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Review

Toward strategies to advance the conductive properties of hydrogel formulations for cardiac tissue engineering

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SUMMARY

This review article aims to elucidate the role of conductive polymers (CPs) in cardiac bioengineering, focusing on scaffolds and biomaterials required for cardiac tissue engineering. It explores the unique features of CPs that make them well-suited for biomedical applications and explores how these polymers have been optimized to exhibit these properties. Moreover, the review provides insight into the importance of conductive biomaterials and their applications for cardiac repair and regeneration. Furthermore, the review seeks to inform and guide readers in this evolving field, highlighting the significant potential of conductive biomaterials in advancing cardiac tissue engineering. By understanding the capabilities and optimization strategies of CPs, researchers can effectively utilize these materials to develop innovative therapies for myocardial repair and regeneration, ultimately contributing to improved outcomes for patients suffering from heart attacks.

INTRODUCTION

Cardiovascular disease (CVD), including myocardial infarction (MI), is a leading cause of death worldwide, claiming approximately 18.6 million lives annually.[1] MI occurs when the heart is deprived of oxygen due to blocked blood flow, resulting in heart muscle damage. This condition presents a significant threat to individuals' lives and health, often leading to pathological and structural abnormalities within the heart ventricles. Immediate medical attention is crucial to reduce further damage and improve outcomes, especially given the limited availability of treatment options such as heart transplants.[2] Moreover, complications like heart failure can arise due to the heart's inability to self-repair. Regenerative medicine research aims to develop therapies for repairing damaged heart tissues, offering hope for enhancing outcomes and improving the quality of life for those affected by CVD.[3]

Currently, available treatment options, such as heart transplants, face challenges due to the scarcity of donor organs, underscoring the urgent need for alternative approaches, such as cardiac tissue engineering using conductive biomaterials.[4] Conductive polymers have emerged as essential materials in supporting and stimulating cells for heart repair. Their engineered properties, along with electrical and electromechanical stimulation, provide various benefits in aiding stem cell function.[5] Optimizing the interaction between cardiac progenitor cells and conductive polymer surfaces is crucial for advancing our understanding of biomaterial interactions with cardiac cells and improving materials for cardiac tissue regeneration.[6]

Furthermore, conductive biomaterials play a pivotal role in post-MI recovery by restoring electrical functions and repairing damaged myocardium. These biomaterials effectively lower scar tissue resistivity, increase field potential, and improve conduction velocity, thereby enhancing heart function.[7] In the field of cardiac tissue engineering, conductive substrates are designed to mimic the electrical properties of the myocardium, thereby improving blood-pumping ability and reducing scar size in heart. These substrates not only enhance cardiomyocyte (CM) maturation and integration with the native myocardium but also contribute to the restoration of heart function. Moreover, conductive scaffolds facilitate stem cell differentiation into CMs, enhancing the expression of cardiac proteins and promoting electrical coupling and contractility of cells, ultimately improving cardiac function post-MI.[8] This review explores the application of various biomaterials and conductive polymers in cardiac tissue engineering.

MEDICAL PROBLEM: HEART FAILURE, CURRENT TREATMENTS, AND CHALLENGES IN CARDIAC REGENERATION

MI, commonly known as a heart attack, is caused by atherosclerosis, a condition in which plaque composed of fatty materials and other substances builds up in the arteries. This accumulation narrows the arterial lumen, reducing or completely obstructing blood flow. As a result, the heart is deprived of oxygen and nutrients, impairing its function and potentially leading to total heart failure,[3,9] as shown in Figure 1. Common medications for treating MI include antiplatelet agents such as aspirin and clopidogrel to prevent blood clots, thrombolytics such as alteplase to dissolve existing clots, and anticoagulants such as heparin.[11]

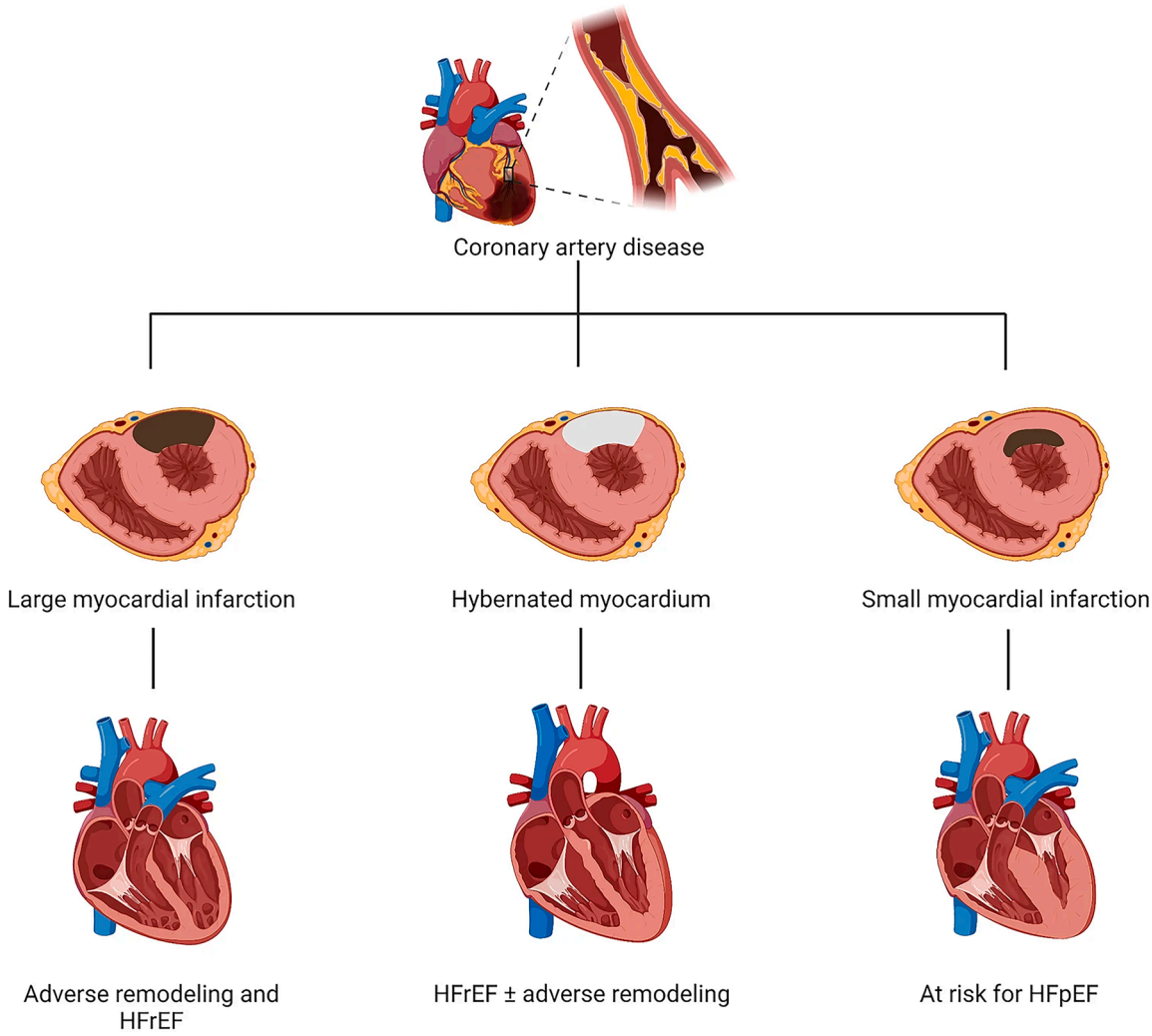

Figure 1. Myocardial infarction in the human heart

The build-up of plaque, composed of fatty materials and other substances, over time in the arteries is the primary cause of myocardial infarction in the human heart, leading to heart failure in patients. Reproduced with permission from Del Buono et al.[10]

Beta-blockers and angiotensin-converting-enzyme inhibitors also help to manage heart workload and blood pressure, while statins lower cholesterol levels. However, if these treatments are insufficient, a heart transplant may be considered for an end-stage heart failure.[12]

Currently, a heart transplant is a crucial treatment option for end-stage heart failures. However, this is associated with risks and limitations. The severe shortage of donor organs significantly restricts its availability, resulting in many patients on the waiting list dying each year.[5] Currently, approximately 3,700 heart transplants are performed globally each year, while approximately 30,000 patients await transplantation. Immunosuppression strategies in heart transplantation adhere to several key principles.[13] First, the risk of graft rejection is at its highest immediately after the surgery, prompting regimens to start with high levels of immunosuppression that are gradually reduced over the first year to the lowest effective maintenance levels.[14] Second, using low doses of multiple drugs is favored over high doses of fewer drugs to avoid overlapping toxicities. Third, excessive immunosuppression is avoided due to its association with increased risks of infection and malignancy. Achieving the right balance of immunosuppression requires a carefully controlled approach by maintaining the right balance between the toxicity and optimum immune response. Immunosuppressive regimens are typically categorized into induction, maintenance, and rejection therapy, with induction providing intense early suppression and maintenance continuing throughout the patient's life to prevent rejection.[15]

An LVAD (left ventricular assist device) is an artificial heart pump used for patients, including pediatric patients, with severe heart failure, particularly those waiting for a heart transplant. It helps the weakened heart pump blood into the aorta, restoring normal blood flow and supporting patients who may not survive until a donor's heart becomes available.[16] In addition, ECMO

(extracorporeal membrane oxygenation) is a life support system for individuals with severe heart or lung dysfunction. It maintains blood circulation and helps regulate oxygen and carbon dioxide levels in the blood.[17] However, LVADs lack in providing the biological support a patient needs.

Current studies have explored innovative approaches to address heart failure, such as using conductive polymers in tissue engineering. Conductive polymers offer promising properties in creating scaffolds that mimic the natural electrical conductivity of cardiac tissues. This supports the integration of implant materials with the host tissue and facilitates electrical signaling essential for proper heart function.[18] Over the last few years, the use of stem cells for cardiac regeneration has provided promising results in preventing ventricular dilation and cardiac dysfunction in preclinical studies.[19] However, there are still some hurdles to overcome, such as challenges in selecting the appropriate cell type for transplantation,[20] mode of cell delivery,[21] cell survival,[22] paracrine signaling, and homing.[23] Furthermore, the absence of efficient engraftment of donor cells with host tissue prevents optimal electrical communication.[24]

Injectable hydrogels for cardiac tissue engineering were investigated by Hasan et al.[25] to close the gap between MI and the shortage of donor heart transplants. These hydrogels can repair damaged cardiac tissues and include natural and synthetic biopolymers, such as collagen, fibrin, alginate, hyaluronic acid, and PEG-based materials. Animal studies have shown increased wall thickness, improved cardiac function, and enhanced angiogenesis. However, further research is needed to optimize hydrogel properties and translate these therapies to human clinical applications. More recently, tissue engineering approaches involving an interactive environment between cells, scaffolds, and bioactive molecules have been explored to generate cardiac patches that improve cell engraftment by providing an optimal growing environment.[25,26]

As the myocardium is an electrically active tissue and cardiac cells have synchronized contractile activity through the propagation of the electrical signals, the bioengineered tissue should be electrically conductive. The absence of electrical conductance in cardiac patches could hinder cell engraftment and prevent the synchronized contractile activity between transplanted cells and host tissues. A wide range of electroconductive biomaterials has already been investigated as potential candidates to improve electrical conductivity in the heart.[25,27]

Biomaterials, whether synthetic or natural, play a crucial role in cardiovascular treatment by facilitating tissue repair and regeneration.[4] Synthetic materials such as polymers and metals offer strength and durability, while natural materials deliver excellent functionality.[28] Combining stem cell therapy with biomaterials shows promise in improving cardiovascular treatment outcomes by enhancing cell engraftment and survival after transplantation.

Advancements in biomaterial-based therapies and 3D bioprinting have the potential to revolutionize cardiac regeneration and significantly improve outcomes for heart failure patients. By providing personalized treatment that overcomes the challenges of traditional heart transplants, these innovations offer hope for a brighter future in cardiovascular medicine.[2,29]

CARDIAC BIOENGINEERING

Cardiac bioengineering aims to create functional cardiac tissues to repair or replace damaged heart tissues.[30] A key component in this field is the use of conductive biomaterials, which enhance the electrical conductivity of engineered tissues and improve their integration and functionality.[31] These biomaterials are critical for ensuring synchronized contractions and effective electrical signaling in engineered cardiac tissues.[32]

Various cell sources, including mesenchymal stem cells (MSCs), cardiosphere-derived progenitor cells, human embryonic stem cells, and human-induced pluripotent stem cells (hiPSCs), are used to generate CMs. hiPSCs are particularly advantageous due to their ethical acceptability and reduced immunogenicity, allowing the production of unlimited autologous CMs.[33]

Successful clinical applications depend on maturation protocols, vascularization, and integration with the host tissue. Conductive biomaterials support these processes by facilitating electrical communication between cells, which is essential for the proper function of cardiac tissue. In addition to cell sources, bioengineering techniques such as cell reprogramming, gene editing, and the delivery of protein factors through engineered particles enhance the properties of both cells and biomaterials.[34]

Innovations in technologies such as protein decoration and the use of cardiac patches embedded with conductive materials are essential for advancing cardiac regenerative medicine. These approaches might help overcome the limitations of live cell therapy and improve the prospects for successful integration and functionality of engineered cardiac tissue in clinical applications.[35]

BIOMATERIALS FOR HEART TISSUE ENGINEERING

Biomaterials are essential in supporting cells and guiding their development into functional tissues.[36] While each type of biomaterial has unique characteristics in tissue engineering, they all function as supportive structures that promote the growth and specialization of targeted tissues, as shown in Table 1.[108] These biomaterials are typically either synthetically engineered or derived from essential natural substances, with subsequent processes used to tailor their morphology and properties for specific applications.[109] This section will explore the various biomaterials used in cardiac tissue engineering.

Alginate

Alginate, a natural compound derived from seaweed, is known for its biocompatibility, biodegradability, non-toxicity, and non-immunogenicity. These advantageous properties make it highly suitable for several medical applications, such as drug delivery, wound healing, and tissue engineering.[110,111]

In cardiac tissue engineering, alginate has been used as an injectable cell delivery system because it can easily form gel when exposed to ions such as calcium. These properties make it effective for delivering cells to the heart tissue during regenerative treatments.[112,113] The gelation process results from the interaction between the alginate molecules and calcium ions present in the surrounding environment. When alginate comes

Table 1. Strengths and limitations of biomaterials used for cardiac tissue engineering

Biomaterial	Strengths	Limitations
Alginate	- biocompatible, biodegradable, non-toxic, and non-immunogenic.[37,38] - forms gels with calcium ions, enabling effective cell delivery and encapsulation.[39] - promotes vascularisation, reduces infarct expansion, and prevents LV enlargement.[40]	- low mechanical strength when used alone.[41] - requires modification or combination with other materials, such as conductive polymers (e.g., polypyrrole and polyaniline), graphene, or carbon nanotubes, for improved structural support and conductivity.[42]
Chitosan	- supports cardiac repair by promoting cell adhesion.[43] - conductive when combined with materials like polypyrrole.[44] - enables controlled scar tissue formation and improves signal conduction.[45]	- conductivity needs enhancement through additional materials like polypyrrole.[46] - variable degradation rate that impacts its stability for prolonged cardiac use.[47,48]
Gelatin	- supports cell recruitment, attachment, and growth.[49] - effective in enhancing heart function when used in cardiac patches.[50] - biodegradable and mimics physiological properties for bone and tissue engineering.[51,52]	- rapid degradation and limited mechanical stability on its own[53] - conductivity may require enhancement through combination with other material such as conductivity may require enhancement through combination with other materials, such as conductive polymers (e.g., polyaniline and polypyrrole) or carbon-based nanomaterials (e.g., graphene).[52]
GelMA (Gelatin Methacryloyl)	- excellent cell compatibility and tunable mechanical properties with UV crosslinking.[54,55] - mimics the ECM and supports cell alignment and tissue structure formation.[56] - effective for cardiac, vascular, and bone tissue engineering.[56,57]	- UV crosslinking is required, which may affect cell viability.[58,59] - limited long-term stability in physiological conditions without modification.[56] - modifications (e.g., incorporation of conductive polymers such as polypyrrole or polyaniline, carbon nanomaterials like graphene oxide or carbon nanotubes, or gold nanoparticles) are required for improved stability and conductivity[60]
Collagen	- naturally supportive of cell attachment and cardiac tissue structure.[61] - provides flexibility and is a key ECM component aiding stem cell differentiation.[62] - useful in injectable hydrogels and cardiac patches.[63]	- it requires conductive materials (e.g., polypyrrole, polyaniline, graphene oxide, or gold nanoparticles) to enhance electrical conductivity in cardiac applications Li et al.[64] - rapid degradation can impact durability in cardiac tissue engineering.[65] - sourcing from animal origins may impact immune compatibility and quality; however, other commonly used biomaterials, such as gelatin, matrigel, fibrin, and chitosan, are also derived from animal sources.[66]
Silk	- excellent biocompatibility, customizable mechanical strength.[67] - supports cell adhesion and proliferation.[68] - enhances mechanical properties when added to other biomaterials.[69]	- higher concentrations may reduce cell viability and affect structural porosity.[70] - it requires complex fabrication steps, such as electrospinning or chemical modification, to improve specific properties like mechanical strength and biocompatibility.[71,72] - biodegradable and can be combined with conductive materials, such as polypyrrole, polyaniline, graphene oxide, or carbon nanotubes, to enhance electrical conductivity and support cardiac tissue function[73]
Fibrin	- high biocompatibility and flexibility in mimicking ECM, not conducive by itself.[74] - enhances cell integration, cardiac patches, and cell retention. - effective in 3D bioprinting applications for cardiac constructs.[75]	- low mechanical strength, degrades relatively quickly,[76] and lacks intrinsic electrical conductivity, often requiring blending with conductive materials (e.g., polypyrrole and graphene oxide) for cardiac applications.[77] - limited cell survival in the middle of the material due to limited diffusion of nutrients and oxygen in thicker fibrin layers.[74] - quick gelation reduces working time in certain applications.[78]

into contact with calcium ions, it undergoes a cross-linking reaction, forming a gel-like structure. This gel can then encapsulate cells, protecting them during delivery and facilitating their release at the target site within the heart tissues.[60]

A study by Leor et al.[114] explored the potential of alginate in cardiac engineering by developing specialized scaffolds to support implanted heart cells in a rat MI model. These alginate-based scaffolds provided a controlled release of therapeutic factors to create an optimal environment for heart cell survival and integration. Additionally, the study examined the effects of specific cytokines, including G-CSF, SDF-1, LIF, LGF-1, and EPO, on promoting tissue healing and reducing scar formation after a heart attack. The results indicated that these cytokine-scaffolds significantly increased cell retention, reduced infarcted area, and improved left ventricle (LV) function, offering promising approaches for heart tissue repair and regeneration.

Landa et al.[115] investigated the potential of alginate's properties by developing absorbable biomaterials using a calcium-crosslinked alginate solution, which transforms into a hydrogel upon injection into an infarcted area. The research focused on alginate's impact on cardiac remodeling and function in the infarcted area. The study used a rat MI model to examine how this alginate hydrogel influenced cardiac tissue recovery and function. The research aimed to understand how the alginate hydrogel specifically affected cardiac remodeling in infarcted tissues.

Echocardiographic and histological analyses showed that the alginate-treated rats had significantly reduced LV dilation compared with the untreated control group in infarcted animals. The control group would have consisted of rats with MI that were not treated with the hydrogel. The results showed comparable or superior benefits to neonatal CM transplantation in rats treated with the alginate hydrogel, improving cardiac function and reducing infarct expansion. Alginate also reshaped the LV, preventing further enlargement and promoting increased arteriogenesis. The hydrogel further promoted neovascularization, with an observed increase in vascular density within the treated infarct area. Compared to fibrin, alginate consistently enhanced LV functional shortening and reduced infarct size, with both materials boosting arteriogenesis[113,115]

A study conducted by Yu et al.[116] investigated the long-term effects of alginate on the heart using a mouse model that mimicked chronic heart disease caused by tissue damage. The study compared modified and unmodified alginate formulations, incorporating arginylglycylaspartic acid (RGD) peptides and calcium chloride, to evaluate their effects on cardiac tissues when administered directly to the damaged area of the LV. Results revealed that the modified alginate combined with RGD promoted angiogenesis and blood vessel formation and that both alginate forms improved LV function. Additionally, Yu developed a method to deliver human MSCs (hMSCs) by encapsulating them in microbeads made from RGD alginate and injecting them into the affected region, which increased stem cell retention, slowed tissue remodeling, and further facilitated angiogenesis. Interestingly, no significant difference was observed *in vivo* between using RGD alginate alone and in combination with cells. This study suggests that RGD alginate is a cell-free approach to stimulate angiogenesis and support functional recovery in cardiac applications.[28,116]

Chitosan

Chitosan is a natural, biocompatible, and non-toxic material derived from chitin, commonly used in controlled drug delivery systems. Its ability to form nanoparticles through ionic interactions with tripolyphosphate makes it ideal for targeted drug delivery and tissue engineering applications. Chitosan nanoparticles are known for their prolonged circulation times in the bloodstream and excellent biocompatibility.[117]

A study by Ye and Qiu[118] focused on using chitosan combined with conductive biomaterials, such as carbon-based nanofibers and nanotubes, to enhance cardiac repair and function following MI. These conductive scaffolds were designed to mimic the heart's electrical environment, thereby supporting improved electrical signal transmission across cardiac cells. The materials were combined to create scaffolds that enhance heart function post-MI by promoting cell adhesion, proliferation, and elongation, key factors in the integration and survival of transplanted cells. These studies did not involve bioprinted tissues; rather, they focused on creating scaffolds that supported cell-based therapies. The scaffolds were intended to facilitate the adhesion and function of transplanted cells (not bioprinted tissues), enhancing the expression of CM-specific markers and leading to improved CM functionality and synchronous contraction, critical for restoring coordinated heartbeats and overall heart performance.[118] Cui et al.[119] further expanded on these findings, exploring how these scaffolds could improve the functionality of CMs and enhance heart tissue regeneration, promoting better outcomes after myocardial injury. The study by Cui et al.[119] also did not involve bioprinted tissues, as it focused on the use of scaffolds as supporting cells.

A study conducted by Mihic et al.[120] examined the effects of chitosan-graft-polypyrrole (CS-g-PPY) hydrogel compositions as implants for treating damaged cardiac tissues and enhancing heart function post-MI. The CS-g-PPY hydrogel was developed to improve electrical conductivity and mimic the natural electrical properties of cardiac tissue. CS-g-PPY demonstrated improved electrical conduction and calcium signal propagation in *ex vivo* tests, enhancing the communication between CMs necessary for synchronized contractions. *In vivo* experiments on rats showed that CS-g-PPY treatment led to echocardiogram readings similar to pre-infarction levels after one week, with faster transverse conduction velocities and elongated rather than rounded scar tissue, indicating better tissue integration and repair. CS and CS-g-PPY reduced scar size and improved various cardiac function parameters compared to saline injections, suggesting CS-g-PPY's potential to restore cardiac electrical and structural integrity after MI,[121] as seen in Figure 2.

Gelatin

Gelatin is a useful biomaterial widely used in medical applications such as wound healing and tissue engineering.[122] Due to its biocompatibility and biodegradability, gelatin provides a supportive environment for various cell types, including cardiac, bone, and cartilage cells, making it highly versatile in tissue engineering.

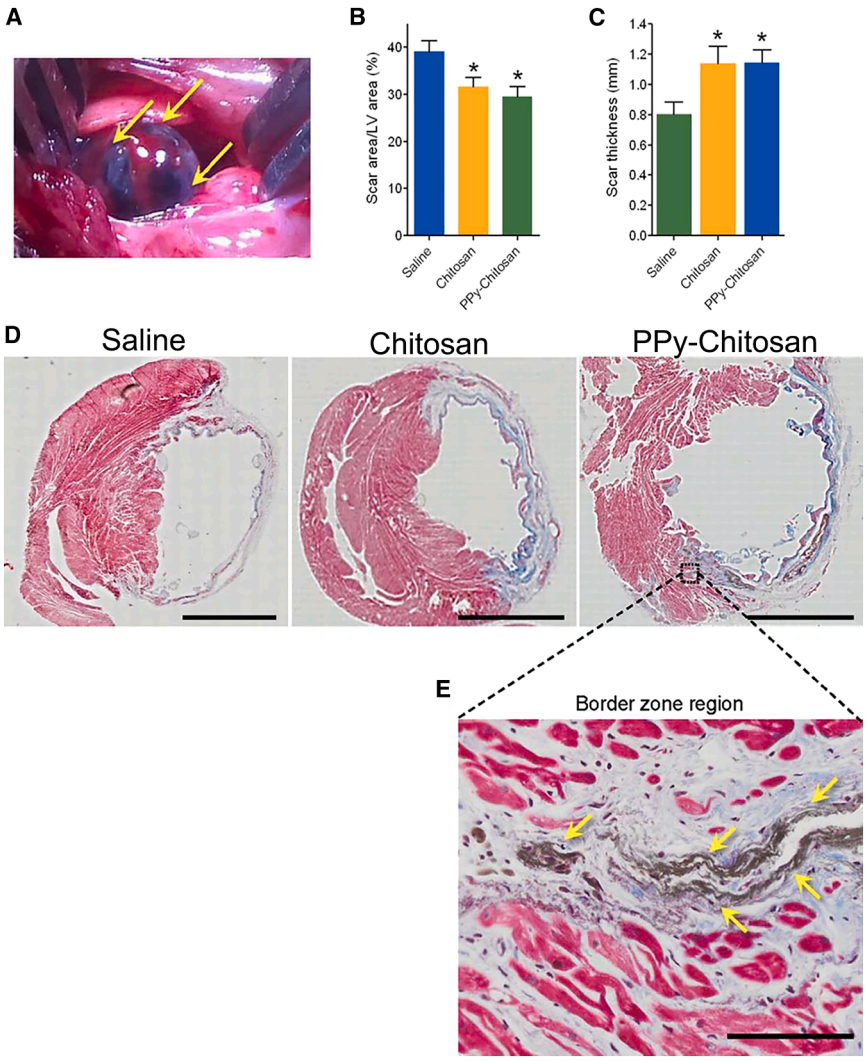

Figure 2. Chitosan-graft-polypyrrole hydrogels reduce scar size in post-MI rat hearts

(A) intraoperative photograph displaying three darker areas for CS-g-PPY was injected into the border area of the rat heart one week post-MI.

(B and C) Eight weeks post-injection, scar area and thickness were measured in a heart treated with saline (n = 6), chitosan (n = 8), and CS-PPY (n = 8). CS-PPY and chitosan significantly reduced scar compared to saline (p <0.05).

(D) Representative heart sections from each group, taken from a similar transverse section below the papillary muscles.

(E) Masson trichrome staining reveals PPy-chitosan particles in the scar and border zone of the heart eight weeks post-injection (arrows). Scale bars: 100 μm. Reproduced with permission from Mihic et al.[120]

Gelatin is derived from collagen, typically from animal connective tissues such as skin, bones, and tendons. It is composed of amino acids like glycine, proline, and hydroxyproline, forming a triple-helix structure. Gelatin is bioactive and demonstrates its ability to support cell recruitment, attachment, and growth, facilitating natural healing processes. Its composition and structure enable it to mimic the extracellular matrix (ECM), which is essential for cellular functions and tissue integration.

Gelatin has successfully been used to transport corneal endothelial cells for transplantation, enhancing cell growth and alignment. Moreover, gelatin-based scaffolds show efficacy in regenerating bone and cartilage tissue, offering properties similar to physiological tissues, which is particularly beneficial for bone regeneration.[120] In cardiac applications, gelatin can be modified or combined with other materials to improve its mechanical strength and stability, enabling its use in cardiac patches and as a supportive matrix for cell delivery,[121] as seen in Figure 3.

A study conducted by Polonchuk et al.[4] showed that the combination of gelatin with alginate produced hydrogels that supported cardiac cell viability, showing promise as a regenerative medicine. The study highlighted that the alginate-gelatin (Alg-Gel) combination created an ECM-like environment, which enhanced cell survival. Another study utilized gelatin in 3D-printed Alg-Gel patches containing cardiac spheroids, which were transplanted onto the outer surface of the heart in a mouse MI model. Gelatin played a crucial role in formulating the bioink for printing the cardiac tissues in another study as well, contributing to their structural integrity and biocompatibility. The results showed that transplanting these gelatin-incorporated patches led to enhanced heart function, likely by upregulating cardiac-specific gene expression and reducing inflammation in the host tissue, which contributed to an improved contractile function and decreased adverse remodeling.[124]

Gelatin methacryloyl

Gelatin methacryloyl (GelMA) is commonly used in heart tissue engineering due to its excellent cell compatibility and tunable mechanical properties, especially with UV crosslinking.[54,55] These hydrogels mimic the natural ECM, promoting cell growth and tissue formation. GelMA's mechanical properties can be finely adjusted with light irradiation in the presence of photoinitiators, allowing it to be microfabricated into controlled structures, such as microchannels or patterned configurations, which support vascularization and tissue integration. Its flexibility to replicate specific tissue stiffness and elasticity makes it particularly suitable for cardiac applications with vital mechanical properties. GelMA has been proven to be effective in bone, cartilage, cardiac, and vascular tissue engineering, as well as drug delivery and biosensing.[57] However, there are some limitations. UV crosslinking, although crucial, can negatively impact cell viability.[58] Additionally, GelMA has limited long-term stability

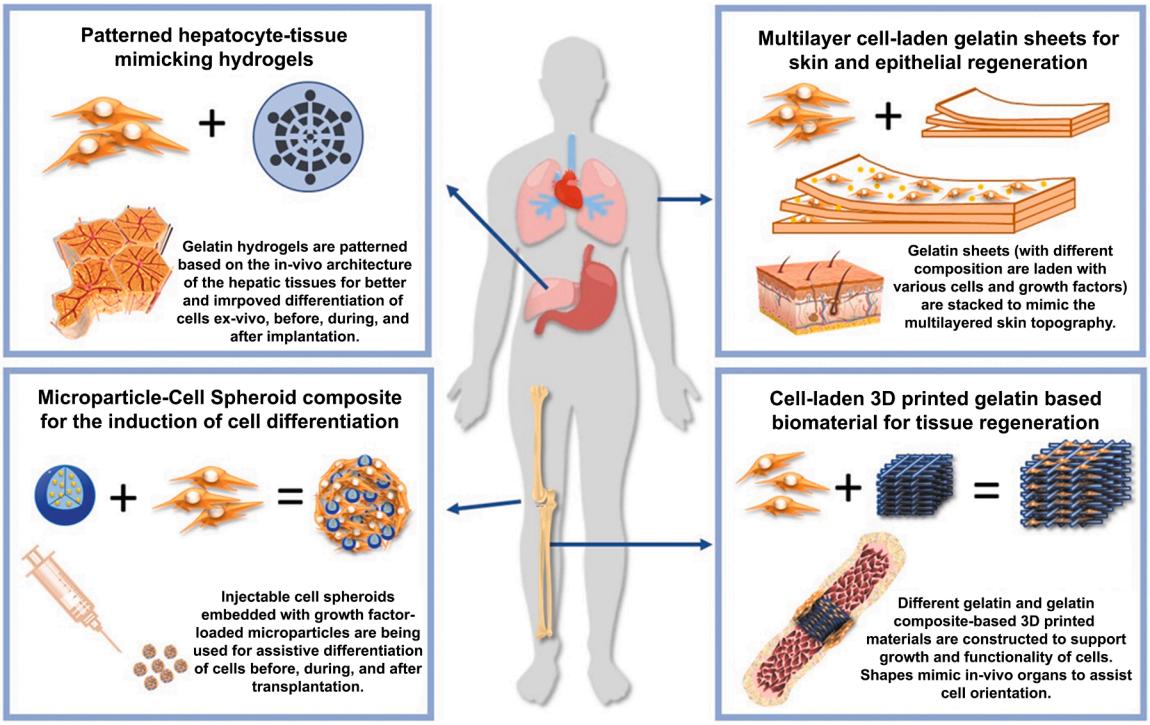

Figure 3. Medical applications of gelatin-based biomaterials

This figure highlights the advancement in gelatin biomaterials, showcasing their use of multi-layered cell-laden sheets for skin and corneal regeneration, patterned hydrogels that mimic natural microenvironments for targeted cell differentiation, injectable spheroids for cell transplantation, and 3D printed scaffolds for repairing bone and cartilage. Reproduced with permission from Bello et al.[123]

in physiological conditions unless further modified,[56] which could hinder its sustained effectiveness in tissue regeneration applications.

A study conducted by Nikkhah et al.[125] investigated the formation of endothelial cord structures using micropatterned GelMA hydrogels. Through precise micropatterning techniques, the researchers created GelMA constructs with varying shapes and heights to examine their effects on endothelial cell behavior and organization. They discovered that the shape of the GelMA constructs was crucial in guiding the development of well-organized and durable cord structures by endothelial cells. Specifically, constructs with optimized heights and geometries provided the most favorable microenvironment, enhancing cell alignment, elongation, and connectivity, which are essential for forming stable vascular networks. Their study underscores the potential of GelMA hydrogels in controlling the morphology of endothelial cells, which is vital for applications in tissue engineering, such as creating vascularized tissue constructs for cardiac and other organ regeneration.

In a study conducted by Lee et al.,[126] the group explored the use of GelMA for cardiac tissue engineering combined with carbon nanotubes (CNTs) and reduced graphene oxides (rGOs), demonstrating improvements in electrophysiological properties, electrical conductivity, mechanical stiffness, and the maturation of CMs. The integration of these conductive materials aimed to replicate the electrical environment of native cardiac tissues, essential for synchronized cell contractions. Additionally, adding fibronectin to GelMA hydrogels enhanced CM survival and spreading, providing an ECM component facilitating cell adhesion and proliferation. The study findings indicated that different functionalizations led to distinct forms of tissue maturation: GO resulted in atrial-like tissues, CNTs in ventricular-like tissues, and rGO-GelMA in a mixed phenotype resembling cardiac muscle cells. This differentiation suggests that tailored functionalization of GelMA with specific conductive materials can guide the formation of specific cardiac tissue types, supporting the development of biomimetic heart models for research and therapeutic applications,[127] as seen in Figure 4.

In another study, CMs in GelMA-coated microchannels displayed organized growth guided by fluid flow, resulting in tissues similar to cardiac fibers with inherent beating capabilities.[55]

Annabi et al.[128] developed a heart-on-chip platform using photo-crosslinked GelMA hydrogels to coat microfluidic devices for drug screening in biomedical engineering. They demonstrated that the GelMA solution could be injected into microchannels and UV-crosslinked to form a coating of controllable thickness. This system allows cell incorporation within the hydrogel, creating a tissue-mimicking microenvironment with physiological conditions, such as oxygen/nutrient supply and shear stress. This microfluidic GelMA platform shows potential for studying cell-biomaterial interactions, biosensing, and drug screening by closely replicating the native tissue environment.

Chen et al.[129] developed a GelMA-based microfluidic platform with a bilayer membrane device to simulate physiological

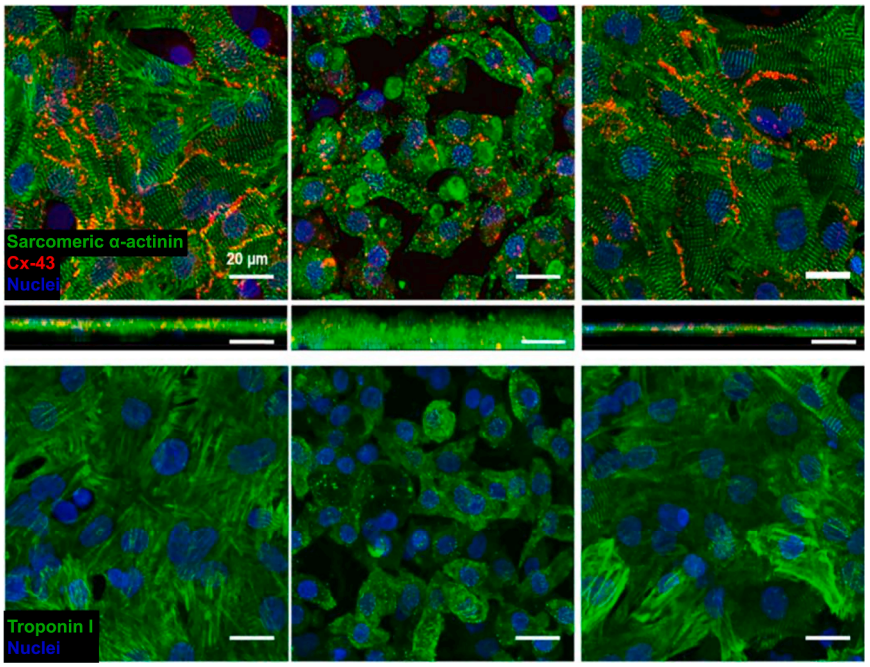

Figure 4. Effects of carbon nanoparticles on GelMA constructs

This image shows GelMA constructs modified with carbon nanotubes, demonstrating increased levels of CX43 and troponin I expression and improved cellular alignment. Reproduced with permission from Nikkhah et al.[126]

cardiovascular cell-cell interactions. While the study does not specifically address conductive polymers or materials, the platform's use of GelMA hydrogel could potentially be combined with conductive materials in future research to enhance the electrical properties of the system. Incorporating conductive polymers into such platforms could help mimic the electrical conductivity of native tissues, which is crucial for studying cardiac and vascular cell behavior under electrical stimulation or flow-induced shear stress. This approach may provide new insights into the role of electrical signals in vascular and valvular biology.

Collagen

Collagen is a structural protein that is primarily derived from the ECM and is found abundantly in connective tissues throughout the body. It plays a critical role in providing structural support to the heart, facilitating stem cell attachment, and transporting essential molecules necessary for heart repair and regeneration.[130] Collagen is typically crosslinked through enzymatic or chemical processes, which help to stabilize its structure and enhance its mechanical properties. These crosslinking methods are crucial for maintaining the integrity of the heart, distributing internal forces, and providing the required strength and flexibility for optimal heart function. Its importance in cardiac function cannot be overstated.[131]

Collagen-based biomaterials for tissue engineering were investigated by Wang et al.,[132] examining their diverse applications, potential avenues for future development, and challenges in the field. The study's emphasis on tissue regeneration underlines the versatility of collagen, particularly its ability to combine with other substances and serve as an ECM, providing structural support and biochemical cues that promote cell adhesion, proliferation, and differentiation. Collagen's adaptability makes it suitable for various tissue engineering applications, from cardiac patches and skin grafts to bone scaffolds, due to its biocompatibility and ability to mimic natural tissue environments.

Regarding the types of collagens, the study likely refers to type I collagen, which is predominant in bone, skin, and tendon, and type II collagen, which is found in cartilage, as these types are commonly used in tissue engineering applications. Additionally, type III collagen, which plays a role in skin and blood vessels, and type IV collagen, found in the basement membrane, are also important in some tissue engineering contexts, especially when mimicking the ECM.

The study also highlighted the potential for enhancing collagen's mechanical and biological properties through crosslinking or incorporation with synthetic polymers, aiming to improve its stability and functionality in dynamic environments, such as the heart. This versatility contributes to collagen's significance in biomaterial development, making it a promising candidate for future advancements in regenerative medicine.

Curley et al.[133] investigated myocardial tissue engineering as a strategy to treat heart failure resulting from MI. They aimed to repair damaged LVs using minimally invasive procedures involving injectable biopolymers combined with cells. These biopolymers included alginate, fibrin, collagen, and chitosan, which served as scaffolds to promote tissue regeneration and improve cardiac function. The study developed biocompatible heart muscle patches that closely resembled the natural myocardium and supported tissue repair in the infarcted area. The injectable biopolymers provided a scaffold that facilitated cell delivery and retention in the damaged tissue, enhancing localized regeneration potential. Collagen emerged as a crucial component in this approach, providing structural support, stiffness, and resistance to deformation, which is critical for maintaining the heart muscle's integrity during contractions. The myocardial collagen matrix, primarily composed of type I and III collagens, is key to preserving heart muscle structure and function. Each collagen type contributes differently to the myocardium's mechanical strength and elasticity, essential for promoting stem cell differentiation into CMs and supporting cardiac tissue regeneration and functional recovery post-MI.[134,135]

Silk

Silk is a natural biomaterial used in cardiac tissue engineering due to its remarkable biocompatibility, mechanical properties, and versatility in forming films, scaffolds, and hydrogels. It comprises silk fibroin (SF) and silk sericin (SS), with SF offering strong

mechanical properties that can be tailored through structural modifications, while the SS enhances cell adhesion and proliferation and controls antioxidant properties beneficial for cardiac tissue repair. The extraction methods employed significantly impact the properties and control antioxidant applications of SF and SS in tissue engineering. Additionally, silk-based materials are cost-effective, durable, and can be utilized for *in vivo* tracking due to their photoluminescent properties.[135,136]

The impact of SF on Alg-Gel hydrogels for cardiac bioink formulations was explored by Vettori et al.[137] The study aimed to improve Alg-Gel hydrogel's structural and functional properties for cardiac tissue engineering. Adding 1% SF enhanced the hydrogel's elasticity and printability without compromising cell viability, allowing the bioink to be extruded smoothly and form stable, well-defined structures suitable for 3D bioprinting. This addition also improved the contractile function of cardiac spheroids, supporting synchronized beating and mimicking native heart tissue functionality. However, a higher SF concentration (2%) negatively affected pore size and cell viability, reducing nutrient and oxygen diffusion, which hindered cell growth and function. The study concluded that 1% SF in Alg-Gel hydrogels optimize mechanical properties and cardiac cell function, showing promise for 3D bioprinted cardiac tissue applications and advancing the development of functional cardiac constructs.

Cetin et al.[138] explored the use of 3D SF scaffolds for cardiac tissue engineering, focusing on the potential of human adipose-derived MSCs (hAD-MSCs) for cardiac regeneration. The research investigates the properties of SF scaffolds, such as their morphology, swelling behavior, and biodegradability. The results show that SF scaffolds can support the proliferation and cardiomyogenic differentiation of hAD-MSCs. The study further demonstrates that SF scaffolds promote the expression of key cardiac biomarkers, such as troponin I, connexin 43, and myosin heavy chain, which are crucial for cardiac tissue function. These findings suggest that SF scaffolds could be a promising material for cardiac tissue engineering, with potential applications in repairing heart tissue damaged by conditions like MI. Integrating conductive materials, such as conductive polymers or nanoparticles, into the scaffolds could improve their electrical conductivity, enhancing cell-to-cell communication and promoting better tissue integration and functionality in cardiac applications.

Fibrin

Fibrin is a natural biopolymer found primarily in the blood, where it plays a crucial role in the blood clotting process. It is produced when fibrinogen, a soluble protein in the blood, is converted into insoluble fibrin strands during coagulation. Fibrin is notable for its biocompatibility, ability to integrate cells and growth factors, and biodegradability. It is essential in the cardiovascular repair mechanism as a scaffold for cardiac tissue engineering. Its flexibility allows for the tailored mimicry of the ECM, making it ideal for crafting heart valves, cardiac patches, and small-diameter vessels. Moreover, fibrin-based injectable cardiac tissue engineering aims to bolster cell therapy outcomes in cardiovascular repairs, leveraging fibrin's capacity to enhance cell therapy efficacy by facilitating specific homing and *in situ* cell retention.[139]

Chang et al.[75] developed a fibrin-based cardiac patch containing neuregulin-1 (NRG-1) for treating MI. Male C57BL/6 mice (6–8 weeks old) were divided into four groups: Sham, MI, Patch, and Patch+NRG-1, which were used to assess the effectiveness of the treatment in improving MI heart function. The patch leverages the biocompatibility and ECM-like structure of fibrin, combined with the regenerative capabilities of NRG-1 via the ErbB signaling pathway, to promote CM proliferation, reduce cell apoptosis, encourage angiogenesis, and inhibit fibrosis. However, a major limitation of fibrin is that it can restrict the exchange of oxygen and nutrients with the outer environment, which may affect the long-term viability of the cells within the patch.

Histology results (Masson's trichrome staining) revealed reduced myocardial fibrosis and infarct size on day 28 after MI. Immunochemistry results for TUNEL staining indicated reduced cell apoptosis (7.06% in the Patch+NRG-1 group vs. 33.02% in the MI group). Also, CD31 staining demonstrated increased blood vessel formation in the infarct border zone, and Ki67/cTnT/DAPI staining revealed increased CM proliferation in the Patch+NRG-1 group. Echocardiography results for M-mode imaging showed improved LV function, with significantly higher LV ejection fraction and LV fractional shortening (LVFS) values in the Patch+NRG-1 group compared with the MI group (36.78% vs. 21.88%, respectively). In clinical practice, LVFS values in heart failure patients often fall below 30%, and values above 30% indicate improved cardiac function, suggesting that the patch may have clinical relevance in improving heart function and patient survival. Higher LVFS values are associated with better survival rates, so the observed improvement in LVFS suggests potential benefits for patients with MI and heart failure. Collectively, all results for the Patch+NRG-1 group showed significant benefits, including reduced cell apoptosis, improved LV contraction, enhanced cardiac function, reduced myocardial fibrosis, and smaller infarcted scar size. These outcomes target different aspects of MI recovery: reducing apoptosis protects CMs, improving contraction and cardiac function enhances heart performance, while reducing fibrosis and scar size prevents further heart damage. Together, these findings highlight the patch's promising potential for MI treatment.

Shaik et al.[140] investigated the development and testing of fibrin-enriched cardiac ECM (Fn-cECM) hydrogels to promote angiogenesis. The cardiac ECM (cECM) is the natural matrix found in cardiac tissues, providing structural and biochemical support to heart cells. It is derived from the heart tissue itself and is crucial for maintaining tissue integrity and functions.[141] The research demonstrated the characteristics of hydrogels by comparing storage moduli, complex moduli, swelling ratios, and degradation rates between cECM and Fn-cECM. Fn-cECM hydrogels exhibited faster gelation times, improved mechanical stiffness, and lower swelling ratios compared to cECM, making them suitable for pre-gel solution mixing and catheter delivery. The study demonstrated that Fn-cECM hydrogels promoted robust vascular network formation in human umbilical vein endothelial cells and enhanced angiogenesis by increasing tube formation and vascular endothelial growth factor (VEGF) secretion. Furthermore, the Fn-cECM hydrogels induced more robust tube network formation and VEGF secretion in hMSCs and promoted angiogenic sprouting in hMSC spheroids.

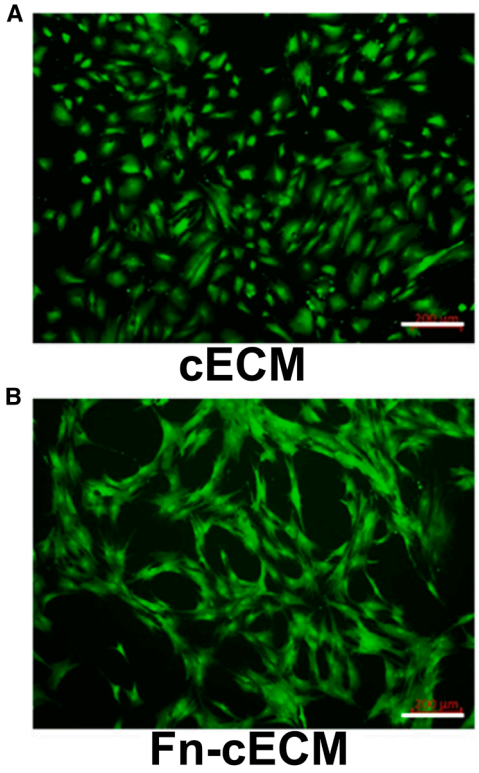

Figure 5. Vascular network formation and VEGF secretion by hMSCs seeded on hydrogels

(A) Representative images of Calcein AM-stained hMSCs seeded on cECM. (B) Representative images of Calcein AM-stained hMSCs seeded on Fn-cECM hydrogels, demonstrating differences in vascular network formation. Scale bars: 200 μm. Reproduced with permission from Shaik et al.[140]

The findings suggest that blending fibrin with cECM hydrogels accelerates gelation and enhances proangiogenic properties, making Fn-cECM a promising material for cardiac tissue engineering. However, rapid degradation observed in Fn-cECM hydrogels may require further modification for improved stability, and the study recommends future optimization and evaluation in MI models as seen in Figure 5.[140]

CONDUCTIVE POLYMERS FOR CARDIAC BIOENGINEERING

Recent research has focused on exploring the potential of conductive polymers in regenerative medicine, particularly in cardiac tissue engineering (Table 2). Conductive hydrogel formulations, for instance, have positively impacted cardiac cells by promoting electrical conduction in non-conductive areas. This property is particularly valuable for mimicking native tissue and preserving the electrical connection between myocardial cells in an infarcted heart. Understanding the critical role of electrical signaling in the native myocardium and cell proliferation during disease, compared to healthy tissues, is paramount. Such insights help to identify similarities and differences between the two cell types, crucial for correcting specific signaling pathways in disease models to restore them to a healthy state.[142,143]

In addition to their role in regenerative medicine, conductive polymers also play an essential role in heart function and the electrical coupling of heart cells within engineered scaffolds, which allows heart cells to communicate and coordinate contraction, restoring heart function in damaged tissues.[144] A variety of conductive polymers, such as carbon nanotubes, gold nanostructures, graphene, polypyrrole, polyaniline, and MXene, have been investigated for their potential to improve electrical conductivity in the heart.[145] This section will describe some of the conductive polymers used in biomedical engineering, including cardiac applications.

Carbon nanotubes

CNTs are derived from carbon atoms and can be produced through methods such as chemical vapor deposition, arc discharge, or laser ablation. They hold promise for regenerating cardiac tissue due to their strong nature and unique mechanical and electrical conductive properties.[146] CNTs are easily chemically modified, making them excellent candidates for creating engineered cardiac structures. Combining CNTs with polymeric scaffolds enhances cardiac regeneration by improving CM behavior, such as synchronized contractility.[147] The elongated shape of CNTs is advantageous for replicating the anisotropic structure of heart muscles, enabling the creation of finely detailed scaffolds to accurately mimic cardiac tissues.[148]

A study by Barrejón et al.[148] investigated the use of CNTs to develop scaffolds to regenerate damaged cardiac tissues. The study highlights that incorporating CNTs significantly enhances the CM synchronous contractility. The elongated shape of CNTs effectively mimics the structural features of the myocardium, enabling the creation of micropatterned scaffolds with nanoscale precision to better replicate cardiac tissue architecture. Micropatterning was achieved by using techniques such as nanoimprinting, laser etching, or electrospinning, which allow for the precise control of scaffold structure at the micro- and nano-scale. This study underscores the potential of engineered CNT constructs as innovative platforms for improving cardiac tissue functionality.

Gold nanoparticles

Gold nanoparticles are small gold particles typically ranging in size from 1 to 100 nm in diameter. Their shape can vary, with common forms including spherical, rod-like, and cylindrical shapes, which contributes to their unique optical, electronic, and chemical properties.[149] These nanoparticles can be customized with different compounds for various medical uses. They are well-tolerated by the body and can be precisely targeted, showing promise for innovative therapeutic applications.[150]

Graphene

Graphene is a highly promising material for tissue engineering due to its exceptional ability to interact with a wide range of biomolecules, including DNA, proteins, enzymes, lipids, and carbohydrates. These interactions make graphene valuable for applications in regenerative medicine, as it can facilitate cell attachment, enhance signaling pathways, and support tissue growth.[151] The ability of graphene to interact with DNA is particularly beneficial as it can aid in the delivery of genetic material

Table 2. Properties and applications of conductive biomaterials

Conductive polymers	Properties	Applications
Carbon nanotube (CNT)	strong mechanical and electrical conductance makes them suitable for improving cardiac regeneration and drug delivery.[79,80]	cardiac regeneration, drug delivery (crosses the blood-brain barrier), biosensors, tissue engineering (cell tracking, microenvironment sensing, stem cell growth), bioimaging (contrast agents in ultrasound/photoacoustic imaging), cancer therapy, infectious disease, and CNS disorder diagnostics and treatment.[81–83]
Gold nanoparticles (GNPs)	biocompatibility and size-dependent toxicity influence their use in drug delivery and bio-imaging.[84,85]	drug delivery (targeted delivery of drugs/DNA), cancer treatment (photothermal therapy), bio-imaging (CT and photothermal microscopy), bone tissue engineering, and biosensors[86–88]
Graphene	exceptional conductivity and mechanical strength support cell growth and bioactive molecule release, essential for drug delivery and biosensors.[89]	drug delivery, biosensors (sensitive electromechanical sensors), tissue engineering (conductive scaffolds), antimicrobials (implant coatings), deep brain implants, neural interfaces (improved brain signal detection), blood glucose sensors[90]
Graphene oxide (GO)	semi-conductivity and antimicrobial properties make it suitable for tissue engineering and biosensors.[91,92]	tissue engineering, biosensors, cardiac regeneration, antimicrobial coatings for medical devices and packaging, drug delivery, clinical diagnostics, and DNA sequence detection.[93,94]
MXene	high conductivity and mechanical properties help in tissue engineering and biohybrid platforms to support cardiomyocyte maturation.[95,96]	tissue engineering, regenerative medicine, and biohybrid platforms to enhance cardiomyocyte maturation and attachment.[97,98]
Polypyrrole (PPy)	conductivity and high biocompatibility make it suitable for cardiac tissue engineering and wound healing[99,100]	cardiac tissue engineering, enhancing electrical signaling in cardiac scaffolds, biodegradable patches for myocardial infarction repair, neural regeneration, drug delivery, biosensors, and wound healing.[101,102]
Polyaniline (PANI)	highly conductive and biocompatible, ideal for cardiac regeneration and conductive scaffolds to restore electrical function.[103–105]	cardiac regeneration, conductive scaffolds for restoring electrical function in injured hearts, promote cardiomyocyte maturation and electrical signaling.[106,107]

and improve gene therapy applications. By embedding graphene into scaffolds, its stability and efficiency in gene delivery are enhanced, allowing for more precise control over cellular behavior, such as promoting cell differentiation, proliferation, and tissue repair.[152]

Furthermore, graphene has become an essential material in biomedical applications due to its unique properties, including its ability to influence cell growth and control the release of bioactive compounds, making it particularly valuable in regenerative medicine. Its exceptional conductivity, mechanical strength, and chemical stability, derived from its honeycomb lattice structure, allow for a wide range of potential applications.[151,152] Graphene can also be engineered into different forms, such as single-layer graphene and GO, which increases its flexibility and adaptability for specific uses.[153] Since its discovery, graphene has garnered significant interest and found widespread use across many scientific disciplines.[154]

Graphene has gained widespread attention across various fields of biomedical engineering due to its unique properties, aiding in extensive cytotoxicity analyses to ensure safe clinical applications. Several studies have assessed the biological toxicity of graphene on different cell types, including fibroblasts, epithelial cells, and neurons.[155–157] A study by Dreanca et al.[158] focused on dental materials, demonstrating graphene's biocompatibility through *in vitro* and *in vivo* tests; the implications extend beyond dentistry. The results revealed that the materials were non-toxic to dental cells and did not cause acute toxicity, inflammation, or systemic organ toxicity in animal models, confirming the material's potential for broad biomedical applications, including tissue engineering and regenerative medicine. In cardiac applications, graphene's biocompatibility holds promise for enhancing heart tissue engineering, where it can support cardiac regeneration and facilitate better integration with heart cells.

A study by Fakhrali et al.[159] focused on creating a composite nanofibrous scaffold that incorporates graphene using electrospinning. These scaffolds were made by the crosslinking of water-soluble polymers, and cells were loaded into them for further testing. The researchers conducted various analyses, including imaging, X-ray diffraction, water contact angle measurement, tensile testing, and biodegradation assessments. The MTT assay was used to assess sample cytotoxicity, and the behavior of human CMs on the scaffold was studied. Results showed that adding PGS (poly[glycerol sebacate]) to poly(ε-caprolactone) (PCL) increased degradation rates, while graphene helped maintain the structural integrity. PGS is a biodegradable elastomer often used in cardiac and vascular tissue engineering due to its flexibility and biocompatibility. PCL increased degradation rates, while graphene helped to maintain structural integrity. Cell

attachment, growth, proliferation, and migration on the scaffolds were observed over 1, 3, and 7 days, indicating promising cell behavior on the hybrid nanofibers.

Graphene oxide

GO, a functional derivative of graphene, has garnered significant attention for its potential in biomedical applications due to its remarkable versatility and biocompatibility.[160] Over time, researchers have increasingly explored its use in a variety of fields, including drug delivery, tissue engineering, biosensors, and medical imaging, owing to its unique properties that enable effective interaction with biological systems and enhancement of therapeutic outcomes.[161]

A study conducted by Choe et al.[162] focused on GO, aiming to create microgel systems for delivering MSCs with strong antioxidant properties to protect them after a heart attack. The research found that MSCs enclosed in rGO/alginate microgels demonstrated higher survival rates under oxidative stress compared to MSCs not enclosed in the microgel, which resulted in better outcomes in heart attack models by reducing damage and improving heart function.

In another study by Li et al.,[163] GO was used to generate bio-inks for tissue engineering applications. By combining GO with alginate and gelatin, 3D printability for cell support was significantly enhanced. The concentration of GO used in the bio-ink formulations ranged from 0.05% to 0.5% (w/w). Compared to traditional bio-inks, the addition of GO improved the structural integrity and bioactivity of the printed scaffolds. Specifically, the researchers found that 0.05%–0.1% (w/w) GO in an Alg-Gel hydrogel improved 3D printability and printing resolution. A concentration of 0.05% (w/w) GO was used to evaluate the effect on bio-ink preparation and performance. The highest achievable GO concentration was 0.5% (w/w), as higher concentrations resulted in undispersed GO content that could cause nozzle clogging during printing. When GO content exceeded 0.2%, the morphology deteriorated due to decreased storage modulus and GO flakes potentially hindered the crosslinking of alginate after printing. These results support that adding GO to the bio-ink can improve cell affinity and viability, making it a promising candidate for novel bio-ink formulations.

MXene

MXene is a 2D material with metallic conductivity, optical and mechanical properties, hydrophilicity, chemical stability, and a large surface area.[164] It is produced by etching the "A" metal layer in the MAX phase, creating 2D nano-layers of MXenes with surface functional groups. MXene is being explored for applications in cardiac repair.[165,166] Additionally, MXene reduces bacterial attachment and proliferation, enhancing its biocompatibility.[167] When paired with electrical field stimulation, these biohybrid platforms, which may include MXene combined with hydrogels, polymeric scaffolds, or other bioactive materials, greatly improve cell growth and maturation, especially in induced pluripotent stem cell-derived CMs (iPSC-CMs).[97] Compared to traditional scaffolds or materials that do not utilize electrical stimulation, these biohybrid systems show significantly enhanced cell differentiation, proliferation, and functional maturation.

Asaro et al.[97] developed a conductive biohybrid platform using collagen type I with MXene (Ti3C2Tx). This platform exhibited enhanced electrical properties and mechanical strength while inhibiting bacterial attachment. It facilitated iPSC-derived CMs' attachment, elongation, and maturation under external electrical stimulation. The study highlights the potential of this biohybrid platform for a range of biological applications that require electrical conductivity, demonstrating promising outcomes for use in tissue engineering and regenerative medicine.

Another study on MXene-based materials for cardiac repair was conducted by Ye et al.[168] This study focused on the potential in biomedical applications, particularly tissue engineering. MXene-based hydrogels exhibit excellent electrical, chemical, and mechanical properties, supporting cardiac tissue regeneration. Studies have shown that MXene-based hydrogels can enhance the expression of cardiac-related genes, improve the synchronous beating of CMs, and have no cytotoxicity, aiding cardiac repair after MI. Additionally, MXene quantum dots in hydrogels offer anti-inflammatory properties and promote cellular activity, making them promising candidate for tissue repair and treatment of inflammatory and degenerative diseases, including cardiac applications[169]

Polypyrrole

Polypyrrole (PPy) is a conductive polymer widely studied in tissue engineering. It is valued for its biocompatibility, conductivity, and ease of synthesis.[101] Several cell types, including neurons, fibroblasts, and endothelial cells, have been shown to adhere and grow on PPy substrates in the laboratory, suggesting potential applications in cardiac tissue regeneration and electrical signal transmission. A study indicates that PPy-containing nanofibers can enhance cell attachment, proliferation, and the expression of cardiac-specific proteins.[170]

Guo and Ma[170] utilized electrically conducting polymers, including PPy, to fabricate conductive biomaterials for tissue regeneration, covering formats such as films, nanofibers, hydrogels, and scaffolds. Their research demonstrated the capacity of conductive polymers to stimulate cells with electrical signals, showcasing the development of degradable conductive composite films and copolymers. These innovations have been shown to enhance cell behavior and promote tissue regeneration in tissue engineering applications.

In a study by Kai et al.,[171] PPy was utilized in cardiac tissue engineering to create bioactive scaffolds for cardiac regeneration. These scaffolds were generated by incorporating various concentrations of PPy into PCL/gelatin nanofibrous scaffolds. Increasing the concentration of PPy (ranging from 0% to 30%) resulted in thinner fibers and higher tensile strength. The PPG15 scaffold, containing 15% PPy in PCL, exhibited an optimal balance of conductivity, mechanical strength, and biodegradability, which enhanced cell attachment, growth, and the expression of cardiac-specific proteins compared to the PPG30 scaffold. The study underscored the critical role of conductivity, mechanical properties, and biodegradability in designing scaffolds for cardiac regeneration.

The study by Ezazi et al.[172] aimed to develop a biodegradable cardiac patch with conductivity and elasticity for heart tissue engineering. They combined PGS, collagen, and PPy using the

evaporation method, which involves dissolving the polymer blend in a solvent, followed by solvent evaporation to create thin, solid films or coatings. This approach was used to treat MI. Results revealed that the composite containing 5% PPy exhibited increased blood wettability compared to pure PGS, indicating its potential for attracting proteins due to PPy's hydrophobic nature. Furthermore, the 0.5%–5% PPy patch demonstrated improved conductivity, reaching 0.06 S compared to lower PPy concentrations. The study also assessed the patches' mechanical properties, degradation rate, protein adsorption, drug release, and cell viability, highlighting their potential in cardiac repair applications.

Polyaniline

Polyaniline (PANI) is a conductive polymer commonly used in cardiac tissue engineering due to its biocompatibility and ability to support cell development and growth.[7] Conductive polymers, such as PANI, are extensively researched for their conductivity and biocompatibility with cardiac tissue regeneration, presenting potential treatment options for MI.[6,7] PANI nanotubes (PANINTs), particularly when dendronized (as PGLD-PANINTs), have been investigated for their potential as scaffolds in cardiac tissue engineering. A study conducted by Moura and de Queiroz[173] showed that PGLD-modified PANINTs could promote cell growth. The study showed that PGLD-coated PANINTs are non-cytotoxic to Chinese hamster ovary (CHO) cells, and microcurrent stimulation supports the differentiation of cardiac cells cultured on these scaffolds. PGLD-PANINTs have shown the potential to serve as a biocompatible, electroactive 3D matrix for cardiac tissue engineering. These findings were confirmed through XPS analysis, which showed the presence of PGLD on the surface of the PANINTs. The study also demonstrated that PGLD-PANINTs electrospun fibers, produced from a 10% w/v dispersion of PGLD-PANINTs in a 50:50 mixture of dichloromethane and dimethylformamide, promoted better proliferation and differentiation of myocardial cells compared to casting PGLD-PANINTs films. The electrospinning process was performed at an applied voltage of 15–20 kV, and the resulting scaffolds showed excellent biocompatibility with no toxicity in CHO cells, indicating high cell viability. These electroactive and biocompatible characteristics suggest the potential use of PGLD-PANINTs in heart tissue engineering, highlighting the material's promising role in advancing cardiac regeneration and offering new avenues for treatment in MI.

Ghovvati et al.[174] explored the incorporation of PANI into electroconductive biomaterials for cardiac tissue engineering. They discovered that integrating PANI into scaffolds made of polymeric materials enhanced cell stimulation, facilitated the controlled release of therapeutic agents, and improved cardiac functions in rat models of MI. The study demonstrated significant improvements in CMs' maturation, contraction, and electrical signaling, underscoring the potential of PANI-based biomaterials for promoting cardiac tissue regeneration and enhancing heart function.

A study by Liu et al.[175] investigated the use of PANI in cardiac tissue engineering applications. They discovered that PANI significantly improves CM adhesion, proliferation, and responses to electrical stimulation, thereby beneficially altering cell electrophysiology and promoting tissue formation.[176] Additionally, PANI was found to form a conductive complex with polymeric materials, resulting in excellent electrical and mechanical properties that support CM growth. This research highlights the critical role of PANI in the repair of MI, specifically by enhancing CM growth, improving electrical conductivity, and fostering tissue development through better cell communication and alignment.

CONCLUSIONS AND FUTURE DIRECTIONS

This review highlighted the significant role of electrically conductive polymers in cardiac tissue engineering. These conducting polymers have numerous advantages, including biocompatibility, adjustable conductivity, ease of synthesis, and flexibility, making them ideal for creating bioactive scaffolds. These scaffolds support cell electrical signaling and enhance cardiac function post-implantation. Unlike hydrogels, conductive polymers provide the necessary electrical conductivity for effective cell communication, which is crucial for integrating implanted materials with native myocardial tissues.

Despite promising results in both *in vitro* and *in vivo* studies, substantial challenges remain in transitioning these materials from laboratory-based modes to clinical applications. Several fabrication techniques have been developed to produce conductive biomaterials, such as composite hydrogels, enhancing their potential for tissue regeneration. However, further research is crucial to fully explore these materials' potential in cardiac regeneration and to ensure their properties align with the dynamic mechanical environment of the beating heart. Future work must refine this material and its applications to develop safe, effective, and reliable CVD therapies.

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AUTHOR CONTRIBUTIONS

W.A.S. and C.G. jointly decided to focus on the topic at the center of the review article; W.A.S. performed the literature search and drafted the original manuscript; C.G. critically revised the work.

DECLARATION OF INTERESTS

The authors claim no competing interests.

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