

## Adipose tissue-derived stem cells as a therapeutic tool for cardiovascular disease

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### Abstract

Adipose tissue-derived stem cells (ADSCs) are

adult stem cells that can be easily harvested from subcutaneous adipose tissue. Many studies have demonstrated that ADSCs differentiate into vascular endothelial cells (VECs), vascular smooth muscle cells (VSMCs), and cardiomyocytes *in vitro* and *in vivo*. However, ADSCs may fuse with tissue-resident cells and obtain the corresponding characteristics of those cells. If fusion occurs, ADSCs may express markers of VECs, VSMCs, and cardiomyocytes without direct differentiation into these cell types. ADSCs also produce a variety of paracrine factors such as vascular endothelial growth factor, hepatocyte growth factor, and insulin-like growth factor-1 that have proangiogenic and/or antiapoptotic activities. Thus, ADSCs have the potential to regenerate the cardiovascular system *via* direct differentiation into VECs, VSMCs, and cardiomyocytes, fusion with tissue-resident cells, and the production of paracrine factors. Numerous animal studies have demonstrated the efficacy of ADSC implantation in the treatment of acute myocardial infarction (AMI), ischemic cardiomyopathy (ICM), dilated cardiomyopathy, hindlimb ischemia, and stroke. Clinical studies regarding the use of autologous ADSCs for treating patients with AMI and ICM have recently been initiated. ADSC implantation has been reported as safe and effective so far. Therefore, ADSCs appear to be useful for the treatment of cardiovascular disease. However, the tumorigenic potential of ADSCs requires careful evaluation before their safe clinical application.

**Key words:** Adipose tissue-derived stem cells; Cardiovascular disease; Acute myocardial infarction; Ischemic cardiomyopathy; Hindlimb ischemia; Stroke

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**Core tip:** Adipose tissue-derived stem cells (ADSCs) have been used for the treatment of cardiovascular disease with the efficacy of ADSC implantation demonstrated in animal models. However, the mechanisms under-

lying the capacity of ADSCs for regenerating the cardiovascular system remain controversial. ADSCs may differentiate into blood vessels and cardiomyocytes, fuse with other cell types, obtaining the characteristics of those cells, and secrete paracrine factors that have proangiogenic and/or antiapoptotic activities. This review also discusses recently initiated clinical trials using autologous ADSCs.

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## INTRODUCTION

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality worldwide. Despite advances in the treatment of acute myocardial infarction (AMI) using percutaneous coronary intervention, the treatment of heart failure (HF), which occurs as a result of the death of myocardial tissues and subsequent tissue remodeling, is still a challenging problem. As cardiomyocytes are terminally differentiated cells with minimal regenerative capacity, heart transplantation is currently the only treatment option for end-stage ischemic heart disease. The development of new therapies for AMI and HF is required to meet this substantial clinical requirement. Thus, stem cell therapy for CVD has recently gained substantial attention.

Stem cells are defined as cells capable of self-renewal and differentiation into a variety of phenotypes<sup>[1]</sup>. Stem cells comprise embryonic stem cells (ESCs) and adult stem cells (ASCs). ESCs were originally isolated from the inner cell mass of blastocysts<sup>[2]</sup>, and are pluripotent stem cells capable of giving rise to all three germ layers. However, several issues, including ethical concerns and teratoma formation, limit the clinical use of ESCs. Induced pluripotent stem (iPS) cells are also pluripotent stem cells that have very similar characteristics to ESCs<sup>[3,4]</sup>. As ethical problems can be avoided, iPS cells represent a potentially promising option for stem cell therapy. However, cancer formation is a major issue that needs to be overcome before widespread acceptance of the use of iPS cells in clinical settings. ASCs are multipotent stem cells that reside in various adult tissues. Among ASCs, bone marrow-derived mesenchymal stem cells (BMMSCs) and adipose tissue-derived stem cells (ADSCs) are the most extensively studied. BMMSCs are reported to have the potential to differentiate into various cell types including bone, cartilage, cardiac muscle, skeletal muscle, vascular endothelial cells (VECs), and vascular smooth muscle cells (VSMCs)<sup>[5,6]</sup>. BMMSCs have been used to treat CVD in clinical settings, with promising results reported in a number of studies<sup>[7-14]</sup>, although other

studies failed to demonstrate positive outcomes<sup>[15,16]</sup>. ADSCs have gained substantial attention recently as subcutaneous adipose tissues are abundant and can be easily harvested using liposuction, a procedure that is less invasive than bone marrow aspiration, with minimal donor discomfort. Adipose tissue contains a significantly greater proportion of stem cells than the bone marrow (5% vs 0.01%) and is therefore a convenient source of stem cells<sup>[17]</sup>. Furthermore, ADSCs reportedly do not express class II major histocompatibility complexes<sup>[18,19]</sup>, suggesting that ADSCs may be suitable for allogeneic transplantation in addition to autologous transplantation. In this review, we discuss the characteristics of ADSCs and their potential use in the treatment of CVD.

## CLASSIFICATION OF ADSCS

ADSCs can be obtained from subcutaneous adipose tissues with the use of collagenase digestion. Freshly isolated ADSCs (fADSCs) are known to be heterogeneous and contain hematopoietic cells (CD45<sup>+</sup> and/or CD34<sup>+</sup>) and VECs (CD34<sup>+</sup>/CD31<sup>+</sup>) in addition to stem cells (CD44<sup>+</sup> and CD105<sup>+</sup>)<sup>[20]</sup>. fADSCs can be cultured on plastic dishes in the presence of fetal bovine serum (FBS). Non-adherent cells, those that do not attach to plastic dishes, can be removed to obtain cultured ADSCs (cADSCs), a relatively homogeneous population that expresses stem cell markers, such as CD44 and CD105, but not hematopoietic lineage markers, including CD11b, CD45, and CD34 or the VEC marker CD31<sup>[21,22]</sup>. Artificially-modified ADSCs (mADSCs) are a type of ADSCs produced through the introduction of specific genes<sup>[23,24]</sup> or pre-treatment with drugs<sup>[25]</sup> before administration. The purpose of artificial modification is to improve the function of ADSCs, such as proangiogenic and antiapoptotic activities. cADSCs have been the most widely used type, particularly in animal studies. However, fADSCs may be more suitable for clinical applications for several reasons. First, fADSCs can be rapidly prepared compared with cADSCs as cell culture is not required while preparing fADSCs. The rapid preparation and administration of stem cells may be required to achieve sufficient recovery from tissue ischemia when treating AMI or critical hindlimb ischemia. Second, the preparation of fADSCs is technically less challenging compared with that of cADSCs as it does not require the use of foreign materials such as FBS. ADSCs used in clinical settings must not contain any foreign materials derived from animals or humans other than the individual patient receiving the stem cell therapy. Therefore, it is desirable to avoid culturing in the preparation of ADSCs for clinical applications.

## DIFFERENTIATION POTENTIAL OF ADSCS IN VITRO

ADSCs have the potential to differentiate into cartilage,

**Table 1** Differentiation potential of adipose tissue-derived stem cells *in vitro*

Cell type	Expression of VEC markers	Expression of VSMC markers	Expression of cardiomyocyte markers	Production of paracrine factors	Ref.
Human fADSCs	CD31, vWF	NE	NE	NE	Miranville <i>et al</i> <sup>[30]</sup>
Human cADSCs	CD31, vWF	NE	NE	NE	Planat-Bénard <i>et al</i> <sup>[31]</sup>
Human cADSCs	NE	SMA, calponin, caldesmon, myosin heavy chain, SM22 $\alpha$	NE	NE	Rodríguez <i>et al</i> <sup>[32]</sup>
Human cADSCs	NE	SMA, calponin, SM22 $\alpha$	NE	NE	Jeon <i>et al</i> <sup>[33]</sup>
Rabbit cADSCs	NE	NE	Myosin heavy chain, sarcomeric $\alpha$ -actinin, troponin I	NE	Rangappa <i>et al</i> <sup>[34]</sup>
Human cADSCs	NE	NE	Sarcomeric $\alpha$ -actinin, desmin, cardiac troponin	NE	Gaustad <i>et al</i> <sup>[35]</sup>
Murine fADSCs	NE	NE	GATA-4, Nkx2.5	NE	Planat-Bénard <i>et al</i> <sup>[36]</sup>
Human cADSCs	NE	NE	NE	VEGF, HGF, TGF- $\beta$	Rehman <i>et al</i> <sup>[44]</sup>
Murine cADSCs	ND	ND	NE	VEGF, HGF	Nakagami <i>et al</i> <sup>[45]</sup>
Human cADSCs	NE	NE	NE	VEGF, IGF-1	Sadat <i>et al</i> <sup>[46]</sup>

NE: Not examined; ND: Not detected; ADSCs: Adipose tissue-derived stem cells; VEC: Vascular endothelial cell; TGF: Transforming growth factor; VSMC: Vascular smooth muscle cell; HGF: Hepatocyte growth factor; IGF-1: Insulin-like growth factor-1; vWF: von Willebrand factor.

bone, tendon, and fat when cultured under lineage-specific conditions<sup>[26-29]</sup>. Furthermore, ADSCs have the potential to differentiate into VECs, VSMCs, and cardiomyocytes *in vitro* (Table 1), the main components of the cardiovascular system. Miranville *et al*<sup>[30]</sup> isolated and examined the characteristics of human fADSCs. Human fADSCs were found to express CD34 (27.6%-63.4%) with CD34 positive cells shown to be composed of two populations: CD34<sup>+</sup>/CD31<sup>+</sup> cells (probably VECs) and CD34<sup>+</sup>/CD31<sup>-</sup> cells. The authors demonstrated CD34<sup>+</sup>/CD31<sup>-</sup> cells expressed CD31 and von Willebrand factor (vWF) when cultured in a medium containing vascular endothelial growth factor (VEGF) and insulin-like growth factor (IGF). Planat-Bénard *et al*<sup>[31]</sup> used relatively fresh human cADSCs cultured on plastic dishes for 3 d without passaging. Approximately 90% of these cells were found to express CD34, and they expressed VEC markers, including CD31 and vWF, when cultured in a semisolid medium. Rodríguez *et al*<sup>[32]</sup> studied human cADSCs cultured in MCDB 131 medium supplemented with 1% FBS. The authors found these cells expressed VSMC markers, including  $\alpha$ -smooth muscle actin (SMA), calponin, caldesmon, myosin heavy chain, and smooth muscle protein 22- $\alpha$  (SM22 $\alpha$ ). Furthermore, differentiated cells contracted in response to carbachol demonstrated contractile capacity. Jeon *et al*<sup>[33]</sup> demonstrated the use of sphingosylphosphorylcholine (SPC) to induce the differentiation of human cADSCs into VSMCs, as determined by SMA, calponin, and SM22 $\alpha$  expression. They also found that SPC-induced differentiation of ADSCs into VSMCs depended on transforming growth factor- $\beta$  (TGF- $\beta$ ), shown to be secreted by ADSCs in an autocrine manner. Rangappa *et al*<sup>[34]</sup> incubated rabbit cADSCs with 5-azacytidine. The authors demonstrated that these cells differentiated into spontaneously beating cardiomyocytes with expression of myosin heavy chain, sarcomeric  $\alpha$ -actinin, and troponin I. Gaustad *et al*<sup>[35]</sup> incubated human cADSCs with rat cardiomyocyte

extracts and demonstrated ADSC expression of cardiomyocyte markers, including sarcomeric  $\alpha$ -actinin, desmin, and cardiac troponin I. Differentiated cells were also shown to beat autonomously. Planat-Bénard *et al*<sup>[36]</sup> cultured murine fADSCs in a semisolid methylcellulose medium without 5-azacytidine and found that ADSCs expressed cardiac-specific markers, such as transcription factors, GATA-4, and Nkx2.5. These cells demonstrated spontaneous beating with acceleration in response to isoproterenol, a  $\beta$ -agonist, and deceleration in response to carbamylcholine, an acetylcholine agonist.

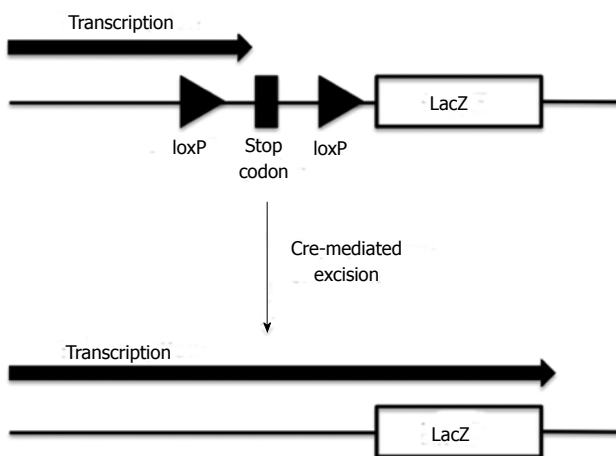
## DIFFERENTIATION POTENTIAL OF ADSCS *IN VIVO*

It has also been suggested that ADSCs express VEC, VSMC, and cardiomyocyte markers *in vivo* (Table 2). For example, cADSCs administered in a hindlimb ischemia model<sup>[31]</sup> and AMI model<sup>[37]</sup> were reportedly incorporated into tissues and were found to express VEC markers, such as CD31 and vWF. ADSC implantation has been shown to improve blood flow in a murine hindlimb ischemia model<sup>[31]</sup>. Jack *et al*<sup>[38]</sup> injected human cADSCs into the bladder and urethra and demonstrated the expression of SMA, a marker for VSMCs, by engrafted cells. Valina *et al*<sup>[37]</sup> injected porcine cADSCs into the coronary artery following the induction of AMI and found that a proportion of engrafted cells expressed SMA. The authors also found that left ventricular function recovered following administration of ADSCs. Strem *et al*<sup>[39]</sup> prepared fADSCs from Rosa 26 mice ubiquitously expressing  $\beta$ -galactosidase and injected these cells into the intraventricular chamber following myocardial cryoinjury. The authors demonstrated co-expression of  $\beta$ -galactosidase with myosin heavy chain, Nkx2.5, and troponin I. Yamada *et al*<sup>[40]</sup> transplanted the CD29 positive fraction of murine cADSCs into the infarct border zone of an AMI model and demonstrated

**Table 2** Differentiation potential of adipose tissue-derived stem cells *in vivo*

Cell type	Animal model	Expression of VEC markers	Expression of VSMC markers	Expression of cardiomyocyte markers	Functional recovery	Ref.
Human cADSCs	Murine hindlimb ischemia	CD31	NE	NE	Yes	Planat-Benard <i>et al</i> <sup>[31]</sup>
Porcine cADSCs	Porcine AMI	vWF	SMA	NE	Yes	Valina <i>et al</i> <sup>[37]</sup>
Human cADSCs	Bladders and urethras of athymic rats and SCID mice	NE	SMA	NE	NE	Jack <i>et al</i> <sup>[38]</sup>
Murine fADSCs	Murine AMI	NE	NE	Myosin heavy chain, Nkx2.5, troponin I	Yes	Strem <i>et al</i> <sup>[39]</sup>
Murine fADSCs	Rat AMI	NE	NE	Sarcomeric actin, GATA-4	Yes	Yamada <i>et al</i> <sup>[40]</sup>
Conditioned medium from human cADSCs	Murine hindlimb ischemia	NE	NE	NE	Yes	Bhang <i>et al</i> <sup>[48]</sup>

NE: Not examined; VSMC: Vascular smooth muscle cell; ADSCs: Adipose tissue-derived stem cells; vWF: von Willebrand factor; VEC: Vascular endothelial cell; SMA: Smooth muscle actin; AMI: Acute myocardial infarction.



**Figure 1** Schematic representation of LacZ expression following the excision of a floxed stop codon by Cre recombinase.

the expression of cardiomyocyte markers, such as sarcomeric actin and GATA-4. Furthermore, improved left ventricular function was observed in this study.

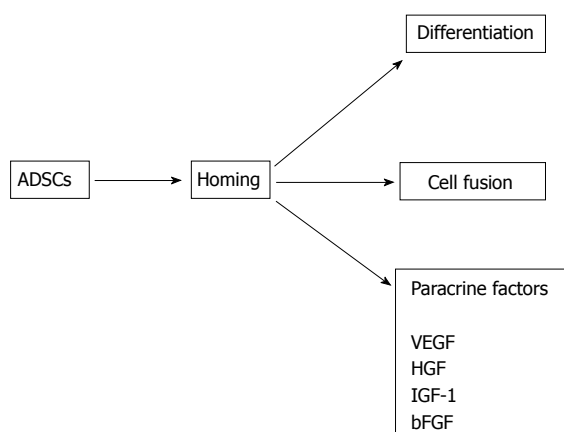
However, cell fusion should be considered carefully before concluding that ADSCs have the potential to differentiate into VECs, VSMCs, or cardiomyocytes *in vivo*. The *in vivo* fusion of administered ADSCs with tissue-resident VECs, VSMCs, and/or cardiomyocytes may lead to ADSCs acquiring the phenotypes of the corresponding fused cell types, making it appear as if ADSCs are directly differentiating into these cell types. In fact, cell fusion has been shown to occur with the *in vivo* administration of BMMSCs. Alvarez-Dolado *et al*<sup>[41]</sup> used R26R mice that contain a *lacZ* reporter gene downstream of a stop codon flanked by loxP sites (floxed). The *lacZ* reporter gene was therefore only expressed when the loxP-flanked stop codon was excised by Cre recombinase (Figure 1). The authors lethally irradiated these mice and transplanted BMMSCs from mice that ubiquitously express Cre recombinase and green fluorescent protein (GFP). If cells from the donor and recipient fused, the Cre enzyme would excise the Lox P-flanked stop codon, thereby allowing the expression of the *lacZ* gene. The results of this

study revealed  $\beta$ -gal<sup>+</sup> (fused) and GFP<sup>+</sup> cells in the brain, heart, and liver of recipients, at 2 and 4 mo post-transplantation. Thus, BMMSCs potentially fuse with other cell types *in vivo*. There have been no reports so far clearly demonstrating the fusion of ADSCs with other cell types *in vivo*. Bai *et al*<sup>[42]</sup> injected both human fADSCs and cADSCs into murine hearts and examined the occurrence of cell fusion using fluorescence *in situ* hybridization to detect human X chromosomes and murine Y chromosomes. The authors did not detect co-localization of human X chromosomes with murine Y chromosomes in individual cells, excluding the possibility of cell fusion events. However, similar techniques used to detect cell fusion by BMMSCs (e.g., the transplantation of ADSCs derived from transgenic mice expressing Cre recombinase into recipients expressing a *lacZ* reporter gene downstream of a floxed stop codon) should be used to conclusively determine whether ADSCs fuse with other tissue-resident cell types. Interestingly, Metzle *et al*<sup>[43]</sup> artificially fused human cADSCs with neonatal rat cardiomyocytes using hemagglutinating virus of Japan. The authors demonstrated spontaneous beating of fused ADSCs and the expression of human troponin I, suggesting fused ADSCs produced cardiomyogenic proteins. Furthermore, fused ADSCs were positive for the cell proliferation marker Ki67, suggesting proliferating capacity in marked contrast to terminally differentiated cardiomyocytes that are unable to proliferate. Therefore, ADSCs may stimulate the regeneration of heart muscles through *in vivo* fusion with cardiomyocytes.

## PRODUCTION OF PARACRINE FACTORS BY ADSCS

ADSCs have been shown to produce a variety of proangiogenic and antiapoptotic factors. Rehman *et al*<sup>[44]</sup> examined the production of paracrine factors by human cADSCs. The authors showed that ADSCs produced VEGF, hepatocyte growth factor (HGF), and TGF- $\beta$ . VEGF production increased five-fold when ADSCs were cultured under hypoxic conditions. Condi-





**Figure 2** Possible mechanisms underlying the effect of adipose tissue-derived stem cells on regeneration of the cardiovascular system. ADSCs: Adipose tissue-derived stem cells; VEGF: Vascular endothelial growth factor; HGF: Hepatocyte growth factor; IGF-1: Insulin-like growth factor-1; bFGF: Basic fibroblast growth factor.

tioned medium (CM) obtained from hypoxic ADSCs significantly increased the proliferation and survival of VECs. Furthermore, the administration of these ADSCs significantly improved perfusion in a hindlimb ischemia model. Nakagami *et al.*<sup>[45]</sup> reported murine cADSCs produce VEGF and HGF. The authors also administered ADSCs in a mouse hindlimb ischemia model and found transplanted ADSCs improved blood flow. However, transplanted ADSCs did not express VEC or VSMC markers, suggesting that ADSCs did not differentiate into vascular components in this study. Sadat *et al.*<sup>[46]</sup> demonstrated human cADSCs produce VEGF and IGF-I and that these cytokines contribute to the antiapoptotic effects of ADSCs on cardiomyocytes. The authors implicated the secretion of VEGF by ADSCs in the ADSC-induced stimulation of tube formation by VECs. Yeghiazarians *et al.*<sup>[47]</sup> administered BMMSCs and their lysates into the heart in a murine AMI model. The authors revealed that both BMMSCs and their lysates improved cardiac function and histology to similar extents, suggesting cytokines produced by BMMSCs, but not cells *per se*, are required for the recovery of cardiac function. Bhang *et al.*<sup>[48]</sup> used a three-dimensional spheroid culture of human ADSCs to prepared CM. The authors injected CM into ischemic regions in a murine hindlimb ischemia model. They detected restoration of blood perfusion in this model. Albersen *et al.*<sup>[49]</sup> injected rat cADSCs and their lysates into the penis in a rat model of cavernous nerve injury. The authors found that both ADSCs and their lysates restored erectile function to similar extents. These results suggest substances secreted by ADSCs, rather than cells *per se*, are critical for their regenerative function. Collectively, these results suggest that paracrine factors produced by ADSCs play a major, if not all, role in the regeneration of the cardiovascular system, although the differentiation and cell fusion of ADSCs may also be involved. The possible mechanisms underlying the regenerative effects of

ADSCs on the cardiovascular system are summarized in Figure 2.

## SURVIVAL OF ADSCS *IN VIVO*

The survival and engraftment of ADSCs *in vivo* have been examined within 30 d of ADSC implantation in the majority of studies<sup>[37,50-53]</sup>. Yin *et al.*<sup>[54]</sup> injected swine cADSCs into the coronary artery following induction of AMI and examined the fate of ADSCs 8 wk after injection. The authors found that many ADSCs expressed troponin T and  $\alpha$ -sarcomeric actin, indicating the ability of ADSCs to survive for 8 wk. Bai *et al.*<sup>[42]</sup> introduced a luciferase reporter gene into human cADSCs and transplanted these cells into the murine heart muscle using an AMI model. The authors detected luciferase-positive ADSCs by bioluminescence imaging. Bioluminescence was observed 16 wk after ADSC transplantation, indicating that some ADSCs survived for 16 wk. However, murine cADSCs transplanted in a hindlimb ischemia model were found to barely remain in ischemic tissues 28 d after transplantation<sup>[45]</sup>. Therefore, the survival and engraftment of ADSCs in recipient tissues appear to vary according to the animal species and experimental models used.

## APPLICATION OF ADSCS TO TREAT CVD

### AMI and ischemic cardiomyopathy

Many studies have demonstrated the efficacy of ADSC administration in recovering cardiac function in AMI models. cADSCs have been predominantly used in animal models<sup>[37,39,40,51-57]</sup>, although fADSCs<sup>[58]</sup> and mADSCs<sup>[23-25,59]</sup> have also been used. ADSCs have been transplanted *via* the coronary artery<sup>[37,53,54,57]</sup> and directly into cardiac muscles<sup>[23-25,39,40,51,55,56,58,59]</sup> in previous studies. Although ADSC implantation into the heart showed efficacy in recovering cardiac function in most studies, the underlying mechanisms remain controversial. Transplanted ADSCs expressed VEC, VSMC, or cardiomyocyte markers in numerous studies<sup>[37,39,40,52-55,57,59]</sup>; however, the "differentiation" of ADSCs was either not detected or examined in other studies<sup>[23-25,51,56,58]</sup>. Bai *et al.*<sup>[42]</sup> transplanted both fADSCs and cADSCs in a murine AMI model and found both cell types recovered cardiac function to a similar extent. A proportion of transplanted fADSCs and cADSCs were found to express cardiomyocyte markers, including troponin I and connexin 43. These results are encouraging as fADSCs may be more suitable for clinical applications than cADSCs for reasons outlined above. ADSCs differentiated into specific cell types have been used to treat chronic MI. Okura *et al.*<sup>[60]</sup> induced the differentiation of human cADSCs into cardiomyoblast-like cells (CLCs) *in vitro* and transplanted these cells into the swine coronary arteries 4 wk following the induction of MI. Cardiac function was

recovered by CLC implantation. Furthermore, implanted CLCs expressed human  $\alpha$ -cardiac actin, Nkx2.5, and GATA-4. Several studies have used a monolayer sheet to transplant ADSCs into chronic MI models. Miyahara *et al.*<sup>[61]</sup> cultured rat ADSCs on a temperature-responsive polymer to prepare a monolayer of ADSCs. The authors transplanted these cells onto scarred myocardium at 4 wk following coronary ligation. Transplanted cells grew *in situ* to form a thick stratum containing newly-formed blood vessels. The transplantation of monolayered cells prevented ventricular wall scarring and improved cardiac function. Okura *et al.*<sup>[62]</sup> induced the differentiation of human cADSCs into CLCs *in vitro* and prepared monolayer sheets of human CLCs and ADSCs using a temperature-responsive polymer. The authors then transplanted these cells onto the infarcted areas of rats 4 wk following the induction of MI. The authors demonstrated that the implantation of CLCs, but not ADSCs, resulted in a long-term recovery of cardiac function and improved survival. Furthermore, CLCs, but not ADSCs, were found to express human troponin I.

Clinical trials of ADSCs in the treatment of AMI have recently been initiated. The AdiPOSE-derived stem cells in the treatment of patients with ST-elevation myocardial infarction (APOLLO) trial is a double-blind, placebo-controlled, phase I/IIa trial<sup>[63]</sup>. Autologous fADSCs were transplanted into the coronary artery of AMI patients with ST-segment elevation following successful revascularization. During the 6-mo follow-up period, improvements in the left ventricular ejection fraction and myocardial perfusion and reductions in the infarct size were demonstrated. The subsequent phase II/III trial, called ADVANCE, is currently ongoing. In this trial, AMI patients with ST elevation are treated with intracoronary implantation of autologous fADSCs. The primary endpoint is reduction in the infarct size as measured by magnetic resonance imaging. The adiPOSE-derived stem cells in the treatment of patients with non revascularizable ischemic myocardium (PRECISE) trial enrolled patients who had chronic ischemic cardiomyopathy (ICM) not amenable to any revascularization procedures<sup>[64]</sup>. Autologous fADSCs were transplanted into cardiac muscles from endocardial sites. Maximal oxygen consumption and total left ventricular mass were significantly improved by ADSCs implantation. The ATHENA trial is an ongoing clinical trial intending to treat patients who have chronic ICM with HF symptoms using autologous fADSCs. The endpoints of this trial include peak oxygen consumption, perfusion defects, HF symptoms, left ventricle end-systolic and diastolic volume, and ejection fraction.

### Dilated cardiomyopathy

Several studies have demonstrated the efficacy of ADSC implantation in the recovery of cardiac function using dilated cardiomyopathy (DCM) models. Lin *et al.*<sup>[65]</sup> used a rat DCM model induced by the injection of porcine myosin and implanted cADSCs into cardiac muscle. The effect of combination therapy with ADSCs

and sildenafil, a phosphodiesterase type-5 inhibitor, was also evaluated. This study found that either ADSCs implantation alone or sildenafil treatment alone was effective for the recovery of cardiac function, with combination therapy being the most effective. Hamdi *et al.*<sup>[66]</sup> transplanted a monolayer sheet of murine cADSCs onto the heart surface in a murine DCM model, in which a floxed serum response factor gene is conditionally deleted using the expression of Cre recombinase. The authors found many blood vessels in transplanted sheets and some transplanted ADSCs in the cardiac muscle, a proportion of which expressed CD31. The authors further demonstrated the recovery of cardiac function and significant reduction of cardiac fibrosis following ADSC transplantation. Pinarlı *et al.*<sup>[67]</sup> transplanted cADSCs into a doxorubicin-induced HF model. They further examined combination therapy of ADSC transplantation with resveratrol, a polyphenolic compound found in red grapes with an antioxidant activity. This study found either ADSC implantation alone, or resveratrol administration alone, was effective in recovering cardiac function, although combination therapy was found to be most effective.

### Hindlimb ischemia

A number of studies have demonstrated that ADSC implantation improves blood flow in animal hindlimb ischemia models. fADSCs<sup>[30,68]</sup>, cADSCs<sup>[31,45,48,69-76]</sup>, and mADSCs<sup>[77]</sup> have all been used in these studies. Although the efficacy of ADSC administration in the recovery of blood flow appears conclusive, the mechanisms underlying the ability of ADSCs to recover blood flow remain controversial. ADSCs have been shown to engraft and express VEC and/or VSMC markers in some studies<sup>[30,31,69,70,72,75,77]</sup>. However, other studies have shown that engraftment was either not observed or examined<sup>[68,76]</sup> or paracrine factors secreted by ADSCs appeared to predominantly mediate the recovery of blood flow<sup>[45,48,70,71,73,74,77]</sup>. Lee *et al.*<sup>[76]</sup> performed the transplantation of autologous cADSCs in 15 patients with critical limb ischemia. Although this was a pilot study, ADSC implantation caused no complications during the follow-up period and clinical improvement was observed in 66.7% patients. Larger-scale clinical studies are required to conclusively evaluate the efficacy and safety of ADSC transplantation in the treatment of limb ischemia.

### Stroke

Several studies have demonstrated ADSC implantation induces functional recovery following brain ischemia in animal models of cerebral infarction (CI)<sup>[78-81]</sup>. Kang *et al.*<sup>[78]</sup> occluded the middle cerebral artery (MCA) to induce CI and transplanted human cADSCs into the lateral ventricle. Transplanted ADSCs migrated to the border zone of the injured area and intact brain tissue and into injured areas. A proportion of ADSCs were found to express microtubule-associated protein 2 (MAP2), a neuron marker, and glial fibrillary acid

protein (GFAP), an astrocyte marker. Furthermore, ADSC implantation improved motor and somatosensory behavior following CI, although no reduction in the area of CI was observed following ADSC implantation. Gutiérrez-Fernández *et al.*<sup>[79]</sup> injected cADSCs intravenously following MCA occlusion in rats and found a significant recovery of motor function, although no reduction in the infarct size or ADSC engraftment into damaged tissues was observed. Furthermore, the expression of VEGF, synaptophysin, a neuron marker, and neurofilament was significantly increased following ADSC injection, although it was not examined whether ADSCs *per se* produced these molecules. Liu *et al.*<sup>[80]</sup> transplanted human cADSCs into the right corpus striatum and cerebral cortex of rats following MCA occlusion. Neurological deficits were significantly attenuated by ADSC administration. Significantly increased expression of brain-derived neurotrophic factor (BDNF), nerve growth factor, and basic fibroblast growth factor mRNA and increased protein levels of BDNF and Bcl-2 were observed following ADSC transplantation, although it was not examined whether ADSCs produced these molecules.

### Coronary artery restenosis

Balloon injury of the carotid artery and wire injury of the femoral artery have been widely used as models of coronary artery restenosis. We implanted rat cADSCs around the femoral artery from the adventitial side following wire injury of the femoral artery and found that ADSC implantation significantly inhibited neointimal formation and stimulated re-endothelialization<sup>[82]</sup>. We also demonstrated that ADSCs produced angiopoietin-1 (Ang-1) and that the effect of ADSC administration diminished when expression of Ang-1 was suppressed using small interfering RNA (siRNA) against Ang-1<sup>[83]</sup> (Figure 3), indicating that Ang-1 produced by ADSCs plays a critical role in the inhibition of neointimal formation. Although drug-eluting stents (DES) are widely used and they potentially inhibit restenosis, the use of DES does not always improve patient outcomes, most likely due to increased risk of late thrombosis<sup>[84,85]</sup>. Because DES inhibit the proliferation of VECs as well as VSMCs by secreting antiproliferative drugs, DES may delay re-endothelialization, resulting in thrombus formation. Therefore, agents that stimulate re-endothelialization, such as Ang-1, may be more suitable for the suppression of neointimal formation than currently used inhibitors of cell proliferation. Systematic analysis of ADSC cytokine production is required to identify molecules that inhibit neointimal formation and stimulate re-endothelialization.

## FUTURE DIRECTIONS

Careful examination of the following points is required before the safe and effective clinical application of ADSCs.

### Tumorigenesis

Although ADSCs may be less prone to forming tumors than ESCs, it has been reported that BMMSCs form tumors *in vivo*<sup>[86]</sup>. Furthermore, several reports have suggested ADSCs promote the proliferation of cancer cells both *in vitro* and *in vivo*<sup>[87-89]</sup>. Therefore, ADSCs may stimulate the growth of pre-existing tumors even if ADSCs *per se* do not form tumors.

### Effects of age and comorbid diseases on the function of ADSCs

Patients suffering from CVD are often older and have comorbid diseases, such as hypertension and diabetes. When considering the autologous transplantation of ADSCs in these patients, it is necessary to examine whether age and comorbid diseases affect the function of ADSCs. Several studies have demonstrated that ADSCs collected from aged patients have less capacity for proliferation and differentiation compared to those collected from young donors<sup>[90-92]</sup>. Furthermore, several reports have shown that ADSCs collected from diabetic mice, hemodialysis patients, and HF patients have less capacity for proliferation, differentiation, or proangiogenic cytokine production<sup>[93-95]</sup>. Therefore, patients requiring ADSC transplantation for the treatment of CVD may not have access to high-quality autologous ADSCs. Allogenic transplantation of ADSCs may be required in these patients.

### Improved ADSC survival and function

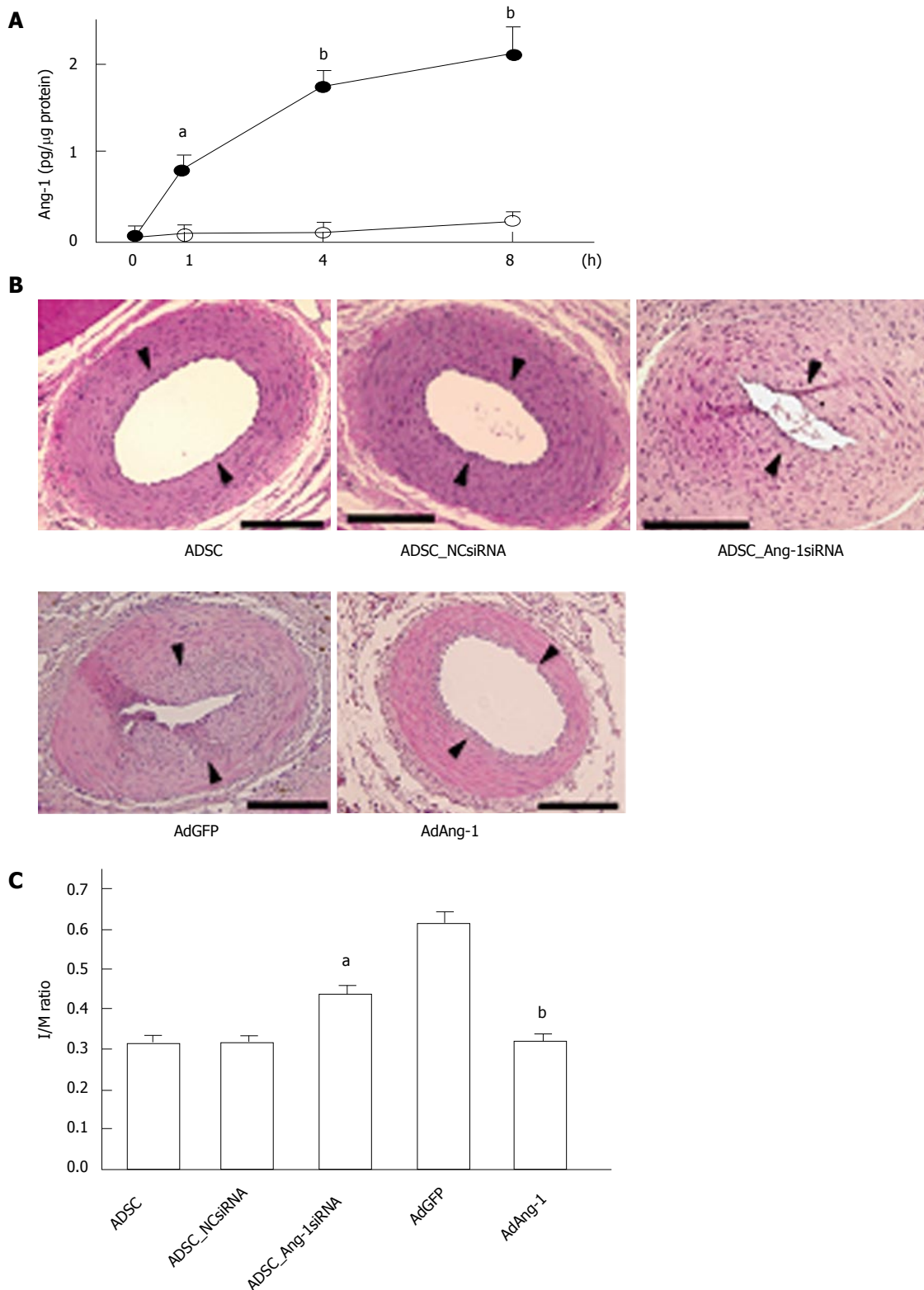
The use of mADSCs may improve the survival and/or function of ADSCs. The incubation of ADSCs with chemical compounds, culture in hypoxic conditions, or the introduction of ectopic genes are all potential methods for the pre-implantation modification of ADSCs. It is noteworthy that ADSCs cultured under hypoxic conditions have demonstrated increased capacity for proliferation, proangiogenic cytokine production, and maintenance of stemness<sup>[96-98]</sup>. The incubation of fADSCs under hypoxic conditions prior to implantation into patients may be a feasible strategy for improving the results of ADSC implantation.

### Identification of paracrine factors

ADSCs produce a variety of paracrine factors, as aforementioned, and these factors appear to play a major role in the regeneration of the cardiovascular system. Elucidation of cytokine combinations with the greatest efficacy in the regeneration of the cardiovascular system may remove the need for ADSC implantation in the future.

## CONCLUSION

Evidence accumulated from animal studies has indicated that ADSCs show efficacy in the treatment of CVD including AMI, ICM, and critical limb ischemia. Clinical trials have reported the safety and efficacy of ADSC



**Figure 3 Ang-1 is implicated in Adipose tissue-derived stem cell-induced suppression of neointimal formation.** A: ADSCs produce Ang-1, particularly when cultured in medium containing growth factors for VECs. Rat ADSCs were plated in 24-well plates and cultured in control medium (open circles) or medium containing growth factors for VECs (EGM: closed circles) for 1 wk. After washing with PBS, the medium was replaced with serum-free Dulbecco's modified Eagle medium and incubated for the indicated periods. Ang-1 accumulation was measured with an enzyme-linked immunosorbent assay kit. <sup>a</sup> $P < 0.05$ , <sup>b</sup> $P < 0.01$  vs 0 h ( $n = 6$  per group); B: Effect of knockdown of endogenous Ang-1 in ADSCs and forced expression of Ang-1 on neointimal formation. ADSCs were infected with lentivirus expressing negative control siRNA (NCsiRNA), which does not suppress the expression of mammalian mRNA, or lentivirus expressing Ang-1 siRNA (Ang-1siRNA). ADSCs not infected with lentivirus were used as positive controls (ADSC). ADSCs were cultured in EGM for 1 wk. ADSCs ( $10^6$  cells) were seeded from the adventitial side immediately after wire injury of the rat femoral artery. Adenoviruses expressing green fluorescent protein (AdGFP) or Ang-1 (AdAng-1) were also injected into the femoral artery from the adventitial side following wire injury. Femoral arteries were harvested 14 d after injury for histological analyses. Arrowheads indicate the position of internal elastic lamina. Bars represent 100  $\mu$ m; C: I/M ratios were compared among the groups ( $n = 8$  per group). <sup>a</sup> $P < 0.05$  vs NCsiRNA infection and <sup>b</sup> $P < 0.01$  vs AdGFP infection. PBS: Phosphate-buffered saline; ADSCs: Adipose tissue-derived stem cells; VECs: Vascular endothelial cells.



implantation in the treatment of CVD. ADSCs may regenerate tissues through a number of mechanisms including direct differentiation into VECs, VSMCs, and cardiomyocytes, fusion with tissue-resident cells, and secretion of proangiogenic and antiapoptotic cytokines. The malignant potential of ADSCs should be carefully examined in the future.

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