

Concise review: Harnessing iPSC-derived cells for ischemic heart disease treatment

Bin Duan^{1,2,3}

¹Mary & Dick Holland Regenerative Medicine Program, Division of Cardiology, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE 68198, USA;

²Department of Surgery, University of Nebraska Medical Center, Omaha, NE 68198, USA;

³Department of Mechanical and Materials Engineering, University of Nebraska-Lincoln, Lincoln, NE 68588, USA

ABSTRACT

Ischemic heart disease (IHD) is one of the most common cardiovascular diseases and is the leading cause of death worldwide. Stem cell therapy is a promising strategy to promote cardiac regeneration and myocardial function recovery. Recently, the generation of human induced pluripotent cells (hiPSCs) and their differentiation into cardiomyocytes and vascular cells offer an unprecedented opportunity for the IHD treatment. This review briefly summarizes hiPSCs and their differentiation, and presents the recent advances in hiPSC injection, engineered cardiac patch fabrication, and the application of hiPSC derived extracellular vesicle. Current challenges and further perspectives are also discussed to understand current risks and concerns, identify potential solutions, and direct future clinical trials and applications.

Key words: Cardiomyocytes, myocardial infarction, heart failure, vascularization, cardiac patch, exosome

INTRODUCTION

Ischemic heart disease (IHD) is a disease caused by blockage of blood flow to the heart arteries, resulting in reduced blood supply to the heart.^[1,2] It is one of the most common causes of death, accounting for more than 9 million mortality per year worldwide.^[3] At an early stage of IHD, many patients may be asymptomatic. However, as the atherosclerosis progresses, the patients may not only experience the initial acute myocardial infarction (MI), but also develop progressive heart failure, which is lethal.^[4] After ischemic insult such as MI, the myocardium undergoes pathological remodeling, resulting in cardiac muscle cell death, scar formation, cardiac dysfunction, and ultimately leading to heart failure.^[5] Cardiac muscle cells, or cardiomyocytes (CMs), have limited regeneration capability and the lost CMs are replaced by a fibrotic scar.^[6]

Current treatment approaches include various procedures to restore and improve blood flow,^[7] pharmacological treatments that slow or reverse cardiac remodeling,^[8]

and various strategies to revascularize or regenerate myocardium.^[9] Among these methods, stem cell therapy using somatic multipotent stem cells (like bone or adipose derived mesenchymal stem cells, MSCs) and pluripotent stem cells (like embryonic stem cells-ESC and human induced pluripotent stem cells-hiPSCs) represents a promising approach to promote cardiac regeneration and myocardial function recovery.^[10,11]

This review aims to provide a state-of-the-art overview of the harnessing of hiPSC derived cells and their derivatives (like secretomes or exosomes) for IHD treatment (Figure 1). First, it will briefly introduce the differentiation of hiPSCs into CMs and vascular cells. Then, it will focus on the recent advances in the injection of hiPSC-CMs and transplantation of hiPSC-CM-based engineered cardiac patch. The delivery or injection of exosomes from hiPSC derived cells will also be presented. Finally, current major technological hurdles and challenges will be discussed, and potential solutions and future directions will be provided.

Address for Correspondence:
Prof. Bin Duan, Mary & Dick Holland Regenerative Medicine Program, Division of Cardiology, Department of Internal Medicine, Department of Surgery, University of Nebraska Medical Center, Omaha, NE 68198, USA; Department of Mechanical and Materials Engineering, University of Nebraska-Lincoln, Lincoln, NE 68588, USA
E-mail: bin.duan@unmc.edu

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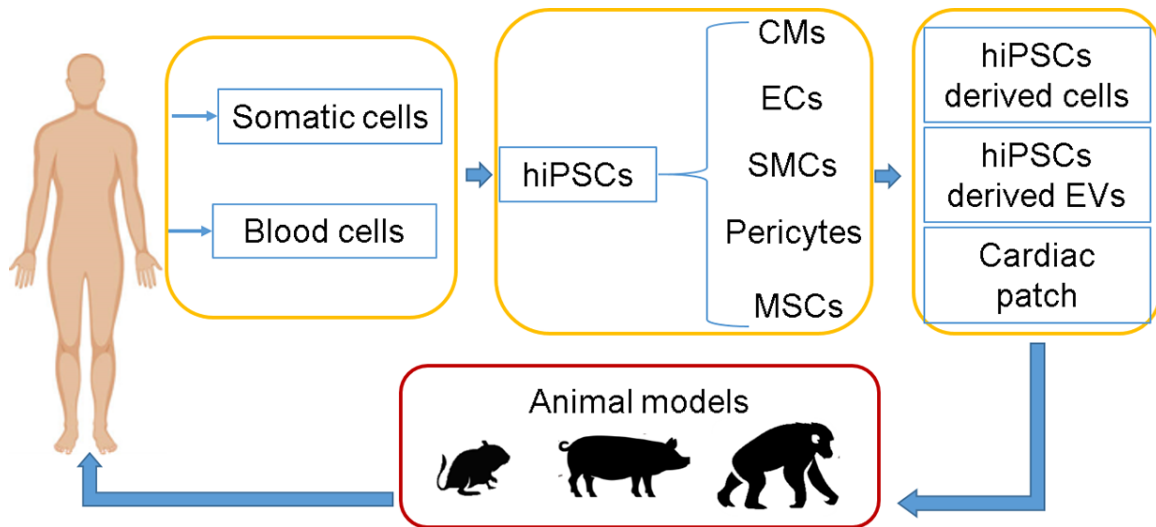


Figure 1: Schematic of how hiPSC derived cells be used for IHD treatment. hiPSCs: human induced pluripotent stem cells; CMs: cardiomyocytes; ECs: endothelial cells; SMCs: smooth muscle cells; MSCs: mesenchymal stem cells; EVs: extracellular vesicles.

HUMAN INDUCED PLURIPOTENT STEM CELL DIFFERENTIATION

iPSCs are pluripotent stem cells that are produced from adult somatic cells or blood cells over a genetic reprogramming process back into an embryonic-like pluripotent state.^[12,13] Table 1 summarizes some advantages and disadvantages/concerns as compared to the use of other stem cells (like MSCs and ESCs). hiPSCs have been successfully demonstrated to be capable of differentiating into beating cardiomyocytes through various protocols.^[14] The cardiac differentiation of hiPSCs can start from embryoid body (EB) or monolayer culture of hiPSCs.^[15,16] Monolayer cultures with Matrigel-coating and/or mouse-embryonic-fibroblast (MEF) feeding layers can result in robust differentiation following pre-differentiation culture, mesoderm induction, early cardiac induction, and maturation process.^[14,17] The differentiated hiPSC-CMs exhibit a functionally immature, disorganized, and fetal-like phenotype.^[18] Some biochemical, biophysical and engineered approaches, like adding soluble factors excreted by MSCs,^[19] applying electrical stimulation,^[20] and 3D culture,^[21] have been used to improve hiPSC-CM maturation *in vitro*.

Table 1: Advantages and disadvantages of hiPSCs

Advantages	Disadvantages/Concerns
No ethical concerns (vs. ESCs)	Require reprogramming process and use reprogramming factors (vs. MSCs and ESCs)
Unlimited proliferative capacity (vs. MSCs)	Risk of tumorigenesis (both for MSCs and ESCs)
Capacity to differentiate into cardiomyocytes and vascular cells (vs. MSCs)	Risk to induce arrhythmias (both for MSCs and ESCs)

Apart from cardiomyocytes, hiPSCs can also be differentiated into vascular cells, that is, endothelial cells (ECs), smooth muscle cells (SMCs), and pericytes.^[22,23] These hiPSC derived vascular cells have also been used, either with hiPSC-CMs or alone, to vascularize the engineered tissue or promote the revascularization of injured myocardium.

INJECTION OF HIPSC DERIVED CELLS

Currently, in various clinical trials, stem cells have been delivered via various routes (Figure 2), including intravenous injection, intracoronary injection, and intramyocardial injection (transendocardial and transepical injection).^[24] The intracoronary approach may be more suitable for patients with acute MI, while the intramyocardial injection may be better for patients with late stage of IHD and completely occluded arteries.^[25] The choice of delivery method should be highly dependent on the patient's disease status. At the current stage, most intravenous/intracoronary injections have been used for MSCs in the clinical or large animal models,^[26,27] whereas hiPSC derived cells are mostly delivered through intramyocardial injection (especially transepical injection) in the preclinical rodent models or large animal models.^[28]

The use of MSCs in the clinical trials and large animal models has much longer history as compared to that of hiPSCs. However, the delivery of MSCs led to only modest benefits for IHD patients, and the results remain controversial without involving a large number of patients.^[29] There are many reasons that contribute to the ineffective efficacy. One of the potential reasons and deficiencies is that MSCs have a limited cardiogenic differentiation capacity. Therefore,

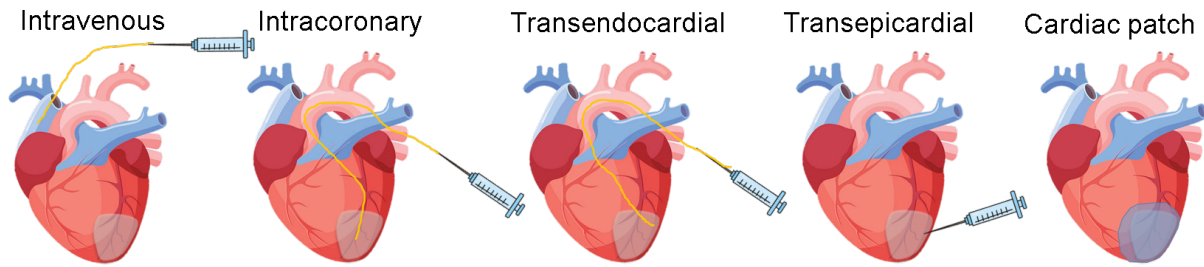


Figure 2: Cell delivery approaches

hiPSCs have obvious advantages as stem cell source to efficiently generate functional cardiomyocytes *in vitro* and to enable further transplantation. The implementation of iPSC-CMs is still in its infancy stage, so most of the pre-clinical studies focus on the transepicaldial injection in rodent,^[30] swine,^[31] and non-human primate^[32] models. In most rodent models, the proximal left anterior descending (LAD) artery is permanently ligated, and then hiPSC-CMs with or without vascular cells are injected immediately or later (1 or 2 weeks after ligation). The animals are either immunodeficient or immunosuppressed due to the use of human/non-human primate cells. The injection of hiPSC derived cells promoted heart remuscularization and facilitated global functional recovery.^[33] However, these results are normally based on short-term experiments (less than 8 weeks after ligation). For large animal models (*i.e.*, swine and non-human primate), due to poor regeneration capacity, temporary occlusion of LAD coronary artery was usually conducted (18–60 min) and then myocardium was reperfused.^[34] Positive results about cell survival and engraftment, and improvements in myocardial wall stress, metabolism, and contractile performance were reported after longer-term observation (several weeks to several months).^[35] Both hiPSC-CMs and non-human primate iPSC-CMs had comparable therapeutic efficacy and were reported to be superior to injection of fibroblasts^[36] and MSCs (in the rodent models).^[31] In addition, the injection of hiPSC-CMs together with hiPSC derived vascular cells (*i.e.*, hiPSC-SMCs and hiPSC-ECs) can further reduce cardiomyocyte apoptosis and enhance endogenous cell survival.^[31] The hiPSC-CMs can also be combined/encapsulated with hydrogel delivery system to improve cardiac function post myocardial infarction.^[30]

ENGINEERED CARDIAC PATCHES

Although cell delivery/injection-based strategies have demonstrated some efficacy in attenuating progressive myocardial damage and in some functional recovery, the injected single cells suffer from several major drawbacks like low cell survival and engraftment rate and unknown cell fate. Therefore, another alternative strategy is to

develop engineered cardiac patch that can be locally implanted to the surface of infarcted area (Figure 2).^[37] Various biomaterials and tissue engineering technologies have been used to generate the engineered cardiac patches. These techniques include molding fibrin/collagen-based hydrogels,^[38] electrospun polymeric meshes^[39], stacked cell sheets^[40], and 3D printed/bioprinted constructs.^[41] As compared to single hiPSC-CM injection, engineered cardiac patches have several advantages. First, the biomaterials and 3D structures provide biomimetic microenvironments for hiPSC-CMs and increase cell-cell and cell-matrix interaction. Second, many other cell types, like fibroblasts and hiPSC derived vascular cells can be incorporated to improve the contractility and angiogenesis. Third, mechanical and/or electrical stimulation can be applied to facilitate hiPSC-CM maturation. For example, electronic cardiac patch was fabricated by embedding gold electrodes in thin mesh, integrating with electrospun meshes, and further seeding neonatal rat CMs and cardiac fibroblasts.^[42] Fourth, the engineered cardiac patches can be fabricated with clinically relevant size and controlled structure (like fiber orientation).^[43] Fifth, various therapeutic factors can also be incorporated within cardiac patch to promote vascularization, maturation, or synergistically improve heart functions.

HIPSC DERIVED EXTRACELLULAR VESICLES (EVs)

Although there is a consensus that stem cell (especially hiPSC) transplantation exhibits beneficial effects on cardiac protection and function, there are many clinical hurdles, like safety issue and ethic issue, for harnessing hiPSC/hESC in the clinical applications. In addition, many studies have demonstrated that the positive effects and efficacy of hiPSC-based transplantation are mediated by paracrine actions.^[44] Therefore, many researches have focused not only on the hiPSC injection/transplantation, but also on their secretomes, which contain cell-secreted EVs.^[45]

The term EV encompasses several subtypes of vesicles that are lipid bilayer-delimited particles and released

by cells.¹⁴⁶ The released EVs are highly heterogeneous in size, biogenesis, cargo, and biological function.¹⁴⁷ Based on the size and biogenesis, EVs include exosomes (~30–150 nm), microvesicles (~100 nm–1 μm), and apoptotic bodies (> 1 μm). EVs contain a wide variety of compounds, such as proteins, lipids, messenger RNA (mRNA), and miRNA and can transfer these bioactive molecules between cells and regulate the functions of the recipient cell.^{148,49} Therefore, EVs secreted by stem cells have gained enormous interest as therapeutic tools. This is because EVs contain therapeutic cargoes and enable to shuttle these cargoes between cells and mediate cell-cell communication. Many studies have shown that cell or plasma derived EVs have cardioprotective effects.^{150,51} EVs from different cell types or cells in different states can generate different sets of cargoes and bioactive components. For example, exosomes isolated from hiPSC-ECs contained miR-199b-5p and promoted angiogenesis.¹⁵² Exosomes isolated from cardiosphere-derived cells with expression of Lamp2b had cardiomyocyte specific peptide on their surface and increased their uptake by cardiomyocytes.¹⁵³ Therefore, the EVs can be engineered by using different cells, co-cultured cells, and biological approaches. Similar to the application of stem cells, EVs can also be injected or combined with cardiac patch for implantation.^{154,55}

CHALLENGES AND FUTURE PROSPECTS

Although hiPSC derived cells have gained more and more attention in the last decades and are promising cell sources for IHD treatment, substantial clinical hurdles restrict their further clinical applications in patients. The barriers include low cell engraftment rate, immaturation of hiPSC-CM differentiation, and risk for tumorigenesis and arrhythmogenesis after injection/implantation.

IHD results in a loss of a large number of cardiomyocytes. However, current methods for cell delivery only achieve very poor engraftment (~0.1% to 5% survive and engraft within 24 h). Long-term results from small animal studies demonstrated that the injected cells were present around the injury site for only a short period of time and then died in situ after migrating to distant organs.^{125,56} The poor engraftment significantly reduces the efficacy. Although the use of engineered cardiac patch significantly improves the engraftment due to the locally suturing onto the infarct bed surface,¹⁵⁷ the viable and functional cells around the infarction area are not sufficient. Future study will focus more on tracking cell fate after transplantation. This knowledge will help to determine the dose of the cells and optimal delivery mode, and to improve the cell retention and survival.

The differentiated hiPSC-CMs and generated cardiac patches based on hiPSC-CMs have immature properties, disorganized structure, fetal-like phenotypes and display important differences from adult human cardiomyocytes and native adult cardiac tissue. Several review articles have systematically compared their differences.^{118,58} Numerous strategies have been developed to improve the maturity of hiPSC-CMs and engineered cardiac tissues. These approaches include varying the culture stiffness,¹⁵⁹ generating biomimetic 3D microenvironment,¹⁶⁰ applying biochemical¹⁶¹ and electrical stimulation,¹⁶² and combining multiple engineered strategies.¹⁶³ Future studies should focus on better understanding of the maturation process, the role of extracellular matrix (ECM) and microenvironment to mimic the physiological environment and promote maturation.

There is also a higher risk of tumorigenesis for the hiPSC-CM transplantation as compared to adult stem cells (*i.e.* MSCs). By increasing the cell maturation during differentiation and applying rigorous testing to ensure the cell purity, quality, and sterility, the tumorigenesis risk can be reduced. Another potential risk is the development of life-threatening arrhythmias. This may be because of the introduction of conduction blocks and electrical heterogeneities and abnormal automaticity of the transplanted cells.¹⁶⁴ The abnormal repolarization or abnormal calcium cycling of the transplanted cells may increase the risk, whereas better coupling and resynchronization in the infarcted area will reduce the arrhythmia risk. Current pre-clinical animal results using various stem cells and clinical trials using MSCs show limited arrhythmia risk. Longer-term clinical trials for using hiPSC-CMs should be conducted to address this concern.

For future translation to clinical application, compliance with good manufacturing practice (GMP) is mandatory before clinical use.¹⁶⁵ Large scale cell manufacture and differentiation are required to obtain large number of cells within a short period of time.¹⁶⁶ Novel biomaterials and biomaterial systems can serve as artificial ECM to promote cell viability, engraftment, and efficacy. For example, large fibrin hydrogel based cardiac patch with hiPSC derived CMs and vascular cells improved recovery from MI in swine model.¹⁵⁷ For another example, Vandergriff *et al.* conjugated exosomes with cardiac homing peptide to increase the delivery efficiency.¹⁶⁷ Apart from biomaterials, development of cutting-edge engineering technologies can also advance the future application of hiPSC-CM-based engineered tissues. For example, 3D printing/bioprinting technique enables the precise fabrication of engineered tissues with clinically relevant size, patient-specific features, and functions.¹⁶⁸ 3D printing/bioprinting has been used to fabricate contractile human cardiac ventricle constructs and even whole heart.^{169,70}

CONCLUSIONS

In summary, the implementation of hiPSC derived cells, the cell-based cardiac patch, and cell-derived exosomes has yielded promising pre-clinical outcomes following IHD. These efforts and results will speed up the development of novel effective regenerative therapies for the clinical setting. However, significant clinical barriers still remain and will not be easily overcome. In order to acknowledge and address the limitations and concerns, the close collaborations between researchers and physicians from multidisciplinary fields are necessary. In addition, due to the complex and sophisticated nature of heart tissue and disease, a combination of multiple therapeutic approaches will be vital to enable successful harnessing of hiPSC-CMs and effectively treating the patients.

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Conflict of Interest

None declared.

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