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ADVANCEMENTS IN CARDIAC TISSUE ENGINEERING THROUGH CONDUCTIVE BIOMATERIALS

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Abstract

Cardiac tissue engineering (CTE) has emerged as a promising strategy to address the limitations of conventional treatments for myocardial infarction and heart failure. A critical challenge in myocardial regeneration is restoring synchronized electrical activity, which is essential for coordinated heart contractions. Conductive biomaterials have gained significant attention due to their ability to combine structural support with electrical conductivity, facilitating cardiomyocyte alignment, signal propagation, and functional integration with native myocardium. This review explores recent advancements in the design and application of conductive biomaterials, including natural polymers, conductive polymers, carbon-based nanomaterials, and metallic nanoparticles. The mechanisms through which these materials promote regeneration are discussed, alongside the challenges related to biocompatibility, degradation control, and vascularization. Furthermore, future perspectives highlight the role of 3D bioprinting, stem cell therapies, and nanotechnology in advancing CTE toward clinical translation. Conductive biomaterials hold great potential to revolutionize cardiovascular therapies, offering new possibilities for personalized and minimally invasive treatments aimed at restoring heart function.

Keywords: cardiac tissue engineering, conductive biomaterials, myocardial regeneration, hydrogels, stem cells, nanotechnology, 3D bioprinting

Introduction

Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide, with myocardial infarction (MI) representing a major clinical challenge due to the irreversible loss of functional cardiomyocytes and the subsequent development of fibrotic scar tissue [1-4]. Following an MI event, the limited regenerative capacity of adult cardiac tissue results in structural and functional deterioration, often culminating in heart failure, a condition with high morbidity and significant economic burden on healthcare systems [5-10]. Conventional therapeutic strategies, including pharmacological interventions, implantable devices, and heart transplantation, are limited by their inability to restore native myocardial architecture and electrical conductivity [4,10]. Heart transplantation remains the gold standard for end-stage heart failure but is hindered by severe donor shortages, risk of immune rejection, and long-term immunosuppressive therapy [4]. These limitations have driven the exploration of innovative approaches, with cardiac tissue engineering (CTE) emerging as a promising interdisciplinary field

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aimed at regenerating damaged myocardium through the integration of biomaterials, cells, and bioactive factors [4,10].

The primary objective of CTE is to create functional cardiac tissue constructs capable of replacing or repairing damaged myocardium, while ensuring the restoration of both mechanical contractility and synchronized electrical signaling [4,10]. The heart's unique electrophysiological properties require engineered scaffolds to support not only cellular adhesion, proliferation, and differentiation but also efficient propagation of electrical impulses to achieve coordinated contractions [5,9]. In this context, biomaterials play a critical role as structural and functional templates that guide tissue regeneration. Natural polymers, such as collagen and chitosan, have been widely investigated due to their biocompatibility and bioactivity, which offer a favorable environment for cell attachment and extracellular matrix (ECM) remodeling [2,3]. Collagen, as the predominant ECM component in the myocardium, provides mechanical support and biochemical cues essential for cardiomyocyte maturation and function [3]. Similarly, chitosan, a polysaccharide derived from chitin, has been employed for its biodegradability, antimicrobial properties, and potential for chemical modification to improve its mechanical and conductive characteristics [2]. However, while natural polymers excel in bioactivity, they lack intrinsic electrical conductivity, which limits their ability to support synchronized myocardial contraction [2,3,4].

To address this limitation, recent advancements have focused on integrating conductive materials into scaffold design, enabling the restoration of electrical communication between cardiomyocytes [5,9]. Conductive biomaterials, including conductive polymers, carbon-based nanomaterials, and hybrid composites, mimic the electrophysiological microenvironment of the native heart, thereby promoting synchronized beating and functional integration of engineered tissue [5,9]. Studies have demonstrated that conductive scaffolds can improve the propagation of electrical signals across damaged tissue, reduce arrhythmic risks, and enhance overall cardiac performance [5,9]. For instance, polypyrrole (PPy) and polyaniline (PANi) are two extensively studied conductive polymers that, when incorporated into scaffolds, significantly improve cardiomyocyte contractility and electrical coupling [8,9]. Cui et al. [9] demonstrated that a polypyrrole-chitosan hybrid biomaterial not only supported cardiomyocyte adhesion and growth but also synchronized their contractions and enhanced electrical impulse propagation, highlighting the potential of combining bioactive natural polymers with conductive synthetic components. Similarly, Borriello et al. [8] reported that PANi-doped electroactive substrates can serve as effective patches for cardiac muscle regeneration, offering both mechanical stability and electrical functionality.

Among conductive materials, carbon-based nanostructures such as graphene and carbon nanotubes have gained attention for their exceptional electrical and mechanical properties [5]. These nanomaterials can be incorporated into hydrogels or polymeric scaffolds to create conductive networks that facilitate electrical signal propagation and mechanical reinforcement [5]. Injectable conductive hydrogels, in particular, represent a minimally invasive therapeutic option for post-MI cardiac repair, allowing for localized delivery and conformal integration with irregular tissue geometries [1,11]. Hasan et al. [1] highlighted the advantages of injectable hydrogels, including their ability to deliver therapeutic cells or molecules directly to the infarcted area while providing a supportive microenvironment for tissue regeneration. Such systems not only restore structural integrity but also address the critical need for synchronized electromechanical function, a hallmark of native myocardium [1,5].

Cardiac tissue engineering also relies heavily on the incorporation of appropriate cell sources to populate the engineered constructs. Stem cells, including pluripotent and mesenchymal stem cells, have been explored for their regenerative potential, offering the possibility of differentiating into cardiomyocytes and promoting vascularization within engineered tissues [4,10]. The success of these cellular therapies depends on the scaffold's ability to provide both biochemical cues and biophysical stimuli that guide cell behavior [4,10]. Recent research

emphasizes the importance of designing biomaterials that actively interact with cells through electrical, mechanical, and biochemical pathways, creating a dynamic environment that closely replicates native cardiac tissue [4,5,9].

Despite the progress achieved, several challenges remain. The integration of engineered tissues with host myocardium requires overcoming immune responses, ensuring vascularization, and achieving long-term stability of the implanted constructs [4,10]. Moreover, many conductive materials face limitations related to biocompatibility, potential toxicity, and degradation kinetics, which must be carefully addressed to meet clinical safety standards [5,9]. Standardizing fabrication methods and meeting regulatory requirements for clinical translation further complicate the pathway toward practical application [4,10].

Types and properties of conductive biomaterials

The development of biomaterials for cardiac tissue engineering (CTE) requires careful consideration of their biocompatibility, biodegradability, mechanical integrity, and electrical conductivity, as these properties collectively determine their ability to support myocardial repair and synchronized contraction [4,10]. An ideal scaffold must provide a structural framework that mimics the native extracellular matrix (ECM), promote cardiomyocyte adhesion and proliferation, and enable the transmission of electrical impulses across the regenerated tissue [5,9,10].

Biomaterials used in CTE can be broadly classified into natural polymers, synthetic polymers, conductive polymers, and nanocomposite systems [10]. Natural polymers, such as collagen and chitosan, have been extensively used due to their inherent bioactivity and resemblance to the native ECM [2,3]. Collagen, the most abundant protein in the myocardium, provides essential mechanical support and biochemical signals that guide cell differentiation and tissue remodeling [3]. Chitosan, a biocompatible and biodegradable polysaccharide, offers versatility through chemical modifications that improve its mechanical and conductive properties, making it suitable for cardiac scaffolds and hydrogels [2,9]. Despite their advantages, natural polymers are inherently non-conductive, which limits their ability to support synchronous electrical activity, a critical requirement for functional cardiac regeneration [2,3,9].

To overcome this limitation, conductive polymers have been introduced into scaffold design. These materials possess intrinsic electrical conductivity while maintaining tunable mechanical and biochemical characteristics. Among the most widely investigated conductive polymers are polyaniline (PANi) and polypyrrole (PPy) [8,9,10]. PANi-doped substrates have been shown to improve cardiac tissue contractility and electrical coupling, making them promising candidates for patch-based therapies [8]. Similarly, PPy can be blended with natural polymers, such as chitosan, to create hybrid scaffolds that combine bioactivity with electrical functionality. Cui et al. [9] demonstrated that a polypyrrole-chitosan composite not only supported cardiomyocyte growth but also synchronized their contractions and enhanced the propagation of electrical signals across the tissue. Such hybrid designs highlight the potential of combining synthetic conductivity with natural biomimicry to address the complex requirements of myocardial repair.

A growing body of research focuses on nanocomposite materials, which integrate conductive nanostructures into polymeric matrices to enhance electrical performance and mechanical reinforcement [5,11-13]. Carbon-based nanomaterials, including carbon nanotubes and graphene, are particularly promising due to their superior conductivity and strength [5,13]. Injectable conductive nanocomposite hydrogels have emerged as a minimally invasive strategy for post-MI treatment, allowing localized delivery to the infarcted region. Behnam et al. [11] reviewed systems incorporating carbon or metal-based nanostructures into hydrogels, emphasizing their role in improving the electrical connectivity between cardiomyocytes and promoting tissue regeneration. These hydrogels can conform to the irregular geometries of

infarcted tissue and integrate with the native myocardium, offering advantages over traditional solid scaffolds [1,11].

Table 1. Types and properties of conductive biomaterials used in cardiac tissue engineering

Type of biomaterial	*Examples*	*Key properties*	*Advantages*	*Limitations*
Natural polymers	Collagen, Chitosan	Biocompatible, biodegradable, bioactive [2,3]	Supports cell adhesion and ECM remodeling, low immunogenicity [2,3,9]	Lack intrinsic electrical conductivity, weak mechanical strength [2,3,4]
Conductive polymers	Polyaniline (PANi), Polypyrrole (PPy)	Intrinsically conductive, tunable mechanical properties [8,9]	Enhances electrical signal propagation, improves synchronized contraction [8,9,10]	Potential cytotoxicity, limited biodegradability [5,8]
Carbon-based nanomaterials	Graphene, Carbon nanotubes (CNTs)	High electrical conductivity, superior mechanical strength [5,13]	Promotes cardiomyocyte alignment and maturation, strengthens scaffold structure [5,13]	Risk of long-term toxicity, complex processing [5,13]
Metallic nanoparticles	Gold nanoparticles (AuNPs)	Excellent conductivity, bioactive interactions [15]	Enhances electrical coupling, can stimulate angiogenesis [15]	High cost, potential inflammatory response [15]
Hybrid hydrogels/ composites	Chitosan-PPy, PANi blends, π-π hydrogels	Combination of bioactivity, elasticity, and conductivity [9,14,17]	Injectable, minimally invasive, conform to tissue geometry, customizable degradation profiles [1,11,16,17]	Complex fabrication, scalability challenges [4,10,11]

Table 1 summarizes the main classes of conductive biomaterials utilized in cardiac tissue engineering, highlighting their properties, advantages, and limitations. Hybrid systems are emerging as a preferred approach, combining the bioactivity of natural polymers with the electrical conductivity of synthetic or nanomaterial components to restore myocardial structure and function.

Recent advances have also explored moldable elastomeric scaffolds with integrated conductive nanomaterials. Ahadian et al. [13] reported on polyester-based scaffolds combined with carbon nanotubes, demonstrating improved mechanical resilience and conductivity suitable for dynamic cardiac environments. Similarly, hybrid hydrogels based on human-derived proteins have been developed to enhance elasticity and mimic the mechanical behavior of native heart tissue. Annabi et al. [14] highlighted the potential of these hydrogels to support synchronous electromechanical function while maintaining biocompatibility.

Moreover, gold nanoparticles (AuNPs) have been incorporated into thermosensitive chitosan-based hydrogels to create electrically conductive systems with strong regenerative potential. Baei et al. [15] demonstrated that these hydrogels improve cardiomyocyte adhesion, electrical coupling, and tissue integration, making them suitable candidates for injectable post-MI therapies. The incorporation of metallic nanostructures provides not only conductivity but also unique bioactive properties that can influence cellular behavior [11,15-17].

In addition to material composition, scaffold design must also consider degradation kinetics, as the gradual resorption of the scaffold should align with the rate of new tissue formation [10,12]. Mechanical properties must be tuned to match those of the native myocardium, preventing stress mismatches that could impair integration or trigger fibrotic responses [4,10]. The development of multifunctional scaffolds that integrate electrical, mechanical, and

biochemical cues is therefore essential to achieve complete functional regeneration of the heart [5,10,11].

Mechanisms of action in cardiac tissue engineering

The successful regeneration of functional myocardial tissue requires not only structural support but also the restoration of the heart's electrical and mechanical functions, which are vital for synchronized contraction and efficient blood pumping [4,10]. Conductive biomaterials play a central role in this process by mimicking the native cardiac microenvironment, enabling cell-to-cell communication, and facilitating the propagation of electrical impulses between cardiomyocytes [5,9,14]. Their mechanisms of action rely on a complex interplay of biochemical, mechanical, and electrical cues that drive cardiomyocyte maturation, alignment, and integration with host tissue [9,14,18].

One of the key pathways through which conductive scaffolds operate is the enhancement of synchronous cardiomyocyte contraction. In healthy myocardium, electrical signals propagate through gap junctions to trigger coordinated contractions. After myocardial infarction (MI), scar tissue disrupts this connectivity, leading to asynchronous contractions and arrhythmias [1,4]. Conductive scaffolds help re-establish these pathways by acting as bioelectronic bridges, transmitting signals between isolated clusters of cardiomyocytes [5,9,15]. Cui et al. [9] demonstrated that a polypyrrole-chitosan scaffold facilitated synchronized beating of cardiomyocytes while improving the speed and uniformity of electrical signal propagation, a crucial factor for functional recovery. Similarly, Baei et al. [15] reported that chitosan hydrogels loaded with gold nanoparticles enhanced cardiomyocyte coupling and improved tissue-level electrophysiological performance.

In addition to electrical conductivity, the mechanical properties of scaffolds significantly influence cardiac tissue regeneration. The heart experiences continuous dynamic stress, and scaffolds must replicate its elasticity to promote proper cardiomyocyte alignment and contractility [4,14]. Annabi et al. [14] introduced highly elastic hybrid hydrogels that supported both electrical activity and mechanical resilience, demonstrating that elasticity plays a synergistic role with conductivity in improving cell function. Moreover, Yao et al. [7] developed multifunctional cardiac patches that not only prevented left ventricle remodeling but also supported mechanical load distribution, showing that conductive scaffolds can modulate both structural and electrical aspects of cardiac repair.

Mechanotransduction, the process by which cells convert mechanical stimuli into biochemical signals, is another critical mechanism influenced by conductive biomaterials. Fibroblasts and cardiomyocytes respond to the stiffness and strain of their environment, which affects tissue remodeling and ECM deposition [18]. Leander and Turner [18] emphasized the role of mechanosensitive ion channels in fibroblasts, highlighting how conductive scaffolds with tunable mechanical properties can regulate pathological remodeling and guide healthy tissue regeneration. This suggests that the integration of conductive and mechanical cues in scaffold design is essential for long-term functional outcomes [14,18].

Furthermore, conductive biomaterials serve as platforms for stem cell-based therapies, enhancing cell survival, differentiation, and integration. Stem cells have demonstrated the potential to differentiate into cardiomyocytes and vascular cells, supporting neovascularization and tissue regeneration [19]. Immacolata et al. [19] highlighted the transformative role of stem cells in cardiac regenerative medicine, emphasizing that their therapeutic efficacy depends on a supportive microenvironment. Conductive scaffolds provide the necessary electrical stimulation to guide stem cell differentiation into excitable cardiac tissue, while simultaneously delivering mechanical stability and biochemical cues [14,19]. For example, Ahadian et al. [13] demonstrated that carbon nanotube-based scaffolds promoted the alignment and maturation of stem cell-derived

cardiomyocytes, illustrating how nanomaterials can bridge the gap between electrical stimulation and biological response.

Injectable conductive hydrogels represent another promising mechanism for post-MI therapy. These systems conform to irregular infarct geometries and deliver therapeutic agents directly to damaged regions [1,11,17]. Bao et al. [17] developed an injectable π-π conjugated hydrogel that integrated with host tissue and efficiently restored cardiac function, showcasing how minimally invasive strategies can leverage conductive networks for rapid functional recovery.

Challenges and limitations

Despite significant progress, the clinical translation of conductive biomaterials in cardiac tissue engineering faces numerous challenges. A primary concern is biocompatibility and potential cytotoxicity, as many conductive polymers and nanomaterials, such as polyaniline (PANi), polypyrrole (PPy), and carbon-based structures, may trigger inflammatory responses or oxidative stress if not properly engineered [5,9,11]. For instance, while carbon nanotubes and graphene significantly enhance electrical conductivity, their long-term effects on cardiac tissue remain insufficiently understood, requiring extensive safety evaluations before clinical use [5,13].

Another major limitation is the stability and controlled degradation of scaffolds. Materials must maintain mechanical and electrical performance during the early stages of tissue regeneration but also degrade gradually to allow complete tissue integration. Achieving this delicate balance remains challenging, particularly with hybrid systems that combine natural and synthetic components [10,12,14].

Moreover, there are engineering and manufacturing obstacles related to scaling up production while maintaining reproducibility and regulatory compliance [4,10]. Injectable hydrogels and nanocomposites must meet strict clinical standards regarding sterility, uniformity, and functionality, which adds complexity to their development [1,11,17].

Finally, limited vascularization within engineered constructs restricts nutrient and oxygen delivery, compromising long-term survival and integration of cardiomyocytes and stem cells [4,19]. Addressing these challenges requires multidisciplinary strategies combining material science, bioengineering, and advanced clinical research to ensure safe and effective cardiac therapies.

Future perspectives and clinical translation

Future advancements in cardiac tissue engineering will focus on developing multifunctional conductive biomaterials that closely replicate the native myocardial environment while ensuring safety and clinical applicability. A promising direction involves 3D bioprinting and advanced fabrication techniques, which allow precise spatial organization of cells and conductive components to create patient-specific cardiac patches or injectable systems [6,10]. Integrating nanomaterials such as graphene or carbon nanotubes into these constructs can significantly enhance electrical conductivity and mechanical stability, leading to improved synchronization of cardiomyocyte contractions [5,13].

Stem cell therapies combined with conductive scaffolds are expected to play a key role in next-generation treatments. These systems can provide both electrical and biochemical cues that guide stem cell differentiation into mature cardiomyocytes and vascular cells, improving tissue regeneration and reducing arrhythmogenic risks [14,19]. Additionally, injectable hydrogels loaded with bioactive molecules or therapeutic cells offer minimally invasive solutions for post-myocardial infarction repair [1,11,17].

To achieve clinical translation, future research must address current limitations related to biocompatibility, scalability, and regulatory compliance [4,10]. Collaboration between

material scientists, clinicians, and regulatory bodies will be essential to establish standardized protocols and safety guidelines. By combining cutting-edge biomaterial science with personalized medicine approaches, conductive biomaterials hold the potential to revolutionize the treatment of heart failure and other cardiovascular diseases [5,10,14].

Conclusions

Conductive biomaterials represent a major advancement in cardiac tissue engineering (CTE), offering innovative solutions for the regeneration of damaged myocardium. By combining structural support with electrical conductivity, these materials enable synchronized contraction, improved signal propagation, and functional integration between engineered tissue and native heart structures. Natural polymers such as collagen and chitosan ensure a bioactive environment, while synthetic polymers, nanomaterials, and metallic nanoparticles contribute to enhanced electrical and mechanical performance.

Recent developments, including injectable hydrogels, hybrid scaffolds, and bioengineered cardiac patches, provide minimally invasive and adaptable strategies for repairing myocardial tissue after infarction. Despite these advancements, several challenges remain, such as ensuring biocompatibility, controlling degradation rates, achieving proper vascularization, and scaling up production for clinical use.

Looking ahead, the integration of 3D bioprinting, stem cell-based therapies, and nanotechnology is expected to revolutionize the field, leading to personalized treatments with higher regenerative potential. Through continuous multidisciplinary collaboration, conductive biomaterials have the potential to transform heart failure management and significantly improve patient outcomes.

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