Heart failure often develops as a consequence of the limited endogenous capacity for cardiac regeneration after acute myocardial infarction (MI). Cardiac progenitor cells (CPCs) that have been transplanted into hearts with MI can repair the damaged myocardium to some degree despite their low engraftment rates and limited evidence of transdifferentiation into myocardial cells. However, as progenitor-based and stem cell–based tissue engineering technologies continue to evolve, it now seems possible to deposit and retain large numbers of therapeutic cells in close proximity to the region of myocardial tissue damage, and even to replace scar tissue, thus preventing scar bulging and LV dilation, reducing wall stress at the border zone (BZ) of the infarct, improving myocardial bioenergetics, and, finally, remuscularizing the heart.

Tissue-engineered cardiomyoplasty, using engineered myocardium or cell sheets, was first introduced at the beginning of the millennium. Importantly, evidence of myocardial salvage has been obtained with both the direct remuscularization and paracrine approaches in rodent and porcine allograft models. Paracrine factors led to significant increases in BZ vascular density and in the regeneration of myocytes from endogenous CPCs. Although these reports suggest that tissue-engineered patches could have therapeutic potential for the repair of myocardial injury, the overall engraftment rate and biophysical integration of grafts need further optimization.

Engineering cardiac patches for heart repair is a challenging biotechnological objective. This review summarizes the progress in cardiac patch engineering (Table) and critically analyzes the problems and considerations that have to be incorporated into the design of an optimal engineered cardiac patch for heart failure therapy. Despite the relatively straightforward biological rationale, the mechanisms responsible for the observed therapeutic effects are, in most cases,
One week after transplantation onto uninjured rat hearts, collagen scaffolds containing cardiomyocytes that had been generated through the controlled differentiation of human embryonic stem cell (hESC)-derived or human-induced pluripotent stem cell (hiPSC)-derived cardiomyocytes, endothelial cells, and stromal cells contained vascular structures derived from the transplanted human cells and were perfused by the coronary circulation of the host animal. In a rat MI model, transplantation of a collagen scaffold containing mesenchymal stem cells was associated with improvements in infarct size, ventricular wall thickness, angiogenesis, perfusion, and contractile function, and with increases in the growth of myofibroblast-like tissue. Collagen scaffolds have also been used to deliver vascular endothelial growth factor both directly, by modifying the protein to include a collagen-binding domain, or indirectly, by seeding the scaffold with cells that have been genetically engineered to express vascular endothelial growth factor, thereby extending the duration of protein delivery and promoting vascular growth in infarcted myocardial tissue.

The fusion of individual EHM rings into multilooop constructs enables the creation of engineered tissues with, in principle, unlimited dimensionality (Figure 1). Implantation of a multilooop patch 2 weeks after MI in rats led to sustained therapeutic benefits with enhanced regional contractility 4 weeks after engraftment. Furthermore, an alternative pattern of EHM ring assembly can be used to generate cardiac tissue pouches that provide restraint and contractile support to failing hearts (Figure 1), and in vitro studies demonstrate that EHM rings can serve as a test bed for receptor pharmacology, growth factor signaling, and target validation through the use of adenoviral transduction and hypertrophic signaling. hESC-derived and hiPSC-derived cardiomyocytes can also be used to generate collagen-based EHM and parthenogenetic stem cells have recently been introduced as another source of stem cells for cardiomyocytes and myocardial tissue engineering. Further advances in collagen-based myocardial tissue will likely involve biomimetic culture platforms that incorporate electrical and mechanical stimulation.

**Fibrin**

Fibrinogen is cleaved and cross-linked by exposure to thrombin and clotting factor XIII to form an insoluble fibrin mesh that captures blood cells to form a blood clot. Fibrin meshes can also be used to capture any target cell for tissue engineering. In vivo, fibrin attracts leukocytes and, in particular, macrophages and is slowly lysed by endogenous proteases. Anisotropic alignment of rat neonatal cardiac cells in fibrin scaffolds was associated with increases in twitch force despite declines in total collagen and protein content. Fibrinogen can also be conjugated with polyethylene glycol to generate scaffolds that covalently bind growth factors and other proteins, and drug screening platforms have recently been established with fibrin-based engineered heart tissue. In a mouse MI model, treatment with a polyethylene glycolylated fibrin patch containing stromal cell–derived factor-1 was associated with increases in CPC recruitment and improvements in infarct size and cardiac function; the patch was placed over

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**Nonstandard Abbreviations and Acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>3D</td>
<td>3-dimensional</td>
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<tr>
<td>BZ</td>
<td>border zone</td>
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<td>CPC</td>
<td>cardiac progenitor cell</td>
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<td>EHM</td>
<td>engineered heart muscle</td>
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<td>ESC</td>
<td>embryonic stem cell</td>
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<td>hESC</td>
<td>human embryonic stem cell</td>
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<td>hESC-VC</td>
<td>human embryonic stem cell–derived vascular cell</td>
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<td>hiPSC-CM</td>
<td>human-induced pluripotent stem cell–derived cardiomyocyte</td>
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<td>LV</td>
<td>left ventricular</td>
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<td>MI</td>
<td>myocardial infarction</td>
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<td>VC</td>
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incompletely understood. Here, we review the available data on tissue-engineered heart repair and highlight evidence of the specific mechanisms of action associated with tissue-engineered patches.
### Table. Summary of Studies

<table>
<thead>
<tr>
<th>Cell Lines and Other Components</th>
<th>References</th>
<th>Summary/Observations</th>
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<tbody>
<tr>
<td><strong>Natural scaffolds</strong></td>
<td>Collagen</td>
<td>Neonatal rat heart cells</td>
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<td>Fetal rat heart cells</td>
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<td>Mouse embryonic stem cells</td>
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<td>Mouse parthenogenetic stem cells</td>
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<td>Human embryonic and induced pluripotent stem cells</td>
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<td>hiPSC-ECs and hiPSC-SMCs</td>
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<td>Fibrin and Matrigel</td>
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<td>Dvir et al</td>
<td>Evaluates methods for optimizing cell seeding and distribution in 3D scaffolds</td>
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<td>Landa et al</td>
<td>Evaluation of a novel perfusion bioreactor that provides a homogenous milieu for tissue regeneration</td>
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<td>Ruvinov et al</td>
<td>Alginate may promote an excellent support for cell transplantation</td>
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<td>Li et al</td>
<td>Contractility↑, angiogenesis↑, scar thickness↑, LV dilatation↓</td>
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<td>Patra et al</td>
<td>Injectable alginate is suitable for cardiac patch engineering</td>
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<td>PGA introduced as synthetic material for myocardial tissue engineering</td>
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<td>Use of PGA seeded with cardiomyocytes as a model for cardiac electrophysiology</td>
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<td>Polyglycerol sebacate forms an accordion-like honeycomb scaffold that promotes heart cell alignment and mechanical properties</td>
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<td>Godier-Furnemont et al</td>
<td>Evaluates the use of a decellularized matrix for delivering ESC-derived cardiac cells</td>
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<td>Haraguchi et al</td>
<td>Electric coupling of CM sheets occurs rapidly</td>
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<td>Bioengineered cardiac cell sheets have intrinsic angiogenic potential</td>
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<td>Hata et al</td>
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<td>Shimizu et al</td>
<td>Spontaneous, macroscopic beating is observed in subcutaneously implanted sheets</td>
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<td>Sekine et al</td>
<td>Contractility↑, angiogenesis↑, fibrosis↓</td>
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<td>Miyahara et al</td>
<td>Contactility↑, angiogenesis↑, LV dilatation, mortality↓</td>
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<td>Bel et al</td>
<td>Angiogenesis↑, cell engraftment rate↑</td>
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<td>Kushida et al</td>
<td>Evaluates a temperature-responsive surface for culturing cell sheets</td>
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<tr>
<td></td>
<td>Masumoto et al</td>
<td>Contractility↑, wall thickness↑, angiogenesis↑, fibrosis↓</td>
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(Continued)
the site of infarction, where it was associated with increases in stromal cell–derived factor-1 levels for up to 28 days.47

Fibrin patches with defined biophysical properties can be created by mixing solutions of fibrinogen and thrombin, and because the mixture typically solidifies in <1 minute, the patch can be created in situ by injecting the 2 solutions into a mold placed over the infarcted site. This method has been used to deliver autologous mesenchymal stem cells to swine26 and hESC-derived vascular cells (hESC-VCs; ie, smooth muscle cells and endothelial cells) to both swine and mice,17,24 after experimentally induced MI. The transplanted mesenchymal stem cells differentiated into myocyte-like cells4 and were associated with greater thickening of the infarcted wall during contraction, whereas the hESC-VC treatments were associated with improvements in myocardial function, perfusion, and energy metabolism, and with declines in left ventricular wall stress and remodeling.91 Furthermore, the proportion of cells retained in the ischemic region was significantly higher when the cells were administered via a patch than when injected directly into the myocardium.91 Thus, a fibrin patch can be used as a unique platform for cell delivery.

Other 3D Biological Scaffolds

Other 3D biomaterials that have been used to engineer myocardial tissue equivalents include alginate50,52 and silks.58 However, preformed matrices do not seem to be ideally suited for the assembly of cardiomyocytes into a functional 3D cardiac syncytium of contracting cells because the rigid structures and pores of the matrix isolate the cardiomyocytes from each other, thereby preventing direct intracellular contact. This caveat also applies to preformed collagen and gelatin sponges; however, gold nanowires have been used to improve the synchronous excitation of engineered cardiac tissue by bridging the electrically resistant pore walls of alginate.53 In addition, it seems essential that the exogenous matrix is rapidly replaced to prevent interference with tissue formation. Vascularization of the matrix occurs quickly in conjunction with the immune response to the presence of foreign materials.

Decellularized Matrix

Recellularization of a previously decellularized rat heart was successfully attempted in 2008, which suggests that whole organs can be reengineered by using a natural extracellular matrix blueprint.54 Natural scaffolds made from decellularized porcine small-intestinal submucosa71 and bladders46 and from human myocardial tissues67 have been used to generate 3D cardiac patches. For example, decellularized small-intestinal submucosa has been layered with multiple sheets of neontal rat cardiomyocytes to produce patches of up to 800 µm thickness, resulting in cardiac muscle constructs that contracted synchronously for up to 10 days.71 Cell sheets broke apart when applied to decellularized bladder matrix, presumably, because of the roughness of the matrix surface, but they remained intact and proliferative when the voids of the matrix were filled with hyaluronan hydrogel; the hydrogel also enabled a greater number of cells to be seeded. Hydrogels made of fibrin and containing suspended human mesenchymal progenitor cells have been applied to decellularized sheets of human myocardium75 to create cardiac patches that were subsequently evaluated in a nude rat model of MI. The patches dramatically increased both the recruitment of mesenchymal progenitor cells and vascular growth in the infarcted region, and measurements of contractility and left ventricular (LV) dimensions were similar to those obtained in uninjured hearts; integration of the patch with the myocardium of the recipient heart was not examined.

Synthetic Polymers

Polycylic acid,64 poly-ε-caprolactone-co-ε-lactide,65 polyglycerol-sebacate,62 and polydimethylsiloxane62 have been extensively used as tissue-engineering substrates. These materials typically must be coated with extracellular matrix proteins to enable cardiomyocyte attachment and have many of the same limitations associated with biological matrices (as described) for heart muscle engineering on a macroscopic scale. However, they may be well-suited for depositing cells with paracrine activity onto the heart and for providing structural support to prevent further ventricular dilatation.

Injectable Systems

Injectable scaffolds have been used to prevent LV wall thinning and bulging of the ischemic myocardium to inhibit LV remodeling66 and to promote angiogenesis by recruiting endogenous CPCs.56,57 The injection of a cell-free, in situ–forming, alginate hydrogel into recent (7 days) and old infarcts (60 days) provided a temporary scaffold that attenuated adverse cardiac remodeling
Scaffold-Free Approaches

The development of scaffold-free cell sheets first became practical after the invention of a temperature-responsive polymer substrate, poly-(N-isopropylacrylamide). Cardiomyocyte cell sheets are grown on the polymer, released by a decline in temperature, and then stacked to yield multilayered tissues. Electric connections between cardiomyocyte sheets form quickly, probably because in contrast to enzymatic sheet release the temperature-responsive plates leave all surface protein structures intact, thus facilitating gap junction formation. Capillary growth can be induced by creating stacks composed of both cardiomyocyte and endothelial cells, and engrafted cell sheets survived and remained contractile for up to 1 year after implantation. Other scaffold-free tissue engineering approaches include the construction of cardiac microtissues by using a hanging drop method or spontaneous aggregation. Both cell sheet and cell aggregation technologies have been successfully used with cardiomyocytes derived from pluripotent stem cells and, recently, composite cell sheets consisting of monkey adipose–derived stromal cells and monkey ESC–derived SSEA-1+ (stage-specific embryonic antigen-1) cells were tested in vivo with encouraging results.

Myocyte Turnover

The concept of cardiomyocyte turnover in the adult heart is relatively new, and whether the limited regenerative capacity of the adult heart is mediated by the proliferation of preexisting cardiomyocytes or through the activity and derivatives of endogenous CPCs remains a matter of intense debate. Several markers can be used to identify endogenous CPCs with cardiogenic potential, including stem cell growth factor receptor, stem cell antigen-1, ATP-binding cassette subfamily G member 2, and Isl1 (islet-1). Once the types of CPCs are fully characterized and their pathways of activation are deciphered, biomaterial patches can be designed to promote CPC activation and cardiomyocyte turnover, and then placed over the site of myocardial injury, leading to the more comprehensive activation of mechanisms for myocyte regeneration both within and outside the myocardium.

Patch-Associated Paracrine Support in Myocardial Protection and the Activation of Endogenous Repair Mechanisms

Cell Patch–Induced and Paracrine Support–Induced Myocardial Repair From Endogenous CPCs

Although CPCs that have been transplanted into hearts after MI can repair the damaged myocardium to some degree, this activity is limited because the engraftment rate is low, and transdifferentiation of the engrafted cells occurs even less frequently. Thus, myocyte regeneration from the transplanted cells and monkey ESC–derived SSEA-1+ (stage-specific embryonic antigen-1) cells were tested in vivo with encouraging results.

Figure 1. Applications of engineered heart muscle (EHM). Schematic presentation of (A) an EHM patch and (B) an EHM pouch (red). C, Illustration of a multiloop EHM with 5 loops fused together to form an asterisk-shaped stack with a solid center surrounded by 10 loops that are used for surgical fixation of the EHM graft. D, The patch was fixed over the site of infarction in rats with 6 single-knot sutures. E, The dimensions of an EHM pouch and an explanted rat heart are shown. F, An EHM pouch was implanted over a healthy rat heart to simulate its use as a biological ventricular assist device. CHF indicates congestive heart failure; and MI, myocardial infarction. C and D are adapted with permission from Zimmermann et al. Authorization for these adaptations has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation. E and F are adapted with permission from Yildirim et al. Authorization for these adaptations has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.
cells has been suboptimal, and additional benefits might be obtained by applying a fabricated cell patch over the perifocal scar to mobilize endogenous repair mechanisms, stabilize the chronically evolving infarct scar, reduce BZ wall stress, and improve myocardial bioenergetics. Xiong et al. used a fibrin patch to enhance delivery of hESC-VCs for myocardial repair. The hESC-VCs that were loaded into the patch released a variety of cytokines that promote angiogenesis and survival and reduce apoptosis. Both in vitro and in vivo experiments demonstrated that the hESC-VCs effectively inhibited myocyte apoptosis, and the patch-enhanced delivery of hESC-VCs alleviated abnormalities in BZ myocardial perfusion, contractile dysfunction, and LV wall stress. These results were also accompanied by the pronounced recruitment of endogenous c-kit+ cells to the injury site and were directly associated with a remarkable improvement in myocardial energetics, as measured by a novel in vivo 31P MR spectroscopy method. Similar findings were obtained with fibrin patches containing VCs derived from hiPSCs. Four weeks after MI and treatment, LV structural and functional abnormalities were less severe in hearts that received the patch-enhanced cell therapy, and these improvements were accompanied by significant reductions in infarct size. hiPSC-VC transplantation also mobilized endogenous progenitor cells into the BZ, attenuated regional wall stress, stimulated neovascularization, and improved BZ perfusion, which led to marked increases in BZ contractile function and ATP turnover rate.

Cytokine-Associated Myocardial Protection and Increased Density of Myocardial Resistant Vessels

It is a rather consistent finding in the literature that only a very small percentage of transplanted cells show long-term engraftment in the recipient myocardium, and an even smaller fraction of the engrafted CPCs transdifferentiate into cardiomyocytes or VCs. These findings have led to the belief that early paracrine interactions between the transplanted cells and native cardiomyocytes, VCs, and (possibly) cardiac and vascular progenitor cells provide much of the benefit associated with cell transplantation. Many reports indicate that cell transplantation performed soon after an ischemia-reperfusion event is associated with early declines in apoptosis of the injured cardiomyocytes. This sparing of native cardiomyocytes that would otherwise have died after the initial ischemia-reperfusion insult likely reduced the size of the infarct and led to the subsequent declines in LV remodeling and dysfunction that were observed in cell-treated animals. Furthermore, evidence reported by Masumoto et al. indicates that cardiomyocytes may be the main source of vascular endothelial growth factor in cardiac-tissue sheets; they found that the omission of cardiomyocytes from transplanted sheets led to the disappearance of neovascularization and functional improvement, suggesting that the beneficial effects of the shed were induced by cardiomyocyte-secreted cytokines.

Although these findings support the view that paracrine effects initiated by the engrafted cells contribute to declines in infarct size by decreasing apoptosis when the therapy closely follows the ischemic event, cardiomyocyte apoptosis may also be reduced at later time points and, if so, this decline may result from the somewhat delayed increase in BZ capillary density after cell patch transplantation. The patch-enhanced delivery of hESC-VCs and hiPSC-VCs was accompanied by significant improvements in myocardial perfusion in both the infarct and the BZ, as well as a significant increase in the number of resistant vessels in the myocardium, which suggests that vessels generated by the transplanted stem cell–derived VCs were functional. Furthermore, these vessels are the smallest muscular arterioles (50–150 μm) that regulate myocardial perfusion, and each arteriole supports capillaries where the exchange of oxygen and carbon dioxide occurs. Thus, because it has been previously reported that LV hypertrophy and failure are associated with subendocardial ischemia during elevated cardiac work states, this increase in resistant-vessel density could provide the structural basis for the increases in myocardial blood flow, declines in apoptosis, and improvements in LV contractile performance that have been observed in preclinical and clinical studies.

Conclusion

Acute myocardial damage is exacerbated by chronic myocardial overload and LV dilatation, which often leads to heart failure. Consequently, the goal for future regenerative/repairative cardiac therapies includes ≥2 components: minimizing oxidative myocardial damage and remodeling secondary to LV chamber dilatation; and rebuilding the muscle of infarcted and chronically failing hearts to improve contractile performance. Although the paracrine mechanisms induced by cytokine administration may be well-suited for delaying and preventing pathological remodeling and disease progression, the repair of significant ventricular scar bulging will likely require the generation of new cardiac muscle. Thus, strategies that combine the administration of paracrine factors with the creation and integration of engineered cardiac tissue are particularly attractive for the treatment of LV dilatation in hearts with postinfarction LV remodeling.

The beneficial effects of engineered cardiac tissue patches have been clearly demonstrated in animal models, and the clinical feasibility of this approach is supported by the successful transplantation of collagen sponges that lack cardiomyocytes and of cell sheets that contain skeletal myoblasts. Nevertheless, cardiac patches have yet to be extensively investigated in clinical studies, primarily because suitable sources for human cardiomyocytes are lacking. The availability of human stem cells, including hiPSCs, and highly efficient protocols for directing differentiation could alleviate this scarcity and may enable patients to be treated with patches engineered from their own cells, thereby minimizing the potential complications that could evolve from the induction of the immune and inflammatory responses. However, the time required to generate hiPSC-derived cardiomyocyte preclones their use in patients who need prompt treatment; thus, many patients who are candidates for cardiac patch therapy will benefit from the continued development of patches that contain autologous stem cells.

Cardiac patch therapy can only be successful if the patch quickly becomes integrated and perfused by the recipient’s coronary circulation. Although current tissue engineering platforms are rapidly vascularized, and many interventions can successfully promote neovascularization in the
myocardium over time, the vessels may not develop quickly enough to prevent a significant fraction of the cardiomyocytes in the patch from initiating necrotic processes and apoptosis, which can occur within 30 minutes of exposure to no flow ischemia. Furthermore, the engineered tissue is less mature than the recipient myocardium, so endogenous mechanisms for sensing and responding to hypoxic conditions within the patch may not be activated by the absence of immediate vascular support. Thus, the integrity and function of the transplanted patch may be improved by the addition of factors that stimulate vessel growth, impede apoptosis, and promote graft maturation.

Engineered cardiac tissue patches possessing both contractile and paracrine activity have been successfully applied in acute and subacute models of myocardial injury, and patches designed to promote CPC activity and cardiomyocyte turnover could be placed over the injury site to stimulate cardiomyocyte regeneration both at the myocardial surface and within the tissue (Figure 2). This strategy can also be extended to include the creation of engineered cardiac tissue pouches that provide paracrine and contractile support over the entire ventricular surface (Figure 1). However, the clinical acceptance of any patch-based therapy will require the development of a practical and minimally invasive delivery method; for example, an endoscope or catheter-based system could be used to access the pericardial sac through the abdomen and diaphragm, and then solutions could be injected through the catheter to form a hydrogel-based patch in situ. Collectively, these advancements could lead to the development of a new generation of patch-based cellular therapies that combine paracrine support and remuscularization to promote cardiac repair from within and from outside the myocardial tissue.

Figure 2. The benefits associated with our in vivo method for cardiac patch application. A circular 3-dimensional (3D) porous biodegradable cardiac patch (blue) is created over the infarcted region by mixing thrombin and fibrinogen solutions that contain different progenitor cell types, such as mesenchymal stem cells (MSCs), vascular cells (VCs) generated through the controlled differentiation of either human embryonic stem cells (hESCs) or human-induced pluripotent stem cells (hiPSCs), or both hiPSC-VCs and cardiomyocytes (hiPSC-CMs). The fibrinogen can be modified to bind peptides for different purposes, such as guiding differentiation or impeding apoptosis. The solution typically solidifies in <1 minute to form a 3D porous cardiac patch that provides structural support, as well as a platform for the transplanted progenitor cells, and ultimately increases the cell engraftment rate. The transplanted cells release growth factors and other cytokines that reduce apoptosis, promote angiogenesis, and activate endogenous mechanisms for cardiomyocyte renewal, which leads to declines in infarct size and to improvements in myocardial perfusion, metabolism, and contractile function. Measurements of in vivo myocardial bioenergetics and the ATP turnover rate (via 31P magnetization saturation transfer) suggest that the patch also protects against adverse changes in cardiomyocyte energy metabolism, perhaps by reducing wall stress and bulging at the site of the infarction. Collectively, these benefits improve cardiac contractile function and impede the progression of left ventricular (LV) dilatation. BrdU indicates bromodeoxyuridine. Panels B and K are adapted with permission from Xiong Q et al.17 Authorization for these adaptations has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation. Panels F, G, I, J, and L are adapted with permission from Xiong Q et al.18 Authorization for these adaptations has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation. cTnl indicates cardiac troponin I; cTnT, cardiac troponin T; α-SA, α-sarcomere actin; SMA, smooth muscle actin; TUNEL, terminal deoxynucleotidyl transferase mediated dUTP-X nick end labeling.

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Disclosures

None.

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