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Review

Therapeutic angiogenesis based on injectable hydrogel for protein delivery in ischemic heart disease

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SUMMARY

Ischemic heart disease (IHD) remains the leading cause of death and disability worldwide and leads to myocardial necrosis and negative myocardial remodeling, ultimately leading to heart failure. Current treatments include drug therapy, interventional therapy, and surgery. However, some patients with severe diffuse coronary artery disease, complex coronary artery anatomy, and other reasons are unsuitable for these treatments. Therapeutic angiogenesis stimulates the growth of the original blood vessels by using exogenous growth factors to generate more new blood vessels, which provides a new treatment for IHD. However, direct injection of these growth factors can cause a short half-life and serious side effects owing to systemic spread. Therefore, to overcome this problem, hydrogels have been developed for temporally and spatially controlled delivery of single or multiple growth factors to mimic the process of angiogenesis *in vivo*. This paper reviews the mechanism of angiogenesis, some important bioactive molecules, and natural and synthetic hydrogels currently being applied for bioactive molecule delivery to treat IHD. Furthermore, the current challenges of therapeutic angiogenesis in IHD and its potential solutions are discussed to facilitate real translation into clinical applications in the future.

INTRODUCTION

According to estimates, 6.2 million Americans suffer heart failure (HF).[1] Ischemic heart disease (IHD) is the most prevalent cause of this disease and continues to be a major cause of morbidity and mortality in industrialized countries.[2] IHD, also known as coronary artery disease (CAD), is defined as stenosis or blockage of arterial lumens and inadequate blood supply to the myocardium, which causes myocardial ischemia, hypoxia, necrosis, and eventually negative ventricular remodeling.[3,4] Traditional treatment strategies include drug therapy, such as antiplatelet drugs, lipid-lowering drugs, drugs to reduce myocardial oxygen consumption, thrombolytic drugs, percutaneous transluminal coronary intervention, and surgical bypass grafting.[5,6] However, some patients may not be suitable for traditional treatments because of severe diffuse coronary disease, complex coronary anatomy, or other factors.[7,8] Therefore, exploring new therapeutic strategies for treating this defect is necessary. Therapeutic angiogenesis, which can accelerate endogenous collateral circulation and ultimately generate more neovascularization, is a promising therapeutic strategy.[9–11] However, the treatment of IHD through therapeutic angiogenesis by growth factors alone has significant limitations, including systemic edema, hypotension due to the diffusion of local growth factors into surrounding blood vessels, and a short half-life of growth factors leading to insufficient therapeutic effect.[12–15] Hydrogels, as new materials, can compensate for this drawback by carrying these bioactive molecules to reduce side effects and prolonging half-life to have a better therapeutic effect.[16–19] This review will focus on the mechanisms of angiogenesis, the major bioactive molecules involved in therapeutic angiogenesis, currently available hydrogels, and future prospects.

THE MECHANISM OF ANGIOGENESIS

Vascular system development is generally considered to involve three critical biological processes: vasculogenesis, angiogenesis, and arteriogenesis. Vasculogenesis typically occurs during the early stages of embryonic vascular development. They are best described as precursor cells called angioblasts that differentiate into endothelial cells (EC) and migrate into avascular areas to form a primitive vascular network.[20–22]

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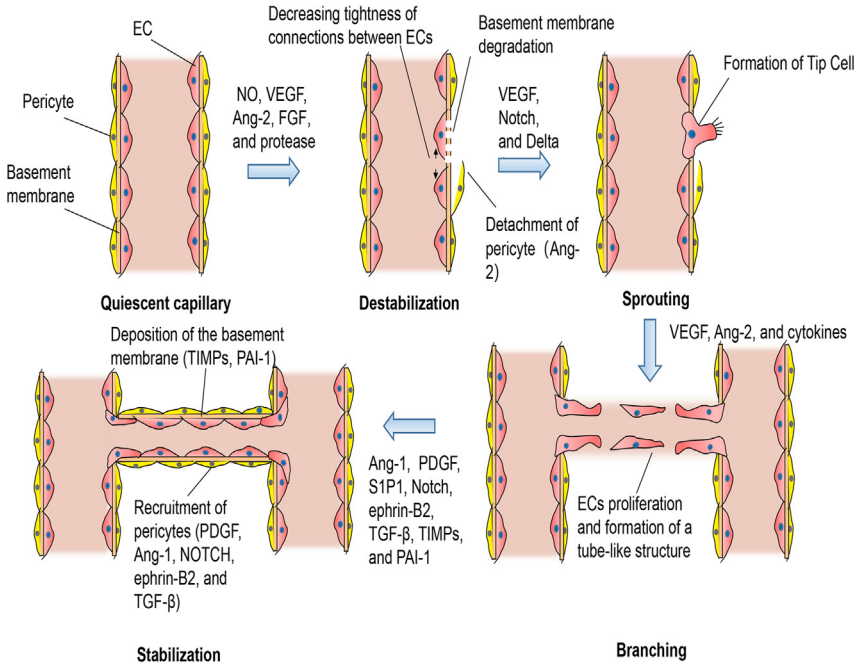

Figure 1. The process of angiogenesis

Under the stimulation of hypoxia, quiescent capillaries enter the step of destabilization, which includes decreasing the tightness of connections between EC, degradation of the basement membrane, and separation of pericytes. The Tip Cells then sprout, and other EC proliferate to form a tube-like structure. Finally, basement membrane deposition and pericyte recruitment stabilized the tube-like structure. EC, endothelial cells; NO, nitric oxide; Ang-2, angiopoietin-2; VEGF, vascular endothelial growth factor; FGF, fibroblast growth factor ; S1P1, sphingosine-1-phosphate-1; TGF-β, transforming growth factor-β; Notch, Notch signaling; Ang-1, angiopoietin-1; PDGF, platelet-derived growth factor; PAI-1, plasminogen activator inhibitor-1; TIMPs, metalloproteinases.

Angiogenesis refers to the formation of microvessels from the existing vascular system due to increased permeability caused by vasodilatation of venules, leading to the proliferation and migration of ECs. Enlarged venules divide through intussusception or bridging to form new capillaries. Pathologically, this process occurs in tumor growth and diabetic retinopathy, and physiologically, in wound healing and along the edge of myocardial infarction (MI).[23] Arteriogenesis is the restoration and remodeling of collateral arteries and the growth of the original musculature arterioles into major arteries. Under hypoxia, hypoxia-inducible factor-1α (HIF-1α) binds to hypoxia-inducible factor-1β (HIF-1β), which subsequently stimulates the hypoxia response element (HRE) and upregulates vascular endothelial growth factor (VEGF) gene, ultimately leading to enhanced angiogenesis.[24] Furthermore, in addition to VEGF, other key biochemical molecules are also upregulated by HIF-1 during angiogenesis, including angiopoietin-2 (Ang-2), platelet-derived growth factor-B (PDGF-B), stromal cell-derived factor-1 (SDF-1), placental growth factor (PGF), and stem cell factor (SCF)[25–30] Angiogenesis is an extremely complex process and can be divided into four stages: destabilization, sprouting, branching, and stabilization (Figure 1). Each stage of angiogenesis is mediated by many bioactive molecules that interact with the cells. Under normal physiological conditions, EC are in a quiescent stable state, which is maintained by VEGF, fibroblast growth factor (FGF), angiopoietin-1 (Ang-1) and Notch.[31,32] Hypoxic conditions can be sensed by EC and other stromal cells, which express hypoxia-inducible factors and oxygen sensors, such as hypoxia-inducible factor 2α (HIF-2α) and prolyl hydroxylase domain 2 (PHD2). When hypoxia is perceived, angiogenic signals, such as nitric oxide (NO), VEGF, Ang-2, and FGF, are released.[31,32] These signals cause pericytes to detach from the vessel wall and the connections of EC to loosen, thereby allowing the vessel to dilate. Angiogenic signals interact with extracellular matrix (ECM) proteases to increase vascular permeability. This is an important step in the process of angiogenesis, which is called destabilization. Subsequently, extravasation of plasma proteins (such as fibrinogen and fibronectin) forms a scaffold to facilitate sprouting, which is mainly the biological manifestation of a specialized endothelial cell, termed a Tip Cell, by Notch receptors and their Delta-like 4 ligand.[33] Subsequently, EC around the tip cell proliferate to promote the formation of a tube-like structure, which is described as branching. The blood begins to flow when two growing

tube-like structures meet and fuse. The final stage is stabilization, which involves the deposition of the basement membrane on the outside of the tube-like structure and the recruitment of pericytes. This process is mainly mediated by Ang-1, PDGF-B, sphingosine-1-phosphate-1 (S1P1), Notch signaling, metalloproteinases (TIMPs), plasminogen activator inhibitor-1 (PAI-1), and transforming growth factor-β (TGF-β)[34,35] For further description and details of the mechanism of angiogenesis, we point the reader to several reviews.[31,36–39]

In the pathophysiological process of IHD, the body compensates for promoting endogenous collateral circulation through hypoxia following coronary artery occlusion; however, this compensatory process is limited. The purpose of therapeutic angiogenesis is to enhance the endogenous collateral circulation process, followed by compensatory restoration of more blood flow, to achieve the purpose of treatment. Therefore, a comprehensive understanding of the role of angiogenesis in IHD and its fundamental molecular mechanisms is essential. By understanding the molecular mechanisms of angiogenesis, we can select important bioactive molecules that can be used to design better therapeutic angiogenesis strategies.

IMPORTANT BIOACTIVE MOLECULES

Vascular endothelial growth factor

VEGF is one of the most widely studied angiogenic growth factors for treating IHD. The functions of VEGF include enhancing the survival, migration, and proliferation of EC; increasing vascular permeability; and producing plasminogen activators, all of which are related to angiogenesis.[40,41] The VEGF family is composed of seven members. However, the term VEGF often refers to the VEGF-A subtype, one of the subfamily members that have been the subject of the most research, along with VEGF-B, C, D, E, F, and placental growth factors. Known VEGF-A spliced isoforms include VEGF121, VEGF145, VEGF165, VEGF189, and VEGF206, among which VEGF165 is the most prominent. VEGF ligands bind to three major receptors (VEGFR-1, VEGFR-2, and VEGFR-3) and two co-receptors (neurophospholipid receptors NP-1 and NP-2). EC generally express VEGFR1 and VEGFR2, which promote endothelial cell migration, proliferation, vascular permeability, and vascular dilatation and control angiogenesis.[42–44] The primary function of VEGFR3, which binds VEGF-C and VEGF-D, is to promote lymphangiogenesis.[45,46] Animal studies have shown that the direct delivery of adenovirus vectors expressing VEGF121 and VEGF165 in the myocardium could enhance collateral formation and restore myocardial perfusion and cardiac function.[47,48] Additionally, intracoronary infusion of VEGF165 significantly increased blood flow to the collateral-dependent ischemic myocardium.[49,50] For example, in a porcine model of MI, John et al. reported that a single intracoronary delivery of VEGF could effectively generate physiologically substantial angiogenesis.[50]

VEGF has also shown potential in clinical trials to treat coronary heart disease (Table 1). In one trial, 15 patients who were not candidates for coronary revascularization but had functional myocardium received increasing doses of intracoronary VEGF165. Clinical improvements in 7 patients' myocardial perfusion, 7 patients' angiographic indications of the density of collateral circulation and 13 patients' symptoms were shown. Increased myocardial flow at rest was also observed in a phase 1 research after intracoronary rhVEGF injection.[51] Because the trial was not blinded and no placebo group was used as a control, no reliable conclusions can be drawn about the clinical benefit of rhVEGF. However, the results suggest that intracoronary infusion of rhVEGF appears to be safe and well tolerated at a dose of 0.050 μg/kg/min.[51] In addition, 178 subjects with stable IHD participated in the VIVA experiment, where they were randomly assigned to receive either intracoronary rhVEGF protein or a placebo. Endpoints included nuclear perfusion imaging at 60 days, exercise treadmill testing, and quality of life evaluation. Both the treatment and placebo groups showed improvements in the subjects' clinical conditions and treadmill tests; however, this trial was terminated prematurely because of a lack of significantly favorable results.[52]

Fibroblast growth factor

FGF is another key growth factor involved in angiogenesis. The human FGF gene family comprises 22 members, ranging from FGF-1 to FGF-23 (except FGF15), and primarily binds to 7 Fibroblast Growth Factor Receptor (FGFR) subtypes: FGFR1b, FGFR1c, FGFR2b, FGFR2c, FGFR3b, FGFR3c, and FGFR4.[57,58] FGF-1, also known as acidic FGF or aFGF, and FGF-2, also known as basic FGF or basic fibroblast growth factor (bFGF), are endothelial cell mitogens that also act on smooth muscle cells and fibroblasts.[59,60] FGF promotes its binding to tyrosine kinase receptors through cell-surface heparan sulfate proteoglycans, induces endothelial cell proliferation, migration, and protease production, and participates in angiogenesis.[61,62] FGF stimulates the synthesis of proteases by EC, including plasminogen activators and

Table 1. Clinical trials of protein for therapeutic angiogenesis in ischemic heart disease

Protein	Active Agent/ Placebo, n/n	Route of administration	Patients	Duration of Follow-up	Results	Reference
VEGF	15/0	Intracoronary administration	Angina, viable underperfused myocardium not able to be revascularized	30 and 60 days	Clinical improvements in 7 patients' myocardial perfusion, 7 patients' angiographic indications of density of collateral circulation, and 13 patients' symptoms	Henry et al.[51]
VEGF	178 total; allocated in a 1:1:1 ratio to the placebo group, low-dose VEGF group, and high-dose VEGF group	Intracoronary injection plus 3 intravenous injections	Angina, viable underperfused myocardium not able to be revascularized	60 and 120 days	Improvements in the patients' clinical conditions and treadmill tests were observed in both the treatment and placebo groups	Henry et al.[52]
FGF-2	52/0	A single intracoronary administration	Advanced CAD, viable underperfused myocardium not able to be revascularized	29, 57, and 180 days	A significant reduction in the angina class, an improvement in exercise endurance, and an increase in regional ventricular wall thickness as evaluated by MRI.	Laham et al.[53]
FGF-2	59/0	Intracoronary (n = 45) or intravenous (n = 14) administration	Angina, viable underperfused myocardium not able to be revascularized	29, 57, and 180 days	Improved resting myocardial perfusion and reduced myocardial ischemia.	Udelson et al.[54]
FGF-2	337 total; allocated in a 1:1:1:1 ratio to receive 0.3, 3, or 30 g/kg FGF-2 or placebo	A single intracoronary administration	Advanced CAD, viable underperfused myocardium not able to be revascularized	90 and 180 days	Not improvement in exercise tolerance or myocardial perfusion but symptomatic improvement trends at 90 (but not 180) days	Simons et al.[55]
FGF-2 + heparin-alginate	16/8	Periadventitial implantation during CABG	Nongraftable artery, undergoing CABG, viable myocardium	3 months (but longer clinical follow-up)	2 deaths during surgery and 3 Q-wave myocardial infarctions; less angina, reduced defect size on nuclear perfusion studies with high dose	Laham et al.[56]

Abbreviation: VEGF, vascular endothelial growth factor; FGF-2, fibroblast growth factor-2; MRI, magnetic resonance imaging; CAD, coronary artery disease; CABG, coronary artery bypass grafting.

metalloproteinases, which are critical for the digestion of the extracellular matrix during angiogenesis.[63] FGF-1/FGF-2 and FGFR expression are upregulated in the infarcted myocardium area in the early stage of MI, which is spatially and temporally consistent with angiogenesis.[64] In addition, FGF-9 has the potential to improve heart function in mice by activating c-Kit progenitor cells, decreasing vascular cell apoptosis, and enhancing angiogenesis and neovascularization.[65]

Clinical trials have assessed the practicability and safety of recombinant FGF (rFGF) for therapeutic neovascularization in humans with chronic coronary heart disease (Table 1). Twenty patients with 3-vessel coronary artery stenosis underwent coronary artery bypass grafting (CABG). FGF-1 was injected into the proximal vascular site. All patients developed a rich capillary network at the injection site, increasing the local blood supply to the myocardium.[66,67] In another phase I clinical trial, subjects with chronic stable angina were well tolerated after a single FGF-2 injection through the coronary artery.[68] In a dose-escalation trial, fifty-two subjects with coronary heart disease who were ineligible for surgical or interventional treatment were administered 0.33 to 48 μg/kg FGF-2 through the intracoronary route. The results demonstrated a significant reduction in the angina class, an improvement in exercise endurance, and an increase in regional ventricular wall thickness as evaluated by magnetic resonance imaging (MRI).[53] However, the occurrence of hypotension was associated with the FGF-2 dose, and 36 μg/kg was considered to be the maximum tolerated dose.[53] Additionally, intravenous or coronary administration of rFGF-2 (rFGF-2) protein can improve resting myocardial perfusion and reduce myocardial ischemia in subjects with advanced CAD.[54] The largest clinical trial of rFGF-2 for chronic CAD, the FGF Initiated Revascularization Trial (FIRST), randomized 337 patients to receive a single coronary dose of 0, 0.3, 3, or 30 μg/kg rFGF-2. Improvement in symptoms, evaluated by myocardial perfusion and exercise tolerance, was reported at 90 days but was not reported at 180 days owing to constant improvement in the placebo group. The incidence of hypotension increased in the 30 μg/kg FGF-2 group. This study clarified the feasibility and safety of rFGF, but the therapeutic efficacy of rFGF was controversial. It is possible that the half-life of FGF in the form of recombinant protein is too short to achieve sufficient angiogenesis for therapeutic purposes when administered through the coronary route.[55]

Platelet-derived growth factor

PDGFs are a family of growth factors comprising four soluble polypeptide chains: PDGF-A, PDGF-B, PDGF-C, and PDGF-D, which form five active homo- and heterodimers: PDGF-AA, PDGF-BB, PDGF-CC, PDGF-DD, and PDGF-AB. PDGF tyrosine kinase receptors have two forms, Platelet-derived growth factor receptor(PDGFR)-α and PDGFR-β.[69,70] PDGFR-α is activated by PDGF-AA, PDGF-AB, PDGF-BB, and PDGF-CC, whereas PDGF-BB and PDGF-DD activated PDGFR-β. PDGF-AB, PDGF-BB, and PDGF-CC can bind to and activate the PDGFRα/β heterodimer complex. The receptor has an intracellular tyrosine kinase domain for downstream signaling pathways, such as phosphatidylinositol 2 kinase, Src family kinase, phosphatidylinositol 3-kinase (PI3K), MAPK, and phospholipase C, and an extracellular area with five immunoglobulin-like domains that bind ligands.[71] PDGFR-expressing cells, particularly pericytes and SMCs, are recruited in developing blood vessels and participate in the maturation of blood vessels by PDGF, which is expressed by ECand acts in a paracrine manner.[72] Furthermore, PDGF mediates the fibroblast production of collagen, induces chemotaxis of inflammatory cells, and recruits stem cells from the bone marrow.[73]

A preclinical study by Zymek et al. illustrated that anti-PDGFR-β resulted in impaired maturation of the infarct vasculature, formation of dilated uncoated vessels, and enhanced capillary density in a mouse model of ischemic reperfusion.[74] In contrast, anti-PDGFR-α did not affect vascular maturation, but significantly reduce collagen deposition in the infarct area.[74] Furthermore, the upregulation of PDGF-A, PDGF-D, and PDGFR expressions in infarcted myocardium demonstrates that PDGF contributes to cardiac repair and recovery.[75] Hao et al. demonstrated that sequential delivery of VEGF-A165 and PDGF-BB resulted in improved cardiac function and formation of mature blood vessels compared to a single factor.[76] These results suggested that PDGF exerts a crucial role in protecting cardiomyocytes after MI.

Transforming growth factor β

TGF-β is a member of the dimeric polypeptide growth factor family. TGF-β and its receptor can be expressed by almost every type of cell in the body, including endothelial, epithelial, connective-tissue, hematopoietic, and neural cells. TGF-β regulates cell proliferation and differentiation, angiogenesis, wound healing, and embryonic development *in vivo*.[77,78] TGF-β has 3 isoforms: TGF-β1, TGF-β2, and TGF-β3. Each isoform performs a specific function, is expressed in a tissue-specific manner, and is encoded

by a separate gene. TGF-β1 is mostly expressed in EC, hematological tissues, and connective tissues.[79] TGF-β2 is primarily expressed in neurons and epithelial cells. TGF-β3 is primarily expressed in mesenchymal cells.[80] The TGF-β receptors include types I, II, and III. In their intracellular protein area, type I and type II receptors comprise serine/threonine kinase domains, which activate intracellular signal transduction through the phosphorylation of Smads to perform specific functions. Type III receptors, however, do not have kinase activity and are generally believed to migrate to type II receptors after binding to the TGF-β ligand.[77] Smad2 and Smad3 are phosphorylated by activated type I TGF-β receptors, while Smad6 and Smad7 prevent Smad2 or Smad3 from being phosphorylated, thereby blocking the TGF-β signaling pathway. TGF-β ligands bind and stimulate type II receptors, which recruit, bind, and phosphorylate type I receptors. The activated type I receptors phosphorylate Smad2 or Smad3, which then binds to Smad4. As a result, Smad complexes are formed. These complexes then migrate into the cell nucleus, where they can interact with various transcription factors to control gene expression in cell-specific manners.[80] Interestingly, when TGF-β expression levels are low, angiogenesis can be promoted by the upregulation of angiogenic factors and proteases. However, high doses of TGF-β can recruit SMCs, stimulate basement membrane reformation, promote differentiation of EC, and inhibit endothelial cell growth. This process is believed to promote the stabilization of neovasculogenesis.[81,82] Additionally, TGF-β can directly promote angiogenesis *in vivo*. TGF-β antibodies can block this stimulation.[83] Selective deletion of TGF-I or type II TGF-β receptors causes reduced vasculogenesis in mice, which is associated with impaired capillary development and endothelial differentiation. These findings demonstrate that TGF-β could be essential for angiogenesis and vasculogenesis.[78,84,85]

The angiopoietin ligand and Tie

Angiopoietin (Ang) ligand and Tie (tyrosine kinase with immunoglobulin-like and epidermal growth factor-like domains-1) receptor tyrosine kinases are essential for maintaining static EC and vascular homeostasis.[86,87] Ang belongs to a family of growth factors necessary for blood vessel development. There are four varieties of Ang: Ang-1, Ang-2, Ang-3, and Ang-4. The most common angiopoietins are Ang-1 and Ang-2. All four angiopoietins bind to Tie-2. The Tie-1 receptors have rarely been studied.[86,88] The dimeric molecular weight of angiopoietins, which are secreted glycoproteins, is approximately 75 kDa. Ang-1 and Ang-2 each have 498 and 496 aa on chromosomes 8q22 and 8q23, respectively. The sequence homology between these two molecules is approximately 60%.[89,90] Perivascular cells such as fibroblasts, vascular SMCs, and pericytes continuously secrete Ang-1. It comprises an N-terminal domain, a central coiled-coil structure, and a fibrinogen domain with its C-terminus linked to the receptor. After Ang-1 binds to the Tie-2 receptor in EC, auto-phosphorylation of the intracellular Tyr split domain of Tie-2 downstream activates protein kinase B (AKT) and PI3K.[91] The Ang-1/Tie2 signaling pathway plays an essential role in vascular maturation during developmental, physiological, and pathological angiogenesis. Ang-2 is synthesized primarily by EC and is pre-stored in vesicles within EC (Weibel Palade bodies, WPBs).[92] Various signals (e.g., trauma, hypoxia, thrombin, and histamine) promote the fusion of vesicles with the cell membrane, leading to the release of Ang-2, which binds to the Tie-2 receptor as an autodimer or polymeric.[92,93] Both Ang-1 and Ang-2 bind to Tie-2, but only Ang-1 induces autophosphorylation of Tie-2, activating the receptor.[89] Ang-2, as an inhibitor of the Ang-1/Tie-2 signaling pathway, does not induce autophosphorylation of the receptor but competes with Ang-1.[94] In therapeutic angiogenesis, VEGF alone induces immature and permeable blood vessels and Ang-1 plays a key role in vascular maturation.[95] Therefore, the combination of VEGF and Ang-1 is commonly used to promote functional angiogenesis.[96]

HYDROGELS FOR DELIVERY OF THERAPEUTIC PROTEINS

Therapeutic angiogenesis strategies in IHD have attempted to increase vascularization and make new vessels more robust by delivering these key signaling proteins. However, since these key signaling proteins are not protected by a carrier, most proteins are quickly cleared from the body.[97] In addition, if these proteins accumulate in other tissues and organs, side effects of angiogenesis may occur, resulting in serious clinical consequences.[98] Moreover, the administration of protein dosages that are too high could result in hypotension, tumor growth, and vascular leakage, while dosages that are too low or temporary could result in the degeneration of neovascularization.[99] Consequently, effective therapeutic angiogenesis requires the precise, tightly controlled, and sustained release of these bioactive molecules.[100] Hydrogels, owing to their ECM-like design, are excellent vehicles for delivering bioactive molecules for treating IHD[101–103] (Table 2). Additionally, hydrogels provide structural support and scaffolds for cellular infiltration. Furthermore, its degradation products can recruit endogenous stem cells.[104,105] Therefore, hydrogels alone are frequently used to treat IHD (Table 3). Hydrogels are mainly made of various biological materials and can be divided

Table 2. Summary of hydrogel for delivery of bioactive molecules in diseased animal models

Biomaterial	Bioactive molecules used	Delivery route	Applications	Time of administration post-animal model	End-point after treatment	Results	Reference
Collagen	CBD-VEGF	Epicardial patch	Rabbit MI model	Immediate	12 weeks	Improved cardiac unction and angiogenesis.	Gao et al.[107]
Collagen-GSH/GST-TIMP-bFGF hydrogel	bFGF	Intramyocardial injection	Rat MI model	Immediate	30 days	Attenuated myocardial remodeling and improved vascularization and cardiac function.	Fan et al.[108]
HA	VEGF or bFGF	Subcutaneous implant	Ear pinnas of mice	Immediate	14 days	Significant improvement in microvessel density	Peattie et al.[109]
HA	VEGF and KGF	Subcutaneous implant	Ear pinnas of mice	Immediate	14 days	Significantly improved microvessel density and robust angiogenic response.	Peattie et al.[110]
Chitosan	bFGF-2	Immobilized on the surface of the myocardium by UV-irradiation	Rabbit chronic MI model	Not mentioned	4 weeks	Significant induction of angiogenesis and collateral circulation and protection of the myocardium.	Fujita et al.[111]
Chitosan	bFGF	Intramyocardial injection	Rat MI model	1 week	4 weeks	Significant improvements in cardiac function, fibrosis, infarct size, and arterioles.	Wang et al.[112]
Disulfide-cross-linked chitosan	bFGF	Intramyocardial injection	Rat MI model	Immediate	28 days	Enhanced left ventricular functions and significantly decreased the fibrotic region of MI. A greater synergistic effect on antiapoptosis and proangiogenesis than either bFGF or the hydrogel alone.	Fu et al.[113]

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Table 2. *Continued*

Biomaterial	Bioactive molecules used	Delivery route	Applications	Time of administration post-animal model	End-point after treatment	Results	Reference
Chitosan, conjugated with poly(N-isopropylacrylamide) and sulfonate groups	VEGF, IL-10, and PDGF	Intramyocardial injection	Mouse MI model	Immediate	28 days	A decrease in macrophage infiltration, an increase in vascularization, and improvements in the ejection fraction and fractional shortening	Rocker et al.[114]
Alginate	VEGF-A165 and PDGF-BB	Intramyocardial injection	Rat MI model	1 week	28 days	Induced mature vessels and improved cardiac function. No increment in capillary density.	Hao et al.[76]
Alginate-Sulfate nanoparticles	HGF/IGF1	Intramyocardial injection	Porcine ischemia-reperfusion injury model	1 week	7 weeks	The infarct size is significantly smaller than in controls. Significantly, LVEF is considerably higher in pigs treated with HGF/IGF1-NP, and myocardial remodeling is improved.	Wu et al.[115]
Heparin-conjugated fibrin	bFGF	Intramuscular injection	Mouse ischemic limb model	1 and 6 days	28 days	Significant mprovement in vessel density in the ischemic region.	Jeon et al.[116]
Heparin-conjugated fibrin	bFGF	Intramuscular injection	Mouse hindlimb ischemia model	1 day	28 days	Significant improvements in neovascularization and reduction in muscle fibrosis and inflammation	Yang et al.[117]
Fibrin	bFGF	Transmyocardial channels	Canine MI model	30 min	8 weeks	Increased and persistent vessel density in the infarct area, improvement in myocardial perfusion and cardiac function.	Nie et al.[118]

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Table 2. *Continued*

Biomaterial	Bioactive molecules used	Delivery route	Applications	Time of administration post-animal model	End-point after treatment	Results	Reference
Fibrin	VEGF and PDGF	Intramyocardial injection	Rat MI model	5 min	28 days	Improvement in LV wall thickness, angiogenesis, cardiomyocyte survival and cardiac function, reduction in inflammation and fibrosis in the infarct region	Awada et al.[119]
Polyethylene glycol-fibrinogen	VEGF and Ang-1	Intramyocardial injection	Rat MI model	Immediate	4 weeks	Greatest degree of cardiac muscle preservation, the best improvement in cardiac function, and arteriogenesis	Rufaihah et al.[120]
dECM extracted from porcine pericardium	HGF fragment	Intramyocardial injection	Rat ischemia-reperfusion injury model	1 week	4 weeks	Improvement in vascularization and attenuation of left ventricular remodeling	Sonnenberg et al.[121]
Porcine cardiac ECM and collagen	CBD-VMP	Intramyocardial injection	Rat MI model	Immediate	3 months	Significant improvement in angiogenesis, cell apoptosis, and cardiac function.	Feng et al.[122]
PEG-maleimide with RGD and VPM	HGF and VEGF	Intramyocardial injection	Rat ischemia-reperfusion injury model	Immediate	21 days	Significant increase in angiogenesis, decrease in fibrosis, stimulation of the migration of c-kit+ progenitor cells, and improvement in cardiac function.	Salimath et al.[123]
Dex-PCL-HEMA/PNIPAAm	VEGF165	Intramyocardial injection	Rat MI model	Immediate	30 days	Improved LVEF, attenuated LV dilation and infarct size, increased angiogenesis, and inhibited cell apoptosis	Zhu et al.[124]

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Table 2. *Continued*

Biomaterial	Bioactive molecules used	Delivery route	Applications	Time of administration post-animal model	End-point after treatment	Results	Reference
NIPAAm/HEMA/AOLA	CTT	Intramyocardial injection	Rat MI model	30 min	4 weeks	Effectively prevented the degradation of the cardiac ECM, attenuated cardiac fibrosis and significantly enhanced heart function.	Fan et al.[125]
NIPAAm/HEMA/AOLA	bFGF	Intramyocardial injection	Rat MI model	30 min	4 weeks	Improved cardiac cell survival, decreased macrophage density, and decreased myofibroblast density and collagen content. Also markedly improved cardiac performance.	Fan et al.[126]
RADA16-II	A peptide mimicking the Notch1 ligand Jagged1	Intramyocardial injection	Rat ischemia-reperfusion injury model	Immediate	21 days	Significantly improved cardiac function, reduced fibrosis, and increased vessel area and Ki67 expression	Boopathy et al.[127]
RADA 16-I peptide with heparin-binding domain sequence(LRKKLGKA)	VEGF	Intramyocardial injection	Rat MI model	30 min	4 weeks	Improved heart function and adequate angiogenesis and reduced collagen deposition and scar size.	Guo et al.[128]
RADA16-I	FGF-2 and PDGF-BB	Intramyocardial injection	Rat MI model	Immediate	8 weeks	Significantly reduced infarct area and cardiomyocyte apoptosis and improved arterial density, capillary density, and cardiac functions.	Kim et al.[129]

Abbreviations: HA, hyaluronic acid; CBD, collagen-binding domain; dECM, decellularized extracellular matrix; MI, myocardial infarction; EF, ejection fraction; LV, left ventricular; VEGF, vascular endothelial growth factor; bFGF, basic fibroblast growth factor ; PDGF, platelet-derived growth factor; IL-10, interleukin-10; KGF, keratinocyte growth factor; HGF, hepatocyte growth factor; VMP, VEGF mimic peptide; Ang-1, angiopoietin-1; AOLA, acrylate-oligolactide; CTT, CTTHWGFTLC.

Table 3. Summary of hydrogel only in diseased animal models

Biomaterial	Bioactive molecules used	Delivery route	Applications	Time of administration post-animal model	End-point after treatment	Results	Reference
Collagen	none	Intramyocardial injection	Rat MI model	1 week	6 weeks	Increased SV, EF, and wall thickness	Dai et al.[130]
MeHA	none	Intramyocardial injection	Ovine MI model	Immediate	8 weeks	Significant reduction in the dilation of the infarct area and increased cardiac function.	Ifkovits et al.[131]
PEG-SH2 crosslinked HA hydrogel after acrylation	none	Epicardial injection	Rat MI model	2 weeks	4 weeks	Reduced LV infarct size and increased cardiac function, heart wall thickness, and vessel formation.	Yoon et al.[132]
Chitosan	none	Intramyocardial injection	Rat MI model	1 h	16 weeks	Increased left ventricular wall thickness, reduced infarct area, attenuated LV remodeling, and preserved LV systolic function.	Henning et al.[133]
Calcium-crosslinked alginate	none	Intramyocardial injection	Rat MI model	7 days and 60 days	60 days	Limited expansion of the LV and increased scar thickness in the recent infarcted model.Increased scar thickness and improved systolic and diastolic dysfunction in the old infarcted heart.	Landa et al.[134]
Calcium-crosslinked alginate	none	Intracoronary injection	Porcine MI model	4 days	60 days	Prevention and even reversal of LV enlargement. Increment in scar thickness.	Leor et al.[135]

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Table 3. *Continued*

Biomaterial	Bioactive molecules used	Delivery route	Applications	Time of administration post-animal model	End-point after treatment	Results	Reference
Fibrin	none	Intramyocardial injection	Rat ischemia-reperfusion injury model	1 week	5 weeks	Significantly improved ventricular wall thickness, FS, and cardiac function.	Christman et al.[136]
Zebrafish dECM	none	Intramyocardial injection	Mouse MI model	Immediate	6 weeks	Increased heart contractile performance and myocardial flexibility, as well as the proliferation of myocardial cells and other cardiac precursor cells	Chen et al.[137]
Porcine acellular myocardium	none	Epicardial patch	Rat MI model	2 weeks	8 weeks	Attenuated myocardial remodeling, improved angiogenesis, and increased left ventricular wall thickness.	D'Amore et al.[138]
Decellularized pericardial-derived scaffolds	none	Epicardial patch	Porcine MI model	30 min	30 days	The formation of nerve fibers and new blood vessels in cell-free cardiac scaffolds applied over infarcted tissue, a significant improvement in LVEF and CO and a decrease in infarct size.	Gálvez-Montón et al.[139]
Dex-PCL-HEMA/PNIPAAm	none	Intramyocardial injection	Rat MI model	4 days	30 days	Increased LVEF, reduced LVEDD and LVESD, and attenuated wall thinning and scar expansion.	Wang et al.[140]

Abbreviations: MeHA, methacrylated hyaluronic acid; HA, hyaluronic acid; dECM, decellularized extracellular matrix; MI, myocardial infarction; SV, stroke volume; FS, fractional shortening; EF, ejection fraction; CO, cardiac output; LV, left ventricular; FS, fractional shortening; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension.

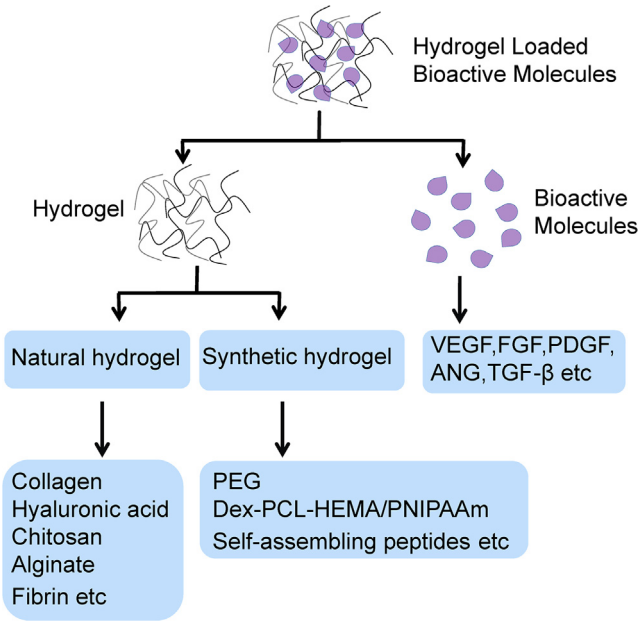

Figure 2. Schematic representation of hydrogels carrying bioactive molecules

into natural and synthetic hydrogels (Figure 2). Natural hydrogels generally have certain bioactivities and biocompatibilities. However, their mechanical strength property is low, causes inevitable inflammatory and immune issues, and are subject to inherent batch-to-batch variations. Furthermore, structural modifications are challenging because of the complexity and fragility of their structures. Despite these defects, natural hydrogels remain promising owing to their bioactivity and the fact that many naturally exist in the human body.[106] Synthetic hydrogels are also important carriers for delivering signaling proteins for therapeutic angiogenesis, owing to their powerful mechanical qualities and readily controlled characteristics, including matrix stiffness, pore size, proteolytic degradability, matrix stiffness, and cell adhesion sites. Herein, we discuss some common natural and synthetic hydrogels for delivering therapeutic proteins.

Natural hydrogel

Collagen

Collagen is a major component of the extracellular matrices (ECMs) of tissues. It is composed of amino acid sequences that can be broken down by enzymes in the presence of collagenases and is biocompatible in terms of cell recognition. The biocompatibility, robust cellular activity, and heat reversibility of collagen are advantages of using collagen. The deficiencies of collagen for hydrogel synthesis include low physical strength, poor mechanical properties, and high synthesis cost.

Only collagen for therapy. Collagen has been utilized as a natural hydrogel for the successful treatment of MI *in vivo*. Dai et al. examined the effectiveness of collagen hydrogels in a rat MI model. They discovered that the collagen hydrogel group had better ejection fraction (EF), stroke volume (SV), and wall thickness than the control group.[130] *In vitro*, endothelial cell proliferation, VEGF production, and tube formation were all stimulated by the bioactive glass (Bioglass® 45S5) placed in collagen gels.[141]

Collagen for drugs delivery. When collagen binds to growth factors, beneficial results have also been observed in animal models. Gao et al. administered collagen-binding domain (CBD)-VEGF to rabbit-infarcted myocardial tissue using a collagen-based cardiac patch. In contrast to VEGF treatment alone, studies have shown that implanting a collagen membrane patch improves cardiac function and angiogenesis.[107] In addition, Fan et al. designed a smart collagen-GSH/GST-TIMP-bFGF hydrogel, targeting matrix metalloproteinase owing to its upregulated expression after MI, for on-demand bFGF delivery. These results demonstrated that this smart hydrogel could attenuate myocardial remodeling and improve vascularization, thus promoting the recovery of MI rats.[108] These beneficial outcomes suggest that collagen hydrogel is a promising biomaterial and scaffold for delivering growth factors in treating IHD.

Hyaluronic acid

Hyaluronic acid (HA) is a polysaccharide in the connective tissues of vertebrates previously known as acid mucopolysaccharides and is now known as glycosaminoglycans. Due to its compatibility and extensive physiological activities, HA is frequently used as a biosynthetic biomaterial.[142] Hyaluronidase is a major enzyme present in cells and serum and plays a crucial role in the degradation of HA. Similar to other natural hydrogels, a significant disadvantage of HA is its poor mechanical properties, which impede its application. However, modifying the molecular structure and composition through various functionalization can improve or control its properties.[106]

Only HA for therapy. Ifkovits et al. cross-linked a methacrylated HA macromere with tetramethylenediamine and ammonium persulfate. This was tested in MI models, which revealed a significant reduction in infarct area dilation and increased cardiac function.[131] In another study, a poly (ethylene glycol) (PEG)-SH2 cross-linked HA hydrogel after acrylation was examined in a rat model of myocardial ischemia. The findings demonstrated a significant reduction in left ventricular (LV) infarct size and improvement in EF, SV index, ventricular wall thickness, and vessel formation compared with the control group.[132]

HA for drugs delivery. In addition, Peattie et al. prepared an HA hydrogel with VEGF or bFGF and tested it in the ear pinnas of mice. The results showed that combining HA hydrogel and VEGF or bFGF resulted in significantly more vessel formation than the HA-only, VEGF-only, and bFGF-only groups.[109] Similarly, they also investigated the cross-linked HA hydrogel loaded with VEGF and keratinocyte growth factor (KGF) in the ears of mice, which promoted the formation of significant microvessel beds and a robust angiogenic response.[110] These results suggest combining growth factors and HA hydrogels can produce synergistic effects.

Chitosan

Chitosan, a natural linear polysaccharide that stemmed from chitin, consists of glucosamine and N-acetyl glucosamine units. Structurally chitosan is similar to glycosaminoglycans contained in the ECM. The molecular weight and level of deacetylation of chitosan are intimately connected with its physical and mechanical characteristics. The benefits of utilizing chitosan in hydrogel preparations include antibacterial quality, low cost, bioactivity, biocompatibility, and biodegradability controlled by changing the level of deacetylation.[143] Parameters such as pH and temperature affect chitosan hydrogels. Its shortcoming is that it has weak mechanical properties; however, this issue can be solved by cross-linking with gelatin or chemical substances.[144]

Only chitosan for therapy. The post-MI scar causes ventricular dysfunction owing to the restriction of electrical impulse conduction. To get around this, polypyrrole was coupled to chitosan, and the efficacy of this conductive biomaterial in the injured heart was examined. The outcomes showed that the biomaterial was biocompatible, conductive, and enhanced electrical conduction in the damaged heart.[145] Additionally, Henning et al. injected injectable chitosan hydrogels around the MI in rats because regions of myocardial necrosis were surrounded by areas of myocardial injury and ischemia.[133] Therefore, avoiding further necrosis in the surrounding area would greatly benefit cardiomyocytes. Chitosan hydrogel reduces LV wall stress by increasing the LV wall thickness, thereby reducing stress-induced cardiomyocyte apoptosis and necrosis. Thus, chitosan hydrogels attenuated LV remodeling and preserved the LV systolic function.

Chitosan for drugs delivery. A previous study by Fujita et al. investigated the synthesis of a chitosan hydrogel incorporating bFGF-2 in a rabbit chronic MI model. The results showed significant induction of angiogenesis, collateral circulation, and protection of the myocardium.[111] Wang et al. utilized a temperature-responsive chitosan hydrogel as an injectable scaffold to slowly release bFGF and tested it in a rat MI model. Four weeks post-injection, the results showed significant improvements were observed in important cardiac parameters, including end-systolic diameter (ESD), end-diastolic diameter (EDD), EF, fractional shortening (FS), fibrosis, infarct size, and arterioles within the infarct region.[112] Furthermore, through a thiol-disulfide exchange reaction, Fu et al. prepared an injectable disulfide-cross-linked chitosan hydrogel that delivered bFGF for MI therapy. Following MI, the bFGF-hydrogel (disulfide-cross-linked chitosan hydrogel loaded with bFGF) was immediately injected into a peri-infarcted region of the heart tissue. After 28 days of treatment, echocardiography showed that the bFGF-hydrogel enhanced LV function.

According to the histological findings, the hydrogel significantly decreased the fibrotic region of MI, which was further improved by the bFGF-hydrogel treatment. The bFGF-hydrogel had a greater synergistic effect on antiapoptosis and proangiogenesis than either bFGF or the hydrogel alone, according to the TUNEL and immunohistochemical staining findings.[113] In addition, a thermoresponsive injectable gel made of chitosan conjugated with sulfonate groups and poly(N-isopropylacrylamide) was prepared by Rocker et al. to deliver VEGF, interleukin-10 (IL-10), and PDGF to treat MI. After injecting the thermal gel and proteins, the results revealed a decrease in macrophage infiltration, an increase in vascularization, and improvements in EF and FS.[114]

Alginate

Alginate, a naturally occurring polysaccharide obtained from brown algae, comprises repeating blocks of polyguluronate and polymannuronate.[146] Alginate can create a hydrogel network with soft protein encapsulation, high water absorption, minimal immunogenicity, biodegradability, and mild cross-linking chemistry; however, it does not enable cellular infiltration without modification.[146–148]

Only alginate for therapy. Landa et al. designed a calcium-crosslinked alginate solution comprising an aqueous sodium alginate and calcium gluconate solution. This novel absorbable biomaterial was injected in a recent MI model (7 days) and an old MI rat model (60 days). The results showed limited expansion of the LV and increased scar thickness in a recent infarct model. This biomaterial increases ventricular wall thickness in an old infarcted heart and improves cardiac function.[134] Alginate, used to treat MI in large animal models, such as pigs, also has promising benefits.[135]

Alginate for drugs delivery. Alginate has been used to deliver drugs to treat MIs. Hao et al. designed an injectable alginate hydrogel delivery system for sequential delivery of VEGF165, followed by PDGF-BB in a rat MI model. This sequential delivery system improves cardiac function and induces mature vessels compared to a single factor.[76] Moreover, hepatocyte growth factor (HGF) and insulin-like growth factor (IGF-1) were encapsulated in alginate-sulfate nanoparticles (AlgS-NP) by Wu et al.[115] They tested this hypothesis in a porcine ischemia-reperfusion model. Pigs (n = 12) with severe LV dysfunction (LV EF, LVEF45%) were randomly assigned to receive intramyocardial injections of either PBS or 8 mg AlgS-NP combined with 200 μg HGF and IGF-1 (HGF/IGF1-NP). Pharmacokinetic investigations of Cy5-labelled nanoparticles(NP) show that intramyocardial injections had superior cardiac retention compared to intracoronary infusion. As determined by MRI, the infarct size was significantly smaller than in controls seven weeks after intramyocardial injection of HGF/IGF1-NP and is linked to enhanced coronary flow reserve. left ventricular ejection fraction (LVEF) was considerably higher in pigs treated with HGF/IGF1-NP, and myocardial remodeling improved. These results provide a novel strategy for treating refractory ischemic cardiomyopathy and demonstrate the viability and usefulness of AlgS-NPs as a growth factor delivery system.

Alginate in human trials. Owing to the promising results of alginate in preclinical studies, clinical trials have been conducted to treat patients with coronary heart disease.[56,149–152] Laham et al. reported epicardial injections of 0, 10, or 100 μg bFGF from heparin-alginate pellets in patients undergoing CABG. As shown by MRI and nuclear perfusion imaging, the ischemic area of the target area was significantly reduced, and vascularization was improved in patients who received 100 μg bFGF (Table 1).[56] Furthermore, alginate alone has been used to treat patients with coronary heart disease in clinical trials.[149–152] Frey et al. conducted a clinical trial of IK-5001, which contained 0.3% calcium gluconate solution and 1% sodium alginate, and was injected into the infarct-related coronary artery within 7 days after MI. At the 6-month follow-up, the trial confirmed the favorable safety of the procedure, with no associated adverse events, blood test abnormalities, serious arrhythmias, or death. Echocardiographic studies demonstrated the preservation of LVEF and LV index. This indicates that intracoronary injection of IK-5001 is feasible.[149] This facilitated the initiation of a multicentre, randomized, and controlled trial to determine the effectiveness and safety of this material in high-risk subjects after ST-segment elevation MI (STEMI).[149] The PRESERVATION I Trial was a double-blind, randomized, controlled trial assessing the safety and efficacy of a bioabsorbable cardiac matrix (BCM), which was composed of an aqueous mixture of calcium gluconate solution and sodium alginate, to prevent ventricular remodeling in patients with advanced STEMI despite receiving the successful percutaneous coronary intervention (PCI)[150] Rao et al. studied the results of the PRESERVATION I trial. The results showed that after 6 months, BCM did not decrease major cardiovascular events or myocardial remodeling compared to the saline group.[151] The AUGMENT-HF trial is an international, multicentre, randomized, controlled, prospective trial to assess the efficacy and safety of a novel

approach to LV modification with alginate-hydrogel. Subjects with advanced chronic HF were randomly divided into two groups (1:1). The experimental group received an alginate-hydrogel combined with standard medical therapy (n = 40), and the control group received standard medical therapy alone (n = 38). The results showed that The experimental group could effectively improve exercise capacity and symptoms in subjects with advanced chronic HF.[152] The safety profile of this treatment was acceptable. Further clinical trials are needed to verify these promising outcomes.[152] These data suggest that alginate as a biomaterial has more potential for treating IHD in future clinical trials.

Fibrin

Fibrin is produced by fibrinogen in response to thrombin. It plays a crucial role in blood clotting.[153] In addition, because of its outstanding biocompatibility, degradability, and ability to stimulate angiogenesis and adjust gel porosity and stiffness,[154–156] fibrin is also one of the main biological materials used for tissue regeneration.[157–160]

Only fibrin for therapy. Christman et al. utilized fibrin glue to treat ischemia-reperfusion injury in a rat model. The results showed that fibrin significantly improved ventricular wall thickness and FS. This was the first time fibrin glue was injected into an ischemia-reperfusion injury model, and it showed promising effectiveness in improving cardiac function.[136]

Fibrin for drugs delivery. Fibrin hydrogels have also been used in tissue engineering to deliver growth factors. A previously utilized heparin-conjugated fibrin hydrogel containing bFGF in a mouse ischemic limb model.[116] Using an immunohistological technique, the findings revealed significant improvement in vessel density in the ischemic region. This study demonstrated that adding heparin could regulate the rate of bFGF release from fibrin hydrogels. Furthermore, a similar study by Yang et al. found significant improvements in neovascularization reduction in muscle fibrosis and inflammation in a hindlimb ischemia model after injecting heparin-conjugated fibrin hydrogel carrying bFGF.[117] The canine MI model was also treated with bFGF. The findings showed that adding fibrin contributed to an increased and persistent angiogenic response in the infarct area compared with the control group, which improved myocardial perfusion.[118] As mentioned in section 2, in the process of angiogenesis, VEGF plays an early role in forming new unstable blood vessels, whereas PDGF acts at a later stage, stabilizing blood vessels by recruiting SMCs and pericytes.[31,161] Therefore, in therapeutic angiogenesis, to achieve the release of VEGF first, then PDGF releases, Awada et al. first embedded VEGF in fibrin gel and then embedded PDGF in heparin-based coacervates distributed in the same fibrin gel.[119] This delivery system was tested in a rat model of MI. The outcomes demonstrated improved LV wall thickness, angiogenesis, cardiomyocyte survival, and cardiac function and reduced inflammation and fibrosis in the infarct region compared with the control groups.[119] Similarly, a single administration of VEGF is insufficient to maintain the stability of newly formed blood vessels, and Ang-1 has been demonstrated to stimulate angiogenesis and promote maturation and stability of blood vessels both *in vitro*[162] and *in vivo*.[163,164] One unique benefit of Ang-1 is its capacity to prevent vascular leakage.[165,166] Rufaihah et al. used polyethylene glycol-fibrinogen (PF) hydrogels for sustained dual delivery of VEGF and Ang-1 in a rat MI model. The results showed that both VEGF and Ang-1 were released in a sustained and controlled manner over 30 days. Furthermore, PF-VEGF-Ang-1-treated animals showed the greatest degree of cardiac muscle preservation and the best improvement in cardiac function and arteriogenesis.[120]

Fibrin in human trials. In a clinical trial, fibrin could be regarded as a secure and efficient therapeutic tool when used appropriately, according to a retrospective analysis of patients with a CABG surgery.[167]

Decellularized extracellular matrix

Decellularized extracellular matrix (dECM) is a naturally occurring polymeric biomaterial generated from the native myocardium (or other tissues), which contains a wide variety of proteins, proteoglycans, glycosaminoglycans, and several other matrix proteins. It provides a foundation for myocardial regeneration, repair, and remodeling owing to its ECM-mimicking abilities.[168] The generation of dECM typically involves removing cells from the heart (or other tissues) by chemical, physical, or enzymatic methods while preserving the content of native ECM.

Only dECM for therapy. The cardiac ECM can accurately match the myocardial microenvironment and thus facilitate proper implantation in the MI region.[169] Because adult zebrafish hearts have such a great regenerating capacity, Chen et al. synthesized zebrafish decellularized cardiac ECM and investigated its

potential in an MI model.[137] These findings demonstrated increased heart contractile performance, myocardial flexibility, and the proliferation of myocardial cells and other cardiac precursor cells. D'Amore et al. studied the preparation of cardiac patches from porcine acellular myocardium and examined their performance in an MI model.[138] Eight weeks after the placement of the cardiac patch in the epicardium, myocardial remodeling was influenced by the mechanical support provided by the cardiac patch, improved angiogenesis, and increased LV wall thickness. Furthermore, Galvez-Monton et al. demonstrated that decellularized pericardial-derived scaffolds could promote the formation of nerve fibers and new blood vessels in a porcine model of MI, which is another advantage of using dECM in the treatment of MI.[139]

dECM for drugs delivery. To improve the retention rate and effectiveness of the growth factor (HGF fragment), dECM extracted from the porcine pericardium was used. The hydrogel used to deliver the HGF fragment was tested using the MI model. The results showed that vascularization and attenuation of LV remodeling improved.[121] Feng et al. tested collagen binding domain peptide with VEGF-mimic peptide(CBD-VMP) peptides with an injectable cardiac ECM in a rat MI model. When injected into the infarcted myocardium, significant improvements in angiogenesis and cell apoptosis were observed, consistent with the improvement in cardiac function.[122]

dECM in human trials. With promising results in animal models, dECM entered its first clinical trial in 2019. VentriGel is a catheter-transportable hydrogel originating from porcine decellularized cardiac ECM. After evaluating its therapeutic effectiveness in animal studies, the safety and feasibility of ventrigel in patients with LV dysfunction were investigated. The promising results of this human trial prompted further investigation in larger clinical trials.[170]

Synthetic hydrogel

Although natural hydrogels have many advantages, their wide application is limited by poor mechanical properties, variability in physical properties, complexity associated with purification, risk of pathogen transmission, and immunogenicity issues. Synthetic hydrogels avoid these disadvantages because they can be tailored to meet specific applications and are biocompatible and biodegradable.[171,172] Moreover, the mechanical, chemical, and physical characteristics of these polymers, such as tensile strength, porosity, and degradation rates, are predictable, adjustable, and repeatable, which enable exceedingly precise construction.[171,173] The synthetic hydrogels for myocardial infarct repair are summarized below.

PEG, poly (ethylene glycol)

PEG is a synthetic biomaterial widely used in tissue engineering because of its biocompatibility, non-immunogenicity, and nontoxicity.[174,175] Salimath et al. developed PEG-maleimide hydrogels with GRGDSPC (RGD) adhesion peptide and a protease-degradable peptide sequence, GCRDVPMSMRGGDRCG (VPM), loaded with hepatocyte growth factor and vascular endothelial growth factor (HGF and VEGF, respectively). They assessed this PEG-based hydrogel in a rat ischemia-reperfusion injury model. These findings showed a significant improvement in angiogenesis in the dual growth factor delivery group. Furthermore, this hydrogel delivery system also decreased fibrosis, stimulated the migration of c-kit+ progenitor cells, and improved cardiac function compared with single growth factor therapy.[123]

Dex-PCL-HEMA/PNIPAAm

A thermosensitive synthetic hydrogel was developed by grafting hydrophobic poly (e-caprolactone)-2-hydroxyethyl methacrylate (PCL-HEMA) into biodegradable dextran and combining it with PNIPAAm.[123,124,176]

Only hydrogel for therapy. The injection of the Dex-PCL-HEMA/PNIPAAm hydrogel into the LV was reported by Wang et al. in 2009.[140] They used a rat model with occlusion of the proximal left coronary artery to test the effect of treatment. Four days after MI, the animals were injected with 200 μL of the Dex-PCL-HEMA/PNIPAAm hydrogel into the LV and analyzed 30 days post-injection. They showed that hydrogel alone could increase LVEF, reduce left ventricular end-diastolic dimension (LVEDD) and left ventricular end-systolic dimension (LVESD), and attenuate wall-thinning and scar expansion. This was the first time that the Dex-PCL-HEMA/PNIPAAm hydrogel alone injected into the MI model was shown to improve cardiac function and inhibit cardiac remodeling. Also, in a similar study by Ren et al., they investigated the efficacy of two Dex-PCL-HEMA/PNIPAAm hydrogels A and B, with different degradation times in a rat MI model.[176] After *in vivo* administration, hydrogel A was fully degraded for 85 days, whereas hydrogel

B, prepared with twice the amount of dextran, degraded in 28 days. They observed significant improvements after injecting the two types of thermo-responsive hydrogels with different biodegradation times in contractility, FS, LV expansion, wall thickness, collagen deposition, infarct size, and neovascularization in the infarct.[176]

Hydrogel for drugs delivery. Zhu et al. injected this hydrogel to deliver VEGF165 in a rat MI model. The outcomes showed that this delivery system improved LVEF, attenuated LV dilation, and decreased infarct size compared with either alone. Furthermore, increased angiogenesis and inhibited cell apoptosis were also observed in the hydrogel/VEGF165 group.[124] Fan et al. designed an injectable, thermosensitive, and quick gelation hydrogel delivery system. NIPAAm, hydroxyethyl methacrylate (HEMA), and the macromer acrylate-oligolactide (AOLA) form the basis of the hydrogel. To prevent MMP-2-mediated ECM degradation, adding the MMP-2 specific inhibitor peptide CTTHWGFTLC (CTT) to the hydrogel delivery system can be precisely administered into infarcted hearts at an early stage of MI. After being injected into the infarcted zone for four weeks, the released CTT effectively prevented the degradation of the cardiac ECM because it improved tissue thickness and maintained a collagen composition similar to that of normal heart tissue. The administration method also significantly enhanced heart performance. Importantly, the administration method does not cause heart fibrosis.[125] Similarly, this team created a NIPAAm/HEMA/AOLA/bFGF delivery system. When injected into tissue, it can immediately solidify and increase bFGF retention. After four weeks of implantation into infarcted hearts, the bFGF release system dramatically improved cardiac cell survival, decreased macrophage density, and decreased myofibroblast density and collagen content. The bFGF release system also markedly improved cardiac performance.[126]

Self-assembling peptides

Self-assembled peptides(SAPs) are short polypeptides that self-assemble into nanofiber gels when combined with salt solutions at physiological pH.[177] This unique property makes SAPs not only slowly degrade and have low immunogenicity but also therapeutic for the sustained release of drugs or growth factors through covalent or non-covalent coupling.[178–182]

Only hydrogel for therapy. Injectable SAPs have been shown to form an intramyocardial microenvironment that promotes the infiltration and maturation of vascular cells.[183,184]

Hydrogel for drugs delivery. RADA16-I (AcN-RADARADARADARADA-CONH2) and RADA16-II (H2N-RARADADARARADADA-OH) have been widely studied as SAPs.[185] Boopathy et al. functionalized the RADA16-II peptide with a peptide mimicking the Notch1 ligand Jagged1 (H2N-CDDYYYGFGCNK FCRPR-OH).[127] When this system was injected into a rat ischemia-reperfusion injury model, cardiac function was significantly improved. Moreover, adding a peptide mimicking the Notch1 ligand Jagged1 reduced fibrosis and increased vessel area and Ki67 expression.[127] For self-assembled peptides delivering VEGF,[128,186] the heparin-binding domain sequence (LRKKLGKA) binds to the RADA 16-I peptide to facilitate sustained delivery of VEGF.[128] According to the data, incorporating the heparin-binding domain sequence improved heart function and adequate angiogenesis and reduced collagen deposition and scar size, when the system was injected into a rat MI model.[128] In addition to VEGF delivery, self-assembled peptides have been used for the delivery of PDGF-BB, stromal cell-derived factor-1 (SDF-1), and insulin-like growth factor 1 (IGF-1).[179,181,187,188] For self-assembling peptides delivering dual factors, FGF-2 and PDGF-BB with self-assembling peptides, RADA16-I, were injected into an MI model. The results showed that the infarct area and cardiomyocyte apoptosis in the dual growth factors with the self-assembling peptides group was significantly reduced compared to those in the other groups. In addition, arterial density, capillary density, and cardiac function improved in this group.[129]

CONCLUSION AND FUTURE PERSPECTIVES

IHD causes millions of deaths worldwide. The IHD burden continues to grow as the population ages. A wealth of accumulated data raises the possibility that therapeutic angiogenesis is promising for patients with symptomatic advanced coronary heart disease who are not candidates for standard revascularization strategies. Therapeutic angiogenesis creates new blood vessels from the existing vasculature to recover blood flow to the afflicted ischemic heart muscle. However, the process of angiogenesis is extremely complex, involving the interaction between multiple growth factors and cells, the extracellular matrix, and each growth factor exerting its function in a specific time and space. Currently, most strategies for therapeutic

angiogenesis are to modify hydrogels by physical and chemical methods to promote the delivery of single or two growth factors. In the future, vascular biology and materials engineering knowledge may need to be combined to design more intelligent and complex hydrogels to precisely release specific key growth factors at a certain time and space to maximize the simulation of the endogenous angiogenesis process and then maximize the therapeutic effect. In addition to the vital role of proteins in therapeutic angiogenesis, gene therapy, cell therapy, and recent exosomal microRNA therapy are exciting prospects. Therefore, a multimodal strategy combining these treatments may offer more significant advantages. In addition, the optimal dosage and selection of the appropriate delivery route should be considered before clinical translation.

To date, some clinical trials have failed to translate these findings into humans. That we should realize that factors such as hypertension, diabetes, and dyslipidemia can make patients face not only the risk of IHD but also damage to EC. It reduces hypoxic stimulation and the reactivity of growth factors for EC, which could damage our efforts in treating new blood vessels and prompt us to rethink our treatment. Optimizing the vascular environment, improving vascular endothelial function, increasing endothelial cell responsiveness, and endothelial progenitor cell production are also future directions for therapeutic angiogenesis in IHD. Therefore, future animal studies may need to involve models of myocardial ischemia and endothelial dysfunction models to simulate endothelial dysfunction in patients with IHD to find new therapeutic targets. Other reasons for the limited results of previous clinical trials may be the short half-life of growth factors, poor biological stability, and rapid diffusion of growth factors in the body. The slow and continuous delivery of growth factors by using hydrogels can compensate for this disadvantage. Therefore, the delivery strategy for hydrogels combined with growth factors needs to be further investigated in clinical trials. Finally, the long-term safety and efficacy of larger animal experiments and clinical trials also need to be carried out, providing more ideas and a basis for real application in patients in the future.

AUTHOR CONTRIBUTIONS

Conceptualization, J.W., Y.W., and W.Y.; Methodology, J.W., W.Y., and Y.S.; Writing – Original Draft, Y.S., W.X., J.Z., and W.Y.; Writing – Review & Editing, J.W., Y.S., Y.W., and W.Y.; Supervision, Y.W. and W.Y.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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