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Review

# Recent Advances in Cardiac Patches: Materials, Preparations, and Properties

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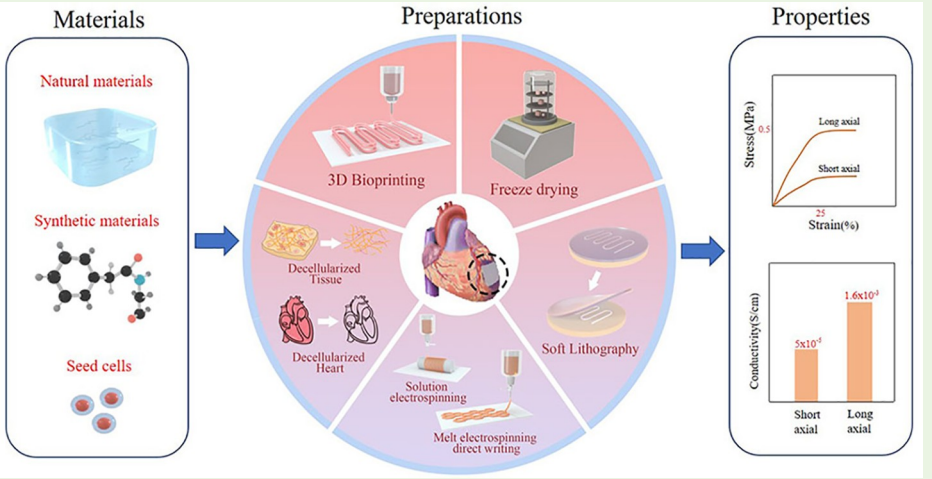


**ABSTRACT:** Cardiac patches are biomaterials that can be used for transplantation and repair of damaged myocardium by combining seed cells with the ability to form cardiomyocytes and suitable scaffold materials. On the one hand, they provide temporary support to the infarcted area, and on the other hand, they repair the damaged myocardium by delivering cells or bioactive factors to integrate with the host, which have gradually become a hot research topic in recent years. This paper summarizes the structural properties of natural myocardium and reviews the recent research progress of cardiac patches, including the seed cells and scaffold materials used in patch preparation, as well as the main methods of scaffold preparation and the structure properties of various scaffolds. In addition, a comprehensive analysis of the problems faced in the clinical implementation of cardiac patches is presented. Finally, we look forward to the development of cardiac patches and point out that precisely tunable anisotropic tissue engineering scaffolds close to natural myocardial tissue will become an important direction for future research.

**KEYWORDS:** *cardiac patch, myocardial infarction, scaffold materials, scaffold preparation method, anisotropy*

## 1. INTRODUCTION

Despite the great progress made by mankind in the past half century in the prevention and treatment of various cardiovascular complications, heart disease still has a high morbidity and mortality rate worldwide, especially in developed countries.[1] Myocardial infarction (MI) is a common cardiovascular disease, which is caused by the lack of oxygen and nutrients in the myocardium due to the obstruction of one or more coronary arteries, resulting in the death of cardiomyocytes (CMs).[2] Myocardial cells have a limited regenerative capacity and cannot repair themselves. The necrotic myocardial cells can only be replaced by fibroblasts and thus form fibrous scar tissue, which leads to loss of contractility in the infarcted area and ultimately to arrhythmias and subsequent heart failure.[3] Currently, heart transplantation is the only treatment option for end-stage heart failure, but this is out of reach for most patients due to a shortage of organ donors. Therefore, new approaches need to be developed to regenerate damaged myocardium and prevent end-stage heart failure.[4]

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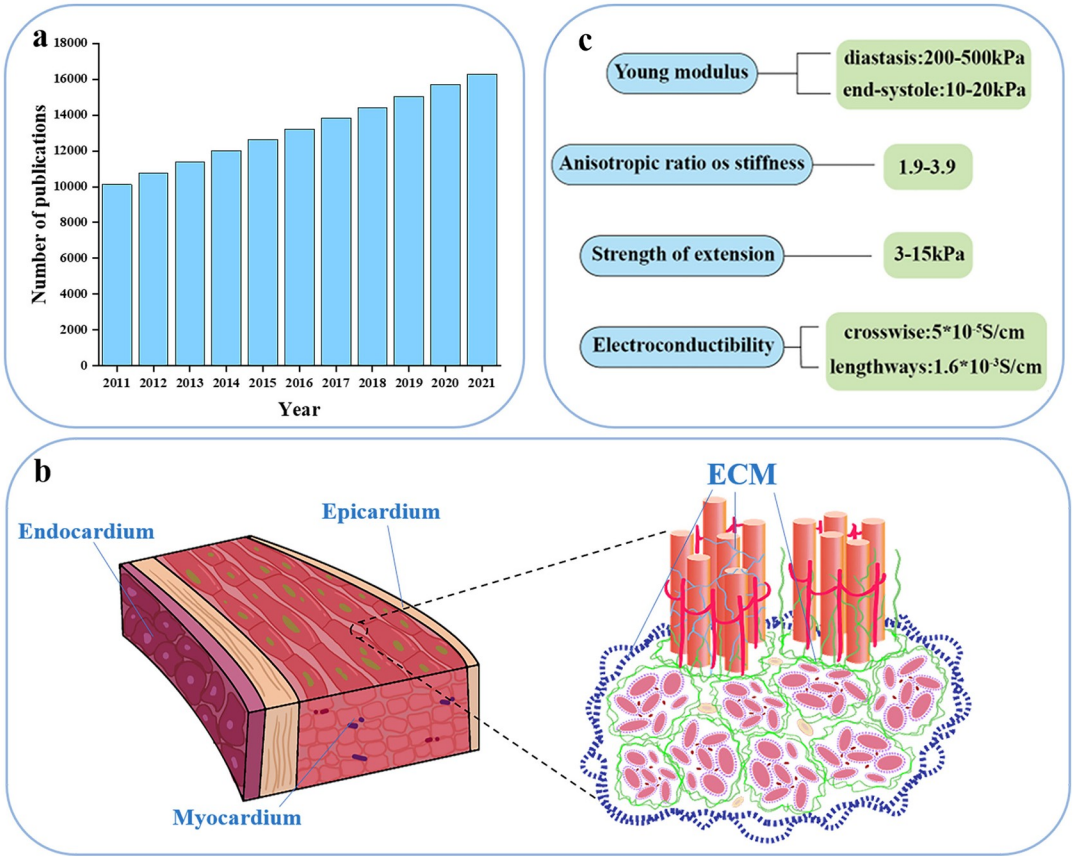


**Figure 1.** (a) Number of publications with the keyword "cardiac patch" in the last 10 years (data source: Web of Science). (b) Natural myocardium microstructure. Left figure adapted from ref 9. Copyright 2020 The Authors. Right figure adapted with permission from ref 10. Copyright 2013 Elsevier. (c) Mechanical and conductive property parameters.[11−13]

Stem cell therapy is currently favored because stem cell transplantation produces paracrine effects and can improve ejection fraction after myocardial infarction,[5] but due to the inflammatory and ischemic environment of the infarcted area, cell survival is low if direct injection is used, thus affecting the therapeutic effect. Tissue engineering (TE) is a multidisciplinary combination of biomaterials, engineering, medicine, and cell biology and is the most promising biotechnology of the 21st century.[6] TE technology consists of three factors: biomaterial scaffold, seed cells, and growth factors. The use of cardiac patches for the treatment and repair of damaged or diseased myocardium is an emerging approach.[7] On the one hand, a biomaterial scaffold similar to extracellular matrix (ECM) can provide temporary mechanical support to the myocardium and limit post-infarct ventricular dilation. On the other hand, it can load bioactive loads such as cells, growth factors, and drugs and deliver them to the infarcted region.[8]

The number of articles published on "cardiac patches" in the last 10 years is shown in Figure 1a. The initial number of 10,135 articles has increased continuously to about 16,284 articles, an increase of nearly 60%, which shows that researchers are paying more attention to cardiac patches. In this Review, we start with natural myocardial structure characteristics, summarize the materials and preparation methods of patch scaffolds, analyze and compare the relationship between structure and performance, review the current research progress of cardiac patches, and point out that precisely tunable anisotropic tissue engineering scaffolds close to natural myocardial tissue will become an important direction for future research.

## 2. STRUCTURAL COMPOSITION AND PROPERTIES OF NATURAL MYOCARDIUM AND EXTRACELLULAR MATRIX

The natural heart is mainly composed of endocardium, epicardium, and myocardium (Figure 1b, left). CMs are the most important functional unit of the myocardium, controlling the contraction and diastole of the heart by conducting electrical signals. CMs account for approximately 75% of the total volume fraction and 33% of the total cell count of the human heart. The main non-myocyte resident cells are endothelial cells (ECs), fibroblasts, pericytes, and resident immune cells (macrophages and a small number of B cells and T cells), etc. ECs account for about 60% of the non-myocyte population, followed by fibroblasts (about 15%). ECs and fibroblasts also play a key role in maintaining the dynamic homeostasis of the heart. ECs form a complex network of capillaries that provide nutrients to the tissues. Fibroblasts produce ECMs that provide structural support and positioning for the tissues.[14−16]

ECM plays a key role in establishing tissue architecture and maintaining the balance of the internal environment from cell to cell or from ECM to cell.[17] Collagen fibers are the main component of the extracellular matrix of the heart and account for approximately 70% of the ECM of the adult heart.[18] There are three main types of collagen fibers that function throughout


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Table 1. Classification and Characteristics of Patch Materials[a]

| | Patch materials | | Characteristics | References |
|---|---|---|---|---|
| Seed cells | ESCs | | Infinite proliferation in vitro, multidirectional differentiation, ethically controversial, morphology of adult cardiomyocytes | 25, 49 |
| | MSCs | | Nonimmune rejection, multidirectional differentiation, high proliferation ability, promotes angiogenesis, low efficiency of differentiation to cardiomyocytes | 28−30 |
| | iPSCs | | Self-renewal, multidirectional differentiation, no immune rejection, no ethical restrictions, tumorigenic risk, functional cardiomyocytes but immature | 31−33 |
| | ADSCs | | Multidirectional differentiation, wide range of sources, insignificant differentiation | 35 |
| Natural materials | Protein | Collagen | Biocompatibility, biodegradable | 39 |
| | | Fibronectin | Biocompatibility, easy cell adhesion, low immune rejection | 29, 42 |
| | | Gelatin | Biocompatibility, good cardiomyocyte adhesion, poor mechanical strength | 43, 44 |
| | | Silk fibroin | Biocompatibility, biodegradable, flexibility, and toughness | 46−48 |
| | Polysaccharide | Chitosan | Biocompatibility, nontoxic, antibacterial, good mechanical properties | 30, 50 |
| | | Alginates | Biocompatibility, easy film formation, low toxicity | 51−53 |
| | | Hyaluronic acid | Biocompatibility, biodegradable, promotes cell proliferation and differentiation | 54, 55 |
| Synthetic materials | Polyester | PGS | Biocompatibility, heat resistance, high elasticity | 56−58 |
| | | PCL | Biocompatibility, mechanical properties, biodegradable, nontoxic | 59, 60 |
| | | PLCL | Good mechanical strength and elasticity, biodegradable | 31, 61 |
| | Polyol | PEG | Antibacterial, water solubility, chemically stable, nontoxic | 62, 63 |
| | | PVA | Chemically stable, nontoxic, easy to form film, good flexibility | 32, 64 |
| | Polyacid | PLA | Biocompatibility, biodegradable, low immunogenicity | 65 |
| | | PLGA | Biocompatibility, high mechanical strength, nontoxic, biodegradable | 66, 67 |

[a]ESCs, embryonic stem cells; MSCs, mesenchymal stem cells; iPSCs, induced pluripotent stem cells; ADSCs, adipose stem cells; PGS, polyglycerol sebacate; PCL, polycaprolactone; PLCL, polypropylene-*co*-*ε*-caprolactone; PEG, polyethylene glycol; PVA, poly(vinyl alcohol); PLA, polylactic acid; PLGA, polylactic acid-glycolic acid.

the myocardium, on bundles of cells, and on individual cells (Figure 1b, right). Epimysial fibers (a few microns) tightly wrap around the entire myocardium and provide external support. Perimysial fibers (~1 $\mu$m) are wavy, are parallel to the long axis of the cell and surround the cell bundle, and are responsible for the contraction of the cell bundle. Endomysial fibers (20−100 nm) wrap around individual CMs, providing mechanical support and guiding their alignment.[10,19] The basement membrane accounts for approximately 20% of the cardiac extracellular matrix and is composed mainly of type IV collagen, but it also has small amounts of aggrecan, polysaccharides, laminin, and nidogen. The structural ECM accounts for 4% of the cardiac ECM and consists mainly of fibrillar glycoproteins and proteoglycans, which play a key role in maintaining the propagation of action potentials generated by pacing cells. In addition, stromal cell components account for approximately 3% of the cardiac ECM and mainly include dermal bridge proteins, periplasmic proteins, emic protein 1, fibrinogenic protein 5, lumican, fibrinogen activator and thrombospondin-2, type VI collagen, and fibronectin.[20]

The complex structural composition of the ECM and the dynamic activity of the cells result in highly variable mechanical properties of the myocardium during a single cycle. It was found that Young's modulus of human myocardium is about 200−500 kPa at end-diastole, about 10−20 kPa at end-systole, and about 3−15 kPa at tensile strength.[12] In addition, myocardium exhibits anisotropic mechanical properties consistent with cell and fiber orientation, and it is stiffer in the circumferential (transverse) direction than in the longitudinal direction (Figure 1c).[13] Cardiac myocytes are short columnar in shape with intercalated discs or gap junction links at the long axis end, which are easier for ionic currents to pass through, while intercellular membrane connections in the short axis direction are sparse and have higher impedance, making it more difficult for ionic currents to pass through, thus leading to anisotropy in myocardial electrical conductivity.[21] The transverse conductivity of natural myocardium is about $5 \times 10^{-5}$ S/cm, and the longitudinal conductivity is about $1.6 \times 10^{-3}$ S/cm.[11] Therefore, the preparation of cardiac patches should take full account of myocardial anisotropy; otherwise, it may lead to increased electrical heterogeneity, which may cause rhythm disturbances.[22] In addition, since cardiac activity is a constant systolic−diastolic process, elasticity should also be a key factor to consider when designing the patch.

## 3. MATERIALS FOR CARDIAC PATCHES

Cardiac patches are mainly composed of seed cells, scaffolds, and other components. Seed cells are generally derived from embryos or subject to induced differentiation. Scaffold components are more complex but can be broadly classified into natural and synthetic scaffolds. The classification of patch materials is shown in Table 1.

**3.1. Cell Source.** Cardiomyocytes are unable to heal themselves by proliferation due to their high degree of differentiation. Seed cells replenish damaged cells and can secrete cytokines. These cytokines improve the biological environment after myocardial infarction and allow repair of the damaged area. The seed cells that are commonly used to obtain cardiomyocytes are generally derived from embryonic stem cells, mesenchymal stem cells, induced pluripotent stem cells, adipose stem cells, etc.

*3.1.1. Embryonic Stem Cells (ESCs).* ESCs are generally isolated from early embryos, can proliferate indefinitely *in vitro*, and can differentiate into cells of all three germ layers of the embryo. Human-ESC-derived cardiomyocytes exhibit a morphology of adult cardiomyocytes expressing myosin.[23,24] Ghazizadeh et al.[25] induced differentiation of ESCs, trans-


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planted them to a mouse infarct model, and subsequently detected myocardial-specific ALCAM protein and a significant increase in ventricular thickness after a period of time, indicating that ESCs differentiated into ISL1+ myocardial progenitor cells and repaired the myocardium. ESCs have a differentiation potential unmatched by other stem cells and are a good choice as seed cells for myocardial repair, but ethical issues and tumorigenic potential have limited their depth of investigation. Researchers therefore have had to look for alternative sources of replacement cells.

*3.1.2. Mesenchymal Stem Cells (MSCs).* MSCs are mainly found in the mesoderm and ectoderm, can be multiply differentiated, and have high proliferative capacity and low immunogenicity, and autologous transplantation can promote neovascularization. Compared to ESCs, such cells are of broader origin, including but not limited to bone marrow, placenta, heart, umbilical cord, peripheral blood, and adipose tissue, and have no ethical restrictions.[26,27] Rou et al.[28] treated MSCs with cell growth factor and transforming growth factor and showed accelerated gene expression and production of spindle-shaped myotubes, suggesting that MSCs can be converted to cardiomyocytes by growth factors and can promote myocardial repair. Studies have also been performed using fibronectin[29] and chitosan[30] to make cardiac patches with MSCs, and both showed that the patches promoted myocardial repair. Numerous studies have demonstrated the ability of MSCs as seed cells for myocardial repair, but the differentiation of MSCs to cardiomyocytes *in vivo* is less efficient. To address this, the best option is to induce MSC differentiation *in vitro* after maturation for transplantation.

*3.1.3. Induced Pluripotent Stem Cells (iPSCs).* iPSCs are obtained by reprogramming exogenous genes introduced into adult somatic cells and have properties similar to ESCs, namely, the ability to self-renew and differentiate into multiple cells. iPSC-derived cardiomyocytes have the actual characteristics of cardiac cells, such as contraction, spontaneous beating, and ion channel expression, but the cardiomyocytes are in an immature state.[23,24] It has been found that iPSCs can be made into patches with various materials such as PLCL[31] and PVA,[32] and the cells can grow normally on the scaffold and can promote myocardial repair. It has also been noted that cardiac fibroblasts (CFs) can be induced into iPSCs and that iPSCs of this origin are more favorable for differentiation into cardiomyocytes.[33] iPSCs can be obtained by induction of patient autologous somatic cells for personalized therapy based on the patient's genetic architecture, which avoids immune rejection and has no ethical restrictions. However, the process of induced differentiation has the potential to be tumorigenic, and mature techniques are needed to guide their directed differentiation to cardiomyocytes.

*3.1.4. Adipose Stem Cells (ADSCs).* ADSCs are stem cells isolated from adipose tissue that are capable of multidirectional differentiation and can proliferate stably *in vitro*.[34] It has been found that injection of ADSCs in patients with acute infarction reduced infarct size and myocardial fibrosis and that SIRT1 gene expression in ADSCs induced angiogenesis and reduced inflammation.[35] The advantages of ADSCs over other stem cells are their easy accessibility and lower cost, but their differentiation is not obvious and long-term cell transplantation is poor.

**3.2. Natural Materials.** Materials for natural scaffolds are generally derived from natural biological tissues, have excellent biocompatibility, and are close to the extracellular matrix environment.[36] Natural polymers used to prepare scaffolds can be mainly classified as protein based and polysaccharide based.

*3.2.1. Protein Based.* Collagen is essentially a protein and is derived from ECM, making it an ideal material for tissue engineering. There are various types of collagen fibers. The most commonly used is collagen fiber type I, which is biocompatible and easy to degrade and provides a good extracellular environment.[37,38] Zhang et al.[39] transplanted type I collagen hydrogel loaded with 7-amino acid peptide (7A) into the infarcted area of the left ventricle. After 2 weeks, attenuated wall fibrosis and reduced wall thinning were found in the infarct area, indicating that the scaffold promoted the formation of neovascularization and reduced apoptosis.

Fibronectin is a class of water-insoluble proteins, which can constitute a cytoskeleton. It is an integral part of the ECM and is biocompatible.[38,40] One study has developed a cardiac patch based on a fibrin composite layer that improves cell orientation and contributes to cell contraction and regeneration of damaged myocardium.[41] By extracting fibrin from the patient's blood, immune rejection can be reduced and the viability of proliferating cells can be improved.[42]

Gelatin and collagen come from the same source, both are proteins from the animal body, and gelatin is obtained through the hydrolysis of collagen. It can improve the adhesion and survival of cardiomyocytes, but the mechanical strength is poor and the mechanical properties are generally enhanced by cross-linking treatment or compounding with synthetic polymers.[43,44] He et al.[45] prepared GelMA−PCL conductive nanofiber membranes containing polypyrrole (PPy) particles by electrospinning using methylacrylylated gelatin (GelMA) obtained by cross-linking. *In vitro* cultures showed good synchronous contraction, and *in vivo* transplantation showed reduced infarct size, increased short-axis shortening of the left ventricle, and increased neovascularization.

Silk fibroin (SF) is derived from silk, which is biocompatible and has excellent degradability. It has a certain elasticity and toughness and can withstand the effect of stress caused by myocardial contraction.[46−48] Dong et al.[47] prepared an ECM/SF composite scaffold using ECM and silk fibroin. Subsequently, gold nanoparticles (Au NPs) and MSCs were distributed into the scaffold to prepare a conductive cardiac patch. The results showed that the patch promoted the proliferation and adhesion of cardiomyocytes, and an increase in ventricular thickness and a decrease in infarct rate were found in mice after transplantation.

*3.2.2. Polysaccharide Based.* Chitosan is derived from mussel shells and is a class of amino polysaccharides. It is nontoxic, has good biocompatibility and mechanical properties, and has antibacterial and cell-repair promoting effects.[68] Baei et al.[30] prepared porous conductive thermosensitive hydrogels using gold nanoparticles (GNPs) and chitosan and inoculated human MSCs onto the hydrogels. After 14 days of incubation, it was found that chitosan hydrogels doped with GNPs resulted in enhanced differentiation of MSCs toward the myocardium compared to chitosan hydrogels alone and that this hydrogel supported cell metabolism.

Alginate is a natural polysaccharide that forms the cell membrane of brown algae. Alginate has a similar structure to extracellular matrix and excellent mechanical and gel properties. After purification, alginate has low toxicity and has broad application prospects.[51] Levit et al.[52] transplanted alginate hydrogels encapsulated with hMSCs into rats with myocardial infarction and showed significant improvement in cardiac


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function with increased ejection fraction and microvessel density and reduced infarct size after 28 days. In addition, to enhance the electrical conductivity of sodium alginate hydrogels, a study added carbon nanofibers (CNFs) to a mixture of sodium alginate and gelatin hydrogels, and the scaffolds prepared had improved electrical conductivity and mechanical properties.[53]

Hyaluronic acid is an acidic polysaccharide that can be derived from animal tissues or obtained by microbial fermentation. It is biodegradable, is biocompatible, and promotes the proliferation and differentiation of cardiomyocytes.[54,55] Gaetani et al.[69] prepared a composite scaffold of hyaluronic acid and gelatin loaded with human cardiac-derived progenitor cells (hCMPCs) to make a cardiac patch. Increased myocardial and vascular markers and a significant reduction in left ventricular remodeling were found after transplantation of the patch into the infarcted region. This suggests that the cardiac patch enhances cell adhesion and survival and improves cardiac function after myocardial infarction.

Cardiac patches made of natural materials have good biocompatibility and easily provide a suitable growth environment for cells, and they help a lot in the reconstruction of cells at the damaged site. However, these natural material scaffolds have a fast degradation rate, low mechanical strength, and poor toughness and are prone to failure with the beating of the heart. To improve their use in the field of cardiac repair, researchers should focus on regulating the properties of scaffolds such as mechanical strength and elasticity, as well as their degradation rate.

**3.3. Synthetic Materials.** Polymeric materials are widely used in the field of tissue engineering due to their low cost, easy synthesis, stable structure, and controlled degradation rate. Synthetic material patches can be classified as polyester, polyol, polyacid, etc., according to the type of matrix.

*3.3.1. Polyester Substrates.* Polyglycerol sebacate (PGS) has the advantages of good biocompatibility, good heat resistance, and high elasticity.[56] It has been found that the honeycomb PGS scaffold helps to solve the problem of mismatch between scaffold structure and myocardium, and the honeycomb scaffold is morphologically stable and close to the natural myocardium, which helps the repair of myocardial tissue.[57] To improve the electrical conductivity and mechanical properties of PGS scaffolds, carbon nanotubes can be added to the matrix material.[58]

Polycaprolactone (PCL) has been widely used in the field of tissue engineering because of its good biocompatibility and mechanical properties, degradability and nontoxic products, and its ability to be applied in drug release.[70] Jana et al.[59] prepared PCL scaffolds with different concentrations and grew porcine valvular interstitial cells (PVICs). The PCL scaffolds with a concentration of 14 wt % were found to have the highest number of infiltrating cells and the best adhesion with low inflammatory response after 14 days of culture, indicating that PCL scaffolds contribute to the regeneration of myocardial tissue.

Polypropylene-*co*-ε-caprolactone (PLCL) has good mechanical strength and elasticity, is degradable, and can be used as a tissue engineering scaffold material when combined with biocompatible materials.[61] Sugiura et al.[31] used 50:50 PLCL and polyglycolic acid (PGA) to make degradable scaffolds and grow human-induced pluripotent-stem-cell-derived cardiomyocytes (hiPSCs-CMs), followed by transplantation of the patches to the infarct site in mice, and after 16 weeks of culture, expression of myocardial-specific proteins was found to be increasing, which promoted the proliferation of cardiomyocytes.

*3.3.2. Polyol Substrates.* Polyethylene glycol (PEG) is nontoxic and has hemostatic and antibacterial properties, and it is water-soluble and chemically stable.[62] It was found that $Ti_3C_2T_x$ MXene imprinted onto PEG hydrogels by spray printing (AJP) produced composite hydrogels with good electrical conductivity and promoted the alignment and proliferation of iPSCs-CMs.[63]

Poly(vinyl alcohol) (PVA) is chemically stable, is nontoxic, and has good film-forming ability, which can improve the overall mechanical strength as a tissue engineering scaffold material.[64] Dattola et al.[32] prepared a porous scaffold using PVA, and after 12 days of growing hiPSCs onto the scaffold, the results were found to show that the scaffold promotes cell differentiation and maturation.

*3.3.3. Polyacid Substrates.* Polylactic acid (PLA) is biocompatible, degradable, and nontoxic and has low immunogenicity, so it can be used for tissue engineering scaffolds.[71] Ren et al.[65] constructed cardiac patch scaffolds with silk protein and polylactic acid (SF/PLA) and surface-functionalized *p*-phenylenediamine with enhanced mechanical properties. Subsequently, rat H9C2 cardiomyocytes were cultured on the scaffold and increased expression of cardiac marker genes such as Tnnc1 was found after 7 days, indicating that this scaffold can show better activity on cardiomyocytes.

Polylactic acid-glycolic acid (PLGA) is biocompatible and nontoxic, with controlled degradation rate, high porosity and good mechanical properties, and is widely used in the field of tissue engineering.[66] Xing et al.[67] grew murine bone marrow mesenchymal stem cells (BMMSCs) induced with 5-Aza on PLGA scaffolds and showed that the scaffold was able to promote cell adhesion and proliferation with increased expression of cardiac-specific proteins.

Compared to cardiac patches made of natural materials, cardiac patches made of synthetic materials are structurally stable, are mechanically strong, and have a controlled degradation rate. However, most of the synthetic patches do not match the mechanical strength of the natural myocardium due to the lesser elasticity and tend to fall off during heart beating after implantation. Moreover, unlike the natural material of the organism itself, they are prone to immune rejection after transplantation, causing inflammation at the damaged tissue sites. Combining with natural materials to prepare composite scaffolds can enhance the compatibility of scaffolds. Except for intrinsically conductive polymers such as polypyrrole (PPy), polyaniline (PANi), and polythiophene (PTH), most polymeric materials are not conductive and often need to be combined with other conductive fillers to enhance the conductive properties of the patch.

## 4. PREPARATION METHOD OF THE CARDIAC PATCH SCAFFOLD

Tissue-engineered scaffolds play a key role in cardiac tissue engineering in that they provide a support framework for cells that can promote cell adhesion, proliferation, and differentiation.[73] The ideal tissue-engineered scaffold should mimic the natural extracellular matrix structure with good mechanical properties, biocompatibility, electrical conductivity, and nontoxic products after degradation to achieve dynamic cardiac function.[74,75] There are numerous techniques used to prepare scaffolds, and the commonly used methods include freeze-


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drying, soft lithography, decellularization, 3D bioprinting, and electrospinning methods. Schematic diagrams and examples of the process of preparing cardiac patches by these methods are shown in Figure 2 and Table 2.

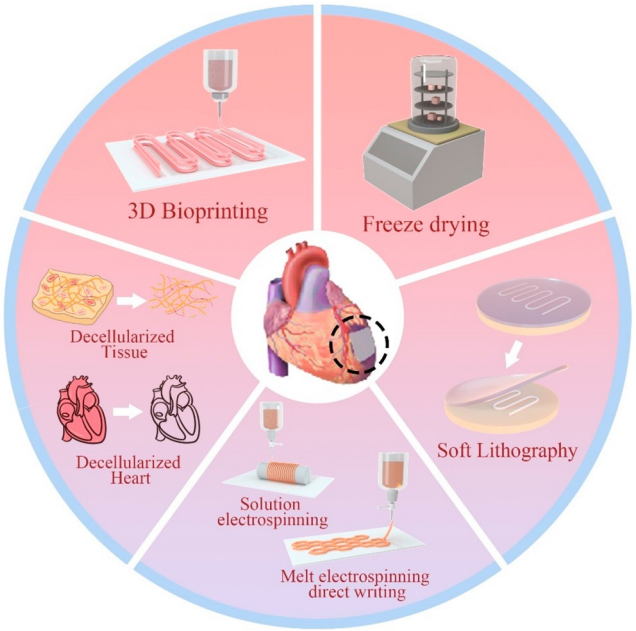


**Figure 2.** Commonly used preparation methods for cardiac patches. Central heart adapted with permission from ref 72. Copyright 2022 Acta Materialia.

**4.1. Freeze-Drying.** Freeze-drying is a drying method in which the material is frozen to below the freezing point of water, then placed in a high vacuum vessel, and then heated to sublimate the material directly from solid to gaseous state. Due to the advantages of high porosity and adjustable pore size of scaffolds prepared by the freeze-drying method, they are widely used in the field of tissue engineering.[76] It was found that high porosity, biodegradable three-dimensional cardiac extracellular matrix−chitosan−gelatin (CECM-CG) composite scaffolds prepared by the freeze-drying method have high water absorption and can promote cell proliferation and differentiation to endothelial cells.[77] PVA has high water retention and bioretention properties, and its mechanical properties are tunable. Dattola et al.[32] prepared a PVA 3D scaffold using foaming and freeze-drying methods, which had mechanical properties similar to those of natural cardiac extracellular matrix. Subsequently, iPSCs were seeded on this scaffold, and the results showed that the cells grew well, successfully differentiated into cardiomyocytes, and were able to produce synchronized beats. Norahan et al.[78] first prepared a collagen 3D porous scaffold by freeze-drying and then covalently coated it with graphene oxide (GO) to prepare a composite scaffold with a pore size of (120−138) ± 8 $\mu$m. The results showed that the scaffold could promote the growth and maturation of cardiomyocytes.

The three-dimensional sparse porous scaffold prepared by the freeze-drying method can provide a suitable growth environment for cells, but its lesser orientation is not good enough to guide cell alignment. The improvement for precise

**Table 2. Examples of Different Methods of Preparing Cardiac Patches**[a]

| Method | Scaffold materials | Seed cells | Effect | | | References |
|---|---|---|---|---|---|---|
| | | | *In vivo/in vitro* | Fibrosis | Angiogenesis | |
| Freeze-drying | Chitosan/carbon nanofiber | Neonatal cardiomyocytes | Enhanced metabolic activity | | | 93 |
| | PVA | hiPSCs | Promotes cell differentiation, produces synchronized beats | | | 32 |
| | Collagen/graphene oxide | Neonatal rat CMs | Promotes cell maturation | | Promotes angiogenesis | 78 |
| Decellularization | Rat decellularized placenta | iPSCs-CMs | Improved left ventricular ejection fraction, fractional shortening, and reduced infarct size | | Increased neovascularization | 89 |
| | Decellularized rat heart | Rat BMMSCs/ECs/primary CMs | Promotes cell adhesion and differentiation, abnormal electrical conduction | | Increased neovascularization | 94 |
| | dECM-BMMSCs | Mouse heart c-kti cells | Promotes cell maturation and boosts antioxidant capacity | | | 95 |
| 3D printing | Gelatin hydrogel | BMMSCs | Promotes cell differentiation, produces synchronized beats | | | 96 |
| | Gelatin/hyaluronic acid | Cardiac progenitor cells | Reduced left ventricular remodeling and infarct size | | Promotes angiogenesis | 97 |
| | Gelatin/sodium alginate | BMMSCs | Improved left ventricular ejection fraction, fractional shortening, reduced infarct size | Reduced fibrosis | Localized vascular hyperplasia | 98 |
| | PCL/dECM | Cardiac progenitor cells/MSCs | Neovascularization of capillaries and reduction of cardiac hypertrophy and fibrosis | Reduced fibrosis | Neonatal capillaries | 99 |
| Electrospinning | PCL/gelatin | hiPSCs-CMs | Synchronized cell contraction and rapid response to cardiac drugs | | | 100 |
| | Carbon nanotube/silk fibroin | Neonatal rat CMs | Promotes cell proliferation and maturation | | | 101 |
| | Gelatin | Cardiac pericyte | Promotes cell proliferation and maturation | | Promotes angiogenesis | 102 |

[a]PVA, poly(vinyl alcohol); CMs, cardiomyocytes; hiPSCs-CMs, human-induced pluripotent-stem-cell-derived cardiomyocytes; BMMSCs, bone marrow mesenchymal stem cells; dECM-BMMSCs, bone marrow mesenchymal stem cell decellularized extracellular matrix; dECM, decellularized extracellular matrix; PCL, polycaprolactone.



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regulation of the scaffold structure of the scaffold is needed to prepare cardiac patches by this method.

**4.2. Soft Lithography.** Advances in microfabrication technology have greatly contributed to the development of biomedical engineering, of which soft lithography is a typical technique. Soft lithography[79] allows precise transfer of patterns from masks to elastomeric substrates, and the technique is currently capable of achieving tiny sizes in the 30 nm to 1 $\mu$m class. This method has proven to be particularly suitable for various biomedical applications.[80,81]

Bian et al.[82] prepared a reticulated cardiac patch scaffold with high aspect ratio using soft lithography. The results showed that increasing the length of the elliptical pores improved the overall alignment of the cardiomyocytes and ECM, thereby enhancing the anisotropic propagation of action potentials and tissue contractile function. In addition, studies have been performed to design soft lithography masks and prepare cardiac patches based on diffusion tensor magnetic resonance imaging (DTMRI) of mouse[83] or human[84] ventricles. Both *in vitro* cultures showed dense, aligned cardiomyocytes and positive electrical signaling. This has important implications in recreating the natural myocardial structure and function. Once a cardiac patch is designed, the assessment of its electrical activity capacity *in vitro* is always limited, which may lead to functional decline of the patch prior to transplantation. Feiner et al.[85] developed a new strategy via a built-in nanoelectronic chip that allows real-time monitoring of functional changes in myocardial tissue and online modulation of electronic devices to deliver electrical stimulation and/or spatial release of biochemical factors to affect the tissue or the surrounding environment as needed.

High-resolution cardiac patch scaffolds can be prepared by soft lithography, and the alignment and growth of cells can be easily regulated by adjusting the pattern and size of soft lithography molds. With the continuous advancement of microfabrication technology, this method is expected to become a key technology in the field of myocardial repair in the future. However, compared with other methods, the preparation of scaffolds using soft lithography is usually time-consuming and requires sophisticated equipment that is more costly.

**4.3. Decellularization.** Generally, natural material scaffolds are made by decellularization methods. The main purpose of decellularization is to generate tissue-engineered scaffolds with natural extracellular matrix structural components and the ability to remove all cellular and genetic material from the original tissue, mainly including physical, chemical, and enzymatic methods.[86] It was found that hydrogels made from porcine heart decellular matrix combined with secreted-derived trophic factor (TF) from human MSCs could well maintain the activity and sustained release of TF. This approach suggests that loading MSC-derived TF with dECM hydrogels could be a potential approach for the treatment of cardiovascular diseases.[87]

Since placenta is rich in extracellular matrix and has a highly vascularized tissue structure, decellularized placenta (DP) is considered an ideal natural tissue engineering scaffold material.[88] Jiang et al.[89] decellularized rat placenta and subsequently implanted iPSCs-CMS. *In vitro* assays exhibited good contractility and synchronized electrical conduction, followed by transplantation of patches into rats with myocardial infarction, which showed significant improvements in left ventricular ejection fraction, short-axis shortening rate, and end-systolic pressure−volume relationships.

Despite current improvements in recellularization methods, validating recellularization efficiency remains a difficult task. Hochman-Mendez et al.[90] developed a unique combination of parameters to quantify the recellularization efficiency of tissue-engineered cardiac patches. They grew cardiomyocytes derived from human ESCs into rat whole heart decellularized extracellular matrix. The results showed that the increased recellularization efficiency promotes cardiomyocyte maturation.

Cardiac patches prepared using decellularization methods retain the natural extracellular matrix structure and some pro-cell-growth biologic factors to the greatest extent possible. However, neither decellularization method can achieve complete removal of ineffective components and effectively avoid structural damage. In addition, cellular residues may also cause inflammatory responses and interfere with endogenous repair.

**4.4. Three-Dimensional Bioprinting.** Three-dimensional bioprinting has developed into a promising technology. It refers to the use of biomaterials and the compounding of cells, growth factors, and other active components into a whole and then printing layer by layer a living scaffold that mimics the structure of the target tissue or organ.[91] Wang et al.[92] mixed young rat primary cardiomyocytes in fibrin bioink and used 3D bioprinting to prepare hydrogel and PCL composite scaffolds. *In vitro* culture showed that cardiomyocytes were uniformly arranged, were dense, could contract spontaneously and synchronously, and showed good physiological response to cardiac drugs. However, the mechanical properties and electrical conductivity of the scaffold were not tested in the paper, and the electromechanical coupling effect with the host after transplantation *in vivo* needs to be further investigated.

The microvascular network is particularly important when printing thicker cardiac patches, which provide oxygen and nutrients to the cells and drain the generated waste products in time for eventual integration with the host vascular network.[102] It was found that three-dimensional heterogeneous multicellular cardiac patches prepared using a hybrid bioink of human umbilical vein endothelial cells (HUVECs) and iPSCs-CMs could be well integrated with the host vascular network after transplantation into mice.[103]

The use of decellularized extracellular matrix (dECM) bioinks can mimic tissue-specific extracellular matrix composition and enhance cell survival, proliferation, differentiation, and migration.[104] Noor et al.[105] processed extracellular matrix extracted from diseased mouse adipose tissue decellularized into specific hydrogels and then reprogrammed the cells into pluripotent stem cells and thus induced differentiation into cardiomyocytes and endothelial cells. A hybrid bioink was prepared, followed by 3D printing of patterned cardiac patches. The good contractility and no immune response after transplantation into mice suggest that a fully autologous material should be the best choice for cardiac patch preparation.

3D bioprinting is currently the mainstream method for preparing cardiac patches. Using dECM as a bioink is the current trend in 3D bioprinting. It can simultaneously deposit cells and biomaterials, improve cell dispersion, and flexibly modulate the scaffold structure according to the needs. However, this method has strict requirements for bioinks,


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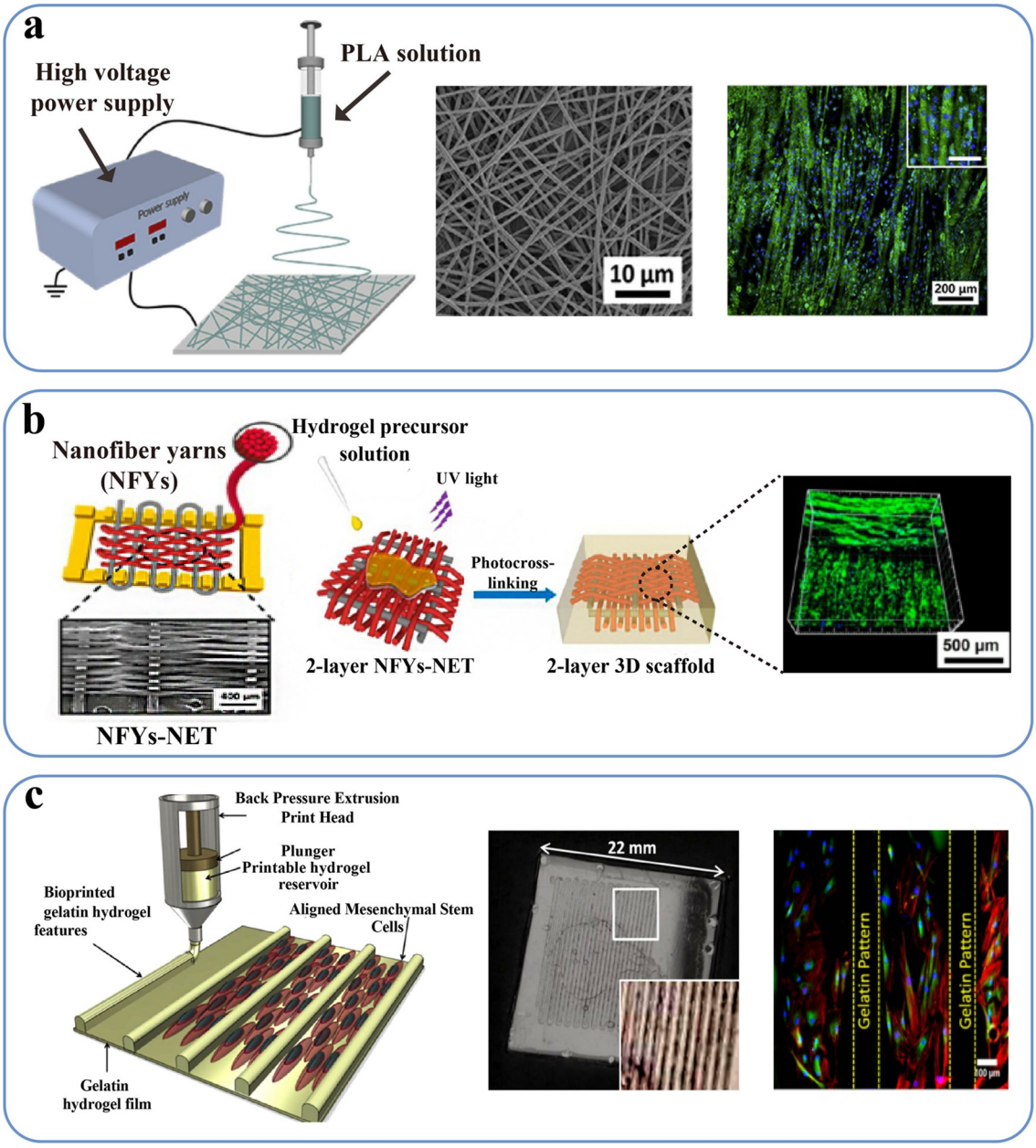


**Figure 3.** Preparation and characterization of random and oriented structured patches. (a) Poly(lactic acid)/poly(aniline) nanofiber cardiac patch scaffolds prepared by solution electrospinning and their biological characterization. Reproduced with permission from ref 110. Copyright 2017 Acta Materialia. (b) Anisotropic cardiac patch scaffolds woven with electrospinning nanofiber yarns (polycaprolactone, silk fibroin, and carbon nanotubes) as weft and surgical sutures as warp and their biological characterization. Reproduced with permission from ref 111. Copyright 2017 American Chemical Society. (c) Gelatin micropatterned cardiac patch scaffolds prepared by 3D bioprinting and their biological characterization. Reproduced from ref 96. Copyright 2018 IOP Publishing.

and the prepared cardiac patches have low mechanical strength and may cause some damage to the cells.

**4.5. Electrospinning.** Electrospinning is divided into solution electrospinning and melt electrospinning. It is a kind of technology that uses high voltage static electricity to make polymer solution or melt spray spinning at the tip.[106] Solution electrospinning has simple equipment and low cost, while melt electrospinning has received much attention in recent years due to its zero solvent and nonpolluting ability to prepare micro- and nanofibers in a green and efficient way.[107,108] The high bionic nature of electrospinning on extracellular matrix makes it one of the most important approaches to prepare tissue engineering scaffolds. Recently, a study was conducted to prepare hybrid electrospinning nanofiber scaffolds using PLA and PGS, and the addition of PGS significantly increased the mechanical properties and hydrophilicity of the scaffolds. Subsequently, cardiac patches were prepared by growing neonatal mouse cardiomyocytes, and the results showed that the patches were able to induce neovascularization after transplantation *in vivo* and did not induce an immune inflammatory response.[109] However, the random structure of this scaffold limits the growth of the cells in an oriented induced alignment, which affects integration


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Table 3. Some Examples of Typical Anisotropic Cardiac Patches[a]

| Materials | Structure | Effect | | Reference |
|---|---|---|---|---|
| | | *In vivo* | *In vitro* | |
| POMAC | Rhombus | Improvement in EF, SF, and end-systolic-diastolic volume, promotes angiogenesis | Effective elasticity close to natural rat myocardium | 126 |
| PGS | Accordion-like honeycomb | | Promotes directional cell alignment, mechanical properties close to adult rat myocardium | 57 |
| Chitosan-polyaniline | Bow-tie | No change in EF, SF, and end-systolic-diastolic volume, reduced cardiac hypertrophy | Close to natural rat myocardial mechanical properties, high electrical conductivity | 127 |
| pHMGCL/PCL | Rectangular | | Promotes directional cell alignment, mechanical properties close to natural human myocardium | 128 |
| mPCL | Honeycomb | No adverse effects | Good mechanical properties, promotes cell maturation, synchronized beating | 117 |

[a]POMAC, poly(octamethylene maleate (anhydride) citrate); EF, ejection fraction; SF, shortening fraction; PGS, poly(glycerol sebacate); pHMGCL, poly(hydroxymethylglycolide-*co*-ε-caprolactone).

with the host myocardium and increases the risk of arrhythmias.

In addition, since cardiomyocytes are electrically active cells that can contract spontaneously under the conduction of electrical signals, it is desirable for the scaffold to have electrical conductivity, thereby facilitating intercellular communication and increasing electrical coupling.[112,113] Zhao et al.[101] prepared a functionalized silk nanofiber scaffold by a solvent-free electrospinning process. Due to the addition of carbon nanotubes (CNTs), the electrical conductivity and mechanical properties of the scaffold were substantially improved. The scaffold was able to induce cell orientation and promote cardiomyocyte maturation.

The melt electrowriting (MEW) technique combines 3D printing and electrospinning technology. By applying electric field force stretches, the molten polymer is stretched from the nozzle tip to the collection plate, and then, the fibers are stacked layer by layer to obtain 3D structures, which provides a new idea for the preparation of tissue engineering scaffolds.[114−116] In our group, we prepared multistage gradient structured electrowriting scaffolds with good biocompatibility and degradability for the microscopic layered structure of bone-chondral bone in our previous work. Zhang et al.[117,118] prepared a conductively anisotropic PCL/Au composite scaffold, which combined with external electrical stimulation improved skeletal muscle cell differentiation and regeneration and achieved synchronous contraction of cardiomyocytes. Castilho et al.[119] printed medical-grade polycaprolactone (mPCL) scaffolds with a honeycomb structure using MEW technology. Compared to the pristine fibrous scaffolds, the cells were more neatly aligned and the pulsation rate and gene expression of cardiomyocytes were exponentially increased.

Scaffolds prepared by electrospinning have high mimicry to collagen nanofibers in the myocardial ECM, which can provide cells with a native-like microenvironment. However, the porosity of electrospinning fiber scaffolds is low, which might hinder the penetration of cells and nutrition though the scaffolds. In contrast, melt electrowriting can precisely regulate the deposition of fibers, which allows flexible and diverse anisotropic structural scaffolds to be prepared. Moreover, the prepared scaffolds have high porosity, which is conducive to cell adhesion, orientation, and diffusion and is expected to be a key technology for the development of future patches.

## 5. STRUCTURE AND PERFORMANCE

**5.1. Random Structure.** Polyaniline (PANi) has recently been extensively studied in biomedicine due to its tunable conductivity, hydrophilicity, and environmental stability.[120] It was found that disordered nanofibrous scaffolds with electrical conductivity were prepared using PLA doped PANi to mimic the microenvironment of the extracellular matrix, and the scaffold conductivity could reach $(2.1 \pm 0.3) \times 10^{-5}$ S/m, showing positive effects in promoting cell differentiation, maturation, and generation of gap junctions (Figure 3a, Figure 5a).[110] The dissolution of PGS is often performed using solvents such as chloroform or dichloromethane, but these solvents have high toxicity and are potentially harmful for medical applications. Vogt et al.[121] used the benign solvent acetic acid as a solvent for solution electrospinning and successfully prepared random PCL/PGS composite nanofiber mats. The mechanical properties of the scaffold decreased with increasing temperature, and the Young's modulus was about 4 MPa at 37 °C. The scaffold was well biodegradable, and the degraded weakly acidic medium is more suitable for cell survival (Figure 5b). Although random structured scaffolds provide a 3D growth environment for cells, they do not induce cell alignment. Due to the orientation of the natural myocardium, the integration of the patch with the damaged site may cause undesirable consequences, so random structure scaffolds are rarely used at present.

**5.2. Orientation Structure.** The myocardium is a highly complex three-dimensional anisotropic structure with a slight shift in the interlayer arrangement from the endocardium to the epicardium,[122] and oriented fibers are important for inducing cell orientation. Wu et al.[111] used electrospinning nanofiber yarns as weft and surgical sutures as warp to prepare structurally anisotropic conductive fiber scaffolds using a braiding process, which were subsequently combined with hydrogels to prepare composite 3D scaffolds, showing that the scaffolds not only induced cardiomyocyte maturation but also controlled the cell orientation of each layer individually (Figure 3b). Usually soluble hydrogels are cross-linked by UV light initiation. It was found that oriented gelatin hydrogels cross-linked using microbial transglutaminase (mTgase) could also produce stable microchannels. The cross-linked scaffolds have an elastic modulus of approximately 80 kPa and can be well suited to induce cardiomyocyte orientation and promote cell maturation (Figure 3c, Figure 5c).[96] A major nuisance of conductive polymers for tissue engineering applications is their brittleness and nondegradability. Hu et al.[123] synthesized an electroactive degradable elastomeric scaffold based on PGS and aniline trimer (AT), and its mechanical and conductive properties were the same order of magnitude as those of natural myocardium. *In vitro* implantation of rat H9c2 cells


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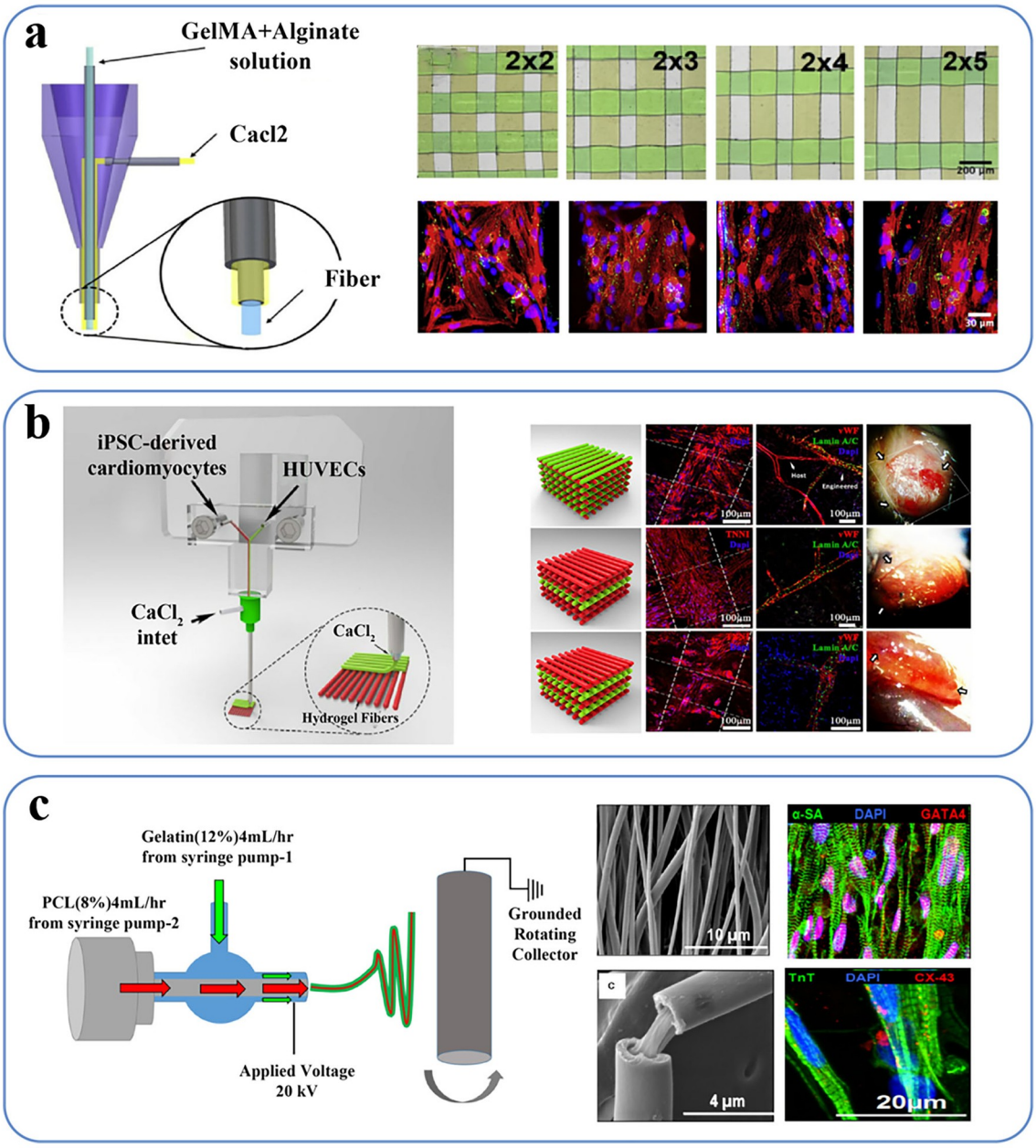


**Figure 4.** Preparation and characterization of coaxial structured patches. (a) Variably spaced microchannel hydrogel cardiac patch scaffolds and their biological characterization using coaxial 3D bioprinting. Reproduced with permission from ref 125. Copyright 2016 Elsevier. (b) Vascularized heterogeneous multicellular cardiac patch scaffolds printed with hydrogel bioinks containing iPSC-CM and HUVEC and their biological characterization. Reproduced from ref 103. Copyright 2018 The Authors. (c) Stretchable coaxial nanofiber cardiac patch scaffolds based on PCL and gelatin and their biological characterization. Reproduced from ref 100. Copyright 2020 The Authors.

showed that the scaffold promoted cell proliferation, differentiation, and maturation and exhibited only a mild inflammatory response after transplantation *in vivo*, and this elastomeric scaffold could be an excellent option in the field of cardiac repair. Recently, Olvera et al.[124] prepared an anisotropic structure of PCL/PPy scaffolds using electro-writing, which had a Young's modulus and electrical conductivity of 2.09 ± 0.26 MPa and 2.51 ± 0.7 S/m in the transverse direction and 1.05 ± 0.13 MPa and 2.07 ± 0.4 S/m in the longitudinal direction, respectively. The anisotropic stiffness ratio of 1.99 is consistent with the anisotropic ratio of natural myocardial stiffness. However, the culture of cardiomyocytes was not addressed in the paper, and subsequent work is pending (Figure 5d). There are also anisotropic cardiac patches that work as shown in Table 3.

**5.3. Coaxial Structure.** The microvascular network has an important role in providing necessary oxygen and nutrients to cells in thick tissues. Zhang et al.[125] used coaxial 3D bioprinting to prepare an anisotropic mesh scaffold by passing gelatin and alginate bioink encapsulating endothelial cells in the inner layer and $CaCl_2$ solution in the outer layer. When the endothelial cells migrated to the periphery of the fibers to form a fused endothelial cell layer, they were implanted into cardiomyocytes to form endothelialized myocardium. The results showed that the grid-spaced anisotropic structure better promoted the growth and maturation of cardiomyocytes and


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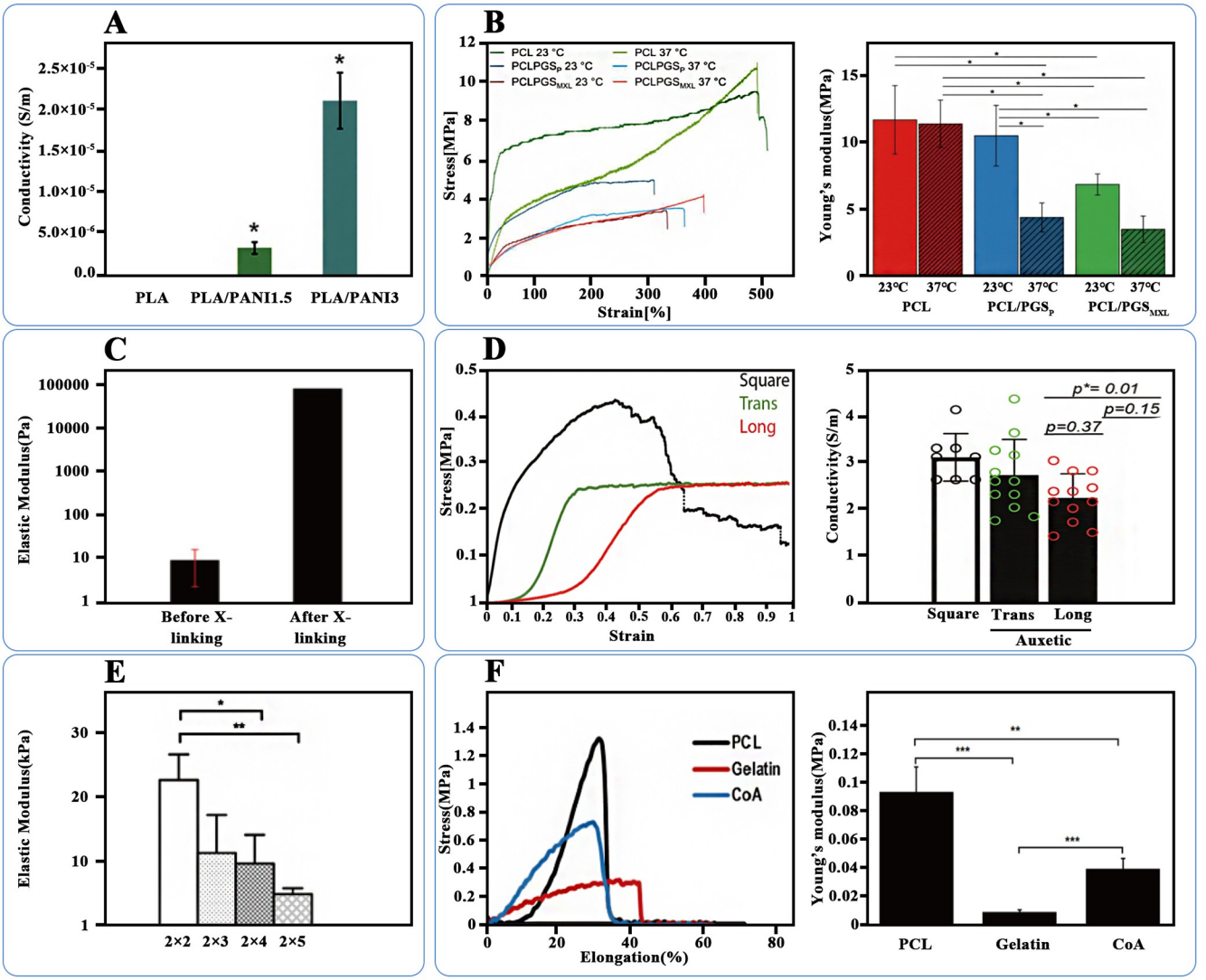


**Figure 5.** Mechanical properties and electrical conductivity of the scaffold. (a) Conductivity of PLA/PANI electrospinning nanofiber scaffolds with different PANI contents. Reproduced with permission from ref 110. Copyright 2017 Acta Materialia. (b) The mechanical properties of electrospinning PCL/PGS fiber scaffolds varied at different PGS contents, cross-linking conditions, and different temperatures. Reproduced with permission from ref 121. Copyright 2019 Elsevier. (c) Changes in THE elastic modulus of 3D bioprinted gelatin hydrogel scaffolds before and after cross-linking with microbial transglutaminase (mTgase). Reproduced from ref 96. Copyright 2018 IOP Publishing. (d) Comparison of the mechanical and conductive properties of melt electrowriting anisotropic scaffolds with square scaffolds. Reproduced with permission from ref 124. Copyright 2020 Wiley. (e) Elastic modulus of 3D bioprinted hydrogel scaffolds with different pitches. Reproduced with permission from ref 125. Copyright 2016 Elsevier. (f) Mechanical properties of PCL, gelatin, and PCL−gelatin coaxial electrospinning fiber scaffolds. Reproduced from ref 100. Copyright 2020 The Authors.

produced spontaneous synchronized beats (Figure 4a, Figure 5e). Similarly, Maiullari et al.[103] prepared cardiac patches with different structures using a customized coaxial needle with an inner layer independently controlling the passage of bioink containing both iPSC-CMS and HUVECs cells and an outer layer with $CaCl_2$ solution. The results compared to the control group without endothelial cells showed that heterogeneous multicellular structures containing endothelial cells played an important role in the improvement of vascularization, where the two interphase Janus structures showed better integration with the host vascular network compared to the other patterned structures (Figure 4b). Recently, a study has prepared a core−shell structured PCL−gelatin nanofiber scaffold using a coaxial electrospinning method. The scaffold was able to achieve a tensile strength and Young's modulus of 0.780 ± 0.098 and 0.039 ± 0.007 MPa, respectively. The hiPSC-CMs spread directionally along the scaffold, and these cells exhibited synchronous contraction and a quick response to cardiac drugs (Figure 4c, Figure 5f).[100]

## 6. SUMMARY AND PROSPECTS

This article first reviews the composition and structural properties of natural myocardium. The anisotropic structural composition of natural myocardium and its extracellular matrix directly lead to the anisotropy of its mechanical and electrical conductivity properties. Then, the seed cell sources, scaffold materials, and processing and preparation methods of cardiac patches were summarized. Differentiation of CMs by induction of autologous somatic cells from patients is the most promising method at present, which not only has no ethical restrictions


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but also avoids immune rejection reactions. However, CMs derived from induced differentiation are not functionally mature enough and often require additional stimulation to enhance their maturation.

Design of scaffolds to recapitulate the composition and architecture of the native cardiac ECM could be a promising approach to generate tissue engineered cardiac patches with the morphology and function similar to native myocardium. Despite the significant advances in cardiac tissue engineering, accurately recreating the complexity of the native myocardial ECM environment is still an ongoing challenge. The "cardiac patch" biomaterial should have good biocompatibility to allow cell adhesion and growth and biomimetic diversity of cell-binding sites to permit physiological functionality. Moreover, after *in vivo* transplantation, the biomaterials should show minimal immunogenicity and their degradation rate should accommodate the speed of tissue remodeling to enhance the therapeutic efficiency. An ideal "cardiac patch" scaffold should not only possess an organized anisotropic fibrillar structure to guide cell anisotropic orientation but also exhibits high elastic deformation (≥25%) to accommodate the continuous heart beating. Additionally, together with the anisotropic mechanical behavior, the scaffold conductivity should be similar to the native myocardium to allow electrical pacing for synchronous contraction.

Cardiac patch scaffolds prepared from natural materials have good biocompatibility and biodegradability. However, their poor mechanical properties lead to processing and handing difficulties and the engineered scaffolds with stiffness less than that of native cardiac tissue, which might not provide ideal conditions for cardiac cell maturation and contraction. Scaffolds prepared from synthetic polymer materials have higher and adjustable mechanical properties and infinite potential for modification to conform the biophysical and biochemical properties to native myocardium. Additionally, they can be designed to take on diverse 3D architectures, such as porous hydrogels or fibrous mesh scaffolds. Therefore, composite scaffolds of multiplex natural and synthetic materials could synergize advantageous characteristics from not only the high density of bioactive sites of natural materials but also mechanical stability and unique geometries from synthetic polymer, which are more suitable for preparation of cardiac patches. However, most of the natural and synthetic polymeric materials are not conductive, which might hinder the electrical integration of a cardiac patch with the host tissue. To this end, a lot of researchers have made an effort to improve the conductivity of patches by combining extroconductive materials (e.g., carbon nanotubes, graphene, metal nanoparticles) or conductive polymers (e.g., polyaniline, polypyrrole),[72,129] showing great potential to enhance cell maturation and electrical signal conduction. However, it is still necessary to precisely control the percentage of conductive fillers to ensure no toxic effects on cells. Scaffolds made by electrospinning cloud closely mimic the microenvironment of natural ECM, but their porosity is low and uncontrollable, which affects cell permeation in thick tissues. Melt electrowriting can precisely regulate the deposition of fibers and prepare flexible and diverse scaffolds with anisotropic structures. Moreover, the scaffold has high porosity, which is conducive to cell adhesion, orientation, and diffusion, and is expected to be a key technology for future patch development.

Cardiac patches have flourished with the rapid development of stem cells, biomaterials, and tissue engineering. The application of cardiac patches provides mechanical support at the site of myocardial infarction and provides reliable cellular or biologically active factors, improving the efficiency of cellular delivery and providing considerable benefits for therapeutic integration. Although cardiac patches have shown promising biological results in preclinical studies, there are no commercially available products for reference and many issues and challenges remain for true clinical application. The biggest obstacle to clinical application and commercialization is that, although a large number of cardiomyocytes are transplanted using a patch for the repair of damaged myocardium, the number of cells that ultimately survive to integrate well with the infarcted region and its function are still far from the desired value. Second, cardiac patches do not achieve good machine−electrical coupling with the host after transplantation and tend to detach with heartbeat and cause arrhythmias. In addition, the diffusion of nutrients limits the thickness of the cardiac patch. Currently, the size of cardiac patches is limited to small animal models, and the clinical size of vascularized patches is an issue that needs further investigation.

The recent emergence of smart biomaterials[130,131] (smart hydrogels, smart nanomaterials, shape-memory materials, and smart bioconjugates) and intelligent biomaterials has greatly advanced the development of modern medicine. It can not only guide stem cells to promote tissue regeneration but also sequester and release cells or drugs in a controlled manner, thus forming a smart system.[132] With the development and application of these new smart biomaterials, the introduction of new concepts in biocytology and medicine, and the involvement of new surgical techniques, cardiac patches have a promising future in the treatment of myocardial infarction. The preparation of conductive anisotropic scaffolds that can be precisely tuned close to natural myocardial tissue should be a key direction for future research.

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### Notes

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