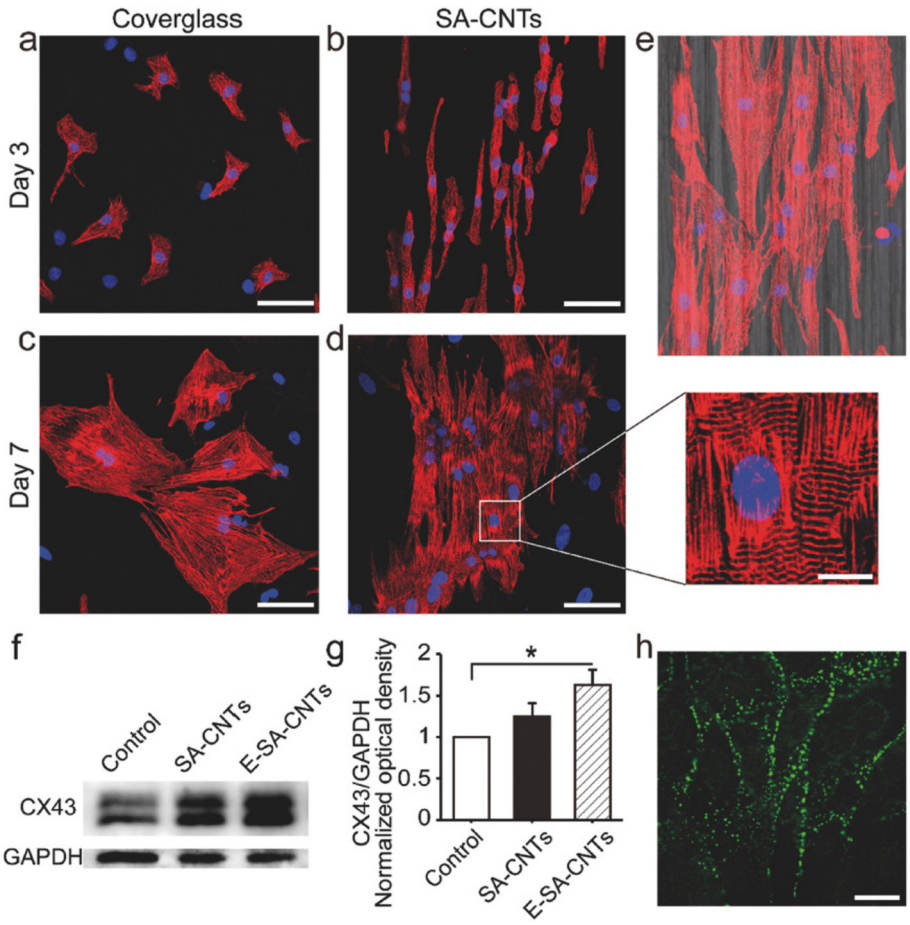


**Fig. 10.** Cell morphology, expression and distribution of CX43 protein. Confocal images of CMs (a, b) after 3 days of culture and (c, d) after culturing for 7 days. CMs grown on (a, c) the cover glass showed random extension, but CMs grown on (b, d) SA-CNTs extended along the alignment of SA-CNTs, with a lot of massive sarcomeric striations perpendicular to the direction of oriented (d, right panel). (e) CMs along the CNT alignment on the SA-CNTs shown in representative superimposed confocal image. (f) CX43 protein expression level in CMs which are grown on the cover glass, SA-CNTs and E-SA-CNTs measured by Western blot. (g) Quantitative data of CX43 protein expression on SA-CNTs with and without electrical stimuli in CMs (n = 6, three independent experiments). Signals of optical-density are standardized to GAPDH and compared to the control (set at 1.0). (h) Representative confocal images of the CMs grown on SA-CNTs after culturing for 7 days, and the CX43 (Green) showed a lateralized linear distribution. *p < 0.05. Scale bars: 50 μm (a–e, h), 10 μm (d, right panel). Reprinted from Ref. [181]. Copyright (2017), with permission from Wiley.

stimulation on adipose stem cells differentiation toward smooth muscle cells. The PPy-coated scaffold could promote proliferation of ASCs as well as expression of smooth muscle cell specific markers. Long pulse and short pulse biphasic electric current was applied to induce the ASC differentiation and they all could support expression of smooth muscle expression markers.

## 4. Mechanism of conductive biomaterials promote muscle tissue formation

The conductive biomaterials have been demonstrated to promote skeletal and cardiac muscle tissue formation by many studies. However, how the conductive biomaterials regulate these specific processes is still remaining to be investigated. To date, researchers only found that the conductive materials provide a specific charge of the cells, which can not happen in other non-conductive scaffolds. Furthermore, cellular behaviors, including cell attachment, cell proliferation and protein expression, can be influenced by the ion transfer and movement across the membrane due to the conducted charge-made local electrical fields inside the scaffolds [64].

A few of these studies investigated the mechanism of how conductive biomaterials help muscle tissue formation. Chaudhuri et al. [188] used the graphene oxide (GO)-poly(ε-caprolactone) (PCL) composite meshes to promote the myoblast differentiation. And they found that the conductive GO/PCL mesh could promote not only the myotube formation, but also the MyoD protein expression. By inhibition of Atk protein expression, the researchers demonstrated the conductive GO/PCL mesh could have effect on the insulin-like growth factor-1 (IGF-1) pathway which is related to the myotube formation and maturation. It has been reported that the Kir2.1- induced hyperpolarization could trigger the activation of calcineurin pathway, leading to the myoblast differentiation by inducing the expression/activation of myogenin and MEF2. Some researchers believed that the electroactive materials could somehow mediate the ion flow and affect the activation of calcineurin pathway, so that they can promote the myoblast differentiation [45,55].

For cardiac tissue formation, Sun et al. [187] found the CNTs-composite hydrogels could promote the intercalated disc assembly in the newly formed cardiac tissue. The β1-integrin-mediated FAK and RhoA signaling pathways are demonstrated to regulate the gap junction and mechanical junction formation. Conductive CNT/GelMA hydrogels could significantly increase the β1-integrin expression and further up-regulate the expression of *p*-FAK and RhoA. Inhibition of FAK pathway reducing the gap junction formation and inhibition of RhoA pathway would impair the mechanical junction formation. In Zhou et al.'s study [151], the GO in the materials could promote isolated cardiomyocytes connection by regulating the Wnt signaling pathway. GO could improve the expression of total Akt and the phosphorylation levels of GSK-3β, resulting in the β-catenin signaling activation and increasing the CX43 expression (Fig. 12).

## 5. Conclusion and outlook

Conductive biomaterials as matrix for muscle tissue engineering have been widely developed in recent years. Various conductive biomaterials were developed, including conductive polymers-, carbon nanomaterials- and metal nanomaterials-based biomaterials. Different forms of conductive biomaterials were fabricated. 2D nanofibrous conductive films could promote myocytes adhesion and proliferation. Conductive hydrogels mimic the native extracellular matrix best to provide 3D conductive environment for myoblasts or cardiomyocytes adhesion and differentiation. 3D scaffolds with porous structures and

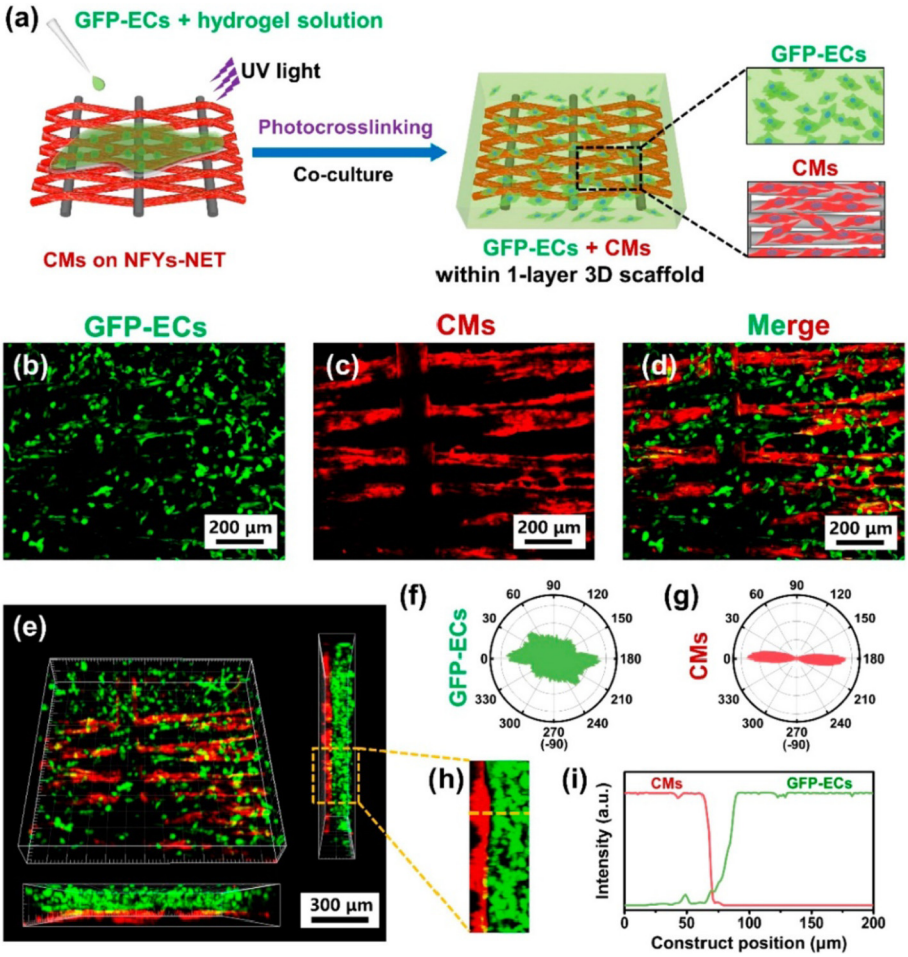


**Fig. 11.** Endothelialized myocardium was constructed based on the co-culture of cardiomyocytes and endothelial cells (ECs) in the 1-layer 3D scaffold. (a) Schematic diagram shows the co-culture process of CMs in NFYs-NET layer, and the hydrogel shell is loaded with GFP- positive endothelial cells (GFP-EC). Fluorescent images of (b) GFP-EC (green) and (c) CM (red) and (d) merged images. (e) Confocal images of GFP-EC and CM in scaffold in a 3D view and the quantitative results of cell orientation distribution of (f) GFP-ECs and (g) CMs. (h, i) Scaffolds' (with cells) cross section fluorescence intensity showing the distribution of ECs in the hydrogel and the distribution of CMs on NFYs-net. Reprinted from Ref. [60]. Copyright (2017), with permission from ACS Publication.

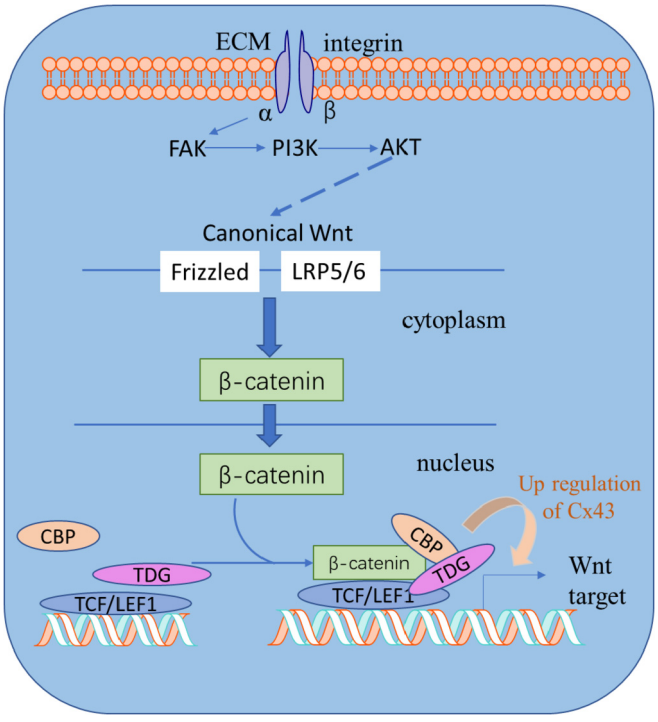


**Fig. 12.** A scheme of the possible mechanism of how conductive ECM affect the cardiomyocytes connection. Reprinted from Ref. [151]. Copyright (2018), with permission from Ivyspring International Publisher.

conductive nanowires or nanoparticles could not only support cell adhesion and differentiation, but also help to generate complicated structures of the newly formed tissues. Conductive polymers-based conductive biomaterials are with good processability and by using oligomers of conductive polymers, the problem of degradability could be solved. However, degradable conductive polymers with high conductivity are still needed to be investigated. Carbon nanomaterials-based conductive biomaterials showed good conductivity and the nanoscale structures help cell adhesion and tissue formation. However, the homogenously dispersion of carbon nanomaterials in the biomaterials is difficult and their non-degradability is another issue in their clinic application. Gold nanomaterials-based conductive biomaterials face the same problems.

As far as the authors concern, the combination of these three different conductive biomaterials to get new composite conductive biomaterials is a new direction to overcome the drawbacks of the present ones. Meanwhile, 3D conductive biomaterials with oriented structures would help the formation of complicated muscle tissue structures, which would be the new trend for the conductive biomaterial's fabrication. Hierarchical conductive scaffolds with nanoscale and micro-/macroscale structures that mimic the native tissue organization are more beneficial for muscle tissue regeneration. Another promising direction is the cell free conductive biomaterials. By modifying the conductive biomaterials with growth factors that may facilitate autologous stem/progenitor cell recruit at the aiming site, the cell free conductive biomaterials could help in vivo tissue formation via triggering the endogenic regeneration.

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