Materials Today Bio 29 (2024) 101295

Contents lists available at ScienceDirect

Materials Today Bio

journal homepage: www.journals.elsevier.com/materials-today-bio

Innovative hydrogel-based therapies for ischemia-reperfusion injury : bridging the gap between pathophysiology and treatment

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ARTICLE INFO

Keywords:
Ischemia-reperfusion injury
Hydrogel
Reactive oxygen species
Therapeutic substance delivery
Mesenchymal stem cells

ABSTRACT

Ischemia-reperfusion injury (IRI) commonly occurs in clinical settings, particularly in medical practices such as organ transplantation, cardiopulmonary resuscitation, and recovery from acute trauma, posing substantial challenges in clinical therapies. Current systemic therapies for IRI are limited by poor drug targeting, short efficacy, and significant side effects. Owing to their exceptional biocompatibility, biodegradability, excellent mechanical properties, targeting capabilities, controlled release potential, and properties mimicking the extracellular matrix (ECM), hydrogels not only serve as superior platforms for therapeutic substance delivery and retention, but also facilitate bioenvironment cultivation and cell recruitment, demonstrating significant potential in IRI treatment. This review explores the pathological processes of IRI and discusses the roles and therapeutic outcomes of various hydrogel systems. By categorizing hydrogel systems into depots delivering therapeutic agents, scaffolds encapsulating mesenchymal stem cells (MSCs), and ECM-mimicking hydrogels, this article emphasizes the selection of polymers and therapeutic substances, and details special crosslinking mechanisms and physicochemical properties, as well as summarizes the application of hydrogel systems for IRI treatment. Furthermore, it evaluates the limitations of current hydrogel treatments and suggests directions for future clinical applications.

1. Introduction

Ischemia-reperfusion injury (IRI) is a complex phenomenon that takes place when blood supply is restored to tissues or organs that have been hypoxic or ischemic. Ischemia typically arises from an obstruction of blood supply due to surgical interventions or diseases such as myocardial infarctions and strokes. Animal experiments and clinical studies have shown that reperfusion can exacerbate tissue and organ damage in some cases [1]. Ongoing research has revealed that although essential for recovery, reperfusion can initiate harmful cellular responses such as oxidative stress, intracellular calcium overload, excessive inflammatory activation, and mitochondrial dysfunction, which worsen tissue damage [2–4].

Research on IRI mechanisms is advancing rapidly, with most preventative and therapeutic strategies still in experimental or clinical observational stages, each facing limitations. Ischemic conditioning, which swiftly restores blood flow and manages reperfusion conditions, emerges as a relatively mature treatment approach. This encompasses ischemic preconditioning and postconditioning, involving repeated short-term ischemic and reperfusion episodes to tissues or organs before or after an extended period of ischemia [5]. Moreover, remote ischemic preconditioning can be applied, where repeated episodes of ischemia and hypoxia are induced in organs other than the heart and brain [6]. These methods activate intrinsic protective mechanisms and enhance hypoxia tolerance. Despite the lack of especially mature and widely accepted pharmacological treatments, several medications have been tested in animal models and small-scale clinical trials. For instance, antioxidants like N-acetylcysteine and superoxide dismutase serve as free radical scavengers [7,8], nucleotidase facilitates the breakdown of Adenosine Triphosphate (ATP) into anti-inflammatory adenosine [9],

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https://doi.org/10.1016/j.mtbio.2024.101295
Received 1 July 2024; Received in revised form 21 September 2024; Accepted 8 October 2024
Available online 10 October 2024

calcium channel blockers diltiazem alleviate calcium overload [10], mitochondria-targeted peptide-131 (MTP-131) stabilizes mitochondrial membranes by binding to specific mitochondrial phospholipids [11], and cyclosporine A prevents the opening of mitochondrial permeability transition pores (mPTP) [12]. Additionally, research has indicated that cytokines and their antagonists, like interleukin-11 (IL-11) and vascular endothelial growth factor (VEGF) can ameliorate IRI in mice [13,14], while IL-6 receptor inhibitors have shown promising therapeutic outcomes in subsequent clinical trials [15]. However, systemic IRI treatments have a brief therapeutic window, necessitating real-time patient monitoring by healthcare systems to guarantee timely medication administration. Additionally, these medications lack target specificity, leading to inevitable adverse effects. For instance, cyclosporine A, while preserving mitochondrial functions, also suppresses the immune system, increasing infection risk [16]. High dosage of N-acetylcysteine for IRI treatment may cause side effects including vomiting, diarrhea and headaches [17].

Recently, there has been a rapid development in emerging therapies for ischemia-reperfusion (I/R). For instance, exosomes (Exo), heterogeneous nanovesicles produced by the reverse budding of multivesicular bodies, can transport proteins, DNA, RNA and other biomolecules. Their rich content of signaling proteins and lipids facilitates the transport of multiple molecules across biomembranes. Studies have shown that Exo play crucial roles in cellular communication, immune modulation, tissue restoration and regeneration, and metabolic adjustment [18]. Owing to their outstanding biocompatibility and low immunogenicity, Exo demonstrate significant therapeutic potential in IRI. However, their application as treatment agents is limited by rapid elimination and brief half-life within the body. Therapeutic gases, including nitric oxide (NO), carbon monoxide (CO), and hydrogen sulfide (H_2S), show promise due to their anti-inflammatory, anti-apoptotic, and antioxidative effects at cellular and tissue levels [19–21]. Nevertheless, effectively delivering these gases to the intended tissues and cells remains a technical challenge. Mesenchymal stem cells (MSCs) are recognized for their extensive self-renewal capabilities, potential for diverse differentiation, regulation of immune responses, and facilitation of tissue repair, significantly enhancing the microenvironment. This makes them promising candidates for IRI treatment [22]. However, their clinical applications are constrained by limitations in targeted delivery, along with low survival and integration rates.

To address these challenges, hydrogels, highly biocompatible and biodegradable, have become dependable vehicles for diverse therapeutic substances delivery and retention [23]. As materials with high water content, hydrogels are characterized by their three-dimensional (3D) network structures. These networks are typically formed from hydrophilic or amphiphilic polymers through processes such as chemical or physical crosslinking [24]. Their matrix protects cells and sensitive biomolecules like proteins, polypeptides and nucleic acids from environmental harm, increasing both stability and bioavailability of these molecules [25–27]. Situ-forming and shear-thinning hydrogels, when administered via localized injections, effectively minimize systemic side effects and enhance therapeutic efficacy [28]. Furthermore, by adjusting the cross-linking density, polymer compositions, and physicochemical properties of hydrogels, controlled release rates of therapeutic agents are facilitated, allowing for sustained and slow medication release for extended effects [29]. Certain intelligent hydrogels respond to environmental stimuli, such as pH shifts, temperature changes and enzymatic activity, triggering substance release at optimal times for precise treatment and improved outcomes [30–34]. Additionally, hydrogels, mimicking the extracellular matrix (ECM), are used to cultivate and recruit pertinent cells, thus widely employed in tissue engineering and regenerative medicine [35,36].

In current IRI treatment strategies, while many therapeutic methods exist, most remain in experimental and clinical trial phases, facing challenges like drug delivery difficulties, short effectiveness duration and significant side effects. Thus, developing a safe, convenient and controllable treatment strategy is crucial. Hydrogels, noted for their functionality and biomimicry, present a promising solution to these challenges. This review explores the applications of hydrogels in IRI treatment, including hydrogel depots for delivering therapeutic agents, hydrogel scaffolds for encapsulating MSCs, and ECM-mimicking hydrogels. By summarizing IRI pathophysiology and detailing hydrogel systems based on polymer composition and therapeutic substance selection, this article analyzes the therapeutic mechanisms of hydrogel systems and evaluates their future directions. It aims to offer fresh perspectives and strategies for clinical practice, enhancing IRI treatment effectiveness and patient survival quality.

2. The pathophysiology of IRI

IRI represents a complex pathological state characterized by oxidative stress, calcium overload, inflammatory responses, and mitochondrial dysfunction [37–40]. In the ischemic phase, tissue impairment occurs due to oxygen deprivation. During reperfusion, the sudden reintroduction of oxygen triggers massive production of reactive oxygen species (ROS), causing widespread cellular structure and function damage. Furthermore, damage to cell membranes facilitates abnormal calcium entry and mitochondrial breakdown, intensifying pathological progression [2]. Inflammatory responses further exacerbate damage to both local and distant organs, rendering the entire sequence a cascade of interconnected pathological events (Fig. 1). These changes manifest as unique pathological characteristics in various organs such as the heart, brain, kidney, liver, lung and intestine, leading to tissue damage and dysfunction [41–46]. A thorough understanding of the mechanisms underlying IRI is essential to devise targeted therapeutic strategies.

2.1. Oxidative stress

During reperfusion, the rapid reintroduction of oxygen supply leads cells to quickly generate substantial amounts of ROS, including superoxide anions, hydrogen peroxide, and hydroxyl radicals [47]. These ROS attack membrane lipids, proteins, and DNA, leading to widespread damage to cell structure and function. This damage leads to the leakage of cellular constituents, dysfunction of cells, and potential cell death. During I/R, key sources of ROS encompass enhanced mitochondrial ROS generation, the xanthine oxidase pathway from vascular endothelial cells, the leukocyte nicotinamide adenine dinucleotide phosphate (NADPH)/nicotinamide adenine dinucleotide (NADH) oxidase system, catecholamine auto-oxidation through monoamine oxidase, and activation of inducible nitric oxide synthase [37,48–50]. The highly reactive nature of ROS facilitates their interactions with cellular components, causing structural and functional metabolic damage. Membrane phospholipids, abundant in polyunsaturated fatty acids, are particularly vulnerable to ROS, which compromises the integrity of cell and organelle membranes, ultimately causing leakage of their contents and cell death [51]. ROS can also react with thiol groups on protein polypeptides, leading to incorrect protein folding, denaturation, aggregation, degradation, and peptide chain breaks [52]. This impairs the function of enzymes, receptors and ion channels. Concurrently, ROS modify bases, break DNA strands, and cross-link DNA, consequently damaging the genetic material in the nucleus and mitochondria [53].

2.2. Calcium overload

Calcium overload plays a significant role in IRI. On the one hand, the substantial ROS generated during I/R damages the cell membrane structure, increasing its permeability to Ca^{2+} [54]. This elevation in intracellular Ca^{2+} activates phospholipases, further degrading membrane phospholipids and increasing the influx of extracellular Ca^{2+} into the cells. On the other hand, ischemia enhances anaerobic metabolism within cells, leading to an accumulation of cytoplasmic H^+ and activating the Na^+-H^+ exchange protein, which elevates intracellular Na^+

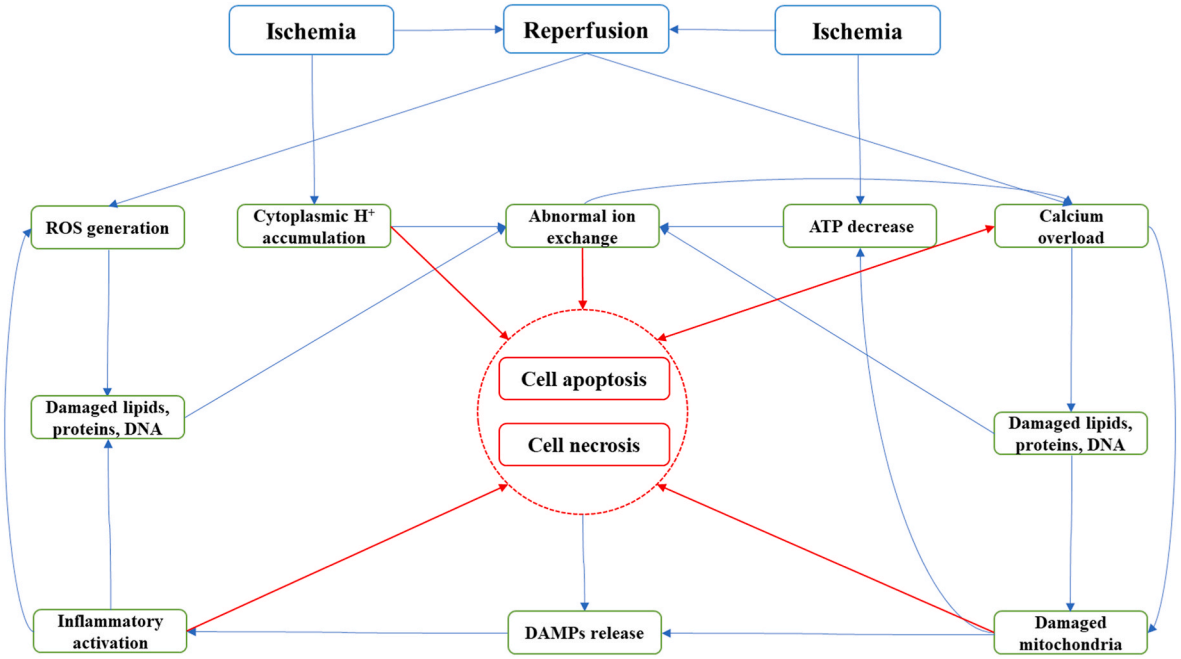

Fig. 1. The illustration of the occurrence process of ischemia-reperfusion and the connection between key pathophysiological mechanisms.

levels [55]. Additionally, ischemic damage to mitochondrial membranes disrupts oxidative phosphorylation, reducing ATP production. It decreases Ca^{2+}-ATPase and Na^{+}-K^{+} ATPase activity, hindering Ca^{2+} efflux and entry into the endoplasmic reticulum as well as leading to the accumulation of intracellular Na^{+}. Upon reperfusion, Na^{+}/Ca^{2+} exchangers are rapidly activated in reverse by oxygen and nutrients, resulting in the expulsion of substantial amounts of Na^{+} from the cells and the influx of large quantities of extracellular Ca^{2+} [56]. Furthermore, tissue damage enhances the release of endogenous catecholamines, which activate protein kinase C, contributing to further calcium overload [57]. The massive influx of Ca^{2+} activates calcium-dependent degradative enzymes, like proteases, phospholipases and endonucleases, resulting in cell damage. Additionally, Ca^{2+} accumulation in the mitochondrial matrix activates mitochondrial cyclophilin D, triggering the opening of mPTP, which leads to cell necrosis and apoptosis [58].

2.3. Excessive inflammatory activation

IRI triggers a sequence of inflammatory reactions that broadly activate the immune system. Typically, this condition does not arise from external pathogenic invasion but from ischemia-induced processes that trigger a cascade of pro-inflammatory signals [59]. Such sterile inflammation stimulates both innate and adaptive immune responses. This involves the interaction of damage-associated molecular patterns (DAMPs) with pattern recognition receptors (PRRs), the activation of the complement system, the enhancement of cell adhesion molecule expression, the release of cytokines, and the mobilization and activation of immune cells [39,60]. The process is characterized by neutrophils and other leukocytes rolling and adhering to the vascular endothelium, accumulating at the endothelium, and, under cytokine influence, migrating through the vessel wall to the site of inflammation [61]. Furthermore, the accumulation of neutrophils, together with endothelial cell swelling, platelet adhesion, microthrombus formation, and tissue edema, contributes to the no-reflow phenomenon, exacerbating tissue hypoxia [62]. Activated leukocytes and injured endothelial cells release substantial quantities of ROS and proteases, damaging adjacent tissue cells. Following cell death, significant DAMPs release occurs during the reperfusion phase, attracting numerous leukocytes into the injured tissue via the bloodstream [63]. This, in turn, further stimulates both the innate and adaptive immune systems, leading to further damage by neutrophils and other immune cells.

2.4. Mitochondria dysfunction

Recent studies indicate that reverse electron transport (RET) at Complex I of the mitochondrial respiratory chain, driven by succinate oxidation, is considered the primary source of ROS during I/R [64–66]. Mitochondrial ROS directly damage cells and tissues via oxidative stress pathways, decreasing ATP production, disturbing energy metabolism, and impairing cell functionality. Concurrently, cellular oxidative stress and calcium overload trigger mPTP opening, causing swelling of the mitochondrial matrix and rupture of the outer mitochondrial membrane (OMM) [67,68]. This results in the release of mitochondrial DAMPs such as cytochrome C, succinate, and N-formyl peptides into the cytoplasm and extracellular space, initiating processes of inflammation-driven necrosis and caspase-dependent apoptosis [69,70]. The necrotic and apoptotic cells discharge mitochondrial DAMPs into their surrounding environment, intensifying damage to cells and tissues.

3. Advantages of hydrogels in IRI

Hydrogels are materials composed of a 3D network, where hydrophilic or amphiphilic polymers form stable structures through either physical cross-linking including physical entanglements, hydrogen bonding, hydrophobic interactions and ionic interactions, or chemical cross-linking in form of covalent bonds [24]. Their unique physicochemical properties enable hydrogels to swell and remain stable in aqueous solutions or biological fluids, providing the foundation for their applications in therapeutic substance delivery and retention, tissue engineering, and regenerative medicine. Although IRI manifests differently across organs, its underlying pathophysiological mechanisms are consistent [2]. Owing to their biodegradability, biocompatibility, excellent mechanical properties, targeting capabilities, controlled release potential, and properties mimicking the ECM, hydrogels present promising prospects for IRI treatment in various organs.

3.1. Biodegradability and biocompatibility

Biocompatibility and biodegradability are essential requirements for hydrogels used in IRI treatment, as they collectively guarantee the material's safety for in vivo applications. The highly hydrated network structure of hydrogels allows for seamless integration with human tissues, minimizing mechanical irritation to cells from foreign materials. This characteristic reduces the stress response on surrounding tissues during application [71]. Natural polymer hydrogels, such as gelatin, hyaluronic acid, and alginate, are derived from biological sources and are typically well-compatible with biological environments [72]. Another promising self-assembling peptide (SAP) hydrogel, which spontaneously forms a 3D network through the physical crosslinking of short peptides, is also designed to exhibit minimal toxicity [73]. Meanwhile, synthetic polymer materials such as poly(ethylene glycol) (PEG) exhibit chemical inertness, effectively preventing immune rejection and inflammatory responses [74]. After fulfilling their therapeutic role, hydrogels naturally degrade into non-toxic byproducts through metabolic pathways, eliminating the need for secondary surgeries to remove the material. PEG-based hydrogels, for example, degrade via hydrolysable bonds such as ester and amide bonds in their network structure, with degradation products excreted through normal metabolic processes [75]. These degradation processes are especially crucial for highly sensitive organs, such as the kidneys, ensuring that the small molecules or oligomers generated from hydrogel degradation can be excreted through urine, thereby preventing potential chronic inflammation or fibrosis.

3.2. Excellent mechanical properties

The mechanical properties of hydrogels are primarily determined by the polymer composition and the crosslinking density of the polymer chains. By selecting base materials of polymers, controlling the amount of crosslinking agents, or adjusting the conditions of the crosslinking reaction, the hardness, strength, and flexibility of hydrogels can be tailored with precision [76]. Through rational design and modulation, hydrogels can be adapted to the mechanical environment of various organs, enabling personalized tissue support and repair strategies, while significantly reducing the risk of damage to organs that are highly sensitive to mechanical stress, such as the brain and kidneys. In treating brain injuries, the softness of the hydrogel is of particular importance [77]. Given the extreme fragility of brain tissue, hydrogels are typically engineered with an appropriate Young's modulus, which mimics the mechanical characteristics of brain tissue and provides adequate support to damaged neurons without exerting excessive pressure on surrounding neural structures [78]. On the other hand, in the treatment of myocardial IRI, the elasticity and toughness of the hydrogel are critical factors. Acute ischemia-induced myocardial infarction can easily lead to mechanical complications, including rupture of a papillary muscle, free wall, and ventricular septum [79]. Although the incidence of these complications decreases during coronary reperfusion, their associated risks remain significant [80]. Hydrogels, due to their tunable mechanical properties, can provide the necessary stiffness and support to the myocardium, which not only helps maintain the heart's functional structure but also creates a stable environment conducive to tissue repair [81,82].

3.3. Targeting capability

In contrast to smaller drug delivery systems, such as nanoparticles (NPs) or liposomes, hydrogels are generally unsuitable for intravenous injection due to their poor fluidity and larger size [83]. Currently, hydrogel-based therapies are primarily designed for oral, topical, and injectable administration [84]. Among them, shear-thinning hydrogels have gained significant attention in the treatment of IRI due to their reversible viscosity changes. These hydrogels exhibit high fluidity under external shear forces and re-solidify into a stable gel structure after injection into the target site, providing support or controlling drug release [85]. Although existing animal studies still rely on highly invasive surgical procedures to directly inject hydrogels into reperfusion regions, catheter-based techniques guided by ultrasound may offer an ideal solution for clinical applications [86]. Delivering hydrogels to deep ischemic organs via minimally invasive catheter injection holds promise for reducing postoperative recovery time and lowing infection risk, though further research is required to substantiate its clinical value. It is worth noting in treating brain injuries, the blood-brain barrier (BBB) poses a major obstacle to drug penetration into damaged areas. Although ROS and inflammatory mediators produced during early reperfusion may transiently open the BBB, conventional drug delivery methods remain limited [87]. Addressing this challenge, intranasal delivery has emerged as a novel method to bypass the BBB. In situ-forming hydrogels can be introduced through the nasal cavity as a liquid precursor, undergoing a sol-gel phase transition at body temperature, gradually solidifying and slowly releasing therapeutic agents into the brain [88]. This approach demonstrates great potential in brain injury treatment.

While macroscopic hydrogels are currently more widely applied in the biomedical field, micro/nano-hydrogel microspheres possess distinct advantages in drug encapsulation and controlled release [89]. Similar to other nanomaterials, they can passively accumulate in damaged organs. Research has shown that 3.5 nm nanoprobes display specific uptake in the kidneys, whereas 7 nm NPs tend to accumulate in the liver [90]. In contrast, larger nanomaterials can be absorbed by kidneys suffering from I/R because of the increased permeability of the glomerular filtration barrier (GFB) , which achieving more effective treatment [91]. Surface charge is another critical factor influencing the in vivo distribution of nanomaterials. Negatively charged nanomaterials can avoid excessive uptake by the reticuloendothelial system in the spleen and liver during circulation. Furthermore, due to the negative charge in GFB, the resulting electrostatic repulsion prolongs nanomaterial retention in the kidney region, thus enhancing therapeutic efficacy [92]. Additionally, micro/nano-hydrogel microspheres can be further functionalized through chemical modifications for targeted therapy. By conjugating targeting ligands such as peptides and carbohydrates on the hydrogel surface, specific binding to receptors on target cells or tissues can be achieved, enabling precise therapeutic substance delivery while minimizing side effects [93].

Although hydrogel systems with targeting and sustained-release features significantly enhance therapeutic efficiency and scope compared to the direct application of drugs, localized injection of hydrogels in larger or denser organs, such as the heart, liver, or brain, still faces the challenge of limited drug diffusion throughout the entire organ. The complex structure of organs and the varying microenvironments in different regions restrict effective drug distribution, potentially resulting in localized treatment with uneven or insufficient efficacy. To overcome these limitations, multi-site injection techniques can offer broader drug distribution, ensuring that the affected areas across the entire organ are adequately covered, thereby improving therapeutic outcomes [94].

3.4. Controlled release potential

The distinct advantage of hydrogels as drug delivery systems lies in their controlled release capability, which allows precise modulation of therapeutic agents release rates according to therapeutic needs. This characteristic is achieved primarily through adjusting the base material, crosslinking method, and crosslinking density, rendering hydrogels suitable for both short-term drug release and long-term sustained-release therapies [95]. In recent years, with the rapid advancement of smart materials, hydrogels have been engineered with environmentally responsive functionalities by introducing groups sensitive to various stimuli, further enhancing their ability to control degradation rates and

drug release [96]. Based on their mechanisms of action, hydrogels can be classified into endogenous factor-responsive, exogenous factor-responsive, and multi-responsive hydrogels [97]. Among them, hydrogels that respond to endogenous factors such as pH, temperature, or enzymes have seen widespread application across various fields, which can automatically adjust drug release according to the physiological changes at the site of injury or disease. In inflamed areas, local acidic or enzyme-active microenvironments can trigger hydrogel degradation and release of the drug, leading to efficient and localized therapeutic outcomes [98,99]. In contrast, exogenous factor-responsive hydrogels provide more precise control over drug release through external stimuli, such as light, magnetic fields, or electric fields [100]. This exogenous responsiveness allows hydrogels to be triggered by external signals at specific times and locations, making them ideal for precision medicine applications. For instance, photo-responsive hydrogels can be activated by external light sources to release drugs at the most appropriate time and site [101]. Furthermore, with technological advancements, multi-responsive hydrogels are rapidly evolving, capable of responding to multiple stimuli, demonstrating significant potential for more refined control, particularly in spatiotemporal drug release [102]. In the complex pathological environment of IRI, where therapeutic needs vary significantly over time, the spatiotemporal control capabilities of multi-responsive hydrogels can optimize the timing and location of therapeutic substance release, effectively addressing the dynamic nature of the disease.

3.5. Properties mimicking the ECM

The ECM is a complex network of biological macromolecules secreted by fibroblasts, located in the extracellular mesenchyme, providing physical support and regulating cellular behavior and function [103]. Key components or degradation products of the ECM, such as collagen, elastin, hyaluronic acid, and gelatin, can serve as polymers in hydrogels, forming a 3D network that partially mimics the composition of natural ECM, thereby regulating cellular functions [104]. Similarly, functionalized synthetic hydrogels can mimic similar effects. For example, the incorporation of the adhesion peptide sequence RGD emulates the adhesive properties of ECM, promoting extracellular vesicles (EVs) and cells adhesion and migration through the RGD–integrin binding [105]. However, an ideal bioactive hydrogel should accurately replicate the ECM's complex microenvironment, which remains challenging to employ with either natural or synthetic polymers alone. Hydrogels derived from decellularized extracellular matrix (dECM) effectively address the limitations of traditional hydrogels, demonstrating unique potential in IRI treatment. The dECM undergoes sequential processes of grinding, dissolution, and enzymatic treatment to acquire gelation capability [106]. The advantage of dECM hydrogels lies in their ability to retain the native structural and functional proteins of the ECM, including collagen, fibronectin, and elastin, which are essential for tissue integrity and function [106]. Furthermore, by employing supercritical fluid technology, dECM hydrogels can preserve critical growth factors (GFs) present within the original ECM. These GFs such as VEGF, Fibroblast Growth Factor (FGF) , and TGF-β are crucial in regulating cell survival, proliferation, differentiation, and migration, promoting a more natural tissue repair process [107]. Additionally, Matrix-bound nanovesicles (MBVs) within the dECM enhance intercellular communication, promoting tissue repair [108]. Owing to these properties, dECM hydrogels present novel therapeutic opportunities in the regenerative medicine area, particularly in treating IRI, enhancing tissue repair as well as providing new possibilities for improving patients' prognosis.

4. Classification and applications of hydrogels

In other reviews, the biomedical applications of hydrogels are typically introduced with a focus on their compositions and properties, while this approach highlights the distinctions among hydrogels. In this article, hydrogel systems are categorized based on their therapeutic substances: hydrogel depots for delivering therapeutic agents, hydrogel scaffolds for encapsulating mesenchymal stem cells (MSCs), and self-functional hydrogels that mimic the ECM. Additionally, therapeutic agents within these systems are further categorized into small molecule drugs, biological macromolecules, NPs, and EVs. A comprehensive analysis of the therapeutic mechanisms of diverse hydrogel systems and their applications against IRI provides valuable insights for directing future research advancements (Table 1).

4.1. Hydrogel depots for small molecule drugs delivery

While excessive ROS are known to drive the oxidative stress process in IRI, they are also significant as cellular signaling molecules. They serve as secondary messengers, regulating critical cell signaling pathways such as MAPKs, NF-κB, and PI3K/Akt, which are essential for cellular growth, differentiation, and homeostasis [135,136]. Consequently, targeting excessive ROS through localized drug delivery seeks to mitigate IRI, thus avoiding the complications associated with high dosage of systemic medications. One notable compound, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), known for its ROS scavenging ability, has been explored in treating neurodegenerative, cardiovascular, and inflammatory diseases [137–139]. Zhu et al. developed a copolymer NIPAAm-co-VP-co-MAPLA-co-MANHS (pNVMN) via free radical polymerization, and further prepared a thermoresponsive injectable hydrogel by reacting copolymers with TEMPO (Fig. 2A) [109]. The TEMPO hydrogel system can be minimally invasively injected into areas of myocardial infarction, effectively reducing inflammation and myocardial fibrosis, and improving cardiac function. In rat models of myocardial I/R, treatment based on hydrogel systems reduced concentrations of malondialdehyde (MDA) and interleukin-1β (IL-1β) compared to treatment with TEMPO alone, indicating enhanced anti-inflammatory and antioxidant effects.

During I/R, mitochondria are the main sites for ROS production. Zhao et al. engineered an SAP hydrogel composed of the anionic peptide KDLL and the mitochondria-targeted antioxidant Mito-TEMPO (MT) [110]. Specifically, MT was composed of TEMPO and triphenylphosphonium cation (TPP^+). The TPP^+ component enhanced MT's penetration through the mitochondrial membrane, facilitating the selective elimination of mitochondrial-derived ROS (mtROS). The KDLL peptides organized into ordered nanostructures via hydrogen bonding, hydrophobic interactions and other non-covalent interactions, which then solidified into 3D network structures. This interaction between the TPP^+ and anionic peptides facilitated a sustained and slow release of MT (Fig. 2B), which significantly reduced the production of mtROS and thereby preserved mitochondrial structural integrity. In mouse kidney I/R models, the hydrogel system suppressed the release of inflammatory cytokines including tumor necrosis factor alpha (TNF-α) and intercellular adhesion molecule-1 (ICAM-1), diminished macrophage infiltration, and ultimately reduced renal tubular cellular apoptosis.

Gas therapy, utilizing gases such as NO, carbon dioxide (CO_2), hydrogen (H_2), and H_2S, has proven highly effective in reducing cell and tissue damage due to their anti-inflammatory, anti-oxidative, and hemodynamic regulatory properties [140]. Traditional inhalation methods often fail to target organs, leading to discomfort from over-inhalation. Consequently, employing hydrogels as delivery vehicles for gas donors presents a viable alternative. For example, NO not only serves as a secondary messenger in inflammation regulation but also plays a role in blood flow regulation [141,142]. In the context of I/R, low concentrations of NO can dilate blood vessels, inhibit platelet aggregation, and preserve endothelial cell function and structure [143]. Although NO donors such as diazeniumdiolates and nitrosothiols show potential in treating I/R, their clinical adoption is limited by low selectivity and significant toxic side effects, making targeted local administration a focus of current research [144,145]. Najafi et al. developed an SAP

Table 1
Polymers and effective substances of hydrogel systems demonstrate significant therapeutic effects.

Code	Polymers	Effective substances	Animal model	Injection site	Therapeutical effects	Ref.
Hydrogel depots for small molecule drugs delivery						
1	NIPAAm，VP，MAPLA，MATEMPO	4-amino-TEMPO	Sprague-Dawley rats, myocardial I/R injury model	Heart	Reduced myocardial infarction/reperfusion injury Preserved left ventricular geometry Reduced fibrosis and inflammation Improved cardiac function Reduced systemic inflammation markers	[109]
2	KLDD (n-KLDLKLDLKLDLD-c)	Mito-TEMPO	C57BL/6 male mice, kidney I/R injury model	Kidney	Reduced renal mitochondrial ROS Improved mitochondrial biogenesis and architecture, decreased apoptosis and inflammation Reduced tubular necrosis and fibrosis, resulting in improved renal function and systemic inflammation markers	[110]
3	Fmoc-FF	SNAP	Male BALB/c mice，kidney I/R injury model	Kidney	Exhibited a controlled release of NO over 7 days Reduced oxidative stress and improved kidney function by decreasing blood urea nitrogen and serum creatinine Reduced histopathological damage and inflammation, leading to better kidney recovery	[111]
4	CS-B-NO	B-NO (a small-molecule NO donor)	Male mice (strain not specified)，myocardial I/R injury model	Heart	Modulated ROS/NO imbalance through dual ROS scavenging and NO release Reduced infarct size and improved cardiac function Downregulated inflammatory markers (IL-1β, IL-6, TNF-α) and upregulated anti-inflammatory cytokines (IL-10) Enhanced the antioxidant defense system via Nrf2-Keap1 pathway regulation	[112]
5	RADA16-I	Curcumin	Male Sprague-Dawley rats, myocardial I/R injury model	Heart	Improved heart function, reduced oxidative stress, and promoted autophagy Enhanced cardiac function (improved LVEF and LVFS) Decreased collagen deposition and apoptosis Reduced reactive oxygen species and mitochondrial damage	[113]
6	Nap-Cur-NO conjugate	NO and curcumin	C57BL/6 mice, myocardial I/R injury model	Heart	Reduced myocardial injury by inhibiting autophagy and apoptosis Improved cardiac functionAlleviated ventricular remodeling after acute myocardial infarction	[114]
7	Rh-DFDFG-ss-ERGD	Rhein and EGCG	Male C57BL/6 mice，myocardial I/R injury model	Heart	Blocked the ROS and inflammation cycle by scavenging ROS and inhibiting TLR4 Resulted in sustained release and treatment, improving cardiac function and reducing scarring Reduced ROS production, inflammation, and apoptosis in cardiomyocytes	[115]
8	EDA, borneol inclusions, P407, PEG400	EDA and borneol	Male Sprague-Dawley rats，middle cerebral artery occlusion model for cerebral ischemia I/R injury model	Nasal cavity	Alleviated neurological deficit symptoms and reduced cerebral infarct size Provided better protection than edaravone alone Increased brain targeting and bypassed the blood-brain barrier	[116]
Hydrogel depots for biomacromolecule delivery						
9	Pluronic F-127	Keratin-based hydrogen sulfide donor	Male Sprague-Dawley rats，myocardial I/R injury model	Heart	Released H_2S at a controlled rate Reduced inflammation by lowering pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) in cardiac tissueReduced microvascular obstruction and fibrosis after myocardial I/R injury Promoted NO production through the activation of endothelial NO synthase, which protected against oxidative stress and inflammation	[117]
10	Gelatin	bFGF	Fischer rats，skin flap I/R injury model	Skin	Improved flap survival area and average number of vessels Promoted expression of vasculogenic growth factors, leading to enhanced tissue regeneration and viability	[118]
11	PEG-MAL	HGF and VEGF	RNU rats，myocardial I/R injury model	Heart	Increased angiogenesis and stem cell recruitment, Decreased fibrosis Improved cardiac function over time	[119]
12	PEG-MAL	CD39 and CD73	Male Sprague-Dawley rats，myocardial I/R injury model	Heart	Decreased immune infiltration (total leukocytes and neutrophils) and NETosis Decreased formation of platelet-leukocyte complexes in circulation Preserved cardiac function, global longitudinal strain, and cardiac output compared to controls Reduced H_2O_2 levels in myocardial tissues, indicating decreased oxidative stress	[120]
13	KLD2R (Ac-KLDLKLDLKLDLRR-CONH2)	TNF-α neutralizing antibody and HGF	Male C57BL/6 mice ，renal I/R injury model	Kidney	Reduced serum creatinine and blood urea nitrogen levels Decreased inflammation (lower IL-1β, IL-6, HMGB1) Reduced tubular apoptosis and renal fibrosis	[121]

(*continued on next page*)

Table 1 (*continued*)

Code	Polymers	Effective substances	Animal model	Injection site	Therapeutical effects	Ref.
					Enhanced tubular cell proliferation and dedifferentiation (higher Ki67, PCNA, and Pax2 expression)	
15	PFA ，PNBA	Mir-196c-3p mimic	Wild-type Sprague-Dawley rats，myocardial I/R injury model	Heart	Controlled miRNA release with NIR-II light Decreased cardiomyocyte ferroptosis by reducing levels of ferroptosis-related genes (NOX4, P53, and LOX) Improved cardiac function and survival rate after myocardial I/R Reduced infarct size and lipid peroxidation, and increased expression of protective genes (GPX4, Fth1)	[122]
Hydrogel depots for NPs delivery						
16	ELP-HA	miNPs (Mir-196c-3p loaded in NPs)	RNU rats ，myocardial I/R injury model	Heart	Improved cardiac function by restoring contractility of damaged myocardium, reducing scar size, increasing capillary density in the infarct border zone	[123]
Hydrogel depots for EVs delivery						
17	KMP2 (Ac-KLDLPVGLIGKLDL-CONH2)	MSC-EVs	Male C57BL/6 mice, kidney I/R injury model	Kidney	Reduced tubular cell apoptosis, pro-inflammatory cytokine expression and macrophage infiltration Enhanced endothelial cell proliferation and angiogenesis Decreased chronic renal fibrosis	[124]
18	AT-EHBPE， HA-SH，CP05	Exo	Sprague-Dawley rats ，myocardial I/R injury model	Heart	Improved cardiac functions, increased ejection fraction and fractional shortening, and reduced fibrosis Upregulated expression of cardiac-related proteins and genes involved in angiogenesis and tissue repair Promoted cell proliferation and angiogenesis, leading to better recovery of myocardial function	[125]
19	L-Glutamine dodecylamide，benzaldehyde	EVs	C57BL/6 male mice，myocardial I/R injury model	Nasal cavity	Reduced inflammation by decreasing pro-inflammatory $Ly6C^{high}$ monocytes/macrophages and neutrophils in the bloodstream Reduced the formation of microvascular thrombi, improved endothelial barrier function, and increased microvascular density in Injured myocardial tissue Improved left ventricular ejection fraction and reduced infarct area	[126]
Hydrogel scaffolds for MSCs encapsulation						
20	PEG derivative	MSCs	Sprague-Dawley rats, myocardial I/R injury model	Heart	Reduced the infiltration of innate immune cells (neutrophils and macrophages), Lowered H_2O_2 formation Improved cardiac function (global longitudinal strain) after 28 days	[127]
21	HA	MSCs	Male BALB/c mice，bilateral and unilateral kidney I/R injury model	Kidney	Improved MSC localization to injured kidneys Reduced urinary NGAL compared to untreated controls Improved renal outcomes: reduced fibrosis and improved GFR	[128]
22	Kidney extracellular matrix	ad-MSCs	Sprague-Dawley rats, kidney I/R injury model	Kidney	Reduced oxidative stress and apoptosis in renal tissue Promoted cell proliferation Reduced tubular necrosis, fibrosis, and inflammation, leading to enhanced renal recovery	[129]
23	Fmoc-FF，Fmoc-RGD	SNAP and WJ-MSCs	Male BALB/c mice， kidney I/R injury model	Kidney	Supported WJ-MSCs, allowing for effective cell proliferation and migration Improved the therapeutic efficiency of the WJ-MSCs Enhanced recovery of renal I/R injury1 Upregulated angiogenesis-related gene expression (VEGF and eNOS) while reducing iNOS and oxidative stress biomarkers	[130]
ECM-mimicking hydrogels						
24	GelMA	MSC-Exo	Male wild-type C57/BL6J mice ，middle cerebral artery occlusion model for cerebral I/R injury	\	The 3D-cultured MSC-derived exosomes significantly reduced the neuroinflammatory response and promoted angiogenesis MSC-Exo improved the prognosis by decreasing infarct volume, improving neurological function, and enhancing blood-brain barrier penetration The exosomes were able to cross the blood-brain barrier and target cerebral ischemia areas, showing better neuroprotective properties than exosomes from traditional 2D cell cultures	[131]
25	RADA16-I	RADA16-I	Sprague–Dawley rats，middle cerebral artery occlusion model	Brain	Promoted neural differentiation of neural stem cells	[132]
26	Type I collagen	Type I collagen	CD1 mice ，healthy model Lewis rats ，kidney I/R injury model	Kidney	Promoted significant regeneration of glomerular and tubular structures Improved renal function Reduced systemic inflammation	[133]
27	Hepatic acellular matrix	Hepatic acellular matrix	Sprague-Dawley rats, liver I/R injury model	Liver	Improved hepatic function Reduced levels of inflammatory markers	[134]

(*continued on next page*)

Table 1 (*continued*)

Code	Polymers	Effective substances	Animal model	Injection site	Therapeutical effects	Ref.
					Decreased liver damage as seen through biochemical and histological analyses Promoted macrophage polarization from the pro-inflammatory M1 to the anti-inflammatory M2 phenotype Reduced TLR4 and NF-κB signaling, contributing to hepatoprotective effects	

Abbr: NIPAAm, N-isopropylacrylamide; VP, vinylpyrrolidone; MAPLA, methacrylate-polylactide; MATEMPO, methacrylate-TEMPO; 4-amino-TEMPO, 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl; ROS, reactive oxygen species; SNAP, S-nitroso-N-acetylpenicillamine; NO, nitric oxide; Fmoc-FF, N-(9-fluorenylmethoxycarbonyl)-L-diphenylalanine; IL-6, interleukin-6; TNF-α, tumor necrosis factor alpha; LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening; I/R, ischemia/reperfusion; TLR4, toll-like receptor 4; EGCG, epigallocatechin gallate; EDA, edaravone; P407, poloxamer 407; PEG, poly(ethylene glycol); bFGF, basic fibroblast growth factor; MAL, maleimide; NETosis, neutrophil extracellular trap formation; HGF, hepatocyte growth factor; VEGF, vascular endothelial growth factor; HMGB1, high mobility group box 1; PFA, paraformaldehyde; PNBA, 4-peroxy nitrobenzoic acid; NPs, nanoparticles; EVs, extracellular vesicles; MSC, mesenchymal stem cells; ad-MSCs, adipose-derived mesenchymal stem cells; ELP, elastin-like polypeptide; Exo, exosomes; AT, aniline tetramer; EHBPE, a hyperbranched epoxy macromer; HA-SH , thiolated hyaluronic acid; CP05 , a peptide sequence; H_2O_2, hydrogen peroxide; NGAL, neutrophil gelatinase-associated lipocalin; HA, hyaluronic acid; Ad, adamantane; Cd, cyclodextrin; GFR, glomerular filtration rate; WJ-MSCs, Wharton's Jelly mesenchymal stem cells; eNOS, endothelial nitric oxide synthase; iNOS, inducible nitric oxide synthase; 3D, three-dimensional; RADA16-I, a synthetic peptide; GelMA, gelatin methacryloyl.

hydrogel formulated with Fmoc-diphenylalanine (Fmoc-FF) as the polymer, delivering appropriate dosage of the NO-releasing donor S-nitroso-N-acetylpenicillamine (SNAP) [111]. Upon injection into the renal parenchyma of I/R mice, the hydrogel system inhibited the endothelial nitric oxide synthase (eNOS) expression and ROS production, alleviating oxidative stress and improving renal function. While NO is a crucial protective gas molecule, excessive ROS reacting with NO results in the formation of the strong oxidant peroxynitrite ($ONOO^-$). This causes the oxidation of thiols and nitration of tyrosine residues, resulting in structural and functional cellular damage [146,147]. Therefore, the combined application of NO donors and antioxidants presents a more viable approach. Hao et al. utilized boronic ester groups, which effectively and specifically cleave under ROS stimulation, to couple with azido-modified diazodicarboxylate, synthesizing a small molecule nitric oxide donor (B-NO) [112]. The donor was subsequently grafted onto the side chains of natural chitosan via click chemistry, creating a CS-B-NO hydrogel(Fig. 2C). In myocardial I/R mouse models, this hydrogel with dual functions of scavenging ROS and releasing NO, thus restrained oxidative stress and inflammatory responses by activating the Nrf2 signaling pathway as well as inhibiting the NF-κB signaling pathway, eventually reducing the myocardial infarction size and improving cardiac function.

Curcumin, a polyphenolic compound extracted from turmeric rhizomes, exhibits multiple pharmacological actions including anti-inflammatory, anti-fibrotic, anti-tumor, antioxidant, anti-apoptotic and cardiovascular protective effects [148]. Liao et al. engineered an SAP hydrogel system based on the polymer RADA16-I and incorporated curcumin [113]. It reduced the generation of ROS as well as suppressed inflammation reactions in myocardial IRI by activating the JAK2/STAT3 signaling pathway. This strategy effectively overcame the challenges associated with curcumin's poor water solubility and rapid degradation, expanding its potential for clinical applications. Furthermore, Deng et al. coupled hydrophobic curcumin with related peptide derivatives to fabricate a novel SAP hydrogel composed of Nap-Cur-NO conjugates [114]. The dual delivery of Curcumin and NO donors not only decreased ROS levels but also significantly inhibited autophagy and apoptosis in cardiac cells during I/R.

As previously discussed, damage-associated molecular patterns (DAMPs) exacerbate the activation of inflammatory mediators, affecting the migration and chemotaxis of leukocytes. The attracted leukocytes further augment ROS production by expressing NADPH oxidase, perpetuating a vicious cycle with inflammation [149]. Therefore, toll-like receptor 4(TLR4), which transmits signals downstream after binding with DAMPs, is identified as a critical target for connecting ROS production with inflammation [150]. Inhibiting ROS production and TLR4 activation offer a promising strategy to break this detrimental cycle. Liao et al. extracted the anti-inflammatory compound rhein from rhubarb and the ROS-scavenging agent epigallocatechin-3-gallate (EGCG) from green tea to develop an injectable EGCG@Rh-gel hydrogel system [115]. EGCG was bonded with the rhubarb peptide hydrogel through π-π stacking and hydrogen, addressing the challenges of poor water solubility and the suboptimal stability of the drugs (Fig. 2D). In myocardial I/R mouse models, EGCG@Rh-gel hydrogel system not only scavenged ROS but also inhibited the activation of the TLR4/NF-κB pathway, thereby improving the prognosis of the damaged myocardium.

Benefiting from the excellent shear-thinning properties of hydrogels, localized injection is the most common and effective application method [151]. Additionally, in situ forming hydrogels, which are injected as a liquid precursor, undergo a sol-to-gel transition at the target site driven by physical interactions and chemical covalent bonding [152]. Teng et al. developed a temperature-responsive PEG-based hydrogel system [116]. This hydrogel formed in the nasal cavity and contained edaravone (EDA) for ROS scavenging and borneol to facilitate drug passage through the blood-brain barrier, specifically targeting cerebral IRI (Fig. 2E). In transient middle cerebral artery occlusion/reperfusion (tMCAO/R) mouse models, the injected solution rapidly transitioned to a gel at nasal temperature and maintained normal physiological state within the nasal cavity. This facilitated sustained drug release, effectively reducing cerebral infarction areas. The approach overcame the drawbacks of administering conventional concentrated solutions of EDA and borneol intravenously, as well as prolonged the retention time of drugs in the nasal cavity.

4.2. Hydrogel depots for biomacromolecules delivery

Biomacromolecules, known for their diverse biological activities and functions, are central to both experimental research and clinical applications in treating IRI. Agents based on nucleic acids, peptides, and proteins offer anti-inflammatory functions, cellular protection, and tissue repair at multiple levels, significantly improving IRI prognosis [153]. Previous studies have utilized hydrogels for localized treatment of IRI with gas donors. Building on this, Zhang et al. prepared a compound to decrease the toxicity of typical H_2S donors, as well as enhance their solubility. They conjugated 4-aminophenylmethanethiol with human hair keratin (KAT) to fabricate a biomacromolecule H_2S donor. When loaded in Pluronic F-127 hydrogel, the conjugate effectively enhanced the stability and periodicity of H_2S release [117]. In rat myocardial I/R models, the hydrogel system significantly reduced pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α, consequently decreasing myocardial infarction size and improving cardiac fibrosis after four weeks.

GFs, pivotal in regulating cell proliferation, migration, and

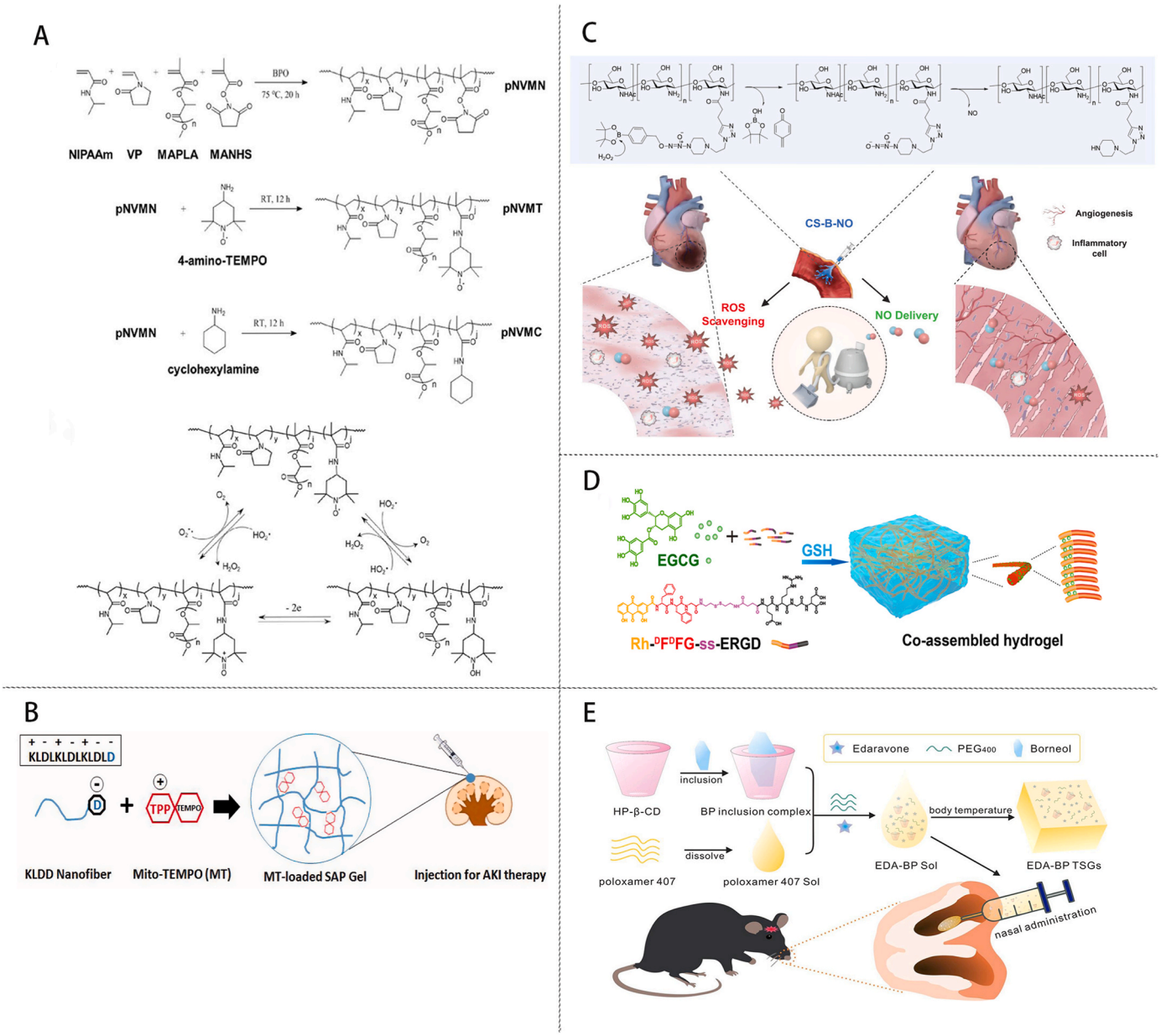

Fig. 2. Schematic illustration of hydrogel depots for small molecule delivery. (A) Synthesis process and ROS scavenging function of pNVMT, the copolymer of the TEMPO hydrogel system, and its mimic pNVMC for controlled experiment [109]. (Adapted with permission; Copyright © 2018 Elsevier). (B) Preparation of the hydrogel for MT delivery [110]. (CC license; Copyright © 2018 by the authors). (C) Fabrication of the CS-B-NO hydrogel and its ability for ROS scavenging as well as NO delivering [112]. (CC license; Copyright © 2022 by the authors). (D) Synthesis of EGCG@Rh-gel hydrogel system. (Adapted with permission; Copyright © 2022 Elsevier) [115]. (E) Schematic illustration of PEG-based hydrogel systems delivery EDA and borneol through nasal administration [116]. (Adapted with permission; Copyright © 2024 Elsevier). NIPAAm, N-isopropylacrylamide; VP, vinylpyrrolidone; MAPLA, methacrylate-polylactide; MATEMPO, methacrylate-TEMPO; 4-amino--TEMPO, 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl; MT, Mito-TEMPO; ROS, reactive oxygen species; EGCG, epigallocatechin gallate; EDA, edaravone; PEG, poly (ethylene glycol).

differentiation, demonstrate considerable potential in treating IRI [154, 155]. Remarkably, members of the FGF family play a critical role in promoting cell proliferation and differentiation, processes indispensable for tissue repair. However, their effectiveness is often limited by short in vivo half-lives [156]. To overcome this, Tabata et al. developed acidic gelatin hydrogel microspheres (AGHMs) that are loaded with basic Fibroblast Growth Factor (bFGF) [157]. Owing to their gradual biodegradation, these microspheres facilitated the slow and sustained release of bFGF. Subsequent studies by Wang et al. indicated that AGHMs enhanced the survival area and angiogenesis in skin flap I/R models, demonstrating that bFGF mitigates IRI by enhancing VEGF and Transforming Growth Factor beta (TGF-β) levels [118]. It is worth noting that PEG hydrogels are favored in current therapeutic strategies due to their superior substance transport and release capabilities [158, 159]. Salimath et al. engineered a novel PEG hydrogel by incorporating RGD sequences for enhanced tissue adhesion and VPM sequences as protease-degradable crosslinkers (Fig. 3A) [119]. In myocardial I/R rat models, the hydrogel system, degradable by matrix metalloproteinases (MMPs), facilitated the sustained release of Hepatocyte Growth Factor (HGF) and VEGF, promoting angiogenesis and progenitor cell migration, ultimately significantly reducing myocardial fibrosis. The synergistic use of both GFs markedly improved therapeutic outcomes compared to single factor treatments. Additionally, Sayegh et al. utilized PEG hydrogels to deliver the enzymes CD39 and CD73, which effectively

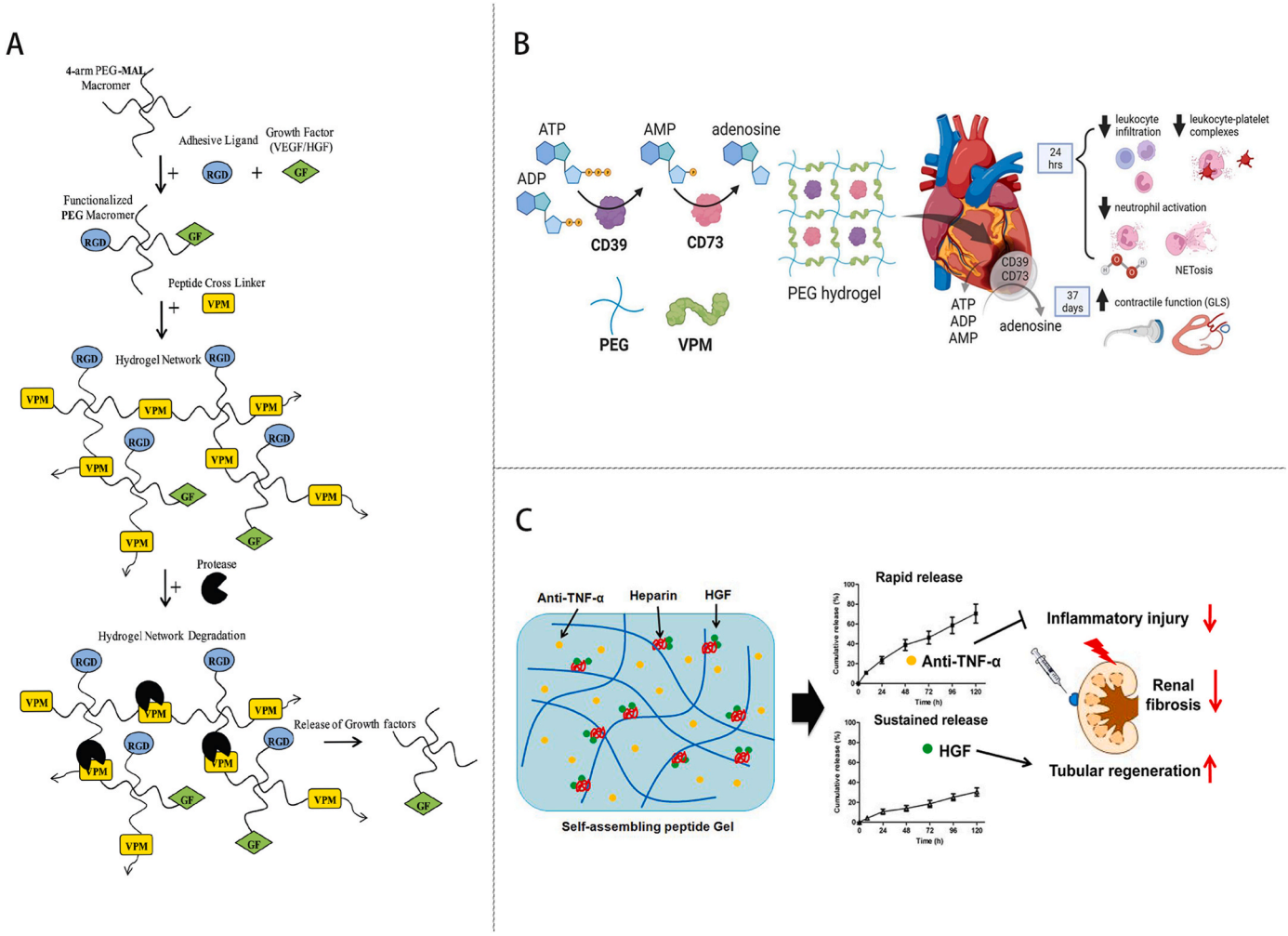

Fig. 3. Schematic illustration of hydrogel depots for biomacromolecule delivery. (A) Synthesis of pre-functionalized PEG hydrogel and release of GFs [119]. (CC license; Copyright © 2018 by the authors). (B) Preparation of PEG hydrogel delivering CD39 and CD73 to converted ATP and ADP into adenosine [120]. (Adapted with permission; Copyright © 2023 Elsevier). (C) Schematic illustration of KLD2R/Hep hydrogel system and its alibility for faster release of anti-TNF-α and sustained release of HGF [121]. (Adapted with permission; Copyright © 2020 Elsevier). PEG-MAL, poly(ethylene glycol) maleimide; GF, growth factor; VEGF, vascular endothelial growth factor; RGD, a peptide sequence used for hydrogel adhesion; VPM, a peptide sequence used for hydrogel cross-linking; ATP, adenosine triphosphate; ADP, adenosine diphosphate; AMP, adenosine monophosphate; HGF - hepatocyte growth factor; TNF-α - tumor necrosis factor alpha.

converted ATP and Adenosine Diphosphate (ADP) into adenosine (Fig. 3B), reducing leukocyte activation, decreasing inflammatory factor release, and enhancing cellular resilience to oxidative stress from I/R [120].

Given the complexity of the I/R process, the body's response to disease progression is dynamic. Therefore, designing appropriate drug delivery systems is crucial to manage the various stages of IRI. Liu et al. developed a KLD2R/Hep hydrogel capable of sequentially releasing anti-TNF-α and hepatocyte growth factor (HGF) [121]. Leveraging the affinity between heparin and HGF, they achieved faster release of anti-TNF-α and sustained release of HGF (Fig. 3C). The hydrogel system effectively reduced apoptosis of renal tubular cells in I/R phase, while also promoting proliferation and differentiation of tubular cells in the repair phase.

In addition to GFs, hydrogels enable targeted delivery of IL-10 to the subcapsular region of an injured kidney. Soranno et al. developed an injectable SAP hydrogel composed of hyaluronic acid (HA) modified with adamantane (Ad) and cyclodextrin (Cd), connected through host-guest interactions [160]. The anti-inflammatory function of IL-10 plays a crucial role in mitigating the infiltration of macrophages, which in turn reduces reducing the progression of acute kidney injury caused by ischemia [161].

Advancements in IRI research have led to the identification of key genetic mechanisms, with therapeutics based on nucleic acids that regulate gene expression offering new treatment perspectives [162]. The microRNA (miRNA) Mir-199a-3p is particularly promising, targeting genes such as HOMER1 and CLIC5 to promote cardiac cell proliferation and cardiovascular regeneration [163]. Further research has revealed that Mir-199a-3p activates the AKT and ERK signaling pathways while suppressing the mTOR pathway, contributing to decreased cell apoptosis and autophagy [164,165]. Although effective, current miRNA carriers like viral vectors, liposomes, and lipid nanoparticles face challenges related to safety concerns, high production costs, and variable delivery efficiency [166,167]. Addressing these issues, Ji et al. developed a photothermal nanoparticle (BTN) and Mir-199a-3p mimic-infused PFA (fructose-containing polymer)/PNBA (BOB-containing polymer) hydrogel [122]. This photo-responsive hydrogel allowed for controlled, non-invasive miRNA release triggered by 1064 nm light exposure, effectively reducing the expression of ferroptosis-related genes such as NOX4, LOX, and P53. In myocardial I/R rat models, this treatment significantly reduced myocardial infarction size and improved survival rates, showcasing the unique advantages of stimulus-responsive, particularly photo-responsive, hydrogels. Compared to thermosensitive hydrogels, photo-responsive hydrogels offered more precise control

over drug release timing and location through external light stimuli, including ultraviolet and near-infrared light [168]. These innovative therapeutic strategies underscore the crucial role of modern technology in addressing the complex challenges of IRI, enabling precise agent delivery and cellular interventions to provide patients with more effective and convenient treatment options.

4.3. Hydrogel depots for NPs delivery

Recently, NPs have gained widespread applications in biomedicine. Polymeric NPs, especially share key attributes with hydrogels, such as biocompatibility, biodegradability, and environmental responsiveness [169,170]. They can be surface-modified for targeted delivery, which minimizes drug toxicity associated with systemic distribution [171]. However, the release kinetics between NPs and drugs often exhibit instability, particularly under biological stimuli such as pH fluctuations or enzymatic activity, which can lead to burst release in NPs drug delivery systems [172,173]. Moreover, the small diameter of NPs makes them more susceptible to hepatic and renal clearance, shortening their circulation time in the body [174,175]. To overcome these limitations, incorporating NPs into hydrogels to form a hybrid system has proven to be an effective strategy. This approach not only prevents NPs degradation and aggregation but also allows the 3D structure of hydrogels to extend their local retention time, thereby enhancing therapeutic precision. Notably, the inclusion of NPs within the hydrogel can enhance the mechanical properties of the entire system. Acting as fillers, NPs can establish physical and chemical cross-links with polymer chains, resulting in hybrid hydrogels that possess superior mechanical strength and elasticity [176]. Furthermore, the introduction of NPs enhances the hydrogel's stimuli-responsive behavior, enabling precise drug release and demonstrating significant potential in the treatment of IRI [177].

The described hydrogel system, which directly encapsulates naked Mir-199a-3p, relies on the physicochemical interactions between the RNA and the hydrogel matrix for its capacity and stability [122]. In contrast, integrating NPs into the hydrogel circumvents the need for chemical modifications to the hydrogel polymers, as their loading capacity is determined by the interactions between the NPs and the hydrogel [178]. Therefore, NPs-hydrogel systems demonstrate enhanced application potential over bare RNA hydrogel systems. Yang et al. fabricated polymeric NPs composed of a poly(9,

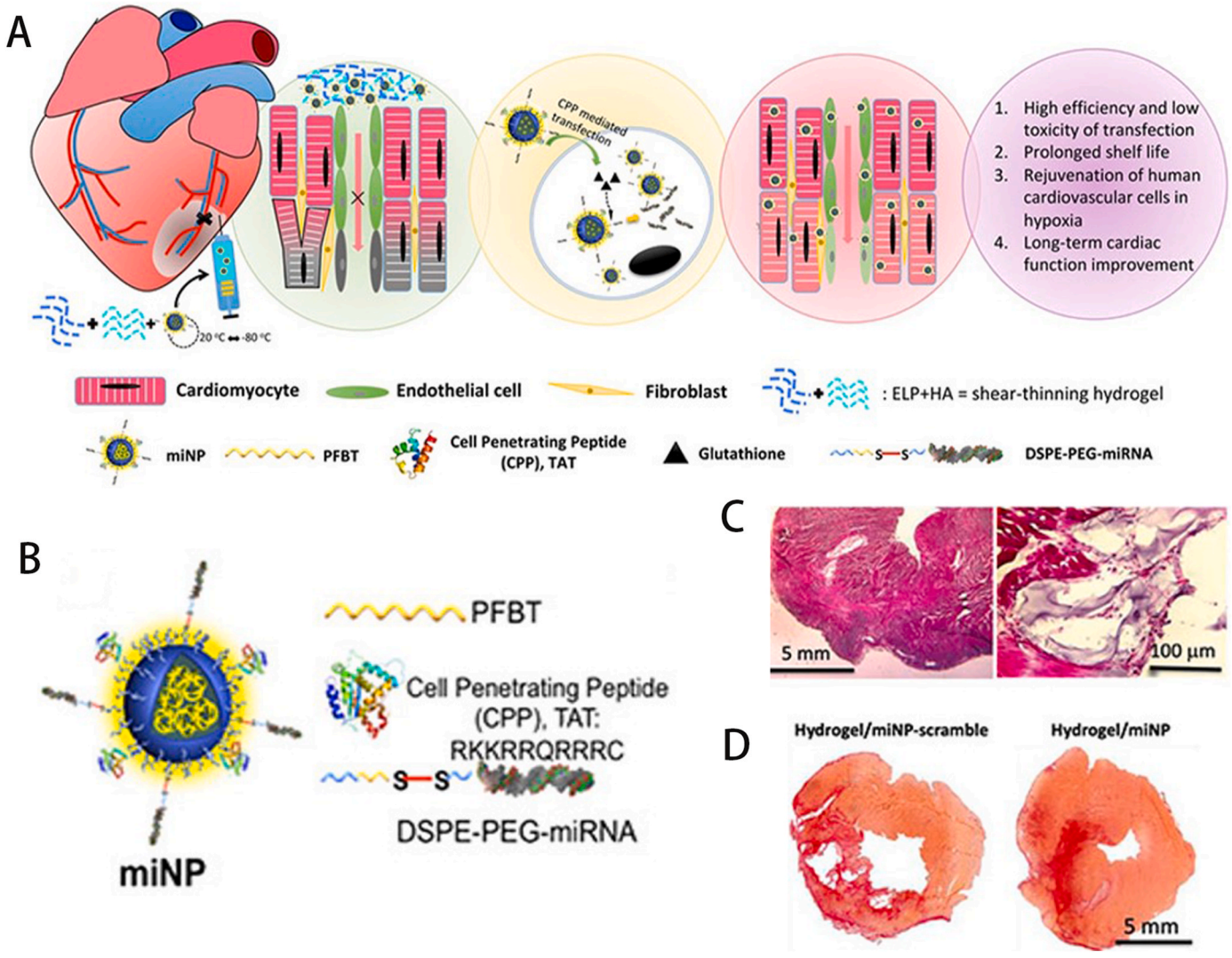

Fig. 4. Schematic illustration of hydrogel Depots for NPs Delivery [123]. (Adapted with permission; Copyright © 2019 American Chemical Society) (A) NPs-hydrogel systems delivering miNPs for restoring infarcted myocardium (B)The structure of the miNP (C) Images of H&E stained left ventricular tissue section with injection of NPs-hydrogel systems at 1 month. A stable engraftment of hydrogel was observed within the myocardium, and no immune response was observed. (D) Images of fibrosis evaluated by Picro Sirius Red staining. The NPs-hydrogel system effectively improved the myocardial fibrosis compared to the hydrogel/miNP-scramble. ELP, elastin-like polypeptide; PFBT, poly(9,9-dioctylfluorene-alt-benzothiadiazole); TAT, a peptide sequence; CPP, cell penetrating peptide; HA, hyaluronic acid. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

9-dioctylfluorene-alt-benzothiadiazole) (PFBT) core, a PEG derivative shell and TAT sequence-miRNA conjugates on the surface, as Mir-199a-3p carriers (miNPs), and encapsulated these within shear-thinning hydrogels to treat myocardial IRI (Fig. 4) [123]. This fluorescent core facilitated in vivo tracking, and the TAT amino acid sequence promoted the uptake efficiency. Encapsulating NPs into shear-thinning hydrogels, these composite materials effectively overcame the low retention rates of drugs associated with cardiac contractions. Through intramyocardial injection, it significantly enhanced the ejection fraction of the I/R hearts in rat models and reduced the infarct size. In conclusion, NPs-hydrogel systems are not only utilized for RNA delivery but also for delivering other therapeutic agents [179]. As advanced multifunctional materials, they exhibit synergistic properties that surpass their individual components, underscoring the need for further exploration to optimize their clinical translation.

4.4. Hydrogel depots for EVs delivery

EVs are nanoscale lipid vesicles secreted by cells, inherently equipped with biomolecules such as nucleic acids and proteins, which

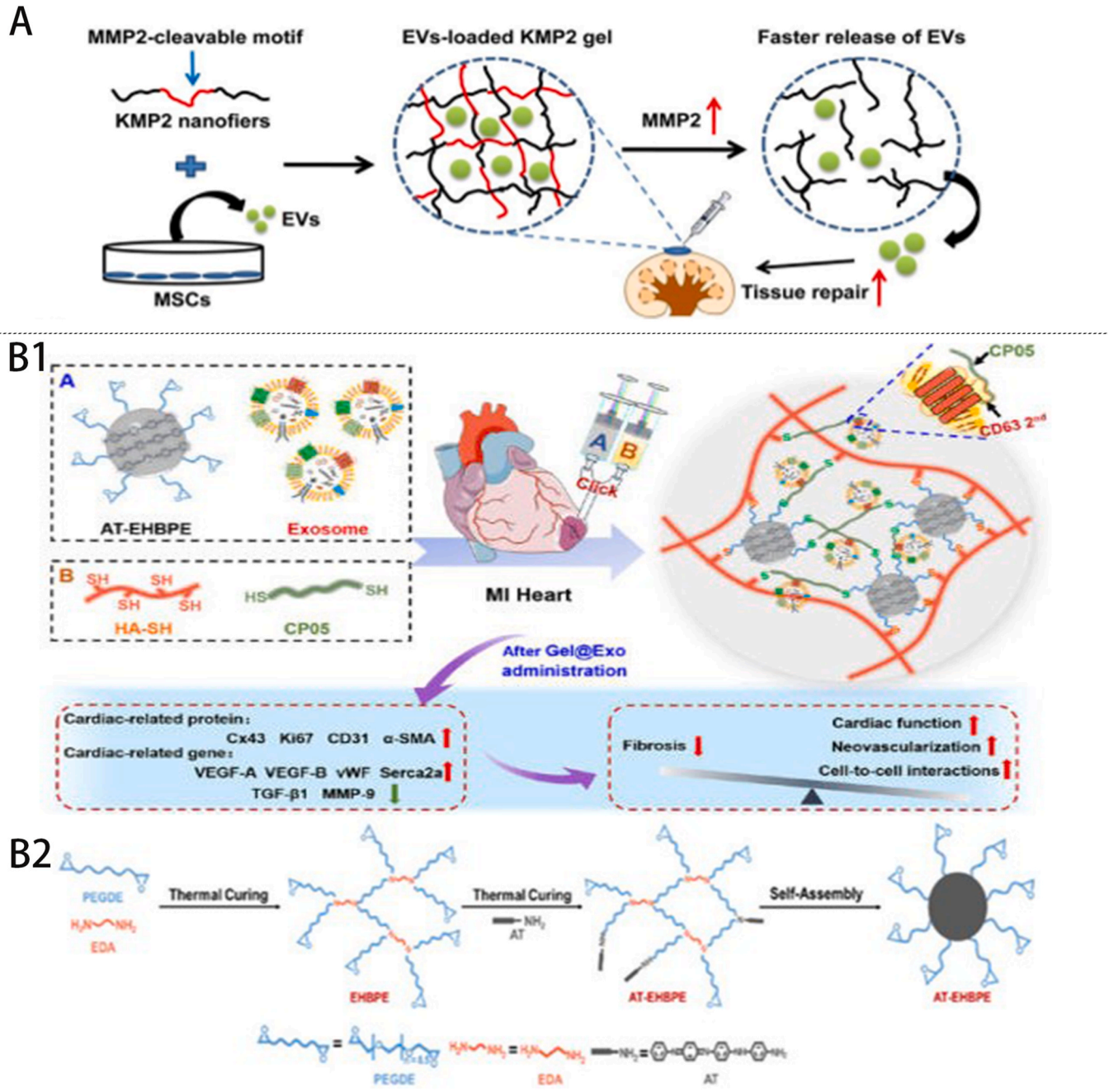

Fig. 5. Schematic illustration of hydrogel Depots for EVs Delivery (A) Fabrication of MMP2-senstive KMP2 hydrogel to deliver MSC-EVs for enhancing tissue repair [124]. (Adapted with permission; Copyright © 2020 Elsevier). (B) Gel@Exo systems for myocardial IRI treatment [125]. (Adapted with permission; Copyright © 2019 American Chemical Society) (B1). Schematic illustration of the Gel@Exo restoring cardiac functions after myocardial I/R and synthesis through mixing precursor solution A and B. (B2) The synthesis of AT-EHBPE. MMP2 , matrix metalloproteinase-2; KMP2 , a peptide sequence; EVs , extracellular vesicles; MSCs , mesenchymal stem cells; AT, aniline tetramer; EHBPE, a hyperbranched epoxy macromer; HA-SH , thiolated hyaluronic acid; CP05 , a peptide sequence; MI , myocardial infarction; Cx43 , connexin 43; Ki67 , a marker of cell proliferation; α-SMA , alpha-smooth muscle actin; VEGF , vascular endothelial growth factor; vWF , von Willebrand factor; Serca2a , sarcoplasmic reticulum Ca^{2+}-ATPase 2a; TGF-β1 , transforming growth factor beta 1.

facilitate intercellular communication [180]. Depending on their size, formation process, and source cells, EVs are classified into categories including Exo, microparticles, and apoptotic bodies [181]. They transfer proteins, lipids, nucleic acids, and other bioactive substances, playing roles in modulating inflammation, enhancing cell repair, and fostering tissue regeneration [182–184]. As natural secretions from autologous or allogeneic cells, they exhibit excellent biocompatibility and minimal immunogenicity, showcasing significant therapeutic potential. The current research and clinical applications engage multiple biological pathways including anti-inflammatory, immunoregulatory, and pro-angiogenic activities [185–188]. However, their short half-life and rapid clearance from biological systems often limit their clinical applications [189–191].

Hydrogels offer protection for EVs against physical and biochemical degradation by encapsulating them, as well as facilitating controlled and localized release, consequently enhancing the efficacy and duration of treatments beyond standard intravenous. Zhou et al. developed an SAP hydrogel composed of KMP2, sensitive to MMP2, which was injected into the renal capsule for prolonged release of MSC-derived EVs (Fig. 5A) [124]. In renal I/R rat models, it effectively reduced tubular cell apoptosis, promoted endothelial cell proliferation, and angiogenesis, subsequently decreasing chronic renal fibrosis. Zou et al. utilized aniline tetramer (AT) grafted onto a hyperbranched epoxy macromer (EHBPE) with MSCs-derived thiolated Exo, thiolated hyaluronic acid (HA-SH) and CP05 peptides, fabricating a Gel@Exo system through a click chemistry (Fig. 5B) [125]. This system demonstrated shear-thinning injectability, controlled gelation kinetics, dynamic stability during heartbeat, outstanding cytocompatibility, and especially conductivity compatible with natural cardiac tissue. The inclusion of CP05 peptides anchored the Exo, addressing low retention issues and extending their retention time, thus effectively enhancing vascular regeneration and improving cardiac function. These strategies underscore that multifunctional hydrogels can optimize local drug concentrations and bioavailability by leveraging their properties such as soft rheological behavior, in situ self-assembly, and controlled release capabilities, thereby reducing systemic side effects and pointing toward further investigative directions.

Additionally, considering the well-vascularized nasal mucosa and its rapid drug absorption capabilities, intranasal hydrogel systems have shown considerable therapeutic potential [116]. Wang et al. mixed glutamine amine derivatives with benzaldehyde to form Schiff base compounds, which then self-assembled into a hydrogel for EVs delivery [126]. Upon intranasal injection in mice undergoing myocardial I/R, this approach significantly reduced the expression of pro-inflammatory factors such as TNF-α, IL-1, and IL-6. The study further showed that EVs derived from endothelial cells reduce inflammation by lowering the neutrophil and Ly6C^{high} monocyte/macrophage levels in the bloodstream, consequently decreasing the extent of myocardial infarction following I/R.

4.5. Hydrogel scaffolds for MSCs encapsulation

Over the past few years, stem cells, especially MSCs, have been widely investigated for treating IRI. MSCs secrete multiple cytokines, including VEGF, which enhances tissue oxygenation and blood flow, thereby promoting tissue repair and regeneration [192]. They also produce anti-inflammatory cytokines like IL-10 and TGF-β, reducing the inflammatory mediators release and leukocyte infiltration [193,194]. By modulating immune responses, MSCs help decrease local and systemic inflammation. While similar to EVs in low immunogenicity, MSCs offer superior repair capabilities and the potential to differentiate directly into damaged cells and tissues, a capability that EVs do not possess. For instance, in the treatment of myocardial infarction or bone injuries, MSCs actively participate in tissue reconstruction [195,196]. However, their post-transplantation survival rate is often low due to the host microenvironment and cell migration, limiting their therapeutic effectiveness [197].

The shear-thinning properties of hydrogels facilitate MSC injection into injury sites, improving cell homing and retention. This requires careful selection and design of hydrogel vehicles to maintain cell viability. For example, Shin et al. utilized ultrapure alginate to encapsulate MSCs, which were subsequently loaded into PEG hydrogels [127]. This method of encapsulating MSCs with composite biomaterials enhanced their retention rate, which significantly improved the long-term prognosis of hearts affected by I/R. They further found that MSCs modulate hydrogen peroxide production and innate immune cell infiltration by converting AMP to adenosine through CD73, thus improving cardiac function. Natural hydrogels, such as those prepared from modified hyaluronic acids (Cd-HA and Ad-HA) via host-guest interactions, show more excellent compatibility with MSCs compared to synthetic hydrogels. Han et al. showed their significant treatment ability in acute kidney injury by improving glomerular filtration rates and reducing renal fibrosis [128]. To enhance the retention and survival rates of transplanted MSCs, Zhou et al. fabricated a decellularized kidney extracellular matrix hydrogel (ECMH) as a biological scaffold for delivering adipose-derived MSCs (ad-MSCs) to ischemic kidneys [129]. The raw material, decellularized rat renal extracellular matrix (ECM) powder, was treated with pepsin and nucleases to remove impurities, significantly reducing its immunogenicity (Fig. 6). In rat models of renal I/R, treatment with ECMH encapsulating ad-MSCs resulted in markedly lower levels of blood urea nitrogen (BUN) and serum creatinine (SCr) compared to other treatment methods. Histological analysis of renal sections revealed a substantial decrease in TUNEL-positive cells and increased expression of proliferating cell nuclear antigen (PCNA) and CD34, highlighting the hydrogel system's profound anti-apoptotic and proliferative effects. Moreover, ECMH enhanced the activity of ad-MSCs, promoting the release of protective cytokines. Most notably, ECMH demonstrated biocompatibility by being absorbed in rabbit models over time, suggesting promising prospects for future applications in human treatments.

To enhance overall therapeutic efficacy, it is advantageous to combine MSCs with other drugs. Najafi et al. developed an SAP hydrogel composed of RGD-functionalized Fmoc-diphenylalanine (30 % Fmoc-RGD + Fmoc-FF) to co-deliver Wharton's jelly-mesenchymal stem cells (WJ-MSCs) and the NO donor, SNAP [130]. This design notably improved the retention of MSCs within the hydrogel via the RGD sequence integration. The sustained release of NO not only mitigated the inflammatory response in damaged tissues but also stimulated the proliferation of WJ-MSCs, thereby enhancing their differentiation into endothelial cells. Compared to using SNAP or WJ-MSCs alone, this synergistic combination of therapeutic agents significantly enhanced the healing effect. Future research should continue to explore various biomaterials to optimize stem cell delivery, aiming to achieve more efficacious clinical outcomes.

4.6. ECM-mimicking hydrogel

ECM is a vital biomaterial in the field of regenerative medicine, and hydrogels with structural and functional similarities to ECM have also been shown to exert therapeutic effects independently. Wang et al. successfully induced cardiac repair and regeneration in a mouse model of myocardial infarction using decellularized zebrafish cardiac ECM [198]. Their research further demonstrated that, compared to mammalian-derived ECM, zebrafish ECM, representing a lower vertebrate, exhibited superior therapeutic efficacy. This finding not only highlights the significant therapeutic potential of cross-species ECM in xenogeneic hosts but also suggests that differences in ECM composition and structure across species may contribute to variations in therapeutic outcomes.

The 3D structure of hydrogels can mimic the ECM, and beyond serving as vehicles for therapeutic agents delivery, they play a pivotal role in cell culture and tissue engineering. Hydrogels not only provide

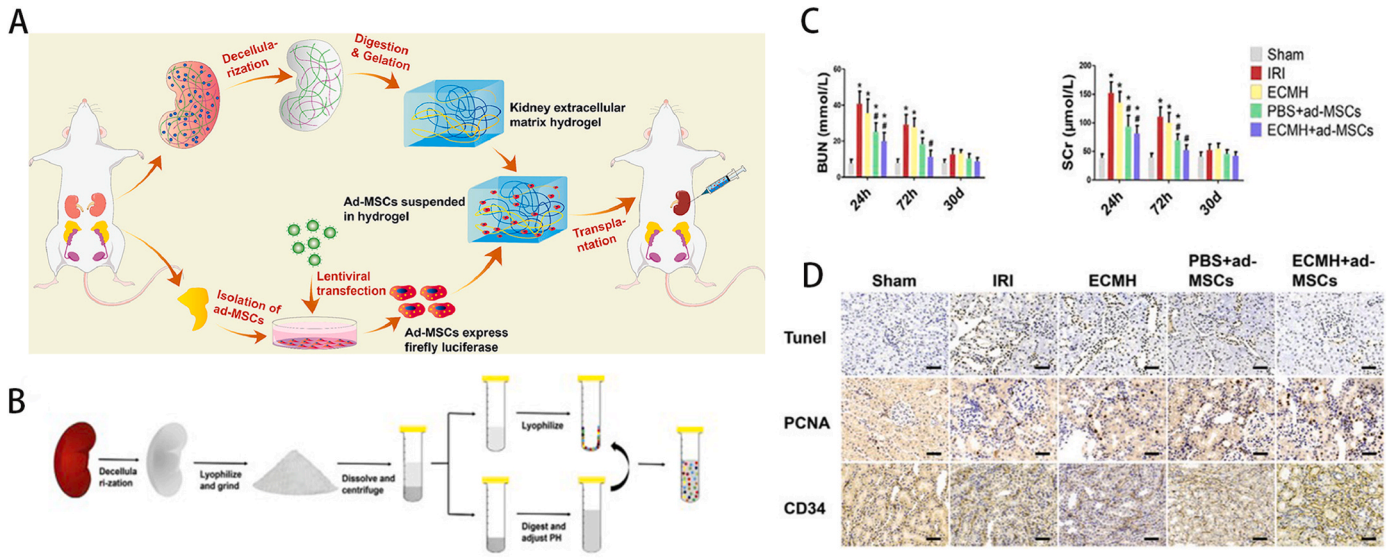

Fig. 6. Schematic illustration of ECMH as Scaffolds for MSCs encapsulation [129]. (Adapted with permission; Copyright © 2020 Elsevier). (A) Schematic illustration of the ECMH encapsulating ad-MSCs for treating renal IRI. (B) The fabrication progress of the ECMH (C) The levels of BUN and SCr at 24 h, 72 h and 30 days after reperfusion with different treatment. (D) Representative images of TUNEL, PCNA, CD34 staining in kidneys at 72 h after reperfusion with different treatment. Ad-MSCs , adipose-derived mesenchymal stem cells; ECMH , extracellular matrix hydrogel; IRI , ischemia-reperfusion injury; BUN , blood urea nitrogen; SCr , serum creatinine; PCNA , proliferating cell nuclear antigen.

cells with support that simulates the in vivo environment, but different types of hydrogels also regulate cell proliferation, differentiation, and migration in various ways [199]. In the field of neural tissue engineering, hydrogels have shown great potential. Han et al.'s study demonstrated that gelatin methacryloyl (GelMA) hydrogels not only offer an ideal 3D culture environment for MSCs but also significantly enhance the production of MSC-derived Exo [131]. Notably, compared to the conventional two-dimensional culture in dishes, 3D-cultured exosomes in GelMA hydrogels exhibited superior neuroprotective effects in treating brain IRI. Additionally, RADA16-I, a short peptide with a nanofiber structure, self-assembles into hydrogels that effectively support neuron growth and axon extension [200]. Liu et al. successfully utilized RADA16-I SAP hydrogels to induce the differentiation of neural stem cells (NSCs) in vitro, and when combined with cerebral dopamine neurotrophic factor (CDNF), they reduced the infarct size in rats with middle cerebral artery occlusion [132]. This process is regulated by the ERK1/2 and STAT3 signaling pathways, indicating that hydrogels not only provide structural support for cell growth but also promote neural regeneration by modulating signaling pathways.

Type I collagen, as one of the main components of the ECM, particularly in connective tissues, plays a critical role in maintaining tissue structure, providing mechanical support, and regulating cellular behavior [201]. Lee et al. utilized natural hydrogels prepared from type I collagen to successfully promote kidney tissue regeneration by recruiting renal stem cells and progenitor cells. The three-dimensional network structure of these natural hydrogels partially mimicked the ECM, creating an ideal microenvironment for cell adhesion and proliferation [133].

In recent years, significant progress has been made in the development of dECM hydrogels in the field of regenerative medicine. Researchers have utilized decellularization techniques to remove cellular components, creating 3D hydrogel scaffolds that closely mimic the natural microenvironment while retaining key bioactive substances such as growth factors and signaling molecules, significantly enhancing their functionality in tissue repair and regeneration [202]. Li et al.'s research further revealed the potential of dECM hydrogels to promote tissue repair by regulating immune responses [134]. Their study demonstrated that hydrogels derived from decellularized liver matrix successfully induced the polarization of macrophages from the pro-inflammatory M1 type to the pro-reparative M2 type through the TLR4/NF-κB signaling pathway. This process not only suppressed the inflammatory response in a mouse model of liver ischemia-reperfusion injury but also promoted hepatocyte proliferation. The immunomodulatory properties of dECM hydrogels show great potential for clinical applications, especially in chronic injury and disease conditions, where inflammation is often a key factor in perpetuating tissue damage [203]. By inducing the resolution of inflammation and promoting the accumulation of reparative macrophages, decellularized hydrogels can simultaneously inhibit chronic inflammation and accelerate tissue regeneration.

Although hydrogels hold great promise for applications in tissue engineering and regenerative medicine, their specific mechanisms of tissue repair in vivo require further investigation. While current studies have demonstrated the role of hydrogels in promoting cell proliferation, differentiation, migration, and survival, the interactions between these processes and the complex physiological environment of the body remain poorly understood. Thus, further research is needed to explore the mechanisms underlying hydrogel function, to optimize their design for more effective clinical applications. Such investigations will advance the broader biomedical application of hydrogels, particularly in simultaneously inhibiting IRI and promoting tissue repair and regeneration.

5. Summary and prospects

5.1. Summary

IRI, a prevalent clinical issue, involves pathophysiological processes including oxidative stress, calcium overload, excessive inflammatory activation and mitochondrial dysfunction. Present systemic pharmacological treatments typically suffer from short duration, poor targeting of the action site, and severe side effects. Utilizing hydrogels to treat IRI mainly involves their role as vehicles for material delivery, enhancing treatment efficacy and reducing systemic side effects by controlling the release location and rate of therapeutic agents. Additionally, hydrogels play a vital role in tissue engineering and regenerative medicine. They provide a 3D natural biological environment for cells, serving as scaffolds to enhance the bioactivity of encapsulated cells, consequently supporting the repair and regeneration of damaged tissues [204].

This article reviews methods of treating IRI based on hydrogels, concentrating on the therapeutic targets for the pathogenesis of IRI development. According to the diverse therapeutic substances, hydrogel systems are categorized into depots delivering therapeutic agents, scaffolds encapsulating MSCs, and self-functional hydrogels that act based on their own intrinsic properties of mimicking the ECM. This classification allows for a detailed analysis of the advantages of various hydrogel systems and their specific applications in IRI treatment.

In conclusion, by refining the classification of hydrogel systems, this review provides a new perspective for evaluating and demonstrating the potential of hydrogels in IRI treatment, aiding readers in comprehensively appreciating their diverse applications and significance in IRI treatment.

5.2. Future prospects

Despite the numerous advantages of hydrogels in treating IRI, clinical translation remains challenging. Future studies need to delve into the following areas.

5.2.1. Explore fundamental mechanisms

The application of hydrogels in IRI treatment is still in the preliminary exploration stage. Generally, by simply encapsulating drugs, bioactive molecules and cells in hydrogels, scholars employ the controlled delivery properties and biocompatibility of hydrogel systems to enhance therapeutic efficacy. Unfortunately, the effects of various polymer hydrogels themselves in IRI are not yet clear. Therefore, it is necessary to further investigate the interactions between hydrogels, therapeutic agents, and damaged tissues. It's a priority to clarify the specific role of hydrogels in regulating cell behavior and repairing tissues, which will provide a theoretical basis for treating IRI.

5.2.2. Develop novel materials

Natural hydrogels ensure excellent biocompatibility, yet their structural limitations restrict modifications of hydrogel systems. Synthetic hydrogels may compromise safety and exhibit matrix heterogeneity. Thus, developing novel hydrogel materials is crucial. Integrating natural and synthetic polymers, along with incorporating microstructures and NPs, can result in hybrid hydrogels [205,206]. These hydrogels balance biocompatibility with mechanical strength, and represent a focal point of current research. And interpenetrating polymer network (IPN) hydrogels composed of two or more polymer networks offer enhanced mechanical strength and stability [207]. These both demonstrate promising applications in biomedicine. Selecting materials tailored to different injury sites improves therapeutic efficacy, such as increasing the conductivity of hydrogels for treating myocardial IRI and incorporating specific functional groups like RGD to improve adhesion to tissues [125,130]. The advancement of 3D printing has brought innovation to the hydrogel domain, enabling researchers to precisely control hydrogel network porosity and pore size via computer-aided design (CAD) [208]. Moreover, future hydrogels employing stimulus-responsive and shape-memory materials for 4D printing hold boundless potential in biomedical engineering [209]. However, 3D and further advanced 4D printed hydrogels are limited by technological and ethical challenges, requiring additional development to meet clinical needs [210].

5.2.3. Optimize treatment strategies

Reflecting on the time-dependence of IRI progression, distinct therapeutic measures should be administered at different stages of the disease. Hydrogel systems should be utilized prophylactically before the onset of localized ischemia to suppress the activation of related inflammatory factors. Monitor the physiological changes during the ischemic period to optimize the medication plan for early intervention. In the early phase of reperfusion, capture the critical therapeutic window to reduce the generation of ROS and suppress related inflammatory responses. Following prolonged reperfusion, prioritize promoting tissue repair and reducing fibrosis. These approaches effectively slow the progression of IRI as well as enhance its prognosis. Therefore, we need to leverage the properties between various hydrogels and diverse therapeutic substances, and judiciously develop hydrogel systems that sequentially release appropriate agents in different phases of I/R. Additionally, it is effective to use combined drug therapy. To be specific, strategic drug combinations enhance treatment efficacy by synergizing effects and reducing the side effects of individual drugs [211].

5.2.4. Advance clinical translation

Bridging the gap between laboratory research and clinical application is key to the success of hydrogel-based IRI treatments. Hydrogels are rapidly advancing in biomedical applications, with successful clinical translations in areas such as ophthalmology and wound dressings [212,213]. Additionally, multicenter clinical trials have revealed that alginate hydrogels can serve as scaffolds to reduce wall stress, thereby improving the prognosis of patients with heart failure [214]. However, in the field of IRI, most studies are still limited to small animal models, lacking advanced studies on large animals analogous to humans and more extensive clinical trials. Additionally,ultrasound-guided catheter-based hydrogel injected into deep organs, along with multi-site injections, offers a promising solution for achieving comprehensive organ treatment. This approach ensures that hydrogel system can be injected precisely into target sites, especially in complex and deep-seated organs like the heart, liver, or kidneys, where single-point delivery might be insufficient. Therefore, to advance hydrogel applications effectively, several essential steps must be taken: fortifying preclinical research and clinical trials, addressing challenges in production standardization and safety evaluations, monitoring long-term effects, and ultimately achieving clinical-grade production and storage.

These approaches further broaden the applications of hydrogels in the treatment of IRI, laying a theoretical and practical foundation for the study of multi-technique and multi-functional hydrogels.

Funding statement

This work was supported by the Health committee project of Anhui Province in China (No. AHWJ2023BAc10007).

CRediT authorship contribution statement

Weibo Wang: Writing – review & editing, Writing – original draft, Visualization, Software, Conceptualization. **Supeng Tai:** Software, Methodology. **Junyue Tao:** Supervision, Conceptualization. **Lexing Yang:** Writing – review & editing. **Xi Cheng:** Validation. **Jun Zhou:** Funding acquisition.

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.

Acknowledgements

The figure in this article, Graphical abstract, were created with BioRender software (https://biorender.com). The authors would like to express their gratitude to BioRender. Figs. 2, 3, 4, 5, 6 have been granted copyright permission by the authors themselves, Elsevier and American Chemical Society. The authors of this paper would like to express their sincere gratitude.

Abbreviation

IRI	ischemia/reperfusion injury

ECM	extracellular matrix
MSCs	mesenchymal stem cells
IRI	ischemia/reperfusion injury
ATP	adenosine triphosphate
MTP-131	mitochondria-targeted peptide-131
mPTP	mitochondrial permeability transition pore
IL-11	interleukin-11
VEGF	vascular endothelial growth factor
I/R	ischemia/reperfusion
Exo	exosomes
NO	nitric oxide
CO	carbon monoxide
H_2S	hydrogen sulfide
MSCs	mesenchymal stem cells
3D	three-dimensional
ECM	extracellular matrix
ROS	reactive oxygen species
NADPH	nicotinamide adenine dinucleotide phosphate
NADH	nicotinamide adenine dinucleotide
RADA16-I	a synthetic peptide
DAMPs	damage-associated molecular patterns
PRRs	pattern recognition receptors
RET	reverse electron transport
OMM	outer mitochondrial membrane
MSCs	mesenchymal stem cells
ECM	extracellular matrix
NPs	nanoparticles
EVs	extracellular vesicles
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
MDA	malondialdehyde
IL-1β	interleukin-1 beta
MT	mitochondrial
TPP^+	tetraphenylphosphonium
mtROS	mitochondrial reactive oxygen species
TNF-α	tumor necrosis factor alpha
ICAM-1	intercellular adhesion molecule 1
CO_2	carbon dioxide
H_2	hydrogen
Fmoc-FF	N-(9-fluorenylmethoxycarbonyl)-L-diphenylalanine
SNAP	S-nitroso-N-acetylpenicillamine
eNOS	endothelial nitric oxide synthase
$ONOO^-$	peroxynitrite
DAMPs	damage-associated molecular patterns
TLR4	toll-like receptor 4
EGCG	epigallocatechin gallate
EDA	edaravone
tMCAO/R	transient middle cerebral artery occlusion/reperfusion
KAT	keratin
GFs	growth factors
FGF	fibroblast growth factor
AGHMs	alginate gelatin hydrogel microspheres
bFGF	basic fibroblast growth factor
TGFβ	transforming growth factor beta
PEG	poly(ethylene glycol)
MMPs	matrix metalloproteinases
HGF	hepatocyte growth factor
HA	hyaluronic acid
Ad	adamantane
Cd	cyclodextrin
miRNA	microRNA
PFBT	poly(9,9-dioctylfluorene-alt-benzothiadiazole)
AT	aniline tetramer
HA-SH	thiolated hyaluronic acid
MSCs	mesenchymal stem cells
ECMH	extracellular matrix hydrogel
ad-MSCs	adipose-derived mesenchymal stem cells
BUN	blood urea nitrogen
SCr	serum creatinine
PCNA	proliferating cell nuclear antigen
WJ-MSCs	Wharton's jelly mesenchymal stem cells
GelMA	gelatin methacryloyl
NSCs	neural stem cells
CDNF	cerebral dopamine neurotrophic factor
IPN	interpenetrating network
CAD	computer-aided design
BBB	blood-brain barrier
GFB	glomerular filtration barrier
dECM	decellularized extracellular matrix
MBVs	Matrix-bound nanovesicles

Data availability

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

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