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INJECTABLE BIOACTIVE HYDROGELS FOR MYOCARDIAL INFARCTION REPAIR: CURRENT STRATEGIES, FUNCTIONAL DESIGN AND TRANSLATIONAL PERSPECTIVES

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Abstract

Myocardial infarction remains a major cause of morbidity and mortality, largely because adult heart tissue has limited regenerative capacity after ischemic injury. Conventional therapies improve survival and reduce acute complications, but they do not completely prevent scar formation, adverse ventricular remodeling, and progressive functional decline. Injectable bioactive hydrogels have become promising biomaterial platforms for myocardial repair because they can be delivered by minimally invasive routes, conform to the irregular geometry of the infarction, and provide localized mechanical and biological support, and this article of ours summarizes current hydrogel-based myocardial infarction repair strategies, with a focus on material composition, injectability, freezing behavior, degradation profile, mechanical compatibility, controlled therapeutic administration, electroconductivity, and microenvironment responsive functionality. Particular attention is paid to hydrogels containing exosomes, nanomaterial-reinforced conductive systems, pH-sensitive platforms, and multifunctional formulations designed to modulate inflammation, enhance angiogenesis, support paracrine signaling, and enhance tissue integration. While preclinical studies are encouraging, clinical translation remains limited by challenges related to retention, reproducibility, safety, scalability, regulatory classification, and long-term performance, and future development should focus on standardized, indication-specific hydrogel systems that integrate mechanical stabilization, bioactive delivery, and functional heart repair.

Keywords: myocardial infarction, injectable hydrogels, cardiac repair, bioactive biomaterials, exosomes, electroconductive hydrogels.

Introduction

Myocardial infarction remains one of the most important cardiovascular events worldwide, not only because of its acute mortality, but also because of the long-term burden created by ventricular remodeling, heart failure, recurrent hospitalization, and reduced quality of life [1-4]. In reviewing the recent literature, we observed that conventional management has improved substantially, yet it still cannot fully replace the cardiomyocytes lost after ischemic injury or restore the native architecture of the infarcted myocardium [2]. This gap explains the

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growing interest in regenerative strategies, particularly injectable biomaterials that can be delivered locally and adapted to the dynamic environment of the injured heart [3-5].

Hydrogels have become especially attractive in this field because they can mimic some features of the extracellular matrix, retain water, fill irregular myocardial defects, and provide temporary mechanical support after injection [4], and their therapeutic value is not limited to passive filling; depending on their composition, hydrogels may also serve as carriers for drugs, growth factors, cells, extracellular vesicles, or nanomaterials [5]. We found that this multifunctionality is central to modern cardiac repair, where the goal is not only to limit scar expansion, but also to modulate inflammation, support angiogenesis, and improve tissue integration [6,7].

Recent studies also emphasize that hydrogel performance depends on a delicate balance between injectability, gelation time, biodegradation, mechanical compatibility, and biological activity [7], and from our perspective, this balance is essential because a material that is easy to inject but mechanically weak, poorly retained, or biologically inert may have limited translational value [3,8]. Newer smart hydrogel systems have therefore been designed to respond to pH, oxidative stress, electrical signals, or inflammatory changes within the post-infarction microenvironment [9].

Preclinical evidence suggests that injectable hydrogel-based combination therapies may improve cardiac repair more effectively than single-component approaches [10], and in particular, exosome-bearing hydrogels have gained attention for their potential to prolong paracrine signaling and enhance myocardial recovery [11,12], and experimental studies further suggest that hydrogel-loaded exosomes can regulate immune responses after infarction [12], while oxygen-releasing and vascularization-supportive systems may improve cell survival in the ischemic myocardium [11-13]. Finally, electroconductive biomaterials introduce an additional functional dimension by enabling electrical communication within engineered cardiac tissues [14], particularly when nanomaterial-based conductive hydrogels are used to enhance signal propagation and tissue repair [15].

Injectable hydrogel platforms: composition, properties, and functional design

Injectable hydrogel platforms used for myocardial infarction repair are no longer viewed simply as passive soft materials, but as adaptable biomaterial systems designed to interact with the mechanical, biochemical, and electrical features of the injured myocardium. In the recent literature, we observed that nanomaterial-based electrically conductive hydrogels are increasingly investigated because they may improve local electrical signal transmission, support cardiac cell communication, and partially compensate for the disrupted conductivity of the infarcted region [15], and this aspect is particularly relevant in cardiac tissue, where mechanical support alone is insufficient unless the material also respects the myocardium's electrophysiological nature.

A second important direction is represented by functional electroconductive hydrogels engineered for targeted therapy of myocardial infarction. These systems combine hydrogel networks with conductive components, bioactive cues, or responsive structures to reduce adverse remodeling and improve tissue integration and therapeutic retention [16], and we found this concept particularly relevant because it directly links material design to post-infarction pathophysiology, including inflammation, fibrosis, impaired conduction, and insufficient vascular regeneration.

More advanced formulations have moved toward intelligent delivery systems. For example, injectable pH-responsive conductive hydrogels can exploit the acidic and inflammatory post-ischemic microenvironment to release therapeutic agents in a controlled manner [17]. This design logic is clinically meaningful because infarcted tissue is not

biologically static; it changes over time, and a material that responds to local signals may offer more precise therapy than a conventional depot system.

In parallel, bioprinting technologies have expanded the design space of cardiac biomaterials by allowing spatial organization of cells, polymers, and bioactive factors into more complex constructs [18], and although bioprinted systems are not always injectable, they provide important principles for hydrogel architecture, vascularization, anisotropy, and tissue-like organization, conductive carbon-based scaffolds, particularly those incorporating carbon nanotubes, further illustrate how nanostructured reinforcement can enhance electrical and mechanical performance in cardiac tissue engineering [19].

Injectable functional hydrogels must therefore be designed around several core requirements: biocompatibility, injectability, in situ gelation, controlled degradation, myocardial mechanical matching, therapeutic loading capacity, and electrical or biochemical functionality [20], and from our perspective, the most promising systems are those that integrate several of these properties into a single platform, rather than optimizing a single feature. Functional hydrogels for myocardial infarction are thus best understood as multifunctional therapeutic matrices that can combine mechanical stabilization, controlled release, conductivity, and regenerative signaling [21].

Table 1. Functional design principles of injectable hydrogel platforms for myocardial infarction repair

Design component	Main role in myocardial repair	Representative functional direction and supporting references	Ref.
Conductive nanomaterials	Improve electrical signal propagation and support intercellular electrical communication	Nanomaterial-based conductive hydrogels for cardiac tissue repair	[15]
Electroconductive polymer networks	Support electromechanical integration and targeted therapeutic activity in infarcted myocardium	Functional electroconductive hydrogels for myocardial infarction repair	[16]
pH-responsive conductive systems	Enable microenvironment-sensitive release of therapeutic agents in ischemic or inflamed tissue	Intelligent delivery of metformin and exosomes through injectable pH-responsive conductive hydrogels	[17]
Bioprinted hydrogel constructs	Improve spatial organization of cells, polymers, and bioactive cues	Advanced bioprinting technologies for engineering cardiac tissue	[18]
Carbon nanotube reinforcement	Enhance scaffold conductivity, mechanical behavior, and cardiac tissue engineering potential	Carbon nanotube-based scaffolds for cardiac tissue engineering	[19]
Injectable functional matrices	Provide local retention, mechanical stabilization, and controlled therapeutic delivery	Injectable functional hydrogel materials for myocardial infarction treatment	[20]
Multifunctional hydrogels	Combine mechanical support, controlled release, conductivity, and regenerative signaling	Functional hydrogels for myocardial infarction therapy	[21]

Therapeutic strategies in myocardial infarction repair

Therapeutic strategies based on injectable bioactive hydrogels have evolved from simple mechanical support systems toward multifunctional platforms designed to influence several stages of post-infarction healing, and after myocardial infarction, the injured region undergoes inflammation, extracellular matrix degradation, fibrosis, scar formation, and progressive ventricular remodeling. In this context, hydrogels are attractive because they can be injected locally, adapt to the irregular infarct geometry, and provide a temporary matrix that supports tissue stabilization and therapeutic retention [3-6].

One of the most direct strategies is the use of acellular injectable hydrogels to reduce wall stress and limit adverse ventricular remodeling, and these systems do not necessarily aim to regenerate myocardium on their own, but they may improve the mechanical environment of the infarcted wall and create a more favorable substrate for repair [4-6], and more advanced formulations incorporate drugs, growth factors, or bioactive molecules, allowing controlled release directly within the damaged tissue, this approach is particularly relevant because systemic therapies often have limited local concentration and may not adequately address the complex microenvironment of the infarct zone [5,10].

Exosome-loaded hydrogels represent one of the most promising current directions. We observed that recent studies increasingly focus on extracellular vesicles because they can transfer regulatory signals without the limitations associated with direct cell transplantation. Hydrogel encapsulation may prolong exosome retention, protect them from rapid degradation, and enhance their paracrine effects on angiogenesis, inflammation, fibrosis, and cardiomyocyte survival [11-13], some experimental systems also combine exosomes with oxygen-releasing or vascularization-supportive components, aiming to improve cell survival in the hypoxic post-infarction environment [13].

Another important therapeutic direction is represented by electroconductive hydrogels. Since the myocardium is an electrically active tissue, conductive biomaterials may support signal propagation, improve electrical coupling, and reduce the functional discontinuity created by scar tissue [14-16]. Newer platforms integrate conductivity with stimuli-responsive delivery, as seen in pH-responsive conductive hydrogels designed to release metformin and exosomes according to local pathological cues [17]. Bioprinting and carbon-based conductive scaffolds further expand this field by improving spatial organization and functional architecture [18-20], and overall, these strategies suggest that the most relevant hydrogel systems for myocardial infarction repair will be those that combine mechanical stabilization, controlled release, electrical integration, and regenerative signaling within a single therapeutic platform.

Translational perspectives, limitations, and future directions

Although injectable bioactive hydrogels have shown encouraging preclinical results for myocardial infarction repair, their translation into routine clinical use remains challenging, and in our review of the literature, we observed that most evidence still comes from experimental models, where infarct size, timing of administration, injection technique, hydrogel composition, and follow-up duration vary substantially [4-6,10], this heterogeneity makes it difficult to directly compare outcomes and to determine which hydrogel properties are truly essential for functional cardiac recovery.

One major translational challenge is delivery, and injectable hydrogels must be retained within the infarcted myocardium without causing tissue disruption, embolic complications, arrhythmias, or excessive inflammation. At the same time, the material must gel rapidly enough to remain localized, but not so rapidly that it blocks injection or produces uneven distribution [3,5,20]. Mechanical compatibility is equally important because a hydrogel that is too soft may fail to support the ventricular wall, whereas an overly stiff material may impair myocardial deformation and integration [6-8].

Biological performance also remains difficult to standardize, and hydrogels may be loaded with drugs, growth factors, exosomes, conductive nanomaterials, or cells, but each additional component increases regulatory complexity and may influence degradation, immune response, sterility, reproducibility, and safety [11-17]. Exosome-bearing systems are especially promising, yet their clinical translation requires better control of vesicle source, dose, purity, storage, and release kinetics [11-13]. Similarly, electroconductive hydrogels may improve electrical integration, but they must be carefully evaluated for arrhythmogenic safety and long-term biocompatibility [14-17].

Future development will probably move toward multifunctional platforms that combine injectable delivery, mechanical stabilization, controlled release, electrical conductivity, and microenvironment-responsive behavior [9,17,21]. Advanced manufacturing, including 3D bioprinting and nanomaterial-reinforced scaffolds, may help improve spatial organization and tissue-like architecture, although scalability and regulatory validation remain important barriers [18,19]. Overall, the most realistic translational path is not the search for a universal hydrogel, but the development of indication-specific systems adapted to infarct stage, delivery route, patient risk profile, and desired therapeutic mechanism.

Table 2. Translational challenges and future directions for injectable bioactive hydrogels in myocardial infarction repair

Translational aspect	Main challenge	Future direction	Ref.
Delivery and retention	Limited localization, leakage, or uneven distribution after injection	Image-guided delivery and optimized in situ gelation	[3,5,20]
Mechanical compatibility	Inadequate matching with the dynamic myocardial tissue	Tunable stiffness and degradation profile	[6-8]
Biological activity	Variable release of drugs, growth factors, or vesicles	Controlled-release and microenvironment-responsive systems	[9,11-13,17]
Exosome-loaded systems	Standardization of vesicle source, dose, purity, and stability	Reproducible exosome-bearing hydrogel platforms	[11-13]
Electroconductive hydrogels	Long-term safety and arrhythmogenic risk	Conductive networks with validated biocompatibility	[14-17]
Advanced manufacturing	Limited scalability and construct reproducibility	3D bioprinting and nanostructured scaffold engineering	[18,19]
Clinical translation	Regulatory complexity and lack of standardized preclinical models	Indication-specific hydrogel systems and harmonized evaluation protocols	[4,10,21]

Conclusions

Injectable bioactive hydrogels represent a promising avenue for myocardial infarction repair because they combine minimally invasive delivery with local mechanical support, controlled therapeutic release, and the potential to modulate the infarct microenvironment, and current evidence suggests that these systems may limit adverse ventricular remodeling, enhance paracrine signaling, support angiogenesis, and improve tissue integration, and their effectiveness depends on careful material design, including injectability, gelation kinetics, degradation profile, mechanical compatibility, biological activity, and, when needed, electroconductive or stimuli-responsive properties.

Future progress should focus on clinically realistic platforms with standardized composition, reproducible manufacturing, and validated safety, and exosome-loaded, electroconductive, and microenvironment-responsive hydrogels are particularly attractive, but translation requires stronger preclinical comparability, long-term biocompatibility data, and clear regulatory pathways before these materials can move from experimental myocardial repair toward routine clinical application.

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