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CHAPTER

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Acellular Injectable Biomaterials for Treating Cardiovascular Disease

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INTRODUCTION

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p0260 Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in western society. In the United States, the overall death rate from CVD was 235 per 100,000 people in 2010 [1]. Among them, coronary heart disease alone caused approximately one of every six deaths [1]. Despite the recent advancements in cardiovascular biology and the developments of new technologies [2], heart transplantation still represents the primary treatment for end-stage heart failure patients. In the last two decades, the idea of using stem cell-based therapies for people suffering from acute myocardial infarction (AMI) or living with congestive heart failure (CHD) has encouraged basic, preclinical, and clinical researches. However, several years after the first human clinical applications using stem cells as a therapy for AMI, heart failure (HF), or refractory angina, the results are contradictory, with benefits ranging from absent to transient or marginal [3].

p0265 Peripheral artery disease (PAD) is another manifestation of CVD which afflicts 12–20% of Americans over age 65 [4]. Although surgical revascularization has become the gold standard treatment for peripheral vessel occlusions, which cause critical limb ischemia (CLI), high rates of restenosis and many ineligible patients have resulted in amputation rates remaining largely unchanged in the last 30 years [5,6]. Many groups have attempted cell or gene therapy for the ischemic limb, but suboptimal results from clinical trials have resulted in none of these therapies yet reaching approval [7,8].

p0270 Safety and feasibility of cell-based therapies have been established. However, poor cell retention, significant cell death, and lack of clear cell differentiation and delivery methods still represent significant obstacles. In addition to stem cells, the use of microRNA [9], exosomes [10], growth factors [11], and small molecules [12] has been proposed as possible tools for cardiovascular tissue regeneration. Tissue engineering and biomaterials have also emerged as an alternative or complementary approach. Tissue engineering offers the possibility to combine cells or molecules with biomaterials; biomaterial scaffolds can give a proper environment for the transplanted cells with the goal of increasing cell survival and differentiation, or provide a controlled delivery of a therapeutic molecule [13,14]. In addition, biomaterial scaffolds can be used alone to stimulate endogenous repair and regenerative responses [15–18].

p0275 There are two main tissue engineering approaches that have been explored: injectables and patches. While injectable approaches employ *in vivo* (or *in situ*) tissue engineering principles, which take advantage of the natural muscle (cardiac or skeletal) milieu to directly stimulate tissue repair at the site of implantation, patches can be generated through both *in vitro* or *in vivo* tissue engineering. The *in vitro* approach focuses on seeding cells onto preformed porous scaffolds. The cells are cultivated under precise culture conditions in order to enhance survival, proliferation, and differentiation. The formed patch is then applied onto the injured muscle. The advantage of the *in vitro* approach is the possibility to control construct shape, size, cell differentiation rate, and organization of the seeded cells. The main limitation of this approach is the need for nutrient diffusion that limits the thickness of the construct, typically only a few hundred microns. For both patch approaches, another limiting aspect is the invasive procedure required for surgical transplantation. With the injectable approach, cells and a biomaterial are mixed and delivered by injection into the ventricular wall or into the ischemic skeletal

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muscle. This approach improves survival and retention of the transplanted cells [19] and has the potential advantage (depending on the biomaterial) of being delivered with a minimally invasive procedure. This approach is easy and feasible, but cell growth and differentiation cannot be controlled as tightly as in the *in vitro* model. Both injectable and patch materials can also be used alone as *in situ* tissue engineering strategies to stimulate endogenous repair and regeneration.

p0280 The focus of this chapter will be on the use of the injectable biomaterials as therapeutic tools in cardiac and skeletal muscle regeneration postischemia, focusing on their properties, mechanism of action and their reported effects on repairing damaged cardiac or skeletal muscle.

s0015 INJECTABLE BIOMATERIALS: MECHANISMS OF REGENERATION AND REPAIR

p0285 In the last decade, the use of injectable biomaterials, either natural or synthetic, has grown exponentially and has emerged as an alternative approach for heart and skeletal muscle regeneration [20,21]. Similarly to the patch-based approach, biomaterials were initially used to increase cell survival after transplantation and provide a favorable environment to the transplanted cells. Christman et al. were the first to demonstrate that the injection of myoblasts in fibrin glue leads to an increase in cell engraftment and survival in the heart [19]. Similarly, Tang et al. showed an increase in cell engraftment and survival when human umbilical vein endothelial cells were transplanted in hyaluronic acid (HA) hydrogel [22]. Since then, similar results were obtained with different cell types [23–25] or biomaterials [26–29].

p0290 An important aspect of many of these initial studies is that injection of the biomaterial alone also preserved cardiac function [30], suggesting that injection of a biomaterial into infarcted myocardium could provide an appropriate environment to recruit endogenous cells to repair and/or regenerate the ischemic region. This may have a beneficial effect on cardiomyocytes survival, neoangiogenesis, and/or cardiac progenitor cell activation and recruitment. This result can also be reconciled with the results Fan et al. saw with fibrin alone in a model of PAD [17]. These findings should not be surprising if we consider the importance of the extracellular matrix (ECM, see Box 25.1) in tissue homeostasis and cell proliferation, differentiation, and migration. During embryonic development, ECM patterns vary in a precise manner and ECM components such as collagen, fibronectin, or laminin are temporally expressed at different stages [31]. These findings could also be translated *in vitro* where 3D cultures altered embryonic stem cell differentiation as compared to 2D, by inducing a more mature phenotype [32]. Accordingly, it was demonstrated that increasing laminin and fibronectin concentrations in a collagen-based matrix drive embryonic stem cell differentiation to cardiac or endothelial lineages, respectively [33]. Similarly, an increase in cardiogenic commitment of cardiac progenitor cells has been demonstrated when the cells were cultured in a 3D environment [34]. ECM is also involved in cardiomyocyte and fibroblast functions in response to the myocardial physical forces and injury and can activate specific intracellular signaling pathways that lead to the pathophysiological response following an injury [35,36]. However, not every injectable material has a beneficial effect on heart function after myocardial infarction (MI). Transplantation of a bioinert material, such as polyethylene glycol (PEG), did not preserve cardiac function compared to the control group despite the significant increase in wall thickness, suggesting that the bioactivity of the injected biomaterial plays an important role in improving cardiac function [37]. This is also evident in PAD, where most efficacy is shown with naturally derived or bioactive materials, or growth factor combination therapies. In PAD, the ECM composition, stiffness, and degradation due to matrix metalloproteinases have also been implicated in angiogenesis [38] following inflammation and injury.

p0295 Another proposed mechanism of regeneration of the injected biomaterial in cardiac applications is the mechanical support to the diseased myocardium. After MI, a progressive dilation of the left ventricle (LV) and wall thinning is often observed, which causes increased wall stress and oxygen consumption leading to a further increase in cardiomyocytes death. Moreover, the altered ECM composition and geometry impair the contraction capability of the remaining cardiomyocytes and further deteriorate LV function. Injection of biomaterials increases wall thickness, thereby potentially reducing wall stress (via La Place's law) with a beneficial effect on global LV remodeling and function as well as on cardiomyocyte death [39]. However, recent studies suggest that injectable materials are not acting predominantly as a mechanical support, but are rather resulting in an endogenous cell response. The mechanical properties of a material, however, undoubtedly influence the cellular response to a material, which is important for tissue repair and regeneration [37,40].

s0020 INJECTABLE BIOMATERIAL PROPERTIES: ENGINEERING DESIGN CRITERIA FOR TREATING MI AND PAD

p0300 When fabricating a material-based therapy for tissue engineering, there are many design criteria to consider.

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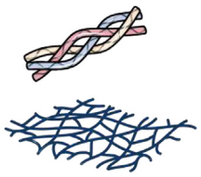
BOX 25.1

MAJOR ECM COMPONENTS

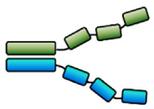
Fibrous proteins

Collagen



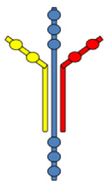
- Main component of the ECM
- Composed of three different polypeptide chains
- Synthesized by fibroblasts and some epithelial cells, and secreted as procollagen in the extracellular space
- 28 different types of collagen. Types I, II, and III account for 90% of total collagen in the body
- Present mostly in form of fibrillar collagen (Type I, II, and III) or network-forming collagen (Type IV, present in the basement membrane)
- Provide mechanical support, tensile and elastic strength to the tissue
- Regulates cell migration

Fibronectin



- Present in the form of a protein dimer
- Can also exist as soluble circulating form in blood plasma
- Has cell binding sites recognized by integrins and regulates cell adhesion, migration, proliferation, and differentiation
- Binds other ECM components such as collagen, fibrin, and heparan sulfate proteoglycans

Laminin



- Large ECM heterotrimetric proteins composed of three polypeptides chains (α, β, and γ)
- Different types of each chain can assemble together and form many types of laminin
- Major component of the basal lamina
- Has cell binding sites recognized by integrins and regulates cell adhesion, migration, phenotype, and differentiation
- Binds other ECM components such as collagen IV, fibronectin, and heparan sulfate proteoglycans

Elastin

- Main component of the elastic fiber properties of the ECM
- Synthesized and secreted as tropoelastin; forms elastic fibers via their lysine residues
- They also bind with fibrillins, another component of the elastic fibers
- Balance between elastin and collagen regulates the mechanical properties of each tissue

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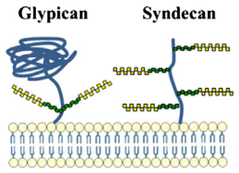
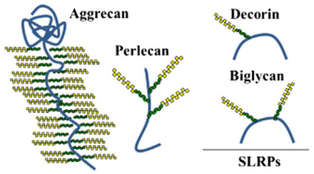
BOX 25.1 (*cont'd*)

Proteoglycans

Cell surface proteoglycans



ECM proteoglycans



- Class of molecules characterized by large carbohydrates (glycosaminoglycans; GAGs) attached to a protein core (except hyaluronic acid)
- GAG chains are composed of repeating disaccharide units that can be divided into sulfated (chondroitin sulfate, heparin sulfate, and keratin sulfate) and nonsulfated (hyaluronic acid)
- Highly hydrophilic due to their negative charge at physiological pH
- Act as a lubricant and space filler in the ECM space
- Can bind many growth factor and cytokines for surrounding cells and limit diffusion of macromolecules
- Act as a barrier to microorganisms
- Hyaluronan is the major component of proteoglycans forming a long negatively charged polysaccharide chain not bound to a core protein

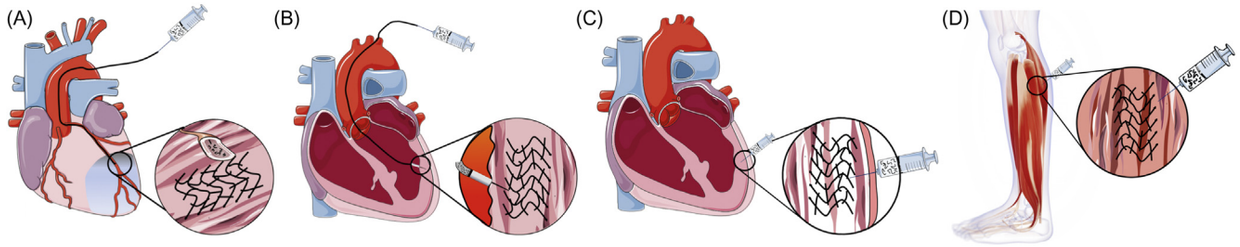
t0010 **TABLE 25.1** Potential Design Considerations for Biomaterials for MI and PAD

- Delivery mechanism
  - Direct injection
  - Catheter based
  - Surgery
- Physical properties
  - Cross-linking
  - Porosity
  - Orientation
  - Stiffness
  - Viscosity
  - Gelation time
- Degradation properties
  - Hydrolysis
  - Enzymatic
  - Degradation time
- Biochemical properties
  - Cell adhesion
  - Bioactive factor release
  - Degradation products
- Electrical properties
  - Conductivity
- Regulatory concerns

Delivery method, as well as mechanical, biochemical, degradation, and electrical properties can all be relevant when developing biomaterials for the treatment of MI and PAD (Table 25.1). Regulatory concerns may also affect material design.

p0305 The optimal delivery method (Figure 25.1) will depend on the application. For example, it may be desirable to deliver a biomaterial as minimally invasively as possible; in this case, an injectable material that assembles into its native architecture *in situ* would be most desirable. Injectable delivery options for cardiac applications are intracoronary injection, epicardial injection, or transendocardial injection [20], with catheter-based options (intracoronary and transendocardial) being more minimally invasive and reduced the need for general anesthesia and surgery as required of epicardial injections. For PAD applications, most injectable therapies are delivered via direct intramuscular injection [41].

p0310 If minimally invasive, delivery is important to a given application, viscosity and gelation kinetics of the biomaterial should be optimized such that the material can be effectively delivered through a small diameter needle (epicardial or intramuscular injection) or a percutaneous catheter (intracoronary or transendocardial injection). In addition, for the latter approach, the material must be hemocompatible since leakage into the systemic circulation can occur. Many injectable materials can be delivered through high gauge needles, but are not compatible for catheter delivery because of either hemocompatibility issues or rapid gelation that does not facilitate the multiple injections required with transendocardial delivery; these considerations should be taken into account early in biomaterial design. In order to assess potential for injectability, viscosity of the liquid form of the material can be measured to ensure that the material is shear thinning (viscosity decreases with increasing shear stress), which could be important for injection through a long catheter. Likewise, gelation kinetics should be determined to ensure the material can withstand a potentially lengthy (~1 h) catheter injection procedure.



AU:4 f0010 **FIGURE 25.1 Delivery approaches for injectable biomaterials.** (A) Intracoronary infusion. A balloon infusion catheter is guided through the aorta into the coronary vessels. The hydrogel is delivered through the leaky vessels after acute MI; it should be hemocompatible and gelation should occur only in the infarcted region to avoid embolisms. (B) Transendocardial delivery through catheter. The injection catheter reaches the endocardium through the aortic valve. The hydrogel is injected directly into the infarct and/or borderline. (C) Direct intramyocardial injection. The hydrogel is directly injected into the infarct or borderline and requires surgical access. (D) Direct intramuscular injection. The hydrogel is directly injected into the ischemic muscle.

p0315 Mechanical characteristics are known to influence cell behavior, and therefore these should also be considered. Healthy myocardial stiffness is around 10 kPa while the stiffness of an infarct is increased to greater than 50 kPa [42]. It is known that stiffness can affect cell behavior, so it may be desirable to design a material that more closely mimics the stiffness of a healthy heart rather than a scarred heart [42,43]; however, the ideal mechanical properties are currently unknown. For example, most injectable materials are weaker than healthy myocardium, yet have shown improvements in cardiac function. This could be partly explained by the fact that embryonic and fetal myocardium, where cardiomyocytes are still proliferative, is softer than adult myocardium [44], and therefore a stiffness less than normal myocardium may in fact be more desirable to stimulate regeneration. Mechanical loading is also a large concern for biomaterials for skeletal muscle regeneration, such as in PAD patients. Skeletal muscle, which also has a stiffness of around 10 kPA [45], sustains significant mechanical loads, and therefore mechanical properties of biomaterials injected intramuscularly may need to be considered for supporting myoblast regeneration and development. To achieve stiffer materials, synthetic materials are often needed since they can be more easily tuned by changing molecular weight of polymer chains, cross-linking density, or branching density. Still, naturally derived materials such as HA or decellularized ECM can also be cross-linked to increase mechanical strength [46,47], although generally these cannot reach the mechanical properties of synthetic polymers.

p0320 Biochemical design considerations are important for regenerative medicine therapies because mechanical support alone can be insufficient for complete tissue regeneration [37]. Natural and synthetically derived materials can have vastly different biochemical properties, so it is important to understand the benefits and optimal uses of each. Natural biomaterials, such as decellularized ECM hydrogels, can already contain many desirable proregenerative cues, such as sulfated glycosaminoglycans or tissue-specific proportions of ECM proteins. Furthermore, naturally derived materials can have domains that can be recognized and adhered to by cells, or embedded with growth factors. However, synthetic materials can also be modified with cell binding peptides (e.g., RGD, KQAGDV, VAPG) or can be functionalized with growth factors or other cytokines [48]. Degradation timeline and degradation products can also have an impact on the success of a biomaterial therapy. Successful resolution of a biomaterial therapy would be either material resorption and degradation or material integration with host tissue with no chronic inflammation or encapsulation. Typically in the myocardium and skeletal muscle, nondegradable materials will cause a nonideal resolution, regardless of how "biocompatible" the material may be. An ideal material for cardiovascular applications will preferably degrade on a similar timescale as the native host healing response, allowing cell migration into the material and resorption of the material concurrently with host regeneration. In this scenario, the material acts as a structurally and biochemically supportive ECM for the nascent healing tissue until the tissue has sufficiently regenerated on its own. Designing a material with controllable degradation properties can affect this resolution.

p0325 Electrical properties are particularly important for cardiac material applications. For example, it is possible that materials injected within the myocardium can interfere with action potential propagation. It is known that cells injected into the myocardium can have effects on action potential propagation [49], so it is important to also understand the effects of biomaterials on myocardial contraction in order to evaluate a material's safety for the clinic.

p0330 Although not an engineering design criteria, regulatory consideration should be given early on when designing a

material for cardiovascular applications to facilitate clinical translation. For example, materials that contain both a mechanical device component (such as an inert, synthetic polymer network) as well as bioactive substances (such as biologics, growth factors, or cells) are regulated as a combination product, resulting in review by multiple branches of the FDA and a longer path to approval [50]. As with any engineering process, resource constraints influence design, and the earlier that regulatory constraints are factored into the design process, the quicker the translational process will be for successful biomaterial solutions.

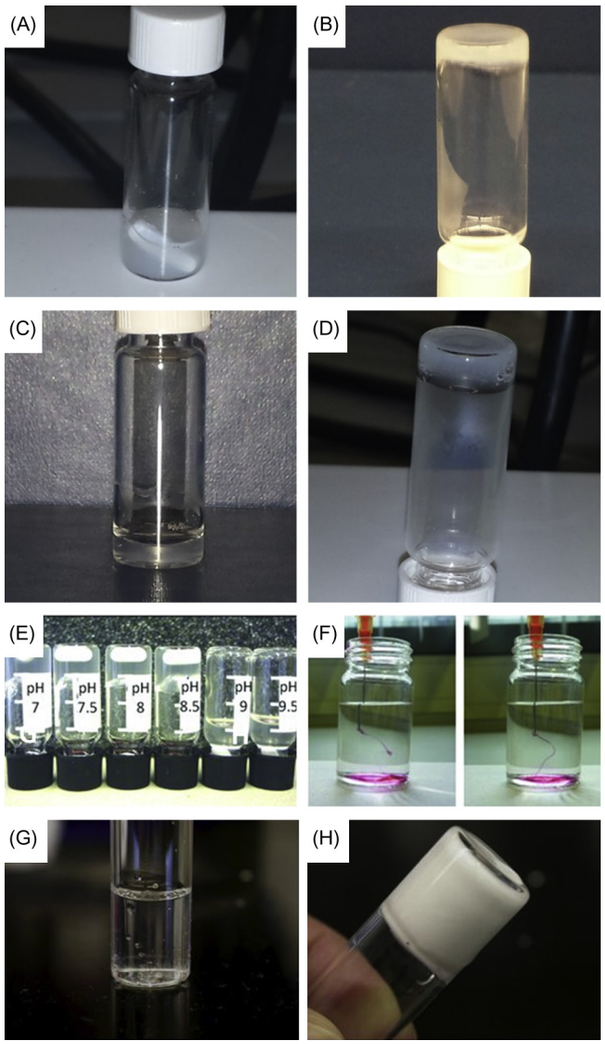
TYPES OF INJECTABLE BIOMATERIALS

s0025

p0335 Many different types of hydrogels have been used as injectable biomaterials, either naturally derived or synthetic. Among the natural biomaterials, collagen, fibrin, HA, alginate, and tissue-derived ECM hydrogels are the most commonly used. Among the synthetic biomaterials, self-assembling peptides, PEG containing materials, and *N*-isopropylacrylamide containing materials are the most used [50]. The majority of these materials are hydrogels (Figure 25.2), which are water swollen cross-linked polymer networks, and many have a nano- to micro-fibrous architecture that mimics the fibers in the native ECM (Figure 25.3).

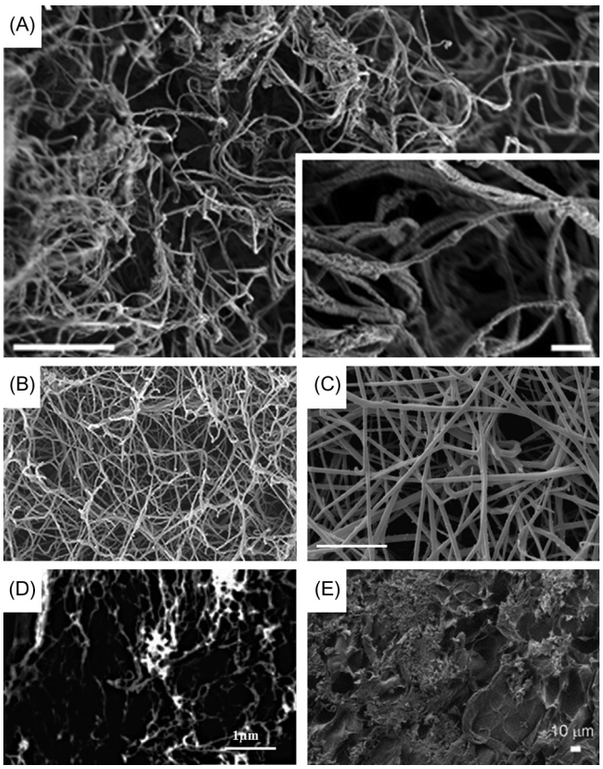
p0340 Collagen is one of the main ECM components in all tissues. It consists of three polypeptide chains (α chain), which form a triple helix. Its structure can be in the form of homotrimers, composed of three identical α chain $(\alpha 1)_3$, or heterotrimers, composed of two or three different α chains. Up to 28 different types of collagen have been identified. In the heart [58], as well as in skeletal muscle [59], collagen I and III are the predominant forms of collagen, and both contribute to the structural integrity of the organs. For example, collagen type I usually forms thick fibers that are responsible for the tensile strength and determines the tissue stiffness [60]. On the other end, collagen type III usually forms thin fibers that are responsible for the elastic properties of the ECM [60]. In the healthy heart, collagen I is the most abundant type of collagen, however, following ischemia the balance of these two types of collagen fibers is shifted. Typically in tissue engineering, hydrogels derived from collagen I are used.

p0345 Rather than using a single component of the ECM, decellularized tissues have also been processed into tissue-specific ECM hydrogels [18,53,61–63]. In 2008, Ott et al. reported the first method to decellularize the myocardium [64], which has spurred significant work in the area of decellularized ECM scaffolds for tissue engineering. While intact decellularized ECM could be used for tissue engineered patches or potentially to regenerate an entire organ, it also can be digested to create ECM hydrogels. While the decellularization process can strip out different ECM components [65], these hydrogels, in general, recapitulate the biochemical complexity of the native ECM and contain both proteins as well as sulfated glycosaminoglycans [53,61]. Both cardiac and skeletal muscle ECM hydrogels have been generated to treat MI and PAD, respectively [16,18].



f0015 **FIGURE 25.2 Hydrogels for cardiac tissue engineering.** Liquid digested cardiac ECM (A, 6 mg/mL) forms a gel (B) after 30 min incubation at 37°C. Solubilized type I collagen (C, 3 mg/mL) also forms a gel (D) after 30 min incubation at 37°C. (E) pH-dependent behavior of Upy hydrogel at a pH range from 7 to 9.5. (F) Injection of liquid 10 wt. % UPy-10k (colored in red) into a neutral PBS solution results in gel formation. Liquid NIPAAm-*co*-AAc-*co*-HEMAPTMC (G) forms a gel (H) after incubation in a 37°C water bath for 30 s. *Reproduced from Refs. [51] ~~(E),~~ [51] ~~(F),~~ [52] (G and H) with permission.*

p0350 Fibrin is a fibrous polymer formed by the cleavage of fibrinogen by the protease thrombin [66]. Fibrinogen, a



f0020 **FIGURE 25.3 Representative scanning electron micrographs of hydrogels.** (A) Cardiac ECM hydrogel, (B) collagen hydrogel at 3 mg/mL, (C) fibrin gel, (D) self-assembling peptide nanofibers, and (E) cross-linked HA hydrogel. *Reproduced from Refs. [53] (A), [54] (B), [55] (C), [56] (D), [57] (E) with permission of the Royal Society of Chemistry.*

soluble plasma glycoprotein, is composed of three polypeptide chains: Aα, Bβ, and γ. The cleavage of Aα and Bβ chains initiates the self-assembling reaction with the subsequent formation of the fibrin network. The γ-chain has a cross-linking site on the C-terminal region recognized by the transglutaminase factor XIIIa, which catalyzes the formation of γ-chain dimers [66]. Fibrin is involved in many tissue physiopathological processes such as blood coagulation, platelet activation, inflammatory response, and signal transduction. Commercially available forms of fibrin, often termed fibrin sealant or fibrin glue, are used in surgical applications, yet have also been employed experimentally as tissue engineering scaffolds.

p0355 HA is a linear polysaccharide that consists of two alternating units, B-1,4-D-glucuronic acid and B-1,3-*N*-acetyl-D-glucosamine, present ubiquitously in all ECM [67]. HA is typically present as a high molecular weight polysaccharide, but it can also be cleaved by hyaluronidase or acid to form low molecular weight HA. The ability to control and tailor its molecular weight is important in the regulation of different physiologic processes. For example, high molecular weight HA is found to act as a physical barrier to cell proliferation and migration and has anti-inflammatory and immunosuppressive properties [63]. Interestingly, once cleaved, low molecular weight HA has been implicated in proinflammatory and proangiogenic properties as well as in cell proliferation [68]. HA interacts with cells through CD44 receptor that is important in tissue organization [67]. In tissue engineering, HA is commonly modified with different chemical groups that can be used to cross-link the polymer into a hydrogel network.

p0360 Alginate is a polysaccharide-based copolymer composed of β-D-mannuronic acid (M) and α-L-guluronic acid (G), and is derived from the cell wall of brown algae [69]. Due to its high biocompatibility and easy gelation in the presence of Ca^{2+} or other divalent cations, alginate has been widely used in tissue engineering applications, as well as the food industry, as emulsifying agent [69]. While it is considered biocompatible, one of the main limitations of alginate is the lack of cell binding sites, although this can be overcome by the use of cell binding peptides [70].

p0365 Synthetic biomaterials are another class of injectable hydrogels for *in vivo* tissue engineering applications. Among them, the most used are self-assembling peptides, PEG and *N*-isopropylacrylamide-based polymers. PEG is a highly hydrophilic polymer that can be easily modified with other functional groups allowing combination of PEG with other biomaterials [71]. This is essential to increase cell interactions with PEG, given that the material is bioinert. Peptide nanofibers are short peptides, 8–16 amino acids, which can form a nanofibrous gel when injected *in vivo* [72]. They show high biocompatibility and can also be modified with adhesion molecules to improve cell–nanofiber interactions. The last class of synthetic biomaterials typically used in these tissue engineering applications is *N*-isopropylacrylamide-based polymers. The main advantage of these materials is their temperature responsive nature, which can be used to form a gel at body temperature [73].

p0370 In general, the main advantage of synthetic biomaterials is that porosity, density, structure, and composition can be controlled and designed as needed for different cell types and applications. However, synthetic materials lack the biological properties that are typical for natural materials, which could potentially influence growth and differentiation of cells in a more physiologic way. For these reasons, different combinations have been tested by combining natural and synthetic materials. One important aspect that should be carefully studied with synthetic biomaterials is the possible inflammatory response to the polymer itself or its degradation products. In particular, the

myocardium has been shown to mount a stronger inflammatory response to biomaterials [74], and therefore testing directly in the myocardium or skeletal muscle should be performed.

s0030

INJECTABLE BIOMATERIALS ALONE: PRECLINICAL AND CLINICAL APPLICATIONS

p0375 The ultimate goal of injectable biomaterial development and testing is to eventually reach a clinical application to improve tissue regeneration after ischemic injury. Since the first report in small animals using fibrin glue as injectable biomaterial post-MI [30], many other hydrogels have been used in small animals and some of them have been tested in large animals (Figure 25.4, Tables 25.2 and 25.3) or moved forward into clinical trials.

s0035

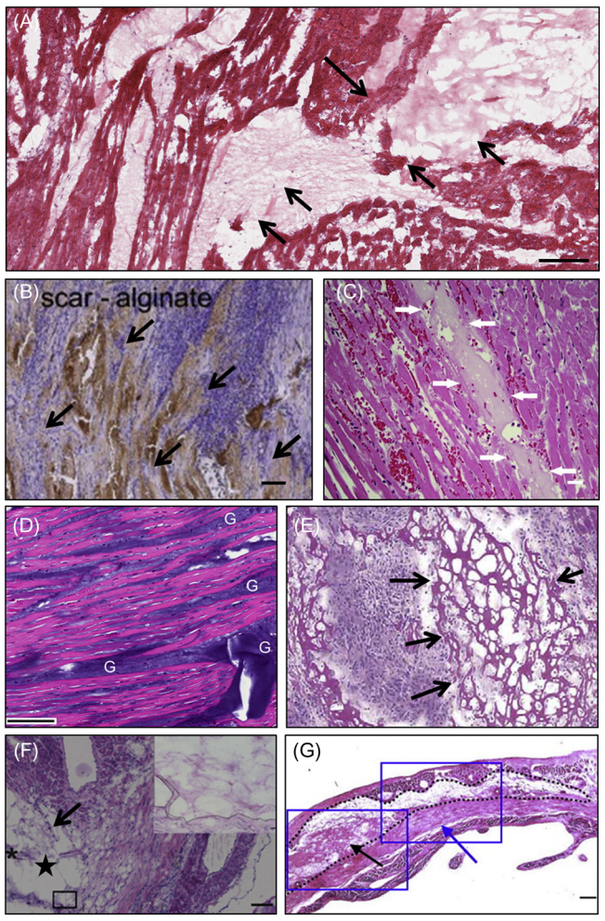
Natural Biomaterials

s0040

Collagen

p0380 Collagen has been widely used as injectable biomaterial, either alone or as cell carrier. These studies have been performed using direct epicardial injection. Given its rapid gelation, catheter delivery, however, is likely to be a challenge. Dai et al. first injected liquid collagen in a rat model of MI 1 week after injury. When compared to saline group, collagen treatment significantly increased wall scar thickness, ejection fraction (EF), and stroke volume (SV), but no significative differences were observed in end-diastolic volume (EDV), end-systolic volume (ESV), or capillary density [78]. In contrast to the previous study, Huang et al. reported a higher number of capillaries 5 weeks after injection when compared to saline groups, which were similar to fibrin or Matrigel [79]. The collagen alone group also showed an increase in myofibroblast infiltration in the infarct area when compared to saline group.

p0385 Collagen has also been examined for the treatment of PAD. Intramuscular collagen injection 10 days after artery ligation in a rabbit model of hindlimb ischemia enhanced capillary density and improved hindlimb perfusion as measured by oxygen saturation ratio after 8 weeks [25]. Kuraitis et al. showed that a combination of two naturally derived materials, alginate microspheres within an injectable collagen hydrogel, prolonged the delivery of stem cell-derived factor 1α (SDF-1α) for 10 days to the ischemic murine hindlimb, improving perfusion, arteriole density, and recruitment of GFP-labeled bone marrow progenitor cells. Although collagen alone also significantly improved perfusion and arteriole density compared with phosphate-buffered saline controls, the SDF-1/alginate/collagen system had higher trends in all metrics and a significantly higher arteriole lumen area and recruitment of GFP-labeled bone marrow cells [86]. Similarly, Suuronen et al. compared the effect of $CD133^{+}$ cell injection within collagen to material alone on vessel density in the ischemic muscle. While cells plus matrix caused an increase in both capillary and arteriole density over PBS controls at 2 weeks postischemia and injection, the material alone reported only an increase in capillary density, but not in the arteriole density over PBS controls [87].



f0025 **FIGURE 25.4** **Injectable biomaterials *in vivo*.** (A) Cardiac ECM hydrogel 20 min after injection. (B) Alginate 2 h after intracoronary infusion. Scale bar is 100 μm. (C) Peptide nanofibers 3 h after injection. Scale bar is 20 μm. (D) Methacrylated HA 24-h postinjection. Scale bar is 100 μm. (E) Fibrin glue and myoblasts 24 h after injection (20X magnification). (F) PEG 6 weeks after injection. Scale bar is 20 μm. (G) pNIPAAm-*co*-AA-*co*-HEMATC 8 weeks after injection. Scale bar is 100 μm. Material location is denoted by a star and surrounded by a dashed line in all images. *Reproduced from Refs. [75] (~~A and~~ B), [76] (C), [77] (D), [19] (E), [37] (F), [52] (G) with permission.*

t0015 **TABLE 25.2** Effects of Injectable Biomaterials Alone in Small and Large Animal Model of Myocardial Infarction (Selected Papers)

Hydrogel	Animal model	Treatment (after MI)	Analysis (after treatment)	Cardiac function	Histological analysis	Refs.
Collagen	Rat	1 week	6 weeks	EF ↑	Wall thickness ↑	[78]
				SV ↑		
				EDV n.d.	Capillary density n.d.	
				ESV n.d.		
Collagen	Rat	1 week	5 weeks	–	Capillary density ↑	[79]
					Myofibroblast infiltration ↑	
Myocardial matrix	Rat	2 weeks	4 weeks	EF ↑	Viable myocardium ↑	[16]
				EDV ↓		
				ESV ↓		
Myocardial matrix	Pig	2 weeks	3 months	EF ↑	Infarct fibrosis ↓	[89]
				EDV ↓	Viable myocardium ↑	
				ESV ↓		
				GMWI ↑		
Fibrin	Rat	1 week	5 weeks	FS ↑	Wall thickness ↑	[30]
Fibrin	Rat	1 week	5 weeks	–	Infarct size ↓	[19]
					Arteriole density ↑	
Fibrin	Rat	1 week	5 weeks	–	Capillary density ↑	[79]
Fibrin	Rat	5 weeks	5 weeks	LVDs ↓	Arteriole density ↑	[80]
				LVDd ↓		
				FS n.d.		
Hyaluronic acid/ thiol-modified collagen	Rat	After MI	4 weeks	FS ↑	Scar size ↓	[81]
				EF ↑		
Hyaluronic acid	Pig	After MI	2 months	EF n.d.	Scar size ↓	[82]
				IVSs n.d.	Capillary density n.d.	
				IVSd n.d.		
Peptide nanofibers	Rat	After MI	3 months	FS n.d.	Infarct volume n.d.	[83]
				LVDs n.d.		
				LVDd n.d.	Vascular density n.d.	
Peptide nanofibers	Pig	After MI	4 weeks	EF n.d.	Infarct size ↓	[27]
				IVSs n.d.	Capillary density ↑	
				IVSd ↑		
PEG	Rat	1 week	6 weeks	EF n.d.	Wall thickness ↑	[37]
				EDV n.d.		
				ESV n.d.		
PEG-vinyl	Rat	After MI	13 weeks	FS n.d.	Wall thickness n.d.	[84]
				EDV n.d.		
				ESV n.d.		

(*Continued*)

TABLE 25.2 (Continued)

Hydrogel	Animal model	Treatment (after MI)	Analysis (after treatment)	Cardiac function	Histological analysis	Refs.
PEG-fumarate	Rat	1 week	4 weeks	FS ↑	Infarct size ↓	[85]
				EDD ↓		
				ESD ↓	Arteriole density n.d.	
N-isopropylacrylamide, acrylic acid, hydroxyethyl methacrylate poly carbonate	Rat	2 weeks	8 weeks	EDA ↓	Wall thickness ↑	[52]
				FS ↑	Capillary density ↑	

SV, stroke volume; GMWI, global wall motion index; EF, ejection fraction; EDV, end-diastolic volume; ESV, end-systolic volume; FS, fractional shortening; LVDs, left ventricular systolic dimension; LVDd, left ventricular diastolic dimension; IVSd, interventricular diastolic septum thickness; IVSs, interventricular systolic septum thickness; ESV, end-systolic diameter; EDD, end-diastolic diameter; EDA, end-diastolic area. ↑: Significant increase; ↓: significant decrease; n.d.: no differences.

t0020 **TABLE 25.3** Effects of Injectable Biomaterials Alone for the Treatment of PAD (Selected Papers)

Hydrogel	Animal model	Treatment (after injury)	Analysis (after treatment)	Perfusion	Histological analysis	Refs.
Collagen	Rabbit	10 days	6 and 8 weeks	Increased oxygen saturation ratio	Cappilary density ↑	[25]
					Arteriole density ↑	
Collagen	Mouse	Immediate	2 weeks	Increased	Arteriole density ↑	[86]
Collagen	Mouse	Immediate	2 weeks	–	Capillary density ↑	[87]
					Arteriole density n.d.	
Skeletal muscle matrix	Rat	1 week	2 weeks	–	Capillary density ↑	[18]
					Arteriole density ↑ Muscle and progenitor cell infiltration ↑	
Fibrin particles	Mouse	1 week	4 weeks	Increased	Capillary density ↑	[17]
					Arteriole density ↑	
Hyaluronic acid	Mouse	1 day	4 weeks	n.d.	Capillary density n.d.	[22]
Peptide nanofibers	Mouse	1 day	4 weeks	n.d.	Fibrosis ↓	[88]
					Capillary density ↑	

↑: Significant increase; ↓: significant decrease; n.d.: no differences.

s0045 ### *Tissue-Derived Extracellular Matrix*

p0390 The use of native tissue as a source of ECM has recently been developed as an alternative naturally derived biomaterial. The main advantage of tissue-derived ECM is the presence of numerous matrix components including proteins and polysaccharides such as glycosaminoglycans, and the ability to create a tissue-specific biomaterial. Singelyn et al. were the first to report the development of a hydrogel from porcine cardiac ECM [61]. The cardiac ECM is processed via partial enzymatic digestion into a viscous liquid solution, which will gel after injection at 37°C. The formed gel has a structure and porosity similar to the native cardiac ventricular ECM and supported the recruitment of endogenous cells, including neovasculature [61]. In a rat model of MI, the myocardial matrix hydrogel was able to preserve EF, EDV, and ESV up to 4 weeks after MI unlike the saline control [16]. Another important advantage of using an ECM hydrogel is its applicability through an NOGA-guided catheter, which allows for minimally invasive delivery [16].

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p0395 Porcine myocardial matrix has been also tested in a pig model of MI and a clinical trial is currently being planned (ClinicalTrials.gov identifier NCT02305602). In this study, Seif-Naraghi et al. injected the myocardial matrix hydrogel via a transendocardial catheter, which has the advantage of local delivery of the material [89]. The hydrogel was injected 2 weeks after MI and the treatment improved EF, EDV, and ESV 3 months after injection compared to controls (saline and nontreated); global motion index also improved in the matrix-treated group. Histological data showed that the treatment increased viable myocardium, mainly at the epicardium, and decreased infarct collagen deposition. Further safety studies also performed by Seif-Naraghi et al. demonstrated that the material is biocompatible despite its xenogeneic source and is also hemocompatible [89], which is important for catheter delivery. The same group also reported the isolation of ECM from human pericardium as a potentially autologous material [62,90] as well as from human hearts [53].

p0400 Tissue-derived ECM as an injectable hydrogel can be also achieved using skeletal muscle as a source of decellularized ECM. DeQuach et al. were the first group to develop a tissue-specific injectable matrix for hindlimb ischemia. This initial study showed that the naturally derived, decellularized skeletal muscle ECM hydrogel injected 1 week after femoral artery ligation improved neovascularization, inducing an increase in arteriole and capillary density when compared to collagen at 2 weeks postinjection [18]. The treatment also increased the recruitment of desmin-positive and MyoD positive cells indicating the potential for increased skeletal muscle regeneration over collagen controls [18].

s0050 *Fibrin*

p0405 The use of fibrin in the clinic is already well established as a hemostatic agent and used as a sealant in surgical procedures or for hemophiliac patients [91]. Moreover, it is also possible to produce autologous fibrin matrix from patients' peripheral blood [91]. As previously mentioned, fibrin glue injection in a rat model of MI preserved fractional shortening (FS) and infarct wall thickness [30], reduced infarct size and increased vessel density [19]. When fibrin glue is injected directly into the scar in a chronic heart failure model (5 weeks after MI), the treatment improved FS and increased wall thickness and left ventricular internal diameter (LVID) at 2 days postinjection. Interestingly, 5 weeks after injection (10 weeks after MI), deterioration of FS was observed in both groups while wall thickness was preserved in the fibrin-injected group [80]. This study also confirmed previously reported results regarding the angiogenic properties of fibrin glue [79].

p0410 A mixture of alginate and fibrin has also been tested in a porcine model of MI and treatment preserved wall thickness and decreased wall stress in the MI region [92]. Histological data showed no differences in capillary density or collagen deposition. One of the main limitations of this approach is the intramyocardial injection of a two-component system, like fibrin glue itself, which requires an invasive surgical approach [92].

p0415 Fibrin was also examined for the treatment of PAD. Fan et al. injected fibrin particles alone intramuscularly in a rabbit model of hindlimb ischemia 1 week after injury and showed improved capillary and arteriole density, as well as improved perfusion measured via angiographic score and calf blood pressure ratio up to 28 days postinjection [17].

s0055 *Hyaluronic Acid*

p0420 Methacrylated HA was tested in an ovine model of MI and injected 45 min after MI. In this study, the authors developed two types of methacrylated HA with either a compressive modulus of 7.7 kPa, which should be similar to the healthy myocardium, or of 43 kPa. Only the stiffer materials showed a reduction in infarct size 8 weeks after application, but no significant differences were observed in EDV, ESV, and EF when compared to the control group [77]. In another study, the authors used the same methacrylated HA hydrogels used in the previous study, but with different degradation properties (3 weeks, 8 weeks, or nondegradable hydrogel). The stiffer nondegradable biomaterial was able to significantly increase wall thickness and reduce ESV at 8 weeks after MI, but no differences were observed for EF and cardiac output among the groups [93]. In another study, HA alone or in combination with bone marrow mononuclear cells was injected in pig after MI. However, injection of the material alone was not able to improve cardiac function, despite a significant decrease in scar size as observed by histology [82]. A HA-collagen hydrogel has also been tested in a rat model of MI; the treatment showed a significant improvement in EF and FS 4 weeks after application [81]. A reduction of infarct size and an increase in capillary density were also demonstrated. However, in this study HA-based hydrogel was combined with a thiol-modified collagen in 1:1 ratio and the effect of HA alone was not investigated [81]. AU:2

p0425 HA was also used in PAD applications to improve cell delivery. The injection of HUVECs in HA immediately after femoral artery ligation prolonged the degree of HUVEC retention, limb perfusion, and angiogenesis up to 4 weeks postsurgery. However, no significant improvement in limb salvage, perfusion, or angiogenesis was observed when HA was injected alone [22].

s0060 ***Alginate***

p0430 The use of alginate is covered in Chapter 37, and therefore we are not fully addressing the use of this injectable biomaterial. Nevertheless, it is important to mention that alginate is the first injectable biomaterial that has moved from small [70,94] and large [75] animal preclinical studies to clinical trials. Preclinical studies showed that alginate increased myofibroblast density, resulting in improvements in LV areas [75,94]. Results from a Phase I study in acute MI patients (NCT00557531) have been reported [95] and a Phase II study is ongoing to address the efficacy of the treatment with a primary outcome measure of LV EDV (NCT01226563).

s0065 Synthetic Biomaterials

p0435 Davis et al. showed for the first time that peptide nanofibers can be injected into the healthy myocardium and promote the recruitment of endogenous endothelial and smooth muscle cells [76]. Since then, peptide nanofibers have been used in combination with several growth factors and cells. When peptide nanofibers were injected alone as a control group, no improvement in cardiac regeneration was observed compared to the MI group only [83]. In a pig model of MI, peptide nanofibers were injected alone or in combination with bone marrow cells intramyocardially after MI. The analysis was performed 2 months after transplantation. The material alone did not significantly improve EF or intraventricular septum (IVS) at systole, but only IVS at diastole. Furthermore, an increase in EDV and EDV was also reported by hemodynamic analysis. Histological data showed a significant increase in capillary density and a decrease in scar size [27]. Similar to the cardiac field, peptide nanofibers were also used in hindlimb ischemia models and mostly in combination with different growth factors, but no regenerative capabilities were reported from the biomaterials alone [88,96].

p0440 Several PEG-based materials have also been tested for treating MI. Once injected into the myocardium in a rat model of MI, PEG alone did not show any improvement in cardiac function despite being able to increase wall thickness compared to the control group [37]. Similar results were reported when a nonbiodegradable PEG-vinyl sulfone hydrogel was transplanted in rats. Despite a significant reduction in left ventricular end-diastolic diameter at 4 weeks postinjection, no differences were observed at 12 weeks [84]. An improvement in cardiac function and a reduction in infarct scar were however reported with a thermoresponsive composite hydrogel of oligo PEG-fumarate [85]. Lastly, Basting et al. demonstrated the applicability of a triblock copolymer, polyurea-block-PEG-block-urea terminated with ureido-pyrimidinone (Upy) units, that can be injected via catheter and conjugated to deliver growth factors [51].

p0445 *N*-isopropylacrylamide polymers have the advantage of being temperature responsive and have been largely used in combination with other materials. A copolymer of poly (*N*-isopropylacrylamide-*co*-acrylic acid-*co*-hydroxyethyl methacrylate-poly(trimethylene carbonate)) (pNIPAAm-*co*-AA-*co*-HEMATC) was injected into rats 2 weeks post-MI showing a positive effect on cardiac function and neoangiogenesis 8 weeks after application [52]. Wall et al. developed a tunable bioactive semi-interpenetrating polymer network hydrogel composed of a copolymer of *N*-isopropylacrylamide and acrylic acid with MMP degradable peptide cross-links for mesenchymal stem cell delivery. FS in the polymer alone group was significantly different compared to the cells alone group at 6 weeks, but no other significant differences in cardiac function or volumes were found [97].

p0450 Synthetic polymers have been used to a lesser extent in PAD, although they have only been used as a vehicle for delivery of angiogenic growth factors. For example, Lee et al. showed the capability of delivering poly (D,L-lactide-*co*-glycolide) (PLGA) microspheres embedded with vascular endothelial growth factor (VEGF) to improve vessel density 4 weeks after intramuscular injection [98].

s0070 INJECTABLE BIOMATERIALS FOR GROWTH FACTOR AND SMALL MOLECULE DELIVERY

p0455 Injectable biomaterials can be also used to deliver cells or bioactive molecules. Many different hydrogels were used as a vehicle for cell delivery and showed to improve cell retention and survival after transplantation. Here, we will focus on the hydrogels used for the delivery of growth factors, small molecules, or other bioactive drugs. Systemic delivery of growth factors or small molecules is relatively simple but has the disadvantages of rapid degradation and potentially harmful side effects in off target organs. Even delivering bioactive molecules via direct injection in the tissue of interest can result in rapid, burst release and degradation profiles, thus limiting the therapeutic capacity of the molecules over a relevant timescale. The advantages of delivering bioactive molecules within a hydrogel are the localized and tunable delivery of the therapeutic molecules. The release profiles from hydrogels can be based on simple diffusion, biomaterial degradation, or enzyme-based cleavage. Targeting cardiomyocyte survival or modulating the inflammatory response should be achieved within the first 2 weeks after MI and therefore a sustained release of the bioactive molecules

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should occur soon after MI and hydrogel injection. On the other hand, delivery of bioactive molecules targeting the remodeling process and collagen turnover should last longer as the remodeling occurs in a later phase of the MI pathophysiological process. This longer delivery timescale is also relevant for PAD, which is a chronic affliction and causes remodeling and collagen turnover over a longer term. In this context, smart biomaterials may play an important role as their delivery is guided by enzymes present in the body or a local change in the microenvironment of the diseased tissue, which allows delivery in the desired time window. Synthetic biomaterials have the advantage of being more easily tunable, so that they can be conjugated with a specific molecule, and the binding type can influence the release kinetics.

p0460 Biotinylation is a common method to modify hydrogels for growth factor binding through streptavidin. Peptide nanofibers have been biotinylated to allow the incorporation of different growth factors such as platelet-derived growth factor (PDGF) [83] or insulin-like growth factor-1 (IGF-1) [99,100]. These studies showed that delivery of growth factors with peptide nanofibers improved cardiac function compared to the material or growth factors alone [83,99,100], prolonged *in vivo* growth factors bioavailability [99] and increased cardiomyocytes [99] or cardiac progenitor cell [100] survival when transplanted in the growth factor hydrogel system. Kim et al. showed that self-assembling bioactive peptides sustained release of substance P, a neuropeptide involved in wound healing, recruit host mesenchymal stem cells and improve limb perfusion in a mouse model of hindlimb ischemia after 4 weeks [88]. Webber et al. designed a synthetic system of peptide amphiphile structures engineered to display a VEGF-mimetic epitope. The construct improved angiogenesis and limb perfusion after 3 weeks compared with all material controls [96].

p0465 Bioactive molecules can be also incorporated into the hydrogel without chemical or enzymatic modification, and their release is mediated by diffusion and/or hydrogel degradation. Alginate has been used to incorporate VEGF [101,102] and PDGF [102]. Similarly MacArthur et al. used a hydroxyethyl methacrylate HA hydrogel to sustain the release of a synthetic analog of SDF-1α [103]. In this context, the use of decellularized biomaterials may be advantageous due to their retention of sulfated GAGs, which allow the binding of heparin-binding growth factors. Seif-Naraghi et al. showed that a pericardial ECM hydrogel can be used to prolong the delivery of basic fibroblast growth factor (bFGF) and showed a significant increase in neoangiogenesis when compared to collagen or saline controls [104]. In another study, the same material was used to sustain the release of an engineered hepatocyte growth factor (HGF) fragment in a rat MI model. When delivered in the hydrogel, the HGF fragment improved fractional area change and increased arteriole density when compared with the other groups [105].

p0470 To better control growth factor binding and release, a sulfated alginate hydrogel, which mimics the high affinity of heparin-binding proteins to heparin/heparan sulfate, was also used to sustain the growth factor's *in vivo* delivery. Ruvinov et al. showed that IGF-1 or HGF can be incorporated into sulfated alginate and that the treatment reduced infarct size and increased angiogenesis *in vivo* [106]. In another application for the treatment of PAD in a preclinical model, a sulfate modified alginate improved the affinity binding of HGF and thus allowed for more sustained release for 7 days [107].

p0475 Eckhouse et al. developed a hydroxyethyl methacrylate HA hydrogel to sustain delivery of a recombinant metalloproteinase inhibitor (rTIMP-3) after *in vivo* injection [108]. The injection of the hydrogel immediately post-MI in a porcine model improved EF and decreased LV volumes compared to the injection of the hydrogel alone. Moreover, the treatment reduced proinflammatory cytokines and increased myofibroblast infiltration in the infarct region [108]. In another study, the same group further modified the HA-based hydrogel with an MMP cleavable domain to regulate rTIMP delivery by the local activity of MMPs [109]. Similar to the previous study, the authors showed the *in vivo* applicability of the new hydrogel as well as the positive effect on ventricular function [109].

p0480 Another strategy to further delay growth factors release is to incorporate them into microparticles that are then embedded in a hydrogel. As previously described, Lee et al. used a combination of PLGA microspheres in alginate hydrogel system to deliver VEGF to the murine ischemic hindlimb [98]. Kuraitis et al. also showed 10-fold increased release kinetics of SDF-1α when embedded in alginate microspheres dispersed in a collagen hydrogel compared to the growth factor in either microspheres alone [86].

p0485 In the first clinical trial for PAD to test a biomaterial-based therapeutic, gelatin hydrogel microspheres were embedded with bFGF and showed improved patient walking distance, transcutaneous oxygen pressure, and ankle-brachial pressure index over pretreatment values at 4 weeks but not at 24 weeks [110].

p0490 Synthetic polymers have been also used to prolong the release of bioactive molecules. PEG has been modified with a thiolated enzymatically degradable peptide for the delivery of HGF and VEGF [111]. In another application, PEG was used as a carrier for thymosin β-4 delivery [112] and α-cyclodextrin/MPEG−PCL−MPEG hydrogel for the delivery of recombinant human erythropoietin [113]. Lastly, Koudstal et al. used a triblock copolymer, polyurea-block-PEG-block-urea terminated

with ureido-pyrimidinone units (urea-PEG-urea), to deliver IGF and HGF intramyocardially. The treatment showed an improvement in cardiac function, an increase in capillary density as well as an increase in cardiac progenitor cell recruitment in the infarct region [114].

CONCLUSION

s0075

p0495 The use of injectable biomaterials has emerged as an alternative approach for the treatment of MI or PAD. In the last decade, several encouraging results have been reported in small animal models and some large animals (Tables 25.2 and 25.3). Although the mechanism of action is not entirely understood yet, it is clear that bioactivity of the material plays an important role. The optimal biomaterial should recruit endogenous cells in the infarct region and orchestrate the cellular response to the injury providing a natural platform to sustain new cardiomyogenesis. Another important aspect is the delivery method, where a catheter-based injectable hydrogel application is likely to be preferred in the clinic for treating MI compared to a direct epicardial injection. This is important for the prevention of adhesions at the surgical site, which is a common problem in many patients, and at the same time, decreases the costs and risks associated with an invasive surgery and postoperative care. Timing of delivery is also an important issue to be considered, as most cardiac studies deliver hydrogels soon after MI, which in most cases, particularly for needle-based injections, does not represent the clinical scenario. In PAD, an ideal material should also stimulate regenerative rather than chronic inflammatory immune response pathways as well as neovascularization to the ischemic muscle. Contrary to cardiac applications, PAD therapeutic delivery strategies are less constrained, although intramuscular injection is preferred over invasive surgical placement (i.e., in cases of material patches applied directly to the muscle).

p0500 Overall, hydrogels provide an attractive alternative approach to regenerative medicine strategies for MI and PAD. When designed appropriately, a biomaterial alone could offer similar, and potentially increased, efficacy compared to cell or other biologics based therapies, yet offer off-the-shelf availability, increased shelf life, and reduced costs. Biomaterials also have the potential to significantly improve the delivery of these biologics by increasing their retention and efficacy. In this context, the choice of the matrix, cells, and bioactive drug is crucial. The targeted patient population also plays an important role in the design of a successful therapy. Different strategies will likely be needed for the treatment of acute MI compared to chronic heart failure, and regenerative capacity of younger patients will be different from that of older patients in both MI and PAD. However, numerous studies are still required to elucidate advantages and disadvantages of the different biomaterials employed and confirm previously reported data. Furthermore, the lack of a standard preclinical animal models in both MI and PAD provides a hurdle for assessing comparative efficacy of different biomaterial therapeutics. However, the recent success of a small number of large animal studies and clinical trials for material-based therapies for both MI and PAD is indicative of the potential of hydrogels as a valid therapeutic approach.

Acknowledgments

s0080

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DISCLOSURE

s0085

p0510 Dr. Christman is cofounder, board member, and holds equity interest in Ventrix, Inc.

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AU:3

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NON-PRINT ITEM

Abstract

In the last decade, the field of tissue engineering has emerged as a potential therapeutic strategy for the regeneration and/or repair of various tissues afflicted by cardiovascular disease, such as myocardial infarction (MI) or peripheral artery disease (PAD). Among the different tissue engineering strategies, injectable hydrogels have been extensively studied and show encouraging results in both small and large animal models. An injectable hydrogel provides a favorable microenvironment for endogenous regeneration or repair, and depending on the material's design can be used either alone or as a carrier to deliver therapeutic molecules or stem cells. The type of injectable biomaterial is key for a successful hydrogel-based treatment, and in this chapter, we will focus on acellular injectable biomaterial approaches for both MI and PAD.

Keywords: Tissue engineering; hydrogels; regenerative medicine; myocardial infarction; peripheral artery disease