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## Cell or cell derivative-laden hydrogels for myocardial infarction therapy: from the perspective of cell types

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Myocardial infarction (MI) is a global cardiovascular disease with high mortality and morbidity. To treat acute MI, various therapeutic approaches have been developed, including cells, extracellular vesicles, and biomimetic nanoparticles. However, the clinical application of these therapies is limited due to low cell viability, inadequate targetability, and rapid elimination from cardiac sites. Injectable hydrogels, with their three-dimensional porous structure, can maintain the biomechanical stabilization of hearts and the transplantation activity of cells. However, they cannot regenerate cardiomyocytes or repair broken hearts. A better understanding of the collaborative relationship between hydrogel delivery systems and cell or cell-inspired therapy will facilitate advancing innovative therapeutic strategies against MI. Following that, from the perspective of cell types, MI progression and recent studies on using hydrogel to deliver cell or cell-derived preparations for MI treatment are discussed. Finally, current challenges and future prospects of cell or cell derivative-laden hydrogels for MI therapy are proposed.

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## 1. Introduction

According to the World Health Organization (WHO), more than 17.9 million people die each year from cardiovascular disease (CVD), and the number is steadily rising.<sup>1</sup> By 2030, the global economic burden of CVD is anticipated to reach \$104.4 billion.<sup>2</sup> Among CVD-related deaths, myocardial infarction (MI) and associated heart failure are the most common causes.<sup>3</sup> MI is triggered by the sudden narrowing or blockage of coronary arteries, which leads to a prolonged reduction or cessation of blood supply to the heart.<sup>4</sup> Myocardial cells undergo necrotic apoptosis during ischemia due to the lack of oxygen or nutrients.<sup>5</sup> The process of fibrous remodeling leads to the formation of scars, which can impede normal cardiac function and ultimately result in severe heart failure.<sup>6</sup> While current

therapeutic methods, such as prompt reperfusion, pharmacological thrombolysis, and surgical intervention, can alleviate the process of MI, they do not address the urgent challenge of regenerating and repairing myocardial tissue. This presents a significant obstacle in the field of MI therapy.<sup>7–9</sup>

Researchers have developed various cell-based MI therapeutic strategies over the years to restore cardiac tissue and reverse cardiac function.<sup>10–13</sup> These strategies have evolved from the initial cell therapy to extracellular vesicles (EVs). (1) Cell therapy. Source cells include mesenchymal stem cells (MSCs), endothelial progenitor cells (EPCs), and cardiac-derived stem cells.<sup>14,15</sup> Mechanisms involved in this therapy are pro-angiogenic factor release and cardiomyocyte differentiation.<sup>16</sup> (2) Cell-derived extracellular vesicle therapy (e.g., MSCs, EPCs, and macrophage-derived exosomes).<sup>17,18</sup> Mechanisms include reduced monocyte invasion and macrophage polarization control.<sup>19,20</sup> However, the clinical application of cell or cell-inspired therapy is hindered by low cell survival rates, inefficient heart targeting, and rapid clearance from cardiac sites.<sup>21,22</sup>

Encapsulating cell or cell-derived preparations in hydrogels or patches is a promising resolution.<sup>23,24</sup> While cardiac patches require surgical implantation and result in low patient compliance, the injectable hydrogel is less intrusive and traumatic, and has preferable biocompatibility due to its structural similarity to the myocardium's extracellular matrix.<sup>25–28</sup> The porous structure of swelling hydrogel also helps maintain cell activity and reduce blood elimination *in vivo*, making it an excellent

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choice for encapsulation.<sup>29,30</sup> Previous studies have demonstrated that injecting hydrogel into myocardial infarction sites can attenuate biomechanical remodeling of the heart, leading to improved 5 year survival rates for MI patients.<sup>31</sup> As such, utilizing an injectable hydrogel delivery strategy in conjunction with cell or cell-derived therapy may be a promising approach to further improve outcomes for MI patients.<sup>32</sup> Moreover, biomimetic nanoparticle (*e.g.*, erythrocyte, neutrophil, and platelet cell membrane-camouflaged nanoparticles) has emerged as a new tool for MI therapy. These delivery systems have the potential to target the site of myocardial infarction and repair endogenous heart tissue by releasing loaded active cytokines or other drugs.<sup>33-36</sup>

In light of the foregoing, this review first presented an overview of the pathological process of myocardial infarction, focusing on the role of each cell type in heart recovery post MI. Then, we discussed the advantages and drawbacks of hydrogel delivery and cell-based therapy, as well as their cooperative relationship in MI treatment. Notably, we reviewed the current studies on using hydrogel delivery technologies to deliver cell or cell-derived preparations for MI treatment. Finally, current challenges and future prospects of cell or cell derivative-laden hydrogels for MI therapy are proposed.

## 2. The role of different cells in heart recovery post MI

Myocardial infarction is closely linked to the interactions and collaboration among various cells in the heart, blood, and bone marrow.<sup>37</sup> The heart, being the primary site of MI, comprises several cell types such as cardiomyocytes, cardiac fibroblasts, endothelium, immune cells, and the myocardium extracellular matrix.<sup>38</sup> During the progression of MI, neutrophils and monocytes, which are the major functional blood or bone marrow cells, also play a critical role.<sup>39</sup> Each cell type has a specific function in the physiological condition, and their interaction and collaboration are essential for the heart to function normally. In the pathological stage of MI, several cascade reactions occur in the specific cells of the heart, blood circulation, and bone marrow, leading to cardiac remodeling and subsequent heart failure.<sup>40-42</sup> This process is mainly divided into four phases: inflammation, proliferation, maturation, and remodeling.<sup>43</sup> This review outlines the biological activity and function of different cells in heart recovery post MI (Fig. 1).

### 2.1 Cardiomyocytes

Myocardial ischemia causes irreparable damage to cardiomyocytes during the inflammatory phase.<sup>44</sup> This process mediates cardiomyocyte death and the release of damage-related molecular patterns through multiple pathways such as necrosis, regulation of death, and autophagy.<sup>45</sup> Cardiomyocytes will hypertrophy with the addition of new myofibrils during the ensuing MI process to adjust to the physical demands of the injured heart.<sup>46</sup>

### 2.2 Macrophages

During the inflammatory phase, resident macrophages receive death signals from cardiomyocytes *via* the pattern recognition receptor.<sup>47</sup> Subsequently, macrophages release pro-inflammatory factors and chemokines into the circulation system, including the chemokine (C-C motif) ligand 2 (CCL2) and interleukin-1 $\beta$  (IL-1 $\beta$ ). In response to cytokines, monocytes are attracted to the ischemic region and then transform into M1-phenotype macrophages with a pro-inflammatory character.<sup>48</sup> At this stage, the inflammatory effect will be amplified in cascades. In the proliferative phase, macrophages are polarized into M2-phenotype macrophages with anti-inflammatory property.<sup>48,49</sup> M2-phenotype macrophages secrete a variety of cytokines, such as TGF- $\beta$ , IL-10, and VEGF, to promote tissue repair and angiogenesis.<sup>50</sup> At the maturation stage, the recruitment of macrophages ends. Macrophages remaining in the ischemic region will undergo apoptosis.<sup>51</sup>

### 2.3 Cardiac fibroblasts

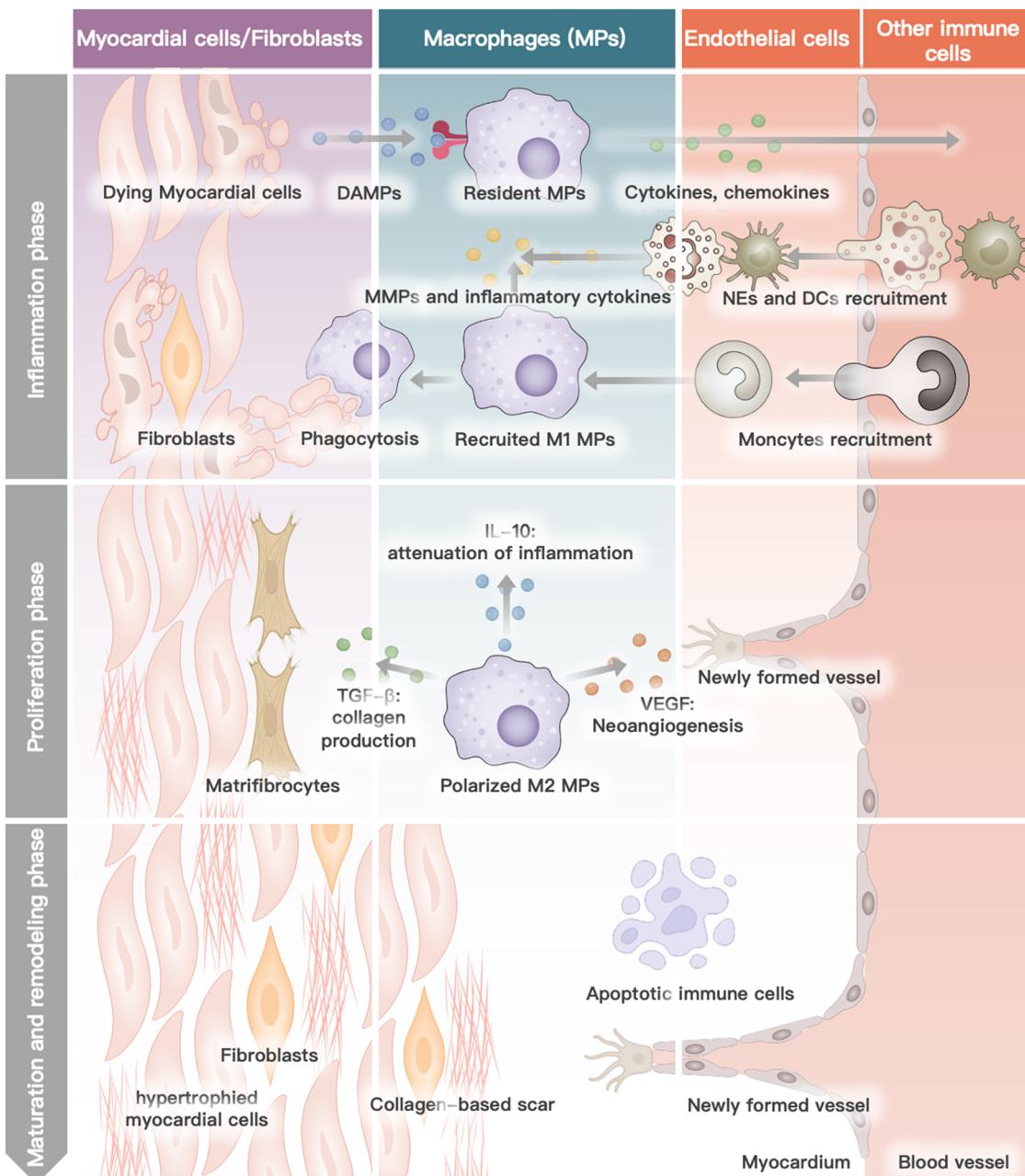
In normal cardiac tissue, cardiac fibroblasts are mainly responsible for the secretion of extracellular matrix, facilitating the infiltration of immune cells.<sup>51</sup> During the proliferative phase, macrophages activate cardiac fibroblasts by releasing TGF- $\beta$ .<sup>51</sup> In the maturation phase, activated fibroblasts transform into matrifibrocytes.<sup>52</sup> The cardiac extracellular matrix is cross-linked to form scar tissue. During the remodeling phase, chronic immune system overactivation will lead to fibrosis and increase tissue stiffness in infarcted and remote myocardium.<sup>53</sup>

### 2.4 Endothelial

Physiologically, the principal function of endothelial cells is to provide a barrier between blood and cardiac tissue by regulating vascular permeability.<sup>54</sup> The initial inflammatory response of MI causes the expression of surface adhesion molecules by endothelial cells and increases the intercellular space between endothelial cells.<sup>55</sup> This action substantially increases vascular permeability and aids immune cell recruitment and infiltration. In the proliferative phase, endothelial cells proliferate in response to cytokines such as VEGF, which mediates vascular regeneration and remodeling at the site of ischemia.<sup>56</sup> Endothelial cells further proliferate during the maturation phase to produce vessel lumens, which are subsequently stabilized by recruited pericytes. During the remodeling phase, as scar tissue continues to form, microvascular rarefied and vascular density is reduced in the heart.<sup>57</sup>

### 2.5 Other immune cells

During heart recovery period post MI, except for macrophages mentioned above, other immune cells (*e.g.*, monocytes, neutrophils, dendritic cells) rapidly coordinate their function to contain inflammation by removing dying cells and promoting cardiomyocyte replenishment. Monocytes and neutrophils from the bone marrow or spleen are recruited to the site of ischemia by endothelial cell surface adhesion molecules and inflammatory chemokines.<sup>58</sup> Among them, induced by pro-inflammatory



**Fig. 1** The role of different cells in heart recovery post MI. Dying myocardial cells release damage-associated molecular patterns (DAMPs). Resident macrophages recognize DAMPs and initialize inflammatory cascade by releasing cytokines and chemokines, leading to the recruitment of neutrophils (NEs), dendritic cells (DCs) and monocytes. Monocytes are differentiated into M1-phenotype macrophages (MPs) and, together with NEs, secrete matrix metalloproteinases (MMPs) and inflammatory cytokines. Resident and recruited MPs are responsible for phagocytosis and degradation of necrotic tissue. In subsequent proliferation phase, MPs are polarized into pro-inflammatory M2-phenotype MPs, releasing transforming growth factor- $\beta$  (TGF- $\beta$ ), interleukin-10 (IL-10), and vascular endothelial growth factor (VEGF). Three cytokines can respectively enhance the collagen production ability of matrifibrocytes, attenuate inflammation, and promote neovascularization. In the maturation and remodeling phase, monocyte recruitment ends. Eventually, the scar tissue is formed by hypertrophied cardiomyocytes and cross-linked extracellular.

cytokines, monocytes transform into M1-phenotype macrophages with a pro-inflammatory character. During the proliferative phase, macrophages polarize into anti-inflammatory M2-phenotype macrophages. The re-emergence of immune cells during the remodeling phase causes inflammation in remote and non-infarcted myocardium.<sup>59</sup> Dendritic cells play a significant role in post-MI antigen presentation, immune

activation, and other processes.<sup>42</sup> Initially, immature DCs migrate through the vascular endothelium into damaged heart tissue, where they are activated by DAMPs. These activated DCs then engulf antigens released by necrotic cardiomyocytes. Subsequently, the DCs migrate to lymph nodes and stimulate the production of CD8+ T cells, triggering specific immunity. On the other hand, EVs released by DCs can activate regulatory

T cells (Tregs), which suppress the activity of CD8+ T cells and regulate the differentiation of monocytes and macrophages. CD8+ T cells, Tregs, and other immune cells work together to maintain the equilibrium of the heart's immune environment post MI.

### 3. Collaborative effects of hydrogel with cell-based therapy

#### 3.1 Necessities and drawbacks of hydrogel in MI therapy

Due to the function of supplying blood to the entire body as a mechanical pump, the homeostasis of the biomechanical environment of the heart matters a lot.<sup>60</sup> The elasticity of each cardiac cell and the extracellular matrix are particularly important. During cardiac systole and diastole, the elastic modulus of the normal heart varies cyclically.<sup>61</sup> The modulus of elasticity in the infarcted region tends to decrease and then increase within 24 hours of the onset of MI.<sup>62</sup> This pattern is associated with the degradation and then increase of extracellular matrix (ECM) during the progression of MI.<sup>63</sup> It has been reported that hydrogels could replace the degraded ECM after being injected into the ischemic region, compensating for the loss of contractility in the acute ischemic region and providing good mechanical support for cardiomyocyte function.<sup>64</sup> Another study found that by increasing the thickness of the ventricular wall in the infarcted region, hydrogel could improve the ejection fraction of the left ventricle, effectively delaying the remodeling process of the myocardium after the onset of MI.<sup>65</sup>

Furthermore, several natural and synthetic hydrogels (e.g., fibrin hydrogels, alginate hydrogels, hyaluronic acid hydrogels, and the cell-interacting peptide RAD16-II hydrogels) have been shown to have bioactivities that can improve the therapeutic efficacy of MI.<sup>33,66</sup> These bioactivities include immune cell recruitment, inflammatory microenvironment modulation, and pro-angiogenic effects. A clinical phase II trial of an alginate hydrogel (Algisy-LVRTM) for intracardiac injection has been completed.<sup>67</sup> Although the hydrogel is able to maintain the biomechanical environment of the heart after the onset of MI and mitigate the MI process, the inability to regenerate cardiomyocytes remains an unresolved issue. In a clinical trial called PRESERVATION-1 (NCT01226563), a total of 231 patients were administered IK-5001 and compared with 102 healthy controls.<sup>68</sup> However, no visible effect was observed after a period of 6 months. It was noted that serious adverse events were more common in the treatment group (5%) than in the control group (2.9%). Additionally, the treatment group also exhibited higher rates of mortality and myocardial infarction compared to the control group. In conclusion, these findings suggest that severe MI patients did not experience significant anatomical changes or improvements in their quality of life but were more prone to severe adverse reactions. This is because there are still many problems with hydrogel alone. On the one hand, the lack of cells makes this therapy only "passive", unable to regenerate new myocardium. On the other hand, since the hydrogel is mainly relied on to maintain the cardiac biomechanical

environment after MI, the injection volume of the hydrogel is relatively large. It may be more likely to cause adverse reactions, such as ventricular ectopy or ventricular arrhythmia.

#### 3.2 Necessities and drawbacks of cell-based therapy

Due to the superior MI therapeutic effects, stem cell therapy has received much attention.<sup>69</sup> In 2011, the first MSCs preparation in the world for myocardial infarction therapy (Hearticellgram-AMI) was launched in Korea.<sup>70</sup> It is prepared by extracting blood from the autologous sciatic bone marrow of patients. MSCs are cultured for three to four weeks before being intracoronary infused. Clinical trials have shown that stem cell preparation injection improved heartbeats in patients with MI. Several autologous bone marrow MSCs administrated by intracoronary infusion for MI therapy are also in phase III clinical trials.<sup>71–73</sup> These findings highlight the significance of stem cell therapy in the treatment of heart diseases such as MI. They stimulate endogenous myocardial activation by secreting a variety of repair and regenerative cytokines. It is characterized by decreased myocardial cell death and hypertrophy, increased neovascularization, and improved function of existing myocardial cells.<sup>74</sup> However, stem cells survive in the heart only for a short time after being infused.

Surprisingly, it is estimated that more than 90% of stem cells infused into the heart do not reach the heart.<sup>75</sup> The situation occurs for two reasons. (1) Because of the abundant blood flow in the heart, stem cells infused are quickly eliminated and cannot be retained for an extended period of time to exert therapeutic effects.<sup>76</sup> (2) Stem cell therapy should be started as soon as an acute injury occurs. However, during acute injury, the infarcted area of the heart has a robust immune and inflammatory response.<sup>77</sup> Therefore, stem cells injected into this area are subjected to a hostile environment, reducing cell viability. As a result, selecting an appropriate delivery system to increase intracardiac retention and cell survival rate is critical to promoting the efficacy of cell-based MI therapy.

Injectable hydrogels, among various biological scaffolds, use the properties of polymeric materials that undergo a sol–gel transition. These hydrogels can incorporate cells and retain them in the infarct site. Furthermore, in the early stages of MI, the hydrogel could effectively separate loading cells from the robust inflammatory and immune environments.<sup>78,79</sup> Additionally, a more suitable *in vivo* microenvironment for stem cell differentiation can be created by adding pro-stem cell differentiation siRNA (e.g., miR-1a) or cytokines to the hydrogel.<sup>80,81</sup> Moreover, it has been reported that the elasticity of the matrix influences the differentiation efficiency of stem cells.<sup>82</sup> Human mesenchymal stem cells differentiate more readily in hydrogels with a higher elastic modulus. Based on this, it is reasonable to speculate that stem cell delivery *via* a hydrogel similar to the elasticity of cardiac tissue is more conducive to stem cell differentiation to cardiomyocytes.<sup>83</sup> In one study, pluripotent stem cells were cultured in a polyacrylamide hydrogel with an elastic modulus of 55 kPa rather than a traditional tissue culture medium.<sup>35</sup> The stem cells were able to differentiate into cardiomyocytes more efficiently.

Notably, some researchers believe that the potential mechanism of MI cell therapy is primarily related to their paracrine function.<sup>84</sup> The paracrine function of stem cells refers to the release of extracellular vesicles from these stem cells into the stroma. Active substances found in extracellular vesicles include stem cell-associated proteins, miRNAs, and DNA fragments.<sup>85</sup> By fusing with the cell membrane of damaged or surviving cardiomyocytes, stem cell-derived exosomes release their active contents into the recipient cells, enhancing cardiomyocyte viability and function at the infarct site. Current research has focused on using extracellular vesicles as drug delivery systems for miRNAs or active proteins that promote angiogenesis for myocardial regeneration.<sup>86,87</sup> However, to date, there is no clinical trial on using extracellular vesicle-loaded hydrogels for MI therapy. Facing the same problem as cell therapy, extracellular vesicles are still rapidly eliminated by the rich blood flow of the heart after intravenous or intracoronary administration.<sup>88</sup> As a result, extracellular vesicle delivery to the infarct site is inefficient. Similarly, sparse drug-loading space combined with the long-term retention ability of hydrogel at the infarct site makes it an ideal vehicle for extracellular vesicle MI therapy.<sup>89</sup>

In conclusion, researches indicate that the use of injectable hydrogels and cell or cell-derived agents can be mutually beneficial and complementary in treating MI. While the cardiomyocyte differentiation ability and paracrine function of cell or cell-derived agents can effectively improve cardiac function after MI, compensating for the inability of hydrogels to reverse cardiac fibrosis, the ECM-like three-dimensional structure of the injectable hydrogel provides mechanical support for the heart. Additionally, the abundant cell-loading space makes hydrogel an ideal microenvironment for cell proliferation and differentiation.<sup>90</sup> The residency of the hydrogel at the site of post-injection infarct provides targeting properties for cell-derived agents, which compensates for the drawbacks of cell or cell-derived preparation. These drawbacks include low cell survival, rapid clearance, and poor targeting properties.<sup>91</sup> In this article, we summarize studies about hydrogel delivery systems that encapsulate cell or cell-derived preparations for myocardial infarction therapy.

## 4. Cell or cell derivative-laden hydrogels for MI therapy

In order to meet the cells or extracellular vesicles delivery requirements of hydrogels, the physicochemical properties of hydrogels need to be carefully considered, including porosity, stiffness, swelling ability, complex mechanical properties, and degradation ability.<sup>92</sup> These physicochemical properties dictate the fate of cells or EVs after being encapsulated and delivered. For example, it has been reported that in order to deliver human embryonic stem cells (hESCs), the stiffness of the hydrogel needs to be around 10 kPa. This is because only hydrogels with this stiffness can maintain hESCs proliferation and pluripotency.<sup>93</sup> Degradability provides the space for cell

stretching and proliferation. According to another study, it has been found that MSCs only spread in a degradable hydrogel made from RGD-modified HA, as opposed to a non-degradable matrix.<sup>93</sup> Therefore, it is necessary to adjust these physicochemical properties and complex mechanical properties of hydrogels to meet the delivery or treatment need for cells or cell derivatives-based MI therapy.

Materials and preparation methods affect the physicochemical properties of hydrogels. Based on the biological material used, hydrogels can be classified as natural or synthetic. Fibrin glue, alginate, hyaluronic acid, and collagen hydrogels are the most commonly used natural hydrogels.<sup>30,92</sup> The majority of synthetic hydrogels are homopolymers and copolymers of acrylamide (AAM) and its derivatives, homopolymers and copolymers of acrylic acid (AA) and its derivatives, followed by polyvinyl alcohol (PVA) and polyethylene glycol (PEG) (Table 1).<sup>92</sup> The preparation methods of hydrogels include physical methods (ultraviolet light,  $\gamma$ -ray irradiation, heating, freeze-drying), chemical methods (modification of functional groups such as carboxyl and amino groups, and addition of crosslinking agents such as glutaraldehyde, *etc.*), and enzymatic methods (glutamine transaminase, *etc.*).<sup>94</sup> Physical crosslinking methods may decrease cell activity, while chemical crosslinking and enzymatic crosslinking require complex modifications or additional reagents. The interactions between the cell or cell-derived agents and the hydrogel matrix must be considered during the preparation of the hydrogels. On the one hand, hydrogels must meet the fundamental requirements for *in vitro* culture and *in vivo* transplantation, such as the absence of small molecule cross-linking agents, moderate cross-linking conditions, and the avoidance of toxic by-product generation.<sup>33,95</sup> As reported, gelation and cryo-gelation hydrogels are less toxic to adipose-derived mesenchymal cells than conventional covalent cross-linked and photopolymerized hydrogels, indicating they are a more promising tool *in vivo* application.<sup>96,97</sup> On the other hand, the physical and mechanical properties of hydrogels are crucial for their application in stem cell tissue engineering.<sup>98</sup> Although the hydrogels have a stable three-dimensional porous structure for encapsulating cells or cell-derived agents, the biotherapeutic adding will inevitably affect the macroscopic properties of hydrogels.<sup>99,100</sup> Herein, we introduced two cell-based approaches for MI therapy from the perspective of cell types.

### 4.1 Cell-laden hydrogels for MI therapy

Cells used in cell therapy primarily consist of bone marrow- or adipose-derived mesenchymal stem cells (ADSCs), blood- or bone marrow-derived endothelial progenitor cells, blood- or bone marrow-derived monocytes, cardiac-derived stem cells, skeletal myoblasts (SkMs), and multi-source-derived cardiomyocytes (Fig. 2). The therapeutic mechanism of cell-based MI therapy is summarized in Table 2.<sup>101–103</sup>

**4.1.1 Bone marrow or adipose-derived mesenchymal stem cells.** MSCs, or mesenchymal stromal cells, are multipotent stromal cells that can differentiate into various cell types, such as osteoblasts, chondrocytes, muscle cells, and adipocytes, among others.<sup>104</sup> MSCs are found throughout the human

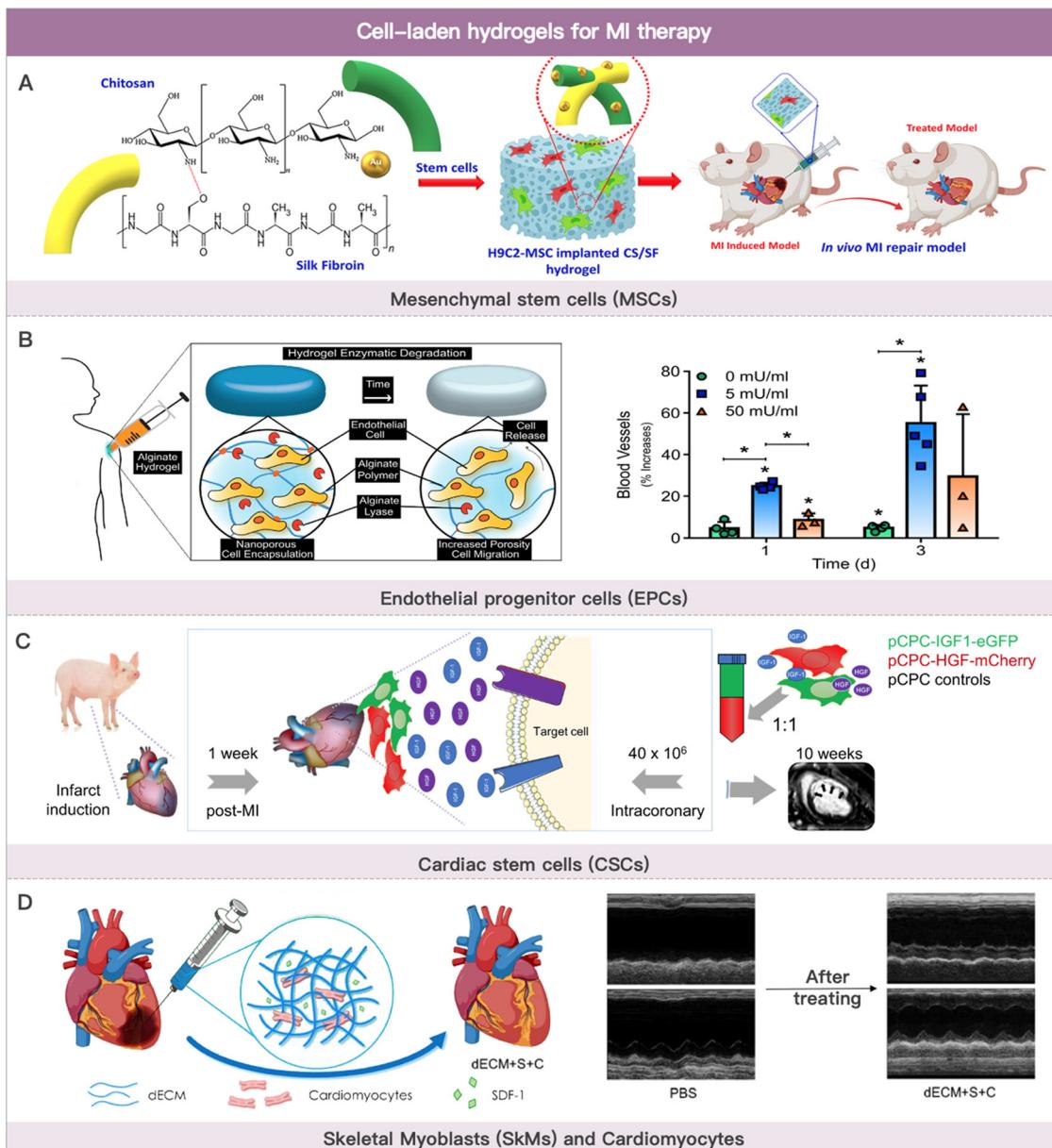
Table 1 Summary of advantages and disadvantages of natural or synthetic hydrogels for cell or cell derivatives encapsulation

| Materials           | Advantages      | Disadvantages  |
|---------------------|-----------------|--|
| Natural hydrogels   | Fibrin          | <ul style="list-style-type: none"> <li>• Good biocompatibility</li> <li>• Good biodegradability</li> <li>• Promotes angiogenesis</li> <li>• Fast gelation</li> </ul> |
|                     | Alginate        | <ul style="list-style-type: none"> <li>• Bio-inert</li> <li>• Fast gelation</li> <li>• Good stability</li> </ul>   |
|                     | Hyaluronic acid | <ul style="list-style-type: none"> <li>• Good biocompatibility</li> <li>• Promotes proliferation and angiogenesis</li> <li>• Fast gelation</li> </ul>                |
|                     | Collagen        | <ul style="list-style-type: none"> <li>• Cell-matrix interactions</li> <li>• Promotes cell attachment</li> </ul>   |
| Synthetic hydrogels | AAM derivatives | <ul style="list-style-type: none"> <li>• Good hydrolytic stability</li> <li>• Similar to the extracellular matrix</li> </ul>   |
|                     | AA derivatives  | <ul style="list-style-type: none"> <li>• Good biocompatibility</li> <li>• Easily functionalized</li> </ul>   |
|                     | PVA derivatives | <ul style="list-style-type: none"> <li>• Promoting cell survival and proliferation</li> <li>• Degradability</li> </ul>   |
|                     | PEG derivatives | <ul style="list-style-type: none"> <li>• Good hydrophilicity</li> <li>• Good biocompatibility</li> <li>• Easily functionalized</li> </ul>                            |

body, most in bone marrow and adipose tissue.<sup>105</sup> MSCs have several advantages in the field of MI therapy: (1) convenient isolation and extraction from bone marrow or adipose tissue; (2) active differentiation and proliferation ability; (3) immune privilege, immunosuppression, and anti-inflammatory ability, which can prevent immune rejection after cardiac infusion; and (4) extensive paracrine effect, which can induce angiogenesis and improve myocardial function by secreting angiogenic and chemotactic factors. MSCs are currently the most commonly used cell type in MI-related clinical trials due to the above-mentioned advantages. In 2008, in a pig model of chronic myocardial infarction, a study was designed to determine whether fibroblast growth factor-contained gelatin hydrogel might improve bone marrow-derived mesenchymal stem cell therapy.<sup>106</sup> Recently, a single study on the use of mesenchymal stem cells encapsulated in epicardial extracellular matrix hydrogel has entered phase II clinical trials for heart failure therapy (NCT04011059).<sup>107</sup>

Wang *et al.* discovered that a cyclodextrin/PEG-PCL-PEG hydrogel could promote bone marrow-derived MSC cell colonization and differentiation in the infarcted area. This hydrogel was absorbed four weeks after administration. Thereby, MSCs were mostly retained in the infarcted tissue.<sup>108</sup> This effectively increased vessel density while inhibiting infarct dilatation and left ventricular remodeling. The pore size of the hydrogel can also influence the paracrine effect of MSCs. Qazi *et al.* reported that medium pore size hydrogels (500 m) promoted pro-angiogenic factor secretion by MSCs more effectively compared with small pore size (400 m) and large pore size (600 m) hydrogels.<sup>109</sup> This class of drug delivery systems has anti-inflammatory properties in addition to cardiac tissue repair. By converting adenosine monophosphate (AMP) to adenosine *via* CD73, bone marrow-derived MSCs encapsulated in hydrogels effectively suppressed acute inflammatory cascade in MI mice

model.<sup>110</sup> MSCs are more abundant in the stromal fraction of adipose tissue than in bone marrow. Adipose tissue is also easily accessible *via* liposuction. As a result, adipose-derived MSCs are a good source of MSCs. Chen *et al.* cultured ADSCs in cross-linked transglutaminase gelatin (Col-Tgel). Col-Tgel created an adaptive microenvironment for ADSCs at the infarct site that is conducive to differentiation and secretion, thereby improving ADSCs cardioprotection.<sup>111</sup> In addition to the commonly used fibrin hydrogels, alginate hydrogels, and hyaluronic acid hydrogels, researchers have developed various other hydrogel systems for MSC cardiac delivery. Koivunotko *et al.* discovered nano-fibrillated cellulose (NFC) as a superior biomaterial scaffold capable of delivering MSCs. NFC maintained the high viability and angiogenic properties of ADSCs *in vitro*. As a result, NFC was able to deliver MSCs for MI therapy.<sup>112</sup> Wu *et al.* co-loaded MSCs and cardioblast cells (H9C2 cells) into chitosan-silk fibroin hydrogel. This co-culture strategy reduced the electrophysiological barriers of native MSCs and released heart-friendly cytokines, which slowed down the acute MI process.<sup>113</sup> Ding *et al.* designed a novel injectable hydrogel to encapsulate MSCs, achieving better therapeutic results in MI treatment. This hydrogel has a dual function of reactive oxygen removal and oxygen generation.<sup>114</sup> The lack of electromechanical coupling of the hydrogel to the host myocardial tissue and the inability to monitor the implantation may compromise optimal treatment outcomes. Zhu *et al.* prepared an injectable conductive nanocomposite hydrogel. The hydrogel consisted of gold nanorods (GNRs), synthetic silicate nanoplatelets (SNs), and PLGA-PEG-PLGA. Among them, SNs supported the proliferation of MSCs.<sup>115</sup> Carbon nanotubes modified poly-(*N*-isopropylacrylamide) (PNIPAAm) hydrogel was prepared by Li *et al.* The hydrogel has good electrical conductivity and mechanical support properties. It can effectively deliver ADSCs to the infarct site and maintain their activity.<sup>116</sup>



**Fig. 2** Cell-laden hydrogels for MI therapy. (A) Schematic illustration of the composited hydrogel formation loaded with MSCs for myocardial functional recovery therapy. Reproduced with permission from ref. 113, Copyright Elsevier 2023. (B) Schematic illustration of hydrogels with various alginate lyase concentrations over the course of three weeks and angiogenesis effect of EPCs-loaded hydrogel. Reproduced with permission from ref. 123, Copyright Elsevier 2018. (C) Safety evaluation of coronary artery injection of porcine cardiac progenitor cells in an acute MI porcine model. Reproduced from ref. 142 under the open access policy of MDPI 2021. (D) Schematic illustration of decellularized porcine extracellular matrix to deliver exogenous cardiomyocytes for MI treatment. Reproduced with permission from ref. 159, Copyright American Chemical Society 2023.

#### 4.1.2 Blood or bone marrow-derived endothelial progeni-

**Endothelial progenitor cells.** Endothelial cells (ECs) are less commonly used in tissue regeneration medicine due to their high differentiation state and limited proliferation rate.<sup>117</sup> In contrast to ECs, angiogenic endothelial progenitor cells play an essential role in physiological and pathological neovascularization and tissue repair.<sup>118</sup> EPCs are mainly derived from peripheral blood, bone marrow, and adipose tissue, expressing cell markers such as CD31, CD34, and CD134. EPCs have the ability to improve myocardial function in preclinical models of ischemic

heart disease. The underlying mechanisms are related to direct incorporation into neovascularization and the release of pro-angiogenic factors.<sup>119</sup> In a prospective crossover study of ischemic heart failure, CD34+ EPCs were infused *via* subcutaneous catheter into ischemic sites.<sup>120</sup> The treatment regimen effectively improved left ventricular ejection fraction and 6 minute walk distance at six months in patients who received high-dose cell injections.

Various materials such as fibrin hydrogels, hyaluronic acid, alginate, self-assembling peptide (SAP), and ECM for hydrogel

Table 2 Summary of the therapeutic mechanism of cell-based MI therapy

| Cell sources                 | Therapeutic mechanism  |
|------------------------------|--|
| Mesenchymal stem cells       | <ul style="list-style-type: none"> <li>Extensive paracrine effect</li> <li>Inducement of angiogenesis by secreting angiogenic factors</li> </ul>                                   |
| Endothelial progenitor cells | <ul style="list-style-type: none"> <li>Differentiation into cardiomyocyte</li> <li>Incorporation into neovascularization</li> <li>Releasement of pro-angiogenic factors</li> </ul> |
| Monocytes                    | <ul style="list-style-type: none"> <li>Differentiation into macrophages and dendritic cells</li> <li>New collateral blood vessel formation</li> </ul>                              |
| Cardiac-derived stem cells   | <ul style="list-style-type: none"> <li>Extensive paracrine effect</li> <li>Modulation of ischemic microenvironment</li> </ul>  |
| Cardiomyocytes               | <ul style="list-style-type: none"> <li>Differentiate into cardiomyocyte</li> <li>Electromechanical integration with host cardiomyocytes</li> </ul>                                 |

delivery of EPCs have been reported.<sup>121–125</sup> For example, Campbell *et al.* reported an alginate hydrogel that can be degraded by lytic enzymes. In this work, alginate lyase and outgrowth endothelial cells (OECs) (a subpopulation of EPCs) were co-loaded in a hydrogel. After injection into the heart, this hydrogel is progressively degraded by enzymatic action, with an increase in pore size and subsequent release of the encapsulated OECs.<sup>123</sup> After MI occurs, adverse remodeling of the ventricles leads to an abnormal biomechanical environment of the heart. For this reason, Gaffey *et al.* designed a novel injectable shear-thinning hyaluronic acid hydrogel. This hydrogel significantly increased the efficiency of intracardiac transplantation and retention of EPCs. In addition, the hydrogel adhered to the infarct site, stabilized the border zone myocardium, and slowed down the adverse myocardial remodeling process. The hyaluronic acid hydrogel, together with encapsulated EPCs reduced left ventricular dilatation, thus improving cardiac function.<sup>126</sup> Cardiac lymphatic vessel damage leads to cardiac lymphedema. Recent studies have shown that stimulation of lymphatic angiogenesis reduces cardiac lymphedema and slows down the MI process. However, little is known about the effect of lymphatic endothelial progenitor cells (LEPCs) on the formation of cardiac lymph nodes. Zhang *et al.* evaluated the safety and efficacy of a self-assembling peptide hydrogel encapsulating LEPCs and VEGF-C for treating MI. The results showed that the cell hydrogel delivery system promoted the survival of transplanted cells and cardiac lymphatic angiogenesis. Notably, cardiac lymphangiogenesis facilitated the clearance of inflammatory cells from the infarct site, thereby alleviating cardiac edema and ventricular remodeling.<sup>125</sup> Engineered heart tissue transplantation requires a good vascular network to provide oxygen and nutrients to the living cells. Based on this, Yang *et al.* proposed spheroids of early vascular cells (EVCs) derived from hESCs rather than single-cell forms as transplant “seeds” for reconstructing microvascular networks. EVCs are capable of forming vascular networks in extracellular matrix hydrogels. After being injected into the ischemic site of the heart in MI mice, this delivery system effectively reduced infarct size and improved cardiac function.<sup>124</sup>

#### 4.1.3 Blood or bone marrow-derived monocytes (BM-MNCs).

Monocytes are the largest type of leukocyte in the blood.<sup>127</sup>

They can differentiate into macrophages and monocyte-derived dendritic cells after migrating into inflammatory tissues.<sup>128</sup> Bone marrow-derived mononuclear cells have been widely used in preclinical and clinical studies for MI treatment due to their accessibility and ease of procurement.<sup>129–131</sup> The therapeutic effect of BM-MNCs infusion in patients with MI or heart failure has been shown in clinical trials to be significantly influenced by trial design diversity and the inherent heterogeneity of BM-MNCs.<sup>132</sup> Overall, BM-MNCs are beneficial in the treatment of MI. Furthermore, using *in vitro* amplification culture techniques, the inherent heterogeneity of BM-MNCs can be overcome. The patented culture technique has been used to boost the culture of BM-MNCs.<sup>133</sup> The techniques can deplete lymphocytes and granulocytes from the initial MNC population and specifically expand mesenchymal cells, monocytes, and M2-phenotype macrophages. Interestingly, M2-phenotype macrophages are considered to assist with tissue repair, angiogenesis, and vascular remodeling.

Fewer studies used hydrogel to deliver MNCs for MI therapy. Li *et al.* discovered that hydrogels enhanced BM-MNC colonization in the infarct site. Hydrogel injection with BM-MNCs promoted angiogenesis and prevented scar expansion in MI rabbits, facilitating cardiac function restoration.<sup>134</sup> In a large animal model, Chen *et al.* assessed the safety and efficacy of BM-MNCs-loaded hyaluronic acid hydrogel. According to the findings, this strategy significantly increased left ventricular ejection fraction, systolic function, and neovascular differentiation in the hearts of the porcine MI model. Notably, the hyaluronic acid hydrogel effectively promoted the differentiation of BM-MNCs at the infarct site.<sup>131</sup>

**4.1.4 Cardiac-derived stem cells.** Based on the foundational studies about isolation, expansion, and therapeutic treatment of resident cardiac cells, various original populations of cardiac-derived stem cells have been identified and isolated.<sup>135</sup> C-kit+, Isl-1+, and Sca-1+ – phenotype cardiac stem cells (CSCs) are plastic to cardiomyocytes and endothelial vascular smooth muscle cells.<sup>132</sup> Other subtypes of cardiac-resident MSCs include epicardium-derived cells (EPDCs) and cardiosphere-derived stem cells (CDCs). Notably, both c-kit + CSCs and CDCs have entered phase II clinical trials for acute myocardial infarction and ischemic heart failure treatment.<sup>136</sup> According to the promising clinical trial results, autologous c-kit + CSCs infusion has a high feasibility and safety profile. Patients in the treatment group exhibited a higher local wall motion score index (WMSI).

In addition, studies have reported a population of progenitor cells derived from resident cardiac stem cells, termed cardiac progenitor cells (CPCs).<sup>137</sup> In contrast to terminally differentiated cardiomyocytes, CPCs are highly proliferative and can theoretically differentiate into all types of cardiomyocytes to efficiently reconstruct damaged cardiac tissue and promote angiogenesis. Cardiospheres are self-adhesive heterogeneous cell populations obtained from *in vitro* cardiac tissue cultures.<sup>138</sup> It typically contains several different types, including endothelial cells, mesenchymal cells, and c-kit, Sca-1, and CD34 expressed stem cells.<sup>139</sup> Because of their feeble differentiation capacity, the

therapeutic potential of CDCs for MI basically relies on their paracrine function. Although CDCs do not significantly improve LV (left ventricle) ejection fraction and LV volume, they reduce scar tissue and increase local ventricular wall contractility after MI.

Phase I clinical trials have been completed with injectable gelatin hydrogels containing human cardiac-derived stem cells and fibroblast growth factor (bFGF).<sup>140</sup> Takehara *et al.* demonstrated that hydrogels co-loaded with bFGF and CDCs could improve post-infarction cardiac function by modulating the ischemic microenvironment and enhancing cardiomyocyte viability.<sup>141</sup> Prat-Vidal *et al.* evaluated the safety of coronary artery injection of porcine cardiac progenitor cells (pCPCs) in an acute MI porcine model.<sup>142</sup> A clinical trial further validated the technical feasibility and short-term safety of using fibrin hydrogel delivery of CPCs.<sup>143</sup> In addition, Masato Kanda reported a three-dimensional hydrogel scaffold (CPC-PRGmx) for culturing CPCs. CPC-PRGmx consisted of RGD peptide-conjugated self-assembling peptide and insulin-like growth factor-1 (IGF-1). This cell hydrogel delivery strategy was potential in MI therapy.<sup>144</sup> The hydrophilic hydrogel environment is more conducive to improving cell viability and achieving uniform cell distribution in engineered cardiac tissues. Chang *et al.* prepared *N*-hydroxysuccinimide-functionalized hyaluronic acid hydrogels to encapsulate CDCs and enhance cell viability. The NHS-activated HA hydrogels reacted with primary amines in the myocardium to form a more stable three-dimensional structure with the infarcted tissue, allowing the hydrogel to remain at the injection site for over 4 weeks. The encapsulated CDCs effectively improved left ventricular ejection fraction after myocardial infarction.<sup>145</sup>

**4.1.5 Skeletal myoblasts.** SkMs are the progenitor cells under the basement membrane of muscle fibers.<sup>146</sup> They can generate new muscle fibers after muscle injury. Due to the easy isolation and intrinsic contraction properties, SkMs were one of the first cell types used in MI cell therapy studies.<sup>147</sup> Although SkMs have been shown to have some function in reducing interstitial fibrosis and improving cardiac performance, the underlying mechanism is not associated with the differentiation of SkMs into cardiomyocytes. SkMs still have a skeletal muscle phenotype after being infused into the heart.<sup>148</sup> In fact, the mechanism of MI treatment of SkMs involves paracrine pathway-mediated ECM and endogenous pro-angiogenic factor release. Previous studies have proposed the use of injectable fibrin hydrogel to enhance SkMs survival in infarcted areas, with the ultimate goal of improving heart function recovery. Despite this, the results of clinical II trials of SkMs were still disappointing.<sup>149</sup> Although percutaneous intramyocardial administration of SkMs improved the 6 minute walking distance, it did not significantly ameliorate the left ventricular ejection fraction at six months.

**4.1.6 Embryonic stem cell-derived cardiomyocytes (ESC-CMs) and induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs).** The structure and function of ESCs are similar to those of cardiac myocytes, including cell markers, sarcomeric organization, and electrophysiological properties.<sup>150</sup> ESCs-induced

pluripotent stem cells and mesenchymal stem cells all have the potential to differentiate into cardiomyocytes.<sup>151</sup> Although ESC-derived cardiomyocytes have been shown to proliferate, differentiate, and electromechanically integrate with host cardiomyocytes after implantation *in vivo*, they have not universally exhibited myocardial remodeling and functional improvement. Nevertheless, there are still clinical phase I studies of MI therapies based on ESCs.<sup>152</sup> Due to concerns about the immune rejection of allogeneic ESC-CMs, autologous iPSCs-derived cardiomyocytes are a safer source of cardiomyocytes. Both undifferentiated iPSCs and iPSCs-CMs have shown repair effects in animal models of MI.<sup>153</sup> However, researchers disagree over the therapeutic effects iPSCs have. Thus, iPSCs are considered more as an experimental platform for mechanistic studies compared with ESCs. The development of clinically available iPSC products still has a long way to go. This process requires overcoming issues such as low efficiency of cell programming and myocardial induction and variabilities between iPSC cell lines.<sup>154</sup>

The hydrogel delivery system is vital to increase cell retention and ameliorate the cell transplantation microenvironment. Oligo [poly(ethylene glycol) fumarate] (OPF) hydrogels were used to encapsulate mouse embryonic stem cells (mESCs) by Wang *et al.* *In vivo* ascorbic acid induces mESCs to differentiate into cardiomyocytes and other cell types in all three lineages. OPF hydrogels effectively increased cell retention and reduced infarct size together with ESC-CMs.<sup>155</sup> Nakajima *et al.* validated that water-soluble gelatin hydrogel was a suitable biomaterial for delivering ESC-CMs.<sup>156</sup> Erythropoietin (EPO) could promote cell survival. Chow *et al.* found that treatment with polyethylene glycol hydrogels encapsulating iPSC-CMs with EPO improved cardiac function and increased infarct thickness and muscle content after MI.<sup>157</sup> Delivery of iPSC-CMs using conventional hydrogels suffered from poor attachment capacity, single function, and inability to control the direction of differentiation of iPSCs. To address these problems, Khazaei *et al.* designed an iPSC-CMs-integrated conductive hydrogel microneedle. The anisotropic structure of the encapsulated parallel-aligned carbon nanotube induced the directional alignment of iPSCs and endowed it with preferable conductivity. MSCs differentiated into cardiomyocytes under the stimulation of MSCs-related genes (*e.g.*, microRNA-1) or differentiation factors (*e.g.*, Myocardin). In addition, hydrogels with three-dimensional structures used for cell culture also improved the induction efficiency of MSC-derived cardiomyocytes (MSC-CMs).<sup>158</sup> Wu *et al.* used a decellularized porcine extracellular matrix to deliver exogenous cardiomyocytes into the infarcted region. The co-loaded stromal cell-derived factor 1 (SDF-1) alleviated the ischemic microenvironment and improved the engraftment environment of cardiomyocytes.<sup>159</sup>

**4.1.7 Other cells.** Furthermore, some cell therapy strategies do not function directly at the site of the myocardial infarction. Cell therapy regimens that combine with other infarct site targeting strategies reduce the need for hydrogel delivery. Platelets have been used to design various functional nanocarriers for treating cancer and bacterial infections in recent years,

owing to their critical role as circulating sentinels for tissue damage.<sup>160</sup> Acute myocardial infarction, in fact, causes vascular damage and exposes the subendothelial matrix, resulting in platelet recruitment from the blood to the infarct site. Shen *et al.* created CD34 antibody-modified platelets (P-CD34) by utilizing the homing ability of platelets to the myocardial infarction site. P-CD34 binds to CD34+ endogenous stem cells and directs cells to the infarct site. This strategy was successful in repairing damaged cardiac tissue following MI.<sup>161</sup> Tang *et al.* discovered that by fusing platelet nanovesicles into CSCs cell membranes, platelet surface markers associated with injury site adhesion were highly expressed on the CSCs surface. The engineered CSCs were able to target and reduce infarct volume in acute MI rat or porcine models.<sup>162</sup> A few studies have been conducted on controlled oxygen-modulating hydrogels for MI treatment. Liu and colleagues created a hydrogel-coated cyanobacteria nano-capsule. The engineered cyanobacteria consumed oxygen *via* respiration, resulting in a hypoxic micro-environment that promoted the upregulation of heat shock protein 70 (HSP70). It resulted in the tolerance of cardiomyocytes to the robust infarction environment. Furthermore, near-infrared (NIR) light could inhibit macrophage M1 polarization by releasing photosynthetic oxygen *via* upconversion luminescence (UCL) effects. This strategy effectively inhibited the pro-inflammatory cytokines Interleukin-6 and tumor necrosis factor- $\alpha$ , thereby repairing myocardial injury.<sup>163</sup>

#### 4.2 Cell-derived extracellular vesicle-laden hydrogels for MI therapy

EVs are natural lipid nanoparticles released by cells that can transport various macromolecular active substances (*e.g.*, cytokines and non-coding RNA).<sup>164</sup> Apoptotic bodies (size between 1 and 4  $\mu\text{m}$ ), microvesicles (size between 50 and 1000 nm), and exosomes (size between 30 and 100 nm) are the three main types of EVs.<sup>165–168</sup> Apoptotic bodies are the remains of cells undergoing apoptosis or programmed cell death. Microvesicles are membrane-bound sacs that are shed from cell surfaces into the extracellular environment in a highly regulated process. Exosomes are generated in the endosomal compartment, which contains the proteins, DNA, and RNA of the cells that secrete them. EVs contain a wide range of biological activities and participate in many physiological or pathological cardiovascular diseases processes, such as angiogenic regulation, blood pressure regulation, cardiomyocyte hypertrophy, and cardiac fibrosis.<sup>169,170</sup>

Most mechanisms of MI therapy with stem cells involve the paracrine release of extracellular vesicles containing bioactive substances. As a result, some researchers have extracted extracellular vesicles from stem cells *in vitro* for MI therapy.<sup>171</sup> Preclinical studies have confirmed the therapeutic potential of EVs in alleviating ischemic heart injury.<sup>172</sup> The therapeutic mechanisms primarily include reduced monocyte infiltration in ischemic cardiac tissue, angiogenesis promotion, and macrophage polarization regulation. Compared with cell therapy, the therapeutic effect of EVs by releasing active contents (*e.g.*, miRNAs and cytokines) in MI is more direct. Furthermore,

EVs are only nanometers in size. Thus, EVs are able to penetrate tissue and cells deeper.<sup>173</sup> It should be noted that EVs (particularly stem cell-derived EVs) are typically less effective due to a lack of targeting ability in the heart and in the infarct region.<sup>174</sup> The recently developed injectable hydrogels show the potential to conquer this issue. EVs-containing hydrogels can be prepared through “sponge absorption,” mix and cross-linking, and *in situ* hydrogel formation.<sup>175</sup> This section summarizes the research on using EVs-loaded hydrogels for MI therapy according to the type of source cells (Fig. 3).

**4.2.1 Stem/progenitor cell-derived EVs.** EVs released from stem/progenitor cells contain a variety of active substances that can improve cardiomyocyte function, which is one of the main MI therapeutic mechanisms of stem/progenitor cell.<sup>176</sup> EVs have several advantages over stem cells, including small size, low toxicity, low immunogenicity, superior tissue permeability, and no cell viability issue. As a result, stem/progenitor cell-derived EVs may be an effective alternative option for stem/progenitor cell therapy. However, fewer clinical trials of cell-derived EVs for MI treatment have yet begun. Only one recent study of cardiovascular progenitor cells-derived EVs entered clinical trials for non-ischemic cardiomyopathy therapy.<sup>177</sup> The reasons for this could be the low yield of EV preparation, poor *in vivo* targetability, and difficulties with quality assessment. Encapsulation by hydrogel has been shown to be effective in overcoming the drawbacks of rapid clearance and insufficient targetability. CPCs, EPCs, and MSCs are currently the most commonly used cell resources of EVs.<sup>19,178,179</sup> For example, Gil-Cabrerizo *et al.* used alginate hydrogels to encapsulate EVs derived from ADSCs to improve EV delivery at the infarct site.<sup>180</sup> Furthermore, researchers have created numerous novel hydrogels for targeted EVs delivery. Yang *et al.* reported an injectable conductive hydrogel. This hydrogel has controllable gelation kinetics, shear-thinning injectability, and conductivity comparable to native myocardium. It relieved myocardial injury after myocardial infarction-ischemia/reperfusion by encapsulating mesenchymal stem cell-derived EVs.<sup>91</sup> Mol *et al.* developed a hydrogel based on ureido-pyrimidinone (UPy) units coupled to poly(ethylene glycol) chains (UPy-hydrogel). The pH-responsive cross-linking ability of UPy-hydrogel allows for *in situ* hydrogel formation after injection into the myocardial infarct region. In UPy-hydrogel, encapsulated EVs can be slowly released.<sup>181</sup> Monguió-Tortajada *et al.* encapsulated MSC-derived EVs into hydrogels to mitigate ventricular remodeling and regulate the immune response in a porcine model of MI.<sup>182</sup> Researchers have also developed other engineered EVs. For example, a strategy that fused EVs with platelet membranes could effectively deliver active contents of EVs to MI inflammation sites. At sites of inflammation, EVs were phagocytosed by macrophages, inducing the formation of M2-phenotype macrophages and thus suppressing inflammation response in acute MI.<sup>183,184</sup>

However, one of the critical limitations of their clinical application is the inefficient production rate of highly active EVs. It has been reported that using three-dimensional hydrogels as the culture medium could significantly enhance the yield of MSC-derived EVs compared to the two-dimensional

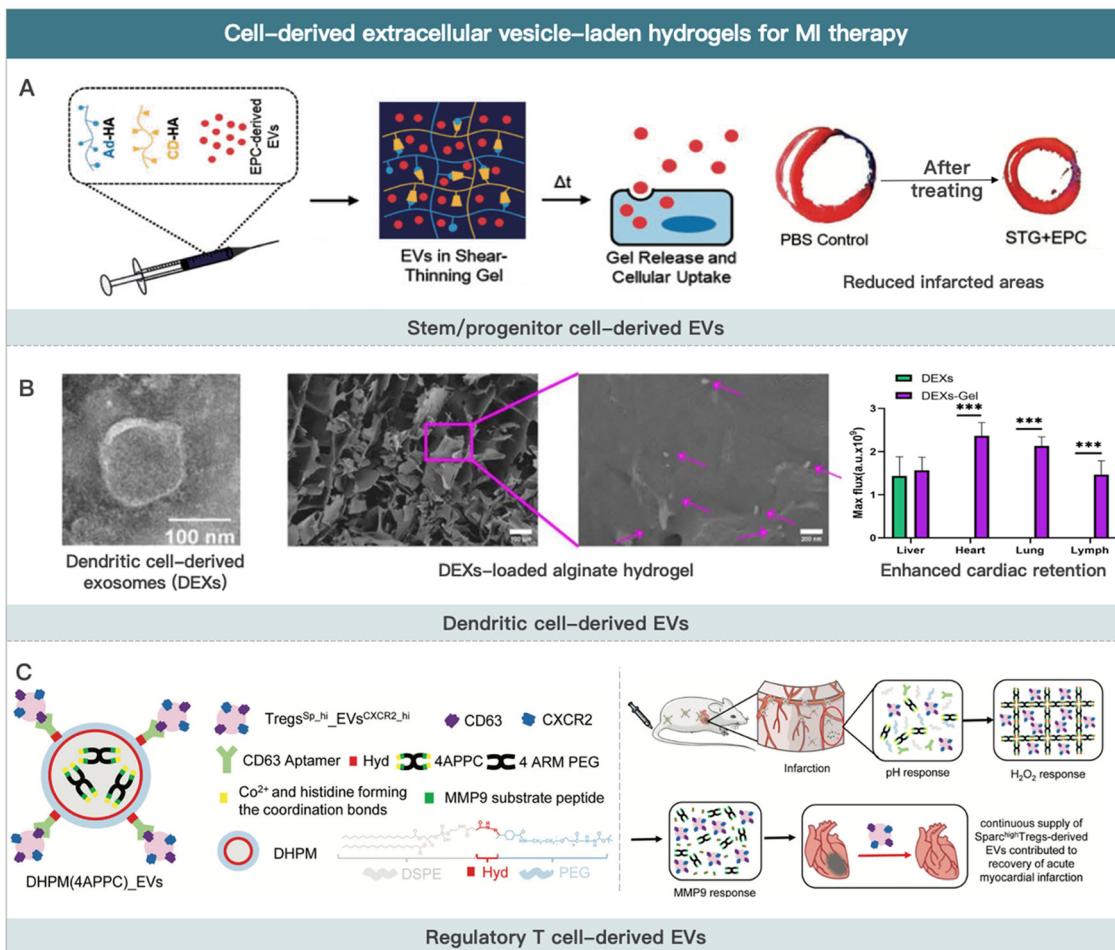


Fig. 3 Cell-derived extracellular vesicle-laden hydrogels for MI therapy. (A) Schematic illustration of EPCs-derived EVs for improving border zone remodeling post-MI. Reproduced with permission from ref. 19, Copyright Oxford University Press 2018. (B) Schematic illustration of dendritic cell-derived EVs loaded alginate hydrogel for improving cardiac function post-MI. Reproduced from ref. 190 under the open access policy of Springer Nature 2021. (C) Schematic illustration of Sparc<sup>high</sup> Tregs derived-EVs loaded hydrogel for promoting the recovery of cardiac function. Reproduced with permission from ref. 192, Copyright Wiley-VCH GmbH 2022.

liquid medium. EVs obtained *via* this method were more potential in terms of cardio-protection due to the similar culture medium structure with the physiological environment. It allowed stem cells to respond positively to exogenous stimuli (*e.g.*, temperature, pH, and nutrition) and produce higher-quality EVs.<sup>185</sup> The expression of *ISL1* could enhance the paracrine function of MSCs. Hu *et al.* used a gene transfection technique to generate MSCs with high *ISL1* expression. This strategy made it possible to prepare MSC-derived EVs (*ISL1*-MSCs-Exo) efficiently. Using angiogenin-1 hydrogel (Ang-1 hydrogel) to encapsulate *ISL1*-MSCs-Exo increased EVs retention at the ischemic site and improved the anti-apoptotic and pro-angiogenic ability of EVs.<sup>186</sup> In addition, researchers demonstrated an approach to prepare high amounts of extracellular vesicles with high bioactivity from endothelial progenitor cells by stimulation with silicate ions derived from silicate ceramics. The engineered EVs encapsulated in hydrogels significantly improved angiogenesis at the post-MI infarct site.<sup>187</sup>

**4.2.2 Dendritic cell-derived EVs.** The immune system is essential in both inflammatory and proliferative phases of MI. Most immune cells (for example, dendritic cells) contribute to the MI process by releasing relevant EVs *via* paracrine mechanisms.<sup>188</sup> Dendritic cell-derived EVs (DEXs) are mainly involved in post-MI antigen presentation, immune activation, and other processes. In detail, mechanisms of DEXs include the activation of regulatory T cells (Tregs) and the induction of anti-inflammatory M2-phenotype macrophage.<sup>189,190</sup> Zhang *et al.* established an alginate-based injectable hydrogel loaded with DEXs. The findings confirmed the role of the hydrogel in increasing DEX retention at the injection site, as well as the therapeutic effect of DEXs in improving cardiac function following MI due to DEX-induced Treg cell activation and macrophage polarization regulation.<sup>190</sup>

**4.2.3 Regulatory T cell-derived EVs.** When acute myocardial infarction occurs, the immune response is highly activated, and both T and B lymphocytes are involved in the inflammatory response, determining the myocardial repair process. Tregs, for

example, can suppress the activity of CD8+ T cells and regulate the differentiation of monocytes and macrophages.<sup>191</sup> SPARC (secreted protein acidic and cysteine-rich) overexpressed Regulatory T cells (Sparc<sup>high</sup> Tregs), in particular, may assist in the repair of infarcted tissues following acute MI. Sparc<sup>high</sup> Tregs-derived EVs have similar cell functions and could thus be a potent strategy for MI treatment. Cheng *et al.* discovered that Sparc<sup>high</sup> Tregs-derived EVs improved cardiac function by inhibiting pro-inflammatory factor secretion and increasing the expression of the collagen synthesis-related gene Col3a1. Furthermore, a novel hydrogel delivery system based on Sparc<sup>high</sup> Tregs-derived EVs was developed. This hydrogel system could respond to environmental pH, H<sub>2</sub>O<sub>2</sub>, and MMP9 and release EVs, allowing EVs to remain in the infarct region and exert repair functions.<sup>192</sup>

## 5. Challenges and future prospects

### 5.1 Challenges

Injectable hydrogels have been highlighted to be the ideal heart tissue analogs. They served as functional myocardial tissue after efficient encapsulation and release of various cells or cell-derived EVs. However, several critical issues need to be addressed and clarified on the road to the commercialization of cell or cell derivative-laden hydrogels for MI treatment.

**5.1.1 Stability and activity issues.** During the manufacturing and clinical application of living cells, freezing and thawing are necessary steps.<sup>193</sup> However, this process can have a significant impact on the differentiation, proliferation, and therapeutic activity of live cells. To avoid this, cell-derived preparations such as EVs and biomimetic nanoparticles may be another reasonable option. Additionally, when using hydrogels for stem cell administration, it is important to carefully examine the hydrogel material, cross-linking agent, and preparation procedure for their potential impact on cell activity.<sup>194</sup> For example, biocompatibility hydrogel material, no introduction of small molecule cross-linking agents, mild cross-linking conditions, and no toxic by-products can improve the stability and activity of cell-based hydrogel delivery systems.

**5.1.2 Large-scale production and quality control issues.** Cell or cell-derived formulations, unlike other medications, require large-scale expansion of cells. Cell source, high costs, technical constraints, and quality control severely limit their application. Using cells from allogeneic sources to prepare cell or cell-derived formulations increased production scalability and saved costs compared to autologous sources.<sup>195</sup>

**5.1.3 Animal model issues.** The bulk of preclinical animals utilized in research are small, adolescent animals.<sup>196</sup> In contrast to clinical patients, these animals often have a favorable body function and a powerful tissue repair potential. Clinical patients are usually middle-aged or elderly. Furthermore, most of them have underlying conditions such as hypertension. Their organism function and tissue repair capabilities are inadequate. Given these distinctions, the animal models for preclinical investigations need to be reconsidered. Medium and big animals such as

rabbits, porcine, and monkeys may be a better choice for animal models.

**5.1.4 Administration timing and mode issue.** Cardiac remodeling following myocardial infarction is a multifaceted pathophysiological process. It comprises four main phases: inflammation, proliferation, maturation, and remodeling (Fig. 1). During the inflammatory and proliferative phases, cardiac fibroblasts secrete extracellular matrix, resulting in scar tissue development. In the early stages of MI, a certain degree of cardiac fibrosis protects the heart by maintaining the structural integrity of cardiac tissue and preventing cardiac rupture. Continuous inflammatory stimulation, on the other hand, aggravates the cardiac fibrosis process during the maturation and remodeling phases, resulting in systolic–diastolic dysfunction and, eventually, heart failure. Different cells or cell-derived vesicles may have a dual function in early inflammation and late scar tissue formation in MI.<sup>197</sup> As a result, while administering cell or cell-inspired preparations, the antifibrotic or profibrotic effects must be considered. Furthermore, the feasibility of the mode of administration requires further investigation. Cell or cell-derived agents are usually administered by intracoronary injection, which is less invasive. However, it might cause vascular obstruction, especially when injecting hydrogels. Instead, hydrogels are administered *via* intramyocardial (IM) injection in animal study, but this route of administration requires thoracic surgery, leading to a higher surgical risk.<sup>198</sup> According to recent preclinical and clinical studies, *trans*-endocardial intramyocardial injection *via* catheter is a minimally invasive approach to deliver potential therapeutic agents directly into the myocardium without the requirement of open chest surgeries.<sup>199</sup>

### 5.2 Prospective future of MI therapy using cell-derived nanoparticles

Plenty of biomimetic targeted drug delivery systems have been developed *via* cell membrane-camouflaged technology.<sup>200</sup> Numerous studies have shown that encapsulating cell membranes onto inner cores can endow nanoparticles with multiple biological functions. For example, erythrocyte membrane-camouflaged nanoparticles have a prolonged *in vivo* half-life due to the high expression of CD47 signaling molecules on the membrane surface.<sup>201</sup> Neutrophil membrane-camouflaged nanoparticles accumulate at MI inflammation sites due to inflammatory chemotactic effects of vascular endothelial adhesion molecules (*e.g.*, P-selectin and chemokine receptors).<sup>202</sup> Compared with cell therapy, cell membrane-camouflaged biomimetic nanoparticles have following several advantages. (1) Multiple adhesion molecules expressed on the cell membrane endow the inner core with prolonged circulation time and infarct/inflammation targetability.<sup>203</sup> As a result, cell membrane-camouflaged nanoparticles exhibited a lower demand for hydrogel delivery compared to cell therapy. Few studies used hydrogel to deliver cell membrane-camouflaged nanoparticles for MI therapy. (2) Cell membrane-camouflaged nanoparticles do not have survival issues, which is unique to cell therapy. Besides, cell membrane-coated camouflaged nanoparticle formulation is more

stable during storage. (3) Cell membrane-camouflaged nanoparticles are commonly nanometer in size. As a result, they can efficiently cross the tissue and cell barrier and penetrate deeper.<sup>204</sup> (4) Cell membrane-camouflaged nanoparticles show lower T-cell immune response levels than cell preparations.<sup>205</sup> Additionally, in contrast to cell-derived EVs, cell membrane-camouflaged nanoparticles have the advantages of various inner core selections, superior drug loading capacity, and high preparation efficiency.

The preparation of cell membrane-camouflaged nanoparticles is primarily divided into four steps.<sup>206</sup> (1) Cell membrane extraction and separation. Freezing or hypotonic are usually employed to lyse cells. Differential centrifugation is used to separate the cell membrane from the rest of the cell contents. (2) Cell membrane vesicle preparation. The lipid co-extrusion method is used to generate nanometer-sized cell membrane vesicles. (3) Inner core preparation. PLGA is the most commonly used core material, prepared using a solvent substitution method. (4) Cell membrane-camouflaged nanoparticles preparation. Lipid co-extrusion, microfluidics, or ultrasonication are commonly used to wrap the cell membrane onto the inner core to fabricate core–shell nanoparticles. Although the preparation process is time-consuming, it has a higher yield than that of cell-derived EVs.

Stem cell membranes express and attach with pro-cardiac or vascular regenerative cytokines.<sup>207</sup> Neutrophil membranes bind inflammatory factors at the site of infarction, reducing inflammation. However, the therapeutic effect of cell membrane-coated nanoparticles for MI is extremely limited due to the lack of paracrine effect and release of endogenous active substances. To compensate for the diminished MI therapeutic activity of cell membrane-camouflaged nanoparticles, researchers usually load drugs in the inner core nanoparticles, including small molecule drugs (*e.g.*, cyclosporine A and celecoxib) and active biomacromolecules (*e.g.*, pro-angiogenic factors and miRNAs).<sup>208,209</sup> Although cell membrane-camouflaged nanoparticles are not in high demand for hydrogel delivery as an emerging cell-derived MI therapeutic strategy, we still summarize the relevant studies in this section due to their potential MI therapeutic effect and intimate connection with cell therapy (Fig. 4).

### 5.2.1 Blood cell membrane-camouflaged nanoparticles.

The blood cells discussed in this paper mainly refer to red blood cells and platelets. The general advantage of using blood cell membranes for encapsulation is to confer the immune escape ability to nanoparticles.<sup>210</sup> Particularly, erythrocytes can circulate in the bloodstream for 120 days.<sup>211</sup> Encapsulation of erythrocyte membranes effectively prevents nanoparticles from being eliminated by the mononuclear phagocytic system during circulation. CD47 is highly expressed on the erythrocyte membrane. Furthermore, as the most numerous blood cells, abundant and easily accessible erythrocytes are an ideal cell membrane type source. As a result, erythrocyte-based drug delivery systems have clinical potential in several disease treatments. In recent years, red blood cell formulations for treating triple-negative breast cancer have entered clinical phase III,

which can provide certain guidance for quality control assessment of cell/cell membrane formulations.<sup>212</sup> Zhang *et al.* constructed a biomimetic drug delivery system with erythrocyte/platelet cell membrane encapsulation. The erythrocyte/platelet membrane wrapping primarily provided extended *in vivo* circulation capability. They could aggregate in the infarct region and responsively form a hydrogel-like structure. Then, encapsulated MSC-EVs released multiple endogenous cytokines. This delivery system showed superior targetability to ischemic tissues and promoted vascular regeneration in acute hindlimb ischemia and myocardial infarction models.<sup>213</sup> Erythrocyte membrane-camouflaged nanoparticles constructed by Huang *et al.* had long circulation and extended drug-release profiles for sustained ischemic myocardium protection.<sup>214</sup> Li *et al.* applied this system to sepsis-induced cardiac injury and achieved similar therapeutic results.<sup>215</sup> Lu *et al.* encapsulated miRNA-208a inhibitors (with a nucleic acid sequence complementary to miRNA 208a complementary nucleic acid sequence) into erythrocyte membrane-camouflaged nanoparticles. The miRNA-208a inhibitors promoted the recovery of cardiac function by silencing miRNA-208a.<sup>216</sup>

Platelets inhibit cardiovascular bleeding injury by forming clots through aggregation.<sup>217</sup> Platelets have a variety of membrane-bound molecules on their membranes, such as GPIIb/IIIa, CD62P, immunomodulatory proteins, CD47, and CD55.<sup>184</sup> During the inflammatory phase of infarction, CD62P on the platelet surface binds to *P*-selectin glycoprotein ligand-1 (PSGL-1) on monocytes, forming monocyte-platelet aggregates (MPA).<sup>218</sup> Thus, platelet membrane-camouflaged nanoparticles can target the ischemic and inflammatory milieu after MI. On the one hand, the damage factors released early in MI recruit platelets/platelet-derived nanoparticles. On the other hand, platelet membrane-camouflaged nanoparticles can bind to monocytes in blood circulation. Monocytes are further recruited to the site of MI inflammation induced by chemokines. These processes enhance the post-MI cardiac targeting ability of platelet-derived nanoparticles. Zhang *et al.* reported a platelet membrane-camouflaged silica nanoparticle to deliver H-D-Arg-Dmt-Ly-Phe-NH2 (SS31) peptide with antioxidant capacity. This strategy effectively delivered SS31 peptide to the damaged heart site to exert antioxidant function.<sup>219</sup> In addition, researchers have delivered non-selective  $\beta$ -blockers (Carvedilol), tissue fibrinogen activator (tPA), and CSCs-derived secretome by platelet membrane-coated nanoparticles for treating MI.<sup>220</sup>

### 5.2.2 Stem/progenitor cell membrane-camouflaged nanoparticles.

Similar to blood cells, stem cells show certain immune escape ability.<sup>221</sup> The encapsulation of stem cell membranes reduces the phagocytosis of nanoparticles by the immune system and increases the blood half-life of nanoparticles.<sup>222</sup> Notably, the stem cell membrane itself also has MI therapeutic activity.<sup>198</sup> Stem cell–cell membranes contact the injected stem cells, triggering intracellular protective/regenerative signal pathways in the host cells.

Tang *et al.* demonstrated the safety and efficacy of CSCs cell membrane-camouflaged nanoparticles (CMMPs), which carry secreted and membrane proteins similar to those of CSCs.

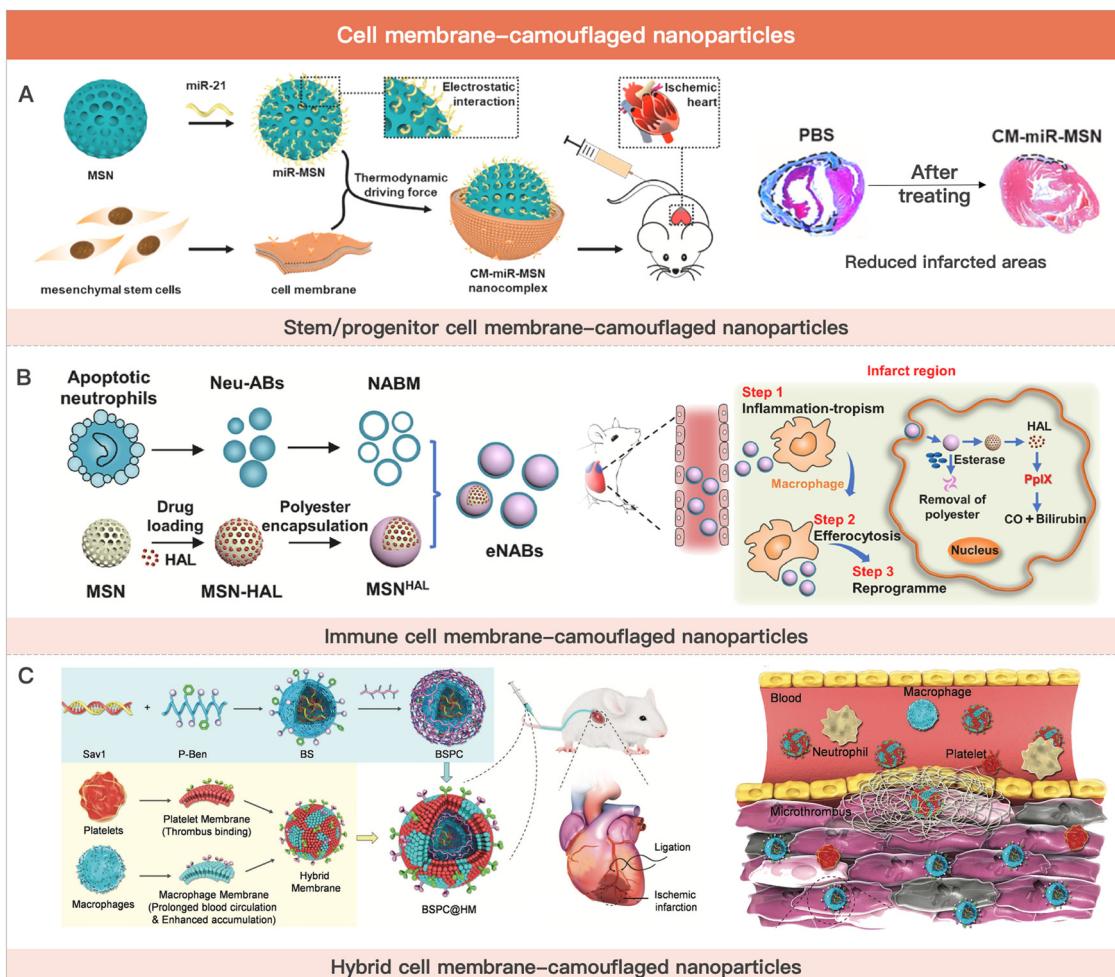


Fig. 4 Cell membrane-camouflaged nanoparticles for MI therapy. (A) Schematic illustration of stem cell membrane-camouflaged exosome-mimicking nano-complex for the miRNA-mediated repair of MI injury. Reproduced with permission from ref. 223, Copyright Elsevier 2020. (B) Schematic of engineered neutrophil apoptotic bodies (eNABs) for MI treatment. Reproduced from ref. 229 under the open access policy of Elsevier 2021. (C) Schematic illustration of the platelet-macrophage hybrid membrane-coated nano-complexes for the myocardial siSav1 delivery and MI/IR injury management. Reproduced with permission from ref. 227, Copyright Wiley-VCH GmbH 2023.

In a mouse model of myocardial infarction, CMMPs enhanced cardiac function without causing infiltration of T cells in mice.<sup>198</sup> Yao *et al.* used this drug delivery system for the cardiac delivery of miRNAs. The nanoparticles effectively encapsulated miRNAs and protected them from *in vivo* protease degradation. miRNAs delivered to the site of ischemic injury inhibited the translation of apoptosis-related proteins, effectively improving cardiac function in MI model mice.<sup>223</sup>

**5.2.3 Immune cell membrane-camouflaged nanoparticles.** Immune cells play a crucial role in developing inflammation and cardiac remodeling after myocardial infarction. This section mainly focuses on monocytes/macrophages, neutrophils, and regulatory T lymphocyte cell membrane-camouflaged nano-delivery systems for MI therapy.

Monocytes/macrophages mediate the innate immune response *in vivo*. After MI occurs, monocytes are recruited to the infarct site and differentiate into macrophages.<sup>224</sup> Together with the cardiac resident macrophages, the recruited macrophages regulate the inflammatory balance at all phases of MI.

They are able to bind to vascular cell adhesion molecule-1 (VCAM-1) on chemically injured vascular endothelial cells.<sup>225</sup> By inheriting the inherent targeting and migration ability of macrophages, the nanoparticle delivery system was able to deliver polydopamine with antioxidant capacity to the infarcted myocardium. It has shown great potential in myocardial ischemia/reperfusion injury (MI/RI) therapy.<sup>226</sup> Based on this, Zhou *et al.* used macrophage cell membrane-camouflaged nanoparticles to deliver Sav1 siRNA. By down-regulating Sav1 expression levels in injured myocardium, the nano complex significantly inhibited cardiomyocyte apoptosis and restored cardiac function.<sup>227</sup>

Neutrophils infiltrate the inflammatory regions of myocardial infarction through the interaction of surface adhesion molecules with endothelial cells. Based on this, Han *et al.* used neutrophil membrane-camouflaged nanoparticles to alleviate ischemic myocardial injury-mediated inflammation and promote angiogenesis. The mechanism involved the pro-angiogenic effect of IL-5 and the inflammatory factor absorption effect of the

neutrophil membrane.<sup>195</sup> During the inflammatory and proliferative phases of MI, neutrophils apoptosis and are phagocytosed by macrophages.<sup>228</sup> This leads to a polarization of macrophages from pro-inflammatory M1-phenotype macrophages to anti-inflammatory M2-phenotype. This process mediates the

transition of MI from the inflammatory phase to the proliferative phase. Administration of neutrophil-derived apoptotic vesicles early in MI to suppress the inflammatory microenvironment in the infarcted region may be an effective strategy for MI treatment. In addition, neutrophils are recruited to the infarcted region

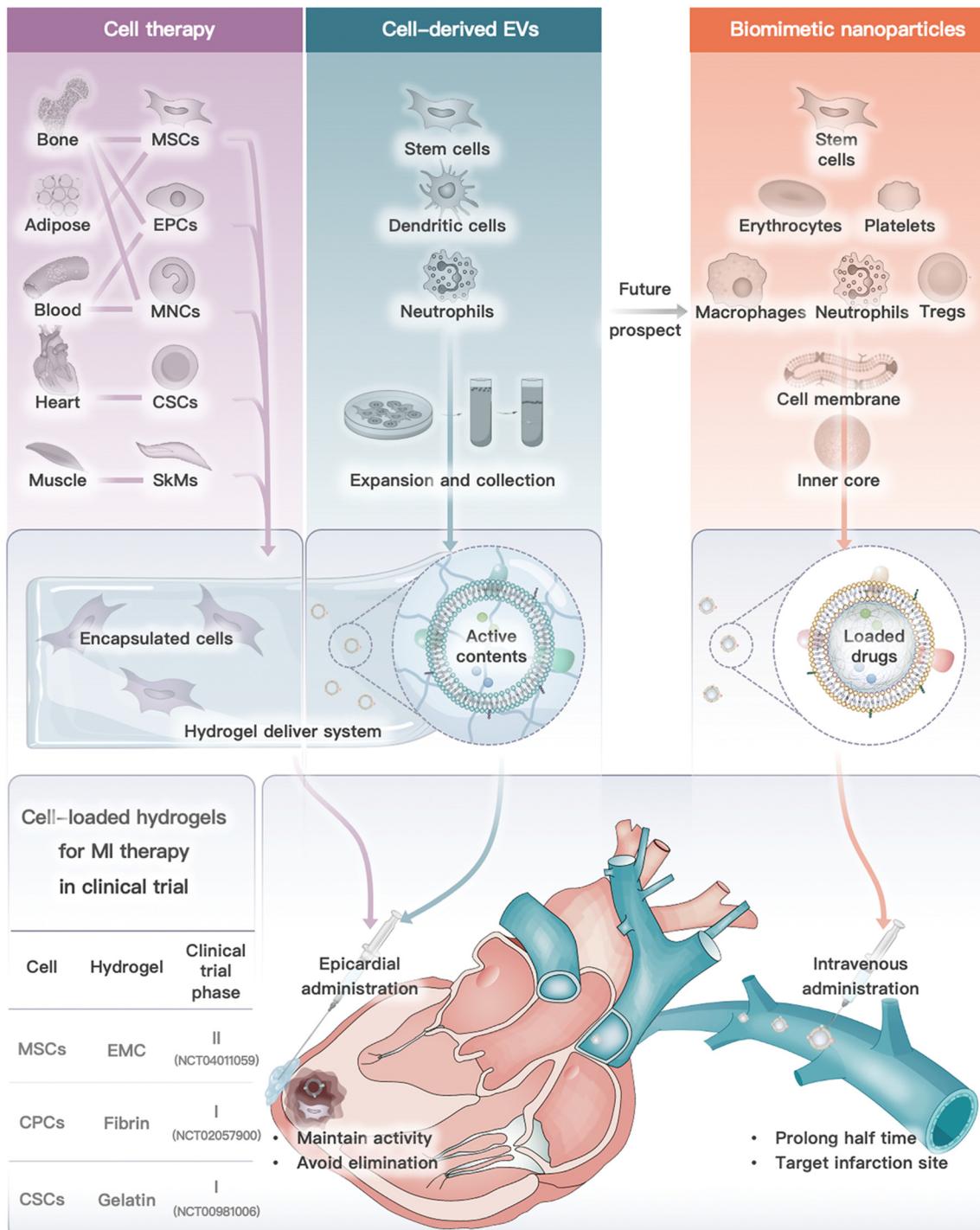


Fig. 5 Cell or cell derivative-laden hydrogels for MI therapy and future prospect on biomimetic nanoparticles. Cell or cell-derived EVs need to be encapsulated into hydrogels and delivered by epicardial administration (or other feasible routes), while cell membrane camouflaged nanoparticles exhibited lower demand for hydrogel delivery, which are commonly administrated by intravenous injection. Notably, three clinical trials of cell-loaded hydrogel for MI therapy are also summarized.<sup>141,143,153</sup>

Table 3 Summary of advantages and disadvantages of cell or cell derivative-laden hydrogels for MI therapy

|                  | Cell sources  | Advantages   | Disadvantages   |
|------------------|---|--|---|
| Cell therapy     | <ul style="list-style-type: none"> <li>• Mesenchymal stem cells</li> <li>• Endothelial progenitor cells</li> <li>• Monocytes</li> <li>• Cardiac-derived stem cells</li> <li>• Skeletal myoblasts</li> <li>• Cardiomyocytes</li> </ul> | <ul style="list-style-type: none"> <li>• High differentiation and proliferation activity</li> <li>• Paracrine effect</li> </ul>  | <ul style="list-style-type: none"> <li>• Low cell viability</li> <li>• Poor formulation storage stability</li> <li>• Fast clearance</li> <li>• Activates local T-cell response</li> </ul> |
| Cell-derived EVs | <ul style="list-style-type: none"> <li>• Stem/progenitor cells (CPCs, EPCS, MSCs)</li> <li>• Dendritic cells</li> <li>• Regulatory T cells</li> </ul>   | <ul style="list-style-type: none"> <li>• No viability issues</li> <li>• Relatively stable formulation storage</li> <li>• High tissue penetration ability</li> <li>• Can release active substances</li> <li>• Weak local T-cell response</li> </ul> | <ul style="list-style-type: none"> <li>• Low yield</li> <li>• Fast clearance, poor targeting</li> <li>• No differentiation and proliferation ability</li> </ul>                           |

during the inflammatory phase. Thus, intravenous infusion of neutrophil-derived apoptotic vesicles is able to target the site of ischemic inflammation in the heart, which greatly reduces the need for hydrogel delivery. Bao *et al.* used neutrophil apoptotic vesicle membranes wrapped in silica nanoparticles to mimic neutrophil apoptosis in the MI state. The functionalized neutrophil apoptotic vesicles had excellent inflammatory targeting ability and enhanced macrophage efferocytosis and reprogramming for inflammation resolution. This strategy could promote cardiac tissue regeneration after MI.<sup>229</sup>

Regulatory T lymphocytes express the Forkhead box P3 (Foxp3) transcription factor, which plays an important role in maintaining immune system homeostasis and suppressing the pro-inflammatory immune responses.<sup>230</sup> Saxena *et al.* reported that Treg depletion increased inflammatory response and dilated left ventricular in mice after myocardial infarction.<sup>231</sup> Another study reported similar results. The adoptive transfer of Tregs attenuated the post-infarction inflammatory response with poor cardiac remodeling.<sup>232</sup> Inspired by this, Li *et al.* prepared Treg biomimetic nanoparticles that mimic Treg to perform various functions, such as targeting ischemic myocardium, anti-inflammation, anti-apoptosis, and scavenging reactive oxygen species. This strategy significantly alleviated left ventricular remodeling and enhanced cardiac function and has the potential to treat MI/RI.<sup>233</sup>

## 6. Conclusion

In conclusion, from the perspective of cell types, we introduced cell or cell derivative-laden hydrogels for MI therapy and the prospective future by using cell-derived nanoparticles (Fig. 5). These therapies have been developed to address the limitations of traditional cell therapy and to move towards engineered cell therapy. However, each therapy modality has its own advantages and disadvantages (Table 3). Cell or cell-inspired MI therapy requires hydrogel delivery, especially cell therapy and cell-derived EVs, as they are rapidly eliminated after *in vivo* infusion and are unable to remain in the ischemic region for long periods of time.<sup>234</sup> Currently, several stem cell intracardiac infusions are in clinical phase III trials for MI treatment.<sup>132</sup>

However, there have been limited clinical trials on the use of cell-derived EVs for MI treatment. A single study on the use of EVs derived from cardiovascular progenitor cells has entered clinical trials for non-ischemic cardiomyopathy therapy.<sup>177</sup> The challenges associated with traditional drug delivery systems include low yield, difficulty in targeting specific areas *in vivo*, and challenges in quality assessment. However, cell membrane-camouflaged biomimetic drug delivery systems, such as those utilizing red blood cells or immune cell membrane-camouflaged nanoparticles, offer potential advantages such as long-term circulation and targeted delivery to inflammatory areas. As a result, cell membrane-camouflaged nanoparticles have a lower demand for hydrogel administration when compared to cell treatment. However, researchers need to address several issues (e.g., stability, large-scale production, animal model selection, and administration timing) before the commercialization of cell or cell derivative-laden hydrogels for MI treatment.

Despite the hurdles and concerns, cell or cell derivative-laden hydrogel formulations for MI are expected to be available soon, owing to the significant potential of cell or cell-inspired techniques in MI therapy, as well as the rapid progress of injectable hydrogels in clinical trials.

## Author contributions

Z. X. mainly contributed to this work, and the manuscript was written through the contributions of all authors. All authors have given approval to the final version of the manuscript.

## Conflicts of interest

There are no conflicts to declare.

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