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Review

The effects of transplanted cells in stem cell therapy for myocardial ischemia

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Abstract

It is known that myocardial infarction (MI) causes damages to the heart tissue and that present medical therapies, such as medication, stenting and coronary artery bypass surgery, cannot recover the injured heart. Fortunately, advances in stem cell research have brought hope of full heart recovery for myocardial ischemia patients. There have been many studies using cell therapies for myocardial ischemia, from preclinical trials to clinical trials. However, the biggest concern is the effect of transplanted cells in myocardial recovery. This review will focus on analyzing both the positive and negative effects of transplanted cells in myocardial recovery to better understand the underlying biological mechanisms and ways to evaluate safety and efficacy of cell transplantation in myocardial ischemia treatment.

Keywords

Biological mechanism, effect, myocardial ischemia, stem cell therapy, transplanted cells

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Introduction

Myocardial infarction (MI) kills cardiac cells and forms scars in the heart tissue. Although the formation of scars helps the injured heart cope with damages quickly, protects healthy tissue from further damage and prevents a cascade of adverse uncontrollable events (Azouz et al., 2004), the biochemical reactions during scar formation remain unclear. In fact, the physical and functional properties during heart tissue scarring is similar to those of normal tissues. Scarring has negative effects on the structure and activity of the infarcted heart (Cregg et al., 2014; Silver and Miller, 2004; Xu et al., 2004).

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Current treatments such as lifestyle changes, medication, stent intervention or artery bypass surgery can only support the heart to slow the failure process, but cannot recover damaged heart tissues. The successful rate of all heart transplantation was very low. The number of novel postnatal heart tisue was low too and it was around 1% of total myocardium and decreased with age (Garbern and Lee, 2013).

Nowadays with the development of regenerative medicine, cell therapy can be expected to completely restore the structure and function of the damaged heart. Cell transplantations into ischemic areas have been investigated in small animal models (Avolio et al., 2015; Kim et al., 2015; Tang et al., 2015), large animal models (Kanazawa et al., 2015; Yee et al., 2014) and in clinical trials (Karantalis et al., 2012; Perin et al., 2015). Various cell types have been used in implantation, including mesenchymal stem cells (MSCs) (Kocher et al., 2001), induced pluripotent stem cells (iPSCs) (Cantz and Martin, 2010), cardiac progenitor cells (CPCs) (Garbern and Lee, 2013), cells derived from fetal tissue and adult cardiomyocytes (Soonpaa et al., 1994; Zhang et al., 2001), skeletal myoblasts (Menasche et al., 2001), muscle cells (Condorelli et al., 2001), embryonic-derived endothelial cells (ECs) (Condorelli et al., 2001), bone marrow-derived immature cells (Hattan et al., 2005), fibroblasts (Galli et al., 2005), smooth muscle cells (SMCs) (Harada et al., 2016) and bone marrow-c-kit positive and negative progenitor cells (Fazel et al., 2008; Fernandez-Aviles et al., 2004). In spite of the fact that results with the above have varied, they were largely similar in that there is a positive impact of cell transplantation on the recipients. It is important to understand how the transplanted cells act in heart wound healing and their efficacy. This review will focus on those issues.

Effects of transplanted cells

Most likely transplanted cells reduce negative remodeling by reducing the stiffness of the ventricular wall scar and restoring the lost heart muscle. Proposed mechanisms for this process include: **(1)** the transplanted cells secrete paracrine factors to protect the cells from apoptosis, mobilize the available cardiac stem cells, activate their proliferation and differentiation into heart cells, partake in neovascularization, reduce scar formation and limit inflammation; **(2)** the transplanted cells can fuse with host graft; **(3)** the transplanted cells can differentiate into cardiac muscle cells (**Fig. 1**).

Secretion of growth factors

Secretion of implanted cells plays an important role in repairing heart tissue damage. Adult stem cells, particularly MSCs, after transplantation can release a variety of cytokines, chemokines and growth factors involved in heart repair process (Deb et al., 2008; Li et al., 2012; Loffredo et al., 2011). These factors, in turn, induce neighboring stem cells to secrete cytokines and induce changes in the microenvironment which promote proliferation and differentiation of stem

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cells (Behfar et al., 2002; Doyle et al., 2016; Gude et al., 2015; Kinnaird et al., 2004). In particular, properties such as myocardial protection and neovascularization of paracrine factors currently have been most widely studied. Moreover, the secreted factors also impact positively on the inflammation process, fibrogenic process, heart metabolism, heart contractions and/or endogenous cardiac regeneration. These effects may occur in different ways and are dependent on the microenvironment after infarction. These factors may also act in an autocrine fashion, impacting the cells which secrete them (Deb et al., 2008).

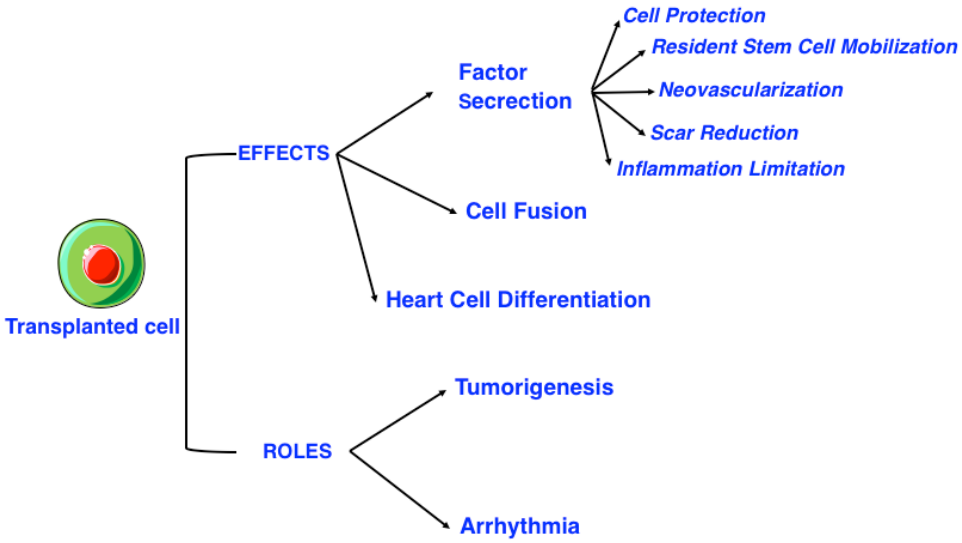

Figure 1. Effects and roles of transplanted cells in myocardial ischemia treatment. Transplanted cells can secrete useful factors to protect cells from appoptosis, mobilize resident stem cells, participate in the process of forming new vessels, reduce the size of the scar in the infarction area or limit the inflammation ; these cells can also fuse with the host cells; or differentiate into heart cells. However, there are some things to consider when choosing the type of cells for transplantation such as their capable of tumorigenesis or arrhythmia causing.

Protection of heart tissue

The immediate impact of stem cells after grafting into the heart muscle is to release cytoprotective molecules to increase myocardial viability. These molecules inhibit apoptosis by activating AKT/PKB signaling pathway (Rosenberg et al., 2012; Yang et al., 2012). Some studies have shown that Akt-overexpressing MSCs and exosomes secreted from CXCR4-overexpressing or GATA4-overexpressing MSCs are able to significantly prevent apoptosis, thereby reducing infarction size (Kang et al., 2015; Noiseux et al., 2006; Yu et al., 2015). Other studies have shown that elements secreted from grafted bone marrow

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stem cells induce cardiomyocyte protection in the ischemic region (Broughton and Sussman, 2016; Dai et al., 2008; Xu et al., 2007). Cardiomyocytes differentiated from bone marrow monocytes (BM-MNCs) cultured under hypoxic conditions show they have inhibitory effects on apoptosis and can reduce infarction size when transplanted into the body (Kubal et al., 2006). When heart muscle cells and BM-MNCs obtained from the same patients were co-cultured, cell necrosis and apoptosis were significantly reduced; cell protection, however, did not occur when heart muscle cells with co-cultured with ECs or keratinocytes (Yoon et al., 2005).

Moreover, transplanted Akt-expressing MSCs also expressed secreted frizzled related protein 2 (Sfrp2), which increases cellular total -catenin of cardiomyocytes. The -catenin protected cardiomyocytes of newborn rats were stable against hypoxia and reoxygenation-induced apoptosis by blocking the pre-apoptotic effects of Wnt3a (Mirotsou et al., 2007; Zhang et al., 2009). Akt-MSCs regulated the increase of vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), hepatocyte growth factor (HGF), insulin-like growth factor-1 (IGF-1), and thymosin 4 (TB4). In turn, these factors promoted neovascularization, protection of myocardium and cardiac contractility (Gnecchi et al., 2006) (**Fig. 2**).

The overexpression of bFGF can enhance the recovery of contractile function and reduce infarction area after reperfusion. In fact, bFGF reduces the protein kinase C delta (PKC-d) displacements but does not affect PKC-alpha (PKC-a), PKC-epsilon (PKC-e), or PKC-zeta (PKC-z). PKC-d reduction protects heart cells and decreases the number of dead cells. In addition, bFGF has been shown to be related to the MAPK/ERK signaling pathway in heart cell protection, although the mechanism remains unclear (Baines et al., 2002; House et al., 2007; Padua et al., 1998; Rose et al., 2010; Srisakuldee et al., 2014). Akt activates a number of substrates, including members of the B-cell lymphoma 2 (Bcl-2) protein family, glycogen synthase kinase 3 beta (GSK-3) and endothelial nitric oxide synthase (eNOS). Nitric oxide (NO) synthesized from eNOS activates PKG through intracellular cGMP increasing. The substrates for protein kinase G (PKG) are thought to include SR regulation proteins and phospholamban, which promotes SR Ca^{2+} absorption thereby reducing the overload of cytosolic Ca^{2+}. PKG is the final component of the signal transduction leading to activation of PKC-epsilon (PKC-e) mitochondrial pool. Activated PKC-e in turn activates mitochondrial ATP-dependent potassium channels (mK_{ATP}), promoting the reactive oxygen species (ROS) formation (**Fig. 2**).

The inhibition of mitochondrial permeability transition pore (MPTP) may occur as a result of PKC-e activation. Sarcolemmal K_{ATP} (sK_{ATP}) and mitochondrial connexin-43 (Cx43) are also considered components of the pre-regulation mechanism. The formation of ROS and reactive nitrogen species (RNS) are the results of mK_{ATP} opening and are mandatory components of the signaling cascade. It seems that ROS /RNS signaling is related to activation of kinases, such as p38, MAPK, PKC and JAK/STAT (Ferdinandy et al., 2007).

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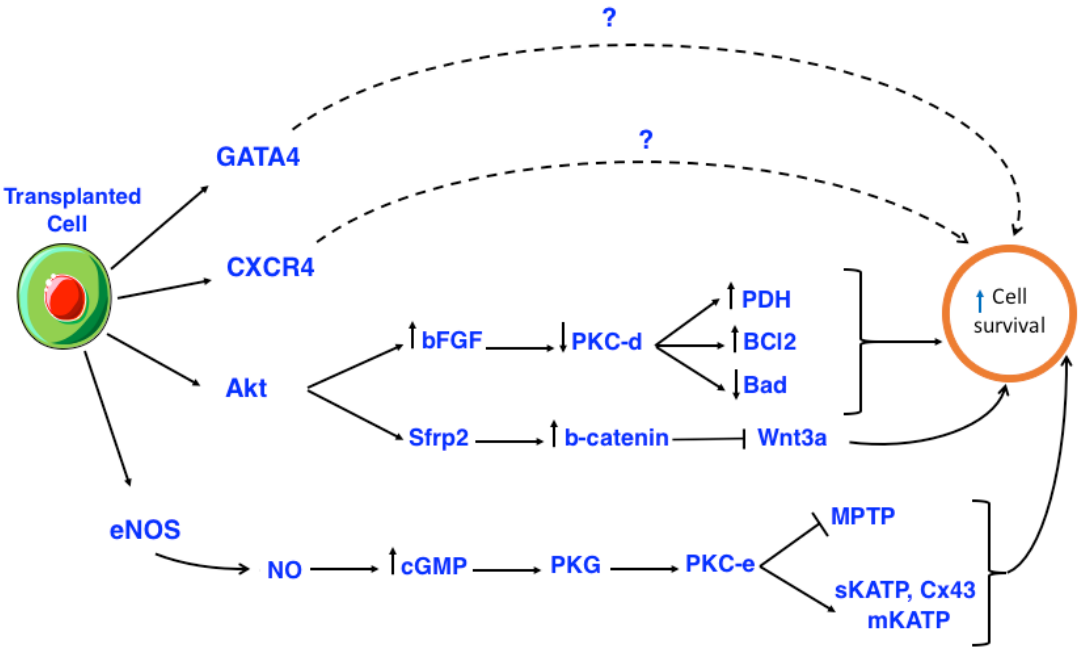

Figure 2. Transplanted cells protect heart tissue by increasing cell survival. CXCR4 or GATA4 overexpressing Mesenchymal Stem Cells released exosomes that prevented cells from appoptosis; the mechenism is unknown. Akt overexpressing MSCs increased bFGF leading to PKC-d reducing that increased PDH, Bcl2 and decreased Bad to protect cell survival. Akt overexpressing MSCs also secreted Sfrp2 which increased cellular total -catenin of cardiomyocytes that blocked pre-apoptotic effects of Wnt3a and thereby protected cardiomyocytes. Akt activated eNOS and NO synthesized from eNOS activated PKG through intracellular cGMP increasing leading to activate PKC-e. PKC-e, in its turn, activate sKATP, mKATP, Cx43 and inhibit MPTP leading to cell protection.

The heart protects extracellular ligands, including adenosine, bradykinin and opioids, while activating multiple kinases, including p42/p44, MAPK/ERK, PI3K/Akt and PKC. The substrates of PKC related to the regulating protective mechanisms are still unknown. There is also evidence that the activation of PKG might occur as part of the post-regulating mechanism downstream of Akt/NO/cGMP, and may play a role in promoting the absorption of sarcoplasmic reticulum Ca^{2+}. It is known that activation of Akt inhibits GSK-3 and members of the chemokine (C-C motif) ligand 2 (Ccl-2) protein family, leading to inhibition of the formation of mK_{ATP}-mediated MPTP (Ferdinandy et al., 2007).

Normally, PKC exists in a non-activated state until it is stimulated by phospholipid diacyl glycerol (DAG)-derived second messengers. Intracellular ROS translocates to the subcellular target locations, including mitochondria, sarcolemmal membrane and gap junctions. Indeed, sK_{ATP}-mediated phosphorylation leads to shortening of the action potential, reducing the Ca^{2+}

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overload during ischemia. Moreover, PKC-mediated phosphorylation of Cx43 reduces connexon permeability and prevents the expansion of damages between co-joined cells. PKC-mediated phosphorylation opens the mK_{ATP}, conserves mitochondria function and forms local ROS. In turn, ROS may initiate PKC signaling via positive feedback. MPTP inhibition can occur by both direct mechanisms (e.g. via PKC phosphorylation) and indirect mechanisms (e.g. via mK_{ATP} opening which reduces cell death after infarction). Receptor for activated c-kinase (RACK) treatment and erythropoietin also promote PKC activation, resulting in heart cell protection (Bearzi et al., 2007; Budas et al., 2007).

In summary, during ischemia reperfusion activated PKC-e in turn activates sK_{ATP} and mK_{ATP}, phosphorylates Cx43 and inhibits MPTP, leading to cell protection. However, activated PKC-d inhibits pyruvate dehydrogenase (PDH), decreases Bcl-2, increases Bcl-2-associated death promoter (Bad) protein, causing apoptosis and necrosis. Thus, transplanted cells protect myocardium by secreting various factors that activate PKC-e and inhibit PKC-d.

Mobilization of resident stem cells

The discovery and recognition of the existence of cardiac stem cells led to a shift by researchers and physicians to explore the use of stem cells for new cardiovascular disease therapies (Bearzi et al., 2009; Hosoda et al., 2009; Urbanek et al., 2006). In the heart, cardiac stem cells (CSCs) have existed in their niches. Normally, these cells have kept "silent" in their niches, and have been nourished and controlled by feeding cells within the niches. Upon receiving trigger signals, CSCs undergo a symmetrical or asymmetrical proliferation; they separate from their niches and migrate to areas where they were needed to replace damaged or dying heart cells. However, the number of CSCs are very rare, at approximately 1 stem cell per 30,000 heart cells (Beltrami et al., 2003; Urbanek et al., 2006). Therefore, based on the normal growth rate of resident CSCs, when infarction occurs the number of cells needed to be replaced is much greater than the number of available cells, leading to a lack of intrinsic cardiac stem cells for replacement. This means that while the injured heart may be delayed in damages in the short term, heart failure cannot be reversed in the long term (Urbanek et al., 2003).

Studies have shown that when MSCs are grafted into the body in the absence of oxygen, they release HGF and IGF-1 to mobilize and activate resident CSCs (Gómez-Mauricio et al., 2016; Linke et al., 2005). Besides MSCs, endothelial progenitor cells (EPCs) play an important role. EPCs activate cardiac regenerative pools and promote the migration, proliferation and differentiation of CSCs (via secretion of cytokines such as VEGF, IGF-1 and SDF-1) (Urbich et al., 2005). These factors induce interstitial CSCs to move through the myocardium to necrotic myocardium and scar areas. There, they divide and differentiate into heart cells and become involved in the process of new blood vessel formation (Bian et al., 2014; Hosoda et al., 2009; Tillmanns et al., 2008). CSC invasion to

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scar tissue is believed to be related to matrix metalloproteinase (MMP)-9 and -14 mediated regulation (Bax et al., 2012; Huang et al., 2011; Rota et al., 2008).

Neovascularization

MSC transplantation improves reperfusion efficiency by increasing the formation of new blood vessels. However, MSCs are rarely present in the new vessels; their main activity is to secrete angiogenic factors, such as VEGF, bFGF, angiopoietin-1, NO and HGF (Kinnaird et al., 2004; Zhao et al., 2010). These factors increase the permeability of the capillary wall, activate MMP, promote the proliferation and migration of ECs and vascular smooth muscle cells (VSMCs), and form new vessels in the lesions (Jiang et al., 2006; Louis and Zahradka, 2010; Nagaya et al., 2004). Besides MSCs, transplanted EPCs also enhance new vessel formation by releasing VEGF and stromal cell-derived factor 1 (SDF-1) into the cellular matrix, thereby promoting the migration and maturation of EPCs into ECs (Cochain et al., 2013; Urbich et al., 2005; Wu et al., 2006). Angiogenic cells have been implanted as hydrogel supplying scaffolds to increase microvasculature along infarction areas, thereby significantly improving coronary blood flow and ejection fraction after MI (Kim et al., 2012; Leblanc et al., 2013; Levit et al., 2013). In addition to angiogenesis factors, adult stem cells secrete TB4 and erythropoietin (EPO) (Lv et al., 2015; Smart et al., 2007). TB4 induces the proliferation and circuit network formation of epicardium-derived cells (EPDCs) and is involved in the intermediate PKC signaling pathway (Smart et al., 2013; Smart et al., 2007). Meanwhile, granulocyte colony stimulating factor (G-CSF) and EPO mobilize hematopoietic stem cells (HSCs) and EPCs from bone marrow for angiogenesis by activating Janus-activated tyrosine kinase 2 (JAK2) through STAT, PI3K/Akt and MAPK signaling pathways (Nagai and Komuro, 2012).

Impact on extracellular matrix (ECM) and reduction of scar formation

After infarction, scars are formed to replace injury tissues damaged by myocardial ischemia. During ischemia, the ECM secretion process is disordered due to heart cells dying and the body's self-regulation. These impact the thickness of the developing scar, leading to an effect on the contraction of the surrounding heart tissue. A decrease in the ECM makes the ventricular wall thinner, causing left ventricular (LV) rupture while an increase in the ECM enhances fibrosis, leading to heart failure over time (Zamilpa and Lindsey, 2010).

From studies, it has been observed that grafted cells are capable of regulating scar formation through inhibition of fibroblast proliferation; furthermore, it has been shown that paracrine factor secretion alters ECM to improve cardiac functions (Berry et al., 2006). Transplanted MSCs reduce myofibroblasts through releasing MMPs (Almalki and Agrawal, 2016; Mias et al., 2009). In MI rat models, implanted MSCs reduce the expression of collagen types I and III, tissue inhibitor of metalloproteinase-1 (TIMP-1), MMP2, MMP9, and transforming growth factor-beta (TGF-beta) (Nagaya et al., 2005; Xu et al., 2005). It is

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interesting that transplanted MSC cardiomyocyte (MSC-CM) also express the ability to reduce the scarring process by downregulating fibroblast proliferation and inhibiting the expression of collagen type I and type III in myofibroblasts (Ohnishi et al., 2007a; Ohnishi et al., 2007b). In addition, embryonic stem cell cardiomyocyte (ESC-CM) also show the ability to reduce scarring after MI (Leor et al., 2007). In sheep, MSCs injected one hour after MI also show changes in MMP-1, -2, -3, -7, -9, -13, membrane type 1-MMP (MT1-MMP), and TIMPs-1, -2, -4, at the border zone and infarct zone (Dixon et al., 2009).

Limiting inflammation

After MI, the inflammatory process is needed to mobilize immune cells to clear out dead heart cells and debris, and to stimulate ventricular remodeling (Frangogiannis, 2012; Frangogiannis et al., 2002). However, prolonged inflammatory responses would be detrimental to the remodeling process and ventricular function due to heart cell loss leading to negative impacts on ECM as well as formation of new vessels (Frangogiannis et al., 2002). Transplanted cells, such as MSCs or MSC-CMs, are able to limit the inflammatory process in the injured tissue. They weaken the proliferation of inflammatory CD^{68+} cells, decrease the expression of monocyte chemoattractant protein (MCP-1), increase the expression of genes involved in DNA repair, increase antioxidant enzymes and stimulate detoxifier systems, thereby improving cardiac function (Fuse et al., 2001; Ohnishi et al., 2007b; Ramalho-Santos et al., 2002).

Transplanted MSCs increase the number of M2 macrophages which were at the anti-inflammatory stage. The mechanism of this process is related to a variety of paracrine factors derived from transplanted MSCs, such as CCL2, galectin-1, interferon-γ, interleukin (IL)-1β, indoleamine-2,3-dioxygenase, IL-4, IL-6, IL-10, IL-13, prostaglandin E2 (PGE2), tumor necrosis factor (TNF)-α, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), NO, heme oxygenase-1, HGF, and TGF-beta (Ben-Mordechai et al., 2013; Bernardo and Fibbe, 2013; Du et al., 2008). Normally, the pro-inflammatory cytokines (e.g. NF-κB, IL-6 and TNF-) poison the heart muscle cells, causing detrimental effects on cardiac contractile function. Transplanted MSCs have been shown to inhibit activation of NF-κB, reduce production of TNF- α and IL-6, and increase the expression of anti-inflammatory cytokine IL-10, thereby limiting inflammation after infarction (Du et al., 2008; Onai et al., 2007). Moreover, the increase of indoleamine-pyrrole 2,3-dioxygenase (IDO) and PGE2 secretion also reduces T-cell activity and NK cell proliferation (Glennie et al., 2005; Nauta et al., 2006; Pradier et al., 2011; van den Akker et al., 2013).

Cell fusion

After infarction, grafted stem cells reduce cardiomyocyte apoptosis and stimulate cell proliferation via cell fusion (Alvarez-Dolado et al., 2003; Yang et al.,

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2012). Studies of bone marrow transplantation have proven that there is cell fusion between donor cells and recipient cells to form multi-nuclear cells (Alvarez-Dolado et al., 2003; Mayourian et al., 2016). Some studies have shown that stem cell transplantation can reprogram recipient cells, causing cardiomyocytes to re-enter the cell cycle; this contributes to regeneration of cardiac muscle and improvement of cardiac function (Yeh and Zhang, 2006).

Manuel Alvarez-Dolado et al. demonstrated that bone marrow stromal cells (BMSCs) derived from R26R mice (i.e. a Cre reporter mouse line) could fuse with Cre+ neurosphere cells after 4 days of co-cuture. Moreover, BMSCs could fuse with Cre+ fibroblasts in primary cuture. In vivo studies have revealed that bone marrow of actin-Cre-GFP mice could be grafted to irradiated R26R mice. The transplanted cells were shown to fuse with and exhibit similar morphology as local mature cardiomyocytes. The fused cells expressed GFP at 2 months after implantation; however, GFP expression was absent in most of the fused cells at 4 months after implantation, suggesting that interesting changes may occur inside the cells (Alvarez-Dolado et al., 2003). In accordance with Manuel et al., Yang et al. reported that transplanted bone marrow cells tend to integrate with local heart cells in infarcted regions rather then in healthy tissues. The infusion contributed to prevention of apoptosis of intergrated cardiomyocytes (Yang et al., 2012). In another interesting study, from Nygren et al., it was shown that transplanted HSC survive but do not transdifferentiate into cardiomyocytes within the infarcted myocardium, whereas X-gal and GFP positive cardiomyocytes or fused cardiomyocytes are seen outside the infarcted zone (Nygren et al., 2004).

Differentiation of transplanted cells into heart cells

Transplantation of stem cells or progenitor cells restore structure and function of heart tissue after infarction; this has been demonstrated both by preclinical studies and clinical trials. One of the proposed mechanisms is that transplanted cells and mobilized cells have the ability to differentiate into heart cells to replace damaged or necrotic cells (Kajstura et al., 2005; Nagata et al., 2016; Suzuki et al., 2015), possibly forming links with neighboring heart cells (Dimmeler et al., 2005).

So far, stem cell differentiation into heart muscle cells is proposed to be related to four major signaling pathways: canonical/non-canonical Wnt signaling pathway, bone morphogenetic protein (BMP) signaling pathway, fibroblast growth factor (FGF) signaling pathway, and Notch signaling pathway. Firstly, when the canonical Wnt pathway is inhibited through Wnt3A and b-catenin inhibition, this stimulates the differentiation of stem cells/precursor cells into cardiomyocytes (Pagliari et al., 2014). In addition, when non-canonical Wnt signaling pathway is activated through Wnt11 and Wnt5A activation, this also increases cell differentiation into cardiomyocytes (Pagliari et al., 2014). Secondly,

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BMP-Smad1 inhibits Wnt/b-catenin and activates non-canonical Smad binding factors, leading to the transcription of activating transcription factor-2 (ATF2), while promoting major histocompatibility complex b (b-MHC) expression, contributing to heart cell differentiation (Parikh et al., 2015). Thirdly, FGF activates the PI3K/Akt signaling pathway to preserve stem cell properties (Parikh et al., 2015); moreover, via the MAPK/ERK signaling pathway they cause proliferation of cardiac progenitor cells but inhibition of their final differentiation into mature cardiomyocytes (Tirosh-Finkel et al., 2010). Repression of FGF signaling, therefore, accelerates the differentiation process of cardiac precursor cells (Tirosh-Finkel et al., 2010). Finally, Notch signaling plays a very important role in the regulation of stem cell differentiation into cardiomyocytes. It affects many kinds of cells- from transplanted cells, such as EPCs, MSCs and CPCs, to resident CSCs, immature cardiomyocytes and quiescent cardiomyocytes. Notch signaling is mediated by Jagged 1, NICD, Wnts, cyclin D1, RBP-Jk and Nkx2.5 (Gude et al., 2015; Luxan et al., 2016; Zhou and Liu, 2014).

Tumorigenesis of transplanted cells

Besides the positive effects of transplanted cells in experimental treatments for myocardial ischemia, there are negative impact, such as fertility tumorigenesis and cardiac arrhythmias.

Almost all adult stem cells and cardiac progenitor cells differentiated from stem cells have been shown to be safe; they did not produce tumors when transplanted into recipients (Ghodsizad et al., 2013; Huber et al., 2007). However, ESCs and iPSCs, have exhibited a high fertility tumorigenesis after transplantation (Ben-David and Benvenisty, 2011; Lee et al., 2013). Nussbaum et al. showed that after injection of undifferentiated-ESCs into rat models, tumor formation developed after transplantation (Nussbaum et al., 2007). In another study, Blin et al. grafted incompletely purified human ESC-derived cardiomyocytes into immune suppressed monkey models and found tumor formation in the transplanted monkeys (Blin et al., 2010). This suggests that unless the ESC-derived cardiomyocyte population is comprised of completely purified embryonic stem cells, it is very easy to form tumors from residual, unpurified ESCs (Tohyama et al., 2013). To date, there has been studies conducted to generate iPSCs without using viral vectors to circumvent the tumorigenesis of iPSCs (Okita et al., 2008).

Arrhythmia

Besides tumorigenesis, the potential of arrhythmia induction from transplanted cells has also received wide attention. In clinical trials, it was shown that transplant of myoblasts could led to arrhythmia occurrence (Leobon et al., 2003).

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Additionally, a number of other studies also confirmed that transplanted beating heart cells could give rise to arrhythmia (Gillum and Sarvazyan, 2008; Menasche et al., 2008), while transplantation of human ESC (hESC)-derived cardiovascular progenitors into human fetal hearts showed harmony of the structure and function between transplanted cells and cardiac host cells (Ardehali et al., 2013). Moreover, the electromechanical coupling of hESC-derived cardiomyocytes and the suppression of cardiac arrhythmias in transplanted pig models seems to be related to the formation of electrical conduction bridges through scar tissues (Shiba et al., 2012). The problem of arrhythmia after transplantation has now become a major problem, attracting scientists and clinicians to investigate mechanisms to overcome it.

Conclusion

In conclusion, transplanted cells delivered by several different pathways have shown that they could recover the structure and function of the damaged heart. These mechanisms include secretion of factors that protect heart cells, neovascularization, prevention of the fibrosis process, limiting the inflammatory processes, and mobilizing resident stem cells to repair the heart (by fusing with host cells or differentiating into heart cells for cell loss replacement). However, in addition to positive effects, transplanted cells can also have undesirable roles, such as induction of tumorigenesis or arrhythmia. The chosen cell type for transplantation needs to be considered carefully before clinical application.

Abbreviations

AKT/PKB: serine/threonine-specific protein kinase/ protein kinase B; ATF2: activating transcription factor-2; b-MHC: major histocompatibility complex b; Bad: Bcl-2-associated death promoter; Bcl-2: B-cell lymphoma 2 ; bFGF: basic fibroblast growth factor; BM-MNCs: bone marrow monocytes; BMP: bone morphogenetic protein; BMSCs: bone marrow stromal cells; Ccl-2: chemokine (C-C motif) ligand 2; cGMP: cyclic guanosine monophosphate; CPCs: cardiac progenitor cells; CPCs: cardiac progenitor cells; CSCs: cardiac stem cells ; Cx43: mitochondrial connexin 43; CXCR4: C-X-C chemokine receptor type 4; DAG: phospholipid diacyl glycerol ; ECM: extracellular matrix; Ecs: endothelial cells; eNOS: endothelial nitric oxide synthase; EPCs: endothelial progenitor cells; EPDCs: epicardium-derived cells; EPO: erythropoietin; ESC-CM: embryonic stem cell cardiomyocyte; FGF: fibroblast growth factor; G-CSF: granulocyte colony stimulating factor; GATA4: GATA Binding Protein 4; GFP: green fluorescent protein; GSK-3: Glycogen synthase kinase 3; GSK-3: glycogen synthase kinase 3 beta; hESC: human embryonic stem cell; HGF: hepatocyte growth factor; HSCs: hematopoietic stem cells; IDO: indoleamine pyrrole 2,3-dioxygenase; IGF-1: insulin-like growth factor-1; IL: interleukin; iPSCs: induced pluripotent stem cells; JAK/STAT: Janus kinase/ signal transducers and activators of transcription; JAK2: Janus-activated tyrosine kinase 2; LV:

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left ventricular; MAPK/ERK: Mitogen-Activated Protein Kinase/ extracellular signal–regulated kinases; MCP-1: monocyte chemoattractant protein 1; MI: myocardial infarction; mK_{ATP}: mitochondrial ATP-dependent potassium channel; MMP: matrix metalloproteinase; MPTP: mitochondrial permeability transition pore; MSC-CM: MSC cardiomyocyte; MSCs: mesenchymal stem cells; NF-kB: nuclear factor kappa-light-chain-enhancer of activated B cells; NICD: Notch intracellular domain; NO: Nitric oxide; PDH: pyruvate dehydrogenase; PGE2: prostaglandin E2; PI3K: Phosphatidylinositol-4,5-bisphosphate 3-kinase; PKC-a: protein kinase C alpha; PKC-d: protein kinase C delta; PKC-e: protein kinase C epsilon; PKC-z: protein kinase C zeta; PKG: protein kinase G; RACK: Receptor for activated c-kinase; RNS: reactive nitrogen species; ROS: reactive oxygen species; SDF-1: stromal cell-derived factor 1; Sfrp2: frizzled related protein 2; sK_{ATP}: sarcolemmal $K_{ATP;}$ SMCs: smooth muscle cells; TB4: thymosin 4; TGF-beta: transforming growth factor-beta; TIMP-1: tissue inhibitor of metalloproteinase-1; TNF: tumor necrosis factor; VEGF: vascular endothelial growth factor; VSMCs: vascular smooth muscle cells; Wnt3a: Wnt Family Member 3A

Author Contributions

Truc Le-Buu Pham wrote and participated in editing the review. Phuc Van Pham oriented, gave important idea and revised the manuscript of this review.

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