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Review article

Engineering functional electroconductive hydrogels for targeted therapy in myocardial infarction repair☆

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ABSTRACT

Myocardial infarction (MI) is characterized by a paucity of cardiomyocyte regeneration, leading to significant morbidity and mortality. Contemporary therapeutic modalities, while mitigating ischemic effects, fail to reconstitute the impaired electromechanical coupling within the infracted myocardium. Emerging evidence supports the utility of electroconductive hydrogels (ECHs) in facilitating post-MI cardiac function recovery by restoring the conductive microenvironment of the infarcted tissue. This comprehensive review delineates the taxonomy of ECHs predicated on their constituent conductive materials. It also encapsulates prevailing research trends in ECH-mediated MI repair, encompassing innovative design paradigms and microenvironment-sensitive strategies. The review also provides a critical appraisal of various implantation techniques, underscored by a thorough examination of the attendant considerations. It elucidates the mechanistic underpinnings by which hydrogels exert salutary effects on myocardial repair, namely by augmenting mechanical and electrical integrity, exerting anti-inflammatory actions, fostering angiogenesis, and curtailing adverse remodeling processes. Furthermore, the review engages with the pressing challenge of optimizing ECH functionality to achieve superior reparative outcomes post-MI. The discourse concludes with an anticipatory perspective on the evolution of ECH scaffolds, advocating for a tailored approach that integrates multifaceted physicochemical properties to cater to the nuances of personalized medicine.

1. Introduction

Myocardial infarction (MI), a critical cardiovascular event, results from the acute rupture of atherosclerotic plaques, precipitating severe complications such as arrhythmias, cardiac rupture, congestive heart failure, and sudden cardiac death, which contribute to a high mortality rate [1]. The limited regenerative potential of cardiomyocytes leads to irreversible cell loss, adversely affecting cardiac conduction and contractility. This pathology often progresses to heart failure. Current therapeutic interventions, including percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), and thrombolytic therapy, mitigate myocardial ischemia but fail to effectively restore cardiomyocyte loss. Cardiac transplantation, albeit a definitive treatment, is hampered by donor scarcity.

Over the past decade, significant research has been dedicated to the implantation of living cells—ranging from non-cardiac to cardiac origin cells and pluripotent stem cells—and biomaterials, such as injectable hydrogels, cardiac patches, nanocarriers, and vascular grafts, into the infarcted myocardium to enhance cardiac function recovery [2,3]. Despite the promising outcomes of cell therapy, challenges persist, particularly the low survival rate of implanted cells and their restricted migration to the infarct area [2]. Among various biomaterials, hydrogels stand out as potential scaffolds for cardiac repair due to their biocompatibility, permeability, tunable mechanical properties, and the capacity

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to carry cells and drugs. Hydrogels can be derived from natural polymers, including collagen, gelatin, fibrin, silk fibroin, alginate, chitosan, cellulose, hyaluronic acid (HA), and acellular extracellular matrix, or from synthetic polymers like polyethylene glycol (PEG), polyacrylamide (PAM), polydimethylsiloxane, polyacrylic acid (PLA), polycaprolactone (PCL), and polyvinyl alcohol (PVA) [4].

Post-MI, the propagation of electrical signals and contractile function in the myocardium are significantly compromised, exacerbating cardiac dysfunction. The integration of conductive materials into injectable hydrogels or hydrogel-based cardiac patches to fabricate electroconductive hydrogels (ECHs) has been shown to be more effective in cardiac function recovery than non-conductive hydrogel scaffolds. The targeting capability of ECHs is often manifested through their ability to modulate electrophysiological properties or provide localized drug release, thereby promoting cardiac repair or regeneration without broadly affecting the entire body. This therapeutic approach can enhance repair outcomes, reduce side effects, and improve treatment efficacy. This review systematically elucidates the progress of ECHs in the context of MI repair, encompassing their classification, emerging research trends, implantation techniques, and mechanisms of myocardial restoration, as summarized in Fig. 1. Various conductive materials have been primarily utilized for the preparation of ECHs, including carbon nanomaterials (e.g., carbon nanotubes, graphene), transition metal carbide (MXene), conductive polymers (e.g., polypyrrole, polythiophene, PEDOT, polyaniline), noble metal nanocrystals (e.g., gold, silver), and bio-ionic liquids (e.g., choline-based Bio-ILs), as detailed in Table 1 and Fig. 2 [5–7]. Additionally, certain materials like melanin nanoparticles, and black phosphorus nanosheets (BPNSs) exhibit conductivity under specific conditions, offering potential for cardiac tissue engineering applications [8–10].

To optimize the efficacy of conductive hydrogels in MI repair, different laboratories have adopted diverse strategies. The incorporation of therapeutic cells, cellular components, and nanodrugs into injectable ECHs has been reported to result in superior repair outcomes compared to non-conductive hydrogel scaffolds [11,12]. The development of smart hydrogels that respond to cardiac microenvironmental cues to enhance their therapeutic efficacy, and the preparation of ECHs with dual functionalities for repair and continuous monitoring, which can facilitate more informed clinical decision-making, have emerged as focal points in recent research. This review consolidates various functional strategies for the designing ECHs and their implantation methods, as detailed in Figs. 3–7 and Tables 2–5.

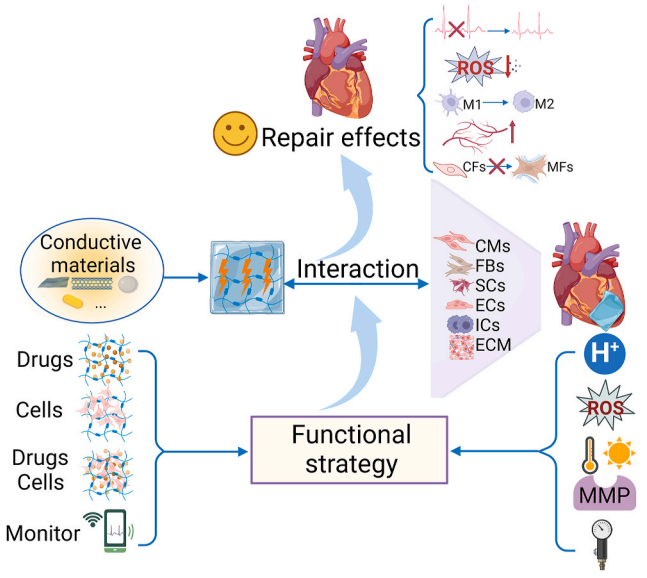

Fig. 1. A schematic illustration of the research progress of engineering functional ECHs for targeted MI Repair (created with BioRender.com).

MI is characterized by inflammation, proliferation, and remodeling during both the early ischemic phase and the subsequent infarct expansion. Elucidating the biological roles of ECH scaffolds in promoting cardiac function recovery post-MI is crucial for refining hydrogel fabrication and advancing clinical applications. Therefore, we summarize the biological roles of ECH scaffolds in cardiac recovery post-MI (Fig. 8) and discuss the challenges associated with their clinical translation. We hope that this review not only assists readers in rapidly grasping the advancements of ECHs in MI repair but also provides valuable insights and information to scholars for the rational design and application of ECH scaffolds for MI treatment.

2. The classification of ECHs

2.1. Carbon nanomaterials-incorporated ECHs

2.1.1. CNTs-incorporated ECHs

Carbon nanotubes (CNTs), characterized by their cylindrical nanostructure derived from graphene sheets, are available in single-walled (SWCNTs) and multi-walled (MWCNTs) configurations. These nanostructures exhibit a substantial specific surface area, which facilitates an increased number of reaction and binding sites. They possess exceptional electrical and thermal conductivities, reaching up to 10^7 S/m and 3000 W/mK, respectively, along with remarkable mechanical strength, with tensile strength approximately 0.85 GPa and a Young's modulus of around 34.65 GPa [13–15]. Integrating these nanofillers into hydrogels enhances fatigue resistance by inhibiting crack propagation and promoting stress transfer between the soft matrix and hard nanofillers. The surface topography of CNTs promotes cardiomyocyte attachment and proliferation, while their fibrillar structure enhances cell alignment, improving longitudinal contraction and emulating the natural cardiac microenvironment [15]. CNTs are often functionalized with polar groups like carboxylic acids to enhance their integration with hydrophilic polymers for ECH fabrication [16]. SWCNTs are particularly advantageous for cardiac scaffold modification due to their superior tensile strength, elastic modulus, surface area, and electron-transfer properties. Post-functionalization, CNTs can be uniformly dispersed within hydrophilic polymer matrices and aqueous solutions [17]. High concentrations of CNTs are toxic and may hinder cardiac cell adhesion and extension, so it's important to control SWCNT levels during hydrogel preparation. The United States National Institute for Occupational Safety and Health (NIOSH) recommends a CNT exposure limit of 7 $\mu g/m^3$. Moreover, activated macrophages within the ischemic myocardium are instrumental in the degradation of SWCNTs through NADPH oxidase, potentially mitigating toxicity [18]. Collectively, These findings suggest that SWCNT-enriched ECH scaffolds are a viable option for cardiac repair.

CNT-enriched ECHs are synthesized through various methodologies, including: (1) the fabrication of CNT-ECM hydrogels via interactions with extracellular matrix proteins [17]; (2) the fabrication of CNT-GelMA hydrogels through UV cross-linking (sandwich replication) or dielectrophoretic techniques [19–21]; (3) the fabrication of CNT-collagen hydrogels by physically blending collagen hydrogels with CNTs [22,23]; (4) the fabrication of alginate-CNT-methacrylated collagen hydrogels using a UV-assisted 3D bioprinting approach [24]; (5) the fabrication of CNT-HA-gelatin hydrogel microcapsules through laccase-mediated crosslinking, coaxial double-orifice microfluidic techniques, and water-in-oil emulsion systems [25]; (6) the fabrication of CNT-incorporated reverse thermal gels via esterification and amidation reactions [26].

In vitro studies have demonstrated that the CNT-enriched ECHs exert a positive influence on the morphology and function of cardiomyocytes, augmenting their contractile capacity [19,22–26], electrophysiological characteristics (owing to physical interactions between CNTs and cardiomyocytes) [27,28], and the expression of cardiomyocyte markers, all

Table 1
A schematic illustration of the properties of conductors and the effects of ECHs in cardial repair.

Conductors	Advantages	Deficiencies	Countermeasures to address the deficiencies	Effects (in vitro/in vivo, vs non-conductive hydrogel)	Ref.
CNTs	High tensile strength, elasticity, large surface area, electrical and thermal conductivity, polar group-modifiable	Cytotoxicity at high concentrations	Monitor CNT level during ECH preparation	In vitro: more favorable for growth in cardiomyocytes and coronary artery endothelial cells CNT-embedded injectable ECHs or cardiac patches: more beneficial for MI repair	[13] [13, 15–17, 20]
rGO	High hydrophilicity, biocompatibility, strong mechanical and electrical properties	Cytotoxicity varies by shape and composition	Use partially reduced GO for ECH preparation	In vitro: more favorable for growth in cardiomyocytes, cardiac fibroblasts, HUVEC, UCMSCs and HEMC-fibroblasts; promote the differentiation of UCMSCs into cardiomyocytes rGO-embedded injectable ECHs or cardiac patches: more beneficial for MI repair	[30,32, 34,39]
MXene	Excellent mechanical and conductivity, biocompatibility, hydrophilicity, high surface area, ease of film formation, antioxidant and antibacterial properties	Cytotoxicity at high concentrations	Monitor MXene level during ECH preparation.	In vitro: more favorable for growth in cardiomyocytes, detection the content of H_2O_2, cTnI, and heart-type fatty acid-binding protein Ti3C2Tx-ECH patch or Ti2C-based cryogel: more beneficial for MI repair	[40, 42–44]
PPy	Electrical conductivity, biocompatibility, easy synthesis, stablity in oxidized form	Poor solubility, mechanical brittleness, cytotoxicity at high concentrations	Add biocompatible/Degradable polymers; monitor PPy levels during ECH prep;	In vitro: more favorable for growth in cardiomyocytes or H9C2 cells PPy-embedded injectable ECHs or cardiac patches: more beneficial for MI repair	[46,47, 49,52, 55]
PEDOT: PSS	Superior chemical and thermal stability, electrical conductivity, biocompatibility, good dispersibility, and light transmittance	Mechanical brittleness, limited extensibility	Add PVA, alginate, or acidic anion liquids for flexibility	In vitro: more favorable for growth in HiPSC-derived cardiomyocytes; PEDOT:PSS-embedded injectable ECHs or cardiac patches: more beneficial for MI repair	[58–62]
PANI	Biocompatibility and adjustable conductivity, easy synthesis, high surface area, ROS scavenging ability	Poor biodegradability, low solubility, mechanical brittleness, and potential cytotoxicity	Add biodegradable polymers; Add lignosulfonate to augment its hydrophilicity and conductivity; monitor PANI levels during ECH preparation	In vitro: more favorable for growth in cardiomyocytes, L929 fibroblast and H9C2 cells PANI-embedded injectable ECHs or cardiac patches: more beneficial for MI repair	[63,64, 66,68]
AuNP	High surface to volume ratio, biocompatibility, easy synthesis, ease of surface modification, tunable electrical and mechanical characteristics, ROS absorption capacity	Poor biodegradability, potential cytotoxicity	monitor AuNP content during ECH preparation	In vitro: more favorable for growth in cardiomyocytes, more favorable for the cardiac differentiation of iPSCs and MSCs AuNP-embedded injectable ECHs or cardiac patches: more beneficial for MI repair	[71,73, 75,77,83, 86]
Bio-ILs	Biodegradable, biocompatible, high ionic conductivity and electrochemical stability, high water solubility and dispersibility, minimal cytotoxicity	Poor long-term stability, not easy to synthesis	Add suitable crosslinkers or stabilizers to enhance gel stability and improve ion stability	In vitro: more favorable for growth in cardiomyocytes and cardiac fibroblast Bio-ILs-embedded ECHs patches: more beneficial for MI repair	[87–90]

of which may foster cardiac repair. Furthermore, stem cells cultured on CNT-ECM or CNT-GelMA hydrogels have shown significantly improved differentiation into cardiomyocytes under electrical stimulation [17,20, 21]. Additionally, human coronary artery endothelial cells cultured on CNT-alginate-methacrylated collagen hydrogel have demonstrated increased proliferation and the formation of lumen-like structures, which are beneficial for vascular regeneration post-MI [24]. Importantly, animal studies have indicated that intramyocardial injection of SWCNT-ECM hydrogel reduces infarction and fibrosis areas in MI rats, improving cardiac function and underscoring its potential as a scaffold for cardiac repair [17].

2.1.2. *Graphene oxide-incorporated ECHs*

The graphene family encompasses several derivatives, including graphene oxide (GO), reduced graphene oxide (rGO), graphene quantum dots (GQDs), graphene nanosheets, monolayer graphene, and few-layer graphene. GO exhibits hydrophilicity and biocompatibility due to its oxygenated functional groups but possesses limited electrical conductivity [19]. Upon chemical reduction, rGO has reduced oxygen content and can be incorporated into hydrogels to enhance their electrical conductivity [29]. The concentration of rGO is directly correlated with the improvement in mechanical and electrical properties of hydrogel scaffolds [30].

In the realm of cardiac tissue engineering, GO/rGO-integrated ECHs are synthesized through various methodologies: (1) rGO-alginate hydrogel via probe sonication and sodium hydrosulfite reduction [30]; (2) rGO-GelMA hydrogel through UV-mediated photocrosslinking and ascorbic acid/dopamine reduction [31–33]; (3) GO-HA hydrogel via physical blending of hyaluronic acid (HA) and GO [34]; (4) GO-oligo (polyethylene glycol) fumarate hydrogel through TEMED/APS-mediated thermal crosslinking [35]; (5) rGO-methacryloyl-substituted tropoelastin (MeTro) hydrogel via UV-mediated photocrosslinking [36]; (6) rGO-dECM hydrogel with NaBH4 reduction and transglutaminase crosslinking [37]; (7) GQDs, made of sp^2 hybridized carbon in a honeycomb lattice with excellent electrical conductivity, are integrated into chitosan/collagen hydrogels through physical blending. Fine-tuning the physicochemical properties of these hydrogels can augment their mechanical, electrical, chemical, and biological functionalities for cardiac repair.

In vitro studies have demonstrated that rGO enhances the

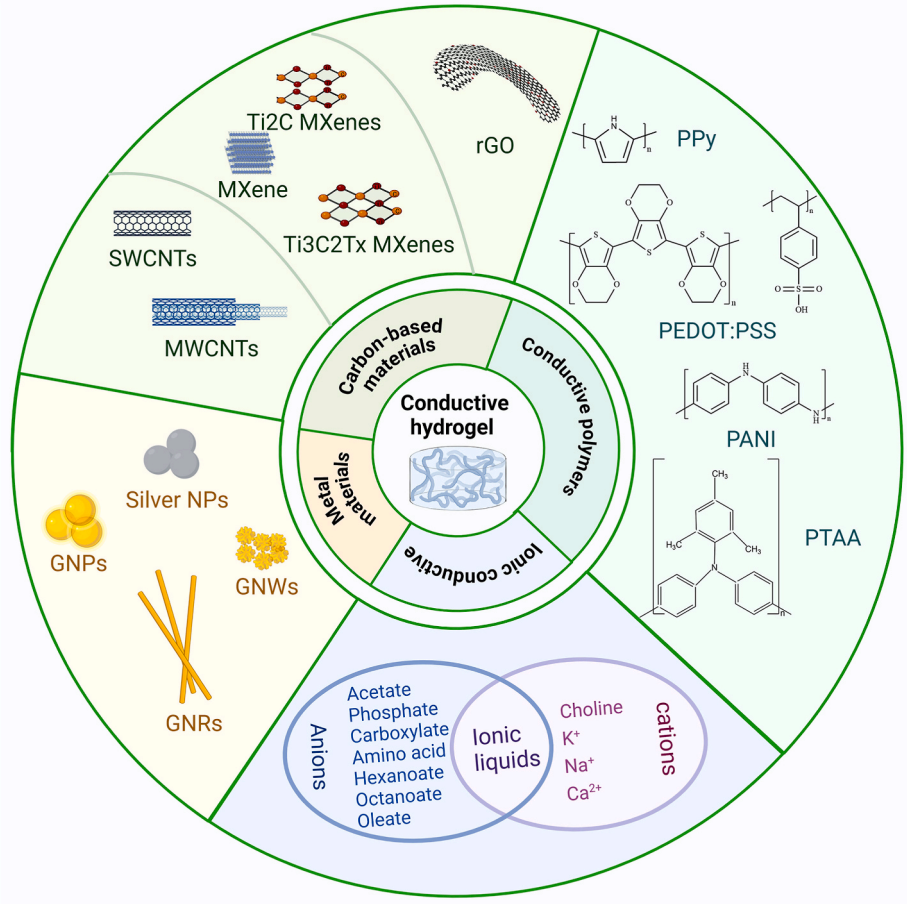

Fig. 2. A schematic illustration of the classification of ECHs for cardiac repair (created with BioRender.com).

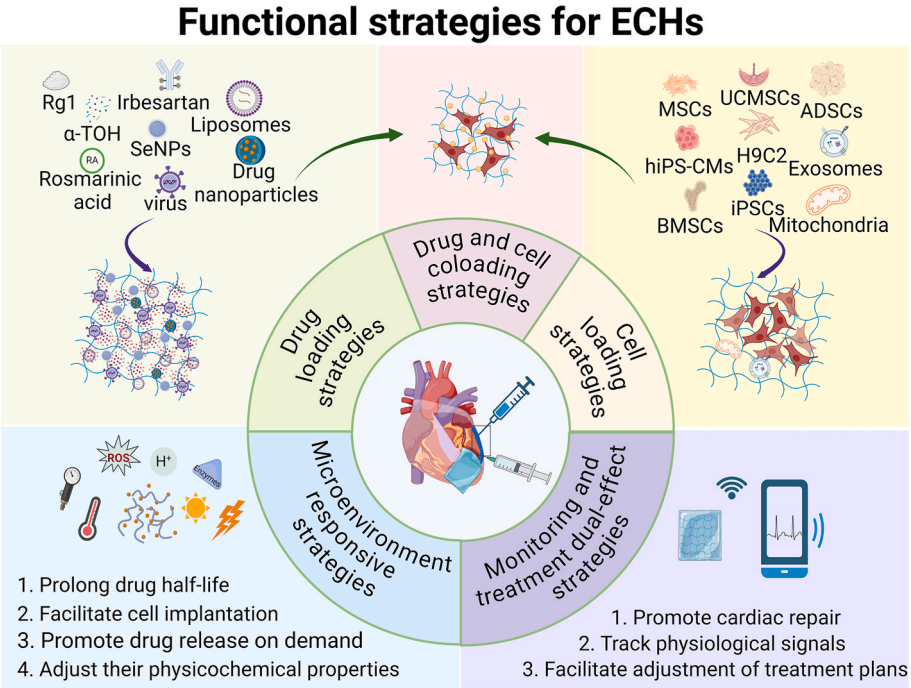

Fig. 3. A schematic illustration of the functional strategies and implantation methods for ECHs in MI repair (created with BioRender.com.).

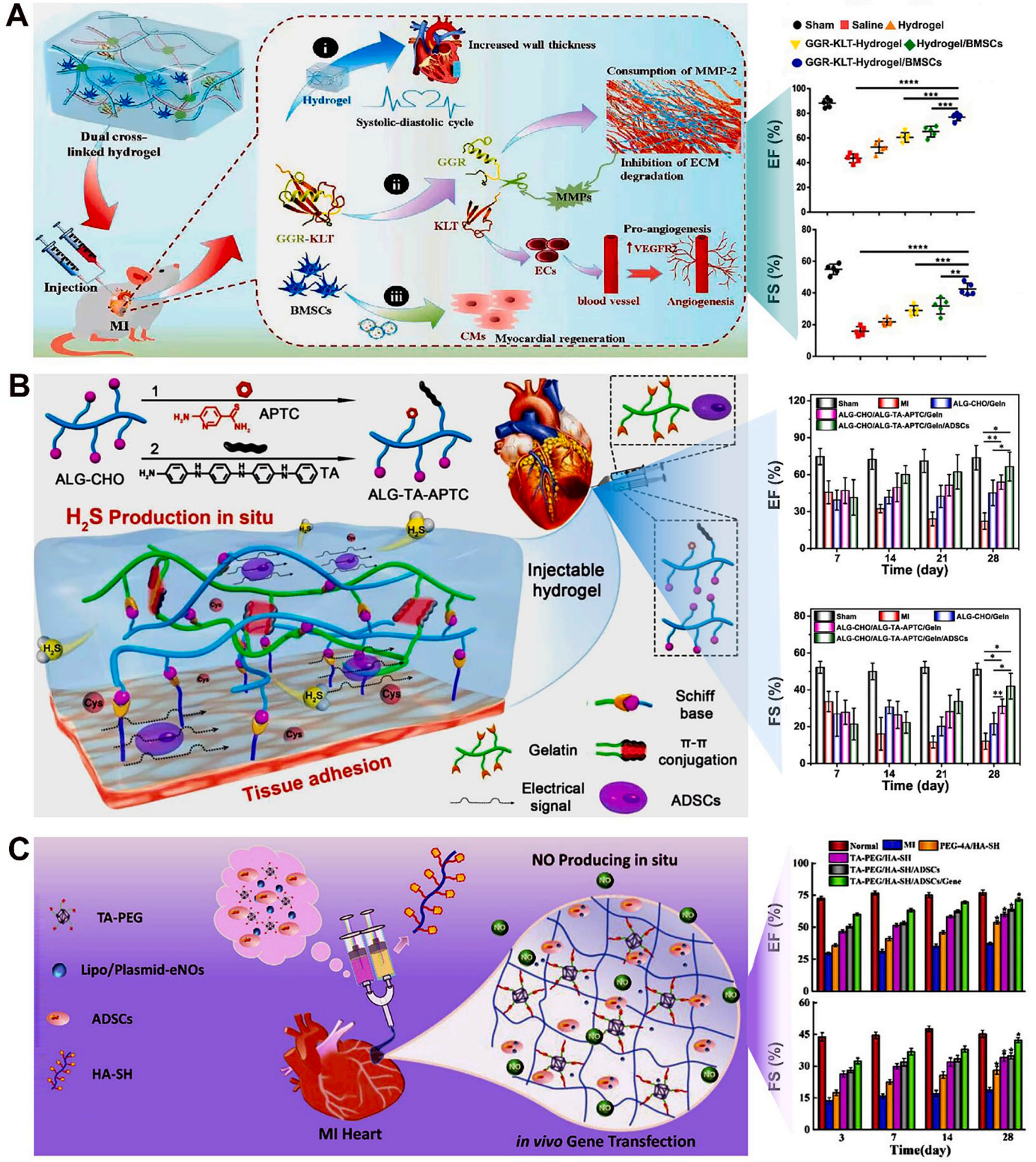

Fig. 4. Schematic diagram of drug and cell co-loaded ECHs for MI repair. **(A)** MaHA/B-G-SH/Fe^{3+} hydrogel co-loaded with GGR-KLT and BMSCs for MI repair (Copyright 2022, Elsevier). **(B)** H_2S-releasing ALG-CHO/ALG-TA/gelatin hydrogel loaded with ADSCs for MI repair (Copyright 2019, ACS Publications). **(C)** TA-PEG/HA-Alginate hydrogel co-loaded with plasmid DNA-eNOs nanoparticles and ADSCs for MI repair (Copyright 2018, Elsevier).

mechanical and conductive properties of hydrogel scaffolds and facilitates cell growth by adsorbing extracellular matrix (ECM) proteins such as fibronectin from the culture medium [31]. For example, cardiomyocytes on rGO-GelMA hydrogels exhibit higher survival rates, stronger contractions, faster beating rates, and greater expression of cardiac-specific proteins compared to those on pristine hydrogel scaffolds [35]. Moreover, Lee et al. evaluated the impact of GelMA hydrogels with CNTs, GO, or rGO on cardiomyocyte structure and function. Their findings indicated that conductive scaffolds (CNT- and rGO-GelMA) improved cardiomyocyte morphology and cardiac marker expression

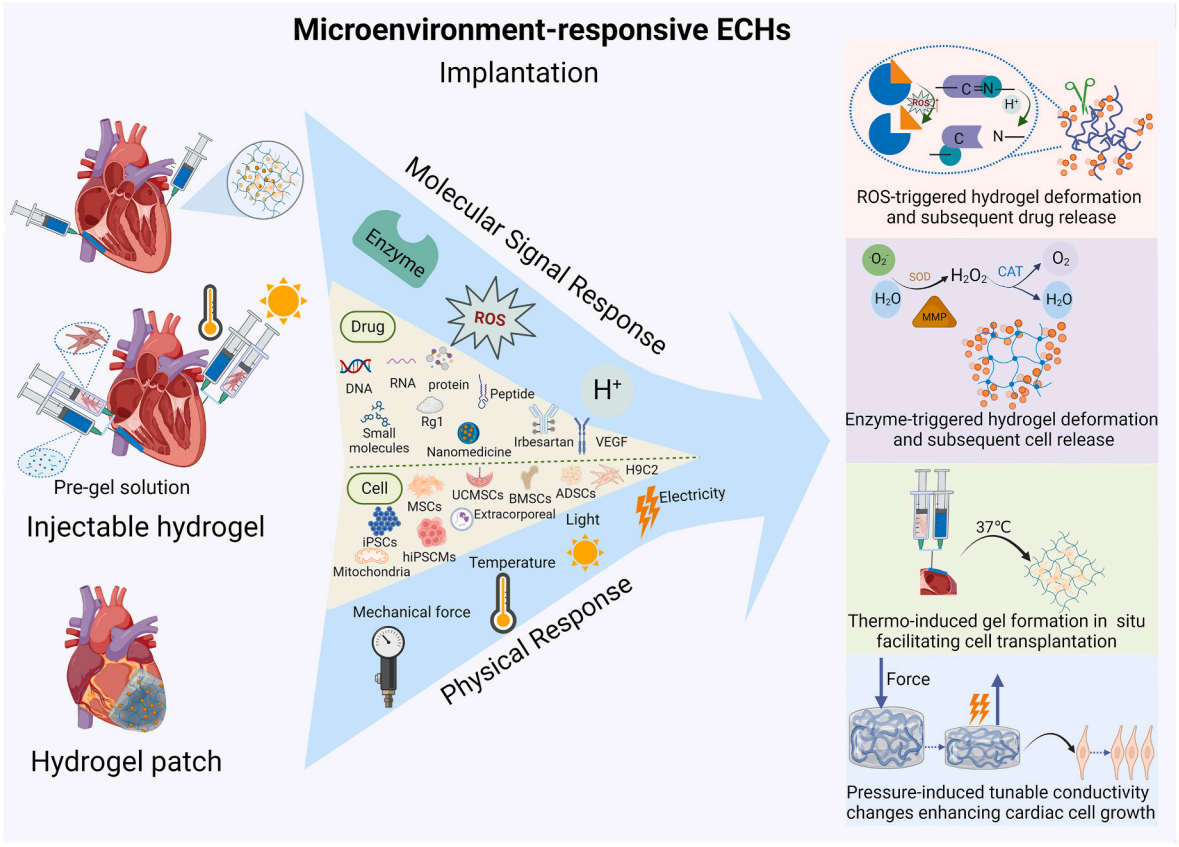

Fig. 5. A schematic illustration of the microenvironment-responsive strategies for MI repair (created with BioRender.com.).

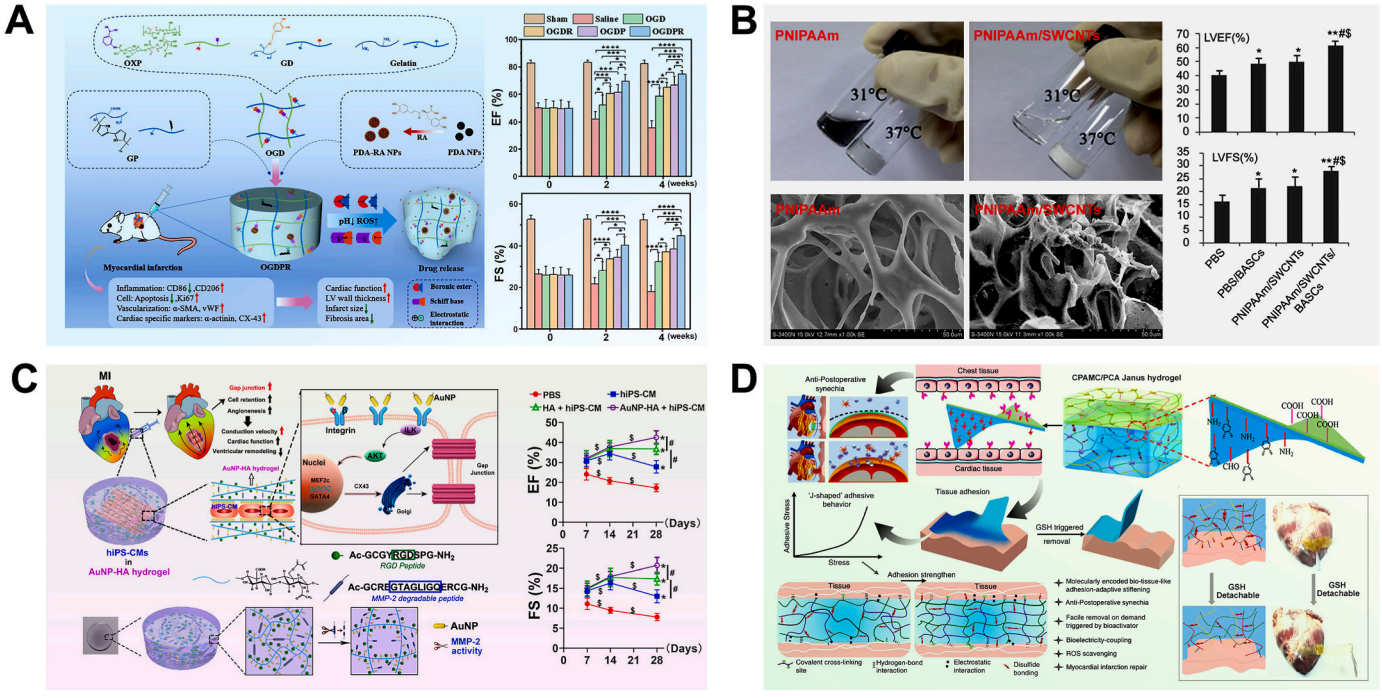

Fig. 6. Schematic diagram of microenvironment-responsive ECHs for MI repair. **(A)** An injectable conductive hydrogel with dual responsive release of rosmarinic acid promotes MI repair (Copyright 2023, Elsevier). **(B)** PNIPAAm-based thermosensitive hydrogel containing SWCNTs for stem cell transplantation promotes MI repair (Copyright 2014, Elsevier). **(C)** Injectable AuNP-HA matrix with localized stiffness promotes MI repair (Copyright 2021, Elsevier). **(D)** A smart adhesive Janus hydrogel for non-invasive cardiac repair and tissue adhesion prevention (Copyright 2022, Nature portfolio).

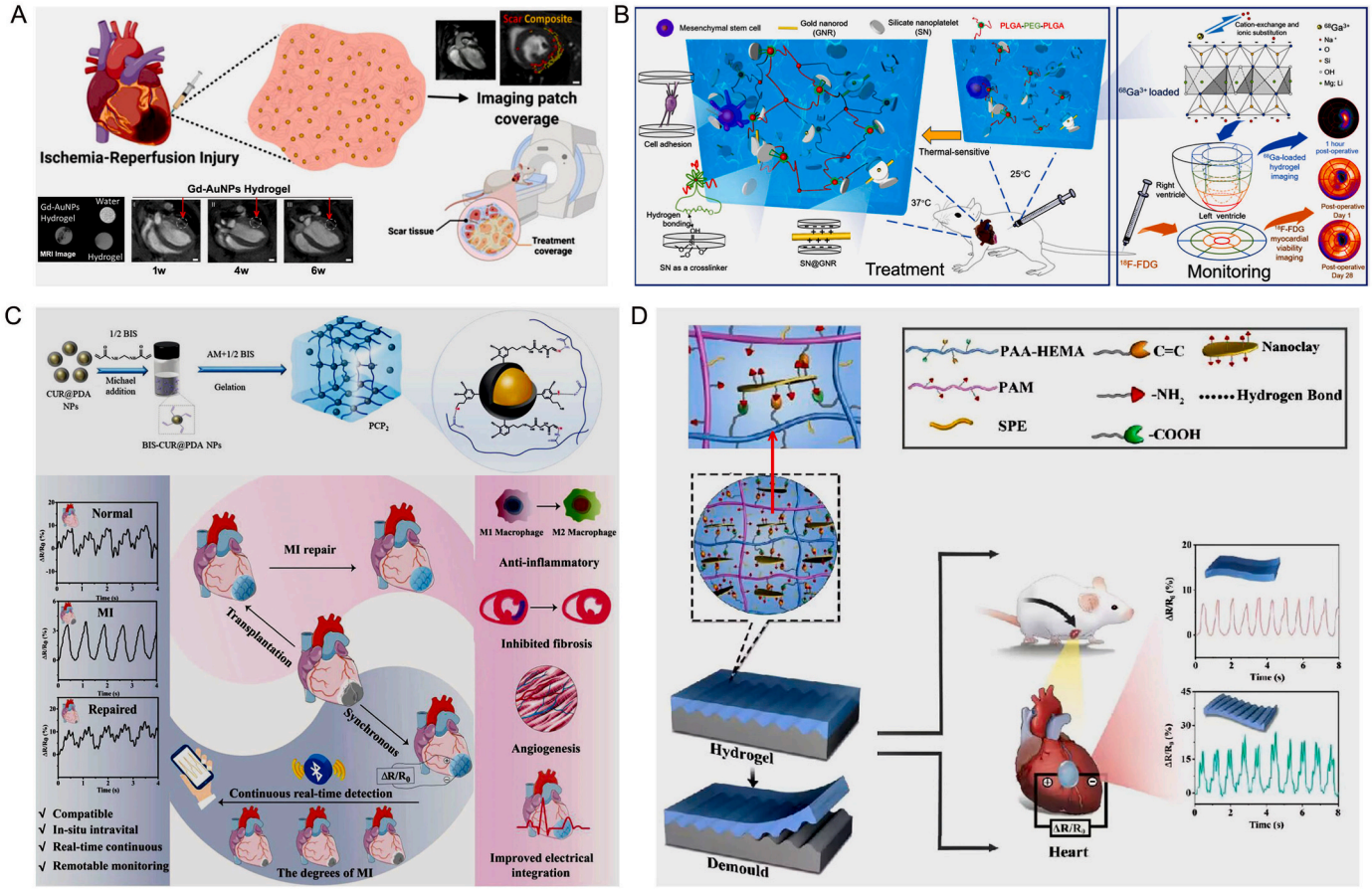

Fig. 7. Schematic diagram of therapy and monitoring bifunctional ECHs for MI repair. **(A)** Imageable AuNP-ECM hydrogel loaded with Gd for MI repair (Copyright 2023, MDPI). **(B)** GNR@SN/Gel hydrogel co-loaded with MSCs and Ga for MI repair (Copyright 2022, BMC). **(C)** PAM/BIS-CUR@PDA NPs (PCP2) hydrogel for MI repair (Copyright 2023, Wiley). **(D)** Wrinkled nanoclay-composite hydrogel for MI repair (Copyright 2023, Wiley).

compared to non-conductive GO-GelMA. Specifically, cardiomyocytes on CNT-GelMA exhibited greater cell spreading, attributed to its electrical and mechanical properties resembling native heart tissue, smaller pore sizes offering more binding sites, and better uniformity with reduced surface roughness [19]. Additionally, rat cardiac fibroblasts on rGO-OPF hydrogels demonstrated good viability and adhesion, positively correlating with rGO content [33]. Human umbilical vein endothelial cells (HUVECs) cultured on rGO-alginate scaffolds showed enhanced viability, adhesion, and increased VEGFR2 expression [30]. The integration of rGO into hydrogels improved the survival of umbilical cord mesenchymal stem cells (UCMSCs) and human embryonic stem cell-derived fibroblasts (HEMC-fibroblasts), stimulated pro-angiogenic factor expression, and facilitated the early differentiation of UCMSCs into cardiomyocytes [38,39]. Concurrently, the intramyocardial injection of rGO-GelMA or GO-OPF hydrogels into MI rats enhances electrical signal propagation in and around the infarcted area, promoting cardiac repair as evidenced by increased gap junction, rhythmic Ca^{2+} transients, subsequently improved ejection fraction (EF), and reduced infarcted area [32,35,39].

2.2. Transition metal carbide-incorpated ECHs

Ti_3C_2 and Ti_2C MXenes, a new class of 2D transition metal carbonitride materials, have gained interest in cardiac tissue engineering for their outstanding electrical conductivity, biocompatibility, hydrophilicity, high surface area, mechanical properties, and ease of film formation. Specifically, Ti3C2Tx MXenes demonstrate advantages such as high flexibility, facile aqueous dispersibility, and superior biocompatibility relative to other metallic meshes and carbon-based nanomaterials [40]. The conductivity of MXenes is temperature-dependent, modulated by their electronic properties and microstructural attributes [41]. Ti3C2Tx-gelatin-dextran aldehyde hydrogels can be synthesized through spontaneous gelation [42], whereas Ti3C2Tx-PEG hydrogels can be generated using aerosol jet printing technology [43]. Additionally, Ti2C-PEGDA cryogels are produced via a TEMED-mediated chemical cross-linking reaction. Polydopamine (PDA) coating enhances the antioxidant and antibacterial properties of MXene and facilitates the cross-linking of MXene nanosheets within hydrogels [44]. A potential limitation of MXenes is their cytotoxicity at high concentrations, highlighting the need for careful monitoring of MXene content during ECH fabrication [45].

The incorporation of MXene into hydrogels confers exceptional electrical, chemical, and mechanical properties, rendering them suitable for establishing an electrically conductive microenvironment and providing mechanical support for cardiac repair. Lee et al. developed a Ti3C2Tx-gelatin-dextran aldehyde hydrogel exhibiting notable properties, including high electrical conductivity (18.3 mS/cm), cardiac tissue-like elasticity (30.4 kPa), robust tissue adhesion (6.8 kPa), and resistance to mechanical deformation. Consequently, the application of this ECH patch could foster the recovery of cardiac function and mitigate pathological remodeling in MI rats [42]. Similarly, Ti2C-based cryogel has been shown to promote cardiomyocyte maturation and facilitate MI repair. Additionally, Ti3C2Tx-PEG hydrogel has been demonstrated to improve cardiac cell alignment and maturation, and to enhance synchronous beating and conduction velocity [43]. Moreover, MXene-based biosensors have been developed for the detection of H_2O_2, cardiac troponin I (cTnI), and heart-type fatty acid-binding protein [40]. It appears that MXene-integrated ECHs may not only facilitate cardiac repair

Table 2
Summary of the drug-loaded ECHs for MI repair.

Materials	Drugs	Loading methods	Repair effects vs ECHs alone	Ref.
Tetraaniline, PEGDA	SeNPs	Blending PEG with TA and doping SeNPs with PEG/TA composite	Intramyocardially injections: The thicker ventricular walls; the smaller infarcted area, the higher expression of IL-10 and the lower expression of IL-18 and CCL2, vs ECHs alone	[95]
Tetraaniline, alginate, HA	DPCA, MMP-SP	1. Incorporate TA into partially oxidized alginate; 2. Decorate DPCA with PDA; 3. Cross-link alginate- CHO and DPCA@PDA with HA-SH and thiolated MMP-SP	Intramyocardially injections: Greater improvement in EF, FS, LVIDd and LVIDs; the thicker ventricular walls; the smaller infarcted and fibrotic area; the higher expression of cTnT, HIF-1α, VEGFA, α-SMA, Ang-1 and α-actinin; the lower expression of IL-1β and TNF-α, vs ECHs alone	[11]
PEDOT:PSS	Irbesartan	1. Mixed PEDOT:PSS with the p(AM-DA-MA) and the CMCS-OHA network; 3. Irbesartan dissolved in stock solution to form hydrogel	Intramyocardially injections (MIRI model): Greater improvement in EF and FS; the smaller infarcted area, vs ECH alone	[62]
PEDOT:PSS, F127DA	α-Tocopherol	1. Use F127DA to disperse and load α-TOH; 2. Polymerize DA to form PDA; 3. Add PEDOT:PSS and photoinitiator for polymerization	Intramyocardially injections: Greater improvement in FS and LVIDd; the higher expression of α-SMA and CD31, vs ECH alone	[96]
PANI, alginate	AAV9-VEGF	Prepare sodium alginate with PANI/LS nanorods and AAV9-VEGF, then crosslink with calcium gluconate solution	Intramyocardially injections: Greater improvement in FS and LVIDs; the thicker ventricular walls; the smaller fibrosis area; the higher arterial density and capillary density; the higher expression of VEGF and VEGFR2, vs ECH alone	[66]
poly-3-amino-4-methoxybenzoic acid (PANI derivative), gelatin	sphingosine-1-phosphate (S1P), elamipretide (SS-31)	1. Mix PAMB-G-TK with 4-arm-PEG-SG; 2. Load liposomes with S1P and SS-31; 3. Mix S1P/SS-31/Lipo nanoparticles with precursor solution to induce gel formation	Intramyocardially injections: Greater improvement in EF, FS, LVIDs and LVIDd; the thicker ventricular walls; the smaller infarcted area; the lower ROS content; the higher expression of vWF, CX43, α-SMA and α-actinin, vs ECH alone	[97]
PPy, gelatin	Rosmarinic acid (RA)	Mix DA-grafted gelatin with oxidized xanthan gum and 3-aminophenylboronic acid, then add PDA-RA NPs to the gel system	Intramyocardially injections: Greater improvement in EF and FS; the thicker ventricular walls; the smaller infarcted and fibrotic area; the lower ROS content and apoptotic cell numbers; enhanced M2 macrophage polarization; the higher α-actinin expression, vs ECH alone	[91]

Table 3
Summary of the cell-loaded ECHs for MI repair.

Materials	Cells or their derivatives	Loading methods	Repair effects vs Cells or ECHs alone	Ref.
rGO, GelMA	UCMSCs	UCMSCs mixed with rGO-GelMA, requires blue light-mediated crosslinking	Intramyocardially injections: Greatest improvement in EF, LVIDs and LVIDd; the thickest ventricular walls; the highest arteriolar density in the scar zone, vs cells or ECHs scaffolds alone	[39]
rGO, alginate	BMSCs	BMSCs mixed with rGO-alginate during gel formation, requires $CaCL_2$-mediated crosslinking	Intramyocardially injections: Greater improvement in EF and FS; the thicker ventricular walls, vs cells alone	[100]
Melamine, GO, HA	ADSCs	ADSCs resuspended in the pre-gel solution, requires PEG-MEL- mediated crosslinking	Intramyocardially injections: Greater improvement in EF, FS, End-diastolic area and End-systolic area; The thicker ventricular walls; the smaller infarcted and fibrotic area, vs ECH alone	[34]
AuNP, chitosan, silk fibroin	H9C2 cells + MSCs	MSCs co-cultured with AuNP-chitosan-silk fibroin hydrogel + H9c2 cells	Intramyocardially injections: Greatest improvements in EF, FS, LVIDs and LVIDd; the smallest fibrotic areas; the highest CX43 expression; the lowest apoptotic cell numbers, vs cells or ECH alone	[99]
AuNP, HA	hiPS-CMs	hiPS-CMs cultured on hydrogel	Intramyocardially injections: Greater improvement in EF and FS; the thicker ventricular walls; the smaller infarcted area and scar thickness; the higher arteriolar density in the infarct zone and border zone; the higher expression of CX43 and VEGF; QRS interval near normal, vs cells alone	[85]
PEDOT:PSS, collagen	hiPSC-CMs	hiPSC-CMs resuspended in the pre-gel solution and incubated at 37 °C to induce gel formation	Intramyocardially injections: Greater improvement in EF and FS, vs ECH alone	[61]
PPY, chitosan	hEMSC-Exo	hEMSC-Exo mixed with PPY-chitosan during gel formation, requires glutaraldehyde-mediated crosslinking	Intramyocardially injections: Greatest improvement in EF, LVIDd and LVIDs; the thickest ventricular walls; the highest arteriolar density in scar zone, vs Exo or ECH alone	[49]
anilinetetramer, HA	hUCMSCs-Exo	hUCMSCs-Exo mixed with pre-gel solution to induce gel formation	Intramyocardially injections: Greater improvement in EF and FS; the smaller infarcted and fibrotic area; the thicker ventricular walls; the higher arteriolar density; the higher expression of CX43, Ki67, VEGF, vWF and serca2a; the lower expression of TGF-β1 and MMP-9, vs Exo alone	[102]
PPY, alginate	MSC-Mitochondrial	Mitochondria mixed with hydrogel	Intramyocardially injections: The thickest anterior ventricular walls; the maximum increase of vWF and α-SMA positive vessels, vs Mito or ECH alone	[54]

Table 4
Summary of the drug/cell-coloaded ECHs for MI repair.

Materials	Drugs/Cells	Loading methods	Repair effects vs cell-loaded ECHs/drug-loaded ECHs alone	Ref.
PABA, Gelatin, HA, Fe^{3+}	GGR-KLT, BMSCs	(1)cross-linked by Michael addition of MaHA and cysteine-modified gelatin; (2) ionic interactions between Fe^{3+} and carboxyl/sulfonic groups of PABA; (3) GGR-KLT conjugation to MaHA via Michael addition and BMSC culture on gel surface	Intramyocardially injections: Greatest improvement in EF, FS, LVEDV and LVESV; the smallest infarcted area; the thickest ventricular walls; the lowest collagen content; the highest vessel intensity; the highest expression of CX43 and α-actinin, vs cell-loaded ECHs or drug- loaded ECHs alone	[103]
tetraanilin, ALG-CHO, gelatin	APTC, ADSCs	(1) Developed a macromolecular H_2S prodrug ALG-TA-APTC; (2) ALG-TA-APTC mixed with ALG-CHO and gelatin to induce gel formation; (3) Cell suspension mixed with precursor solution and injected into the heart to induce in situ gel formation.	Intramyocardially injections: Greater improvement in EF, FS and ESV; the higher expression of α-SMA, VEGFA, Ang1, CX43 and cTnT, vs drug-loaded ECHs alone	[104]
TA, PEG, HA alginate	plasmid DNA-eNOs nanocomplexes, ADSCs	(1) in situ Michael addition reaction between TA-PEG and HA-SH; (2) Lipo/plasmid DNA-eNOs nanoparticles and ADSCs cultured on gel surface	Intramyocardially injections: Greater improvement in EF, FS, EDV and ESV; the thicker ventricular walls; the smaller infarcted and fibrotic areas; the higher expression of eNOS, VEGFA and Ang1, vs cell-loaded ECHs alone	[12]

Table 5
Fabrication, responsive mechanism and repair effects of microenvironment-responsive ECHs in MI repair.

Materials	Fabrication methods	Responsive mechanism	Repair effects vs non-responsive ECHs/cells alone	Ref.
ROS-sensitive ECH: PAMB-G-TK, 4-arm-PEG-SG, S1P/SS-31/Lipo	(1) Mix PAMB-G-TK and 4-arm-PEG; (2) Combine S1P/SS-31-loaded liposomes with precursor solution and inject into the heart to form hydrogel in situ.	ROS-cleavable thioketal links break in the presence of ROS, initiating drug release	Intramyocardially injections: Greatest improvement in LVIDd and LVIDs; the smallest infarcted areas; the thickest ventricular walls; the lowest ROS content; the lowest apoptotic cell numbers; the highest expression of α-SMA, vWF, α-actinin and CX43, vs drug-free ECH/single-drug loaded hydrogel	[97]
ROS-sensitive ECH: BPNSs, DTPH, OHA, GelMA	Disperse BPNSs in GelMA/DTPH/LAP solution and mix with OHA for Schiff base cross-linking.	Incorporate DTPH with ROS-responsive disulfide bonds into the hydrogel for ROS scavenging	Intramyocardially injections: Greater improvement in EF, FS, LVSd and LVDd; the thicker ventricular walls; the smaller infarcted areas; the lower ROS content and apoptotic cell numbers; the lower expression of iNOS and the higher expression of CD206, CX43 and α-actin; the higher level of blood vessel density; QRS interval near normal, vs non-responsive ECHs alone	[10]
pH/ROS dual-sensitive ECH: PPY, xanthan gum, gelatin, rosmarinic acid (RA)	(1) Mixing of OXP, gelatin, and PPy-modified gelatin; (2)PDA-RA NPs incorpated to OGDP gel system by forming boronic ester bonds	Boronic ester bond cleavage induced by high ROS and acidic environment, facilitating on-demand drug release	Intramyocardially injections: Greater improvement in EF and FS; QT interval, the inducibility quotient and tissue resistivity near normal; the smaller infarcted and fibrotic areas; the lower ROS content and apoptotic cell numbers; the higher $CD206^+/CD86^+$ ratio, the higher α-actinin expression, vs non-responsive ECHs alone	[91]
Thermo-sensitive ECH: PEG diacrylate, piperazine, dodecylamine, NIPAm, SWCNTs, BASCs	(1) Combine PEG diacrylate, piperazine, and dodecylamine to achieve Michael reaction. (2) Added SWCNTs to NIPAm to form ECHs via chemical crosslinking; (3) BASCs culture on hydrogel	NIPAm, a temperature-sensitive material, polymerizes upon temperature changes, aiding in gel formation	Intramyocardially injections: Greater improvement in EF and FS; the improved hiPS-CMs viability; the thicker ventricular walls; the smaller infarcted area, vs cells alone.	[109]
MMP-responsive ECH: MMP-2 degradable peptide, HA, AuNP, RGD, hiPS-CMs	(1) MA-HA functionalized with RGD peptides and AuNP@PEG-SH; (2) Mix with MMP-2 degradable peptide and gelled; (3) Culture hiPS-CMs on hydrogel	The MMP-2 degradable peptide-loaded hydrogel responds to MMP-2, leading to hydrogel deformation and subsequent cell release	Intramyocardially injections: The improved hiPS-CMs viability; the wider distribution of hiPS-CMs and the lower apoptotic cell numbers in the infarction area, vs non-responsive ECH.	[85]
Smart adhesive Janus ECH: PAA, PEI, CNC-CHO, CA, BAC	(1) Fabrication of CPAMC hydrogel; (2) Fabrication of CPAMC/PCA Janus hydrogel	Oxidized glutathione cleaves the redox-responsive disulfide bond in BAC, enabling rapid hydrogel separation from the adhesive site	Cardiac patches: Greater improvement in EF and FS; the *anti*-synechia performance vs non-responsive hydrogel	[110]

but also serve as real-time dynamic monitoring tools for MI progression. Research in this domain is currently in its nascent stages, and further detailed studies are warranted in the future.

2.3. Conductive polymers-incorporated ECHs

2.3.1. PPy-incorpated ECHs

Polypyrrole (PPy), an electronically conductive polymer under physiological conditions, is characterized by its non-thermoplasticity, mechanical rigidity, and brittleness. These intrinsic properties can be ameliorated through covalent conjugation with other biocompatible substrates during the ECHs fabrication [46–48]. Collagen has been reported to enhance cell adhesion when incorporated into PPy hydrogels [47]. Although high concentrations (30–50 %) of PPy-modified hydrogels can be cytotoxic, conductive nanofibers with 15 % PPy provide an optimal balance of conductivity, mechanical integrity, and biodegradability for cardiac repair applications [47].

In the domain of cardiac tissue engineering, a variety of different

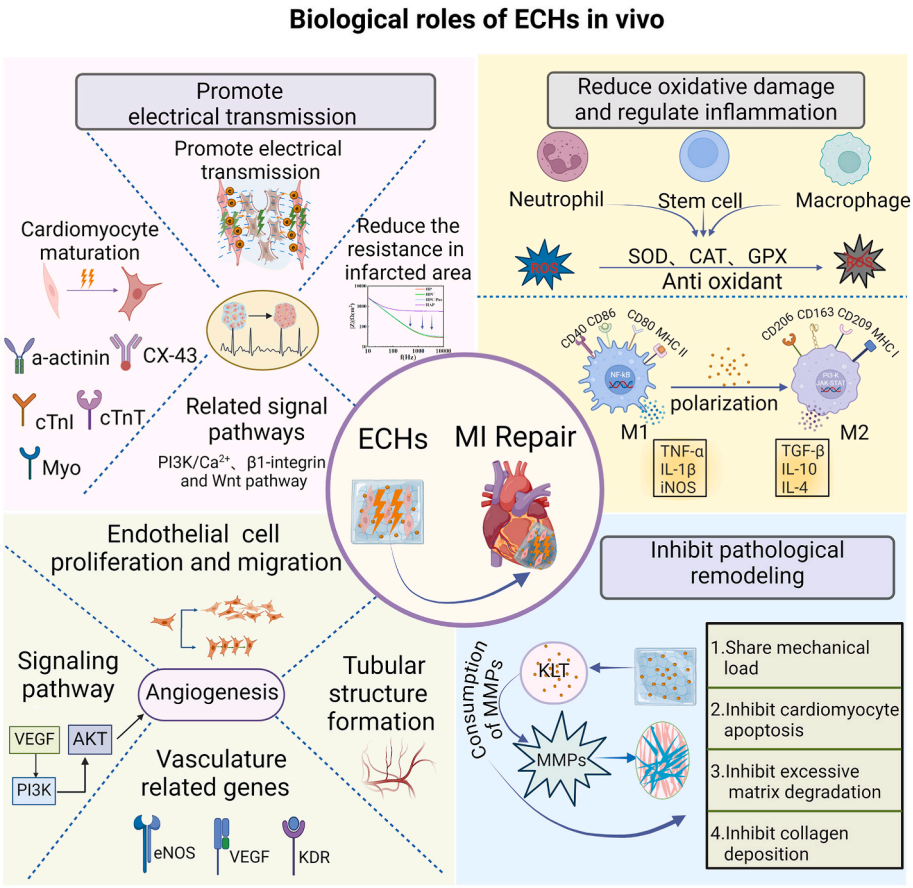

Fig. 8. A schematic illustration of the biological roles of ECHs scaffold in MI repair (created with BioRender.com.).

crosslinking agents and polymerization techniques have been utilized to synthesize PPy-embedded ECHs: (1) PPy-chitosan hydrogels generated via glutaraldehyde-mediated chemical oxidative polymerization [47,49] or through the grafting of PPy onto chitosan [50,51]; (2) PPy-PCL/gelatin hydrogels produced using electrospinning techniques [48]; (3) PPy-dopamine-gelatin (GelDA) hydrogels formed through Fe^{3+}-induced ionic coordination and Schiff base reactions [52]; (4) PPy-gelatin hydrogels created by grafting PPy onto gelatin [53]; (5) PPy-alginate-gelatin hydrogels synthesized via Fe^{3+}-induced oxidative polymerization and polysaccharide oxidation [54]; (6) PPy-GelMA hydrogels produced through self-crosslinking and dopamine-MBA-mediated crosslinking [55]; (7) PPy-GelMA-alginate-graphene hydrogels developed via UV-mediated photocrosslinking [56]. These ECHs have demonstrated appropriate gelation times, superior biocompatibility, and elastic moduli and electrical conductivities analogous to native myocardium, without impeding the proliferation of cardiomyocytes or H9C2 cells. Rat cardiomyocytes cultured on PPy-chitosan or GelMA-alginate-PPy-graphene hydrogels have exhibited enhanced electrical conductivity (increasing from 0.0615 ± 0.007 S/cm to 0.124 ± 0.04 S/cm) and improved Ca^{2+} signal propagation from peripheral to central populations compared to chitosan alone [47,50,56]. Furthermore, He et al. crosslinked GelMA-PPy nanoparticles in an ES-GelMA/PCL membrane, improving cardiomyocyte viability compared to pristine membranes [55].

Meanwhile, injectable PPy-embedded ECHs and cardiac patches have demonstrated greater efficacy in cardiac repair compared to unmodified scaffolds in MI animal models. Injecting chitosan-based or OXG-gelatin-PPy hydrogels enhances impulse propagation and improves ventricular contraction [50,51,53]. Additionally, PPy-GelDA hydrogel patches have facilitated cardiac function recovery in MI rats by modulating electrical signal conduction in the infarcted area [52].

2.3.2. *PTH-incorpated ECHs*

Polythiophenes (PTH), a class of conductive polymers, includes notable derivatives such as poly(thiophene-3-acetic acid) (PTAA), poly (3,4-ethylenedioxythiophene) (PEDOT), and its poly(styrene sulfonate) complex (PEDOT:PSS), all recognized for their excellent chemical stability, electrical conductivity, aqueous dispersibility, and light transmittance. PTAA incorporates carboxyl groups within its backbone, which can be exploited to create cross-linked network hydrogels. Yang et al. synthesized a PTAA-methacrylated aminated gelatin hydrogel using N,N′-carbonyldiimidazole (CDI) and UV-mediated crosslinking techniques, promoting the survival, proliferation, and cardiac differentiation of brown adipose-derived stem cells (BADSCs) and highlighting its biomedical potential [57].

PEDOT:PSS surpasses other conductive polymers, such as PPy and polyaniline (PANI), in terms of chemical and thermal stability. However, its application in hydrogel fabrication is constrained by inherent brittleness and limited extensibility (up to 10 %). Nonetheless, the incorporation of PVA, alginate, or acidic anion liquids can augment its flexibility and self-healing attributes, rendering it more amenable for hydrogel applications. In the context of cardiac tissue engineering, a variety of crosslinking agents and polymerization techniques have been harnessed to fabricate PEDOT:PSS-integrated ECHs, including: (1) PEDOT:PSS-PVA hydrogel with high electrical conductivity (40 S/cm) and up to 50 % stretchability, further enhanced by an N-cadherin mimic peptide to promote cell adhesion [58]; (2) PEDOT:PSS-alginate hydrogel utilizing H_2SO_4 as the initiator for alginate polymerization while encapsulating PEDOT:PSS [59]; (3) PEDOT:PSS-collagen hydrogel created through physical mixing, with lithium bis(trifluoromethanesulfonyl)imide (LiTFSI) added to enhance conductivity and stability [60,61]; and (4) PEDOT:PSS-chitosan-HA-catechol-branched polyacrylamide hydrogel formed via acrylamide-, TEMED-, and

APS-mediated chemical crosslinking reactions [62].

Although research is nascent, PTH-embedded ECHs manifest promise for cardiac repair. HiPSC-derived cardiomyocytes within PEDOT:PSS-collagen hydrogels exhibit near-adult sarcomeric lengths, improved contractility, superior calcium handling, and augmented conduction velocity [60]. Moreover, the injection of a PEDOT:PSS-chitosan-HA hydrogel, which boasts superior mechanical strength and electrical conductivity, has been shown to effectively reduce infarct size in mice following MI-reperfusion injury compared to pristine hydrogel treatment [61].

2.3.3. PANI-incorpated ECHs

Polyaniline (PANI) is recognized for its exceptional biocompatibility and adjustable conductivity through the doping process, which facilitates cell viability, adhesion, proliferation, and differentiation. PANI possesses distinctive attributes such as stability, facile synthesis, and a porous morphology that provides an expanded surface area. However, it also exhibits limitations including poor biodegradability, low solubility, mechanical brittleness, and potential cytotoxicity due to the release of precursors and impurities into the extracellular milieu [63–65]. To mitigate these issues, strategies have been implemented, such as blending PANI with biodegradable polymers, like PVA, PEGDA, and alginate, and employing lignosulfonate to augment its hydrophilicity and conductivity, while also promoting the formation of conductive hydrogel networks [66].

PANI can be integrated with natural biocompatible polymers or synthetic materials to fabricate ECHs: (1) PANI-alginate hydrogel formed via calcium gluconate-mediated chemical crosslinking [66]; (2) PANI-P/PEGDA hydrogel formed via the 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC)/N-hydroxysuccinimide (NHS) chemical coupling method and APS/TEMED-mediated crosslinking [67]; (3) PANI-PVA hydrogel formed via dynamic covalent/noncovalent interactions between functionalized f-PANI and PVA [68]; (4) PANI-N-fluorenylmethoxycarbonyl diphenylalanine hydrogel formed via APS-mediated in situ oxidative polymerization [69]; and (5) PANI-di-Fmoc-Arg-Gly-Asp (RGD) fragment hydrogel, advantageous for cell adhesion, through physical mixing [70].

Komeri et al. developed a PANI-PEGDA hydrogel with a porous surface, robust mechanical stiffness, elastic properties, and electrical conductivity comparable to native myocardium, coupled with free radical scavenging ability, which fosters the growth of L929 fibroblast and H9c2 cardiomyoblast cells [67]. Similarly, cardiomyocytes cultured on PANI-Fmoc-FF or PANI-di-Fmoc-RGD hydrogels have demonstrated high cell viability, confirming their non-cytotoxic profile [69,70]. In vivo studies have indicated that the PANI-PVA hydrogel cardiac patch significantly ameliorates cardiac repair in MI models compared to unmodified scaffolds, as evidenced by enhanced cardiomyocyte Ca^{2+} transient velocity and improved electrical conduction in fibrous tissue, which mitigates MI-induced ventricular electrophysiological dysfunction, underscoring its potential for cardiac repair [68].

2.4. Noble metal nanoparticles-incorporated ECHs

Noble metal gold nanomaterials can form particles with various sizes, shapes, and surface properties, absorb reactive oxygen species (ROS), and exhibit tunable electrical and mechanical characteristics, making them promising for cardiac repair [71,72]. Gold nanoparticles (AuNPs) are used to produce ECHs due to their inertness, ease of surface modification, and ability to convey electrical signals that support stem cell differentiation [71]. Hosoyama et al. found that AuNPs have better electrical conductivity and stability than silver nanoparticles (AgNPs) under physiological conditions, likely due to AgNPs' partial oxidation affecting signal propagation [73]. Larger gold nanoparticles (~15 nm) are non-toxic even at high concentrations [71] and can be easily adjusted to various forms, including gold nanorods (GNRs), gold nanospheres (GNPs), and gold nanowires (GNWs), which are widely utilized in cardiac tissue engineering [74].

AuNPs can be integrated with various natural biocompatible polymers to form hydrogels through processes, including in situ particle formation within scaffolds, deposition on scaffolds, or dispersion within them [71]. This involves various physical and chemical reactions, including: (1) AuNP-ECM hydrogels formed via physical encapsulation [72] or electron beam evaporation [75]; (2) AuNP/AgNP-collagen hydrogels formed via UV-mediated photocatalytic reactions [73]; (3) AuNP-alginate-chitosan hydrogels formed via adsorption and sonication [76]; (4) AuNP-decorated cellulose nanofiber-pluronic-chitosan hydrogels formed via EDC/NHS chemistry [77]; (5) GNR/GNW-GelMA hydrogels formed via UV-mediated photocrosslinking [78–80]; (6) GNPs-chitosan hydrogels formed by using β-glycerophosphate or trisodium citrate [81,82]; (7) AuNP-aminated guar gum (AGG) or AuNPs-HA hydrogels formed via physical mixing [83–85]; (8) GNR-fibrin hydrogels formed via charge-driven interactions [86].

When integrated with natural polymers, AuNPs provide scaffolds with mechanical strength and conductivity akin to myocardium, supporting cardiac cell growth and facilitating faster, anisotropic electrical signal propagation through organized Cx43 staining, indicating that the electrical conductivity features positively influence the cardiac tissue phenotype and function [72,73,75–79,85]. Additionally, AuNPs-incorporated ECHs promote the differentiation of stem cells (induced pluripotent stem cells and mesenchymal stem cells) into cardiomyocytes [72,81]. When implanted in MI models, both injectable and cardiac patch ECHs loaded with AuNPs restore cardiac function by improving electrical signal propagation, maintaining hemodynamic stability, reducing fibrotic scarring, and mitigating pathological ventricular remodeling [70,72,73,75,85].

2.5. Bio-ionic liquids (bio-IL)-incorporated ECHs

Bio-ionic liquids are organic salts with high water solubility, excellent ionic conductivity, and electrochemical stability, synthesized from renewable biological sources by combining cations like choline, piperidinium, pyrrolidinium, or amino acid esters with various anions [87–89]. Bio-ionic liquids have been explored as biocompatible materials for a wide range of applications, including multi-responsive drug delivery systems, solvents for biopolymers, and ion gels for sensors and actuators. Bio-IL conjugated hydrogels exhibited a wide range of highly tunable physical properties, remarkable in vitro and in vivo biocompatibility, and high electrical conductivity without the need for additional conductive components [87]. The hydrophilic hydroxyl (-OH) and amine (-NH_2) groups in Bio-ILs contribute to higher swelling ratios in hydrogel structures with increased Bio-IL concentrations. The electrical conductivity of Bio-IL-enriched hydrogels is contingent upon ionic strength, migration rates, and the choice of polymer matrix [87,88]. Compared to hydrogels modified with carbon and metal materials, incorporating Bio-ILs can stabilize temperature and pH fluctuations, ensure homogeneous distribution within hydrogels, and mitigate tissue damage risks [88].

Choline-based Bio-ILs, synthesized from choline bicarbonate and acrylic acid, are notable for their low cytotoxicity and superior biocompatibility. These are integrated into GelMA hydrogels through a visible-light-induced photopolymerization process. By fine-tuning the polymer concentration and the polymer-to-Bio-IL ratio, the electrical characteristics of the ECHs can be precisely adjusted. For instance, a 20/80 GelMA-to-Bio-IL ratio results in a hydrogel with a conductivity of 516×10^{-5} S/m, closely matching that of native myocardium. This formulation supports cardiomyocyte and cardiac fibroblast growth while enhancing their viability, metabolic activity, and contractile function compared to GelMA controls [87]. Additionally, GelMA-based cardiopatches containing higher Bio-IL concentrations also exhibit accelerated degradation, enhanced elastic moduli, and improved adhesive strength. In a rat MI model, these patches adhered well to the epicardial surface, creating a conductive microenvironment that

reduced myocardial remodeling [90]. Further long-term studies in animal models are warranted to translate these findings into clinical practice.

3. Functional strategies for ECHs fabrication

3.1. Drug loading strategies in ECHs

The pathological cascade in response to MI initiates with an inflammatory phase, progressing subsequently to a fibrotic phase. Given that oxidative stress and the accumulation of inflammatory cytokines expedite MI progression [91], there is a pronounced research focus on incorporating anti-inflammatory and antioxidant pharmaceuticals into hydrogel scaffolds to ameliorate myocardial damage. Localized drug delivery from these scaffolds minimizes adverse effects of high systemic drug concentrations and allows targeted delivery to the affected myocardium. Conductive materials such as CNTs [27], PANI [66], PPY [92], and PEDOT:PSS [93] exhibit inherent antioxidant properties. Dopamine-derived catecholic moieties oxidize to form quinone, which polymerizes into a PDA layer that encapsulates nanodrugs for controlled release [93]. This layer scavenges ROS and serves as a crosslinking agent for thiol and amine groups, enhancing drug loading via chemical bonding (Schiff base reaction and Michael addition) and physical interactions (hydrogen bonding and π-π stacking) [91]. Polyethylenimine (PEI) enhances nucleic acid binding and cellular uptake due to its cationic properties, making it widely used in gene delivery [32]. Consequently, these conductive materials, in conjunction with PDA, PEI, and therapeutic agents, are frequently embedded within hydrogels for MI treatment. Drug release occurs as water gradually enters the 3D hydrogel matrix, causing swelling that disrupts hydrogen bonds and van der Waals forces, allowing the drug to be released into the surrounding environment [94]. Moreover, hydrogel swelling creates a more porous 3D structure, facilitating drug release from the internal matrix.

Recent research has demonstrated that ECHs laden with therapeutic agents achieve superior outcomes in the treatment of MI compared to non-drug-loaded ECHs (as depicted in Fig. 3 and Table 2). For instance, tetraaniline (TA, a conductive and antioxidant tetrameric form of aniline), α-tocopherol (also known as Vitamin E) and selenium nanoparticles (SeNPs) that exert antioxidant effects during MI progression, have been investigated. DPCA, a hypoxia-inducible factor-1α (HIF-1α) stabilizer, curbs the unwarranted proliferation of cardiac fibroblasts by modulating mitochondrial ROS. Consequently, SeNPs-loaded TA/PEG hydrogels and alginate-HA/TA hydrogels co-encapsulating DPCA@PDA and matrix metalloproteinase (MMP)-sensitive peptides (MMP-SP) have been engineered [11,95]. The findings indicate that TA-modified ECHs loaded with DPCA/SeNPs exhibit enhanced therapeutic efficacy in MI treatment, reducing infarct size by 33.8 % with DPCA@PDA and by 17.1 % with SeNPs compared to non-drug-loaded TA-modified ECHs [11,95]. The heightened efficacy of DPCA@PDA TA hydrogels is attributed to the reduction of ROS levels by TA, PDA, and MMP-SP components, which in turn diminish inflammatory mediators [11]. Moreover, the MMP-SP segments enable controlled degradation, promoting gradual DPCA release and stabilizing HIF-1α to enhance angiogenesis in the infarcted region. Similarly, the PDA/α-tocopherol-loaded PEDOT:PSS hydrogel showed superior treatment efficacy compared to the pure PEDOT:PSS hydrogel, indicated by improved left ventricular EF and reduced infarct area, due to the effective synergy of PEDOT:PSS, PDA, and α-tocopherol in reducing ROS levels and cellular apoptosis in MI rabbits [96].

Beyond their antioxidant effects, therapeutic angiogenesis has emerged as a promising strategy in MI treatment. Irbesartan (an angiotensin receptor blocker recommended for MI treatment), or adeno-associated virus encoding vascular endothelial growth factor (AAV9-VEGF) have been incorporated into ECHs to enhance treatment efficacy. AAV9-VEGF-loaded PANI-alginate hydrogel restored systolic function in MI rats, shown by improved EF, fractional shortening (FS), and near-normal ECGs, compared to the pure PANI-alginate group with abnormal ECGs. This enhancement likely results from the strong ROS-eliminating capacity and electrical conductivity of PANI/LS nanorods, which aid AAV9-VEGF transfection in cardiomyocytes to promote angiogenesis [66]. Furthermore, an irbesartan-loaded PEDOT:PSS hydrogel integrated with a catechol-branched polyacrylamide network and a chitosan-HA covalent network was administered intramyocardially to a mouse model of myocardial ischemia-reperfusion injury (MIRI) [62]. The irbesartan-loaded PEDOT:PSS hydrogel, PEDOT:PSS hydrogel, and MIRI rats showed reduced left ventricular EF (51.42 %, 46.92 %, 37.41 %) and FS (25.92 %, 23.19 %, 17.77 %), while infarct sizes increased (12.55 %, 21.3 %, 32.65 %), indicating a synergistic therapeutic effect of the combination of irbesartan and PEDOT:PSS.

The majority of drug-loaded hydrogel systems target one or two pathological factors in MI. A multifactorial approach may enhance therapeutic efficacy. For instance, a poly-3-amino-4-methoxybenzoic acid (PANI derivative)-gelatin hydrogel encapsulating sphingosine-1-phosphate (S1P, to activate angiogenesis) and elamipretide (SS-31, a mitochondria-targeted antioxidant peptide) significantly improved cardiac function by reducing ROS, enhancing mitochondrial function, and promoting angiogenesis [97]. Furthermore, rosmarinic acid (RA) demonstrates strong cardioprotective potential due to its diverse biological activities, which include anti-inflammatory, anti-apoptotic, and anti-fibrotic effects. PDA-RA nanoparticles integrated into a PPy-gelatin hydrogel combine electrical conductivity with RA's therapeutic properties and demonstrate superior cardiac function compared to unmodified hydrogels, as evidenced by increased wall thickness, reduced infarct size, and diminished fibrotic area in MI rats [91].

However, a lingering challenge is the need to screen drugs on ECHs to identify compounds that facilitate optimal myocardial repair when incorporated into ECHs. In recent years, organ-on-a-chip systems, built on microfluidics to mimic human organ physiology and functionality, have emerged as an innovative approach to accelerate drug development and clarify biological mechanisms. Sun et al. developed an ECH with a structural color colloidal array on one side and a SACNTs-GelMA film on the other. This integration of cardiomyocyte-driven hydrogels and microfluidics created a visual heart-on-a-chip system, enabling consistent beating frequencies for dynamic sensing and effective drug screening [98].

3.2. Cell loading strategies in ECHs

Although stem cell therapy has been shown to improve cardiac function, regenerate myocardium, reduce infarct size, and inhibit heart failure in preclinical and clinical studies, challenges remain, including low cell retention and survival, poor tissue integration, and incomplete differentiation after transplantation [39]. Encouragingly, recent studies have shown that the encapsulation of various cellular entities [(MSCs [39,99,100], induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) [61,85], adipose tissue-derived stromal cells (ADSCs) [101], or H9C2 cardiomyoblast cells [99] within diverse ECH formulations enhances cellular retention, survival, and facilitates stem cell differentiation into cardiomyocytes, leading to superior therapeutic outcomes compared to the use of pristine ECH scaffolds or cells in isolation (as depicted in Fig. 3 and Table 3). The encapsulation strategies for ECHs encompass three primary approaches (see Table 3): (1) The incorporation of cells or their derivatives into polymer matrices with the subsequent addition of a crosslinking agent to induce gelation; (2) The physical blending of cells or their derivatives with a pre-gel solution to achieve in situ gelation through temperature modulation; (3) The cultivation of cells directly onto ECHs. These ECHs have a highly porous structure that promotes the exchange of fluids and nutrients while providing support in the peri-infarct region [39]. As the ECH degrades, the therapeutic cells are gradually released to the MI site.

Intramyocardial injection of UCMSC-loaded rGO-GelMA hydrogel enhances myocardial conduction, improves cell retention, prolongs stem

cell survival, supports sustained release of stem cells, and promotes differentiation into cardiomyocytes, aiding myocardial repair in MI rats. Notably, the infarct sizes in the PBS, GelMA, rGO-GelMA, and UCMSCs/rGO-GelMA groups were 33.4 %, 22.3 %, 16.8 %, and 7.1 %, respectively, with the UCMSCs/rGO-GelMA group demonstrating end-diastolic volume (EDV) and end-systolic volume (ESV) values closest to normal levels [39]. Similarly, the injection of human bone marrow MSCs (BMSCs)-loaded rGO-alginate hydrogel significantly enhanced myocardial repair compared to BMSCs injection alone. Microscopic analysis revealed that the microvessel densities for the control, MSC/alginate, and MSC/rGO-alginate groups were 4.2, 8.6, and 19.6, respectively, indicating that the incorporation of cells or rGO into the hydrogel scaffold substantially enhances neovascularization in the infarcted area of MI rats [100].

Meanwhile, the AuNP-chitosan-silk fibroin hydrogel, capable of co-loading MSCs and H9C2 cells, has demonstrated improved fiber alignment, increased collagen levels, elevated Cx43 expression, reduced infarct size, and decreased inflammatory marker expression compared to the use of MSCs alone [99]. The hiPS-CMs delivered via AuNP-HA or PEDOT:PSS-collagen ECHs showed enhanced angiogenesis in the infarcted area, improved sarcomere alignment and width, and synchronized ventricular electrical conduction after MI, aiding recovery [61,85].

ADSCs can be incorporated into melamine-HA/GO or PVA/poly(β-N-acrylamido-L-alanine):gelatin (PVA/b-PANi:Gel) hydrogels, which, when injected intramyocardially or intrapericardially into MI rats, significantly improve the transmission of mechanical and electrical signals, resulting in enhanced heart function, including increased EF and vessel density, along with reduced infarcted and fibrotic area [34,101]. In MI rats treated with cell-free ECH scaffolds, these positive outcomes were not observed, indicating that ECHs significantly enhance cardiac repair when therapeutic cells are encapsulated.

Cell transplantation faces challenges such as the necessity for ex vivo expansion, the risk of allo/xeno-reactive immune responses, and cell mortality shortly after transplantation. Utilizing cell derivatives instead of whole-cell transplantation may be more feasible, potentially avoiding side effects and enhancing patient acceptance. Prior results suggest that exosomes (Exo)/mitochondria derived from stem cells possess robust capabilities to promote cardiac repair. Exo-loaded ECHs offer benefits such as sustained exosome release and cardiac signal conduction, leading to a synergistic therapeutic effect. The human endothelial MSC-derived exosome-loaded PPy-chitosan hydrogel effectively enhances post-MI cardiac function by promoting angiogenesis, inhibiting apoptosis, reducing ventricular remodeling, and resynchronizing electrical transmission to alleviate arrhythmias [49]. Zou et al. synthesized a hyperbranched epoxy macromer to cross-link thiolated hyaluronic acid and thiolated exosomes. When injected into injured rat hearts, the Gel-Exo composite system improved exosome retention in the ischemic myocardium and enhanced cardiac function by increasing EF and reducing fibrosis [102]. Encapsulating mitochondria in Alg-Gel-PPy hydrogel enhances cell attachment, proliferation, migration, and junction formation due to its high porosity. MI rats treated with this ECHs showed thicker ventricular walls and more α-SMA$^+$ vessels and vWF$^+$ capillaries in the infarct border zone than those treated with mitochondria or hydrogel alone, likely due to mitochondrial uptake by cardiomyocytes [54].

3.3. Drugs and cells co-loading strategies in ECHs

The integration of therapeutic cells and pharmacological agents within ECHs has been shown to elicit superior therapeutic outcomes relative to monomodal treatments (refer to Figs. 3–4 and Table 4). In this context, Zheng et al. have engineered a poly-3-aminobenzenesulfonic acid (PABA)-derived gelatin-HA hydrogel co-encapsulated with BMSCs and the therapeutic peptide GGR-KLT (to foster angiogenesis). The second cross-linked network utilized $FeCl_3$ and PABA to confer electrical conductivity and self-healing properties to the ECH. This innovative approach significantly improves myocardial architecture, prevents adverse left ventricular remodeling, enhances cardiac function recovery, and promotes myocardial regeneration in MI rats, outperforming hydrogels loaded with drugs or cells alone [103].

Moreover, the combination of macromolecular H_2S prodrugs APTC (a thiol-dependent H_2S-releasing compound) or plasmid DNA nanocomplexes encoding endothelial nitric oxide synthase (eNOS) with ADSCs has led to the development of a TA-based ECH scaffold, which was subsequently injected into MI rats [12]. The TA-ECH scaffold co-encapsulated with APTC and ADSCs significantly improved therapeutic outcomes by enhancing cardiac function, as evidenced by increased EF and reduced infarct size [104]. The H_2S released from ADSC-loaded ECHs further improved therapeutic outcomes, including improved EF and reduced infarct size, thereby promoting cardiac function in MI rats. Similarly, the plasmid DNA-eNOS nanocomplexes loaded within the hydrogel can transfect the encapsulated ADSCs or deliver these cells to the myocardium, enabling persistent NO production over an extended period, which is crucial for promoting neovascularization, thereby demonstrating significant improvements in heart function, including increased EF, shortened QRS interval, reduced infarct size, decreased fibrosis, and higher vessel density [12].

As shown in Fig. 4, these results underscore the potential of injectable hydrogels to simultaneously transport both cells (BMSCs or ADSCs) and drugs within the same organism, representing a promising therapeutic option [12,103,104]. Previous studies indicate that ADSCs are easier to obtain than BMSCs, with adipose tissue yielding 500 times more stem cells than an equivalent amount of bone marrow, and ADSCs demonstrating higher proliferation capacity [105]. Clinically, patients prefer harvesting ADSCs from autologous adipose due to the less traumatic procedure, making ADSCs more favorable for clinical applications. Additionally, exosomes derived from ADSCs also have strong capabilities to promote cardiac repair [106]. Therefore, future strategies may involve co-delivering therapeutic drugs with exosomes derived from ADSCs to enhance MI repair while reducing side effects associated with cell transplantation, such as ex vivo expansion, the risk of allo/xeno-reactive immune responses, and cell mortality shortly after transplantation.

3.4. Microenvironment-responsive strategies in ECHs

The development of microenvironment-responsive ECHs, also known as stimuli-responsive or smart ECHs, is a cutting-edge approach that addresses the dynamic changes in the cardiac microenvironment following MI. These smart ECHs enhance cardiac repair by adjusting their properties and releasing therapeutic agents in response to physical cues (temperature, mechanical stress, electrical stimulation) and chemical factors (pH, ROS, enzymatic activity) [107]. They can be designed as injectable gels or patches that detect changes in the microenvironment and modulate their properties or release therapeutic payloads (see Figs. 3, 5 and 6, and Table 5).

In the infarcted region, the localized low pH or hypoxic environment triggers the hydrogel to release the drug, ensuring targeted delivery to the damaged site while minimizing release in healthy areas and reducing potential side effects. Microenvironment-responsive hydrogels can adjust the timing and rate of drug release based on physiological changes following MI, ensuring timely drug delivery to enhance therapeutic efficacy. In contrast to non-responsive ECHs, microenvironment-responsive hydrogels enable precise, on-demand drug release at the lesion site, improving drug efficacy by prolonging half-life, enhancing local pharmacological effects, reducing dosing frequency, and minimizing side effects [91]. As a result, they demonstrate superior performance in MI repair, as evidenced by more pronounced restoration of wall thickness, improved cardiac function, reduced infarction size, and enhanced pro-angiogenesis near the injection sites (Table 5). For instance, an injectable ROS-responsive ECH has been engineered by

combining poly-3-amino-4-methoxybenzoic acid, TK-NH2-modified gelatin (PAMB-G-TK, known for its excellent electrical conductivity), and 4-arm-PEG-succinimidyl glutarate (4-arm-PEG-SG), featuring ROS-cleavable thioketal crosslinks that reduce excess ROS, triggering hydrogel deformation and drug release for MI repair [97]. An injectable BPNSs-loaded hydrogel was developed using a ROS-sensitive disulfide bridge to protect BPNSs from degradation, along with a photomediated cross-linking reaction, effectively reducing ROS levels in the infarcted area, inhibiting oxidative stress damage, and promoting MI repair [10]. For instance, a pH/ROS dual-responsive injectable ECH was designed by crosslinking xanthan gum and PPy-modified gelatin with reversible imine and boronic ester bonds. These boronic ester bonds allow for the controlled release of the antioxidant RA in high ROS and low pH environments, promoting cardiac repair (Fig. 6A) [91]. Additionally, sodium alginate, a pH-sensitive material, rapidly forms gels via ion exchange with cations, making it a promising candidate for pH-responsive ECHs. However, this ion exchange may cause uncontrolled hydrogel dissolution, limiting its applications [108].

In addition to facilitating drug therapy, microenvironment-responsive ECHs can also be utilized to enhance cell therapy. Thermo-responsive ECHs have garnered attention due to their ability to retain delivered cells and form gels in situ. The pre-gel solutions are liquid at room temperature but form a gel upon injection into the myocardium at body temperature, facilitating cell incorporation into the ECHs and creating a suitable 3-D environment for cellular behaviors. For instance, thermo-responsive GNP-chitosan hydrogels have been shown to enhance MSC/H9C2 cell viability, metabolism, migration, and proliferation, and support the development of uniform cellular constructs better than chitosan alone, indicating their potential for MI repair [77,81]. Similarly, injectable thermo-responsive SWCNTs-modified PNIPAAm hydrogel demonstrates enhanced bioactivity, promoting BASC engraftment and survival in infarcted myocardium, thereby augmenting therapeutic efficacy post-MI compared to PNIPAAm alone (Fig. 6B) [109]. Furthermore, there are enzyme-sensitive ECHs that can gradually release cells to the infarcted area as the gel degrades, thereby continuously exerting their MI repair effects. For instance, as shown in Fig. 6C, the AuNP-HA hydrogel co-loads hiPS-CMs and MMP-2 degradable peptides, allowing it to degrade in response to elevated MMP-2 levels in the ischemic heart, thereby enabling effective delivery of hiPS-CMs to the MI area and promoting cardiac repair [85].

Another advantage of smart hydrogels is their ability to adjust their physicochemical properties in response to changes in the external microenvironment, making them more suitable for MI treatment. For instance, PANI-incorporated N-fluorenylmethoxycarbonyl diphenylalanine (Fmoc-FF) hydrogels exhibit pressure-responsive conductivity, which aids cardiac cell growth [69]. To prevent secondary damage and tissue adhesion from suturing during cardiac patch implantation, we developed an ECH cardiac patch that adheres securely to the heart (Fig. 6D). Its adhesion can be toggled by elevated oxidized glutathione levels, which break the redox-responsive disulfide bonds, allowing the ECHs to be removed [110].

3.5. Dual-effect strategies for monitoring and treatment

Recent studies show that integrating therapeutic agents or stem cells into ECHs is effective for cardiac repair, but there is a clinical need for real-time monitoring of MI progression after ECH interventions to optimize treatment protocols and achieve personalized therapeutic outcomes (Fig. 3). Gadolinium (Gd) is known to enhance magnetic resonance imaging (MRI) by shortening T1 relaxation times. Encapsulated $^{68}Ga^{3+}$ cations in injectable GNR-SN-Gel or AuNP-ECM hydrogels were administered to MI rats, allowing in vivo localization via PET/CT imaging while preserving the electrical conductivity of GNRs (Fig. 7A and B). Meanwhile, the strong affinity between $^{68}Ga^{3+}$ and AuNPs enables long-term tracking of the treatment for up to six weeks [72,111].

Ion-conductive hydrogels with superior mechanoelectrical sensitivity can track physiological signals in real time by detecting changes in electrical characteristics due to minor mechanical deformations. In this context, our laboratory has developed two types of ECH cardiac patches that integrate therapeutic and diagnostic functionalities (Fig. 7C and D). One type is a nanoclay-composite ionic-conductive hydrogel with a wrinkled surface and hierarchical structure, designed as a strain biosensor with strong protein resistance and accurate detection of MI regions. It contains amphiphilic sulfobetaine-based acrylate monomer ions, enhancing ionic mobility, conductivity, and biosafety for implantation [112]. Another synthetic strategy develops a core-shell curcumin-nanocomposite-reinforced ion-conductive hydrogel for MI repair and simultaneous electrophysiological signal monitoring. A PDA coating on curcumin with ammonium persulfate as an initiator creates a nanocomposite-enhanced ECH. The ionic bonds and protons in the hydrogel ensure high ionic conductivity. This hydrogel has excellent elasticity, low hysteresis, fatigue resistance, and strong mechanical properties, allowing it to differentiate MI degrees through resistance signals for real-time monitoring [113].

These ECH scaffolds, when implanted, excel not only in repairing MI but also enable real-time monitoring of MI status in vivo without exacerbating the original pathological condition at the MI site [72,112,113]. However, studies on acute MI models in small animals have limitations, as they detect varying degrees of MI but lack precise disease-related data and focus on short-term treatments. Future efforts should aim to develop ECH scaffolds for long-term treatment and continuous monitoring of MI progression in larger animal models.

4. Implantation methods for ECH scaffolds

4.1. Attached hydrogel cardiac patch

Engineered ECH cardiac patches can be attached to damaged myocardium via suture or autonomous adhesion, bypassing conduction issues and restoring sinus rhythm. Unlike intramyocardial injections, they avoid invasive procedures. Traditional attachment methods, such as surgical suturing, stapling, or photothermal adhesion, carry risks of hemorrhage and inflammatory responses. The adhesive properties are key to stabilizing the patches on the epicardium, aided by interactions between hydrogel and myocardial tissue [5]. The presence of free carboxyl and aldehyde groups within hydrogels enhances integration with myocardial tissue, diminishing the reliance on sutures [94]. The surface topography (including pore size, porosity, and interconnectivity) and physicochemical properties (such as anisotropic mechanical and electrical characteristics) of ECH scaffolds substantially influence cell adhesion, proliferation, metabolic activity, and angiogenesis post-implantation [110]. ECHs with optimal degradation kinetics provide temporary mechanical support to prevent cardiac dilation and remodeling, ultimately being resorbed without perturbing cardiac function [114]. To fabricate ideal ECH patches for MI treatment, several criteria must be satisfied: 1) elasticity analogous to cardiac tissue with appropriate degradation kinetics; 2) structural and mechanical homology to cardiac tissue; 3) facilitation of myocardial electrical conduction; 4) capacity to adhere directly to the epicardium without reliance on sutures, metallic clips, or photothermal activation; and 5) capability for drug delivery for MI therapy [5,94,110,114].

To date, naturally-derived biomaterials such as collagen (comprising approximately 80 % of myocardial tissue), alginate, gelatin, chitosan, fibrin, matrigel, and ECM components have garnered significant interest for ECH patch fabrication due to their favorable biocompatibility and degradability [115–121]. Conductive biomaterials like CNT, PPy, PANI, rGO, or MXenes are integrated into ECH patches to achieve the anisotropic structural, mechanical, and electrical attributes essential for cardiac repair [30,42,78]. Various physical (photocrosslinking, thermal crosslinking) and chemical (dynamic covalent/noncovalent) cross-linking reactions are employed in the fabrication of ECH cardiac patches.

Natural biomaterials hold substantial potential for clinical MI treatment but also face risks and challenges. In patients with acute MI, left ventricular free wall rupture can lead to cardiac tamponade, which can be treated with external pericardial patches like fibrin sealants or gelatin hydrogels. However, results show a 30-day mortality rate of 57 %, with 1- and 2-year survival rates of 42 %, indicating that these biological materials still need further improvement before clinical application [122]. Harnessing biomaterials to develop a cardiac-adaptive ECM with anisotropic properties, along with mechanical and electrical characteristics, facilitates 3-D cell assembly and tissue regeneration, which are vital for effective cardiac repair. Inspired by this, our laboratory has converted a rigid swim bladder film rich in type I collagen fibers into a flexible anisotropic hydrogel with the PPy. This ECH displays high flexibility, anisotropic properties, and ionic conductivity, improving the viability, electrophysiological activity, maturation, elongation, and orientation of cardiomyocytes, making it more suitable for cardiac patch applications [123]. Similarly, Srinivasan et al. have improved the tensile strength, surface roughness, and wettability of ECHs by in situ synthesis of PPy nanoparticles within a bacterial cellulose fiber network, rendering them appropriate for use as cardiac patches [124].

Adhesive ECH patches should be easily applied to the beating heart, effectively augmenting the transmission of electrophysiological signals. Liang et al. developed a paintable hydrogel via Fe^{3+}-triggered polymerization of pyrrole and dopamine, achieving myocardium-like conductivity and strong adhesion to the beating heart within four weeks, enhancing electrical conduction and revascularization in the infarcted area [124]. Wu et al. also fabricated a self-adhesive ECH patch predicated on Fe^{3+}-induced ionic coordination between GelDA and DA-PPy [52]. GelMA hydrogel exhibits robust adhesion to various tissues, and the GelMA-Bio-IL patch adheres securely to the myocardium, surpassing other synthetic sealants and eliminating the need for sutures or additional adhesives [90]. However, in ECH cardiac patches, stronger adhesion does not always lead to better performance, as excessive adhesion may cause secondary tissue damage. Then, our laboratory developed an asymmetrically adhesive ECH cardiac patch, which adheres to the heart surface and can be selectively detached through stimulation, thereby preventing postoperative tissue adhesion [110].

Various novel methods such as electrospinning, aerosol jet printing, micropatterning (e.g., excimer laser microablation), and 3D printing have been employed to enhance the structure of ECH patches, optimize alignment of cardiac muscle cells, and facilitate the formation of functional heart tissue [24,43,90,117,125,126]. Electrospinning facilitates the fabrication of fibrillar scaffolds with high surface area-to-volume ratios, precise spatial density, and controlled 3D orientation. Walker et al. created cardiac patches with excellent adhesion and electrical properties by electrospinning GelMA and conjugating it with a choline-based bio-ionic liquid [90]. Similarly, electrospun CNF/gelatin ECH cardiac patches have also been developed [125]. Basara et al. utilized aerosol jet printing to pattern conductive Ti3C2Tx MXene on PEG hydrogels, creating physiologically relevant cardiac patches for MI repair [43]. Excimer laser microablation was employed to micropattern a re-entrant honeycomb design into chitosan-PANI composites, yielding patches with adjustable mechanical strength and anisotropy to emulate native heart tissue properties [126]. There have been reports of utilizing a UV-integrated 3D bioprinting technique to fabricate ECH patches consisting of CNT-incorporated alginate frameworks and cell-laden MeCol, which significantly improved the viscoelastic behavior and electrical conductivity of photo-cross-linked MeCol [24].

ECH cardiac patches must exhibit biocompatibility, biodegradability, bioprintability, mechanical robustness and elasticity, electrical conductivity, and the ability to promote cellular growth, proliferation, and differentiation. However, these experimental studies have primarily been conducted on small animal models of MI, and there are even fewer clinical trials employing ECH for MI treatment. Research on loading drugs into ECH patches for MI repair is also relatively limited. A crucial yet unresolved issue is that cardiac patches are typically applied to the epicardium, without direct contact with the myocardial surface. In the future, new strategies must be explored to eliminate the heterogeneity of charge distribution in the infarcted area.

4.2. Intramyocardial injection

Injectable ECHs facilitate targeted delivery of therapeutic drugs or cells to compromised myocardium, providing structural reinforcement, attenuating wall stress, augmenting myocardial stiffness, diminishing left ventricular cavity dimensions, and restoring left ventricular geometry while activating bioactive signaling cascades to ameliorate cardiac performance. Compared with non-conductive hydrogel-treated MI models, multiple intra-scar injections of ECH post-thoracotomy significantly enhance conduction velocity in the peri-infarct zone and reinstate electrical coupling, bolstering cardiac function [47]. Lee et al. found that injectable ECHs create a 3D electrical bypass around the MI site, enhance the conductive properties of fibrotic tissue, reduce infarct thinning and dilation, and improve stem cell engraftment and survival, thereby boosting ventricular function in MI models, supported by electrocardiography and histological examination [5].

Injectable ECHs derived from natural or synthetic polymers exhibit potential for cardiac reparative endeavors. Natural polymers-based hydrogels have slow gelation times (15 min–24 h), rapid degradation, and poor mechanical properties, which limit the retention of encapsulated cells or biomolecules. Conversely, synthetic polymers-based hydrogels gel much faster, ranging from a few minutes to a few seconds [127]. Both natural- and synthetic polymers-derived hydrogels can undergo gelation through either physical or chemical cross-linking mechanisms. The gelation time of ECHs is influenced by a variety of factors, including the type of material, cross-linker concentration, temperature, pH, ionic conditions, molecular weight, and mechanical stress. Natural hydrogels are typically more dependent on environmental factors, leading to more variable gelation times, while synthetic hydrogels are more controllable and consistent due to their design flexibility.

Conductive materials such as SWCNTs, PANI, PPY, and rGO have been incorporated into injectable ECH systems using methods like physical or chemical crosslinking, including photo-crosslinking, click chemistry, boronate ester formation, Schiff base condensation, and Michael addition reactions [91]. Physical cross-linking, which is based on non-covalent interactions like entanglement or secondary forces, tends to be reversible and leads to weaker mechanical properties and faster degradation. Chemical cross-linking, achieved through light, heat, or enzymatic reactions, forms stable covalent bonds, resulting in stronger mechanical properties and slower degradation [127,128]. For cardiac tissue engineering applications, injectable ECHs should undergo a rapid phase transition from a liquid solution to a gel state, while ensuring optimal cellular engraftment, hydrogel deployment, and retention of cells and/or biomolecules throughout the sol-gel transition [129,130]. Furthermore, the degradation time of ECHs used for MI treatment can be also influenced by factors such as the type and concentration of cross-linkers, the polymer's molecular weight, pH, temperature, ionic strength, and the presence of enzymes or other degrading agents.

ECHs regulate drug release through diffusion and degradation, with hydrogel porosity and structure affecting diffusivity. To ensure uniform distribution in the infarcted area, ECHs are delivered via multiple injections and show favorable volumetric expansion in vivo. The rheological properties of the ECH formulation must be controlled for smooth syringe injection [131]. For example, the incorporation of fGO enhances the mechanical robustness and injectability of GelMA hydrogels, yet precise control of gelation timing is essential [32]. Prolonged gelation may result in solution loss due to cardiac contractions, while rapid gelation can lead to needle obstruction [132].

During the hydrogel injection process, ensuring the uniform distribution of ECHs in the infarcted area is crucial. This uniformity provides

evenly distributed mechanical and electrical support to the damaged region and facilitates the consistent delivery of therapeutic drugs or cells, which is essential for MI repair. If ECHs are unevenly distributed, certain local areas may not receive adequate mechanical or electrical support, potentially hindering the maintenance of myocardial structure and leading to a decline in the synchronization of cardiac contractions and overall heart function. Limited hydrogel dispersion may create arrhythmogenic foci, delay left ventricular activation, and reduce gap junction density, adversely affecting cardiac conduction [133]. Additionally, if ECHs are not evenly distributed, it may lead to either over-accumulation or insufficient delivery of therapeutic drugs or cells in the infarcted areas, which would be detrimental to MI repair. To enhance the uniform distribution of ECHs in the infarcted area, several strategies can be considered. A multi-channel injection system can be designed, or a dynamic flow rate adjustment device can be employed. This approach allows for the uniform injection of ECHs at multiple points and in various directions, ensuring even distribution within the infarcted area. Additionally, ECHs with good biocompatibility and low surface tension can more easily conform to the shape of the infarcted region, thereby reducing uneven distribution caused by surface tension or incompatibility after injection. In the future, 3D printing technology shows promise for designing ECH scaffolds that fit the shape of the infarcted area prior to injection, enabling precise injection or implantation into the myocardium, which is expected to improve the uniform distribution of hydrogels in the infarcted area.

If the gelation process is too slow, the injection volume is excessive, or the injection speed is too fast, hydrogel leakage into healthy tissue may occur when ECHs are injected into the border region of the damaged myocardium. This could result in several adverse effects. For example, it may provoke an immune response, leading to inflammation in the surrounding healthy myocardium. The ECHs could also interfere with the heart's electrical signaling, causing arrhythmias or other abnormal heart rhythms. In more severe cases, leakage of hydrogel components could disrupt the heart's normal electrical conduction or mechanical properties, impairing its ability to pump blood effectively. To prevent leakage of ECHs into normal myocardial tissue, it is essential to individually adjust the infarct area and the hydrogel injection volume [134]. Meanwhile, the polymerization time should range from a few minutes to several tens of minutes to ensure that the hydrogel is effectively delivered and successfully localized at the injection site, rather than being completely washed out [135]. Utilizing ECHs with strong adhesion properties enhances their stability and localization in the damaged area, which also helps prevent hydrogel leakage.

Injectable ECHs can be delivered to compromised myocardial regions via direct visualization during thoracotomy or minimally invasive thoracic surgical procedures. Leor et al. exemplified this by administering Ca^{2+}-crosslinked alginate solutions into the infarcted area at the distal aspect of the occluded left anterior descending coronary artery within a swine MI model [136]. This technique utilizes the differing permeability of vessels in the infarcted area versus healthy coronary vessels, preventing substances in normal vessels from entering the myocardium or distant organs. However, challenges remain with injection methods, as limited hydrogel dispersion may create arrhythmogenic foci, delaying left ventricular activation and reducing gap junction density, which impacts cardiac conduction.

Recent reports also introduced a new hydrogel implantation approach in animal experiments. Epicardial patches and injectable hydrogels provide different support: patches interact with external cells, while hydrogels act internally. Wu et al. demonstrated that sequentially administering HA hydrogel via intramyocardial injection, followed by a conductive PPy-GelDA patch, greatly improved cardiac function compared to single-mode systems, suggesting that combining these hydrogels could be a promising strategy [52]. Similarly, biocompatible microneedle (MN) patches applied to the injured myocardium have emerged as an advanced technology platform for sustained drug release, providing mechanical support and preventing cardiac rupture during MI repair [117]. The microneedle patch can be securely fixed to the epicardium without causing significant tissue reactions while possessing sufficient mechanical strength to penetrate the myocardium, thereby delivering drugs to the infarcted area and demonstrating superior therapeutic effects. Although there are currently no reports on the use of conductive materials in hydrogel microneedle patches for MI treatment, we look forward to significant advancements in this new cardiac repair technology in the future.

Previous clinical studies suggest that intracardiac injection of alginate hydrogel is more beneficial for patients with advanced chronic heart failure than conventional therapies. The injections were executed along a single mid-ventricular line or within 1 cm of it, circumventing visible coronary vessels [137]. Subsequent research has demonstrated that intramyocardial injection of rGO-ALG or PANI-ALG hydrogel has been shown to be safe and efficacious in enhancing left ventricular function, neovascularization, and electrical properties in MI rats [66,100]. A clinical study by He et al. confirmed the safety and feasibility of injecting collagen hydrogel laden with hUC-MSC at 5 to 10 sites in the central and peripheral zones of infarcted regions for MI treatment [138]. Future research is anticipated to integrate conductive materials into alginate or collagen hydrogels for clinical cardiac repair.

4.3. Intrapericardial injection

The pericardium is a fluid-filled, two-layered sac that protects the heart and aids contraction. Intrapericardial interventions are commonly used for epicardial catheter mapping and ablation. Implanting a drug-eluting system in the pericardial space provides sustained, localized delivery of multiple agents, reduces proteolytic degradation, and improves myocardial retention. Conductive hydrogels with inherent adhesive properties can firmly adhere to the myocardium. Zhu et al. showed that intrapericardial injection of HA hydrogels containing IPSC-derived cardiac progenitor cells or MSC-derived exosomes effectively delivers therapies to infarcted myocardium in mice. These hydrogels form patch-like structures, enhancing therapeutic cell retention, activating epicardium-derived cells, and improving cardiac function after MI [139].

The injection of ECHs into the pericardial sac offers mechanical support to the heart and enables compliant coupling with the cyclically deformed myocardium. This approach enhances electrical connectivity between healthy and infarcted regions, ameliorating the velocity and synchrony of electrical signal propagation, thereby restoring normal cardiac function [5,101]. Yu et al. have implanted an injectable mechanical-electrical coupling PANI-gelatin ECH patch into the pericardial space, achieving highly compliant interfacial coupling with the cyclically deformed myocardium. This strategy not only fosters neovascularization and restores electrical signal propagation and synchronized pulsation but also effectively inhibits ventricular dilation and prevents ventricular fibrosis and remodeling [101]. Research on intrapericardial injection of ECHs for MI treatment is limited. Future studies should develop biocompatible, biodegradable, low-swelling, conformable, and soft ECHs, while reducing the risk of cardiac effusions and adhesions.

5. Biological roles of ECHs scaffold in cardiac repair

ECHs may serve multiple functions in the myocardial reparative process post-infarction: (1) offering mechanical and electrical support to the compromised myocardium; (2) mitigating oxidative stress and inflammation; (3) fostering neovascularization; and (4) curtailing pathological remodeling [110,134]. Moreover, ECH scaffolds can augment the targeted delivery of therapeutic cells, drugs, peptides, and genetic material to discrete cardiac regions, thereby amplifying their therapeutic efficacy. The subsequent section will provide a succinct overview of the biological roles of ECHs in cardiac repair subsequent to MI (as depicted in Fig. 8).

When ECHs are implanted in the infarcted region, the conductive materials and matrix gel components work together to provide appropriate mechanical support for the damaged myocardium. The mechanical properties of ECHs are highly tunable, and their stiffness can be increased by incorporating various conductive nanoparticles or decreased through the addition of Bio-IL, enabling the formation of an optimal scaffold for cardiac differentiation and maturation. By integrating conductive biomaterials with hydrogels, a local conductive microenvironment is created, which enhances electrical signal transmission in the infarcted areas [85]. The desirable mechanical properties, combined with electrical conductivity, lead to improved functionality, as evidenced by larger beating areas and increased expression of specific cardiac markers [74].

ECH scaffolds enhance electrical signal transmission between cardiomyocytes through several mechanisms: (1) Conductive materials accelerate the maturation of electrically responsive cells, such as stem cell-derived cardiomyocytes, while the porous architecture of ECHs improves oxygen and nutrient transport, thereby supporting cardiomyocyte growth and electrical coupling [91,140]; (2) The combination of electrically conductive biomaterials with hydrogels facilitates ion transfer within the porous framework and enhances ionic conductivity, promoting the propagation of cardiac action potentials by ensuring close contact with cell membranes [74]. Furthermore, the intrinsic electrical signals of cardiomyocytes serve as stimuli that activate adjacent cells and promote synchronized beating through the ECH scaffold. (3) ECHs reduce resistivity in the fibrous tissues of the infarcted myocardium and increase tissue conduction velocity [53]. On the other hand, incorporating conductive materials into hydrogels can activate intracellular signaling pathways, including PI3K-Ca^{2+}, β1-integrin, and Wnt, to improve electrical signal propagation in cardiac tissue [137–139].

Curtailing the accumulation of ROS and inflammatory factors may alleviate MI-induced cardiac dysfunction. Throughout the degradation of ECHs, conductive materials (e.g., CNTs, PPy, rGO, PANI, PEDOT:PSS, BPNSs, melanin nanoparticles) along with anti-inflammatory antioxidants are gradually released, effectively mitigating oxidative stress [27,94,97,141–143]. Meanwhile, implanting hydrogels can alleviate myocardial chronic inflammation and fibrosis by promoting the transition of macrophage phenotype from M1 to M2 [144]. This process is influenced by the electroconductive properties of ECHs, matrix components, encapsulated bioactive molecules, or scaffold cells. Previous studies have demonstrated that both HA and GelMA facilitate macrophage infiltration, migration, and M2 polarization [145,146]. Direct electrical stimulation upregulates M2-associated genes in M0 and M1 cells, while inhibiting the expression of M1-related genes and the secretion of inflammatory cytokines in M1 cells. Conversely, M2 cells appear to be less responsive to the electrical stimulation [147]. Graphene, BPNSs, magnesium, and electrical stimulation synergistically promote M2 macrophage polarization, with potential applications in cardiac repair [147–149].

Hydrogels that replicate the ECM can be injected into the MI site to enhance endothelial cell migration within the myocardial matrix, thereby promoting neovascularization and improving the function of the infarcted myocardium [150–153]. In engineered biomimetic human cardiac tissue, exposure to continuous electric fields enhances the length of tubular structures, suggesting improved vascular stability [154]. Compared to non-conductive scaffolds, ECHs that incorporate conductive materials such as rGO, PPy, PANI, and BPNSs create an electrically conductive microenvironment, thereby promoting endothelial cell communication, migration, and tubular structure formation in ischemic regions [30,54,55,66,91]. Of course, the pro-angiogenic effect becomes more pronounced when the ECHs are loaded with pro-angiogenic drugs or therapeutic cells.

In MI, cardiomyocytes undergo irreversible injury, resulting in non-contractile scars, collagen deposition, and ECM degradation, which lead to ventricular remodeling [144]. Electrical stimulation of the border zone can alter local stress-strain patterns in the border zone-MI region and reduce MI expansion and LV dilation. This effect may be associated with the presence of ion channels and resting membrane potentials in fibroblasts, which enabling them to respond to electrical stimulation [155]. The inhibitory effect on pathological remodeling may become more pronounced when ECHs are loaded with therapeutic drugs or cells. Thus, injectable ECHs or cardiac patches can target and fill inaccessible pathological tissue post-MI, provide a local conductive microenvironment, reduce left ventricular wall stress, increase myocardial thickness, and share the mechanical load, thereby helping to mitigate ventricular remodeling [149].

6. Future challenges

This review categorizes ECHs by their conductive scaffold materials and highlights emerging research trends, including innovative design paradigms and microenvironment-responsive strategies. Although current studies in rodents and pigs have raised hope for the potential of ECHs for cardiac repair in primates and humans, no ECHs have demonstrated exceptional performance sufficient to enter clinical trial phases yet. This is primarily due to the following reasons. First, assembling ECHs that meet all the necessary requirements for effective MI repair remains a significant challenge. The unique structural characteristics of the human heart have contribute to the relatively slow progress in developing clinical trials and exploring indications and contraindications. Additionally, it is required to determine which drug, cell, or combination of both, when loaded onto the ECHs, is more effective in promoting MI repair [156]. Furthermore, it's crucial to highlight that animal studies do not fully reflect clinical realities, which creates challenges for application. Animal experiments are often performed on young, healthy animals lacking the risk factors, co-morbidities and co-medications characteristic of acute MI patients [157]. In these animal models, injections occur immediately after infarction, while patients usually receive treatment hours later. Evaluating the therapeutic effect of hydrogels in MI requires considering factors like cardiac function, tissue repair, material safety, clinical symptoms, and imaging. The design, implementation, and evaluation criteria of animal studies and clinical trials may differ due to variations in experimental conditions, pathological characteristics, treatment methods, and the subjects involved (animals vs. humans). Moreover, in vivo studies have been limited to short-term studies, leaving many unresolved questions regarding the long-term toxicity of these materials in vivo and their interactions with both the innate and adaptive immune systems [6]. The development, production, and approval of hydrogels not only require a long time and high costs, but the production and storage processes of the hydrogels themselves also face various challenges [158]. Concerns about patient infection and batch-to-batch variability have impeded the transition of ECHs from the laboratory to clinical applications. The preparation of multifunctional ECHs and their clinical translation in the MI treatment rely on further optimization of the preparation methods and improving the safety and efficacy of drug or cell delivery systems [156]. Meanwhile, by applying chemical engineering principles to develop large-scale manufacturing processes, it will improve manufacturing efficiency, reduce product variability, and lower costs, which would be beneficial for clinical translation [159].

The pathophysiology of myocardial damage following MI is intricate and multifactorial. To enhance therapeutic efficacy, adjustable ECH scaffolds are combined with cellular, genetic, and pharmacological strategies, enabling them to respond rapidly to the microenvironment, and are implanted at the MI site to improve cardiac function. Future advancements should focus on the development of ECHs that can concurrently tackle multiple etiological factors implicated in MI repair, with the potential to dynamically interface with the microenvironment. Such an integrated strategy could yield superior reparative efficacies compared to those targeting isolated or dual factors. On the other hand, customizing ECH scaffolds for individual MI patients, along with

integrating smart biosensors for precise drug and cell release modulation, is crucial for improving repair outcomes. Combining injectable ECHs with myocardial patches for therapeutic and diagnostic purposes may enhance myocardial repair. The compatibility of ECHs with existing bioelectronic devices in MI patients warrants careful examination. Preliminary research is limited, necessitating extensive long-term studies in large animal models to evaluate compatibility and mechanical alignment.

Currently, there is no consensus on the optimal timing for ECH intervention in MI treatment. The timing of ECH intervention should fully consider the MI repair process, as well as the properties of the hydrogels. Most animal studies involve injecting hydrogels into the infarcted area immediately after MI, which may not accurately reflect clinical practices. In the absence of sufficient safety evidence, performing a transendocardial injection procedure in early MI patients remains challenging. Thoracotomy is not an option for patients with mild to severe heart failure. It may be an appropriate time to inject hydrogel or implant myocardial patches during surgeries such as coronary artery bypass grafting (CABG) or left ventricular assist device (LVAD) implantation. On the other hand, hydrogel intervention is not necessarily limited to early stages of MI. Recent study reported that transendocardial injection of the hydrogel was performed in patients between 3 months and 35.5 months post-MI. Post hoc analysis showed that improvements in left ventricular remodeling data, useable mass, and BNP levels primarily occurred in patients with infarcts >12 months prior to treatment. No improvements were observed in early MI patients (<12 months post-treatment), possibly due to baseline differences and ongoing recovery from ischemic injury in the infarct and peri-infarct regions [160]. Future studies may need to select and implant the most effective ECHs based on the pathology of the specific stage of the disease.

Despite advancements in ECH scaffold fabrication, the precise mechanisms underlying the in vivo interactions between ECHs and resident cells within the myocardial microenvironment, including cardiomyocytes, fibroblasts, stem cells, and immune cells, are not yet fully understood. The interfacing between ECH scaffolds and cardiac tissue implicates targeted interactions with cardiomyocytes. Mechanosensitive ion channels pivotal for cardiac function and pathophysiology are potential therapeutic targets. The influence of ECH scaffolds on ion channel kinetics and ECM dynamics remains obscure. Clarifying these interactions is imperative for the evolution of higher efficacy, multifunctional composite hydrogels that can address the complex reparative challenges posed by MI.

The development of ECH scaffolds for myocardial repair requires a comprehensive consideration of their physicochemical properties, including mechanical strength, elasticity, porosity, biodegradability, hydrophilicity, adhesiveness, cytotoxicity, and drug delivery effectiveness. These properties significantly influence the behavior of cardiomyocytes and stem cells within hydrogels, thereby affecting the efficacy of MI treatment. In the future, an intelligent hydrogel-based drug and cell delivery system that integrates diagnostic and therapeutic functions is expected to show promising potential for personalized medicine and tailored treatment outcomes.

7. Conclusion

Various conductive materials have been employed in the preparation of ECHs for cardiac tissue engineering applications. ECHs have emerged as a promising therapeutic option for repairing infarcted myocardium by providing mechanical and electrical support, reducing inflammation, promoting angiogenesis and alleviating pathological remodeling. The application of various functionalization strategies, such as innovative design paradigms and microenvironment-responsive approaches for preparing ECHs, has resulted in improved efficacy in MI animal models. Future advancements should focus on the development of ECHs that can concurrently tackle multiple etiological factors implicated in MI repair, with the potential to dynamically interface with the microenvironment. The preparation of multifunctional ECHs and their clinical translation in MI treatment depend on further optimization of preparation methods and improvements in the safety and efficiency of drug or cell delivery systems.

CRediT authorship contribution statement

Qianqian Lv: Writing – original draft. **Dandan Zhou:** Writing – original draft. **Yutong He:** Writing – original draft. **Tao Xu:** Writing – original draft. **Xiaozhong Qiu:** Writing – review & editing, Supervision. **Junwei Zeng:** Writing – review & editing.

Declaration of generative AI and AI-assisted technologies in the writing process

The authors declare that they have not employed these technologies.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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