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REVIEW ARTICLE

Functionalization of soft materials for cardiac repair and regeneration

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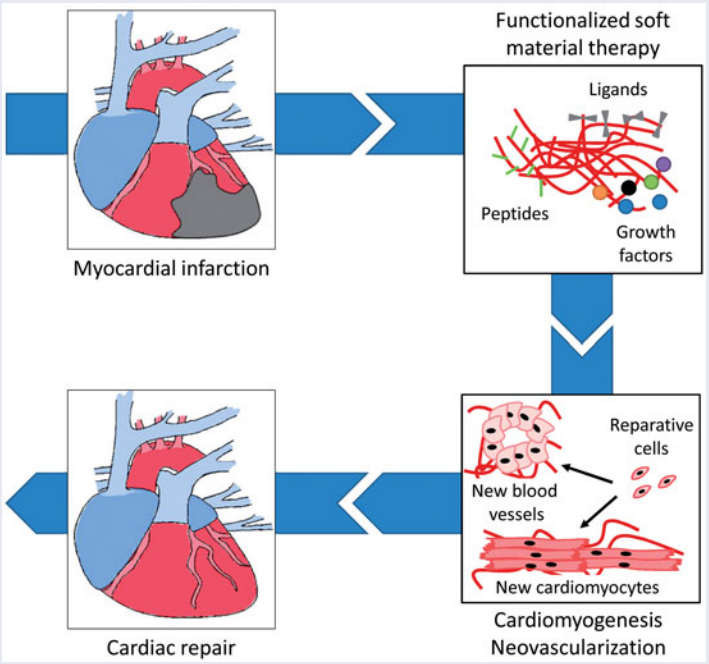
ABSTRACT

Coronary artery disease is a leading cause of death in developed nations. As the disease progresses, myocardial infarction can occur leaving areas of dead tissue in the heart. To compensate, the body initiates its own repair/regenerative response in an attempt to restore function to the heart. These efforts serve as inspiration to researchers who attempt to capitalize on the natural regenerative processes to further augment repair. Thus far, researchers are exploiting these repair mechanisms in the functionalization of soft materials using a variety of growth factor-, ligand- and peptide-incorporating approaches. The goal of functionalizing soft materials is to best promote and direct the regenerative responses that are needed to restore the heart. This review summarizes the opportunities for the use of functionalized soft materials for cardiac repair and regeneration, and some of the different strategies being developed.



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Introduction

Coronary artery disease represents a significant problem in developed nations. Disease progression leads to a loss of blood flow in the heart and ultimately cell death and loss of heart function. Initial clinical trials of stem cell therapy to restore the heart have produced modest results, often citing poor cell engraftment and survival, or a lack of persistent beneficial effects [1].

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To address this, biomaterial therapies have emerged. Soft materials are currently being tested, whether as injectable hydrogels, meshes to wrap around a heart, or scaffolds for implantation. Many studies have reported them to be efficacious and safe and, to date, a few clinical trials have been initiated to investigate their use in patients for the treatment of ischemic cardiomyopathy [2–5]. On their own, soft materials may have regenerative effects, but they can be further modified to enhance regenerative signaling; in other words, soft materials may be *functionalized*. Such methods include the incorporation of growth factors, ligands and peptides, and have demonstrated success at restoring cardiac perfusion and improving the natural stem cell response in the damaged heart. Here, we will review how the endogenous responses to myocardial infarction (MI) may be exploited for the functionalization of soft materials aimed at enhancing cardiac regeneration.

Pathophysiology of heart disease

In order to design functional materials to treat heart disease, one must first have an understanding of the dysfunctional myocardium that develops after ischemic injury.

The physiological response to ischemic injury

Coronary artery disease persists as a leading cause of death in developed nations [6,7]. Over time, the coronary arteries that supply the heart with blood become constricted, reducing local perfusion, impeding normal heart function, and possibly leading to MI. Infarcted tissue is hypoxic leading to a rapid loss of cardiomyocytes through necrosis, and the accumulation of dead cells and debris [8]. The myocardium then releases chemoattractants to recruit circulating inflammatory and progenitor cells, which are guided to the damaged regions by cytokine, adhesion molecule and extracellular matrix (ECM) signals [9]. The inflammatory cells participate in the clearance of dead cells and debris and in the recruitment of wound-healing cells [10,11]. Slightly delayed is the progenitor cell response, whereby stem/progenitor cells attempt to repair/regenerate the myocardium [12–14]. Unfortunately, the stem cell response is short-lived, results in poor accumulation of therapeutic cells in diseased tissue, and contributes minimally to *de novo* cardiomyocytes [15–20]. Myofibroblast activation also accompanies these changes leading to the deposition of a rigid collagen-based scar [21–23], which is a leading cause of diastolic dysfunction and hinders myocardial regeneration [24].

The heart has long been considered an organ of terminally differentiated cells; however, recent reports suggest some capacity for self-renewal, providing hope that adult human cardiomyocytes may be able to divide and contribute to regenerating myocardium [25–28]. In models of skeletal muscle injury and ischemia, it has been shown that vascular regeneration precedes events of muscle regeneration [29–31]. Thus, in order to improve cardiac function, it may be first necessary to restore perfusion, as this is a stepping-stone to further recovery and regeneration [32–34]. To this effect, *therapeutic angiogenesis* centers on the hypothesis that myocardial vasculature must be regenerated in order for other tissue types (e.g. muscle) to regenerate [33,35].

Many different biomaterials are being investigated to support cardiac regeneration. The heart's endogenous repair processes provide insights into what the body is capable of doing on its own, albeit to a limited extent. Much research has focused on exploiting these endogenous regenerative axes. The goal is to design therapies using biocompatible materials to minimize host immune responses, allow for functional integration and promote gradual replacement of constructs as tissue turnover occurs [36–39].

Windows of opportunity and inspiration for therapy

Following MI, several sequential and/or overlapping repair processes are activated, presenting various windows of opportunity for treatment and different strategies to enhance endogenous regenerative efforts.

Inflammatory cell response

Within minutes of myocardial ischemia, inflammatory cytokines are produced and secreted into the circulation [40]. These signals aid in the recruitment of leukocytes and monocytes. During this inflammatory phase is an ideal time for the use of biomaterial therapy designed to capitalize on the reparative potential of circulating mononuclear cells. In particular, monocyte chemoattractant protein-1 (MCP-1) recruits macrophages, some of which will adopt the anti-inflammatory "M2" phenotype [41] and promote wound healing [42]. To aid cell recruitment, the vasculature of damaged zones increases its adhesion molecule expression, including vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1) and E-selectin [43–45]. These ligands can be incorporated into biomaterial therapy as a functionalization strategy to promote cell recruitment and retention, as discussed in

the section "Functionalization of soft materials for cardiac repair".

Growth factor response

Following the production of inflammatory cytokines, there is coordinated release of growth factors [45–47]. Among the most studied are vascular endothelial growth factor (VEGF), insulin-like growth factor-1 (IGF-1), fibroblast growth factor-2 (FGF-2), hepatocyte growth factor (HGF) and stromal cell-derived factor-1 (SDF-1). These cytokines are temporally released and peak at different periods post-MI, aiding in cell recruitment. FGF-2 is a potent stimulator of proliferation and regulates angiogenic progenitor cell activity after infarction [48,49], while SDF-1 recruits progenitor cells to ischemic tissue [46,48]. The incorporation of growth factors may functionalize materials and better support progenitor cell-mediated regeneration in the infarcted heart.

Dynamic ECM changes

Immediately post-MI, soluble and tissue proteases accumulate in the heart [50,51]. These proteases degrade the local ECM, in particular structural collagens I and III [52]. Imbalances in these proteases and their inhibitors precede negative remodeling post-MI, a hallmark of heart failure. Neutrophils and macrophages clear the ECM debris in the MI heart, a process that occurs up to a week post-MI [10,53]. As scar tissue is deposited, the myocardium becomes less elastic and also less permissive of cell infiltration [54,55]. Targeting the early events that characterize ECM remodeling may be a window of opportunity for biomaterial therapy prior to stable scar formation [56–58]. For example, one group delivered a hydrogel designed to release an inhibitor of tissue proteases, TIMP-3, which restored MMP/TIMP imbalances in the myocardium and improved ventricular dimensions and cardiac function [56,57,59]. Therefore, the dynamically changing ECM environment post-MI presents a period when structural preservation is needed, a strategic time and target for biomaterial therapy.

Soft materials for myocardial repair

Ideal physical properties of soft materials for myocardial regeneration

The mammalian myocardium has an elastic modulus that differs among species, but ranges from 20–40 kPa. After infarction, elasticity is reduced and the myocardium becomes stiffer [60]. This is an important consideration since Engler et al. [54] have demonstrated that the elastic modulus is an integral parameter in determining how well regenerating tissues respond to soft materials. In another study, the authors showed that the elastic modulus of a soft material determines the cell type that differentiates from pluripotent cells cultured on the material [61]. In other studies, they demonstrated that the myocardium becomes too stiff after infarction to support the function of new cardiomyocytes [54]. Plotkin et al. tested several fibrinogen-based materials of different stiffness in an infarct model, showing that the material with the highest modulus offered the best functional improvement [62]. It was also reported that a supraphysiological hydrogel modulus may be required to effectively attenuate LV remodeling [63]. Furthermore, Rodell et al. reported on a dual-crosslinking hyaluronic acid hydrogel, which changes modulus from <1 kPa to 40 kPa after local injection, and demonstrated an improvement in LV remodeling following application in an ovine MI model [64].

Aside from matrix stiffness, other important material properties may also play a significant role in mediating the repair process of the myocardium, such as topography, porosity, and viscosity. For example, for preformed scaffolds, modification of the porosity or surface structure has been reported to be a strategy for improving the biointegrity of a material [65]. However, control over topographical features is not as easily achieved for injectable materials since their formation is determined by the space within the tissue into which they are injected. For injectable materials, adjustments made to their viscosity or gelation time can be used to control their injectability, retention and distribution upon injection [66,67]. Recently, some approaches to image materials transplanted into the heart have emerged, such as ultrasound imaging, magnetic resonance imaging, positron emission tomography, and bioluminescence technologies [64,68,69]. Such methods are expected to greatly advance our understanding of how the physical properties of materials can affect their retention and integration with the host tissue. For more in-depth review about how the physical properties of materials can be tuned for repairing the heart, we direct the reader to other reviews on the topic [70–72].

Together, these studies support the hypothesis that ideal materials for regeneration are ones that are recognized as "natural" and "healthy" by the body, not only in chemical composition, but also in physical properties. Thus, soft materials should possess an elasticity that closely matches that of native cardiac muscle, they should allow for nutrient diffusion and cell infiltration, and should integrate with the tissue and cells of the myocardium.

Ideal biochemical properties of soft materials for myocardial regeneration

Ideal biochemical properties of soft materials for myocardial regeneration are those that are considered to be "natural". Soft materials should be minimally immunogenic [73–75]. Immune responses may result from exposure to non-biocompatible synthetic soft materials, or to natural materials derived from species with poor homology, for example. Even if the introduced foreign material is made of components native to the host tissue (as many hydrogels are), there will be a response mounted by the immune system. Actions by the innate and humoral immune systems are varied, and are dependent on the material's antigenicity, composition, and physical properties such as density, porosity, texture, sterility, and physiologic binding sites or recognition sequences [76–78]. At one extreme, the foreign body response leads to rapid surrounding of the introduced material by macrophages, eventually forming a granuloma that effectively walls off the material from the surrounding tissue without any integration [79]. The other end of the spectrum is what researchers are aiming for, i.e. to be able to create materials that illicit minimal inflammation while promoting rapid integration. To achieve this, one needs to consider the multiple aforementioned factors that dictate the host immune response. The entirety of the foreign body response is beyond the scope of this review; however, we direct the reader to recent reviews on this topic [80–82]. Some important points that relate to the functionalization of soft tissues are discussed below.

The first cell to respond to the transplantation of a material is the neutrophil, followed by macrophages and then interstitial cells and stem cells, depending on the composition of the material [83,84]. Each of these cell types is instrumental in determining the degree to which the material will be integrated with the host vs. degraded. If the material is derived from natural components but contains residual DNA, granuloma and scar formation is more likely. However, properly decellularized products have a greater likelihood of being integrated into the functional tissue [85]. Additionally, materials that are better able to promote the anti-inflammatory M2 macrophage phenotype are more likely to be integrated into the host and will promote repair [86,87]. Recently, D'Amore et al. showed that the incorporation of decellularized cardiac ECM to a polymeric biodegradable patch led to a greater M2:M1 macrophage ratio, which was associated with decreased scar, increased angiogenesis, and greater ventricular compliance in the infarcted rat heart [88].

Consideration should also be given to the degradation profile of cardiac soft materials [89]. The heart displays a significantly greater rate of metabolism, when compared to other tissues in the human body [90]. Materials should be recognized by host cells and enzymes, and be subjected to natural degradation as turnover proceeds. Examples of polymers that are commonly used in soft tissue engineering approaches, that also fulfill the requirement for natural degradation and turnover, are the synthetic poly(lactic-*co*-glycolic) acid (PLGA), collagen derived from mammalian sources, and alginate derived from sea kelp [73,75,91–93]. These materials have also been investigated clinically and are considered to have minimal-to-no adverse effects. Notably, it has been shown that the degradation rate of a material can affect the functional benefits associated with its implantation in the infarcted myocardium [89]. In addition, one may wish to consider the degradation products, such as matricryptins, which can be biologically active ECM fragments. For example, the collagen matricryptin p1158/59 was shown to improve LV remodeling and cardiac function post-MI [94]. In summary, a material's immunogenicity and degradation properties are factors involved in determining its *in vivo* performance.

Functionalization of soft materials for cardiac repair

Biofunctionalization serves to modify a material to have a biological function, whether permanent or temporary, while at the same time being biocompatible. Many techniques are available for functionalizing a material including passive soaking, electrospinning, bioprinting, and nanoengineering. However, discussing their technical challenges and unique advantages and disadvantages is outside the scope of this review. Therefore, we refer the reader to the following reviews for more information on different fabrication techniques [95–97]. In terms of cardiac repair, the biological functions that bioengineers hope to impart are those that promote the endogenous repair of the ischemic myocardium, which are supportive of efficacious vascular and cardiomyocyte regeneration. Interaction between the biomaterials and the cells it supports is important for improving the efficacy of the therapy [98,99], and thus functionalizing materials may serve to further enhance this. Figure 1 summarizes the strategies to functionalize soft materials for myocardial applications.

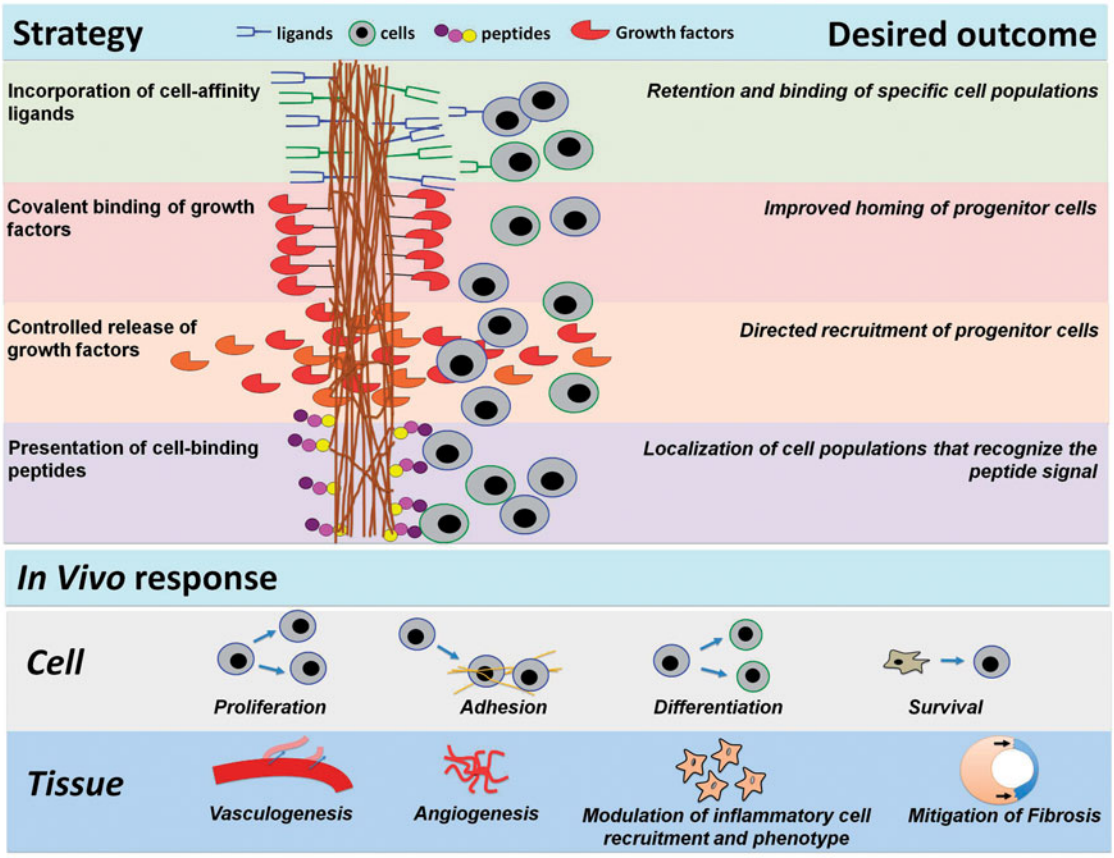

Figure 1. Strategies to functionalize soft materials for improved mobilization, recruitment, and engraftment of regenerative cells for cardiac repair.

Ligand binding strategies

Ligand binding strategies aim to improve the retention and engraftment of cells or the delivery of therapeutics to host cells. For example, Shi et al. [100] incorporated anti-stem cell antigen-1 (Sca1) antibodies into a collagen scaffold (Sca1 is a marker of cardiac progenitor cells). Transplantation of this scaffold into a heart defect model yielded greater numbers of local $Sca1^{+}$ cells, improved vascular density and also provided evidence of cardiomyogenesis [100]. Another group covalently bound the ligand for L-selectin, a receptor found on circulating angiogenic cells (CACs), to an injectable collagen scaffold. Although tested in skeletal muscle, the addition of this ligand improved progenitor recruitment, accelerated reperfusion and also provided evidence of myogenesis [31,101]. They have also reported that CACs cultured on a collagen-based matrix conjugated with the matricellular protein CCN1 (CYR61/CTGF/NOV family member 1, which targets integrin αV and β3) exhibited enhanced cell proliferation, greater incorporation into capillary-like structures *in vitro*, and substantial blood flow recovery after intramuscular injection into ischemic hind limbs in mice [102].

There are many other ligand-based approaches that may be effective for promoting endogenous repair/regeneration responses, but are yet to be tested in relevant models of myocardial ischemia. For instance, the antibody against CD34, an endothelial progenitor cell marker, has been used to functionalize heparin/collagen multilayer polymers to promote attachment, growth and function of endothelial cells to vascular stents [103]. This strategy may also be useful for attracting circulating angiogenic progenitors to participate in the repair/regeneration of the ischemic myocardium. The West group has reported that immobilizing ephrinA1 to poly(ethylene glycol) diacrylate hydrogels enhanced endothelial cell tubule formation *in vitro*, and promoted greater neovascularization *in vivo*, compared to non-functionalized hydrogels [104,105]. Another approach is to use the ligand-receptor system to deliver a therapeutic product to cells in the myocardium. In one study, a primary cardiomyocyte-specific ligand was conjugated to bioreducible poly(cystamine bisacrylamide-diaminohexane) for targeted delivery of Fas siRNA to inhibit apoptosis in cardiomyocytes [106]. In other studies, polyamidoamine dendrimers were functionalized by conjugation with adenosine agonists, which

were successfully applied to prevent the death of cardiomyocytes in apoptosis-inducing conditions [107]. More recently, the delivery of IGF-1 complexed PLGA nanoparticles was shown to reduce cardiomyocyte apoptosis and infarct size and to improve function in a mouse infarct model [108]. One can envision the use of such polymer systems for customized and effective delivery of small molecules for a variety of functions in multiple cell types in the diseased heart based on the specificity of the chosen ligand.

Growth factor incorporation

The functionalization of soft materials can take advantage of growth factor signaling to recruit specific cell types and augment local regeneration. For example, the delivery of SDF-1 using collagen- [109], hyaluronan-based hydrogels [110], and decellularized skeletal muscle-derived scaffolds [111] has been shown to recruit greater numbers of bone marrow-derived progenitor cells to zones of ischemic damage, resulting in improved tissue morphology and/or function. In separate studies, VEGF and FGF released from a PLGA system improved vascular density and also heart function up to 3 months post-injury [112–114]. A poly-L-lactide (PLLA) scaffold releasing granulocyte colony-stimulating factor (GCSF) induced angiogenesis and ECM re-organization leading to connective tissue deposition, scar remodeling, and improved cardiac performance in a rabbit chronic model of MI [115]. A commercially available ECM biomaterial patch (CorMatrix Cardiovascular Inc.) enhanced with FGF-2 was shown to improve function and parameters of remodeling in a rat model of infarction [116]. The release of an HGF fragment from an ECM-derived hydrogel was able to prevent negative remodeling post-MI [117]. As another example, a microsphere/hydrogel combined approach was used to deliver a heat shock protein (HSP27) to the myocardium, which reduced infarct size and apoptosis, and improved function [118]. Likewise, VEGF-loaded materials, delivered either as a cardiac patch or an injectable hydrogel, in a rat MI model led to improved angiogenesis and cardiac function [119,120]. Steele et al. [121] reported on a polyethylene glycol vinyl sulfone-based shear-thinning, self-healing, bioengineered hydrogel (SHIELD) that flows as a solution when subjected to shear force (i.e. injection) and then rapidly returns to a gel state once the force is removed. When HGF was encapsulated, the hydrogel increased arteriole density and reduced infarct size in the rat MI model [121]. Similar to growth factor release, biopolymer mediated gene delivery or RNA interference has also shown promise for salvaging the myocardium [122–126].

Research is evolving towards recapitulating the endogenous regenerative response *in vivo*, and therefore the delivery of 2 or more growth factors is being investigated with greater frequency. For example, Projahn et al. used a combined fast and slow biodegradable synthetic hydrogel approach to spatially and temporally deliver Met-CCL5 and CXCL12 [127]. Their strategy was to delay early neutrophil invasion using the fast degradable polymer (Met-CCL5), while promoting the recruitment of hematopoietic progenitors with the slow degradable polymer (CXCL12). This strategy suppressed initial neutrophil invasion, improved neovascularization, reduced apoptosis, and preserved function post-MI [127]. In another approach, Ruvinov et al. used a soft alginate system to deliver IGF-1 and HGF in a model of MI [128]. Combined growth factor delivery best preserved cardiac structure, reduced fibrosis and also led to more blood vessels in the infarcted myocardium. Evidence of cardiomyocyte regeneration was also present, suggesting an effect on cardiomyogenesis. Similarly, Salimath et al. used a PEG hydrogel system to co-deliver HGF and VEGF [129]. Combined delivery led to improved progenitor cell recruitment, reduced scar tissue, increased vascular density and improved cardiac function. Interestingly, few benefits were observed with single growth factor delivery. Another combined delivery approach used gelatin microspheres containing IGF-1 and VEGF [130]. The results suggested that IGF-1 reduced remodeling, and improved cardiac function and capillary density while reducing inflammation and apoptosis. Animals receiving only VEGF did not display such marked improvements, but co-delivery of both factors synergistically enhanced vascular regeneration. Another combination of FGF-2 and HGF using an alginate-based system also reduced scar formation and improved vascular regeneration and heart function [131]. FGF-2 has also been combined with VEGF for delivery and release from a modular starPEG (multi-armed polyethylene glycol)-heparin hydrogel system [132,133]. Their combined delivery resulted in pro-angiogenic effects both *in vitro* and *in vivo* compared to either growth factor alone. In another report, FGF-2 and VEGF were embedded into nanofibrous scaffolds made of poly (L-lactide-co-caprolactone) and poly (2-ethyl-2-oxazoline), and improved neovascularization and left ventricular wall motion in a rabbit acute MI model [134]. VEGF has also been combined with angiopoietin-1 using polyethylene glycol-fibrinogen (PF) hydrogels or with platelet-derived growth factor using fibrin gels, and showed improved

cardiac function in rat MI model via enhanced angiogenesis [135–137]. Co-delivery of SDF-1 and angiogenic peptides (Ac-SDKP) also showed synergistic benefits when delivered to the infarcted myocardium with superior angiogenesis, reduced infarct size, and improved function compared to either factor delivered alone [138]. A novel approach using platelet rich plasma (PRP) combined with allopurinol, ascorbic acid, and ibuprofen in a hyaluronic acid based hydrogel was shown to improve vascular density, cardiac function and ventricular volumes in surgically infarcted Yorkshire pigs [139]. All of the growth factors described in these studies are normally released by local cells after infarction and confer some survival or functional advantage to the recovering myocardium. It is likely that the ideal strategy to functionalize materials using growth factors will involve multiple factors and controlled delivery. These studies have shown that combination treatment of at least 2 growth factors is superior to the delivery of one alone.

Although growth factor functionalization studies typically aim to improve regeneration via controlled release, some studies have attempted to localize growth factors to the site of injury. For example, Zhang et al. created a VEGF fusion protein that has a collagen-binding domain [140]. Delivery of this fusion protein retained the VEGF signal in the heart and reduced scar size, improved vascular density and preserved cardiac function. In other work, FGF-2 was immobilized into an ECM-derived hydrogel by binding it to sulfated glycosaminoglycans [141]. This system prolonged FGF-2 retention and when applied to a rodent MI model, it increased neovascularization with the generated blood vessels forming anastomoses with the preexisting vascular network. Schesny et al. recently reported on a tunable approach to release and preserve the bioactivity of SDF-1 using a glycoprotein VI domain to anchor SDF-1 to collagen type 1 in the myocardium [142].

Functionalization using cell-responsive peptide sequences

Some large ECM molecules, such as collagen and fibronectin, have multiple peptide sequences that are recognized by cells and may induce multiple regenerative responses. Therefore, it may be advantageous to specify where and when particular cells bind, and how they behave in response to their interaction with their substrate. The concept of designing a biomaterial to control a cell's localization and function has been well-described [143]. For example, the RGD sequence (Arginine-Glycine-Aspartic acid tripeptide) has been identified as the major cell-binding domain in fibronectin [144]. Thus, functionalization of materials by presenting the RGD sequence may confer advantages to the regenerating myocardium via better adhesion and cell integration. RGD incorporation into collagen scaffolds has been shown to improve cardiomyocyte contractility and viability [145]. Similar effects were observed when RGD was combined with an alginate delivery system that reduced apoptosis, improved cell adhesion and cardiomyocyte morphology similar to those of normal cells [146]. An RGD-alginate system was also able to improve vascular cell adhesion and proliferation, and increase blood vessel formation *in vivo* [147]. Recently, alginate scaffolds modified with cyclic RGDFK (Arg-Gly-Asp-D-Phe-Lys)-peptides improved survival of transplanted mesenchymal stem cells (MSCs) and promoted angiogenesis in rat MI model [135,148]. Other ECM-derived peptide sequences that have been investigated as functional additions to soft materials include YIGSR (laminin-derived) [149] and QHREDGS (angiopoietin-1-derived) [150–152]. In one study, YIGSR was immobilized into a self-assembled peptide amphiphile nanomatrix in combination with a nitric oxide donor system [153]. This functionalized material was superior in capturing endothelial progenitors and inducing their differentiation to endothelial cells. In another approach, Zachman et al. used soluble peptides delivered in a polymeric scaffold to mimic ECM degradation products, which can act in a cytokine fashion [154]. Two functional peptides, the pro-angiogenic laminin-derived C16 and the anti-inflammatory thymosin β4-derived Ac-SDKP, were loaded in collagen hydrogels. Subcutaneous implantation of the scaffolds up-regulated the angiogenic response, while down-regulating inflammation, thus holding promise as a strategy for addressing ischemia and inflammation post-MI. Thymosin β4 has also been successfully incorporated into collagen-chitosan hydrogels for release in the heart post-MI, resulting in superior vascular growth and myocardial repair compared to unmodified hydrogels [155]. In another study, RoY, a 12 amino-acid synthetic peptide specifically binding to the 78 kDa glucose-regulated protein (GRP78) receptor, which is largely expressed on vascular endothelial cells under hypoxia, was conjugated to a thermosensitive chitosan chloride hydrogel. The material induced angiogenic activity and attenuated myocardial injury in rat MI model [156]. Although peptide-based strategies allow for control over cell adhesion signal localization and density, the peptides are often highly ubiquitous and not specific to particular cell types. For example, many cell populations will respond to the RGD signal, and it is therefore

difficult to identify which cell types is directing regeneration *in vivo*.

Alteration of soft material composition

Changing the base composition is another strategy to functionalize materials [89]. For example, many studies have incorporated chitosan into soft material systems. Chitosan has been reported to have anti-microbial and pro-angiogenic properties, while being biocompatible and biodegradable [157–159]. As the amount of chitosan increased in a collagen-based hydrogel, the recruitment of $CXCR4^+$ cells, angiogenesis and the frequency of VE-$cadherin^+$ and vWF^+ vascular cells all increased [160]. Incorporation of chitosan into a hyaluronan/silk fibrin patch that was applied to infarcted myocardium led to increased wall thickness and improved function, perhaps attributed to the improvements in vascular density and paracrine secretion [161]. Xu et al. investigated a thiolated collagen and OAC-PEG-OAC copolymer as either stand-alone therapy or as an adjuvant to cell therapy [66]. Delivering the hydrogel alone improved vessel density, scar thickness and size, and cardiac function, and delivering the hydrogel with MSCs further augmented the benefits achieved [66]. Francis et al. reported that a human placenta-derived hydrogel, rich in collagens, laminin, fibronectin, and growth factors (e.g. VEGF-B, HGF) significantly reduced scar volume and maintained electrophysiological activity of the surviving tissue in a rat MI model [162]. This approach to functionalization offers an infinite amount of combinations, and many types of ECM components have been investigated as potential additions to soft materials, such as laminin, heparan sulfate, chondroitin sulfate and collagen IV [36]. However, the focus here was not to detail all the various polymers being investigated. For more information on this subject, please refer to the following reviews [36,163–165].

Biofunctionalization for predicted cellular responses

As many strategies for functionalization now employ multiple methods (ligand/antibody, growth factor & material incorporation), it is useful to summarize what is known so far for each functionalization strategy. Biofunctionalization strategies can be separated into 3 categories: (i) improving the regenerative response via cell recruitment (Table 1); (ii) promoting vascular or cardiac regeneration (Table 2); and (iii) improving heart function and morphology (Table 3). These examples are not exhaustive, but they are of importance to the field because they are studies that demonstrate: (i) soft material functionalization; (ii) application of the functionalized material to a mammalian model of cardiac ischemia, and (iii) morphological and/or functional improvements that can be directly attributed to the functionalization.

Biofunctionalization for cardiomyocyte regeneration

Many of the benefits of biomaterial therapy for cardiac repair can be attributed to myocardial salvage or preservation, neovascularization, and/or mechanical support. The *de novo* production of cardiomyocytes to replace lost ones has proven to be a far more challenging problem. Consideration must be given to what material properties will be necessary to drive myogenesis and to ensure long-term survival and the function of new myocytes. Achieving cardiomyogenesis will likely require a combinatorial approach taking advantage of a number of soluble and insoluble cues, summarized in Figures 2 and 3.

Pre-cardiac myocytes and mature cardiomyocytes

Cells respond to the elastic modulus, or stiffness, of their environment. It is a critical guide for progenitor/stem cell differentiation and the phenotype [166], and it is also important for maintaining cardiomyocyte function and contraction [54,167]. Thus, materials to promote the endogenous repair program post-MI should be designed with this in consideration. Recently, Young and Engler improved cardiac maturation from pre-cardiac cells using collagen I coated hydrogels on a thiolated-hyaluronic acid (HA) template that possessed time-dependent properties achieved via a Michael-type

Table 1. Methods of soft material functionalization to improve cell recruitment in the ischemic myocardium and the time (phase) that treatment was applied.

Functionalization	Time	Effect on cell recruitment	Reference
Chitosan-containing hydrogel	Inflammatory phase	↑ $c\text{-}kit^+$ recruitment ↑ SDF-1 production	[194]
SDF-1-releasing PEG/fibrin patch	Inflammatory phase	↑ $c\text{-}kit^+$ recruitment	[195]
Sca-1 affinity collagen hydrogel	n/a (LV free wall repair)	↑ $sca\text{-}1^+$ recruitment	[100]
SDF-1 and Ac-SDKP releasing hydrogel	Maturation phase	↑ $CXCR4^+$ recruitment	[138]
SDF-1-conjugated muscle-derived scaffold	n/a (femoral muscle implantation)	↑ $CXCR4^+$ recruitment	[111]

Table 2. Methods of soft material functionalization to improve vascular and cardiac regeneration in the ischemic myocardium and the time (phase) that treatment was applied.

Functionalization	Time	Effect on regeneration	Reference
Chitosan-containing hydrogel	Inflammatory phase	↑ Vascular density	[159,194]
Chitosan & FGF-2-containing hydrogel	Proliferative phase	↑ Vascular density	[196]
FGF-2-releasing PLGA scaffold	Inflammatory phase	↑ Vascular density ↑ Perfusion	[113]
FGF-1-releasing PEG-PLGA microparticles	Inflammatory or proliferative phase	↑ Vascular density	[113,114]
FGF-2 and VEGF-embedded PLCL patch	Inflammatory phase	↑ Vascular density	[134]
HGF & IGF-1-releasing alginate microbeads	n/a (hindlimb ischemia model)	↑ Vascular density	[197]
IGF-1-releasing gelatin	Inflammatory phase	↑ Vascular density	[130]
VEGF-bound collagen patch	n/a (RV free wall repair)	↑ Vascular density	[198]
VEGF-releasing PLGA	Inflammatory phase	↑ Vascular density	[199]
VEGF & PDGF-BB-releasing alginate hydrogel	Proliferative phase	↑ Vascular density	[200]
VEGF-releasing calcium-alginate patch	Proliferative phase	↑ Vascular density	[119]
VEGF-releasing hydrogel	Inflammatory phase	↑ Vascular density	[120]
VEGF and ANG-1-releasing hydrogel	Inflammatory phase	↑ Vascular density	[136]
VEGF and PDGF-releasing fibrin gel	Inflammatory phase	↑ Vascular density	[137]
Sca-1 affinity collagen hydrogel	n/a (LV free wall repair)	↑ Vascular density	[100]
RGD-containing alginate hydrogel	Maturation phase	↑ Vascular density	[147]
Thymosin B4-releasing collagen/chitosan hydrogel	Inflammatory phase	↑ Vascular density	[155]
SDF-1 & SCF- containing gelfoam patch	Maturation phase	↑ Vascular density	[201]
HGF & IGF-1-releasing alginate microbeads	n/a (hindlimb ischemia model)	↑ Ki-67^{+} (dividing) cardiomyocytes	[197]
HGF-releasing shear-thinning injectable hydrogel	Inflammatory phase	↑ Vascular density	[121]
Thiolated collagen and OAC-PEG-OAC hybrid hydrogel	Inflammatory phase	↑ Vascular density	[66]
SDF-1 and Ac-SDKP releasing hydrogel	Maturation phase	↑ Vascular density	[138]
PRP releasing hydrogel	Inflammatory phase	↑ Vascular density	[139]
HGF fragment releasing ECM-derived hydrogel	Maturation phase	↑ Vascular density ↑ Cardiomyocyte area	[117]
Engineered CCL5 and CXCL12 releasing biodegradable hydrogel	Inflammatory phase	↑ Vascular density	[127]
SDF-1-conjugated muscle-derived scaffold	n/a (femoral muscle implantation)	↑ Vascular density	[111]
GCSF-releasing PLLA patch	Maturation phase	↑ Vascular density	[115]
RoY-conjugated chitosan chloride hydrogel	Inflammatory phase	↑ Vascular density	[156]

Table 3. Methods of soft material functionalization to improve heart function and morphology after ischemic injury and the time (phase) that treatment was applied.

Functionalization	Time	Effect on heart function/morphology	Reference
Chitosan-containing hydrogel	Inflammatory phase	↑EF, FS; ↓Fibrosis	[159,194]
Chitosan and FGF-2-containing hydrogel	Proliferative phase	↑EF, FS; ↓Fibrosis	[196]
FGF-2-releasing PLGA scaffold	Inflammatory phase	↑FS	[113]
FGF-1-releasing PEG-PLGA microparticles	Proliferative phase	↑EF	[114]
FGF-2 and VEGF-embedded PLCL patch	Inflammatory phase	↑EF	[134]
HGF and IGF-1-releasing alginate microbeads	n/a (hindlimb ischemia model)	↓Fibrosis	[197]
HGF-releasing shear-thinning injectable hydrogel	Inflammatory phase	↑EF	[121]
VEGF-releasing PLGA	Inflammatory phase	↑Wall thickness	[199]
Thymosin B4-releasing collagen/chitosan hydrogel	Inflammatory phase	↑Wall thickness	[155]
Heat shock protein-releasing alginate hydrogel	Inflammatory phase	↑EF	[118]
VEGF-releasing calcium-alginate patch	Proliferative phase	↑FS	[119]
VEGF-releasing hydrogel	Inflammatory phase	↑EF ↓Fibrosis	[120]
VEGF and ANG-1-releasing hydrogel	Inflammatory phase	↑EF, FAC; ↓Fibrosis	[136]
VEGF and PDGF-releasing fibrin gel	Inflammatory phase	↑FAC; ↓Fibrosis	[137]
SDF-1 and SCF-containing gelfoam patch	Maturation phase	↑Wall thickness	[201]
PEG-DMA polymeric microstructures	Proliferative phase	↑EF; ↓Fibrosis	[65]
Tetronic-fibrinogen and PEG-fibrinogen conjugates	Inflammatory phase	↑EF	[62]
GCSF-releasing PLLA patch	Maturation phase	↑EF, FS	[115]
QHREDGS-conjugated collagen hydrogel	Inflammatory phase	↑EF, FS	[152]
RoY-conjugated chitosan chloride hydrogel	Inflammatory phase	↑EF	[156]

EF: ejection fraction; FS: fractional shortening.

addition reaction with poly(ethylene glycol) diacrylate cross-linker [168]. This dynamic material stiffened gradually over time, and in culture produced a 3-fold increase in mature cardiac specific markers and up to 60% more maturing muscle fibers from pre-cardiac cells, compared to a control static hydrogel. Thus, time-dependent stiffening, akin to the developing heart, may prove to be an important functionalization parameter in regenerating cardiomyocytes. Similarly, Boothe et al. reported that cardiomyocytes cultured on

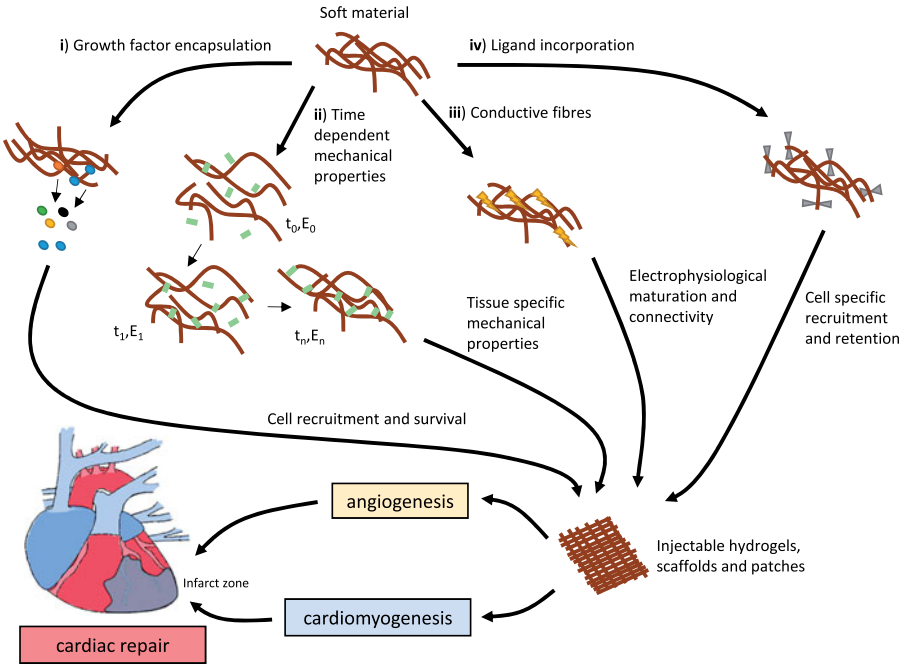

Figure 2. The next generation of "smart" materials for repair and regeneration of the myocardium. A combinatorial approach for the next generation of soft materials is likely required for achieving *in situ* cardiomyogenesis. Naturally-derived or synthetic materials as scaffolds, patches or injectable hydrogels will likely require both angiogenic and cardiomyogenic properties. (i) The encapsulation of soluble growth factors can generate chemical gradients and signals to attract and cue endogenous progenitors. (ii) Tuned mechanical properties provide the necessary structure for lineage specific differentiation and time-dependency may more closely mimic the native developmental program. (iii) Conductivity will be necessary to ensure proper electrophysiological maturity and cell-to-cell coupling. (iv) Ligand incorporation ensures cell-specific attachment in the micro-environment. Together, these various design elements may serve to preserve host myocardium and attract local progenitors to the site of injury, promoting both cardiomyogenesis and neovascularization, and ultimately replacing scarred myocardium with *de novo* myocardium.

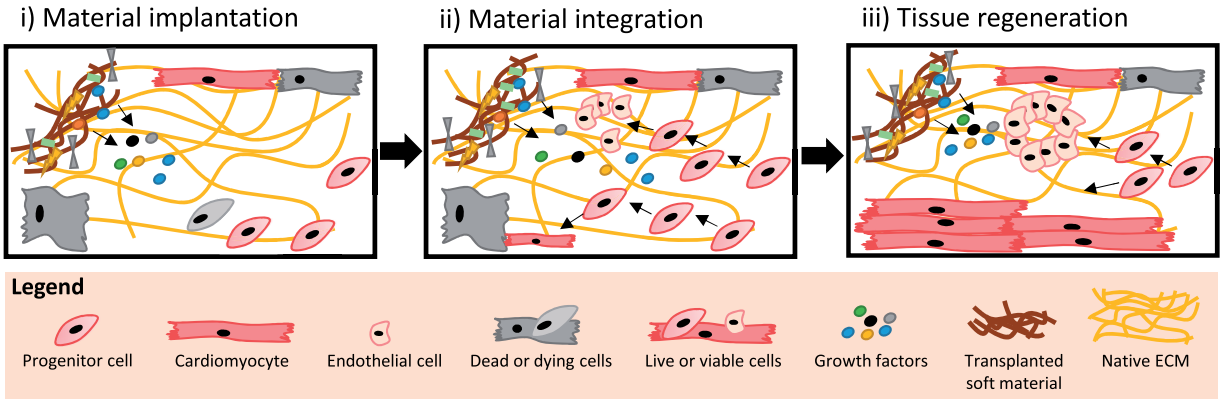

Figure 3. Possible mechanisms for biomaterial-mediated cardiac repair. For optimal cardiac repair/regeneration, transplanted soft materials will need to activate efficient reparative processes. Ideally, on a broad scale, this will consist of (i) implantation of a material with bio-mimicking properties followed by possible growth factor release and/or host cell recognition of incorporated ligand(s); (ii) integration of the material with the host tissue including progenitor cell infiltration, proliferation, and differentiation; and (iii) cardiomyogenesis and neovascularization resulting in replacement of the lost/damaged tissue.

polyacrylamide hydrogels with a 9 kPa elastic modulus (in the range of native myocardium) had the longest action potential duration [169]. In contrast, Chopra et al. suggested that material stiffness mimicking the physiological heart may be unnecessary [170]. Using HA hydrogels functionalized with integrin ligands, it was demonstrated that cells did not respond to traditional mechanical cues [170]. Cardiomyocytes reassembled myofibrils and produced well-developed and functional sarcomeres on a material with mechanical properties far from what is considered conducive to cardiomyogenesis. This suggests that the need for static or

dynamic mechanically optimized soft materials could, potentially, be circumvented. Altogether, the functionalization of soft materials will likely require time-dependent mechanical and topographical properties, or chemical cues to activate intersecting signaling cascades.

Embryonic stem cells and induced pluripotent stem cells

Embryonic stem cells (ESCs) and inducible pluripotent stem (iPS) cells offer a unique opportunity to study post-mitotic cells such as cardiomyocytes [171–173]. However, cardiomyocytes derived from either cell source are, appreciably, different. Much work has been conducted on tuning biomaterials to correct some of these deficits *in vitro*. Borrowing from these studies, we may derive insights into how soft materials could be functionalized for *in vivo* applications to drive endogenous cardiomyogenesis. For example, Nunes et al. demonstrated that iPS cells were able to mature into more functionally representative cardiomyocytes on a collagen I biowire platform when the cells were subjected to a high frequency electrical stimulation protocol [174]. Compared to non-stimulated or low frequency stimulated controls, cardiomyocytes derived from the high frequency protocol demonstrated pronounced sarcomeric organization including more H zones per sarcomere, desmosomes along the plasma membrane, and mitochondria localized closer to the contractile apparatus. For more regarding electrical stimulation systems for cardiac tissue engineering, readers are referred to Tandon et al [175]. Mechanical stimulation alone does not produce electrophysiologically mature cardiomyocytes [176]. Chang et al. demonstrated that electrical stimulation increased the expression of cardiac genes (e.g. HCN1, MLC2V, SERCA, and GATA4), promoted ventricular-like phenotypes, and improved the calcium handling of ESC-derived cardiomyocytes [177]. Likewise, Ma et al. reported that electrical stimulation accelerated cardiac differentiation of human iPS cells and facilitated the functional maturation of cardiomyocytes through activation of Ca^{2+}/PKC/ERK pathways. In addition, the transplantation of derived cardiomyocytes pretreated with electrical stimulation effectively incorporated and repaired the infarcted heart of MI mice [178]. Another challenge to consider is the isolation of islands of cells within polymer scaffolds, separating them from their neighbors and in turn impeding electrical signal propagation through a network of cells. Engineered conductive materials are presenting as potential strategies to solve this issue [179–182]. Using gold nanowires within alginate scaffolds, Dvir et al. showed calcium transient propagation and improved cardiac myocyte alignment, compared to non-conductive scaffold controls [180]. Similar results were reported by Hsiao et al. via culturing neonatal cardiomyocytes on their conductive polyaniline (PANI) poly(lactic-co-glycolic acid) (PLGA) nanofibrous meshes [179]. Other types of conductive materials, such as a polypyrrole-chitosan hydrogel [181] and a π-π conjugation-containing hyaluronic acid hydrogel [182], were also reported to improve electric signal propagation resulting in preserved cardiac function. Thus, future materials may need to be functionalized with electrophysiological properties in order to best support cardiac regeneration.

Challenges that limit clinical application

Despite the promising results of biomaterial treatment for MI in preclinical models, only a limited number of materials have moved forward with clinical trials and the results can be considered, at best, modest so far [2,183–185]. Although not the focus of this review, we provide the following section as a brief introduction to the hurdles currently limiting the translational of materials to the clinic for the treatment of MI. Very few clinical trials for cardiac biomaterial therapy have been undertaken, and the discrepancy between the preclinical benefits and the less encouraging clinical trials identifies some issues that need to be considered. For one, the limited number of clinical trials may be a consequence of the low availability of the needed clinical grade primary materials or the difficulty/cost associated with generating and manufacturing them. In this regard, some functionalized biomaterials may be more easily and/or quickly translated if new more affordable manufacturing procedures could be developed. For example, one group used an engineered fragment of hepatocyte growth factor, which was less expensive to produce and yet possessed superior stability while maintaining its therapeutic effects [117,186], and delivered it to the MI heart in an injectable ECM hydrogel. Similar engineering principles could be applied in generating peptide fragments of other growth factors or ECM proteins for use in functionalized materials.

Other considerations that may not always be at the forefront during the material design phase include the sensitivity of the composite materials to sterilization, the generation of standard operating procedures to ensure quality control of the biomaterial product, together with the optimal time window and delivery route to be used for administering these strategies. Failure to incorporate these factors into material

development at the early stages may limit or delay translational research once pre-clinical evaluation is complete. Another issue to contend with is the regulatory requirement(s) for translating biomaterials to the clinic. Due to the inherent complexity of biomaterials and their functionalized products, it can be difficult to regulate them under the same criteria used for more traditional drug therapies. This in turn makes it difficult to navigate the process of moving a biomaterial product from the laboratory to the patient. As a result, many regulatory bodies, including those in the U.S., Europe and Japan, have been implementing changes to help regenerative therapies gain accelerated and conditional approval to better conduct clinical trials and to better meet the demands of patients [187–189]. While future efforts should focus on optimizing the therapeutic potential of biofunctionalized materials, it may be equally important to consider the above-mentioned challenges in order to maximize the chance of clinical success. For further information on this subject, please refer to the following reviews [71,95,190–193].

Conclusions

For soft materials to yield effective cardiac therapies, methods must be developed to maximize their regenerative potential. Such strategies may employ the incorporation of regenerative signals, in the form of growth factors, peptides and progenitor cell signals. With a better understanding of what regenerative processes exist in the body and which ones are insufficient, our repertoire of soft materials can be further enhanced via functionalization.

The ultimate goal of cardiac tissue engineering is to regenerate a tissue that mimics the healthy myocardium. The ideal biomaterial will incorporate into the host tissue, turnover and be replaced with healthy, viable tissue. Functionalization allows biomaterialists to guide the regeneration process by providing functional cues that direct the cellular response, from invading inflammatory cells to cardiomyocyte renewal/replacement and recruited circulating progenitor cells. As these functional cues are evaluated in the pre-clinical setting, future studies will be able to draw from them and better improve the soft materials that are being used today.

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