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BIODEGRADABLE HYDROGELS AND POLYMERS IN CARDIAC TISSUE REGENERATION

Luiza Camelia NECHITA[1], Iulia Alecsandra SĂLCIANU [2,*], Luciana Carmen NITOI[1]

[1] Faculty of Medicine and Pharmacy, University "Dunarea de Jos", Galati, Romania
[2] Carol Davila University of Medicine and Pharmacy, Bucuresti, Romania
[3] Umberto I Hospital Frosinone in Frosinone, Viale Mazzini, 03100 Frosinone, Italy

Abstract

Cardiac tissue regeneration is a major challenge in cardiovascular medicine, given the myocardium's limited ability to repair itself after a heart attack. Biodegradable hydrogels and polymers have demonstrated significant potential in supporting cardiac regeneration by mimicking the extracellular matrix, facilitating cell proliferation, and controlled delivery of bioactive factors. Natural hydrogels, such as collagen, fibrin, and alginate, provide a biocompatible environment that stimulates angiogenesis and cell regeneration, but have limitations in terms of mechanical stability. Synthetic hydrogels, such as PEG, PCL, and PLGA, allow better control over degradation and mechanical properties, being used in three-dimensional structures or in injectable form. Biodegradable polymers support regeneration by providing temporary structural support and gradual delivery of bioactive factors. New approaches, such as 3D bioprinting and the development of smart hydrogels, open up promising prospects for personalized therapies. However, challenges related to the optimal integration of these materials and the control of the immune response require further research to facilitate large-scale clinical application.

Keywords: Cardiac regeneration, hydrogels, biodegradable polymers, biomaterials, 3D bioprinting, angiogenesis

Introduction

Cardiovascular diseases are one of the main causes of morbidity and mortality globally, having a major impact on the health system and on the quality of life of patients [1]. In particular, myocardial infarction and heart failure are conditions in which regeneration of heart tissue is essential for restoring heart function [1,2]. However, unlike other types of tissues, the adult myocardium has a limited capacity for regeneration. Mature cardiomyocytes show extremely low mitotic activity, which causes myocardial damage to be repaired predominantly by the formation of fibrotic tissue. This ineffective repair can lead to ventricular remodeling, decreased contractile performance, and ultimately progressive heart failure [3].

In recent years, tissue engineering has provided new directions for cardiac regeneration, using biocompatible materials capable of supporting cell proliferation and differentiation. Among these materials, biodegradable hydrogels and polymers have attracted special attention due to their favorable properties in stimulating myocardial regeneration. These biomaterials are designed to mimic the structure and function of the extracellular matrix (ECM), facilitating cell integration and promoting the formation of new functional cardiomyocytes [4].

Corresponding author: iulia.salcianu@umfcd.ro

Hydrogels are three-dimensional networks of polymers that can retain large amounts of water, thus maintaining a hydrated environment conducive to tissue regeneration. They can be natural (such as collagen, fibrin, and alginate) or synthetic (such as polyethylene glycol – PEG, polycaprolactone – PCL, and biodegradable copolymers) [5].

A major advantage of hydrogels is their ability to be injected directly into the affected area, adapting to the shape of the damaged tissue and providing temporary structural support for the transplanted cells. In addition, hydrogels can be functionalized to deliver growth factors, proteins, and other bioactive molecules necessary for the regeneration process [6].

On the other hand, biodegradable polymers have been widely used in medical devices and implants, due to their ability to gradually degrade in the body without inducing an adverse immune response. They are used to manufacture scaffolds (three-dimensional structures) that support cell proliferation and cardiomyocyte differentiation. Polymers such as polylactic acid (PLA), polyglycolic acid (PGA), and their copolymers, such as PLGA, are commonly used for tissue regeneration, including in cardiac applications [7]. These structures can be formed by 3D bioprinting methods or can be injectable, combining the flexibility of hydrogels with the mechanical stability of polymers [8].

Currently, combining hydrogels with biodegradable polymers offers a promising strategy for cardiac regeneration. These materials can be used either to deliver stem cells and growth factors or to support endogenous regeneration of heart tissue. For example, collagen-based hydrogels can be combined with polymeric structures from PLGA to create mechanical supports capable of withstanding the biomechanical stress of the heart [8].

At the same time, advanced controlled delivery systems of growth factors allow the optimization of the cardiac microenvironment, thus improving the survival and differentiation of transplanted cells [9].

Another important aspect is the potential of these biomaterials to be used in combination with emerging technologies, such as 3D bioprinting and cell therapy. For example, work is being done on the development of smart hydrogels, capable of modifying their properties according to biological or mechanical stimuli, which could allow a more efficient integration into cardiac tissue [9].

In addition, recent studies have demonstrated that the combined use of biodegradable hydrogels and polymers can reduce post-implantation inflammation and improve the vascularization of newly formed tissue [10].

Biodegradable hydrogels and polymers represent a promising research direction in cardiac tissue regeneration. These materials have the potential to improve the prognosis of patients with cardiovascular disease, providing effective solutions for repairing myocardial damage. However, there are still many challenges related to optimizing the properties of these biomaterials, integrating them into clinical therapies, and validating them through long-term studies. In the coming years, research focused on the development of biomimetic materials and the application of advanced technologies, such as nano-engineering and artificial intelligence, could lead to significant advances in this field, facilitating the clinical implementation of effective cardiac regeneration strategies [10].

Properties and requirements of materials for cardiac regeneration

The regeneration of cardiac tissues requires the use of biocompatible materials capable of mimicking the functions of the extracellular matrix (ECM) and facilitating the process of myocardial restoration [8]. To be effective in this context, biodegradable hydrogels and polymers must meet a number of essential requirements related to biocompatibility, biodegradability, mechanical properties, interaction with cells, and delivery of bioactive factors [9].

Biocompatibility and biodegradability

The materials used in cardiac regeneration must be biocompatible, i.e., they must not induce an adverse immune response or an excessive inflammatory reaction. Any foreign implant inserted into the body can trigger an immune reaction, which could lead to fibrosis and failure of myocardial regeneration. Therefore, hydrogels and polymers must have a chemical composition that is accepted by the body and does not generate toxicity during degradation [10].

Biodegradability is also an essential criterion, as materials must progressively break down into non-toxic products as newly formed cardiac tissue replaces them [7,11]. The degradation must be controlled and correlated with the rate of myocardial regeneration, thus avoiding the accumulation of byproducts that could induce inflammation or side effects [8-11]. Materials such as PLGA (polylactic-co-glycolic acid), PCL (polycaprolactone), and natural hydrogels (collagen, fibrin, alginate) have demonstrated favorable properties from this point of view [11].

Mechanical properties and resistance to cardiac stress

Cardiac tissue is under constant biomechanical stress, needing materials that can withstand repeated cycles of contraction and relaxation without losing its structural integrity [12,13]. The elasticity and rigidity of biomaterials are critical parameters, as the materials must have sufficient elasticity to adapt to heart movements, but also a rigidity to prevent structural collapse [12].

Natural hydrogels such as collagen and fibrin provide a hydrated and flexible environment, but may have low mechanical strength, requiring combination with synthetic polymers such as PCL or PLGA to improve stability [12,13]. Three-dimensional polymer scaffolds are designed to provide both initial mechanical support and progressive degradation with cardiac tissue regeneration [13].

Interaction with stem cells and cardiomyocytes

To facilitate cardiac regeneration, biomaterials must be able to support the attachment, proliferation, and differentiation of cells involved in regeneration, such as cardiomyocytes and mesenchymal stem cells [4,14]. Hydrogels can be modified by adding bioactive sequences that promote cell adhesion and stimulate cardiomyocyte maturation [14]. For example, RGD peptides (Arg-Gly-Asp) are used to enhance the interaction between material and cells [12-14].

Another important aspect is the vascularization of the implanted material [11,15]. Cardiac tissue requires a constant supply of oxygen and nutrients, which requires the use of materials that support the formation of new blood vessels [12-15]. Hydrogels functionalized with proangiogenic factors, such as VEGF (vascular endothelial growth factor), can stimulate this process, thus improving the survival of transplanted cells [15].

Delivery capacity of bioactive factors

To support myocardial regeneration, biomaterials must be able to deliver growth factors, proteins, and bioactive molecules in a controlled and sustained manner [13,16]. For example, injectable hydrogels can be used as delivery systems for factors such as insulin-like growth factor (IGF-1) or TGF-β (transforming growth factor beta), which stimulate cell regeneration and reduce inflammation [16].

Smart materials, capable of responding to biological stimuli (pH, temperature, mechanical stress), represent an emerging direction of research. They can ensure a controlled release of therapeutic factors, adapting in real time to the needs of cardiac tissue [15-17]. For example, pH-sensitive polymers can only release anti-inflammatory substances in the affected areas, thus preventing adverse effects [18].

Table 1. The table presents the main properties of the materials used in cardiac regeneration, including the description of each feature, relevant examples, advantages, and limitations. This information is essential for the selection of suitable biomaterials in cardiac tissue regeneration therapies [2,4,5,7,12-18].

Property	Description	Material examples	Advantages	Limitations
Biocompatibility	Materials should not induce an adverse immune response and must be accepted by cardiac tissue.	Collagen, alginate, PEG, PCL	Reduces inflammation risk, promotes integration into cardiac tissue.	Some materials may induce an inflammatory response or require additional modifications.
Biodegradability	Controlled degradation is essential to allow optimal tissue regeneration without generating toxicity.	PLGA, PCL, synthetic copolymers	Naturally degrades, eliminating the need for surgical removal.	Too rapid degradation may compromise regeneration, while too slow degradation may affect tissue integration.
Mechanical strength	Materials must be elastic enough to support heart movements but rigid enough to maintain tissue structure.	PCL, PLGA, functionalized hydrogels	Maintains cardiac tissue architecture and prevents structural collapse.	Too rigid materials may interfere with heart contractions, while too soft materials may collapse.
Cell interaction	They should support cell attachment, proliferation, and differentiation, including cardiomyocytes and stem cells.	Modified collagen, hydrogels with RGD peptides	Facilitates tissue regeneration, enhances vascularization, and functional integration.	Cellular response may vary depending on the material, requiring optimization for each application.
Bioactive factor delivery capacity	Materials should enable the gradual delivery of growth factors, proteins, and other bioactive molecules necessary for regeneration.	Smart hydrogels, polymers with controlled release	Optimizes cardiac microenvironment, supports cell differentiation and angiogenesis.	Risk of uncontrolled release of bioactive factors, which may affect regeneration efficiency.

Hydrogels used in cardiac tissue regeneration

Hydrogels represent one of the most promising classes of biomaterials used in cardiac tissue regeneration due to their ability to mimic the extracellular matrix and support cell proliferation [1,4,6]. These are three-dimensional networks of polymers capable of retaining large amounts of water, providing a hydrated microenvironment conducive to myocardial regeneration [2,5]. Due to their versatility, hydrogels can be injected directly into the affected tissue or used as structural support for the delivery of stem cells and growth factors [3,9].

One of the main advantages of these materials is their high biocompatibility, especially in the case of hydrogels of natural origin, such as collagen, fibrin, alginate, and hyaluronic acid, which interact effectively with cells and stimulate the regeneration of heart tissue [6,7,10].

Natural hydrogels have demonstrated significant potential in myocardial regeneration through their ability to promote angiogenesis and reduce inflammation in the affected area [5,8]. Collagen, a major component of the extracellular matrix, is often used to create three-dimensional structures that facilitate cell attachment and cardiomyocyte proliferation [6,11]. Fibrin, another natural biomaterial, provides excellent support for transplanted cells and plays a crucial role in the formation of new vascular networks, essential for oxygenating regenerated heart tissue [7,12]. Alginate, derived from seaweed, has been used in preclinical studies to prevent negative remodeling of the ventricle post-infarction, demonstrating significant functional improvements [2,13]. Hyaluronic acid, known for its moisturizing properties and interaction with endothelial cells, is frequently used in combination with bioactive peptides to stimulate cell proliferation and extracellular matrix regeneration [8,14].

In addition to natural hydrogels, synthetic materials such as polyethylene glycol (PEG), polycaprolactone (PCL), and PLGA copolymers are used due to their superior mechanical stability and precise control over degradation [9,15]. These hydrogels can be chemically modified to improve interaction with cells and allow for the controlled release of bioactive factors [10,16]. PEG is commonly used in combination with adhesive peptides to improve cell attachment, while PCL and PLGA are used in the manufacture of more rigid three-dimensional structures capable of providing more solid mechanical support [11,17]. Thermoreversible hydrogels, such as poloxamers, have attracted attention due to their ability to remain liquid at room temperature and gel at body temperature, thus facilitating injection and uniform distribution into heart tissue [12,18].

The use of hydrogels in myocardial regeneration has both advantages and limitations [13,16]. These materials are able to provide an optimal cellular environment, allow the delivery of proangiogenic factors, and reduce inflammation in the affected area [5,14,19]. Also, injectable hydrogels are a minimally invasive solution, eliminating the need for complex surgeries [3, 10]. However, the mechanical stability of natural hydrogels is limited, and their degradation rate may vary depending on the specific composition [15,18]. Degradation too fast can compromise the efficiency of regeneration, while degradation too slow can interfere with the formation of new tissue [17]. In addition, synthetic hydrogels, although more stable, may require further modifications to improve biocompatibility and prevent inflammatory reactions [6,20].

The clinical applicability of hydrogels is constantly developing, with numerous preclinical and clinical studies demonstrating their benefits in post-infarction myocardial repair [1,4,13]. For example, recent research has shown that collagen and fibrin-based hydrogels combined with stem cells can significantly improve heart function and reduce negative ventricular remodeling [7,11]. Alginate-based injectable hydrogels are clinically tested for the prevention of heart failure by structurally supporting the damaged myocardium [2,13]. In parallel, 3D bioprinting opens up new perspectives for the use of personalized hydrogels, which can be adapted according to the specific needs of patients [19,20].

Biodegradable polymers in cardiac regeneration

Biodegradable polymers have become an essential component in cardiac tissue regeneration, providing temporary mechanical support and facilitating the myocardial healing process [1,9]. They are used for the manufacture of three-dimensional structures (scaffolds) that mimic the extracellular matrix (ECM) and provide a favorable environment for the proliferation and differentiation of cells involved in regeneration [2-4]. Biodegradable polymers must be biocompatible, degrade at a controlled rate, and have adequate mechanical properties to withstand the biomechanical stress exerted by the heartbeat [5,10]. Among the most widely used polymers in cardiac tissue engineering are polylactic acid (PLA), polyglycolic acid (PGA), PLGA copolymers, and polycaprolactone (PCL) [6,11].

These polymers are approved for medical use and have demonstrated efficacy in numerous clinical and experimental applications [7,13].

One of the major advantages of biodegradable polymers is the ability to create custom structures through 3D bioprinting, providing solutions tailored to the specific needs of patients [8,14]. Bioprinting allows the design of scaffolds that reproduce the architecture of the myocardium, thus facilitating cell migration and attachment [9,15]. In addition, these polymers can be combined with hydrogels and growth factors to improve regeneration and integration with heart tissue [3, 16]. The controlled degradation of polymers allows the gradual release of bioactive factors, reducing inflammation and stimulating cell proliferation in the affected area [10,17].

Polymeric scaffolds can be used in combination with stem cells to support myocardial regeneration [12,18]. Studies have shown that implanting structures made of PLGA or PCL can improve the survival of transplanted stem cells and favor their differentiation into functional cardiomyocytes [7,13]. These materials provide temporary mechanical support, preventing tissue collapse in the regeneration process and allowing for a progressive integration of new cells [11,17]. Over time, polymers degrade into non-toxic products, being gradually replaced by newly formed cardiac tissue [6,12].

Another important area of research is the use of biodegradable injectable polymers, which can be administered minimally invasively directly to the affected area [3,15]. These polymers are designed to form three-dimensional structures *in situ*, dynamically adapting to the cardiac microenvironment [14,18]. Thermoreversible polymers, such as Pluronic F127, can remain liquid at room temperature and solidify at body temperature, thus providing an efficient method of delivering cells and growth factors [12,19]. These materials can be used to treat myocardial infarction and heart failure, providing a less invasive alternative to traditional surgeries [1,10].

Although biodegradable polymers have many advantages, there are also challenges associated with their use in cardiac regeneration [5,7]. One of the main difficulties is to achieve an optimal balance between degradation and regeneration, so that the scaffold provides sufficient mechanical support until functional tissue is formed [6,13]. Also, certain polymers can induce an inflammatory response, affecting the regeneration process [8,16]. The optimal integration of materials with cardiac tissue remains a challenge, as the myocardium is a dynamic environment, exposed to constant biomechanical forces [9,17]. In this regard, recent research focuses on the development of intelligent polymers capable of responding to biological stimuli and adapting their properties according to the needs of the tissue [15,18].

Prospects in the use of biodegradable polymers include optimizing their composition to improve biocompatibility and functionality [19,20]. Advanced bioengineering technologies allow the development of polymers that can release proangiogenic factors, favoring the formation of new blood vessels in the ischemic areas [16,20]. Also, combining polymers with nanomaterials offers the possibility to create hybrid structures with superior mechanical properties and better integration with cardiac tissue [14,18]. The integration of these solutions with artificial intelligence and computational modeling will allow the optimization of scaffold design, accelerating the transition from research to clinical applications [18-20].

Conclusion

Biodegradable hydrogels and polymers represent a promising direction in the regeneration of cardiac tissues, offering innovative solutions for repairing damaged myocardium. These biomaterials can mimic the extracellular matrix, support cell proliferation, and provide bioactive factors in a controlled manner, thus facilitating the functional regeneration of the heart. Natural hydrogels, such as collagen, fibrin, alginate, and hyaluronic acid, provide excellent biocompatibility and stimulate angiogenesis, but are limited by reduced mechanical stability and

rapid degradation. On the other hand, synthetic hydrogels such as PEG, PCL, and PLGA allow for more precise control of degradation and can be modified to improve interaction with cells; however, they may require additional adjustments to prevent inflammation and ensure optimal integration into cardiac tissue.

Biodegradable polymers play an essential role in cardiac regeneration by providing temporary mechanical support and facilitating cell attachment and differentiation. They can be used in the form of three-dimensional scaffolds or in injectable form, which allows for minimally invasive methods of treatment. 3D bioprinting and the development of intelligent materials capable of responding to biological stimuli open up new perspectives for personalized therapies. However, challenges related to controlled degradation, optimal integration into heart tissue, and the risk of immune reactions need to be addressed through further research.

Preclinical and clinical studies are already demonstrating the benefits of biodegradable hydrogels and polymers in preventing heart failure and improving post-infarction ventricular function. The integration of these materials with cell therapies and emerging technologies, such as nanotechnology and computational modeling, will accelerate the clinical deployment of these solutions. In the future, optimizing the composition and structure of these biomaterials will allow the development of more effective and affordable treatments, reducing the impact of cardiovascular diseases and improving patients' quality of life.

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