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Patching the scarred heart

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Acute myocardial infarction (AMI) and heart failure (HF) that often follows remain the leading causes of morbidity and mortality worldwide. Following MI, lost cardiomyocytes (CM) are replaced by non-contractile scar tissue that increases ventricular wall stress while diminishing myocardial performance. With the negligible regenerative capacity of the heart, the field of heart engineering and regenerative therapy for MI remains a challenge. Cardiac patch often combines the use of cells and synthetic/biomaterials with the ultimate aim of improving myocardial function. Through the years, there have been remarkable breakthroughs in the fields of stem cell and biomaterials research. The advent of human-induced pluripotent stem cells provides a potentially unlimited source of cardiomyocytes for regenerative therapy. By combining this with 3D bioprinting, it was possible to generate a cardiac patch with cell and structural organizations similar to that of the native heart. Even with vast technological advancements, the promise of the cardiac patch to treat MI has not been fulfilled. Subsequent studies revealed that exosomes, rather than the cellular component of the cardiac patch, is one of the main contributors to its cardioprotection. In this review, we present and discuss perspectives of the cardiac patch and its drawbacks and future relevance as a promising intervention for MI patients.

Keywords: Cardiac patch, engineered heart tissue, regenerative medicine, acute myocardial infarction, cardioprotection, stem cell therapy

Acute myocardial infarction

Acute myocardial infarction (AMI) and the often-ensuing heart failure (HF) are leading causes of morbidity and mortality globally, exerting huge burdens on healthcare and economy (Reed et al., 2017). MI occurs as a result of cardiomyocyte death due to prolonged ischemia and is clinically classified based on the presence or absence of ST-segment elevation on the electrocardiogram (ECG) – ST-elevation MI (STEMI) and non-STEMI (NSTEMI) (Anderson and Morrow, 2017).

Reperfusion, using either thrombolytic therapy or percutaneous coronary intervention (PCI), is mandatory following AMI to salvage ischemic cell death and improve clinical outcome (Saleh and Ambrose, 2018), with the latter being the method of choice (Grines et al., 2003). With reperfusion along with appropriate medical and lifestyle intervention, most patients can be discharged within two to three days and resume normal or near normal lives (Saleh and Ambrose, 2018). While reperfusion reduces myocardial ischemic injury and limits the infarct size, the process of reperfusion independently activates a cascade of cellular injuries and exacerbates myocardial injury (Shin et al., 2017), causing excessive cardiomyocyte cell death and increasing the infarct size. This phenomenon, termed myocardial reperfusion injury, was shown to contribute to up to 50% of the final infarct size (Yellon and Hausenloy, 2007). The lost cardiomyocytes are replaced by non-contractile scar tissue consisting of cardiac fibroblasts and collagen (Jugdutt, 2009). Though scar formation preserves structural integrity, excessive collagen deposition can cause cardiomyocyte atrophy and arrhythmogenicity (Leask, 2015). Therefore, despite effective reperfusion therapy, survivors remain at risk of severe sequelae, including sudden cardiac death (SCD), HF, and left ventricular systolic

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dysfunction (Docherty et al., 2020), prompting the need for new therapies against AMI.

Given that the heart has very limited capacity for regeneration (van Berlo and Molkentin, 2014), stem cell transplantation has emerged as a promising avenue to improve function following myocardial insult (Bartunek et al., 2013; Suncion et al., 2014; Perin et al., 2015; Bartunek et al., 2017; Emmert et al., 2017; Yau et al., 2019). Some clinical trials have yielded positive results, showing improved left ventricular ejection fraction (LVEF) – a major determinant of long-term prognosis for STEMI – following administration of mesenchymal stem cells (MSC) (Kim et al., 2018) and bone marrow mononuclear stem cells (Stamm et al., 2007; Laguna et al., 2018). The benefit of stem cell transplantation extends beyond myocardial regeneration, and include angiogenesis (Tse et al., 2003; Li et al., 2010), and improvements in tissue perfusion and fibrotic burden (Karantalis et al., 2014). However, several recent clinical trials have yielded neutral results with no significant LVEF improvements (Nasseri et al., 2014; Wollert et al., 2017; Laguna et al., 2018; Nicolau et al., 2018; Traverse et al., 2018) (see Table 1).

Stem cell transplatation

Following MI, up to one billion cardiomyocytes in the infarct zone are lost (Lin and Pu, 2014). Over the past two decades, studies have attempted to replace the lost myocardial cells using cell injection. However, poor inferior cell engraftment and cell survival at the ischemic region coupled with rapid (hours to days following transplantation) cell loss have resulted in the low efficacy of stem cell therapy (Nguyen et al., 2016).

Stem cell transplantation has yielded promising results (Liu et al., 2018). However, it appears current stem cell transplantation has yet to reach its full potential of alleviating cardiac injury. Several limitations have been eluded from previous studies, with the major limitation being poor cell survival and retention at the intended site (Hou et al., 2005; Sekine et al., 2011; Wang et al., 2013; Lepperhof et al., 2014; Roche et al., 2014; Yan et al., 2017) limiting the regenerative application of stem cell therapy. Furthermore, the harsh ischemic microenvironment of the injured myocardium is not favorable for the transplanted cells (Hu et al., 2016). Efforts to circumvent this include the use of intrinsic cellular homing (such as sphingosine-1 phosphate-sphingosine-1 phosphate receptor 2 (S1P-S1PR2) axis in Muse cells) (Yamada et al., 2018), nanoparticles to facilitate homing of cells (Huang et al., 2013; Lee et al., 2020), and cardiac patch (Roche et al., 2014; Bellamy et al., 2015; Zhang, 2015; Sugiura et al., 2016). While the former two entail a less invasive approach to improve cell retention, they do not necessarily improve the microenvironment to encourage cell survival. On the other hand, cardiac patch, which employs the use of biomaterials, may require more invasive procedures, but the use of biomaterials could provide a more favorable microenvironment to improve cell survival (Sun et al., 2020). Herein we review the recent progress on cardiac patches and discuss how it remains a promising endeavour to alleviate post-MI sequelae.

Cardiac patch

In contrast to cell therapy alone, cardiac patch is a three-dimensional heart tissue engineered in vitro and implanted over the infarcted tissue. It has been widely reported to enhance cell retention and survival at the implanted sites, thereby increasing the success of cell therapies (Madonna et al., 2019). Several animal studies have shown the effectiveness of cardiac patch in alleviating cardiac injury in MI (Table 2). A recent study has demonstrated the high degree of retention and vascularization over 14 days of transplanted cardiac patches that were printed with bioinks (composed of cardiac extracellular matrix (cECM), human heart progenitor cells (hCPCs), and gelatin methacrylate (GelMA) in rat models of MI (Bejleri et al., 2018). The effectiveness of cardiac patches was also seen in a study using a porcine model of MI, where a pair of clinically relevant cardiac patches containing trilineage cardiac cells had engraftment rates beyond 10% at four weeks post-implant and was associated with significant improvements of the left ventricular function coupled with reduced infarct size and myocardial wall stress in the peri-scar boarder zone of the myocardium (Gao et al., 2018). To date, there are only a few human studies being done that used cardiac patch to alleviate post-infarct sequelae (Menasche et al., 2015; Menasche et al., 2018; Prat-Vidal et al., 2020).

The earliest cardiac patch that was implanted in a human contained cardiac-committed human embryonic stem cells (hESCs) – Isl-1+ SSEA-1+ (stage-specific embryonic antigen-1) cells – embedded in a fibrin scaffold. The 68-year-old patient presented with HF as a result of a previous MI, and was designated for surgical anterior myocardial revascularization via coronary artery bypass graft (CABG). During the CABG, the cardiac patch was secured between the pericardium and epicardium with the use of sutures. Functional improvements were observed after three months, with the patient having increased LVEF, 6 min walking distance, and decreased LV end-diastolic and end-systolic volumes (Menasche et al., 2015). Though these improvements were only seen in one patient, the authors conducted a similar study subsequently on six patients with severe ischemic LV dysfunction resulting from previous MI. That study yielded similar optimistic results in the aforementioned parameters (Menasche et al., 2018), demonstrating both the efficacy as well as safety of cardiac patches. Moving forward, the recent first-in-human study scaled up a 2 cm2 preclinical construct (Galvez-Monton et al., 2017) to a 16 cm2 decellularized human pericardial matrix colonized with 12.5 million human viable Wharton's jelly-derived MSCs (WJ-MSCs) (Prat-Vidal et al., 2020). The cardiac patch was applied by surgical glue over non-revascularizable myocardial scar tissue while CABG was being performed for revascularizable regions. The patient showed ~9% reduction in scar mass in the treated area (Prat-Vidal et al., 2020). Cardiac patches offer a promising integrative approach to repair the injured heart following MI, with optimistic results ranging from improvement of cell retention and engraftment to reducing adverse LV remodeling, preventing LV dilation, and thinning, and enhancing LV function (see Table 3). Nonetheless, cardiac patch has its limitation, and is currently not applicable for clinical application (Zhang et al., 2018).

The challenges of patching the heart

The main challenges in engineered heart tissue (EHT), or cardiac patch, includes but are not limited to (1) the optimization of scaffold mechanics and biocompatibility, (2) cell maturation and contractile ability, (3) electromechanical integration, (4) immune rejection, (5) tissue vascularization and oxygen supplementation (Jackson et al., 2020).

Scaffold mechanics and biocompatibility

An ideal scaffold for cardiac tissue engineering should possess excellent mechanical properties and electrical conductivity to perform normal physiological functions of the heart (Qasim et al., 2019b). Thus, an ideal scaffold must possess sufficient porosity for cell ingrowth (Loh and Choong, 2013; Bruzauskaite et al., 2016), architecture that facilitate proper cardiomyocyte alignment (Homma et al., 2020), mechanical properties to withstand surgical implantation, and surface characteristics to support firm cell adhesion and growth (Prasad and Krishnan, 2008; Khalili and Ahmad, 2015). Recent advances in biomaterials have provided a variety of different approaches to create scaffolds for tissue engineering, which include the use of nanofibers (Joshi and Kothapalli, 2015), hydrogels (El-Sherbiny

Table 1. Clinical trials of stem cell therapy against MI in the recent five years

Year	Randomized	Trials	Arms	Number	Type of cells	Route of delivery	Follow-up	LVEF variation (Study vs Control)	Reference
Positive Results									
2020	Yes	NCT02870933	Receive $CD133^+$ cells and CABG; CABG alone	30	$CD133^+$ bone marrow stem cells	Trans-epicardial and transseptal implantation	6 months	Δ=8.69% vs 1.43%, p=0.04	(Soetisna et al., 2020)
2020	Yes	MSC-HF (NCT00644410)	Bone marrow-derived mesenchymal stem cells (MSCs); Placebo	60	Bone marrow-derived mesenchymal stromal cells	Intramyocardial injection	12 months	Δ=5.2% vs -1.0%, p<0.0001	(Mathiasen et al., 2020)
2018	Yes	COMPARE CPM-RMI (NCT01167751)	$CD133^+$ cells; bone marrow mononuclear cells; Placebo	77	$CD133^+$ bone marrow stem cells or bone marrow mononuclear cells	Intramyocardial injection	18 months	Δ ($CD133^+$, placebo) = 8.962 p=0.011; Δ (MNC, placebo) = 6.917 p=0.022	(Naseri et al., 2018)
Neutral Results									
2021	Yes	CardiAMP Heart Failure (NCT02438306)	Bone marrow mononuclear cells; Sham	250	Bone marrow mononuclear cells	Trans-endocardial injection	12 months	Outcome pending	(Raval et al., 2021)
2020	Yes	CHART-1 (NCT01768702)	Cardiopoietic stem cells; Sham	315	Cardiopoietic stem cells	Intramyocardial injection	2 years	Neutral at 52 weeks	(Bartunek et al., 2020)
2019	Yes	TEAM-AMI (NCT03047772)	Routine atorvastatin (ATV) (20 mg/d) with placebo or bone marrow MSCs (MSC^{INJ}) and intensive ATV (80 mg/d) with placebo or MSC^{INJ}	100	Bone marrow mesenchymal stem cells	Intracoronary infusion	12 months	Outcome pending	(Xu et al., 2019)
2019	Yes	MyStromalCell (NCT01449032)	Adipose-derived stromal cell in border zone; Placebo	60	Adipose-derived stromal cells	Intramyocardial injection	3 years	Exercise tolerances benefit not clear	(Qayyum et al., 2019)
2019	Yes	SCIENCE (NCT02673164)	Allogeneic cardiology stem cell centre-adipose derived stem cells; Placebo	133	Allogeneic cardiology stem cell centre-adipose derived stem cells	Intramyocardial injection	6 months	Outcome pending	(Paitazoglou et al., 2019)
2018	Yes	CAREMI (NCT02439398)	Allogeneic cardiac stem cells; Placebo	49	Allogeneic cardiac stem cells	Intracoronary infusion	12 months	Δ=7.7% vs 8.6%, p=ns	(Fernandez-Aviles et al., 2018)
2018	Yes	TIME (NCT00684021)	Bone marrow mononuclear cells post PCI (3 days); placebo	120	Bone marrow mononuclear cells	Intracoronary infusion	2 years	Δ=2.8% vs 4.7%, p=ns	(Traverse et al., 2018)
2017	No	NCT02387723	Allogeneic adipose derived stem cells	10	Allogeneic adipose derived stem cells	Intramyocardial injection	6 months	Δ=2.9% (95% CI: 0.2 to 6.1; p =0.065)	(Kastrup et al., 2017)
2017	Yes	PERFECT (NCT00950274)	$CD133^+$ cells and CABG; Placebo and CABG	82	$CD133^+$ bone marrow stem cells	Intramyocardial injection	180 days	Δ=10.4% vs 8.8%, p=ns	(Steinhoff et al., 2017)
2017	Yes	BOOST-2 (ISRCTN17457407)	High-dose (hi)BMCs, low-dose (lo)BMCs, irradiated hiBMCs, or irradiated loBMCs; Placebo	153	Nucleated bone marrow cells	Intracoronary infusion	6 months	Δ=(hiBMCs) 4.3% vs (Control) 3.3%, p=ns	(Wollert et al., 2017)
2016	Yes	SWISS-AMI (NCT00355186)	Bone marrow mononuclear cells post PCI (5-7 days OR 3-4 weeks); Sham	200	Bone marrow mononuclear cells	Intracoronary infusion	12 months	Δ=-0.9% vs -0.7% vs -1.9%, p=ns	(Surder et al., 2016)
2016	Yes	REGENERATE-AMI (NCT00765453)	Bone marrow-derived cells within 24h post PCI; Placebo	100	Bone marrow-derived cells	Intracoronary infusion	1 year	Δ=5.1% vs 2.8%, p=ns	(Choudry et al., 2016)

and Yacoub, 2013; Radhakrishnan et al., 2014), injectable gels (Alagarsamy et al., 2019), decellularization (Rana et al., 2017; Daley et al., 2018), and 3D printing (Mosadegh et al., 2015; Qasim et al., 2019a). Among which, generating scaffolds from decellularization have been particularly attractive as it preserves the structural "blueprint" of the actual heart. In a breakthrough study in 2008, researchers successfully created a physiologically functional heart by first decellularizing the rat whole heart via coronary perfusion and later incorporating the decellularized scaffolds with cardiac and endothelial cells (Ott et al., 2008). Subsequently, in 2016, researchers successfully repopulated decellularized human myocardial slices (200 µm thick with hiPSC-CMs) to generate myocardial tissue capable of spontaneous contraction (Guyette et al., 2016). More recently, a pre-clinical study on swine models of MI demonstrated that the implantation of such cardiac patch led to restoration of ventricular function and better recovery following MI. The cardiac patch was made of decellularized myocardial and pericardial tissues that were repopulated with adipose tissue derived MSCs (Perea-Gil et al., 2018).

However, decellularization and repopulation of cells are not without imperfections. The balance between the removal of cellular components and preservation of structural and biomechanical integrity of the three-dimensional extracellular matrix remains to be optimized (Di Meglio et al., 2017; Kc et al., 2019). Other challenges of using decellularized extracellular matrix (dECM) includes the homogenous distribution of repopulated cells within the scaffold compartments, and the diffusion limit of thick cardiac dECM (Kc et al., 2019).

Other noteworthy innovation includes the recent three-dimensional (3D) bioprinting, which uses a layer-by-layer approach to deposit bioink filaments to generate cardiac patches (Gardin et al., 2020). The advent of additive manufacturing 3D bioprinting technology allows heterogenous cell types,

Table 2. Recent preclinical studies of cardiac patch

Year	Species	Material of patch	Type of cells	Route of delivery	Follow -up	LVEF improvement	Infarct size reduction	Other benefits	Reference
2021	Rat	Oxidized alginate(OA)/gelatin(Geln)/ polyacrylic acid(PAA) hydrogel	Rat neonatal cardiomyocytes	Epicardial implantation	4 weeks	Around 25% increase in LVEF compare to MI group, p<0.001	Decreased from 82.73% (in MI group) to 33.25%, p<0.01	Increased arterioles and micro-vessels densities	(Song et al., 2021)
2021	Rat	ECJM hydrogel (made by decellularized heart tissues)	hiPSC-CPCs	Intrapericardial injection	4 weeks	Increased from 29.4% (in MI group) to 45.4%, p<0.0001	Decreased from 38.99% (in MI group) to 18.97%, p<0.0001	Mitigated immune response and increased cells retention	(Zhu et al., 2021)
2021	Rat	Decellularized placenta	hiPSC-CMs	Epicardial implantation	4 weeks	Around 15% increase in LVEF as compared to MI group, p<0.05	Decreased from 20% (in MI group) to 12%, p<0.05	Promoted neovascularization	(Jiang et al., 2021)
2021	Rat	Acetylated chitosan hydrogel	-	Epicardial implantation	1 month	Maximum 40% increase in LVEF as compared to MI group, p<0.01	-	Attenuated fibrosis and inflammation	(Domenge et al., 2021)
2020	Mouse	3D printed scaffold with gelatin methacrylate(GelMA) and polyethylene glycol diacrylate(PEGDA) inks	hiPSC-CMs, hECs, hMSCs	Epicardial implantation	4 months	Increased from56.1% (in MI group) to 64.1%, but no change as compared to cell only group	Decreased from 14.3% (in MI group) to 5.6%	Increased vascularization and vascular remodelling	(Cui et al., 2020)
2020	Rat	Alginate microspheres and collagen	hiPSC-CMs	Epicardial implantation	1 month	18.6% increase in LVEF as compared to MI group, p=0.006	No significant change in infarct area size	Robust angiogenesis and neovascularization	(Munarin et al., 2020)
2020	Rat/Pig	Decellularized porcine myocardial extracellular matrix	Secreted factor from human cardiac stromal cells	Epicardial implantation	21 days (rats); 7 days (pigs)	Rat-around 20% increase in LVEF as compared to MI group, p<0.0001; Pig-around 5% increase in LVEF as compared to MI group, p<0.05;	Rat-decreased from 30% (in MI group) to 18%, p<0.01; Pig-decreased infarct area on some heart slices	Promoted angiomyogenesis	(Huang et al., 2020)
2019	Rat	Dopamine(DOPA)-coated Polypyrrole(PPy)/poly(glycolic acid)(PGA)	-	Epicardial injection	4 weeks	Around 20% increase in LVEF as compared to MI group, p<0.01	Decreased from 55% (in MI group) to 20%, p<0.001	-	(Song et al., 2019)
2018	Mouse	Elastic hydrogel(EH) /aligned nanocollagen fibrous(AF)/nanogold(AuNPs)	Rat neonatal ventricular myocytes	Epicardial implantation	4 weeks	Around 12% increase in LVEF as compared to MI group, p<0.001	Decreased the scar size of around 25%, p=0.04	Increased vascularization and positive connexin-43 discs	(Hosoyama et al., 2018)
2018	Rat	Hyperbranched poly(amino ester)(HPAE)-pyrrole(Py)/Gelatin and Fe^{3+}	-	Epicardial painting (a novel technique)	4 weeks	Around 25% increase in LVEF as compared to MI group, p<0.01	Decreased from 50% (in MI group) to 15%, p<0.01	Boosted the transmission of electrophysiological signals and promoted revascularization	(Liang et al., 2018)
2018	Pig	Fibrin	hiPSC-CMs, hiPSC-SMCs, hiPSC-ECs	Epicardial implantation	4 weeks	Around 10% increase in LVEF as compared to MI group, p<0.05	Decreased from 10% (in MI group) to 8%, p<0.05	Promoted angiogenesis and cell survival in the peri-scar border zone	(Gao et al., 2018)

biomaterials, and signalling factors to be precisely deposited and arranged in organized geometries similar to those found in the native counterparts (Alonzo et al., 2019). Some of the biomaterials that were utilized for myocardial tissue printing include alginate ((Rastogi and Kandasubramanian, 2019), collagen (Jakab et al., 2008), gelatin (Gaetani et al., 2015), fibrin (Barsotti et al., 2011), and synthetic biomaterials (Ho et al., 2017). Not surprisingly, 3D bioprinting has been explored in the context of dECM (Pati et al., 2014). Three-dimensional printed dECM-based cardiac patch retains the microenvironmental cues that facilitates cardiomyocyte differentiation and maturation (Das et al., 2019). Such results were echoed in another recent study that derived dECM from porcine heart. Human MSCs were then printed onto porcine dECM to generate the cardiac patch, which was implanted on the epicardial infarct region of a rat model of MI. The implanted patch provided a conducive microenvironment and paracrine factors that promote vascular regeneration, resulting in restoration of cardiac function (Park et al., 2019).

Cell maturation and contractile ability

One of the early limitations of using human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) is their immature phenotype. Since then, many have attempted to facilitate the maturation of hiPSC-CMs to achieve a more adult-like phenotype – including extended culture, electrical and mechanical stimulation, extracellular matrix modulation, and using microRNAs (Ramachandra et al., 2021). In the context of serum-free culture, several factors were identified to be crucial for the maturation of hiPSC-CMs. These include triiodothyronine (T3), insulin-like growth factor 1(IGF-1), and glucocorticoid dexamethasone. T3 is essential for cardiomyocyte excitability and contractibility was found to enhance the resting membrane potential while IGF-1 and dexamethasone produce synergistic effects on cellular bioenergetics and traction force (Birket et al., 2015). Additionally, further functional and metabolic maturation of hiPSC-CMs were observed when these three factors were coupled with peroxisome proliferator-activated receptor alpha (PPAR-α) activation and hypoxia inducible factor-1 alpha (HIF-1α) inhibition (Gentillon et al., 2019). Direct supplementation of metabolic substrate such as palmitate/oleate (fatty acids) was also found to promote metabolic maturation of hiPSC-CMs, with better mitochondrial oxidative phosphorylation, and ATP production (Ramachandra et al., 2018).

Interestingly, 3D cultures of hiPSC-CMs generate greater mitochondrial mass as compared to 2D hiPSC-CMs cultures, and produce mitochondrial proteomic profiles similar to adult human cardiomyocytes (Ulmer et al., 2018). By combining different cell populations – hiPSC-CMs, cardiac fibroblasts, and cardiac endothelial cells – maturation is further enhanced, where 3D cultures of hiPSC-CMs exhibit improved sarcomeric structures with transverse tubules, greater contractility and mitochondrial respiration, and more mature electrophysiological properties. The study found that the enhanced maturation was associated with the coupling of hiPSC-CMs with cardiac fibroblast via connexin 43 (CX43) gap junctions and increased intracellular cAMP (Giacomelli et al., 2020). Similarly, co-culturing hiPSC-CMs with MSCs showed improved contractile properties, with the hiPSC-CMs exhibiting aligned myofibrils

Table 3. Clinical trials of cardiac patch implantation against MI

Year	Randomized	Trials	Intervention	Number	Type of cells	Route of delivery	Follow-up	LVEF variation (Study vs Control)	Reference
2020	No	PERISCOPE (NCT03798353)	Decellularized pericardial matrix colonized with human viable Wharton's jelly-derived mesenchymal stromal cells	1	Allogeneic Wharton's jelly-derived MSCs	Surgical epicardial surface delivery	3 months	Reduction of scar mass, LVEF benefit not clear	(Prat-Vidal et al., 2020)
2018	No	ESCORT (NCT02057900)	hESC-derived cardiovascular progenitors embedded fibrin patch	6	hESC-derived cardiovascular progenitors	Epicardial delivery during CABG	12 months	26%(IQR:22-32%) to 38.5%(IQR:33.5-41%) p=ns	(Menasche et al., 2018)
2017	No	UMIN000003273	Scaffold-free cell sheets derived from skeletal muscle	15	Skeletal muscle	Surgical epicardial surface delivery	12 months	26.74±8.0% to 30.7±10.0% p<0.01	(Miyagawa et al., 2017)

with A-, H-, and I-bands that are able to contract and relax rapidly (Yoshida et al., 2018).

Remarkably, the microenvironment has a huge impact on cardiomyocyte maturation, where myocardial-grafted cardiac patch resulted in nascent tissue-like organization with aligned cardiomyocytes in the scaffold that was accompanied by a greater degree of neovascularization and microvascular maturation as compared to the peripherally grafted cardiac patch (Ja et al., 2018). In addition, hiPSC-CMs alone may not be optimal for cardiac regeneration. In particular, a stem cell study showed that when injected into the peri-infarcted anterior free wall of a murine model of MI, hiPSC-derived cardiac progenitors provided greater protection compared to hiPSC-CMs, resulting in greater functional recovery of the heart (Ja et al., 2016). By incorporating hiPSC-CMs with human dermal fibroblasts into fibrin hydrogels and applying electrical stimulation to induce auxotonic contractions, the cardiac patch exhibit adult-like gene expression profiles, organized ultrastructure, sarcomere length, and mitochondrial density. Functionally, these cardiac patches have a positive force-frequency relationship and functional calcium handling. Cardiomyocyte elongation and alignment were facilitated by the passive tension created by the stretching motion within the cardiac patch (Ronaldson-Bouchard et al., 2018). Also, instead of electrical stimulation, a separate study has stimulated similar cardiac patch using a dynamic (rocking) platform, and also resulted in matured cardiomyocytes – with presence of intercalated disk-like structures (Gao et al., 2018).

Moreover, it seems that the presence of other cell population, such as endothelial cells, smooth muscle cells, and MSCs, may significantly improve the contractility (Burridge et al., 2014) and therapeutic effects (Ye et al., 2014) of cardiac patches.

Electromechanical Integration

Besides the cellular immaturity of cardiac patches, another important hurdle to overcome is the electromechanical integration between the implanted cardiac patch and the host myocardium since contraction-competent cardiac patches may disrupt the cardiac syncytium and de-synchronize cardiac rhythm, and potentially exacerbate cardiac arrhythmia, which could lead to pathological conditions (Puig-Sanvicens et al., 2015). Non-human primate studies have shown that the direct injection of hiPSC-CMs has the potential to cause dangerously abnormal ventricular electrical activities (Chong et al., 2014), while epicardial injection of hESC-CMs resulted in graft-induced arrhythmias (Liu et al., 2018).

To tackle this, conductive polymers – such as polydimethysiloxane (Jackman et al., 2018), polypyrrole (Cui et al., 2018), and poly-3-amino-4-methoxybenzoic acid (Zhang et al., 2020) – were incorporated into the scaffolds (Solazzo et al., 2019). A recent study has demonstrated that an injection of conductive polypyrrole-chitosan hydrogel into the scar zone following MI improved the electrical conduction across the fibrotic scar and resynchronized the cardiac contraction of the rat's heart (He et al., 2020). Another study conjugated a choline-based bio-ionic liquid onto gelatin methacryloyl to generate a scaffold with better conductive and adhesive property. After which, primary cardiomyocytes and cardiac fibroblasts were incorporated into the scaffold, and the resulting cardiac patch attenuated post-MI remodeling in murine hearts (Walker et al., 2019).

Taken together, conductive scaffolds offer a platform to improve the electromechanical integration of cardiac patches while improving the synchronization of cardiac contraction. Nonetheless, further research is required to optimize the conductivity of cardiac patches to achieve similar properties of the native heart (Baei et al., 2020).

Immune rejection

Immunogenicity is expected to be less of a problem in clinical practice because hiPSC-CMs can be generated from the patient's own somatic cells. However, the urgency for prompt treatment following MI to minimize cardiac injury (Lesneski, 2010) precludes the use of autologous hiPSC-CMs as a substantial amount of time is needed for hiPSC reprogramming and subsequent differentiation into hiPSC-CMs (Blair and Barker, 2016; Lipsitz et al., 2016). On the other hand, while using pre-made allogenic hiPSC-CMs for cardiac patches is more practical, it runs the risk of immune rejection due to the human leukocyte antigen (HLA) – the human major histocompatibility complex (MHC) (de Rham and Villard, 2014). Thus, the risk versus benefit ratio of the use of hiPSC-CMs remains highly debatable.

By inactivating MHC class I and II genes and overexpressing CD47, researchers were able to generate hypoimmunogenic hiPSCs that retained the ability to differentiate into spontaneously beating hiPSC-CMs (Deuse et al., 2019). This opens the exciting possibility of having a universally compatible source of readily available hiPSC-CMs for regenerative medicine. Alternatively, the use of MHC haplotype homozygous cells could also overcome immunorejection for allogenic hiPSC-CM transplantation (Kawamura et al., 2016), with a recent clinical study demonstrating the usefulness of hiPSC banking for hematologic and nonhematologic malignancies (Morishima et al., 2020). All of the paired 39 donor HLA homozygous donor to patient heterozygous, except one (early death), engrafted neutrophils (the primary outcome of the study) with incidence of acute graft-versus-host disease of 17/38 (grades II to IV) and 3/38 (grades III to IV). The study concluded that HLA-homo hiPSC transplantation led to favorable engraftment (Morishima et al., 2020). More interestingly, a recent study demonstrated that syngeneic MSCs reduces immune rejection after transplantation of allogenic hiPSC-CMs in mice (Yoshida et al., 2020). Such findings add to the aforementioned benefits of incorporating MSCs (i.e., enhanced maturation and cardioprotection) in cardiac patches. Furthermore, syngeneic MSCs can be readily harvested using methods such as AdiPrep® (Dragoo and Chang, 2017).

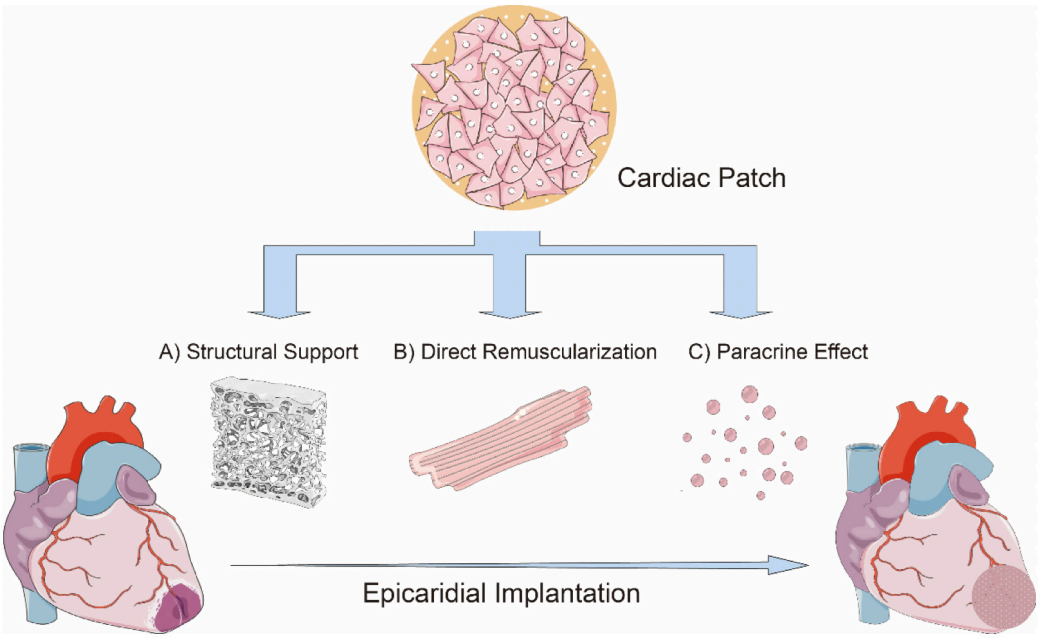

Figure 1. Schematic description of the mechanistic action of cardiac patch. The major mechanisms include (A) providing structural support, (B) promoting direct myocardial remuscularization, and (C) producing cardioprotective paracrine factors. (A) Since a thin fibrotic scar replaces the myocardium at the infarct zone, the rigid scaffold of the cardiac patch provides additional wall thickness and rigidity, which could enhance myocardial function while preventing detrimental left ventricular remodeling. (B) With the tremendous loss of cardiomyocytes following AMI, early studies focus on regenerating the injured myocardium by introducing cells with therapeutic properties. While there were optimistic results that implanted cells were able to reduce the infarct size and stimulate vascularization, there were also contrasting results that showed partial remuscularization with suboptimal biophysical integration of the cardiac patch. Currently, more evidence is attributing the cardioprotective effects of cardiac patch to the paracrine factors produced by the implanted cells. (C) The implanted cells such as adult stem cells which secrete a variety of paracrine factors which is capable of altering the myocardial microenvironment and influence myocardial remodeling.

Vascularization and oxygen supply

Poor perfusion of cardiac patches remains a major issue for cells-containing cardiac patches. Previously, because of the lack of vasculature, the viable cardiac cell sheet-layered tissues were limited to three layers (~80 μm) (Shimizu et al., 2006). Moreover, the suboptimal neovascularization and microvascular maturation could be an intrinsic limitation of the current hiPSC-CMs as a study showed that cardiac patch containing human embryonic stem cell-derived cardiomyocytes (hESC-CMs) generated significantly more robust and mature microvasculature as compared to cardiac patches containing hiPSC-CMs (Ja et al., 2018).

Strategies to rapidly perfuse thick, cell-dense cardiac patches to avoid hypoxia and necrosis are critical to support the long-term survival of the implanted cardiac patches (Chang and Niklason, 2017; Tang et al., 2018). Recent advancements have improved the perfusion of cardiac patches. By incorporating different cell types besides hiPSC-CMs, such as endothelial cells and MSCs, the hybrid cardiac patch was able to generate micro-vessels and integrate rapidly with the host (Huang et al., 2019). Recently, the use of microfluidic hydrodynamics focusing has become an interesting strategy to vascularize cardiac patches as researchers were able to construct biomimetic microvessels. Subsequently, these biomimetic microvessels were incorporated into the cardiac patch resulting in a vascularized cardiac patch that has the natural architecture and function of capillaries. When implanted in a rat model of AMI, the cardiac patch induced cardiomyocyte proliferation at the peri-infarct region four-weeks post-treatment with a significant increase in myocardial capillary density as compared to the conventional cardiac patch (Su et al., 2018).

The mechanism of aciton

Structural Support

Following MI, the injured myocardium is replaced by a thin fibrotic scar that increases wall stress in the surrounding tissues. Thus, the addition of wall thickness and rigidity by a cardiac patch may improve myocardial performance and prevent detrimental LV remodeling (Domenech et al., 2016). Decrease infarct size and reduced wall thinning were also seen (in rat model of MI) from a cardiac patch without cardiomyocytes. This fibrin-based, stretch-conditioned cardiac patch served as a proof-of-concept of the benefits conferred by structural support by the scaffold rather than the replenishment of cardiomyocytes (Wendel et al., 2014). In another study, acellular cardiac patches, generated using type I collagen, attenuated LV remodeling with reduced fibrosis and formation of an interconnected blood vessels at the infarct site, resulting in significant protection against cardiac injury at both the anatomical and functional levels following MI (Serpooshan et al., 2013).

Direct remuscularization

The original goal of the cardiac patch is to replace fibrotic scar tissue with electromechanically functional and vascularized tissue (Lakshmanan et al., 2012; Ye et al., 2013). While a study has shown that cardiac patches containing hiPSC-CMs, fibroblasts, and endothelial cells were able to reduce the infarct size and increase the vessel numbers following MI (Yeung et al., 2019), another study (employing a cryo-injury guinea pig model) demonstrated that cardiac patches only resulted in partial remuscularization of the injured heart (Querdel et al., 2021). Given the poor retention and survival of transplanted cells, multiple stem cell transplantation studies

concluded that the functional improvements seen were not due to direct remuscularization but rather the paracrine effects by the transplanted cells (Gnecchi et al., 2006; Takahashi et al., 2006; Uemura et al., 2006; van der Spoel et al., 2012; Zuo et al., 2012; Bao et al., 2017; Wu et al., 2017; Dougherty et al., 2018; Zhu et al., 2018). As more data has emerged, it appears that remuscularization by the cardiac patch is controversial, especially with the suboptimal biophysical integration of the cardiac patch and the host myocardium (Huang et al., 2019). Current research attributes the main contributor of cardioprotective effects by cardiac patches to be the paracrine factors (Hodgkinson et al., 2016). Such a turn of events could be seen as a blessing since clinically relevant cell-based therapy would require billions of cardiomyocytes (Chong et al., 2014; Liu et al., 2018), making it highly laborious and time-consuming.

Paracrine Effect

Current evidence suggests the majority of the benefits associated with cardiac patches likely revolves from the paracrine activity of implanted cells (Qasim et al., 2019b), with a recent study showing the secretome from hiPSCs and MSCs is able to produce significant improvement of cardiac function and remodeling following MI (Alrefai et al., 2019), thereby circumventing the need for exogenous cell implantation. Furthermore, a cardiac patch containing hiPSC-CMs, fibroblasts, and endothelial cells, produced improvement of heart function that is correlated with patch production of extracellular vesicles (i.e. exosomes). In addition, the cardiac patch led to regeneration of cardiac tissues, angiogenesis in the infarcted area, and reduced scar tissue formation (Yeung et al., 2019).

Adult stem cells secrete a variety of growth factors and chemokines - including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and IGF-1 – which alters the microenvironment of the myocardium and regulate remodeling following MI (Hodgkinson et al., 2016; Broughton et al., 2018). To facilitate the direct delivery of the secreted regenerative factors into the injured myocardium, microneedles were engineered on a cardiac patch incorporated with cardiac stromal cells. The resulting cardiac patch effectively augmented the myocardial function and enhanced angiomyogenesis (Tang et al., 2018).

Future directions

With many optimistic results thus far, the cardiac patch remains a promising avenue to pursue to attenuate cardiac injury associated with MI. However, more evidence suggests that the beneficial effects of the cardiac patch are largely due to the non-cellular part of the cardiac patch (Domenech et al., 2016; Qasim et al., 2019b). Therefore, we envision that the next generation of cardiac patch would be an acellular one that is focused on providing structural support while serving as a delivery vehicle for the continuous release of cardioprotective secretomes. Being cell-free not only reduces the risk of immune rejection but overcomes the need for perfusion, electromechanical integration, and cell maturation – all of which are the major roadblocks of today's cardiac patch.

Conclusion

AMI remains as one of the leading causes of death despite tremendous leaps in medical advancements. Over the years, research has led to mechanistic insights on the cardioprotective benefits conferred by cardiac patches. These include (1) providing structural support, (2) promoting direct remuscularization, and (3) secretion of cardioprotective paracrine factors (see Figure 1). Earlier studies have focused on "direct remuscularization", optimizing the delivery and incorporation of cardiomyocytes and other cell types to the infarct zone in an attempt to regenerate and repair myocardium. Soon, it became clear that cardiomyocytes were not the only important cell type. Other important cell types include MSCs, cardiac fibroblasts, and endothelial cells. However, increasing evidence have suggested that the key contributors to the protective effects of cardiac patches are the secretomes or exosomes produced by the implanted cells rather than the cells themselves. Therefore, we envision that the next generation of cardiac patches would be an acellular one that deliver protective secretomes. Being acellular would help overcome most of the major obstacles faced by the current cardiac patches. With optimistic data of cardiac patches presented by numerous studies, we believe that the cardiac patch remains a promising avenue to attenuate post-MI sequelae.

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