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Cardiac tissue engineering for myocardial infarction treatment

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ABSTRACT

Myocardial infarction is one of the major causes of morbidity and mortality worldwide. Current treatments can relieve the symptoms of myocardial ischemia but cannot repair the necrotic myocardial tissue. Novel therapeutic strategies based on cellular therapy, extracellular vesicles, non-coding RNAs and growth factors have been designed to restore cardiac function while inducing cardiomyocyte cycle re-entry, ensuring angiogenesis and cardioprotection, and preventing ventricular remodeling. However, they face low stability, cell engraftment issues or enzymatic degradation *in vivo,* and it is thus essential to combine them with biomaterial-based delivery systems. Microcarriers, nanocarriers, cardiac patches and injectable hydrogels have yielded promising results in preclinical studies, some of which are currently being tested in clinical trials. In this review, we cover the recent advances made in cellular and acellular therapies used for cardiac repair after MI. We present current trends in cardiac tissue engineering related to the use of microcarriers, nanocarriers, cardiac patches and injectable hydrogels as biomaterial-based delivery systems for biologics. Finally, we discuss some of the most crucial aspects that should be addressed in order to advance towards the clinical translation of cardiac tissue engineering approaches.

1. Myocardial infarction and currently available treatments: First-line pharmacological treatments and surgical procedures

Myocardial infarction (MI) is one of the major causes of death and disability worldwide, involving three million deaths in 2021 (Mechanic et al., 2022). Most of the patients who survive require lifelong medical therapy and, in many cases, repeated invasive cardiovascular procedures (Berman and Miller, 2020). MI occurs commonly due to a thrombus formation in a coronary artery causing a reduction in myocardial perfusion and prolonged ischemia. This results in massive cardiomyocyte (CM) necrosis and the appearance of an infarcted area (Boateng and Sanborn, 2013). The hypoxia condition leads to ATP deficiency, calcium homeostasis imbalance and the release of damage-associated molecular patterns, which activate the innate immune system and the generation of reactive oxygen species (ROS) while inducing cytokine and chemokine upregulation. This cascade of molecular events eventually results in the appearance of a fibrotic area and ventricular remodeling.

Current pharmacological treatments focus on removing blockade and restoring blood supply to the damaged area of the heart. They include the use of painkillers to treat chest pain (Erhardt, 2002), oxygen supply to restore normal O_2 levels and antithrombotic therapy to prevent blood from clotting and mitigate the risk of ischemic events. In addition, nitroglycerin and β-blockers are used to decrease blood pressure and reduce myocardial oxygen demand. Furthermore, lipid-lowering therapy is used to control LDL cholesterol levels and ACE inhibitors and aldosterone antagonists to improve post-infarction remodeling (Reed et al., 2017).

Reperfusion therapy remains the most effective clinical approach and consists of restoring blood circulation to the heart (Lu et al., 2015). Unfortunately, reperfusion may induce subsequent injury in the ischemic tissue, a phenomenon termed "ischemia-reperfusion injury" (Wu et al., 2018), which causes the death of reversibly injured CMs and can contribute to up to 50% of the final myocardial infarct size (Virmani et al., 1990). In this sense, coronary angioplasty allows for the restoration of the blood flow in narrowed or blocked vessels that supply blood

Abbreviations: ADSCs, Adipocyte tissue-derived stem cells; bFGF, basic fibroblast growth factor; BM-MNCs, Bone marrow mononuclear cells; CDCs, Cardiosphere-derived cells; CM, Cardiomyocytes; CPCs, Cardiac progenitor cells; CSCs, Cardiac stem cells; dECM, decellularized Extracellular Cardiac Matrix; ECs, Endothelial cells; ESCs, Embryonic stem cells; EVs, Extracellular Vesicles; GelMA, Gelatin methacryloyl; GF, Growth factors; GMPs, Good Manufacturing Practices; HA, Hyaluronic acid; HGs, Hydrogels; iPSCs, induced pluripotent stem cells; LNPs, Lipid nanoparticles; MI, Myocardial infarction; microRNAs, miRNAs.

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to the heart. After this surgical procedure, a stent, usually coated with a drug (drug-eluting stent), can be left in place to help to keep the artery open and decrease the chance of the artery becoming blocked in the future. However, in some cases, due to the anatomy of the coronary artery or the presence of multiple lesions, it is necessary to resort to coronary artery bypass surgery, which involves bypassing the blood flow interrupted by a blocked coronary artery by using the patient's own vessels (grafts), either from the leg (saphenous graft) or from the chest (mammary artery).

Current MI treatments can therefore relieve the symptoms of myocardial ischemia but cannot repair the necrotic myocardial tissue. Undoubtedly, myocardial regeneration offers the best solution to restore cardiac function and avoid the surgically derived problems of current MI treatments (Peng et al., 2017). Novel therapeutic strategies have been designed to promote CM cycle re-entry, prevent ventricular remodeling, and induce angiogenesis and cardioprotection. These include the use of cells (cellular therapy) and different types of therapeutic molecules (acellular therapy) such as growth factors (GFs), extracellular vesicles (EVs) or microRNAs (miRNAs). However, once administered *in vivo,* both approaches face many challenges (i.e., low stability and cell engraftment, enzymatic degradation and off-target effects) requiring combination with biomaterial-based delivery systems.

In this paper, we provide an overview of the recent advances made in cellular and acellular therapies used for cardiac repair after MI. Additionally, we highlight preclinical and clinical studies performed over the last five years using microcarriers and nanocarriers, cardiac patches and injectable hydrogels (HGs) as biomaterial-based delivery systems for cells and cardiac therapeutic agents. Finally, we discuss some key aspects that should be addressed before their translation into the clinic.

2. Novel therapeutic strategies for the treatment of myocardial infarction

In physiological conditions, CMs self-renewal in the human adult heart has an estimated turnover of 1% per year at the age of 25 and 0.45% at the age of 75 (Bergmann et al., 2015, 2009). This proliferative capacity is insufficient to recover the damaged ischemic tissue after MI. Novel cardiac therapeutic strategies have been designed to repair the damaged myocardium and restore the function of the heart while minimizing adverse ventricular remodeling. These can follow two different approaches: a) the exogenous regeneration approach focused on the transplantation of exogenous cells and b) the endogenous regeneration approach, based on the evidence that adult myocardium has a population of resident multipotent cardiac stem cells (CSCs) whose differentiation and proliferative activities can be enhanced by the administration of therapeutic agents (i.e. GFs, EVs and miRNAs (Leite

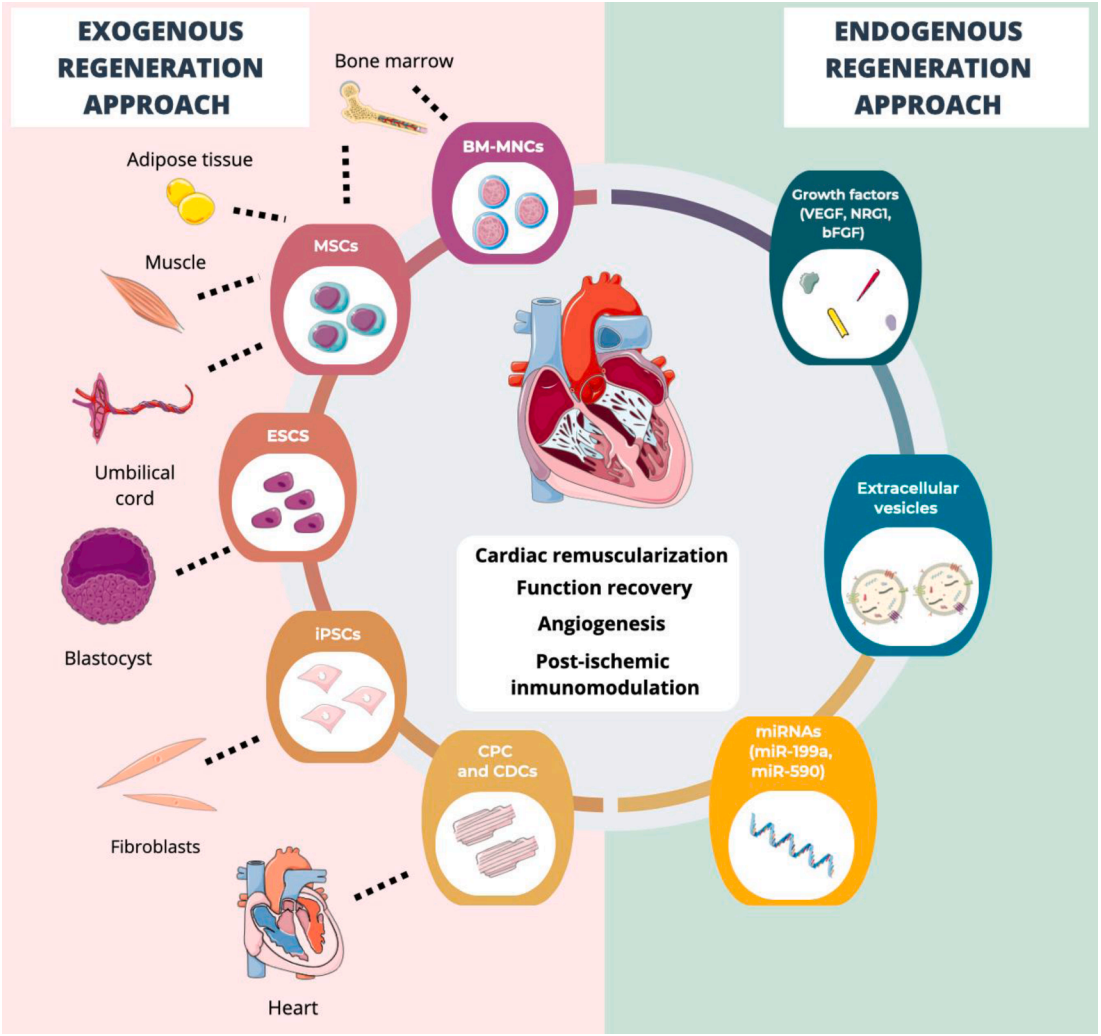

Fig. 1. Novel therapeutic strategies for cardiac repair: exogenous and endogenous regeneration approaches. The exogenous approach is based on cellular therapy and aims to induce cardiac repair by the transplantation of exogenous cells (i.e., BM-MNCs, MSCs, ESCs, iPSCs, CPCs or CDCs). The endogenous regeneration approach aims to enhance cardiac remuscularization, angiogenesis and modulate the immune response by the administration of therapeutic agents (GFs, EVs and miRNAs). The figure includes original elements from Servier Medical Art.

et al., 2015) (Fig. 1).

2.1. Exogenous regeneration approach: cellular therapy

Cellular therapy emerged as a novel cardiac regenerative strategy to replace infarcted tissue while enhancing perfusion and contributing to angiogenesis (Carbone et al., 2021). Several cell sources have been used for these purposes including bone marrow-derived mononuclear cells (BM-MNCs), mesenchymal SCs (MSCs), embryonic SCs (ESCs), induced pluripotent SCs (iPSCs), cardiac progenitor cells (CPCs) and cardiosphere-derived cells (CDCs).

In the early stages, BM-MNCs appeared very attractive, as they demonstrated cardiac regenerative capacity in preclinical studies (Deb et al., 2003). These promising results made it possible to study BM-MNCs potential in humans, but although small randomized clinical trials initially demonstrated safety and a modest increase in the ejection fraction, multiple well-randomized and double-blinded clinical trials did not reproduce these successful results (Hosseinpour et al., 2022). Then, researchers shifted towards the use of MSCs, multipotent cells that can be isolated from different stromal sources (i.e., bone marrow, adipose tissue, umbilical cord, muscle) with reported cardioprotective effects (Jiang and Zhang, 2017). Nowadays, MSCs are by far the most widely researched SC source for the treatment of cardiac injury (Golpanian et al., 2016). Likewise, CPCs are precursor multipotent cells found in the heart which have been associated with the ability to proliferate and differentiate into CMs, smooth muscle cells and vascular ECs (Arbatlı et al., 2017). Additionally, pluripotent stem cells such as ESCs and iPSCs are gaining attractiveness because of their differentiation potential into functional CMs. ESCs are pluripotent SCs derived from totipotent cells from the inner mass of a blastocyst. The transplantation of CMs derived from ESCs induced the remuscularization of the heart while enhancing cardiac function (Liu et al., 2018). However, there are ethical and legal issues that limit their use in research and translational medicine. In contrast, iPSCs are reprogrammed cells originally generated from fibroblasts, with reduced ethical requirements, high dedifferentiation and proliferation rates as well as self-renewal ability (Kumar et al., 2017). In addition to their potential for inducing *in vivo* cardiac regeneration and function after MI (Sadahiro, 2019), human iPSC-derived CMs have the advantage of being derived from patients allowing for the development of personalized-based therapy (Osada et al., 2021). Finally, CDCs are another cell source which has been studied as an "off-the-shelf" therapy for patients in the acute setting of MI. They are undifferentiated cells obtained from postnatal atrial or ventricular heart tissue (Smith et al., 2007; Chimenti et al., 2010). Several studies demonstrated that CDCs have cardiomyogenic differentiation potential *in vitro* and the ability to improve cardiac function, reduce scar size and increase the viability of the infarcted myocardium (Lee et al., 2011).

Given their promising therapeutic potential, SC's main effect was first thought to be a consequence of cell engraftment and replacement of the damaged cells in the infarcted tissue. However, functional benefits were often observed despite the lack of sustained cell engraftment suggesting the existence of another mechanism of action based on paracrine signaling (Phinney and Pittenger, 2017). SCs appear to release diverse therapeutic factors (i.e., GFs, nucleic acids and EVs) able to increase CM survival, angiogenesis and cardiomyogenesis, reduce fibrosis and potentially preserve the cardiac function (Nikfarjam et al., 2020; Sid-Otmane et al., 2020; Xu et al., 2019).

2.1.1. Main challenges of cellular therapy

Although major advances have been made in cardiac cell therapy, up to now, no SC-based therapy has passed all the clinical phases for MI treatment. One of the major limitations of cell therapy is low cell engraftment. Most of the cells do not survive in the infarcted environment after transplantation and therefore do not have enough time to proliferate by themselves and send pro-regenerative paracrine signals to the surrounding damaged cells. Oxidative stress, inflammation, cell leakage, and wash-out are among the identified causes of cell loss and death (Selvakumar et al., 2022). Therefore, optimizing delivery techniques is vital for improving cell engraftment. In addition, ventricular arrhythmias have sometimes been identified post-cell transplantation (Higuchi et al., 2017). Moreover, patients who may require cell therapy have had a large infarction resulting in the loss of hundreds of millions of CMs. The selected cell source must allow a feasible scale-up and the production of large numbers of cells endowed with cardiomyogenic potential. Additionally, the inability to non-invasively monitor the transplanted cells and trace their therapeutic effects during the period of ventricular remodeling constitutes another challenge. Given these limitations, most research is now focused on the combination of cellular therapy (Chimenti et al., 2010; Smith et al., 2007) with biomaterial-based delivery systems to provide an environment that protects cells from the extreme conditions of the infarcted tissue while favoring engraftment and allowing the infiltration of endothelial and smooth muscle cells. Finally, for a feasible translation of cellular therapies to the clinic, regulatory guidelines such as those recently published by the FDA on the development of cellular therapies in an Early-Phase Clinical Trial should be considered (FDA-2021-D-0776).

2.2. The endogenous regeneration approach: acellular therapeutic strategies

While CMs from lower vertebrates have a significant ability to differentiate and proliferate allowing the recovery of the damaged myocardium, it is thought to decrease after adolescence in the adult human heart (Mollova et al., 2013; Naqvi et al., 2014). Clearly, after MI, adult mammalian CMs can replicate DNA, but they rarely advance to the step of cytokinesis (Sdek et al., 2011). The endogenous regeneration approach aims both to induce CM cell cycle re-entry and increase the regeneration properties of endogenous CPCs by the administration of different therapeutic agents. Among them, GFs, EVs and non-coding RNAs (i.e., miRNAs) constitute the most promising candidates.

Experimental evidence suggests that therapies with GFs, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and neuregulin-1 (NRG-1), have drawn considerable attention to timely induce angiogenesis, suppress fibrosis and alleviate inflammation post-MI. VEGF has been shown to stimulate de novo vessel formation and preserve cardiac function in the setting of ischemia-reperfusion (Räsänen et al., 2021). Otherwise, bFGF can inhibit collagen synthesis and improve cardiac remodeling by decreasing the expression of a series of inflammatory interleukins and fibrosis-related factors (Khosravi et al., 2021). NRG-1 plays an important role during cardiac injury being involved in angiogenesis, cell survival and cardiac regeneration (Cacciapuoti et al., 2020).

EVs are cell-derived nanosized particles surrounded by a lipid bilayer that transport a large variety of biomolecules (i.e., soluble proteins, mRNAs, microRNAs or long non-coding RNAs) able to trigger important downstream signaling pathways involved in cardiac repair (Saludas et al., 2021). They have been associated with proangiogenic and anti-apoptotic effects, cardioprotection, modulation of the immune response and cardiac repair, which makes them interesting candidates for the treatment of MI (Deng et al., 2019; Estes et al., 2022; Li et al., 2021b).

Finally, miRNAs are highly conserved, single-strand, small non-coding RNAs that regulate gene expression post-transcriptionally by annealing with complementary sequences of mRNAs. They recognize multiple target mRNAs, thereby controlling a variety of biological processes, including heart development and disease (Liu et al., 2021). For example, hsa-miR-590 and hsa-miR-199a were shown to promote cell cycle re-entry of adult CMs *ex vivo* and to promote CM proliferation in both neonatal and adult animals in response to MI (Eulalio et al., 2012). In this sense, several studies have been performed using miRNAs as therapeutic agents to stimulate cardiac endogenous regeneration with satisfactory results in different animal MI models (Gao et al., 2019; Nugroho et al., 2022). Additionally, the levels of some miRNAs may

increase after MI, and some these are involved in post-infarction remodeling processes. For example, miR-132 levels are increased in patients with heart failure and mechanistically drive cardiac remodeling processes (Zhou et al., 2021). Recently, a first-in-class miR-132 inhibitor (CDR132L) able to attenuate and even reverse heart failure in preclinical models has been developed (Batkai et al., 2021). This miR-132 inhibitor has been tested in patients with heart failure in a first-in-human-Phase 1b randomized, double-blind, placebo-controlled study (NCT04045405) without apparent dose-limiting toxicity. CDR132L treatment induced significant QRS narrowing, encouraging positive trends for relevant cardiac fibrosis biomarkers (Baker and Giacca, 2021). This study represents a huge transformation in the treatment of patients with heart disease and offers a new possibility to treat not only the symptoms but to cure the disease even in the chronic stage (Nicholls, 2022).

2.2.1. *Main challenges of acellular therapies*

Although significant advances have been made, there are still several challenges that need to be addressed before GFs, EVs, and miRNAs can be used clinically. GFs face instability *in vivo*, poor penetration across biological barriers, and rapid clearance by the reticuloendothelial system (J. Li et al., 2021). EVs' main challenges include the need to establish standard operating procedures (SOP) for large-scale isolation and purification. Additionally, a deeper characterization and understanding of their mechanism of action is needed (Saludas et al., 2022; van Niel et al., 2022). Moreover, EV safety and pharmacokinetic/-pharmacodynamic (PK/PD) studies are still in a preliminary state, being necessary to establish a therapeutic dose before clinical translation (Reiner et al., 2017). Most studies use animal models. However, *in vitro* multi-organ chip platforms combined with microfluidics are emerging as alternative methods to evaluate the mechanism of action of EVs and their PK/PD profiles (Wagner et al., 2021). For instance, a body-on-a-chip platform that allows interorgan communication has been developed, in which EVs could be profiled in each tissue compartment allowing for the assessment of EVs efficacy, targeting and off-target effects (Novak et al., 2020). Further, independently of their route of delivery, EVs suffer instability and low retention rates once administered *in vivo,* leading to multiple dosing. Finally, the main limitations of miRNAs include the establishment of safe and effective concentrations in the target tissue (Laggerbauer and Engelhardt, 2022).

Despite the specific challenges of each therapy, all of them share poor stability and low retention rates in the infarcted heart. Therefore, their combination with biomaterial-based-delivery systems is essential to improve their therapeutic effect and reduce off-target effects.

3. Cardiac therapeutic strategies combining biomaterial-based delivery systems: therapeutic potential and current challenges

In the last decade, tissue engineering has transformed the area of cardiac regenerative medicine (Edgar et al., 2020; Garbayo et al., 2020). The use of different biomaterials as scaffolds and delivery systems has contributed to overcome the main clinical limitations of cellular therapy and acellular therapies (Fig. 2). Novel and efficient methods of cell delivery are required to enhance cell retention and promote electrical and mechanical coupling into the host myocardium. Furthermore, biomaterial-based delivery vehicles are indispensable for increasing the half-life of proteins and nucleic acids *in vivo* while allowing sustained release. Currently, micro and nanocarriers, cardiac patches and injectable HGs are the most common delivery systems for cardiac applications (Guan et al., 2021; Saludas et al., 2018; Lu Wang et al., 2021). In this section, recent trends in cardiac tissue engineering related to the use of biomaterial-based delivery vehicles are presented.

3.1. *Microcarriers and nanocarriers*

Microscale and nanoscale carriers can be designed to improve targeting and overcome systemic drug administration hurdles such as instability, poor bioavailability, absorption, burst release and adverse side effects. In addition, as a consequence of their size, nanocarriers enable the intracellular delivery of nucleic acids, allowing them to successfully escape before endo-lysosomal degradation.

Given their bigger size, most of the studies with microcarriers use them as systems to enhance cell survival while delivering cardiac therapeutic proteins. In this sense, Díaz-Herráez et al. investigated the reparative potential of a system that combined adipose-derived SCs (ADSCs) and biomimetic microparticles (MPs) loaded with NRG-1 (Díaz-Herráez et al., 2017). MPs improved the survival of ADSCs, allowing them to act in synergy with NRG-1, which led to an improvement in cardiac regeneration and angiogenesis in a rat MI model. In another study, MPs were combined with hiPSC—CMs to enhance

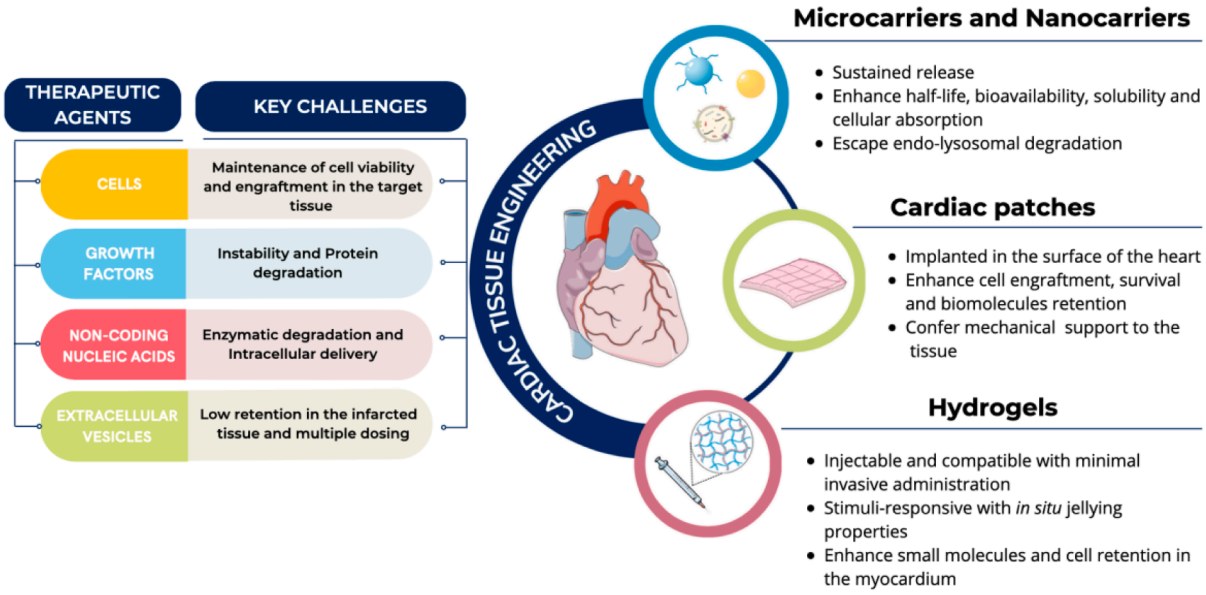

Fig. 2. Biomaterial-based delivery systems (micro and nanocarriers, cardiac patches and HGs) as the perfect strategy to overcome the key challenges of free-administered therapeutics (cells, GFs, non-coding nucleic acids or EVs) after *in vivo* administration. The figure includes original elements from Servier Medical Art.

long-term cell survival and retention in the heart and consequently improve cardiac repair (Saludas et al., 2019). The efficacy of the system was confirmed in a mouse MI model in which cells not only maintained the cardiac phenotype but also showed *in vivo* maturation and signs of electrical coupling while improving cardiac function. Likewise, the transplantation of CPCs adhered to MPs within the infarcted myocardial microenvironment improved cell viability and long-term engraftment for up to one month (Garbayo et al., 2021). The enhancement of cardiac cellular retention correlated with an increase in functional recovery, better tissue remodeling and vasculogenesis. Another interesting and different approach was given by Tang et al., where cell-mimicking MPs loaded with therapeutic proteins were studied as a "synthetic SC-based strategy" (Tang et al., 2017). Intramyocardial injection of cell-synthetic MPs in a mouse MI model reproduced the paracrine activities of natural SCs in therapeutic cardiac regeneration leading to the preservation of cardiac function. Finally,

On the other hand, nanocarriers constitute one of the most common delivery systems used in cardiac repair. Accordingly, a wide variety of nanocarriers have been reported, including polymeric nanoparticles (NPs), lipid NPs (LNPs), inorganic NPs and EVs (Borrelli et al., 2021; Dong et al., 2018). Among these, polymeric NPs stand out for their excellent biocompatibility, their tunable mechanical properties, and their ability to encapsulate a large variety of cardiac therapeutic agents (Karam et al., 2022). The most frequently used polymer is polylactide-co-glycolide (PLGA), which is non-immunogenic, biodegradable and has Food and Drug Administration approval. For example, the local administration of VEGF loaded-PLGA NPs allowed the sustained delivery of VEGF for at least one month in a murine MI model (Oduk et al., 2018). Greater vascular density in the peri-infarct region, a reduction in infarct size, and an improvement in left ventricle contractile function were observed. In addition, Chen et al. demonstrated that the encapsulation of TT-10, a pharmacological product that increases CM proliferation, into PLGA NPs improved cardiac function and infarct size while reducing off-target effects (Chen et al., 2021). Another interesting biomaterial is hyaluronic acid (HA), an abundant polymer of the extracellular matrix, which can influence cell proliferation as well as angiogenesis and inflammation (Passi and Vigetti, 2019). Recently, miR-21 was encapsulated into hyaluronan-sulfate NPs to study whether boosting the miR-21 transcript level in macrophage-enriched areas of the infarcted heart could switch their phenotype from pro-inflammatory to reparative (Bejerano et al., 2018). NPs allowed the targeted delivery of miR-21 to cardiac macrophages after MI and induced their modulation towards an anti-inflammatory state, which resulted in increased angiogenesis, reduction of apoptotic cells and attenuation of left ventricle remodeling.

Besides polymeric NPs, LNPs are also considered promising cardiac delivery vehicles due to their cell membrane's similar morphology and ability to carry proteins and nucleic acids, minimizing toxicity and immunogenicity. Furthermore, they can be tuned to reduce their capture by the reticuloendothelial system and increase their circulation time. Recently, the ability of LNPs to effectively deliver modified mRNA to the myocardium upon ischemia-reperfusion injury was demonstrated in a mice model of MI (Evers et al., 2022). LNPs administered intravenously accumulated in the infarcted area of the heart, proving the ability to functionally deliver mRNA therapeutics to the damaged myocardium.

Furthermore, albeit less frequently, inorganic NPs can also be used in cardiac repair due to their electrical conductivity properties (Li et al., 2023). Gold, silver and copper are among the most widely used materials. In this regard, intravenous administration of gold-NPs was found to decrease infarct size, improve systolic function and inhibit cardiac fibrosis in a mouse MI model (Tian et al., 2018). Additionally, copper-NPs and exercise training either alone or in combination diminished oxidative stress, inflammatory cytokines, apoptosis and increased serum bioavailability of nitric oxide (NO) in a rat model of ischemic/reperfusion (Sharma et al., 2018).

In addition to their therapeutic potential, EVs can be used as lipid-based and cellular-derived delivery systems (Cheng et al., 2020; Fu et al., 2021). One potential advantage of using EVs for the delivery of biologics rather than synthetic carriers is that the bilipid membrane of EVs protects their contents from degradative enzymes and that endogenous cellular machinery can be used to produce the desired cargo inside EVs (Elsharkasy et al., 2020). This is particularly interesting for protein and nucleic acid-based therapeutics, whose stability is sensitive to changes in temperature, solvents and pH. Several studies have demonstrated that encapsulating therapeutic agents into EVs by indirectly incorporating the cargo into the cell culture medium or directly to EVs are feasible strategies to strengthen their therapeutic outcomes (Luan et al., 2017). Moreover, EVs can be engineered and modified to increase their organ-targeting ability by presenting specific surface ligands of the target tissue (Vandergriff et al., 2018; Xu et al., 2022). Targeting modifications improve the efficiency of EV uptake by specific cell lineages, increase EVs stability in circulation, reduce the injected doses and enhance the therapeutic effects (Herrmann et al., 2021). For instance, Zhu et al. improved the targeted delivery of EVs containing miR-125b-5p by conjugating them with "CSTSMLKAC" peptide. After systemic administration, EVs specifically accumulated in the ischemic zone and exerted a marked cardioprotective function post-MI (Zhu et al., 2018). Another study employed an EV membrane anchoring platform termed "cloaking" to directly embed tissue-specific antibodies or homing peptides on EV membrane surfaces *ex vivo* and enhance vesicle uptake by the cells of interest (Antes et al., 2018).

3.1.1. Main challenges of microcarriers and nanocarriers

The use of micro and nanocarriers in cardiac repair still presents some challenges. Optimization of nanocarriers would require the adherence of ligands to the surface and their combination with secondary release systems such as cardiac patches or HGs to enhance retention (Borrelli et al., 2021). Furthermore, regarding particle fabrication issues, microfluidics has improved the scalability and reproducibility concerns of synthetic particles. Nevertheless, NP and MP production following Good Manufacturing Practices (GMP) guidelines remains a challenge. In the case of EVs, given their cellular origin, SOP for isolation and purification have not been established yet, which would be essential for their full clinical translation along with their further characterization and the elucidation of their mechanism of action.

3.2. Cardiac patches

Cardiac patches are generally a small disk or square-shaped platform used to deliver therapeutics (cells or bioactive molecules) locally to the ischemic zone of the heart while providing a protective environment that attracts ingrowth cardiac cells (Yang et al., 2020). They are developed to adhere to the surface of the heart and require elasticity and mechanical strength to integrate with host cardiac tissue, provide structural support and promote its pumping function. Ideally, the mechanical properties of a cardiac patch should match those of healthy native heart tissue whose Young's modulus ranges from 8 to 15 KPa in diastole (Reis et al., 2016). In addition to mechanical strength, cardiac patch biomaterials should be able to conduct electrical signals to promote the heart's contractions and achieve an efficient recovery after MI. Furthermore, they must be biodegradable with a degradation consistent with new tissue formation to avoid side effects of long-term existence (Leor et al., 2006). In the last five years, several cardiac patches have been developed and tested at a preclinical level yielding promising results in cardiac repair (Table 1) and some of them are under evaluation in clinical trials. According to the origin of the biomaterial used for their synthesis, cardiac patches can be classified as natural or synthetic.

3.2.1. Natural cardiac patches

Natural cardiac patches can be synthesized from *in vivo* sources like proteins (i.e., collagen, fibrin and gelatin), polysaccharides (i.e.,

Table 1
Preclinical studies with cardiac patches and their combination with cardiac therapeutic agents for MI treatment.

	Biomaterial	Therapeutic agent	MI animal model	Therapeutic effect	References
CELLULAR PATCHES	Neonatal rat CMs	–	Rats	Increased vascularization and maintained electrical function	(Jackman et al., 2018)
	Fibrin, Thrombin and hiPSC—CM/EC/MSCs	–	Swine	Reduced infarct size and improved cardiac function	(Gao et al., 2020)
	CDCs	–	Rats	Reduced CM apoptosis, restored myocardium volumes, and reduced fibrosis	(Yeung et al., 2019)
	Fibrin and hiPSC—CMs	–	Rabbit	Improved function and reduced scar size	(Jabbour et al., 2021)
	PECUUS and porcine dECM	hADSCs	Rats	Enhanced cardiac function and neovascularization in the peri-infarct zone	(Kashiyama et al., 2022)
	Polyaniline, Gelatin and PVA	hADSCs	Rats	Prevented ventricular fibrosis and remodeling	(Yu et al., 2022)
	Porcine dECM	hiPSCs-ECs and MSC (SDF-1α)	Rats	Induced neovascularization	(Kim et al., 2022)
	Chitosan and Fibroin	hADSCs	Rats	Improved cardiac function and alleviated cardiac fibrosis	(Chen et al., 2018)
	Fibrin and Engineered microvessels	CDCs	Rats and swine	Promoted cardiac function, reduced scar size, promoted neovascularization and suppressed inflammation	(Su et al., 2020)
	GelMa and PGDA	hiPSC—CMs, hECs and hMSCs	Mice	Increased cell engraftment and vasculogenesis	(Cui et al., 2020)
	Ionically crosslinked starch	–	Rats	Reduced pathological cardiac remodeling	(Lin et al., 2019)
ACELLULAR PATCHES	Porcine dECM	–	Rats	Improved cardiac function	(Shah et al., 2019)
	GO and Silk fibroin	–	Rats	Repaired the infarcted myocardium	(Zhao et al., 2022)
	GelMA and Choline-based bio-ionic liquid	–	Rats	Minimized cardiac remodeling and preserved normal cardiac function	(Walker et al., 2019)
	PLGA and Gelatin	Adenosine	Swine	Decreased fibrosis	(Cristallini et al., 2019)
	PCL	NO	Rats and swine	Reduced cardiac injury, suppressed adverse cardiac remodeling and ameliorated heart function	(Zhu et al., 2021)
	GO and PVA	VEGF	Mice	Promoted neovascularization, reduced myocardial fibrosis, and restored cardiac function.	(Fan et al., 2020)
	PCL and Collagen I	Substance P and IGF-1C peptide	Mice	Enhanced heart function and attenuated adverse cardiac remodeling	(Shafiq et al., 2018)
	GelMA	Galunisertib	Rats	Improved long-term cardiac function and reduced cardiac fibrosis	(Chen et al., 2022)

GelMA: Gelatin methacryloyl; **GO:** Graphene oxide; **IGF-1C:** C domain peptide of insulin-like growth factor-1; **NRG1**: Neuregulin-1; **NO**: Nitric oxide; **PECUUS:** poly (ester carbonate) urethane urea; **PEGDA:** Polyethylene glycol diacrylate; **PCL:** Polycaprolactone; **PVA:** Polyvinyl alcohol.

alginate, chitosan and HA), decellularized extracellular cardiac matrix (dECM) and even cell sheets, which confer higher biocompatibility compared to synthetic biomaterials.

Although the therapeutic effects of various cardiac patches *per se* have been reported on MI, the optimum patch design is still unknown due to the lack of understanding of the mechanisms involved in limiting left ventricular remodeling and restoring cardiac function. In this sense, Lin et al. demonstrated that a patch made of an ionically crosslinked starch HG with unique gel-point properties induced transcriptomic changes in the cells of the infarcted tissue leading to decreased fibrosis, apoptosis, inflammation and improved mitochondrial metabolism (Lin et al., 2019). As stated before, cell therapy has been a promising strategy for cardiac repair after MI. Seeding scaffold materials with cells to create cellular cardiac patches transplanted onto the heart's surface can overcome these limitations. A recent proof is the development of highly functional cellular patches made with neonatal rat ventricular cells which were able to robustly engraft on the epicardial surface (Jackman et al., 2018). They induced vascularization and maintained the heart electrical function for at least 6 weeks in a rat MI model. Additionally, a cellular cardiac patch composed of a layer of human iPSC-derived ECs sandwiched between two layers of human iPSC—CMs suspended in a fibrin matrix was efficiently designed (Wang and Zhang, 2022). The local application of the patch in a rat MI model was associated with significantly better cell engraftment, cardiac function, infarct size and vascularity. Similarly, a cellular cardiac patch based on fibrin and three cardiac cell lines (CMs, smooth muscle cells and ECs) derived from human iPSCs significantly reduced infarct size and improved cardiac function in swine (Gao et al., 2018). These studies confirmed that the implantation of cardiac patches on the infarcted zone of the heart efficiently enhanced cell retention while contributing to cardiac repair. Given the promising results of cellular cardiac patches in preclinical models, preliminary clinical trials have been initiated. The potential of a patch seeded with autologous CMs and amnion epithelial SCs is being evaluated in patients suffering MI as a consequence of COVID-19 disease (ClinicalTrials.gov #NCT04728906). Furthermore, the safety and efficacy of a collagen-based patch combined with ADSCs are being tested in patients with ischemic heart disease and left ventricular dysfunction (ClinicalTrials.gov #NCT03746938). Notably, PERISCOPE (ClinicalTrials.gov #NCT03798353) studied the efficacy of PeriCord ™, a clinical-size pericardial matrix colonized with human viable Wharton's jelly-derived mesenchymal stromal cells, showing a ~9% reduction in scar mass in the treated area once implanted (Prat-Vidal et al., 2020)

Another interesting purpose of cardiac patches is to induce vascularization as a strategy to provide oxygen and nutrient delivery to the cells within the patch while restoring the injured vasculature of the ischemic zone. Regarding this, Su et al. developed a pre-vascularized cardiac stromal cell patch based on fibrin integrated with CDCs and engineered microvessels (Su et al., 2020). After epicardial implantation, the cellular cardiac patch sustainably released cardioprotective factors secreted by the CDCs, promoted cardiac function recovery and limited pathological ventricular remodeling post-MI injury. Increases in CM proliferation, new blood vessel formation, endogenous progenitor cell activation, and alleviation of proinflammatory cytokine expression were also reported. Likewise, a dual strategy was successfully developed to

effectively reconstruct the vasculature of ischemic hearts by delivering iPSC-derived EC and genetically modified BM-MSCs secreting SDF-1α within a 3D dECM-based cardiac patch (Kim et al., 2022; Park et al., 2019). The patch consisted of porcine dECM, which provided a protective microenvironment that allowed the intramyocardial injection of SCs. The system favored a synergistic effect of both cell types ultimately achieving complete vascular regeneration of rat MI hearts. Finally, Huang et al. developed an off-the-shelf therapeutic cardiac patch composed of a porcine dECM scaffold and synthetic cardiac stromal cells generated by encapsulating secreted factors from isolated human cardiac stromal cells (Huang et al., 2020). This fully artificial cardiac patch supported cardiac recovery by reducing scarring, promoting angiogenesis and boosting cardiac function in a rat model of acute MI.

3.2.2. Synthetic cardiac patches

Synthetic cardiac patches can be fabricated with a great variety of polymers such as polymer poly (vinyl alcohol), PLGA, poly-(L-lactic) acid, and polyurethanes which allow more reproducible synthesis processes, functionalization and confer electrical properties.

Most of the developed cardiac patches are sutured in the epicardium requiring surgical implantation, and if injectable, they do not maintain their shape or function. As an alternative, microneedle synthetic cardiac patches are constituted of a kind of microchannels to allow for communication between the patch and the host myocardium without requiring a suture. In this regard, a PVA microneedle cardiac patch integrated with CSCs was developed for heart repair (Tang et al., 2018). Microneedles were designed as channels to allow the secretion of CSC regenerative factors into the injured myocardium and promote heart repair. After administration, the cardiac patch promoted angiogenesis, reduced scar size, and augmented cardiac functions in a porcine model of MI. Likewise, a biocompatible microneedle patch using gelatin methacryloyl (GelMA) and loaded galunisertib, a transforming growth factor-beta-specific inhibitor, was engineered to treat excessive cardiac fibrosis after MI (Chen et al., 2022). The patch could sustainably release galunisertib for more than 2 weeks and provided mechanical support to the fragile ventricular wall. After the administration in a rat model of MI, the galunisertib-loaded patch improved long-term cardiac function and reduced cardiac fibrosis.

Cardiac patch functionalization can confer interesting properties such as conductivity, ROS scavenging and enhanced therapeutic agent anchoring. Regarding this, a nitrate-functionalized patch demonstrated optimized therapeutic efficacy in a rat model of MI (Zhu et al., 2021). Reduced cardiac injury at an early stage, suppressed adverse cardiac remodeling and ameliorated heart function after long-term treatment were among the therapeutic outcomes observed. The translational potential of nitrate-functionalized patches was further evaluated in a porcine ischemia/reperfusion MI model which showed enhanced cardiac function after their implantation. Additionally, a microporous cardiac patch made of elastomeric polyurethane containing ROS-sensitive poly(thioketal) and unsaturated poly (propylene fumarate) segments and further clicked with proangiogenic Arg-Glu-Asp-Val-peptides was synthesized for the delivery of rosuvastatin into the infarcted myocardium (Yao et al., 2022). The mechanical support and multifunctional effects were confirmed in a rat model of MI leading to reduced cell apoptosis, suppressed local inflammatory response, alleviated fibrosis, induced angiogenesis and maintained cardiac function demonstrating the advantages of the integrated and orchestrated treatment strategy for MI therapy.

Incorporating electrical conductivity into these patches is found to be an efficient method to improve cardiac tissue function. Electroconductive materials have been extensively investigated and developed for various biomedical applications over the past few decades including graphene, carbon nanotubes, metallic NPs, polyaniline, polypyrrole (PPy), and poly(3,4-ethylendioxythiophene) (Ghovvati et al., 2022; Solazzo et al., 2019). In this way, an injectable, shape-memory and conductive patch consisting of methacrylated elastin and GelMA combined with carbon nanotubes was designed as a novel scaffold for cardiac repair (Leyu Wang et al., 2021). The implantation of cell-free patches or patches seeded with rat CMs led to functional repair after four weeks in a rat model of MI. Functional recovery was observed also in minipigs after the delivery of cell-free patches or patches incorporating hiPSC—CMs. Likewise, Liang *et al.* developed a conductive HG which could be conveniently painted as a patch onto the heart surface without adverse liquid leakage (Liang et al., 2018). The functional patch whose conductivity was equivalent to that of the normal myocardium strongly bonded to the beating heart within 4 weeks and efficiently boosted the transmission of electrophysiological signals. The reconstruction of the cardiac function and revascularization of the infarct myocardium remarkably improved. Finally, a composite cardiac patch based on chitosan electrospun nanofibers was synthesized and loaded with neonatal rat CMs (Wang et al., 2019b). *In vivo* studies demonstrated that the scaffold improved cardiac function by limiting the scar area and promoting angiogenesis in post-MI rats.

3.2.3. Main challenges of cardiac patches

Cardiac patches have shown the potential to improve cardiac function after MI in relevant animal models and some of them have entered clinical trials. Although these studies suggested the possibility of a near-translation to the clinic, some points need to be improved to achieve an optimal clinical translation (Chang et al., 2021; McMahan et al., 2020). The biggest obstacle to clinical application and commercialization is that, although many CMs can be transplanted using a patch, the number of cells that ultimately survive and integrate within the infarcted region is still quite low (Ghovvati et al., 2022). Additionally, cardiac patches do not achieve good electrical coupling in the heart after transplantation and tend to detach with the heartbeat causing arrhythmias. Currently, the size of cardiac patches is mostly limited to small animal models, and the clinical size of vascularized patches is an issue that needs further investigation. In most cases, epicardial suture-based implantation is the first choice for heart attachment requiring open-chest surgery, which may lead to increased damage in the infarcted tissue and slow down cardiac recovery. In this sense, compatibility with minimally invasive approaches such as cardiac catheters would be essential. Furthermore, greater efforts need to be made to enhance their adhesive properties to achieve higher retention rates once they are placed in the heart as well as long-term storage *ex vivo*.

3.3. Injectable hydrogels

HGs are cross-linked 3D networks that can serve as effective therapeutic molecule depots to afford local delivery and respond to endogenous or exogenous triggers. Stimuli-responsive HGs can efficiently overcome the hurdles of small therapeutics systemic delivery (Zheng et al., 2021). Furthermore, they rapidly undergo a phase change from solution to gel in response to a change in temperature, pH, light or mechanical forces, thus enabling the release of encapsulated therapeutic cargoes via minimally invasive techniques into the target site (Buwalda et al., 2014; Gu et al., 2017).

To date, injectable HGs developed for cardiac tissue regeneration applications have become increasingly safer, smarter and more multifunctional (Saludas et al., 2017). Ideally, HGs should be biocompatible and biodegradable, preferably with a biodegradation rate similar to the regeneration rate of the damaged tissue. In addition, they should mimic the mechanical properties of myocardial tissue to provide mechanical support and maintain the contractile function of the heart. Furthermore, they should have a sol-gel transition time suitable to support their injectability and allow their compatibility with cardiac catheters, spray and intramyocardial injection (Fig. 3). Finally, injectable HGs should have electrical conductivity properties able to support cardiac contraction and diastole. As in the case of cardiac patches, a great variety of biomaterials with different origins has been tested for HG synthesis in the last few years (Table 2) and some are currently being evaluated in

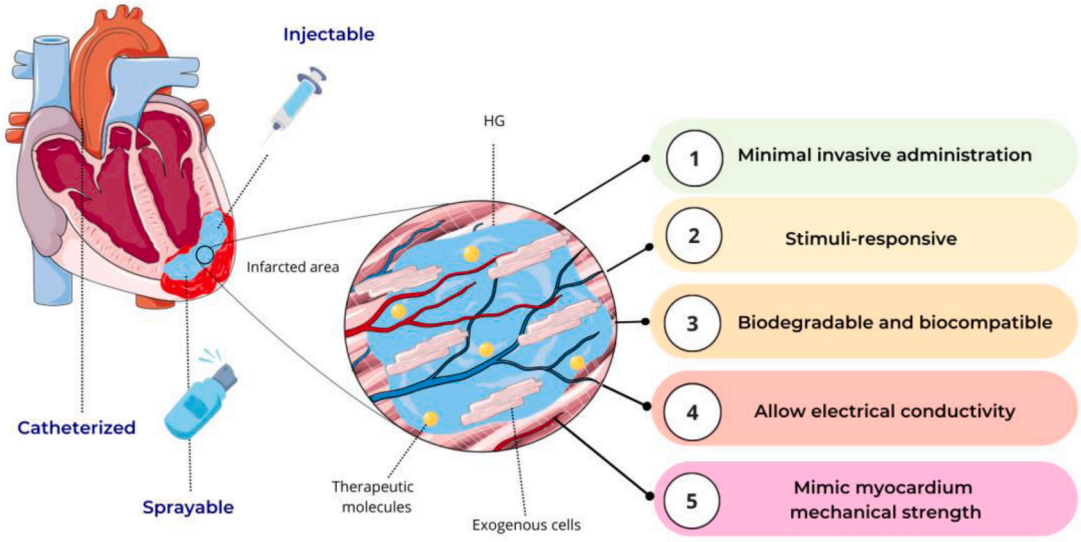

Fig. 3. Main features of HGs for cardiac tissue regeneration application include minimal invasive administration, stimuli-responsiveness, biodegradability and biocompatibility, conductivity and heart-compatible mechanical properties. The main routes for HG delivery (catheter, spray and injection) are also indicated. The figure includes original elements from Servier Medical Art.

Table 2
Preclinical studies with hydrogels and their combination with cardiac therapeutic agents for MI treatment.

Biomaterial	Therapeutic agent	MI animal model	Therapeutic effect	References
Recombinant human collagen I and Collagen III	–	Mice	Restored the myocardium's mechanical properties and reduced scar size	(McLaughlin et al., 2019)
ROS-cleavable hyperbranched polymers and MA-HA	–	Rats	Promoted angiogenesis, reduced infarcted area, and improved cardiac function	(Ding et al., 2020)
Elastin-like recombinamers	–	Sheep	Functional recovery of EF, decreased fibrosis, increased angiogenesis and marked functional recovery	(Contessotto and Pandit, 2021)
HA-chitosan/β-glycerophosphate	–	Mice	Enhanced cardiac function and increased vascularization	(Peng et al., 2022)
Alginate, HA and platelet-rich fibrin	–	Rats	Promoted angiogenesis and increased vascular density	(Qian et al., 2022)
4-Aminobenzothioamide and Keratin	–	Rats	Cardioprotection	(Zhang et al., 2022)
Chitosan	–	Mice	Attenuated cardiac damage and adverse cardiac remodeling, promoted cardiac repair and function	(Hao et al., 2022)
Selenium and polymers	–	Mice	Promoted cardiac function recovery	(Yang et al., 2022)
Collagen-GSH	GST-TIMP-bFGF	Rats	Promoted cardiac recovery by enhancing vascularization and ameliorating myocardium remodeling	Fan et al., 2019
HA	HGF and SDF-1α	Rats	Improved cardiac function	(Steele et al., 2020)
PLGA-PEG-PLGA	Colchicine	Mice	Alleviated cardiac inflammation, inhibited myocardial apoptosis and fibrosis, improved cardiac function and increased mice survival	(Chen et al., 2020b)
HA	miRNA-29B	Mice	Improved cardiac function	(Monaghan et al., 2018)
Transglutaminase cross-linked Gelatin and Collagen	hADSCs	Mice	Induced cardioprotection	(Chen et al., 2020a)
PLA-PEG-NIPAAM	hESC—CMs	Rats	Reduced infarct size, stimulated vascularization and recovery of cardiac function	(Zhao et al., 2020)
Matrigel ™/ HA/ Alginate	hESC—CMs	Rats	Cardiac regeneration	(Tan et al., 2020)
Chitosan/DEX/β-glycerophosphate	MSCs	Rats	Increased EF and vessel density and decreased the fibrotic area and infarct size	(Hua et al., 2020)
Chitosan	BM-MSCs	Mice	Promoted cardiac function recovery	(Liu et al., 2020)

CRAMP: Cathelin-related antimicrobial peptide; **DEX:** Dextran; **EDC**: 1-Ethyl-3-(−3-dimethylamino propyl) carbodiimide hydrochloride; **EF**: Ejection fraction; **FS**: Fractional Shortening; **GSH:** Glutathione; **GST:** Glutathione S Transferase; **HA:** Hyaluronic Acid; **HEMA:** (Hydroxyethyl)methacrylate; **HGF**: Hepatocyte Growth Factor; **MAPLA**: Malleated polylactide; **MMP**: metalloproteinase; **NIPAAMm:** Poly(*N*-isopropyl acrylamide; **PANI–AMB:** poly-3-amino-4-methoxy benzoic acid; **PEG**: Polyethylene glycol; **PCLGA**: Poly(ε-caprolactone-*co*-glycolic acid; **PGA**: Polyglutamic acid; **PLA**: Polylactic acid; **PDGF**: Platelet-derived growth factor;); **rTIMP3**-: recombinant TIMP metalloproteinase inhibitor 3; **SDF1**: Stromal derived factor 1.

clinical trials.

3.3.1. *Natural-based hydrogels*

Several smart natural polymer-based HGs including temperature, pH, light, electricity, ions and multiple responsive HGs have been reported. Among them, temperature responsive HGs are one of the most widely investigated. They represent a promising vehicle to deliver cells and small therapeutic molecules by direct injection since they can undergo a reversible phase transition at body temperature, allow fast gelation, and controlled degradation while providing a protective environment for encapsulated cells or a reservoir for protein delivery (Sheridan et al., 2014). In this regard, Liu et al. explored whether transplantation of chitosan/β-glycerophosphate thermosensitive HG with BM-MSCs could maximize the therapeutic effect of the embedded

cells in a mouse model of MI (Liu et al., 2020). The HGs enhanced cell survival, engraftment and the recovery of cardiac function by increasing the number of vascular ECs. Transplanted BM-MSCs inhibited the inflammatory response and alleviated the pyroptosis of vascular ECs. As a double therapy, a thermosensitive chitosan-IGF-1C HG improved human placenta-derived MSCs survival and increased angiogenesis, reduced collagen deposition, ameliorated left ventricular expansion, and further promoted the recovery of cardiac function in a rat model of MI (Yao et al., 2020).

Alternatively, another frequently used method for inducing HG sol-gel transition is the addition of a crosslinking agent. Interestingly, a thiolated HA crosslinked with polyethylene glycol-diacrylate was developed to efficiently deliver exogenous miR-29B (Monaghan et al., 2018). Delivering miR-29B locally resulted in the maintenance of myocardial function at 2- and 5-weeks following MI in mice. Histological analysis revealed a significant decrease in elastin, new collagen fibers and increased vascularity at the border zone of the infarct. Additionally, a new type of HG composed of alginate and HA with lyophilized platelet-rich fibrin was designed for GFs release. Since HA cannot be cross-linked it was combined with alginate (Qian et al., 2022). When injected into the infarcted myocardium, the HG promoted angiogenesis and increased vascular density in both the infarcted and border zone, which rescued the ischemic myocardium. These beneficial effects were also accompanied by macrophage polarization and regulation of myocardial fibrosis. Regarding alginate potential, AUGMENT-HF, a clinical trial involving alginate-based HGs proved the safety and cardiovascular effects of Algisyl-LVR™, an alginate-based HG, as a method of left ventricular augmentation in patients with dilated cardiomyopathy (ClinicalTrials.gov #NCT01311791). The epicardial implant placed during open thoracotomy led to decreased myofiber stress, restored LV geometry and improved cardiac function (Diaz et al., 2021).

3.3.2. Synthetic hydrogels

Synthetic polymers are biomaterials that have attracted considerable interest due to their strong mechanical properties, stability and easily controlled physical and chemical properties, but they have the drawback of being less biocompatible than natural materials. However, they can be tuned by the attachment of specific molecules to face these limitations. Moreover, they usually confer electrical properties to the HG necessary to improve the heart's electrical signals and conduction.

Recently, a conductive, biocompatible and injectable HG was generated by conjugating conductive PPy onto chitosan backbones. PPy is a well-known conductive polymer. Unless it is non-thermoplastic, mechanically rigid and brittle, when conjugated with other biocompatible materials, such as collagen, its biocompatibility is improved without significantly affecting its conductivity (Ateh et al., 2006). In this sense, PPy was successfully immobilized in chitosan via a chemical oxidative polymerization method. The intra-myocardial injection of the HG following cardiac injury improved electrical impulse propagation of scar tissue in a rat model of MI. Future studies including therapeutic agents should be of interest.

Related to ADSC-loaded synthetic-based HGs, an alginate HG modified with 2-aminopyridine-5-thiocarboxamide was developed to vehicle a macromolecular hydrogen sulfide (H_2S) prodrug as a strategy to mimic H_2S continuous endogenous release, which has been proven to produce extensive anti-inflammatory effects, mitochondrial function preservation, vasodilation, and protection against oxidative stress in cardiovascular systems (Liang et al., 2019). Tetraaniline (a conductive oligomer) and human ADSCs were also embedded to form a stem cell-loaded conductive H_2S-releasing HG. Echocardiography and histological analysis revealed a remarkable improvement in cardiac function in a rat model of MI. Additionally, Yoshizaki et al. developed an HG based on PCLA and PEG with temperature-responsive sol-to-gel transition, biodegradability and injectability properties (Yoshizaki et al., 2021). Human ADSC embedded within the HG showed enhanced retention rates accompanied by a recovery of the cardiac function once injected *in vivo*.

HGs have also been investigated as GF and protein delivery vehicles. A bFGF-loaded HG based on NIPAAm, HEMA and macromer acrylate-oligolactide was developed with suitable release kinetics (Z. Fan et al., 2019). Increases in blood vessel density, cell survival, decreased myofibroblast density and reduced macrophage density were observed 4 weeks after implantation in a rat model of MI. In addition, the bFGF release system significantly enhanced cardiac function was found. As a triple GF therapy, Rocker et al. developed a thermo-responsive injectable gel composed of chitosan, conjugated with poly (N-isopropyl acrylamide) and sulfonate groups for the spatiotemporal delivery of VEGF, IL-10 and PDGF (Rocker et al., 2022). The thermoresponsive HG delivered GFs in a sequential and sustained manner *in vitro*. Additionally, it allowed the controlled delivery of the therapeutic proteins in a mouse model of MI, which led to reduced macrophage infiltration and increased vascularization, and eventually triggered cardiac function recovery.

3.3.3. Main challenges of hydrogels

Despite substantial improvements in the field of cardiac HGs (Correa et al., 2021), one of the major issues is the full optimization of their viscoelastic and mechanical properties to be easily administered via cardiac catheters. In addition, ensuring cell survival and engraftment in the cardiac environment and SC differentiation into the required cell phenotypes (i.e., beating cardiac CMs) in minimal time from the time of injection would be essential. Moreover, the absence of electrical coupling is also among the challenges that can compromise the success of injectable HG-based SC therapy and cardiac repair. Finally, most HGs are currently fabricated in small batches, but large-scale production must be optimized under GMPs before approval and commercialization.

3.4. Hybrid therapeutic strategies

The combination of nanoparticles with other biomaterials to form hybrid systems has arisen as a novel nanotechnology approach to optimize single-delivery-system-based therapies (Table 3). For instance, a novel therapeutic strategy based on a cardiac conductive patch combining gold NPs with extracellular matrix/silk proteins and MSCs was recently developed (Dong et al., 2020). The system proved to favor cell growth and led to higher CM survival and retention rates once implanted in the heart while decreasing infarct size and enhancing cardiac function. In another study, a contracting fibrin-based cellular cardiac patch containing CHIR9902 and FGF1-loaded PLGA-NPs significantly increased hiPSC—CM cell cycle activity, improved cardiac function, reduced infarct size, induced angiogenesis and diminished apoptosis four weeks after its administration in a mouse MI model (Fan et al., 2020). Cardiac patches have gained recent interest in efficiently delivering exosomes to the ischemic myocardium. An injectable HA HG-based patch combined with MSC-derived exosomes efficiently reduced LV chamber size and preserved wall thickness in a rat model of heart failure. Additionally, the feasibility and safety of the patch injection were further confirmed in swine (G. Cheng et al., 2022).

The combination of HGs and nanocarriers has also been investigated demonstrating enhanced delivery properties compared to those obtained when administered separately (Table 4). These hybrid biomaterials have shown superior capabilities in modulating drug release kinetics and releasing drugs in a remotely controlled fashion while assisting site-specific drug targeting. Regarding the type of nanocarriers embedded, EVs represented the most frequently used. For example, an alginate-based HG enhanced cardiac retention of EVs in the infarcted heart in a rat model of MI (Lv et al., 2019). EVs-HG combination significantly decreased cardiac cell apoptosis and promoted the polarization of macrophages, increased scar thickness and angiogenesis and significantly improved cardiac function. Likewise, an in situ jellifying alginate and collagen-based HG enhanced EVs retention in the infarcted

Table 3
Preclinical studies with cardiac patches and nanocarriers for MI treatment.

Biomaterial type	Nanocarriers	Therapeutic effect	Type of implantation	MI animal model	Therapeutic effect	Reference
Collagen	AuNPs	–	Sub-pericardial	Mice	Enhanced vasculogenesis	(Hosoyama et al., 2018)
ECM/silk proteins	AuNPs	–	Epicardial	Rats	Decreased infarct size	(Dong et al., 2020)
Chitosan and PANI	AuNPs	–	Epicardial	Rats	No detrimental effect on cardiac function and negligible fibrotic response	(Kapnisi et al., 2018)
dECM, PuraMatrix® and peptide	ADSC-EVs	–	Heart surface	Swine	Modulation of short-term post-ischemic inflammation	(Monguió-Tortajada et al., 2022)
HA	MSC-EVs	–	Pericardial	Mice	Reduced LV chamber size and preserved wall thickness	(G. Cheng et al., 2022)
Elastin-like polypeptide gel and HA	PLGA NPs	MSCF	Epicardial	Rats	Reduced CMs apoptosis and fibrosis	(Hu et al., 2022b)
Fibrin	PLGA NPs	CHIR9902, hiPSCs and FGF1	Epicardial	Mice	Improved cardiac function, reduced infarct size and induced angiogenesis	(Fan et al., 2020)

MSCF: mesenchymal stromal cell factor; **PANI**: Polyaniline.

Table 4
Recent preclinical studies with hydrogels and nanocarriers for MI treatment.

Biomaterial type	Nanocarriers	Therapeutic cargo	MI animal model	Therapeutic effect	References
NIPAAm/HEMA/AOLA	PLGA-PVP/H_2O_2 microspheres	–	Rats	Stimulated angiogenesis and improved cardiac function	(Fan et al., 2018)
HA	PLGA microparticles	MSCs	Rats	Efficient reconstruction of cardiac function, structure and revascularization	(Lyu et al., 2020)
MMP sensitive PEG	PLGA-NPs	F and R (hydrophobic drugs)	Rats	Improved LV functions, increased angiogenesis and reduced fibrosis and inflammatory response	(Fan et al., 2019)
CMC and PhB $(OH)_2$	PLGA NPs	Curcumin and Collagen III	Rats	Reduced inflammation and induced angiogenesis	(C. Hu et al., 2022)
Alginate	Silk fibroin microspheres	VEGF and BMP9	Mice	Promote angiogenesis and enhanced heart function.	(Wu et al., 2021)
Alginate	Silk fibroin microspheres	IGF-1	Rats	Reduced the infarct size and improved cardiac function	(Feng et al., 2020)
PEG	Mesoporous silica NPs	miR-21–5p	Pigs	Promoted local neovascularization and reduced infarct size	(Li et al., 2021c)
PVA	Melanin NPs	–	Rats	Enhanced the cardiac repair and promoted vascularization	(Guan et al., 2022)
Extracellular matrix	AuNPs	–	Mice	Reduced infarct size and the inflammatory response and significantly prevented the deterioration of heart function	(Shilo et al., 2021)
ROS responsive PAMB-G-TK/4-arm-PEG-SG	Liposomes	Elamipretide and S1P	Rats	Improved cardiac function and promoted angiogenesis	(Zheng et al., 2022)
ROS-sensitive macromer and HA	PDA-NPs	Tanshinone IIA	Rats	Improved cardiac functions and decreased infarct size	(W. Wang et al., 2019)
Alginate	EVs	miRNA-126 and miRNA-146a	Rats	Reduced inflammation and fibrosis	(Shafei et al., 2022)
Alginate	MSC-EVs	–	Rats	Improved cardiac function and infarct size.	(Lv et al., 2019)
(RADA)4-SDKP	MSC-EVs	–	Rats	Improved cardiac function	(Firoozi et al., 2020)
Gelatin and Methacrylic anhydride	MSC-EVs	–	Mice	Significant cardiac function recovery	(Tang et al., 2022)
Alginate	Dendritic cell-EVs	–	Mice	Reduced inflammatory response	(Zhang et al., 2021)
RGD-biotin	MSC derived EVs	HIF-1α	Rats	Angiogenesis	(Q. Wang et al., 2021)
4APPC and DHPM	Treg-EVs	–	Rats	Reduced myocardial injury and improved cardiac function	(Cheng et al., 2022b)
Gelatin and Laponite®	hADSC-EVs	–	Rats	Promoted increased angiogenesis, reduction in cardiac remodeling and cardioprotection	(Waters et al., 2018)

AOLA: Acrylated olygolactide**; BMP9:** Bone morphogenetic protein-9; **CMC**: Carboximetyl cellulose; **HEMA:** Hydroxyethylmethacrylate; **NIPAAm**: methacrilated Poly (N-isopropylacrylamide); **PAMB-G-TK:** poly-3-amino-4-methoxybenzoic acid with TK-NH2-modified gelatin; **PDA**: Polydopamine; **PVP**: Polyvinylpyrrolidone; **S1P:** sphingosine-1-phosphate; **4-arm-PEG-SG:** 4-arm-PEG-succinimidyl glutarate ester; **PhB(OH)₂:** Phenylboronic acid.

myocardium (Gil-Cabrerizo et al., 2022). After administration in a rat MI model, the HG allowed the sustained release of EVs for at least 7 days. Regarding NPs-HG systems, an injectable and thermosensitive HG based on chitosan, gelatin, β-glycerophosphate and Arg-Gly-Asp-peptide was synthesized to confer a protective microenvironment for VEGF-loaded NPs and SDF-1α -loaded NPs. The advanced system was injected into a rat model of MI showing increased angiogenesis and cardiac function recovery.

Thus far, these studies demonstrate that hybrid therapeutic strategies combining NPs with cardiac patches or HGs constitute novel promising approaches with an enormous potential to improve the delivery efficiency of biologics to the infarcted heart. With appropriate compositions, these hybrid strategies could be the ideal approach to preserve the structural integrity and the functionalities of the embedded NPs while offering additional engineering flexibility to improve the overall therapeutic efficacy.

4. Routes of administration of biomaterial-based therapies for MI treatment

Different administration routes can be used to deliver biomaterial-based therapies for MI treatment. Systemic administration of therapeutics often faces challenges such as limited efficacy due to off-target effects or short circulation times needed to select more invasive routes. The most frequently used delivery route in preclinical studies is intramyocardial administration, which can be performed by open chest surgery or by transendocardial injection catheter. Another alternative is intracoronary infusion which can be done via catheterization. Catheter-based techniques are less invasive and therefore preferred for the cardiac delivery of therapeutics.

Specifically, for microcarriers, particle size plays an important role in the selection of the delivery route. Generally, MPs are mostly administered via intramyocardial injection, which requires open-chest surgery. However, MPs with a size of 5 μm can be delivered via percutaneous catheters in infarcted pigs demonstrating the feasibility of using a minimally invasive administration route for microcarrier delivery to the heart (Garbayo et al., 2016). Additionally, if the particle size is comprised between 1.5–3 μm, they can be administered via inhalation (El-Sherbiny et al., 2015). On the other hand, nanocarriers allow non-invasive or minimally invasive delivery routes, including both intravenous administration and inhalation. Recently, a novel delivery approach for heart targeting and treatment based on the inhalation of drug-loaded CaP-NPs absorbed through the lung has been proposed (Miragoli et al., 2018). The therapeutic delivery of an active mimetic peptide targeting the Cavβ2 cytosolic subunit of the L-type calcium channel directly to the cardiomyocytes using inhalable CaP-NPs was demonstrated in a murine model of diabetic cardiomyopathy (Rusconi et al., 2016). Later, another proof-of-concept study showed how inhaled CaP-NPs loaded with a synthetic miRNA-133 efficiently mimic limited heart failure progression in a mouse model of ventricular pressure overload (Modica et al., 2021). Furthermore, inhalable microparticles embedding CaP-NPs loaded with bioactive mimetic peptide have also been successfully developed for cardiac delivery (Quarta et al., 2022). Altogether, these studies demonstrate that inhalation could be a pioneering non-invasive approach for NPs and MPs delivery to treat MI.

Regarding cardiac patch delivery, these are mainly adhered or sprayed to the epicardial surface of the heart and therefore require invasive open-chest surgery (Table 3). In contrast, HG administration depends on the biomaterial composition, and those synthesized with in situ jellifying biomaterials are the most suitable for delivering therapeutics directly to the infarcted region via minimally invasive routes.

5. Concluding remarks

In the last few decades, the cardiac regeneration field has seen some major advances. Nowadays, there is a growing understanding of the biological pathways underlying MI, and consequently, novel therapeutic strategies have been proposed to achieve heart remuscularization and restore cardiac function. While in the early twenties SC based therapy came onto the scene with promising potential, the research has now shifted towards the use of EVs and miRNAs. However, these biomolecules need to be combined with delivery systems to augment their stability, control their release and help them to traverse the barriers towards the target site. Currently, a broad variety of delivery systems have been developed to maximize the potential of numerous biologic molecules, nanocarriers, cardiac patches and HGs being the ones that have met with greater success at a preclinical level. Particularly, naturally based cardiac patches and HGs are currently being evaluated in clinical trials with high expectations for MI treatment. Although great

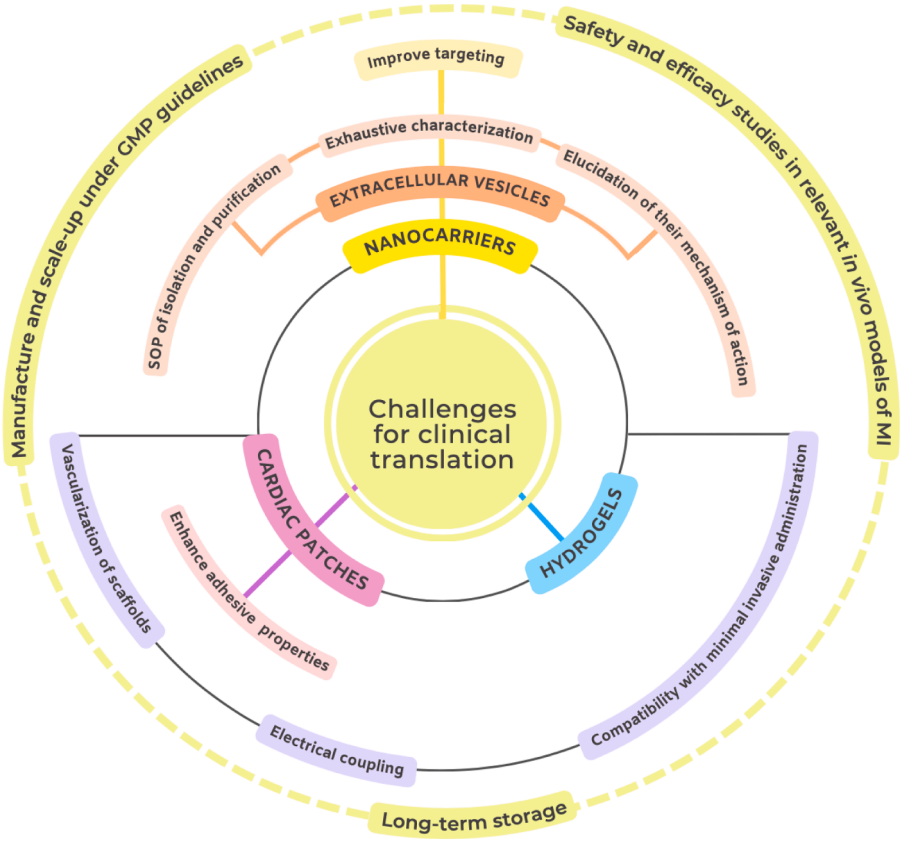

Fig. 4. Challenges for clinical translation. The main challenges of nanocarriers, cardiac patches and HGs include manufacture and scale-up under GMP guidelines, long-term storage, and safety and efficacy studies in relevant *in vivo* models of MI. In addition to these, each delivery vehicle faces its own specific challenges (i.e. targeting improvement, enhancing adhesive properties).

efforts have been made, there are still some common challenges that must be overcome (Fig. 4). These include the need for more studies assessing safety and efficacy in relevant preclinical models (i.e., swine), and for optimization of the fabrication process following GMP guidelines and improvements in long-term storage. Furthermore, each delivery system has specific limitations. In the case of EVs, an exhaustive characterization, the establishment of SOP for efficient isolation and purification, and elucidation of their mechanism of action are considered the major challenges. Regarding nanocarriers, improving their targeting ability is essential to avoid off-target effects and diminish multiple dosing. Cardiac patches sometimes adhere to the epicardial heart surface, and so they must improve adhesiveness to achieve higher retention rates. Finally, both HG and cardiac patches should be developed to allow vascularization, in order to increase the survival of the embedded cells and an appropriate integration into the target tissue, increase electrical coupling to avoid the appearance of arrhythmias and allow their administration via minimally invasive techniques. The combination of nanocarriers with HGs or cardiac patches to form a synergistic hybrid system would be the most complete and promising cardiac therapeutic strategy, as it would confer the advantages of both biomaterial-based delivery systems. Therefore, once the aforementioned challenges are solved, novel hybrid therapeutic strategies based on cardiac tissue engineering will be able to become powerful MI treatments.

Credit author statement

Paula Gil-Cabrerizo and Ilaria Scacchetti, Preparation and presentation of the published work by those from the original research group; critical review ad first draft writing. Elisa Garbayo: reviewing; María J. Blanco-Prieto: Reviewing and Editing, supervision, funding acquisition.

Data availability

No data was used for the research described in the article.

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