Regenerative Therapy 26 (2024) 859–866

Contents lists available at ScienceDirect

Regenerative Therapy

journal homepage: http://www.elsevier.com/locate/reth

Review

Regenerative medicine in cardiovascular disease

Takasumi Goto [a, b, 1], Yuki Nakamura [a, 1], Yoshito Ito [a, 1], Shigeru Miyagawa [a, *, 1]

[a] Department of Cardiovascular Surgery, Osaka University Graduate School of Medicine, Osaka, Japan
[b] Department of Cardiovascular Surgery, Toyonaka Municipal Hospital, Osaka, Japan

ARTICLE INFO

Article history:
Received 30 July 2024
Received in revised form
4 September 2024
Accepted 11 September 2024

Keywords:
Heart failure
Cellular regenerative therapy
Endogenous regenerative therapy
Stem cell

ABSTRACT

Owing to the rapid increase in the number of people with severe heart failure, regenerative medicine is anticipated to play a role in overcoming the limitations inherent in existing surgical interventions. There are essentially two types of cardiac regenerative therapies for a failing heart. Cellular regenerative therapies using various stem cells improve the functional recovery of the heart mainly by cytokine paracrine effects. The implantation of induced pluripotent stem cell–derived cardiomyocytes can contribute not only to the inhibition of adverse heart remodeling by paracrine effects but also to the supply of newly born functional myocytes with the recipient myocardium as "mechanically working cells." Cell transplantation, including autologous myoblast transplantation, reduces heart failure exacerbations and benefits patients without the need for other treatment options. Although cellular therapy is currently the mainstream approach, it requires an in-house cell-processing center with an aseptic environment. In addition, these stem cells are usually introduced via several invasive delivery methods, including intracoronary administration, and cellular sheet implantation. Simplifying the culture methods for these cells is a crucial problem that needs to be resolved.

Drug-induced regenerative therapy is another option that enhances self-endogenous regenerative systems in the human body and does not require invasive methods or cell cultures. Therefore, drug-induced regenerative therapies may overcome the disadvantages of these cellular therapies. The purpose of this report is to summarize cell transplantation therapy in the cardiovascular system and regenerative therapy for heart failure using an autologous endogenous regenerative system.

Contents

* Corresponding author. 2-2, Yamadaoka, Suita, Osaka, 565-0871, Japan.
E-mail address: miya-p@surg1.med.osaka-u.ac.jp (S. Miyagawa).
Peer review under responsibility of the Japanese Society for Regenerative Medicine.
[1] All authors contributed equally to this work and share first authorship.

https://doi.org/10.1016/j.reth.2024.09.004

Abbreviations

MI	myocardial infarction
LVAD	left ventricular assist device
iPSC	induced pluripotent stem cell
BM	bone marrow
BM-MSC	BM-derived mesenchymal stem cell
BM-MNC	bone marrow mononuclear cell
ICM	ischemic cardiomyopathy
DCM	dilated cardiomyopathy
LVEF	left ventricular ejection fraction
NYHA	New York Hear Association
ESC	embryonic stem cell
hiPSC	human iPSC
EHT	engineered heart tissue
HLA	human leukocyte antigen
CRISPR	clustered regularly interspaced short palindromic repeats
NK	natural killer
MSC	mesenchymal stem cell
HMGB1	high-mobility group box 1 protein
LV	left ventricle
CXCR4	C-X-C chemokine receptor 4
SDF1	stromal cell–derived factor 1
PDGFRα	platelet-derived growth factor receptor alpha
GFP	green fluorescent protein
VEGF	vascular endothelial growth factor
HGF	hepatocyte growth factor
LAD	left anterior descending artery

1. Introduction

Heart failure is a life-threatening disorder that is typically caused by various cardiac diseases, including myocardial infarction (MI), valvular heart disease, and cardiomyopathies [1–3]. Mild heart failure can be effectively treated with medications, including beta-blockers, angiotensin-converting enzyme inhibitors, and diuretics. The efficacy of pharmacological interventions is limited in patients with more severe heart failure resulting from adverse left ventricular remodeling. Consequently, surgical interventions such as left ventricular assist device (LVAD) implantation and heart transplantation are required [4,5]. However, these surgical options have limitations. Heart transplantation is the most effective treatment for severe heart failure but faces an extremely serious donor shortage worldwide. Complications associated with LVAD, such as infection and cerebral thrombosis, have a significant effect on patient outcomes. Consequently, there is an urgent need to develop new therapies to assist heart transplantation and LVAD.

Over the past two decades, cell therapies using myoblasts [6,7], bone marrow (BM) cells [8], and other stem cells [9] have emerged as promising alternatives to conventional therapies for heart failure. These therapies are thought to improve the functional recovery of failing hearts primarily through paracrine effects [6–12]. Additionally, the implantation of induced pluripotent stem cell (iPSC)–derived cardiomyocytes can contribute to the inhibition of adverse heart remodeling through paracrine effects and the supply of newly born functional myocytes to the recipient myocardium as “mechanically working cells” [10–12]. Nevertheless, concerns persist regarding cellular engraftment because these are allogeneic cell transplants. Therefore, it is necessary to consider methods that control immune rejection.

On the other hand, a number of stem cells, including BM-derived mesenchymal stem cells (BM-MSCs) and tissue stem cells, play a pivotal role in the repair of damaged tissues [13,14]. In particular, BM-MSCs can repair damaged organs by recruiting other host cells, secreting effective growth factors, or differentiating into various cells, including endothelial cells [15], thereby promoting angiogenesis and inhibiting adverse fibrosis in various injuries and diseases, including MI [8,16], injured muscles [17], and cerebral infarction [8,16–18]. By enhancing endogenous repair mechanisms with stem cells or pharmacological agents or by accelerating endogenous regenerative function, a less-invasive regenerative treatment could be offered rather than conventional cellular therapy in the future.

This article reviews the field of cardiovascular medicine with a focus on regenerative medicine. It introduces the concept of heart failure treatment using somatic cells or iPSC-derived cardiomyocytes and introduces a novel concept of regenerative medicine, namely: in vivo regenerative therapy.

2. Regenerative medicine in the cardiovascular field

Initially, regenerative therapy in the field of cardiovascular medicine was applied to arteriosclerotic obliterans, in which BM mononuclear cells (BM-MNCs) were transplanted into the affected limb by using a syringe. Angiography revealed new blood vessels, indicating an improved blood flow [19]. The therapeutic mechanism was found to involve angiogenesis via the cytokines produced by the cells, which were then applied to ischemic heart disease. In addition to BM-MNCs, autologous myoblasts have been transplanted using a syringe for ischemic cardiomyopathy (ICM) simultaneously with coronary artery bypass surgery. However, no improvement in cardiac function has been reported, and lethal arrhythmias have occurred. It has been demonstrated that reentry occurs because of myocardial tissue damage caused by the injector as a cause of arrhythmia [20]. Consequently, a methodology that does not cause myocardial tissue damage at the time of transplantation was proposed: myoblasts are cultured in vitro, processed into sheets in a temperature-responsive culture dish, and transplanted onto the heart surface [6,21]. This method was applied to patients with dilated cardiomyopathy (DCM) fitted with an LVAD, with two of four cases demonstrating improved cardiac function and LVAD weaning [22]. The sheet was also transplanted into patients with ICM, and the transplanted patients were divided into two groups: one group responded to the same treatment, whereas the other group did not respond [23,24]. Furthermore, patients

with heart failure transplanted with this tissue were shown to have a significantly prolonged life expectancy compared with a control cohort [25]. Recently, iPSC-derived cardiomyocytes have been employed to treat ICM, not only with cytokines but also to mechanically support the failing heart [26,27].

In a more recent study, the POSEIDON-DCM Trial was conducted on patients with DCM who had undergone allogeneic or autologous BM-MSC transplantation [28]. Both groups were safe, did not elicit an immune response, and demonstrated consistent therapeutic efficacy. Furthermore, the allogeneic group exhibited superior improvements in left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) classification, and other parameters compared with the autologous group. This indicates that the discrepancy in cellular functionality is attributable to the fact that autologous cells are mesenchymal stem cells (MSCs) of patients with DCM themselves, whereas allogeneic cells are derived from healthy donors. Additionally, the anti-inflammatory properties of MSCs are diminished in patients with DCM. Furthermore, genetic analysis of the patients enrolled in this clinical study and comparison of prognoses revealed that patients with pathogenic genetic abnormalities, such as titin, exhibited a less favorable response to MSC transplantation therapy than patients without such abnormalities [29].

These studies indicate that cell-based regenerative medicine is not an effective treatment for all patients with heart failure. Therefore, it is essential to identify patients who will benefit from this approach by analyzing their genetic and clinical data.

3. The current status of heart failure treatment using iPSCs and ESCs

For patients with severe heart failure who have lost a significant number of cardiomyocytes because of extensive fibrosis, it is necessary to replace the lost healthy cardiomyocytes. One potential treatment is cardiomyocyte transplantation, which involves replacing healthy cardiomyocytes at the infarction site where cardiomyocytes have been depleted. Recently, it was reported that iPSCs can be induced from somatic cells and differentiated into various cell types. It is now possible to induce high physiological and anatomical homology in cardiomyocytes from these cells [30].

Cardiomyocyte sheets can be created using iPSC-derived cardiomyocytes. A proof of concept for the same tissue was obtained using a large animal model of heart failure [10,31]. The transplanted iPSC-derived cardiomyocyte cell sheet can repeatedly contract and relax in the recipient heart and may function as the working myocardium, as the iPSC-derived cardiomyocyte sheet behaved synchronously with the recipient heart, thus indicating that tissue beating may directly affect the recipient heart [32]. iPSC-derived cardiomyocyte sheets not only function as working tissue but also secrete cytokines, including hepatocyte growth factor (HGF), which induces angiogenesis in the transplanted organ and improves blood flow [31].

To improve the efficiency of in vivo engraftment, it is necessary to suppress the immunogenicity of iPSCs and construct trophic vessels for the transplanted tissue. Neovascularization, which is the formation of new blood vessels, requires functional blood vessels with smooth muscle cells lining vascular endothelial cells. Nonclinical studies have demonstrated that the simultaneous transplantation of a large mesh with a rich vascular network and iPSC-derived cardiomyocyte sheets can maintain the viability of cardiomyocytes [33].

Prior to the application of these cells in heart failure, it is essential to examine their safety and to develop a method for their mass culture. The fundamental technology for the mass culture method has already been developed, and a clinical application of this technology is already underway [34]. Therefore, verifying their safety is crucial. A safety verification system for undifferentiated cell markers and tumorigenesis that uses non-obese diabetic/Shi-scid/IL-2Rγnull mice has already been established [35]. Furthermore, a system has been established to verify the safety of tumorigenesis and the occurrence of genetic abnormalities that promote tumorigenesis after differentiation induction [35]. The aforementioned system validated the nonclinical safety and efficacy of iPSC-derived cardiomyocyte sheets. A clinical trial led by a doctor for the transplantation of iPSC-derived cardiomyocyte sheets in patients with ICM has commenced, with reports of improvement in cardiac function at the site of transplantation [26,27].

In addition to sheet transplantation, clinical studies on the transplantation of "human iPSC (hiPSC)–derived cardiac spheroids" [36]. To further enhance clinical efficacy, research is being conducted on "iPSC-derived cardiovascular cell multilayers," which are sheets of three types of cells (cardiomyocytes, vascular endothelial cells, and vascular mural cells) layered with gelatin hydrogel microspheres and transplanted into a rat MI model. In a preclinical safety study, no tumor formation or arrhythmia was observed, thus confirming the safety of the graft [37]. Zimmermann et al. developed engineered heart tissue (EHT) by seeding cardiomyocytes in a collagen hydrogel. The EHT is a rubber band–like tissue that contracts autonomously in response to mechanical stretching stimulation. EHTs were implanted to cover the heart, and a significant improvement in cardiac function was observed in an MI model [38].

In addition to iPSCs, ESCs have been used as a source of cardiomyocytes. A clinical study of the transplantation of cardiac progenitor cells produced by differentiation induction from ESCs was conducted in 2013 for six patients with heart failure with LVEF of 35% or less and NYHA class III or IV. The transplantation of cells embedded in a fibrin patch inserted between the epicardium and the anterior wall of the heart demonstrated the absence of tumor development until six months after the procedure. Additionally, the NYHA and 6-min walk performance improved, thus indicating a certain level of efficacy [39].

The first report on the creation of BioHeart using the decellularization–recellularization method with rat hearts was published in 2008 [40]. Subsequently, in 2013, hiPSC-derived mesoderm progenitor cells were recellularized in a decellularized mouse matrix and cultured to differentiate into cardiomyocytes and other cells [41]. Furthermore, it has been reported that hiPSC-derived cardiomyocytes were transplanted into a decellularized heart of a deceased human patient [42]. To date, no human-sized decellularized cardiac matrices have been produced. There are still many issues to be addressed, such as the number of cells, cell quality, and culture system.

4. Immunological examination of iPSCs transplantation

When transplanting iPSC-derived products, it is essential to prevent immune rejection after transplantation to ensure the long-term viability of the transplanted cells. The expression pattern of cell surface glycans, such as N-glycans, expressed on iPSCs has been demonstrated to be similar to that of mature cardiomyocytes during their differentiation into cardiomyocytes; this finding may be crucial in verifying the immunogenicity of iPSC-derived cardiomyocytes [43,44]. Currently, owing to the cost of iPSC establishment and safety concerns, such as tumorigenicity, it is assumed that other established iPSCs will be used for clinical applications [45]. Human leukocyte antigen (HLA) compatibility is crucial for preventing rejection after allogeneic transplantation because HLA is a molecule that distinguishes between self and non-self in the body. HLA compatibility is correlated with organ survival after transplantation [46,47]. Therefore, it is essential to match the HLA

haplotypes during the transplantation of iPSC-derived products [45]. iPSC-derived cardiomyocytes suppress immunogenicity in allogeneic transplantation experiments in cynomolgus monkeys [48]. With the advent of gene editing technology, such as clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 [49–51], attempts have been made to establish universal iPSC lines that can avoid immune rejection after allogeneic transplantation by adjusting HLA expression on the iPSC surface with CRISPR/Cas9. Therefore, it is anticipated that the transplantation of HLA-homologous iPSCs established by the Center for iPS Cell Research and Application of Kyoto University to HLA-matched patients will be immunologically effective in clinical applications. HLA can be broadly divided into class I (HLA-A, HLA-B, HLA-C, HLA-E, HLA-F, and HLA-G) and class II (HLA-DP, HLA-DQ, and HLA-DR). These functions can be classified into two major categories. The first is to trigger an immune response by $CD8^+$ and $CD4^+$ T cells via antigen peptides. The second is to function as a ligand for T cells or natural killer (NK) cells to recognize non-self and self [52,53]. In the latter function, T cells recognize HLA haplotypes that are different from the self and consider them as non-self. Conversely, NK cells cannot recognize HLA, which is identical to the self; therefore, these cells are excluded from the body [54,55]. To suppress immunogenicity, it is essential to conduct basic research to elucidate the mechanism of immune response when iPSC-derived cardiomyocytes are transplanted.

4.1. Regulation of posttransplantation immune responses by T cells

To control immune rejection by T cells, iPSCs with a homozygous tridentate HLA haplotype are banked, and iPSC lines established from these iPSC lines are used for allogeneic transplantation in clinical settings [45]. However, only approximately 40% of the Japanese population can be covered by the banked iPSC lines [56]. Furthermore, although HLA-compatible dopaminergic neuron transplantation in monkeys has been demonstrated to suppress immune rejection by T cells without the use of immunosuppressive agents [57], it has been reported that immunosuppressive agents must be employed in HLA-compatible cardiomyocyte transplantation [48]. In HLA-compatible allogeneic transplantation, immunogenicity varies depending on the differentiation products. Although methods to suppress posttransplantation immune responses by T cells are being established by combining HLA matching with immunosuppressive agents as needed, it has been reported that HLA expression is poor in some differentiation products such as iPSC-derived cardiomyocytes and dopamine cells [57,58]. Furthermore, HLA-matched transplants have been reported to cause immune rejection by NK cells [48,57,58]. Immune responses using HLA-negative iPSCs generated using CRISPR/Cas9 have been investigated to avoid T cell–mediated immune responses. HLA class 1 expression can be suppressed by the deletion of its subunit, namely, the *B2M* gene [59], and HLA class 2 expression can be suppressed by the deletion of its transcription factor, namely, the *CIITA* gene [60]. Despite the ability of iPSC-derived cardiomyocytes and vascular endothelial cells lacking the *B2M* and *CIITA* genes to suppress immune responses to other T cells, they do not express HLA class 1 or 2, thus resulting in NK cell activation [61,62]. Therefore, immune rejection by T and NK cells should be avoided after transplantation by editing HLA expression on iPSC surfaces, and universal cell lines that can be used for transplantation regardless of HLA haplotypes or differentiation products should be established. Two approaches were proposed. The first is the complete suppression of HLA expression on the cell surface, which suppresses the immune response of T cells. The second mechanism involves the expression of ligands that suppress NK cell cytotoxicity.

4.2. Regulation of the posttransplant immune response by NK cells

Reports on immune responses by NK cells include iPSC-derived cardiomyocytes and dopamine cells with low HLA expression [48,57,58]. NK cell–activating ligands, such as CD112 and CD155, are expressed in iPSC-derived cardiomyocytes [58]. Regardless of HLA expression, activating ligands such as major histocompatibility complex class I chain-related protein A, nectin cell adhesion molecule 2, and poliovirus receptor are present in iPSC-derived fibroblasts, and immune responses by autologous NK cells have also been observed. Additionally, iPSC-derived cardiomyocytes or vascular endothelial cells without HLA expression have been established as universal cell lines that are targets of NK cells [61,62]. Some reports have indicated that certain ligands may be required for NK cells to evade posttransplant immune responses. For example, Gornalusse et al. reported that ESCs selectively expressing only HLA-E could evade the immune response of $CD45^+$ NK cells [63]. Additionally, iPSC-derived cardiomyocytes and vascular endothelial cells overexpressing CD47, which is the inhibitory ligand of NK cells, evaded rejection by NK cells after transplantation, and long-term engraftment was achieved [64]. Furthermore, in a study using iPSC-derived $CD43^+$ blood cells in which only HLA-A/B was deleted by CRISPR/CAS9 while retaining HLA-E/F/G in addition to HLA-C, immune responses associated with NK cells and T cells were avoided by matching only HLA-C [65]. This report suggests that matching only HLA-C may avoid immune responses associated with NK cells in addition to immune responses associated with T cells. It has also been reported that the 12 HLA-C haplotypes cover approximately 95% of the population, and iPSCs of these 12 HLA-C prototypes are being investigated for use as semi-universal iPSCs [66]. Numerous activating and inhibitory ligands are involved in the immune response of NK cells, which is defined by the balance of the signals mediated by these ligands. The extensive variety of ligands makes it challenging to eliminate all activating ligands or induce the expression of all inhibitory ligands in cells. Therefore, it is essential to determine the combination of ligands that most efficiently and effectively suppresses the immune response of NK cells after transplantation.

4.3. Other reports of immune tolerance after transplantation

In addition to HLA matching with immunosuppressive agents and the generation of universal iPSCs, several methods have been reported to induce a state of posttransplant immunity and achieve long-term engraftment. Autologous MSCs can be transplanted simultaneously with iPSC-derived cardiomyocytes to induce post-transplant immune tolerance [67]. There are also reports of a method to induce specific immune tolerance to iPSC-derived cardiomyocytes by establishing mixed chimerism in the recipient [68], and a method to induce immune tolerance after organ transplantation by inducing regulatory T cells from recipient-derived T cells and reinjecting them [69,70].

5. Current status and prospects of regenerative therapies in the body

In the human body, several endogenous regenerative mechanisms repair damaged organs. Several stem cells, including BM-MSCs, have the potential to repair damaged organs by recruiting other host cells [13–15]. The activation and augmentation of endogenous repair mechanisms with pharmacological agents harboring stem cells are promising because they are less invasive than conventional cellular therapies.

Herein, we summarize several self-endogenous regenerative therapies for heart failure.

5.1. High-mobility group box 1 protein (HMGB1) recombinant fragment

HMGB1, which is a non-histone nuclear protein that regulates chromatin structure [71–73], has two opposing effects: HMGB1 released from necrotic cells activates macrophages and neutrophils, thereby accelerating inflammation in injured tissue [73]. By contrast, HMGB1 also plays an important role as a regenerative factor that enhances the mobilization of alpha platelet-derived growth factor receptor-positive (PDGFRα+) mesenchymal cells from the BM to damaged organs [71–75]. PDGFRα is a representative marker of BM-MSCs [76]. The inflammatory responses induced by HMGB1 are mediated by the binding of specific HMGB1 domains to toll-like receptor-2/-4 or the receptor for advanced glycation end products [77,78]. A novel HMGB1 fragment was created by removing the previously reported functional domains of HMGB1 associated with systemic inflammatory responses [71]. Several studies have demonstrated the potential of this HMGB1 fragment to inhibit the deterioration of cardiac performance in various models of heart failure [42,72]. Kido et al. reported that an improvement in LVEF and a reduction in myocardial fibrosis were achieved by the systemic injection of the HMGB1 fragment in a DCM hamster model [72]. Similar results, including an improvement in left ventricle (LV) contraction and inhibition of adverse LV remodeling, have also been observed in a rat MI model [72].

HMGB1 plays a role in the aggregation of PDGFRα+ BM-MSCs around vessels in the BM and that these BM-MSCs migrate via the blood circulatory system [75]. With regard to the mechanism by which BM-MSC home to damaged tissue via HMGB1 fragment, C-X-C chemokine receptor 4 (CXCR4), which is a receptor of stromal cell–derived factor 1 (SDF1), plays a pivotal role in the migration and proliferation of various stem cells, including BM-MSCs [79,80]. In vivo and in vitro studies have demonstrated that HMGB1 can induce the overexpression of CXCR4 on the surface of BM-MSCs [13]. In ischemic lesions, the tumor microenvironment, fibroblasts, epithelial cells, and endothelial cells secrete SDF1 [75,79–81]. Indeed, significant elevations in SDF1 levels have been observed in the hearts of rats with MI, particularly in the peri-infarct region [71].

In the MI model, rats with green fluorescent protein (GFP)–positive BM cells exhibited a significant recruitment of GFP+/PDGFRα+ BM cells to the peri-infarction area in response to HMGB1 fragment administration [71]. Real-time polymerase chain reaction analysis also demonstrated significant expression of various growth factors, including vascular endothelial growth factor (VEGF) A, HGF, and tumor necrosis factor–stimulated gene 6, in the damaged heart following the injection of the HMGB1 fragment [71,72]. Therefore, it can be concluded that the HMGB1 fragment induces BM-MSC homing to damaged cardiac tissues via the SDF1-CXCR4 signaling complex, which in turn promotes vasculogenesis in ischemic lesions.

The differentiation ability of recruited BM-MSCs is also a crucial factor associated with regenerative effects in damaged heart tissue. Several in vitro and in vivo studies have revealed the multipotency of BM-MSCs as endothelial cells, pericyte, and smooth muscle cells [15]. The recruited GFP+/PDGFRα+ cells may have differentiated into vessel constituent cells, such as vascular endothelial cells or pericytes, in the peri-infarcted area [71].

HMGB1 also exerts a regenerative effect on adverse LV remodeling [82]. Takahashi et al. demonstrated that direct injection of HMGB1 into the myocardium can attenuate local myocardial inflammation, thus leading to the inhibition of cardiomyocyte hypertrophy and the expansion of fibrosis [82].

5.2. SDF1

The SDF1 or “SDF1 to CXCR4” (its receptor) complex is one of the most representative regulators of endogenous tissue repair in the human body [80–84]. Ischemic cardiac damage causes SDF1 overexpression in ischemic cells, which induces the recruitment of both BM-MSCs and cardiac stem cells to the damaged heart tissue [71,82–84]. In addition to the homing ability of these stem cells to ischemic heart tissue, SDF1 inhibits cardiomyocyte cell death, thereby promoting angiogenesis and preventing adverse fibrosis [85–87].

This has led to the development of gene therapy using SDF1 at various dosages. JVS100, which is a non-viral DNA plasmid encoding human SDF1, is used in regenerative clinical trials with SDF1 [84,87,88]. On the basis of the results of a preclinical study and a subsequent phase I clinical trial with JVS-100 that assessed its safety and potential efficacy [87,88], a randomized phase I clinical trial using JVS-100 was initiated in patients with ICM [84]. Compared with the placebo group, there was an improvement in LVEF and N-terminal pro-brain natriuretic peptide serum levels and an increase in cardiac output at one year after a single administration of JVS-100 [84]. Although no adverse events were observed, the present study was performed using an endomyocardial injection of SDF1. This study aimed to facilitate progress in regenerative drug discovery. Future studies should focus on developing methods of drug administration in a more systematic and safer manner.

5.3. ONO1301: a synthetic prostacyclin agonist

Prostacyclin is an endogenous factor that facilitates the regeneration of damaged tissues and organs [89–91]. Although the therapeutic effects of prostacyclin analogs could theoretically be useful for adverse LV remodeling after ischemic heart damage, the use of these agents in clinical practice has been limited by their short half-lives [92–94].

ONO-1301 is a novel synthetic prostacyclin agonist that exhibits prolonged prostacyclin activity and thromboxane synthase inhibitory activity. Their chemical stability was attributed to the absence of typical prostanoid structures [93,94]. ONO-1301 stimulates the production of intracellular cyclic adenosine monophosphate by binding to the prostaglandin I2 receptor in vascular endothelial cells, smooth muscle cells, or fibroblasts. This leads to the release of various growth factors, including VEGF, HGF, and SDF1, into damaged heart tissue [92–97]. In our department, a slow-release system for ONO-1301 was developed using the polylactic co-glycolic acid polymerization technique. The sustained-release delivery of ONO-1301 (ONO-1301SR) demonstrated the robust inhibition of LV fibrosis following MI and improved cardiac function through neovascularization in the peri-infarction area [94,95,97]. Additionally, several preclinical studies employing ONO-1301SR have demonstrated its therapeutic effects in various tissue injury models, including aortic valve stenosis, pulmonary hypertension, and critical limb ischemia [96,98,99].

ONO-1301 has also been shown to promote tissue repair by inducing the migration of BM-MSCs into ischemic heart tissue [93]. An in vitro study demonstrated that BM cell migration was significantly enhanced by ONO-1301 and was inhibited by the use of BM cells with CXCR4 antagonist (AMD3100) [93]. The intravenous administration of ONO-1301 significantly enhanced the recruitment of BM cells to the peri-infarction area. Although SDF1 expression is generally increased in ischemic tissues, including MI [71], ONO-1301 can enhance SDF1 expression in fibroblasts, endothelial cells, and smooth muscle cells in the infarct border zone. ONO-1301 treatment improves cardiac function by inducing

neovascularization and inhibiting fibrosis in damaged tissue in acute or chronic MI models [93,95,97]. ONO-1301 has been demonstrated to enhance the recruitment of BM cells to ischemic heart lesions via the SDF1/7CXCR4 signaling pathway. This may lead to tissue repair via paracrine effects or differentiation activity of the recruited BM cells.

5.4. Large animal study of HMGB1 and ONO-1301

The purpose of large animal studies is to evaluate the efficacy and safety of mechanisms demonstrated in vitro and in small animals in a manner that is similar to clinical practice. A major advantage of large animal studies is the ability to perform multimodal imaging evaluations for efficacy assessment.

Our primary animal model used was porcine ICM. This model was created by placing a special ring called an Ameroid Constrictor, which gradually occluded the lumen by absorbing moisture at the ostium of the porcine left anterior descending artery (LAD), thus ultimately creating an ICM model because of LAD occlusion.

Yajima et al. have evaluated the efficacy of ONO-1301 in a porcine ICM model [97]. This study demonstrated an improvement in cardiac function compared with the control by applying an omental flap to the surface of the heart, in addition to the administration of ONO-1301. Other than histological and molecular biological assessments, the following have been used as imaging modalities to macroscopically demonstrate improvements in cardiac function and myocardial blood flow: echocardiography, cardiac MRI to assess myocardial strain, ^{13}N-ammonia positron emission tomography to assess myocardial blood flow, and coronary catheterization to assess myocardial blood flow reserve.

Ito et al. conducted a study evaluated the efficacy of the HMGB1 fragment in a porcine ICM model (submitted for publication). This study demonstrated that systemic intravenous administration of HMGB1 fragment improved cardiac function compared with the control. In this study, echocardiography, histologic evaluation, and molecular biological evaluation, as well as quantitative assessment of damaged and fibrotic myocardial tissue using late gadolinium–enhanced cardiac MRI and coronary pressure wire study to assess coronary flow reserve and resistive reserve ratio, were performed to macroscopically demonstrate improvements in myocardial blood flow, myocardial fibrosis suppression, and cardiac function.

ONO-1301 and HMGB1 both activate the self-tissue repair capacity of MSCs via minimally invasive intravenous administration. Large animal studies have shown an improvement in myocardial blood flow reserve through angiogenesis, suppression of myocardial fibrosis around the infarct site, inhibition of myocardial cell hypertrophy, and reactivation of the hibernating myocardium. In addition, the improvement in cardiac function appears to extend beyond the LAD region, where the infarction occurs, which may benefit multivessel ICM in clinical practice.

These data provide a more macroscopic understanding of the mechanisms demonstrated in vitro and suggest potential clinical efficacy. Given that similar imaging assessments can be performed in clinical practice, these findings may support the mechanisms of therapeutic effects in clinical settings. Additionally, regenerative therapy achieves efficacy through the interaction of various factors, and there are both responders and non-responders to treatment [24,29]. When exploring responders and their predictive factors, focusing on imaging modalities that have shown efficacy in large animal studies may allow for a more efficient evaluation. Research on the predictive factors for responders is crucial for expanding the indications for regenerative therapies, and large animal studies play an important role in this regard. On the basis of these studies, the first human phase I/IIa clinical trial using ONO-1301SR for patients with ICM was performed [100], and the use of HMGB1 has been initiated and is ongoing.

Drug-induced regenerative therapy is a good alternative option for heart failure, particularly in patients with refractory heart failure who are using conventional medication. It can easily be combined not only with medication but also with surgical procedures such as coronary artery bypass grafting or LVAD implantation. Further clarification of the mechanism of cell-based regenerative therapy will facilitate progress in regenerative drug discovery and will lead to an increase in the use of drug-induced regenerative therapy and minimally invasive therapy for patients with heart failure.

6. Conclusion

This review discusses the fundamental clinical applications of regenerative medicine in cardiovascular medicine. Regenerative medicine covers a wide range of areas, including cell and tissue transplantation, treatment based on regenerative mechanisms in the body, and organ creation using regenerative medicine technology. We hope that these technologies will be applied clinically in the future and become a goal for patients with intractable circulatory diseases.

Declaration of competing interest

This work was partially funded by StemRIM Inc.

Acknowledgments

This work was supported by AMED (grant numbers: 22bm0204003h, and 17ek0109095h), KAKENHI (grant numbers: 15K10212, 21249075, and 26293311), and MHLW Research (grant number: 201415027). This work was also funded by StemRIM Inc. partially.

References

[1] Appoo J, Norris C, Merali S, Graham MM, Koshal A, Knudtson ML, et al. Long-term outcome of isolated coronary artery bypass surgery in patients with severe left ventricular dysfunction. Circulation 2004;110:II13–7.
[2] Cohn JN. Heart failure in 2013: continue what we are doing to treat HF, but do it better. Nat Rev Cardiol 2014;11:69–70.
[3] Jessup M, Brozena S. Heart failure. N Engl J Med 2003;348:2007–18.
[4] Miyagawa S, Sawa Y. Building a new strategy for treating heart failure using Induced Pluripotent Stem Cells. J Cardiol 2018;72:445–8.
[5] Miyagawa S, Toda K, Nakamura T, Yoshikawa Y, Fukushima S, Saito S, et al. Building a bridge to recovery: the pathophysiology of LVAD-induced reverse modeling in heart failure. Surg Today 2016;46:149–54.
[6] Miyagawa S, Sawa Y, Sakakida S, Taketani S, Kondoh H, Memon IA, et al. Tissue cardiomyoplasty using bioengineered contractile cardiomyocyte sheets to repair damaged myocardium: their integration with recipient myocardium. Transplantation 2005;80:1586–95.
[7] Saito S, Miyagawa S, Sakaguchi T, Imanishi Y, Iseoka H, Nishi H, et al. Myoblast sheet can prevent the impairment of cardiac diastolic function and late remodeling after left ventricular restoration in ischemic cardiomyopathy. Transplantation 2012;93:1108–15.
[8] Nagaya N, Kangawa K, Itoh T, Iwase T, Murakami S, Miyahara Y, et al. Transplantation of mesenchymal stem cells improves cardiac function in a rat model of dilated cardiomyopathy. Circulation 2005;112:1128–35.
[9] Yang L, Soonpaa MH, Adler ED, Roepke TK, Kattman SJ, Kennedy M, et al. Human cardiovascular progenitor cells develop from a KDR+ embryonic-stem-cell-derived population. Nature 2008;453:524–8.
[10] Kawamura M, Miyagawa S, Miki K, Saito A, Fukushima S, Higuchi T, et al. Feasibility, safety, and therapeutic efficacy of human induced pluripotent stem cell-derived cardiomyocyte sheets in a porcine ischemic cardiomyopathy model. Circulation 2012;126:S29–37.
[11] Miki K, Uenaka H, Saito A, Miyagawa S, Sakaguchi T, Higuchi T, et al. Bioengineered myocardium derived from induced pluripotent stem cells improves cardiac function and attenuates cardiac remodeling following chronic myocardial infarction in rats. Stem Cells Transl Med 2012;1:430–7.
[12] Miyagawa S, Fukushima S, Imanishi Y, Kawamura T, Mochizuki-Oda N, Masuda S, et al. Building A new treatment for heart failure-transplantation of

induced pluripotent stem cell-derived cells into the heart. Curr Gene Ther 2016;16:5–13.
[13] Kucharzewski M, Rojczyk E, Wilemska-Kucharzewska K, Wilk R, Hudecki J, Los MJ. Novel trends in application of stem cells in skin wound healing. Eur J Pharmacol 2019;843:307–15.
[14] Maxson S, Lopez EA, Yoo D, Danilkovitch-Miagkova A, Leroux MA. Concise review: role of mesenchymal stem cells in wound repair. Stem Cells Transl Med 2012;1:142–9.
[15] Oswald J, Boxberger S, Jorgensen B, Feldmann S, Ehninger G, Bornhauser M, et al. Mesenchymal stem cells can be differentiated into endothelial cells in vitro. Stem Cell 2004;22:377–84.
[16] Golpanian S, El-Khorazaty J, Mendizabal A, DiFede DL, Suncion VY, Karantalis V, et al. Effect of aging on human mesenchymal stem cell therapy in ischemic cardiomyopathy patients. J Am Coll Cardiol 2015;65:125–32.
[17] Linard C, Brachet M, L'Homme B, Strup-Perrot C, Busson E, Bonneau M, et al. Long-term effectiveness of local BM-MSCs for skeletal muscle regeneration: a proof of concept obtained on a pig model of severe radiation burn. Stem Cell Res Ther 2018;9:299.
[18] Fukuda Y, Horie N, Satoh K, Yamaguchi S, Morofuji Y, Hiu T, et al. Intra-arterial transplantation of low-dose stem cells provides functional recovery without adverse effects after stroke. Cell Mol Neurobiol 2015;35:399–406.
[19] Tateishi-Yuyama E, Matsubara H, Murohara T, Ikeda U, Shintani S, Masaki H, et al. Therapeutic angiogenesis for patients with limb ischaemia by autologous transplantation of bone-marrow cells: a pilot study and a randomised controlled trial. Lancet 2002;360:427–35.
[20] Menasche P, Alfieri O, Janssens S, McKenna W, Reichenspurner H, Trinquart L, et al. The Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) trial: first randomized placebo-controlled study of myoblast transplantation. Circulation 2008;117:1189–200.
[21] Okano T, Yamada N, Sakai H, Sakurai Y. A novel recovery system for cultured cells using plasma-treated polystyrene dishes grafted with poly(N-isopropylacrylamide). J Biomed Mater Res 1993;27:1243–51.
[22] Yoshikawa Y, Miyagawa S, Toda K, Saito A, Sakata Y, Sawa Y. Myocardial regenerative therapy using a scaffold-free skeletal-muscle-derived cell sheet in patients with dilated cardiomyopathy even under a left ventricular assist device: a safety and feasibility study. Surg Today 2018;48:200–10.
[23] Miyagawa S, Domae K, Yoshikawa Y, Fukushima S, Nakamura T, Saito A, et al. Phase I clinical trial of autologous stem cell-sheet transplantation therapy for treating cardiomyopathy. J Am Heart Assoc 2017;6.
[24] Kainuma S, Miyagawa S, Toda K, Yoshikawa Y, Hata H, Yoshioka D, et al. Long-term outcomes of autologous skeletal myoblast cell-sheet transplantation for end-stage ischemic cardiomyopathy. Mol Ther 2021;29:1425–38.
[25] Miyagawa S, Kainuma S, Imanishi Y, Shimamoto T, Nitta Y, Matsuo C, et al. Prognosis of patients with heart failure receiving autologous myoblast patches - comparison of single-arm trial data to registry data. Circ J 2022. https://doi.org/10.1253/circj.CJ-22-0319.
[26] Miyagawa S, Kainuma S, Kawamura T, Suzuki K, Ito Y, Iseoka H, et al. Case report: transplantation of human induced pluripotent stem cell-derived cardiomyocyte patches for ischemic cardiomyopathy. Front Cardiovasc Med 2022;9:950829.
[27] Kawamura T, Ito Y, Ito E, Takeda M, Mikami T, Taguchi T, et al. Safety confirmation of induced pluripotent stem cell-derived cardiomyocyte patch transplantation for ischemic cardiomyopathy: first three case reports. Front Cardiovasc Med 2023;10:1182209.
[28] Hare JM, DiFede DL, Rieger AC, Florea V, Landin AM, El-Khorazaty J, et al. Randomized comparison of allogeneic versus autologous mesenchymal stem cells for nonischemic dilated cardiomyopathy: POSEIDON-DCM trial. J Am Coll Cardiol 2017;69:526–37.
[29] Rieger AC, Myerburg RJ, Florea V, Tompkins BA, Natsumeda M, Premer C, et al. Genetic determinants of responsiveness to mesenchymal stem cell injections in non-ischemic dilated cardiomyopathy. EBioMedicine 2019;48:377–85.
[30] Yu T, Miyagawa S, Miki K, Saito A, Fukushima S, Higuchi T, et al. In vivo differentiation of induced pluripotent stem cell-derived cardiomyocytes. Circ J 2013;77:1297–306.
[31] Ishida M, Miyagawa S, Saito A, Fukushima S, Harada A, Ito E, et al. Transplantation of human-induced pluripotent stem cell-derived cardiomyocytes is superior to somatic stem cell therapy for restoring cardiac function and oxygen consumption in a porcine model of myocardial infarction. Transplantation 2019;103:291–8.
[32] Higuchi T, Miyagawa S, Pearson JT, Fukushima S, Saito A, Tsuchimochi H, et al. Functional and electrical integration of induced pluripotent stem cell-derived cardiomyocytes in a myocardial infarction rat heart. Cell Transplant 2015;24:2479–89.
[33] Kawamura M, Miyagawa S, Fukushima S, Saito A, Miki K, Ito E, et al. Enhanced survival of transplanted human induced pluripotent stem cell-derived cardiomyocytes by the combination of cell sheets with the pedicled omental flap technique in a porcine heart. Circulation 2013;128:S87–94.
[34] Matsuura K, Wada M, Shimizu T, Haraguchi Y, Sato F, Sugiyama K, et al. Creation of human cardiac cell sheets using pluripotent stem cells. Biochem Biophys Res Commun 2012;425:321–7.
[35] Miyagawa S, Kawamura T, Ito E, Takeda M, Iseoka H, Yokoyama J, et al. Preclinical evaluation of the efficacy and safety of human induced pluripotent stem cell-derived cardiomyocyte patch. Stem Cell Res Ther 2024;15:73.
[36] Soma Y, Tani H, Morita-Umei Y, Kishino Y, Fukuda K, Tohyama S. Pluripotent stem cell-based cardiac regenerative therapy for heart failure. J Mol Cell Cardiol 2024;187:90–100.
[37] Osada H, Kawatou M, Fujita D, Tabata Y, Minatoya K, Yamashita JK, et al. Therapeutic potential of clinical-grade human induced pluripotent stem cell-derived cardiac tissues. JTCVS Open 2021;8:359–74.
[38] Jebran AF, Tiburcy M, Biermann D, Balfanz P, Didie M, Karikkineth BC, et al. Transmural myocardial repair with engineered heart muscle in a rat model of heterotopic heart transplantation - a proof-of-concept study. J Mol Cell Cardiol 2022;168:3–12.
[39] Menasche P, Vanneaux V, Hagege A, Bel A, Cholley B, Parouchev A, et al. Transplantation of human embryonic stem cell-derived cardiovascular progenitors for severe ischemic left ventricular dysfunction. J Am Coll Cardiol 2018;71:429–38.
[40] Ott HC, Matthiesen TS, Goh SK, Black LD, Kren SM, Netoff TI, et al. Perfusion-decellularized matrix: using nature's platform to engineer a bioartificial heart. Nat Med 2008;14:213–21.
[41] Lu TY, Lin B, Kim J, Sullivan M, Tobita K, Salama G, et al. Repopulation of decellularized mouse heart with human induced pluripotent stem cell-derived cardiovascular progenitor cells. Nat Commun 2013;4:2307.
[42] Guyette JP, Charest JM, Mills RW, Jank BJ, Moser PT, Gilpin SE, et al. Bioengineering human myocardium on native extracellular matrix. Circ Res 2016;118:56–72.
[43] Kawamura T, Miyagawa S, Fukushima S, Yoshida A, Kashiyama N, Kawamura A, et al. N-glycans: phenotypic homology and structural differences between myocardial cells and induced pluripotent stem cell-derived cardiomyocytes. PLoS One 2014;9:e111064.
[44] Kawamura T, Miyagawa S, Fukushima S, Kashiyama N, Kawamura A, Ito E, et al. Structural changes in N-glycans on induced pluripotent stem cells differentiating toward cardiomyocytes. Stem Cells Translational Medicine 2015;4:1258–64.
[45] Nakatsuji N, Nakajima F, Tokunaga K. HLA-haplotype banking and iPS cells. Nat Biotechnol 2008;26:739–40.
[46] Trowsdale J, Knight JC. Major histocompatibility complex genomics and human disease. Annu Rev Genom Hum Genet 2013;14:301–23.
[47] Montgomery RA, Tatapudi VS, Leffell MS, Zachary AA. HLA in transplantation. Nat Rev Nephrol 2018;14:558–70.
[48] Kawamura T, Miyagawa S, Fukushima S, Maeda A, Kashiyama N, Kawamura A, et al. Cardiomyocytes derived from MHC-homozygous induced pluripotent stem cells exhibit reduced allogeneic immunogenicity in MHC-matched non-human primates. Stem Cell Rep 2016;6:312–20.
[49] Jinek M, Chylinski K, Fonfara I, Hauer M, Doudna JA, Charpentier E. A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity. Science 2012;337:816–21.
[50] Cong L, Ran FA, Cox D, Lin S, Barretto R, Habib N, et al. Multiplex genome engineering using CRISPR/Cas systems. Science 2013;339:819–23.
[51] Mali P, Yang L, Esvelt KM, Aach J, Guell M, DiCarlo JE, et al. RNA-guided human genome engineering via Cas9. Science 2013;339:823–6.
[52] Felix NJ, Allen PM. Specificity of T-cell alloreactivity. Nat Rev Immunol 2007;7:942–53.
[53] Siu JHY, Surendrakumar V, Richards JA, Pettigrew GJ. T cell allorecognition pathways in solid organ transplantation. Front Immunol 2018;9:2548.
[54] Long EO, Kim HS, Liu D, Peterson ME, Rajagopalan S. Controlling natural killer cell responses: integration of signals for activation and inhibition. Annu Rev Immunol 2013;31:227–58.
[55] Martinez-Lostao L, Anel A, Pardo J. How do cytotoxic lymphocytes kill cancer cells? Clin Cancer Res 2015;21:5047–56.
[56] Okita K, Matsumura Y, Sato Y, Okada A, Morizane A, Okamoto S, et al. A more efficient method to generate integration-free human iPS cells. Nat Methods 2011;8:409–12.
[57] Morizane A, Kikuchi T, Hayashi T, Mizuma H, Takara S, Doi H, et al. MHC matching improves engraftment of iPSC-derived neurons in non-human primates. Nat Commun 2017;8:385.
[58] Nakamura Y, Miyagawa S, Yoshida S, Sasawatari S, Toyofuku T, Toda K, et al. Natural killer cells impede the engraftment of cardiomyocytes derived from induced pluripotent stem cells in syngeneic mouse model. Sci Rep 2019;9:10840.
[59] Riolobos L, Hirata RK, Turtle CJ, Wang PR, Gornalusse GG, Zavajlevski M, et al. HLA engineering of human pluripotent stem cells. Mol Ther 2013;21:1232–41.
[60] DeSandro A, Nagarajan UM, Boss JM. The bare lymphocyte syndrome: molecular clues to the transcriptional regulation of major histocompatibility complex class II genes. Am J Hum Genet 1999;65:279–86.
[61] Mattapally S, Pawlik KM, Fast VG, Zumaquero E, Lund FE, Randall TD, et al. Human leukocyte antigen class I and II knockout human induced pluripotent stem cell-derived cells: universal donor for cell therapy. J Am Heart Assoc 2018;7:e010239.
[62] Deuse T, Hu X, Gravina A, Wang D, Tediashvili G, De C, et al. Hypoimmunogenic derivatives of induced pluripotent stem cells evade immune rejection in fully immunocompetent allogeneic recipients. Nat Biotechnol 2019;37:252–8.

[63] Gornalusse GG, Hirata RK, Funk SE, Riolobos L, Lopes VS, Manske G, et al. HLA-E-expressing pluripotent stem cells escape allogeneic responses and lysis by NK cells. Nat Biotechnol 2017;35:765–72.
[64] Han X, Wang M, Duan S, Franco PJ, Kenty JH, Hedrick P, et al. Generation of hypoimmunogenic human pluripotent stem cells. Proc Natl Acad Sci U S A 2019;116:10441–6.
[65] Xu H, Wang B, Ono M, Kagita A, Fujii K, Sasakawa N, et al. Targeted disruption of HLA genes via CRISPR-cas9 generates iPSCs with enhanced immune compatibility. Cell Stem Cell 2019;24:566–578 e7.
[66] Koga K, Wang B, Kaneko S. Current status and future perspectives of HLA-edited induced pluripotent stem cells. Inflamm Regen 2020;40:23.
[67] Yoshida S, Miyagawa S, Toyofuku T, Fukushima S, Kawamura T, Kawamura A, et al. Syngeneic mesenchymal stem cells reduce immune rejection after induced pluripotent stem cell-derived allogeneic cardiomyocyte transplantation. Sci Rep 2020;10:4593.
[68] Yoshida S, Miyagawa S, Matsuzaki T, Ishii Y, Fukuda-Kawaguchi E, Kawamura T, et al. Chimerism through the activation of invariant natural killer T cells prolongs graft survival after transplantation of induced pluripotent stem cell-derived allogeneic cardiomyocytes. PLoS One 2022;17:e0264317.
[69] Todo S, Yamashita K. Anti-donor regulatory T cell therapy in liver transplantation. Hum Immunol 2018;79:288–93.
[70] Thomson AW, Humar A, Lakkis FG, Metes DM. Regulatory dendritic cells for promotion of liver transplant operational tolerance: rationale for a clinical trial and accompanying mechanistic studies. Hum Immunol 2018;79:314–21.
[71] Goto T, Miyagawa S, Tamai K, Matsuura R, Kido T, Kuratani T, et al. High-mobility group box 1 fragment suppresses adverse post-infarction remodeling by recruiting PDGFRalpha-positive bone marrow cells. PLoS One 2020;15:e0230392.
[72] Kido T, Miyagawa S, Goto T, Tamai K, Ueno T, Toda K, et al. The administration of high-mobility group box 1 fragment prevents deterioration of cardiac performance by enhancement of bone marrow mesenchymal stem cell homing in the delta-sarcoglycan-deficient hamster. PLoS One 2018;13:e0202838.
[73] Lotze MT, Tracey KJ. High-mobility group box 1 protein (HMGB1): nuclear weapon in the immune arsenal. Nat Rev Immunol 2005;5:331–42.
[74] Aikawa E, Fujita R, Kikuchi Y, Kaneda Y, Tamai K. Systemic high-mobility group box 1 administration suppresses skin inflammation by inducing an accumulation of PDGFRalpha(+) mesenchymal cells from bone marrow. Sci Rep 2015;5:11008.
[75] Tamai K, Yamazaki T, Chino T, Ishii M, Otsuru S, Kikuchi Y, et al. PDGFRalpha-positive cells in bone marrow are mobilized by high mobility group box 1 (HMGB1) to regenerate injured epithelia. Proc Natl Acad Sci U S A 2011;108:6609–14.
[76] Takashima Y, Era T, Nakao K, Kondo S, Kasuga M, Smith AG, et al. Neuroepithelial cells supply an initial transient wave of MSC differentiation. Cell 2007;129:1377–88.
[77] Park JS, Gamboni-Robertson F, He Q, Svetkauskaite D, Kim JY, Strassheim D, et al. High mobility group box 1 protein interacts with multiple Toll-like receptors. Am J Physiol Cell Physiol 2006;290:C917–24.
[78] Yanai H, Ban T, Taniguchi T. High-mobility group box family of proteins: ligand and sensor for innate immunity. Trends Immunol 2012;33:633–40.
[79] Nagasawa T, Hirota S, Tachibana K, Takakura N, Nishikawa S, Kitamura Y, et al. Defects of B-cell lymphopoiesis and bone-marrow myelopoiesis in mice lacking the CXC chemokine PBSF/SDF-1. Nature 1996;382:635–8.
[80] Orimo A, Gupta PB, Sgroi DC, Arenzana-Seisdedos F, Delaunay T, Naeem R, et al. Stromal fibroblasts present in invasive human breast carcinomas promote tumor growth and angiogenesis through elevated SDF-1/CXCL12 secretion. Cell 2005;121:335–48.
[81] Kinoshita H, Yashiro M, Fukuoka T, Hasegawa T, Morisaki T, Kasashima H, et al. Diffuse-type gastric cancer cells switch their driver pathways from FGFR2 signaling to SDF1/CXCR4 axis in hypoxic tumor microenvironments. Carcinogenesis 2015;36:1511–20.
[82] Yamaguchi J, Kusano KF, Masuo O, Kawamoto A, Silver M, Murasawa S, et al. Stromal cell-derived factor-1 effects on ex vivo expanded endothelial progenitor cell recruitment for ischemic neovascularization. Circulation 2003;107:1322–8.
[83] Askari AT, Unzek S, Popovic ZB, Goldman CK, Forudi F, Kiedrowski M, et al. Effect of stromal-cell-derived factor 1 on stem-cell homing and tissue regeneration in ischaemic cardiomyopathy. Lancet 2003;362:697–703.
[84] Chung ES, Miller L, Patel AN, Anderson RD, Mendelsohn FO, Traverse J, et al. Changes in ventricular remodelling and clinical status during the year following a single administration of stromal cell-derived factor-1 non-viral gene therapy in chronic ischaemic heart failure patients: the STOP-HF randomized Phase II trial. Eur Heart J 2015;36:2228–38.
[85] Cheng K, Malliaras K, Smith RR, Shen D, Sun B, Blusztajn A, et al. Human cardiosphere-derived cells from advanced heart failure patients exhibit augmented functional potency in myocardial repair. JACC Heart Fail 2014;2:49–61.
[86] Dong F, Harvey J, Finan A, Weber K, Agarwal U, Penn MS. Myocardial CXCR4 expression is required for mesenchymal stem cell mediated repair following acute myocardial infarction. Circulation 2012;126:314–24.
[87] Penn MS, Pastore J, Miller T, Aras R. SDF-1 in myocardial repair. Gene Ther 2012;19:583–7.
[88] Penn MS, Mendelsohn FO, Schaer GL, Sherman W, Farr M, Pastore J, et al. An open-label dose escalation study to evaluate the safety of administration of nonviral stromal cell-derived factor-1 plasmid to treat symptomatic ischemic heart failure. Circ Res 2013;112:816–25.
[89] Majed BH, Khalil RA. Molecular mechanisms regulating the vascular prostacyclin pathways and their adaptation during pregnancy and in the newborn. Pharmacol Rev 2012;64:540–82.
[90] Miller SB. Prostaglandins in health and disease: an overview. Semin Arthritis Rheum 2006;36:37–49.
[91] Narumiya S, Sugimoto Y, Ushikubi F. Prostanoid receptors: structures, properties, and functions. Physiol Rev 1999;79:1193–226.
[92] Fukushima S, Miyagawa S, Sakai Y, Sawa Y. A sustained-release drug-delivery system of synthetic prostacyclin agonist, ONO-1301SR: a new reagent to enhance cardiac tissue salvage and/or regeneration in the damaged heart. Heart Fail Rev 2015;20:401–13.
[93] Imanishi Y, Miyagawa S, Fukushima S, Ishimaru K, Sougawa N, Saito A, et al. Sustained-release delivery of prostacyclin analogue enhances bone marrow-cell recruitment and yields functional benefits for acute myocardial infarction in mice. PLoS One 2013;8:e69302.
[94] Kubota Y, Miyagawa S, Fukushima S, Saito A, Watabe H, Daimon T, et al. Impact of cardiac support device combined with slow-release prostacyclin agonist in a canine ischemic cardiomyopathy model. J Thorac Cardiovasc Surg 2014;147:1081–7.
[95] Masada K, Miyagawa S, Sakai Y, Harada A, Kanaya T, Sawa Y. Synthetic prostacyclin agonist attenuates pressure-overloaded cardiac fibrosis by inhibiting FMT. Mol Ther Methods Clin Dev 2020;19:210–9.
[96] Sougawa N, Miyagawa S, Kawamura T, Matsuura R, Harada A, Sakai Y, et al. Combined administration of laminin-221 and prostacyclin agonist enhances endogenous cardiac repair in an acute infarct rat heart. Sci Rep 2021;11:22243.
[97] Yajima S, Miyagawa S, Fukushima S, Sakai Y, Isohashi K, Watabe T, et al. A prostacyclin agonist and an omental flap increased myocardial blood flow in a porcine chronic ischemia model. J Thorac Cardiovasc Surg 2018;156:229–241 e14.
[98] Kanaya T, Miyagawa S, Kawamura T, Sakai Y, Masada K, Nawa N, et al. Innovative therapeutic strategy using prostaglandin I(2) agonist (ONO1301) combined with nano drug delivery system for pulmonary arterial hypertension. Sci Rep 2021;11:7292.
[99] Nakagawa T, Miyagawa S, Shibuya T, Sakai Y, Harada A, Watanabe K, et al. Administration of slow-release synthetic prostacyclin agonist promoted angiogenesis and skeletal muscle regeneration for limb ischemia. Mol Ther Methods Clin Dev 2020;18:119–30.
[100] Kawamura T, Yoshioka D, Kawamura M, Matsuura R, Kawamura A, Misumi Y, et al. Enhanced myocardial blood flow in ischemic cardiomyopathy by a slow-release synthetic prostacyclin agonist combined with coronary artery bypass grafting: the first human study in a Phase I/IIa clinical trial. Front Cardiovasc Med 2023;10:1047666.