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Therapeutic Cardiac Patches for Repairing the Myocardium

Benjamin W. Streeter and Michael E. Davis

Abstract

The explosion of stem cell research in the past several years has made its presence known in the field of cardiology and has been recently tasked with solving one of the largest health problems to afflict humanity: cardiovascular disease (CVD). Although stem cell therapy has shown glimmers of promise, significant problems remain that need to be addressed if these therapies are to ever find true success. One way to achieve this success is to take engineering principles and apply them to fabricate engineered cardiac tissues, composed of the aforementioned therapeutic stem cells and biomaterials to bolster the tissue's reparative capacity. In this review, the authors examine advancements in cardiac cell therapy and biomaterial research and discuss how their combination has been used to create tissue-engineered patches capable of restoring function to the damaged or failing myocardium.

Keywords

Cardiac patch · Cardiac tissue engineering · Stem cells · Biomaterials · Myocardial repair

Abbreviations

BMMNCs	bone marrow-derived mononuclear cells
CDC	cardiosphere-derived cell
CM	cardiomyocyte
CSC	cardiac stem cell
CTE	cardiac tissue engineering
CVD	cardiovascular disease
EC	endothelial cell
ECM	extracellular matrix
EHT	engineered heart tissue
ESC	embryonic stem cell
HF	heart failure
HSF1	heat shock factor 1
iPSC	induced pluripotent stem cell
Isl-1	Islet-1
LV	left ventricle
MI	myocardial infarction
miRNA	micro-RNA
MSC	mesenchymal stem cells
PCL	polycaprolactone
PGS	poly(glycerol serbate)
PLGA	poly(lactic-co-glycolic) acid
PLLA	poly-(L-lactic) acid
Sca1	stem cell antigen-1
SIS	small intestinal submucosa
SkMBs	skeletal myoblasts
SMC	smooth muscle cell

B. W. Streeter and M. E. Davis (✉)
Wallace H. Coulter Department of Biomedical Engineering, Emory University and Georgia Institute of Technology, Atlanta, GA, USA
e-mail: michael.davis@bme.emory.edu

1 Introduction

CVD is the number one cause of death in the United States and claims more lives each year than cancer and chronic lower respiratory disease combined. Around 11.5% of American adults (27.6 million) have been diagnosed with some form of CVD, and, despite many advances in cardiovascular research and medical treatment, many of these patients still succumb to the disease (Benjamin et al. 2018). The limited capability of the heart to regenerate following injury remains a major hurdle to effectively restoring heart function in CVD patients. Specifically, the loss and replacement of cardiomyocytes (CMs) by fibrotic scar and CMs' extremely low turnover rate in the endogenous myocardium leaves the heart unable to perform contractile functions and eventually leads to end-stage heart failure (HF) (Bergmann et al. 2009, 2015 Porrello et al. 2011; Eschenhagen et al. 2017). The only current treatment for end-stage heart disease is heart transplantation. However, several complications including infection, rejection, and malignancies can occur following heart transplant procedures (Wilhelm 2015). Further, many HF patients never receive a transplant and die while on the waitlist due to a shortage of donor hearts (Goldstein et al. 2016). Therefore, there is still a significant need to develop new techniques and therapies to combat CVD and repair injured myocardium.

Recently, cell therapy has emerged as an alternative therapeutic option to transplantation. Several preclinical studies have illustrated the potential of injected stem cells to repair injured myocardium, but this potential is limited due to low engraftment into the native myocardium and lack of differentiation to new, functional CMs (Zhang et al. 2001; Terrovitis et al. 2010; Wu et al. 2011; Nguyen et al. 2016). Many current research efforts are geared towards solving these problems and improving cell therapy's therapeutic benefit, specifically using cardiac tissue engineering (CTE). Tissue engineering combines knowledge from physiology and cellular biology with engineering principles to create scaffolds *in vitro* whose purpose is to improve cell survival, retention, and reparative capacity following implantation. Researchers often use native matrix composition and architecture as blueprints for the construction of scaffolds in laboratory conditions. Combining these scaffolds with the appropriate cell source can lead to the creation of functional tissue and other therapeutic products. In the case of CTE, engineered cardiac patches can be generated to help reverse many of the deleterious effects of CVD (Ye et al. 2013; Hirt et al. 2014; Best et al. 2016; Zhang et al. 2018). This article reviews several different recent CTE and cardiac patch advancements, particularly in the context of restoring contractile function of the myocardium.

2 Cell Sources

It is estimated that CM turnover in the human heart is only about 0.5–2% (Eschenhagen et al. 2017). Although this rate may increase following injury (Hsieh et al. 2007), endogenous CM renewal is not sufficient to restore contractile function. Stem cells from many different sources have been investigated to both replace lost CMs in the native heart as well as to galvanize cardioprotective events through paracrine signaling following their implantation (Dimmeler et al. 2007). Cell sources used in cardiac cell therapy include skeletal myoblasts, bone marrow-derived cells, mesenchymal stem cells, embryonic stem cells, induced pluripotent stem cells, and cardiac stem cells (Chavakis et al. 2010; Zhang et al. 2018). In this section, we review previous work that has utilized these different cell sources to treat the failing heart and highlight important preclinical and clinical findings.

2.1 Skeletal Myoblasts

The first clinical study investigating cell therapy for myocardial repair was published in 2001 by Menasché et al. The authors delivered autologous skeletal myoblasts (SkMBs) to a myocardial infarction (MI) patient. Several SkMB injections were administered in and around sites of necrosis on the LV wall, and the patient's contractile

function improved upon a 5-month follow-up (Menasché et al. 2001). The same group performed a much larger clinical trial in MI patients, The Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) Trial, in 2011, but found that SkMB injection showed no improvement in cardiac function compared to a placebo control injection. Additionally, a greater number of arrythmias were reported in patients receiving SkMB patients (Menasche et al. 2008). Further pre-clinical research investigating SkMBs' potential as a therapeutic cell type for myocardial repair has focused on *ex vivo* engineering of SkMBs to prevent arrhythmic events upon implantation and to improve their reparative paracrine signal secretion. SkMBs do not naturally express the gap junction protein connexin 43 that CMs use to propagate electrical signals through the myocardium. Therefore, several studies have investigated overexpressing connexin 43 in SkMBs to enhance electrical coupling and engraftment to host CMs. These studies have shown that this strategy leads to attenuation of arrythmias and improvement in ventricular function following treatment with connexin-43-overexpressing SkMBs (Abraham et al. 2005; Kolanowski et al. 2014; Antanavičiūtė et al. 2015). SkMBs have also been used in tissue engineered constructs to produce functional tissue and production sources of reparative paracrine signals. Both Blumenthal et al and Siepe et al used polyurethane-based scaffolds seeded with SkMBs as a cardiac patch that was implanted onto the epicardium of MI animal models. Further, the SkMBs used in these constructs overexpressed the pro-survival gene *Akt1*. Implantation of these patches led to increased angiogenesis and reductions in infarct size (Blumenthal et al. 2010; Siepe et al. 2010). Recently, scaffold-free SkMB cell sheets have been shown in clinical trials to decrease arrythmias, improve LV injection fraction, and increase angiogenesis in ischemic and dilated cardiomyopathy (Sawa et al. 2015; Yoshikawa et al. 2018). The results from these studies suggest that the use of SkMB cell sheets and SkMB-based tissue-engineered patches may circumvent some of the safety and efficacy issues that plagued earlier injection-based trials and may make them more successful in larger clinical studies.

2.2 Bone Marrow-Derived Cells

Bone marrow-derived mononuclear cells (BMMNCs) are a heterogeneous group of cells composed of several cell types including hematopoietic progenitor cells, bone marrow mesenchymal cells, and monocytes (Yoon et al. 2010). They have been studied extensively as a candidate to regenerate and repair the damaged myocardium and, to date, are the cell type most commonly used in cardiac cell therapy clinical trials. The first clinical application of BMMNCs took place in 2001, when Strauer et al. delivered BMMNCs to an acute MI patient via intracoronary injection. At follow-up 10 weeks later, the patient had a reduced infarct area and improved cardiac function (Strauer et al. 2001). This study set the stage for several other clinical trials that later used BMMNCs to treat acute MI, including the BOOST (Wollert et al. 2004) and TIME (Traverse et al. 2012) trials, and subsequent follow-ups to these trials, BOOST-2 (Wollert et al. 2017) and LateTIME (Traverse et al. 2011). Additionally, BMMNCs have been used in clinical trials to restore myocardial function in other cardiac disorders including ischemic cardiomyopathy (Perin et al. 2003, 2004, 2012; Assmus et al. 2006; Heldman et al. 2014) and dilated cardiomyopathy (Fischer-Rasokat et al. 2009; Seth et al. 2010; Martino et al. 2015; Xiao et al. 2017) along with others focused on addressing acute MI similar to the BOOST and TIME trials (Sürder et al. 2016). Although many of these studies report modest improvement in left ventricle (LV) function following BMMNC injection in certain areas, these results have not often translated to improvement in clinically meaningful outcomes (Simari et al. 2014). Because of this, other research efforts have been driven toward modifying BMMNC therapy through enhanced delivery methods. One previous study by Lin et al. used self-assembling peptide nanofibers to increase BMMNC retention

following injection and showed improved systolic and diastolic function in pig models of MI (Lin et al. 2010). BMMNC populations have also been enriched by sorting cells for the stem cell marker c-kit, and this enriched cell population has been modified via tissue and genetic engineering methods to enhance the bone marrow-derived c-kit$^+$ cells' efficacy (Quijada et al. 2012; Liu et al. 2016b).

2.3 Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) are multipotent fibroblast-like cells have the ability to differentiate into osteoblasts, adipocytes, and chondroblasts (Dominici et al. 2006). MSCs can be derived from many different organ and tissue sources in the body, but the most common sources are bone marrow and adipose tissue. They are an attractive cell source due to their immunoprivileged nature, as they lack major histone compatibility complex class II markers and due to their many pro-reparative functions including attenuating fibrosis, enhancing angiogenesis, and kickstarting endogenous cardiac repair mechanisms (Golpanian et al. 2016). Because MSCs have limited retention at target sites when injected (Bahr et al. 2012), these functional improvements are often attributed to the secretion of paracrine effectors (Banerjee et al. 2018). MSCs are the most commonly used cell type in preclinical CTE studies, and several clinical trials have been conducted investigating MSCs as a feasible and efficacious cell source for cardiac cell therapy (Zhang et al. 2018). The POSEIDON trial conducted by Hare et al. compared the use of allogenic and autologous MSCs as a therapy for ischemic cardiomyopathy. The authors injected MSCs transendocardially at three different doses: 20 million, 100 million, or 200 million cells. They found that both autologous and allogenic MSCs significantly reduced infarct size and that the lowest dose, 20 million cells, led to the greatest reduction in LV volume and increase in ejection fraction (Hare et al. 2012). MSCs have also been used in combination with other cell types including BMMNCs and cardiac progenitor cells in preclinical and clinical studies (Heldman et al. 2014; Quijada et al. 2015; Bolli et al. 2018). MSCs may be able to enhance the proliferation and cardiac reparative capacity of these cell types, while also improving therapy through immunomodulation. Further, MSCs are being explored as a cell therapy candidate in pediatric patients with hypoplastic left heart syndrome in the ELPIS clinical trial (Kaushal et al. 2017). Other preclinical work has used computational modeling to better understand MSCs' ability to couple to host myocardium and to elucidate the underlying mechanisms of MSC paracrine secretion that leads to functional benefit (Mayourian et al. 2016, 2017). MSCs have been used extensively in combination with biomaterials for CTE applications, and several of these studies will be discussed later in this review.

2.4 Embryonic Stem Cells

Embryonic stem cells (ESCs) are stem cells isolated from the inner cell mass of an embryo and can give rise to any cell type in the body, excluding those in placental tissue (Evans and Kaufman 1981). ESCs have been used both in their undifferentiated, pluripotent state as well as differentiated into many different cell types for cardiac cell therapy and tissue engineering purposes. Kofidis et al. combined undifferentiated mouse ESCs with Matrigel and injected this mixture into a mouse infarct model. Injected ESCs formed colonies in the infarcted area, showed expression of connexin 43 at contact sites with host cells, and improved fractional shortening (Kofidis et al. 2005). Although in this study no teratoma formation was observed, the tumorgenicity of undifferentiated ESCs, along with ethical issues, immunogenicity, and scaling up of ESC isolation and production, remains a major concern for their clinical translation (Zimmermann 2011). To bypass some of these issues as well as produce more cardiac-like cells, ESCs are often differentiated to cardiac progenitors, CMs, and endothelial cells (ECs). A fibrin patch embedded with ESC-derived SSEA1$^+$ progenitor cells was shown to increase

ejection fraction and angiogenesis when implanted onto infarcted rat hearts (Bellamy et al. 2014). ESC-derived CMs have been a highly investigated topic of cardiac cell therapy, and many studies have shown their efficacy in both rodent and non-human primate models (Laflamme et al. 2007; van Laake et al. 2008; Shiba et al. 2012; Chong et al. 2014). ESC-derived ECs and CMs have been used together with one another to form vascularized cardiac muscle, illustrating the versatility and flexibility of ESCs as a cell source (Caspi et al. 2007). Ongoing research focuses on further maturation of ESC-CMs so that they more closely mimic the mechanical properties of natural CMs *in vivo*. A variety of methods including modulating substrate stiffness (Jacot et al. 2010), electrical stimulation (Martherus et al. 2010), and delivering biochemical cues (Földes et al. 2011) are currently being explored to increase ESC-CM maturation.

2.5 Induced Pluripotent Stem Cells

The Yamanaka laboratory first demonstrated the creation of induced pluripotent stem cells (iPSCs) in 2007. The authors of this study retrovirally transduced human dermal fibroblasts with four key transcription factors: Oct3/4, Sox2, c-Myc, and Klf4. These "Yamanaka factors" converted human dermal fibroblasts into pluripotent stem cells with similar characteristics, including gene expression and morphology, to ESCs (Takahashi et al. 2007). This landmark work set the stage for the use of iPSCs throughout the field of regenerative medicine, including CTE. Because iPSCs are patient-derived from adult fibroblasts, they circumvent the immunogenic and ethical concerns associated with the use of ESCs, while still providing the versatility of a pluripotent cell source. iPSCs have a similar differentiation potential to ESCs (Mauritz et al. 2008) and have been differentiated to a variety of different cardiac cells for use in cell therapy. Ye et al differentiated iPSCs into ECs, CMs, and smooth muscle cells (SMCs) and implanted this tri-lineage combination with a fibrin patch into a porcine model of MI. The iPSC-derived CMs integrated into the host myocardium, while the ECs and SMCs contributed to endogenous vessels, leading to improvements in LV function (Ye et al. 2014). This same group later reported a similar tri-lineage cell patch approach with larger, more clinically relevant dimensions and more advanced maturation of iPSC-CMs through dynamic culture on a rocking platform (Gao et al. 2018). Other studies have shown improvements in iPSC-CM therapy and maturation using anisotropic scaffolds (Khan et al. 2015), naturally-derived extracellular matrix (ECM)-based materials (Fong et al. 2016; Wang et al. 2016), and 3D spheroid aggregation (Beauchamp et al. 2015). Despite their promise, issues with iPSCs, including partial reprogramming that can lead to genetic and epigenetic changes, remain a challenge for clinical translation, and are being addressed by ongoing research (Okano et al. 2013).

2.6 Cardiac Stem Cells

The first population of cardiac stem cells (CSCs) was discovered in 2003 when cells marked by the tyrosine kinase c-kit were isolated from the adult mammalian heart. These cells were clonogenic, self-renewing, and multipotent with the ability to differentiate into CMs, ECs, and SMCs (Beltrami et al. 2003). Since this discovery, several other cardiac stem cell populations have been studied including cardiosphere-derived cells (CDCs), stem cell antigen-1^+ ($Sca1^+$) cells, and Islet-1^+ (Isl-1+) cells (Le and Chong 2016). However, the true nature of these stem cells' role in cardiac biology, specifically that of c-kit+ CSCs, and their contribution to the functional cardiomyocyte population *in vivo* has been hotly debated and shown to be very minimal (Ellison et al. 2013; van Berlo et al. 2014; Sultana et al. 2015; Liu et al. 2016a; Vicinanza et al. 2017, 2018; Gude et al. 2018). Nonetheless, CSCs' ability to provide therapeutic benefit has been shown extensively in both preclinical and clinical studies. SCIPIO, a Phase I clinical trial, was the first in-human clinical trial using autologous c-kit^+ CSCs. The CSCs were used to treat patients

with ischemic cardiomyopathy undergoing coronary artery bypass grafting. Results from the trial showed encouraging outcomes including an increase in LV ejection fraction and a decrease in infarct size (Bolli et al. 2011; Chugh et al. 2012). CADUCEUS, another Phase I clinical trial, employed CDCs to treat patients 2–4 weeks following an MI. Although initial results showed no changes in LV ejection fraction with CDC therapy, CDC treatment did lead to a decrease in infarct size and an increase in viable myocardium (Makkar et al. 2012). As is true with other cell therapy, the functional benefit provided by CSCs is thought to be due largely to paracrine factor secretion. Therefore, current research has employed computational methods to elucidate the paracrine factors most important for cardiac repair (Gray et al. 2015; Agarwal et al. 2017; Sharma et al. 2017). Additionally, our laboratory and others have shown an age-dependent decline in the reparative capability of CSCs (Agarwal et al. 2016; Sharma et al. 2017). Other arms of CSC research have focused on *ex vivo* conditioning through hypoxic growth conditions (Gray et al. 2015), genetic manipulation (Fischer et al. 2009), and combinatorial cell therapy (Avolio et al. 2015; Bolli et al. 2018).

3 Material Considerations

While a sufficiently therapeutic cell source is vitally important to the success of CTE strategies, a biomaterial that can effectively act as a carrier of this therapeutic cell source is equally essential. Further, cell-free materials that bolster the function of endogenous cells and tissue may be a similarly effective option to cell-laden patches. Because of this, research uncovering the optimal parameters of a biomaterial's formulation as well as the most therapeutic combination of material and cell source is paramount for advancing CTE. In this section, we review the considerations for cardiac biomaterials, including material source and fabrication technique, that have been explored in literature.

3.1 Material Sources

3.1.1 Natural Materials

Natural biomaterials are those derived from naturally occurring, biological sources, giving them many advantages for their use in CTE. Most notably, because these materials are derived from *in vivo* sources, they retain much of the microenvironmental architecture cells experience in native tissue. Cues from this biomimetic microenvironment can help improve stem cell maturation and therapeutic function. Additionally, natural materials often have superior biocompatibility, allowing them to avoid immune reaction and thrombosis once implanted. Natural materials that have been used in CTE applications include collagen, chitosan, fibrin, alginate, Matrigel, hyaluronic acid, gelatin, and decellularized ECM (Reis et al. 2016). Decellularized ECM has been derived previously from both cardiac sources, including the myocardium (Singelyn et al. 2012; Seif-Naraghi et al. 2013; Dai et al. 2013) and pericardium (Wei et al. 2006, 2008; Rajabi-Zeleti et al. 2014; Vashi et al. 2015), as well as from non-cardiac sources, including small intestinal submucosa (SIS) (Tan et al. 2009; Okada et al. 2010) and urinary bladder matrix (Kochupura et al. 2005; Robinson et al. 2005). Cardiac decellularized matrix was first harvested by Ott et al in 2008 when the authors delivered detergents including PBS, SDS, and Triton X-100 through coronary perfusion to rat cadaveric hearts. This process eliminated virtually all cellular contents in each heart but retained ECM content such as collagens I and III, laminin, and fibronectin and maintained ECM fiber composition and architecture. Further, the researchers were able to repopulate the decellularized hearts with neonatal cardiac rat cells and produced hearts that displayed expected electrical and contractile responses to electrical stimulation (Ott et al. 2008). The Christman group then expanded upon this decellularization principle and used it to process soluble porcine myocardial ECM that gelled at 37 °C, allowing the ECM to be used as an injectable material (Singelyn et al. 2009). Although decellularized ECM and other natural

materials confer better mimicry of the native cell microenvironment, use of these materials still often faces the challenge of being too mechanically weak to successfully function as a cardiac patch. The human myocardium can range in stiffness from 20 kPa (end of diastole) to 500 kPa (end of systole), while many natural materials have stiffnesses in the tens of Pa range (Reis et al. 2016). Moreover, batch-to-batch variation of natural materials is largely dependent on variations in material sources. Engineering natural materials to more closely mimic *in vivo* stiffnesses and creating consistent material processing practices are needed to continue to push these materials towards clinical use.

3.1.2 Synthetic Materials

While natural materials often provide a ready-made cell microenvironment that closely mimics that seen *in vivo*, synthetic materials offer modular building blocks that can be combined in myriad ways to create scaffolds with more clearly-defined physical and mechanical properties. Additionally, use of synthetic materials allows for more reproducible fabrication processes and often have enough mechanical strength for implantation as a patch. Synthetic materials commonly used in CTE include polycaprolactone (PCL), poly(glycerol serbate) (PGS), polyurethane, poly-(L-lactic) acid (PLLA), and poly(lactic-co-glycolic) acid (PLGA), among several others (Reis et al. 2016). PCL has been used in combination with neonatal rat CMs to form cardiac grafts where CM beating was maintained, cell-to-cell contact occurred, and cardiac specific markers such as connexin 43, cardiac troponin I, and α-myosin heavy chain were expressed (Shin et al. 2004; Ishii et al. 2005). PCL has also been combined with other co-polymers, including those from synthetic sources like carbon nanotubes (Wickham et al. 2014) and PGS (Tallawi et al. 2016) and from natural sources such as chitosan (Pok et al. 2013) and gelatin (Kai et al. 2011), to form more complex constructs. PGS is another particularly attractive synthetic polymer due its elastic nature, making it ideal for mimicking the mechanically dynamic environment of contracting CMs. Additionally, mechanical characterization of PGS scaffolds has shown its Young's modulus to more closely mimic that of native myocardium compared to several other synthetic polymers (Chen et al. 2008). PGS has also been shown to provide a viable environment for a variety of cells including fibroblasts and ESC-CMs (Chen et al. 2010). While synthetic materials offer many benefits for CTE, there are also problems with their use that still need to be solved. Synthetic materials provide a great deal of mechanical support, but this often means that their stiffnesses can be orders of magnitude greater than that seen in the native myocardium. This may cause a mechanical mismatch with the heart upon implantation and could induce additional burden on the pumping function of the heart. Additionally, due to many of these materials' bioinert nature, they may not be able to fully propagate electrical signals to the heart and could cause arrythmias when implanted. Continuing research into properly tuning the properties of synthetic polymers and co-polymers is needed to address these issues.

3.2 Material Fabrication Techniques

3.2.1 3D Bioprinting

Several different techniques for fabricating biomaterials exist, and each technique can significantly impact material properties. 3D bioprinting, one such technique, is the process of depositing sequential layers of biological materials (often a biomaterial/cell mixture) on top of one another to form 3D structures. Utilizing this technique allows for precise control of cardiac patch geometry and modulation of properties such as strand diameter and pore size (Murphy and Atala 2014). Further, one major issue with cardiac patches is delivery of a clinically relevant number of cells. Patches may suffer from either low proliferation of cells or insufficient oxygen and nutrient delivery to cells within the patch, leading to a high degree of cell death. 3D printing allows for the creation of complex porous networks that permit efficient nutrient delivery, and ensures a uniform distribution of cells throughout the patch

(Mosadegh et al. 2015). 3D printing has been used with many combinations of materials and different cell types, often termed "bioinks", for cardiac applications. Gao et al. recently printed a methacrylated gelatin-based patch with CMs, SMCs, and ECs, all differentiated from iPSCs. To precisely control the architecture of their patch, the authors used multiphoton-excited 3D printing and mapped the blueprint for the printed scaffold to the distribution of fibronectin within the mouse myocardium (Fig. 1). This technique produced printing with a resolution of <1 μm, giving a highly accurate approximation of native ECM structure. Following printing and seeding with the three cell types, the patch beat synchronously after just 1 day and improved cardiac function, infarct size, and vessel formation when implanted into a mouse model of MI (Gao et al. 2017). Our laboratory has also used gelatin methacrylate as a bioink for 3D printing, and recently combined gelatin methacrylate with porcine-derived cardiac ECM and neonatal c-kit^{+} CSCs to create a cardiac patch for right ventricular heart failure (Bejleri et al. 2018). Another recent study used 3D printing to print gelatin microchannels to improve MSC differentiation and CM alignment and beat synchronicity. MSCs aligned and elongated at a higher rate in microchannel constructs than unpatterned constructs, leading to a higher expression of cardiac specific proteins. CMs also showed more pronounced alignment and display synchronous beating on microchannels (Tijore et al. 2018). These studies highlight the ability of 3D bioprinting to produce complex and highly defined architectures to influence cell behavior and function.

3.2.2 Electrospinning

Electrospinning is another fabrication process that has garnered a great deal of attention recently in CTE. During scaffold fabrication, a high voltage (~1–30 kV) is applied to the needle of a syringe containing a polymer of choice. As the polymer is extruded out of the needle, the electrostatic force at the surface of the polymer droplet and the Coulombic force from the surrounding electric field overcome the surface tension of the droplet, leading to the formation of a polymer jet that is deposited onto a grounded collector (Li and Xia 2004). Electrospinning produces polymer patches with nanoscale fibers and high porosity, mimicking the fiber composition of native ECM and allowing for efficient nutrient diffusion throughout the patch (Liu et al. 2012). Additionally, electrospinning is a highly reproducible, tunable, and cost-effective process. Electrospinning was first used in CTE by Shin et al. to create PCL patches seeded with neonatal rat CMs (Shin et al. 2004). Since this initial study, electrospinning has been used expansively with both natural and synthetic materials for cardiac applications (Kitsara et al. 2017). Notably, electrospinning has been employed to create patches with highly aligned fibers to align cells, more closely mimicking CM morphology and spatial organization in the myocardium. For example, neonatal rat CMs seeded on aligned PGS/gelatin electrospun patches showed greater anisotropic sarcomere formation and synchronized beating compared to random patches (Kharaziha et al. 2013). Electrospun scaffolds are also easily modifiable with other components to improve cell attachment, survival, and reparative function. These components include gold nanoparticles (Shevach et al. 2013; Ravichandran et al. 2014; Fleischer et al. 2014), growth factors such as VEGF (Ravichandran et al. 2015; Chung et al. 2015), and ECM proteins such as fibronectin (Badrossamay et al. 2010; Fleischer et al. 2015) and laminin (Yu et al. 2014).

3.2.3 Engineered Heart Tissues

While 3D bioprinting and electrospinning precisely control material architecture to mimic *in vivo* tissue, creating engineered heart tissues (EHTs) capitalizes on cells' inherent ability to self-assemble and form tissue. The first EHT was created by Eschenhagen et al. in 1997 when CMs from chick embryos were blended with a collagen matrix and seeded between two Velcro-coated glass tubes. The EHT that formed was able to beat in response to electrical pacing and increased contractile strength with increased pacing frequency (Eschenhagen et al. 1997). Since this initial work, EHTs have been produced in a variety of geometries with an abundance of

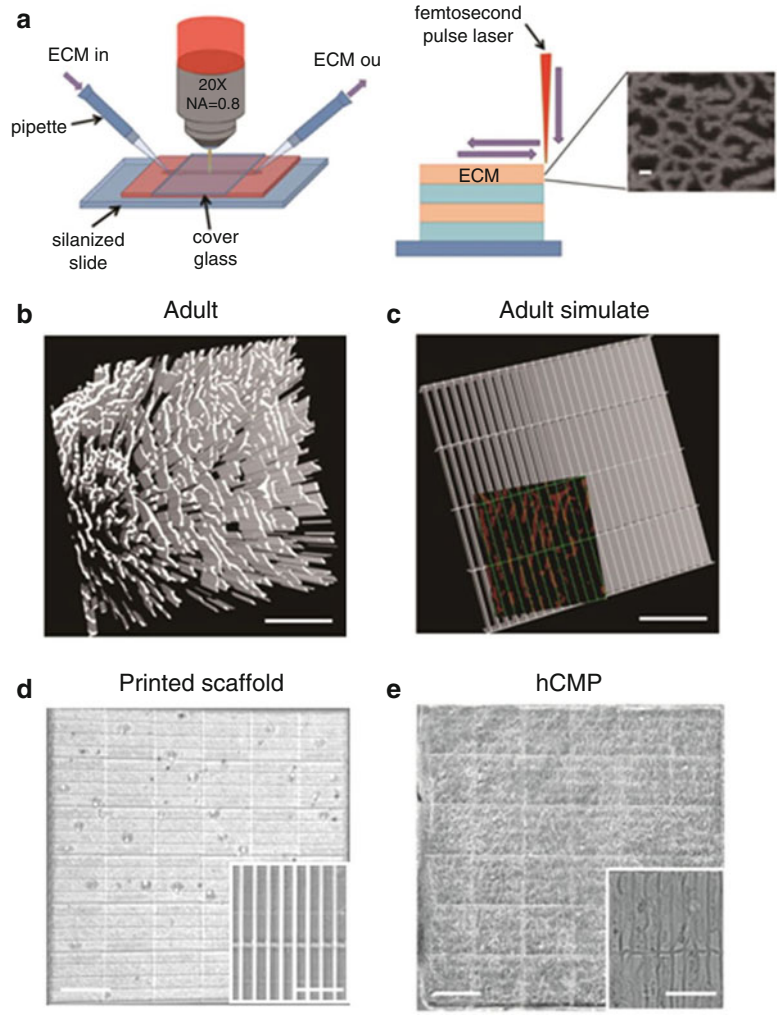

Fig. 1 Human-induced pluripotent stem cell–derived cardiac muscle patch (hCMP) fabrication via 3-dimensional multiphoton excited (3D-MPE) printing. (**a**) The extracellular matrix (ECM) and associated crosslinking solution are passed through the optical interrogation path, although the laser power and dwell time are modulated to deposit ECM at each x, y location in each z plane. The submicron scale features produced in the ECM scaffold are displayed in the inset (scale bar = 1 μm). Three-dimensional structures can be generated by combining multiple layers with the same or different ECM patterns. (**b**) Sections from the heart of an adult mouse were immunofluorescently stained for the presence of fibronectin and scanned via MPE (scale bar = 200 μm); then, (**c**) the distribution of fibronectin in the native tissue was simulated in a template. The simulated channels (green, 100 × 15 μm) are shown overlaying the fibronectin pattern of the native tissue (red) in the inset (scale bar = 100 μm). (**d** and **e**) The simulated template was used to determine the position of crosslinks in a solution of gelatin methacrylate, thereby producing a native-like ECM scaffold (**d**); then, the scaffold was seeded with human-induced pluripotent stem cells (hiPSC)–derived cardiomyocytes (CMs), endothelial cells (ECs), and smooth muscle cells (SMCs) to generate the hCMPs (**e**) The complete hCMP is shown in the larger image (scale bar = 400 μm), whereas the individual channels and incorporated cells are visible in the inset (scale bar = 50 μm). (Reused with permission from Gao et al.)

different cell types. For instance, one study generated EHTs from a combination of Matrigel and a mixed population of cardiac cells including CMs, fibroblasts, ECs, and SMCs. These EHTs were then formed into many different shapes including stars, horizontal tubules, a mesh

network, and a "rope" structure (Fig. 2) (Naito 2006). EHTs have also been investigated as a therapy for chronic MI. Loop-shaped EHTs formed from ESC-CMs and collagen I matrix were mechanically stretched and implanted into a rat model of MI. The EHTs showed high engraftment rates and significantly improved the ejection fraction of rat hearts (Riegler et al. 2015). More recently, a square patch EHT generated from neonatal rat ventricular cells and a gel mixture of thrombin, fibrinogen, and Matrigel was formed using a large (18 mm X 18 mm) PDMS mold. The patches were epicardial implanted onto rat ventricles and electrically coupled to healthy host myocardium without altering any electrophysiology of the heart (Jackman et al. 2018). Because it is very difficult to couple EHT patches to unexcitable, damaged myocardium, ongoing research will continue to work towards more effectively forming effective cell-cell contacts between patch and native cells to allow for more functional integration of patches into hearts.

3.2.4 Hydrogels

Hydrogels are water-insoluble polymers that are formed through crosslinking of synthetic and/or natural precursor polymers. These gels are often at liquid phase *in vitro* but, following injection to a site *in vivo*, will gel and can help replace damaged ECM and deliver therapeutic cells (Sun and Nunes 2015). Hydrogels used in CTE have been both in cell-free and cell-laden forms. Cell-free alginate hydrogels were implanted into rat MI models and were shown to replace up to 50% of the scar tissue area. Additionally, alginate gel injection attenuated LV dysfunction and achieved similarly therapeutic outcomes to neonatal rat CM injection (Landa et al. 2008). Another acellular approach used a cell-free collagen I patch and found that when implanted, the collagen patch attenuated remodeling and fibrosis and enhanced angiogenesis in infarcted LVs (Serpooshan et al. 2013). Hydrogels have also been utilized to facilitate differentiation of stem cells into more mature cardiac phenotypes through methods such as

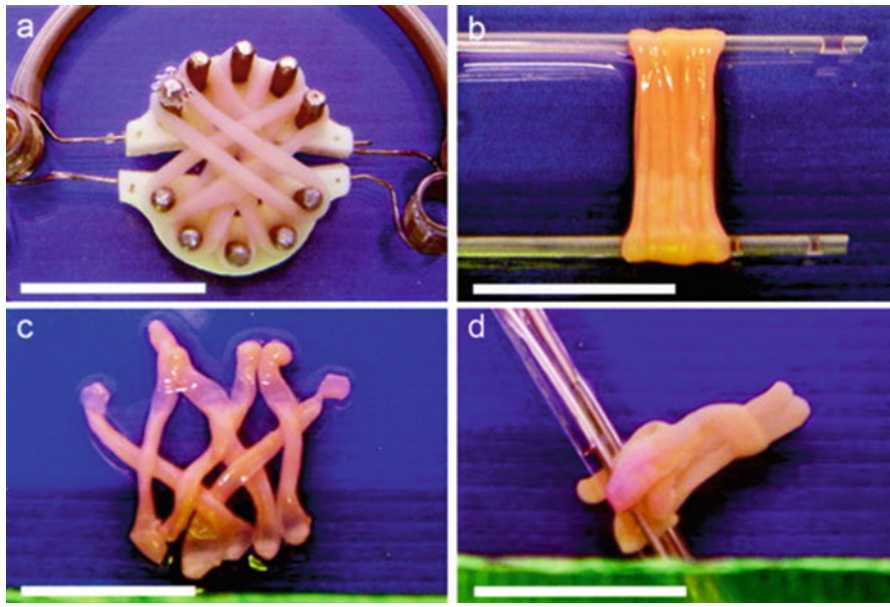

Fig. 2 Generation of different EHT geometries. EHTs fuse after sustained contact to form in-unison contracting complex cardiac muscle constructs. Star-shaped EHTs (**a**) were generated by stacking 5 EHTs on a custom-made holder. Single-unit EHTs fused in the center. 5 EHTs (**b**) were grown on horizontal glass pipettes. Adjacent EHTs fused to form a tubular construct. 6 EHTs (**c**) were cut open and layered to form a contracting network. 3 EHTs (**d**) were twirled together to form a longitudinal "rope" structure. Bars: 10 mm. (Reused with permission from Naito et al.)

cellular aggregation (Kerscher et al. 2016) and incorporation of important signaling molecules such as Notch1 (Boopathy et al. 2014). Continuing research focuses on finding the right combination of cells and hydrogel polymer and introducing components to hydrogels to modulate their mechanical and bioactive properties.

4 Cardiac Patch Clinical Trials

Previous sections of this review discussed several cell therapy clinical trials. These trials used cell injections, separate from any supportive material. However, there are other previous clinical trials have been carried out using biomaterials, both with and without cells. The first such clinical study, the MAGNUM trial, was accomplished by Chachques et al. and used a patch consisting of BMMNCs seeded onto a collagen I matrix to treat infarct patients. Specifically, 250 ± 28 million BMMNCs were injected into several infarcted sites on the heart, and then a patch consisting of the same number of BMMNCs and a collagen I matrix was sutured on the epicardium on top of the scarred area. Results showed that the patch therapy enhanced ejection fraction, increased scar thickness, and improved LV filling (Chachques et al. 2007). The same group later compared their injection/patch procedure to BMMNC injection alone and found that injection/patch group significantly improved ventricular filling compared to cell injection alone (Chachques et al. 2008). The next cardiac patch clinical study investigated the use of CorMatrix®, a cell-free, porcine SIS-derived ECM. The first in-human studies used CorMatrix® to repair cardiac and vessel defects in 37 congenital heart patients (Scholl et al. 2010). It was then shown to be a clinically feasible option for repairing LV complications following MI in 11 patients (Yanagawa et al. 2013). CorMatrix® has also been studied as an epicardial patch in both rat and pig models of MI and shown to improve myocardial recovery following MI (Mewhort et al. 2014; Mewhort et al. 2016). A clinical trial applying the CorMatrix® epicardial patch to 8 MI patients undergoing coronary artery bypass grafting has also taken place, although results have not been made available (Fedak 2017). Another acellular therapy was used in the AUGMENT-HF trial, in which Algisyl, an injectable calcium alginate hydrogel, was delivered to patients with advanced heart failure. Algisyl was administered to the LV wall via 12 to 15 injections during left anterior limited thoracotomy. At 12-months follow-up there was statistical improvement in VO_2 and 6-minute walk test distance (Anker et al. 2015; Mann et al. 2016). Finally, the PRESERVATION clinical trial used a bioabsorbable scaffold made up of sodium alginate and calcium gluconate, IK-5001, to treat ST-segment-elevation MI patients. A pilot study in 27 patients showed that use of the IK-5001 was safe and feasible in ST-segment-elevation MI patients and reported no IK-5001-related adverse events upon 6 months follow-up (Frey et al. 2014). A larger study involving 201 similar patients was later undertaken, but results showed that implantation of IK-5001 did not improve LV function or attenuate LV remodeling at 6 months follow-up (Rao et al. 2016). These clinical studies illustrate the feasibility of tissue-engineered constructs to be used to improve cardiac function in the failing heart and show the opportunities for promising preclinical work to be effectively translated to clinical settings.

5 Challenges and Outlook

5.1 Current Issues

Although significant progress in creating efficacious cardiac patches has been made, several issues persist that ongoing research is working to address. Extensive loss of CMs following cardiac injury and low CM renewal means that a high rate of cell engraftment upon patch implantation is necessary to effectively restore the loss of contractile function. However, it is estimated that only 0.1–10% of cells engraft into the host myocardium following injection (Zhang et al. 2018). This loss of cells can be attributed to cell leakage at the injection site, which is pushed further out as the heart contracts and transported away from the injection site due to blood flow (Terrovitis et al.

2010). Biomaterials, along with methods such as genetic modification and *ex vivo* preconditioning, certainly improve cell engraftment, but present issues of their own that must be addressed (Wu et al. 2011). Even with adequate cell engraftment, the engineered tissue of a cardiac patch must be able to both electrically and mechanically couple to the host myocardium. Perhaps the biggest concern with lack of integration of cardiac patches is formation of arrythmias. Previous studies have shown that implantation of cell types such as MSCs can lead to significant development of arrhythmias and adversely affect the electrophysiology of the heart (Zheng et al. 2013). Further, in contrast to small-animal models, implantation of ESC-CMs in non-human primates led to ventricular arrythmias (Chong et al. 2014). Beyond integration with the native myocardium, immunological issues with implanted cardiac patches may also hamper any therapeutic benefit achieved. Implanted materials can cause both innate and adaptive immune responses and may exacerbate acute inflammation that is occurring at the site of injury (Crupi et al. 2015). Further, xenogeneic materials and allogeneic stem cell sources can often illicit damaging immune responses (Papalamprou et al. 2016). All these issues must be addressed in future research to engineer a successful cardiac patch.

5.2 Future Directions

5.2.1 Strategies for Advanced Cardiac Maturation

While maturation of cells on cardiac patch constructs has improved greatly over the years, more techniques to further advance this maturation are needed to produce true-to-form CMs *in vitro*. Research has focused on subjecting CM precursor cells, such as CSCs, and immature pluripotent cell-derived CMs to similar physical forces native CMs experience in the myocardium, namely mechanical strain and electrical stimulation. French et al. cultured c-kit^{+} CSCs on various ECM proteins and subjected the CSCs to cyclic strain. The CSCs aligned more efficiently when subjected to higher strain, and this led to an increase in angiogenic paracrine factor production on many of the ECM substrates (French et al. 2016). Similar maturation of CSCs and induced calcium handling was also seen following electrical stimulation (Maxwell et al. 2016). This phenomenon has also been seen in neonatal rat CMs, where electrical stimulation induced calcium handling once again and increased CMs' expression of cardiac differentiation markers, independently of contractile effects (Martherus et al. 2010). While both of these maturation techniques can have profound effects on their own, they are often used in combination with one another (Ruan et al. 2016) and with other techniques, including perfusion culture (Lux et al. 2016) and cellular coculture with cell types such as ECs and fibroblasts (Tulloch et al. 2011). Importantly, these techniques not only induce increased maturation and cardiac differentiation, but also confer enhanced cardiac benefit *in vivo*. Tissues engineered from hESC-CMs and ECs and pre-conditioned with mechanical stress showed increased engraftment into the hearts of athymic rats (Tulloch et al. 2011). A similar patch using the elastic polymer poly(lactide-co-caprolactone) and hESC-CMs preconditioned with cyclic strain attenuated fibrosis in a rat infarct model (Gwak et al. 2008). Following mechanical preconditioning, SkMBs were also shown to electrically couple to host myocardium upon implantation and expressed the cardiac-specific gap junction protein connexin 43 (Treskes et al. 2015). More recently, Ronaldson-Bouchard et al. achieved the greatest degree of maturation in engineered cardiac tissue to date using iPSC-CMs and physical conditioning with increasing intensity. Specifically, tissues formed from early iPSC-CMs, just after the cells began to beat, were subjected to electrical stimulation from 2 Hz to 6 Hz, with the stimulation increasing 0.33 Hz each day (Fig. 3). Following 4 weeks of stimulation, the engineered tissues showed sarcomere length and mitochondria density at physiological levels, had formed transverse-tubules, and had functional calcium handling (Ronaldson-Bouchard et al. 2018). Contuining optimization of electrical and mechanical stimulation techniques and fabrication of complex bioreactors

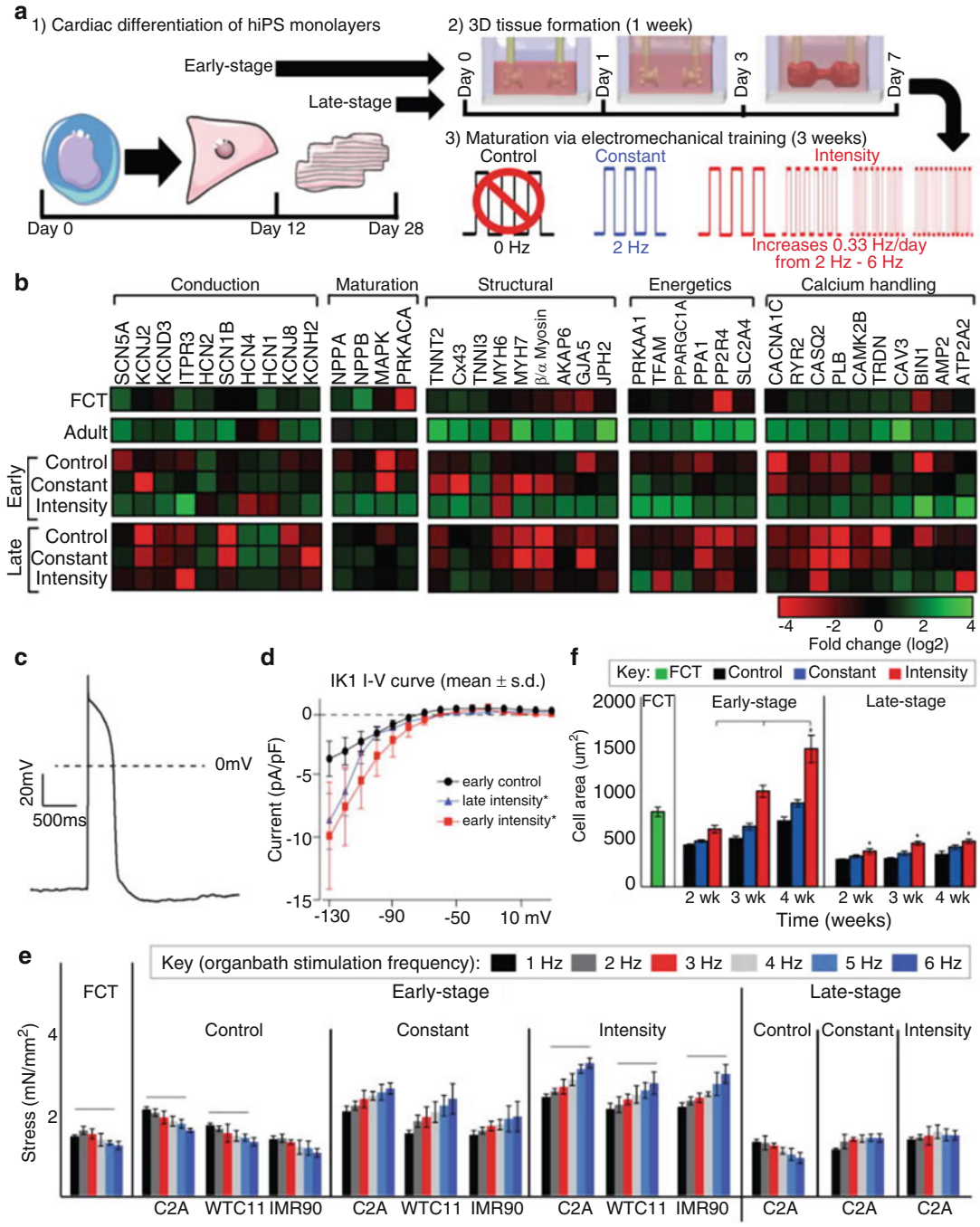

Fig. 3 Intensity training of cardiac tissues derived from early-stage hiPS-CMs enhances maturation. (**a**) Experimental design: early-stage or late-stage hiPS-CMs and supporting fibroblasts were encapsulated in fibrin hydrogel to form tissues stretched between two elastic pillars and made to contract by electrical stimulation. Gradual increase in frequency of stimulation to supra-physiological levels (intensity regime) was compared to stimulation at constant frequency (constant regime), unstimulated controls and human adult and fetal heart ventricles. (**b**) Gene expression data for six groups of cardiac tissues, and adult and fetal heart ventricles. (**c**) Action potential for the early-stage intensity-trained group. (**d**) IK1 current–voltage (I–V) curves (mean ± s.d.). (**e**) Early-stage intensity-trained tissues from all three iPSC lines (C2A, WTC11, IMR90), but not the other groups, developed a positive force–frequency relationship after 4 weeks of culture. Line above graph indicates $P < 0.05$ versus other timepoints using two-way ANOVA followed by Tukey's HSD test; *P < versus control group using one-way ANOVA followed by Tukey's HSD test. (Reused with permission from Ronaldson-Bouchard et al.)

combing these techniques may be needed to more effectively mature stem cell-derived CMs and tissue-engineered grafts.

5.2.2 Cell-Free Products

While cell therapy has been shown to provide functional benefit in the injured heart, exogenous cell engraftment into host myocardium is very low (Zhang et al. 2018). These observations have led researchers to believe that the benefit exhibited following cell therapy must be attributable to paracrine mechanisms from implanted cells, prior to the cells being washed away from the site of injection. Therefore, a recent push has been made to both define the secretory factors responsible for cardiac improvement and to use these reparative factors as their own therapy, separate from the cells that produce them. Informatics and systems biology methods have proved to be powerful tools for elucidating the functional units of many different cell types. Sharma et al. used informatics techniques to identify upregulated growth factors and signaling pathways in the secretome of c-kit^{+} CSCs from adult and neonatal patients. Using this analysis, the authors were able to pinpoint heat shock factor 1 (HSF1) as a crucial regulator of the secretome of CSCs and demonstrated that knockdown of HSF1 led to decreased secretion of important pro-reparative factors such as VEGF, ANG1, and SDF1 (Sharma et al. 2017). While growth factors such as these certainly play an important role in the reparative secretome, other research has focused on characterization of another important player in the secretome: exosomes. Exosomes are small (30–120 nm in diameter) extracellular vesicles that form within larger multivesicular bodies and release from the cell upon fusion with the cell membrane. Exosomes can contain proteins, lipids, RNA, and/or DNA, and it is this cargo that can provide reparative effects to the heart (Garikipati et al. 2018). Both Gray et al and Agarwal et al used systems biology methods to distinguish what exosomal cargo from rat and human pediatric c-kit+ CSCs, respectively, correlated most strongly with improvement in functional outcomes such as angiogenesis, fibrosis, and ejection fraction (Gray et al. 2015; Agarwal et al. 2017). Specifically, these studies correlated the presence of different micro-RNAs (miRNAs) with these functional changes. It has been shown that miRNAs alone improve heart function, making them one of the most important pieces of exosomal cargo. A recent study identified miR-21-5p as the functional miRNA of the MSC secretome and showed that delivery of miR-21-5p alone was enough to increase expression of calcium handling genes and, consequently, contractility in EHTs (Mayourian et al. 2018). To avoid the issues with implantation of cells, other cell-free delivery methods have been explored to deliver reparative secretome products. In one study, the complete secretome from adipose-derived stem cells was loaded into a gelatin and Laponite® hydrogel and injected into a rat acute MI model and shown to reduce scar area, increase angiogenesis, and improve several cardiac functional parameters (Waters et al. 2018). Another innovative method to deliver therapeutic secretome components is the use of "synthetic stem cells", a method created by Tang et al. Synthetic stem cells are PLGA microparticles loaded with stem cell conditioned media and coated with stem cell membranes. They have been fabricated using the secretomes and membranes from both MSCs and CDCs, and both sets of synthetic stem cells have been shown to repair the heart in mouse models of MI (Tang et al. 2017; Luo et al. 2017). Future work on cell-free products will continue to identify the functional units of different therapeutic cells' secretomes and will work to find efficient ways to deliver and scale up the production of these factors.

6 Conclusion

CVD has been and continues to be the number one cause of death in the world. Even with the technologies at the disposal of modern medicine, there remains an immensely significant need to treat those with CVD and to restore the pumping force of failing hearts. CTE holds promise as the missing piece to the puzzle of treating CVD.

Significant advances have been made in recent years to both identify therapeutic cell types and to combine these cells with supportive materials to further enhance their therapeutic potential. Because current cell-based therapies suffer from a lack of engraftment into the host myocardium, paracrine effectors are currently the main source of providing functional benefit for these therapies. As the CTE field continues to progress, engineered cardiac tissues will become more and more complex and will more closely mimic the native myocardial structure. It will be important in the future to understand how to properly strike a balance between working towards integrating functional, lab-engineered tissue into host tissue and modulating tissue-engineered constructs to maximize their paracrine effects. If paracrine effects prove to be the most beneficial route of research, further research into the therapeutic potential of various cell-free secreted factors alone could prove to be the future of cardiac repair. Other practical considerations including implantation method, manufacturing concerns, and scalability of new patches and therapies will also need to be considered. As CVD continues to plague the world, CTE research will continue to harness the power at the intersection of engineering and cardiac biology and use it to tackle the complex problems that CVD presents.

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