Review Article

Conductive biomaterials in cardiac tissue engineering

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Abstract: Conductive biomaterials (including conductive polymer, carbon-base materials, nanogold, and conductive silicon nanowires etc.) with prominent electrical conductivity, good cellular response, and promotion of cell-cell signaling transduction are possibly more suitable for cardiac tissue engineering. To date, their excellent properties catch more attention of the researchers to investigate their roles in life science research. Due to the limited therapeutic approaches of myocardial infarction (MI), engineered cardiac patches have received more attention in the treatment of MI. While, conductive biomaterial taken as a scaffold for cardiac tissue engineering is a promising strategy to repair infarct myocardium and improve the cardiac function. In this review, we summarized the fabrication of various conductive biomaterials for cardiac tissue engineering, and discuss the interaction between the conductive biomaterials and the cells [cardiomyocytes (CMs) and stem cells]. The advance of conductive biomaterials in tissue engineering, regenerative medicine and bio-sensing are also demonstrated.

Keywords: Conductive biomaterials; cardiac tissue engineering; myocardial infarction (MI); review

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Introduction

Heart is a strong power pump in human body owing to the myocardium consisting of tightly packed uniaxial cytoarchitecture and electrically conductive Purkinje fibers, which provide electrical conductive signal through the whole heart (1). Myocardial infarction (MI), which can lead to heart dysfunction and heart failure, is still one of the major causes of human death in the worldwide (2). Pathological change in MI such as cardiac infarct scar generation and cardiomyocytes (CMs) death through necrotic processes is always irreversible. More structural and functional changes in the heart lead to the formation of stiff ventricular wall, conductive disorders and reduced oxygen diffusion (2).

To date, the effect of thrombolytic therapy or coronary artery bypass grafts, widespread used to the treatment of MI, is still unsatisfied since adult CMs are terminally differentiated cells and have minimal intrinsic ability to self-regenerate (3). If there is no regeneration of new CMs, transplantation is a merely long-term treatment to cure end-stage heart failure. Besides of the above reasons, due to the limited source of heart donors and the challenge of the allograft rejection, heart transplantation is still not the most optimum selection in the therapy of MI (4). Today, researchers pay more attention on developing a new approach that can promote myocardial regeneration.

Cardiac tissue engineering is an emerging approach in cardiac regeneration research. The aim of cardiac tissue engineering is to develop a viable cellular harbor through utilizing excellently biocompatible materials and suitable biochemical factor for the seeded cells (CMs or stem cells) to improve or replace cardiac tissues, promote the regeneration of myocardium (5). Cardiac tissue engineering depended on the biomaterial scaffold and the therapeutic cells (CMs or cardiac progenitor cells)

are promising approaches for MI therapy (6-8). Electrical conductivity is a particular characteristic of the heart that is a key factor in structuring therapeutic biomaterials for cardiac repair. Engineered cardiac tissues, developed in electrically conductive nanomaterials, featuring biomimetic topographical cues have received more attention. Lots of conductive biomaterials used to be incorporated into cardiac scaffolds for restoring the disorder electrophysiological function of damaged heart. These conductive stuff include carbon-based nanomaterials [such as grapheme (9,10) and carbon nanotubes (CNTs) (11)], metal derived materials (such as gold nanoparticle) (12) and conductive polymers (such as polyaniline, polythiophene and polypyrrole) (13). As to the formation of engineered conductive cardiac tissue, the effective method employed for preparation of scaffolds using the conductive biomaterials is a key issue. To date, electrospinning and hydrogel fabrication are available methods to synthesize conductive cardiac scaffolds. In this review, we summarized the fabrication of various conductive biomaterials for cardiac tissue engineering, and the interaction between the cardiac cells and these biomaterials.

Fabrication of conductive cardiac scaffold

Electrospinning

Electrospinning technology is a facile method and has widely applied to fabricate nanofibrous-formed scaffolds using different polymers. Producing conductive nanoscale fibres require organic conductive polymers including polypyrrole (PPy), polyaniline (PANi), polythiophenes and poly (para-phenylene vinylene). Li *et al.* had incorporated conductive camphorsulfonic acid-doped emeraldine PANi (C-PANi) with gelatin to fabricate the electrospun fibers. The PANi could increase homogeneous electrospun fibers and regulate the fiber size in the fibrous scaffolds. Tensile modulus of this submicron-sized fibrous scaffold can be regulated depended on the concentration of the C-PANi. After being crosslinked with EDC, the electrospun C-PANi-gelatin blend fibers seeded with rat cardiac myoblast H9c2 showed excellent cell elongation and proliferation (14). Ravichandran *et al.* had developed the gold nanoparticles (AuNPs) loaded BSA/PVA nanofibrous scaffolds to study the functional activity of bone-marrow derived mesenchymal stem cells (MSCs). They found that the MSCs could differentiated into cardiomyocyte-like cells on AuNPs-embedded nanofibers, which exhibited multinucleated morphology and cardiac-related protein expression, such as actinin, Troponin-T and Cx43 (15). To endow the electrical conductivity to the electrospun patches, a mass of CNTs (6%) was electrospun into fibers. For instance, blend and coaxial electrospinning was utilized to fabricated line up PELA fibers with CNTs. The CNTs integrate-fibers could sustain the cell viabilities, promote the cell elongation, as well as the expression of contractile proteins, and promote the synchronous beating behaviors of CMs (16,17). Recently, Wang *et al.* had blend PANI into PLA polymer to prepare PLA/PANI conductive nanofibrous sheets and found that the sheets with homogeneous conductive nanofiber could promote cardiac cell viability and maturation, and even generate functionalized CMs-based bio-actuators (18).

Hydrogel-based conductive biomaterials

The hydrogel can provide a certain mechanical property and a swollen 3D environment with a high water content, adequate diffusion of nutrients through its network (19). Conductive biomaterials incorporated into hydrogel networks have allowed to create electrical conductive hydrogels. Poly(ethylene glycol)-dimethacrylate (PEG-DMA) derived consistent PEG nanopillars hydrogels with a novel 3D guiding construction, via a simple Ultraviolet-assisted capillary molding technique, could induce the proliferation of CMs and maintain their conductive properties (20). CNTs based gelatin methacrylate (GelMA) hydrogel could simultaneously address the beneficial properties of organic porous scaffolds, such as biocompatibility, biodegradability high porosity, and high electrical conductivity. The CNTs can lead to widespread nanofiber crisscrossed in the porous GelMA scaffold and promoted cell spreading and elongation. A photocrosslinkable derivative (GelMA) could be served as protective cardiac scaffolds through preventing or reducing cardiac tissues damages (21). A biocompatible gel composite formed by multi-walled CNT-dispersed sheet and an aqueous polyrotaxane-based gel with cyclodextrin/polyethylene as crosslinker could be taken as a gel electrode for epicardial electrocardiography (22).

The Engineered cardiac tissues based on conductive biomaterials could recover heart function after MI via integrated with damage heart, effectively inhibited the further deterioration of the infarcted heart (23). Mihic *et al.* conjugated the conductive polypyrrole (PPy) onto chitosan side chains to generate an electrically conductive PPy-chitosan hydrogel and the formed conductive hydrogel could coordinate myocyte function ex vivo, and leads to significantly improved heart function when injected into

rat hearts after MI (24). Our group had also introduced a mussel-inspired dopamine as a crosslinker to produce a PPY-based conductive GelMA/PEGDA cryogel. It is interesting that the conductive Ppy nanoparticles could remove onto the CMs cytomembrane from the cryogel. The developed PPY-based conductive GelMA/PEGDA cryogel was confirmed to improve cardiac repair and function *in vivo* (25).

The graphene oxide (GO) nanoparticles derived conductive and elastomeric MeTro/GO hybrid hydrogels was reported to bear more strong cyclic tensile and torsional forces. Through a two-step process, a light-sensitive, highly elastomeric, conductive and injectable scaffold with homogeneous spreading of GO was obtained. This MeTro/GO hybrid hydrogels could support CMs growth and function (26). Bao *et al.* had developed a PEG-MEL/HA-SH/GO hydrogel by simple mix with PEG-MEL (a cross-linker), thiol-modified hyaluronic acid and GO. This soft (storage modulus =25 Pa) and anti-fatigue hydrogel with appropriate conductive property via easy synthesis process could be a promising scaffold for cardiac tissue engineering. As a result, the adipose tissue-derived stromal cells (ADSCs)-encapsulated hydrogel could increase the ejection fraction, reduce the scar generation, and enhance higher neovascularization (27).

Poly(thiophene-3-acetic acid) (PTAA), one kind of derivatives of conductive polythiophene, is easy to form cross-linked network hydrogel due to its carboxyl groups in the backbone. The conductive PTAA photocrosslinking with methacrylated aminated gelatin (MAAG) via Irgacure 2959 addition and exposure to UV light for 15 min endowed the well-proportioned PTAA/MAAG-based hydrogel with conductive properties and excellent biocompatibility *in vitro* and *in vivo*, which meet the essential requirement for cardiac repair (28). With similar synthesis approach, the gold nanorod (GNR) incorporated into gelatin methacrylate (GelMA) hydrogels via photosynthesis also could form an excellent biocompatible cardiac patch (29).

The thickness of the human myocardium is up to 2 cm and the sufficient nutrients and oxygen support is essential to the thick tissues. The oxygen support in the core of scaffold is the key issue in construction of engineering heart tissue. Attributable to the porous property of electrospun membranes, the cardiac patches could be assembled layer-by-layer up to five layers without inward hypoxia (30). Aligned electrospun nanofibers can mimic the anisotropic organization of cardiac tissue and their excellent mechanical properties were benefited to the maturation of myocardial cells (31). Wu *et al.* had encapsulated electrospun conductive nanofiber yarns network (NFYs-NET) into hydrogel shell to fabricate anisotropic and endothelialized 3D multilayer cardiac tissues. The interwoven conductive aligned NFYs-NET structures can induce aligned and elongated CMs maturation, and the GelMA hydrogel shell that can provide a suitable 3D microenvironment (32).

Application of conductive biomaterials

Interactions between the cardiac cells and conductive biomaterials

The conductive biomaterials including carbon-based (33) and gold-based (29) nanomaterials, conducting polymers (34,35) were introduced into the fabrication of cardiac scaffold. The conductive scaffolds could indeed upregulate the expression of the cardiomyocyte specific markers, including cTnT/cTnI, connexin 43 and sarcomeric, leading to the enhanced CMs functionalization and excellent synchronous contraction (29,33).

To investigate the behavior of the CMs on a conductive scaffold and the potential of conductive biomaterials to improve function of CMs, chitosan doped with carbon nanofibers (36) and CNTs embedded with the Poly (lactic-co-glycolic acid) scaffolds (37), were used to be taken as scaffolds and were seeded the CMs on them. Interestingly, the CMs seeded on a conductive biomaterial-combined scaffold not only exhibited a synchronous beating behavior but increased levels of the proteins related to cardiac contraction and electrical coupling. Wang *et al.* demonstrated that the conductive biomaterials (Ppy) can be observed on the cytomembrane surface of the CMs which indicate that conductive biomaterial may enhance function of CMs through spontaneously intimate contact with them (34). The cardiomyocyte-seeded CNTs integrate-fibers patch could electrically contract nearby 270 beats/min, which was similar to the physiologic rates of rats (17). Taken together, the above studies demonstrated that conductive biomaterials not only promote expression of Cx43 protein, but evoked spontaneous synchronous beating of the bionic cardiac tissue and can be taken for developing promising scaffold for the cardiac tissue engineering.

Interactions between the stem cells and the conductive biomaterials

Stem cells play a vital role in the repair and regeneration of injured myocardium, and different stem cell types,

including mesenchymal stem cells (MSCs), embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and cardiac stem cells (CSCs), have achieved remarkable effects in myocardial regeneration (38-42). A mountain of work demonstrated that stem cells have potential capability to restore the CMs, and stimulate neovascularization in the infarcted area, which may enhance myocardial perfusion and contractile functionality in the injured heart (43).

A growing number of studies indicate that the cell-fate determination of stem cells can be regulated by the specific microenvironment (44). Constructing specific microenvironment with conductive materials (conducting polymers, gold-based or carbon-based biomaterials etc.) can guide stem cells differentiating into electroactive lineages and enhance the capabilities of stem cells in electroactive tissue regeneration (45).

The combination of stem cell with a supportive conductive scaffold is a promising approach to construct cardiac tissue engineering. The fate of stem cells cocultured with conductive biomaterials *in vivo* could be controlled by enhancing the electrical conductivity of the matrix since the great electrical conductivity and biocompatibility of conductive biomaterials (46).

In MI area, TGFβ1 overexpression resulted in atrial fibrosis, which limits the adhesion of CMs and progenitor stem cells (47). An *in vitro* study showed that the Poly (N-isopropylacrylamide) (PNIPAAm) hydrogel modified with single-wall carbon nanotubes (SWCNTs) encapsulated BASCs significantly promoted cell adhesion and proliferation compared with PNIPAAm hydrogel. Also the PNIPAAm/SWCNTs hydrogel significantly enhanced the retention of BASCs in infarct myocardium and achieved therapeutic efficacies in MI (48).

Recent studies have demonstrated that simply culturing MSCs on the graphene monolayers, the cardiomyogenic differentiation in MSCs could be observed (49). The poor survival of CMs or cardiac progenitor cells in the MI area is possibly due to the generation of reactive oxygen species (ROS). After MSCs were combined with GO flakes, their survival rate improved significantly due to the protection to the seeded cells of GO from ROS. To sum up conductive biomaterial may protect the implanted stem cells from ROS-mediated death and thereby improve the function of the stem cells in cardiac repair (50).

Furthermore, addition of electrically conductive silicon nanowires (e-SiNWs) effectively stimulated the cellular maturation of hiPSC-CMs and enhanced the functions of the cardiac spheroids (51). The hMSC committed differentiation could be more easily observed by culturing in excellently conductive, CNT-integrated scaffolds in the presence of myocardia inducing medium 5-azacytidine compare to the hMSC only culture in the 2D plate in the presence of 5-azacytidine (52).

Application of conductive biomaterials in vivo

Following the observations above, conductive biomaterials have also been studied the function in cardiac injured animal. In a mouse model of MI, implanting hybrid rGO-hMSC spheroids more enhanced cardiac repair and function than either rGO or hMSCs group. Additionally, echocardiographic parameters showed significantly improvement of cardiac function (10 folds higher in ejection fraction (EF) than PBS group) through injection of hybrid rGO-MSC spheroids (53).

A significant upgrading of ventricular function, such as significantly increase of EF, smaller scar area, and higher blood supply, was achieved by injecting pi-pi conjugation-containing PEG-MEL/HA-SH/GO hydrogel into the MI rats (27). Similarly, Zhou *et al.* demonstrated that more myocardium and neovascular can be observed in the conductive biomaterial implanted-heart compare to the MI rats via tissue section staining (23).

Conductive biomaterials in diagnosis of the cardiac disease

Biomarkers have played an important role in rapid diagnosis and accurate diagnosis of myocardial injury (54,55). Cardiac markers are protein molecules increased from damaged heart muscle that can be detect in the blood (56). Various type of cardiac markers within the blood include the following: cardiac troponins (cTnI and cTnT), C-reactive proteins (CRP), creatine kinase-MB (CK-MB), creatine kinase MM (CK-MM), myoglobin (Myo) and etc. (57).

Due to the advantage of the conductive biomaterial, which can perform electron-transfer activities and improve the sensitivity of electrochemical detection, researcher focus on using conductive biomaterial as a sensor for cardiac biomarkers detection (58). Buch *et al.* (59) applied multi-walled CNTs/screenprinted carbon electrodes (MWCNTs/SPE), modified with polyethylenimine and glutaraldehyde, bonding with the anti-CRP to develop a bio-sensing electrode for measuring concentrations of CRP biomarker in blood serum. In another research, a nanoscale immunosensor based on a conductive polyethyleneimine film combined with CNTs was structured for sensitive detection of cardiac Troponin T (cTnT), the most sensitive and specific cardiac

marker for myocardial damage. The immunosensor which is able to detect a low concentration (0.033 ng/mL) of cTnT in serum is significantly suitable for acute MI diagnosis (60).

Prospection

The key to take advantage of conductive biomaterials is the appropriate and effective method to fabricate the conductive scaffold. An ideal conductive scaffold should be able to promote the adhesion and the bio-function of seeded cells (such as synchronous contraction ability of CMs, differentiation of CSCs) with simple-stepped and effective method. We have reviewed that electrospinning and hydrogel fabrication were used to develop the proper microenvironment for cardiac engineering. Otherwise self-assembly and 3D print nanotechnology also provide a window to structure functional organoids and complex 3D tissues. Electrical conductivity of biomaterials has been designed to mimic the native properties of the heart as well as promote the cardiac marker expression of CMs and enhance differentiation to cardiomyocyte-like cells in stem cells.

Additionally, the electrical conductivity of these biomaterials is expected to stimulate the adhesion, spreading, and proliferation of electrical related cells such as CMs as well as enhance the interaction between cells. However, utilize conductive biomaterials to properly mimic the electrical conductivity of the native heart is still a challenge. Future studies are expected to focus on regulation of the behavior of the seeded cells on the conductive scaffold by applying conductive biomaterials. Using conductive biomaterials to improve the cellular response and cell-cell signaling transduction as well as enhance the enhanced CMs/stem cells functionalization in scaffold can lead to the optimization of cardiac tissue engineering for regeneration medicine and clinical application.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/biotarget.2017.08.01). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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