

WJSC 6th Anniversary Special Issues (2): Mesenchymal stem cells**Mesenchymal stem cells for treatment of aortic aneurysms**

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Abstract

An aortic aneurysm (AA) is a silent but life-threatening disease that involves rupture. It occurs mainly in aging and severe atherosclerotic damage of the aortic wall. Even though surgical intervention is effective to prevent rupture, surgery for the thoracic and thoraco-abdominal aorta is an invasive procedure with high mortality and morbidity. Therefore, an alternative strategy for treatment of AA is required. Recently, the molecular pathology of AA has been clarified. AA is caused by an imbalance between the synthesis and degradation of extracellular matrices in the aortic wall. Chronic inflammation enhances the degradation of matrices directly and indirectly, making control of the chronic inflammation crucial for aneurysmal development. Meanwhile, mesenchymal stem cells (MSCs) are known to be obtained from an adult population and to differentiate into various types of cells. In addition, MSCs have not only the potential anti-inflammatory and immunosuppressive properties but also can be recruited into damaged

tissue. MSCs have been widely used as a source for cell therapy to treat various diseases involving graft-versus-host disease, stroke, myocardial infarction, and chronic inflammatory disease such as Crohn's disease clinically. Therefore, administration of MSCs might be available to treat AA using anti-inflammatory and immunosuppressive properties. This review provides a summary of several studies on "Cell Therapy for Aortic Aneurysm" including our recent data, and we also discuss the possibility of this kind of treatment.

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Key words: Aortic aneurysm; Mesenchymal stem cells; Cell therapy; Elastin; Chronic inflammation; Extracellular matrices; Macrophages; Matrix metalloproteinases

Core tip: Aortic aneurysm (AA) is caused by an imbalance between synthesis and degradation of extracellular matrices (ECMs) such as collagen and elastin in the aortic wall. The chronic inflammation enhances the degradation of ECMs directly and indirectly. We hypothesized that administration of mesenchymal stem cells (MSCs) might be able to treat AA given the anti-inflammatory and immune-suppressive potential of MSC. In this article, we review papers that attempt to treat AA using MSCs with our recent results, as well as review the molecular pathogenesis of AA and characteristics of MSC.

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INTRODUCTION**Trend of aortic aneurysm**

An aortic aneurysm (AA) occurs mainly in aging and

chronic inflammation associated with atherosclerosis. It is a common and silent disease but also a life-threatening one involving rupture. AA has an incidence of 6%-9% in men over the age of 65 in abdominal aorta^[1,2]. AA larger than 55 mm in diameter in the abdominal aorta and 60 mm in diameter in the thoracic aorta increase the risk of rupture. Therefore, patients of the kind require surgical intervention such as prosthetic graft replacement to prevent rupture^[3]. However, surgery for thoracic and thoraco-abdominal aorta is a highly invasive procedure with high mortality and morbidity rate. On the other hand, abdominal or thoracic endovascular aneurysm repair (EVAR, TEVAR), which are catheter-based interventions, called internal aortic stent grafting, might be used for conventional surgically inapplicable patients with a high risk for surgical repair. However, EVAR and TEVAR have drawbacks such as limitations of anatomic and clinical criteria, complications of endoleaks, and graft migrations^[4]. Thus, an alternative less invasive strategy is required for treatment of AA.

Development of medical treatment for aortic aneurysm

Recently, the molecular pathology of AA has been clarified, and control of chronic inflammation is crucial for AA progression. AA is caused by an imbalance between synthesis and degradation of the extracellular matrices (ECMs) such as collagen and elastin in the aortic wall. Chronic inflammation enhances the degradation of ECMs directly and indirectly. Therefore, control of inflammation may be an alternative strategy for treatment of AA. A number of experimental investigations and clinical studies have attempted to treat AA using various drugs and factors to control the inflammation; for example, angiotensin converting enzyme inhibitor and statin associated with reduced abdominal AA (AAA) rupture in a case-control study^[5,6], doxycycline decrease in aneurysmal expansion rate in an experimental model^[7] and in a randomized double-blinded clinical trial^[8], nonsteroidal anti-inflammatory drugs decrease AAA expansion rate in a case control study^[9], and c-jun N-terminal kinase inhibitor regresses AAA in a CaCl₂-treated mice model^[10]. However, these pharmacotherapies have still not been established for clinical application because of their array of side effects caused by systemic administration of these agents. Another disadvantage of using these agents is that special equipment might be required to deliver them locally for treatment of AA.

Mesenchymal stem cell therapy

Meanwhile, the recent progress in stem cell research in regenerative medicine is remarkable. Stem cell is one of the most important cell sources for treatment of damaged organs using regenerative technology. Mesenchymal stem cells (MSCs) can be obtained from adult tissue such as bone marrow^[11,12], adipose tissue^[13,14] and others. MSCs can be differentiated into various types of cells such as osteoblast, adipocyte and chondrocyte. In addition, MSCs have anti-inflammatory and immunosuppressive proper-

ties as well that can be recruited into damaged tissue^[15,16]. By utilizing their unique potential, MSCs have been widely used as a cell source for cell therapy to treat various diseases involving graft-versus-host disease, stroke, myocardial infarction (MI), and chronic inflammatory disease such as Crohn's disease clinically^[17-21].

In this article, we review papers that attempt to treat AA using MSCs with our recent results, and we also discussed the update status of the molecular pathogenesis of AA and characteristics of MSC.

MOLECULAR PATHOGENESIS OF AORTIC ANEURYSMS

The molecular pathology of AA is a failure in the balance between synthesis and degradation of ECMs in the aortic wall. These phenomena are induced by chronic inflammation associated with atherosclerosis. Aortic ECMs are mainly composed of elastin and collagen and play an important role in the aortic strength and flexibility to withstand arterial blood pressure. Especially, elastin is a major fibrillar component in the arterial wall, and destruction of elastin fiber directly leads to expansion of AA^[22]. Elastin polypeptide is known to be synthesized by vascular smooth muscle cells (VSMCs)^[23], and its gene expression is modulated by transforming growth factor (TGF)- β 1 and insulin-like growth factor (IGF)-1^[24,25]. On the other hand, degradation of ECMs is caused by mainly secretion and activation of matrix metalloproteinases (MMPs), leading to the weakening of the aortic wall. In particular, MMP-2 and MMP-9 are known as a powerful proteinase that degrades elastin fiber, and they are secreted from macrophages which have infiltrated the inflammatory site^[26,27]. Macrophage plays a major role of inflammatory cells in the development and progression of AA, and also secretes various cytokines, chemokines and proteinases. Many studies have been reported that interleukin (IL)-1 β , IL-6, tumor necrosis factor (TNF)- α and monocyte chemoattractant protein (MCP)-1 were up-regulated in the AA wall of human or experimental animal aortic aneurysm^[28-30]. These cytokines and chemokines induce recruitment of monocytes^[31], apoptosis of VSMCs^[32] and regulation of MMP secretion^[33]. On the other hand, failure of ECM synthesis is reportedly due to a disability of ECM synthesis and decrease of cell number by apoptosis of VSMCs in the AA wall^[34]. Therefore, the inhibition of excessive inflammation and the recovery of ECM synthesis are key factors for treatment of AA.

DETERMINATION OF MSCS

Surface maker of the MSCs

MSC is one of the adult somatic stem cells which can be isolated from adult organs including bone marrow and adipose tissue^[13,35]. Early in culture, the spindle-shaped plastic-adherent cells do not appear uniformly by contamination of hematopoietic cells, but this heterogeneity gradually decreases influenced by culture conditions and

Table 1 Mesenchymal stem cells phenotypic characteristics

		Positive marker	Negative marker	Pluripotency	Ref.
ISCT criteria	Human MSC	CD73, CD90, CD105	CD34, CD45, CD11b or CD14, CD19 or CD79 α , HLA-DR	Osteogenic Chondrogenic Adipogenic	[38]
In AA experimental studies	Mouse BM-MSC	CD44, CD106, Sca-1	CD11b, CD31, CD34, CD45, CD86, CD117	Osteogenic Chondrogenic Adipogenic	[51,53]
	Human placental-MSC	CD29, CD44, CD73, CD90, CD105	CD14, CD19, CD34, CD45, HLA-DR	Data not shown	[54]
	Rat BM-MSC	CD44, CD73, CD90, CD105	CD11b, CD45	Data not shown	[56]
	Pig ASC	CD73, CD90, CD105	CD14, CD11b	Osteogenic Chondrogenic Adipogenic	[57]
	Pig BM-MSC	CD13, CD29	CD31, CD34, CD45	Data not shown	[58]

ISCT: International society of cell therapy; MSC: Mesenchymal stem cell; AA: Aortic aneurysm; BM-MSC: Bone marrow-derived MSC; HLA-DR: Human leukocyte antigen-DR; ASC: Adipose tissue-derived MSC.

consecutive passages^[36,37]. The International Society of Cell Therapy criteria propose (ISCT) that human MSCs should be positive for the expression of CD73, CD90 and CD105 ($\geq 95\%$ positive), and lack expression of CD34, CD45, CD11b or CD14, CD19 or CD79 α , and HLA-DR ($\leq 2\%$ positive). Also, MSC should differentiate into osteogenic, adipogenic and chondrogenic lineage (Table 1)^[38]. However, CD73 and CD105 are also expressed on fibroblast and endothelial lineage cells and CD90 is also expressed on haematopoietic stem cells^[39,40]. To improve purity of the human MSC population, several studies have been performed using a combination such as Stro-1, CD271, CD146 and PDGFR- α , not only CD73, CD90 or CD105^[41-43].

Migration mechanism of MSCs

Through a CXCR4 signaling pathway of damaged tissue stimuli migration and activation of MSC *via* stromal cell-derived factor-1, MSCs are known to accumulate in damaged tissue sites^[44]. In addition, it also has been reported that the migration of MSCs is accelerated through up-regulation of pro-MMP-2 and membrane-type 1-MMP complex by stimulation of the inflammatory cytokines IL-1 β ^[45,46].

Immunosuppression and anti-inflammation properties of MSCs

MSCs have the capability of immunosuppression and anti-inflammation properties. Several investigations were reported regarding the mechanisms of immunosuppression and anti-inflammation of MSCs. MSCs do not express the costimulatory molecules CD80, CD86 and CD40, which have been identified to play a role in the initiation of immune responses by T and B lymphocytes^[47,48]. Also, MSCs can inhibit activation of T-cells immune response and proliferation by expression of indoleamine 2,3-dioxygenase, which degrades tryptophan and suppresses T-cell proliferation. Moreover, MSCs reduce the secretion of interferon (IFN)- γ , which regulates several aspects of the immune response, from T-helper 1 (Th1) cells, and conversely increase secretion of IL-4, which plays a cen-

tral role in the inhibitory regulation of immune response, from Th2 cells. In addition, MSCs inhibit proliferation of natural killer cells through soluble factor prostaglandin E₂ (PGE₂), which inhibits actions on T cells depending on their maturation and activation state, and TGF- β which were secreted from MSC, and reduce the proinflammatory potential of dendritic cell-1 (DC1) by inhibition of their secretion TNF- α , IFN- γ and IL-12 and conversely increase IL-10 secretion from DC-2^[49,50].

TREATMENT OF AORTIC ANEURYSMS USING MSCs

Recently, several studies using MSCs as a cell source for treatment of AA have been reported including our own studies. Published experimental studies were summarized in Table 2.

Implantation of bone marrow-derived MSC cell-sheet for aortic aneurysm

We earlier reported that AA formation and growth were attenuated by intraperitoneal implantation of bone marrow-derived MSC (BM-MSC) cell-sheet using an angiotensin II (AT II)-infused apolipoprotein E-deficient (apoE^{-/-}) mouse model^[51]. The BM-MSC cell-sheet was prepared using an Upcell[®] which is a thermoresponsive polymer-grafted dish surface, and the BM-MSC cell-sheet was implanted into the nearby abdominal aortic adventitia at the time of implantation of Alzet osmotic minipump to infuse the AT II (Figure 1). Four weeks after implantation of BM-MSC cell-sheet, the aortic diameter of the BM-MSC cell-sheet implanted group was significantly lower than that of the apoE^{-/-} + AT II group at the infrarenal aorta (Figure 2A). The enzymatic activities of MMP-2 and MMP-9 were suppressed in the BM-MSC cell-sheet implanted mice group. The downregulation of MMP enzymatic activity may be influenced *via* the paracrine effect of soluble factors secreted from BM-MSC because we showed that gene expression of MMPs in macrophages was decreased by indirect co-culture

Table 2 Animal studies for treatment of aortic aneurysm using mesenchymal stem cells

Experimental AA model	Cell source	Number of cells	Injection time	Delivery	Efficiency	Ref.
AT II -infusion mouse model	BM-MSC	Cell-sheet	Same time as AT II -infusion	Implantation of MSC-sheet around infrarenal aorta	4 wk after implantation, inhibition of AA development and growth, and elastin degradation downregulation of IL-1 β , IL-6, MCP-1 and TNF- α protein expression, and MMP-2 and -9 enzymatic activity Up-regulation of IGF-1 and TIMP-1 protein expression Positive for MSC specific surface marker	[51]
AT II -infusion mouse model	BM-MSC	1 \times 10 ⁶ /every week, 4 times	Same time as AT II -infusion	<i>iv</i> -administration	4 wk after injection, inhibition of AA development and growth, elastin degradation, M ϕ infiltration downregulation of IL-1 β , IL-6 and MCP-1 protein expression, and MMP-2 and -9 enzymatic activity Up-regulation of IGF-1 and TIMP-1 protein expression Detection of MSC in the aortic wall	[53]
Elastase-perfusion mouse model	Placental- MSC	1 \times 10 ⁶	1 d after elastase-perfusion	<i>iv</i> injection	2 wk after injection, inhibition of AA expansion, inflammatory cell infiltration, and elastin degradation, downregulation of IL-17, IL-23, INF- γ , TNF- α , RANTES and MCP-1 protein expression Increase of α -SMA expression	[54]
Xenograft rat model	BM-MSC	1 \times 10 ⁶	Same time as surgical intervention	Catheter	1 wk after surgical intervention inhibition of inflammatory cells infiltration and <i>MMP-9</i> gene expression, and increase of <i>TIMP-1</i> gene expression, after 4 wk, inhibition of AA expansion, increase of α -SMA expression, elastin and collagen content	[56]
Dacron-patch pig model	ASC	1 \times 10 ⁶	Same time as surgical intervention	Catheter	Attenuation of inflammation reaction, detection of ASC 3 wk after surgical intervention	[57]
Balloon injury with type 1 collagen and elastase-perfusion porcine model	BM-MSC	1 \times 10 ⁶	Same time as balloon-injury	Direct injection into aortic wall	72 h after injection, Increase of VEGF-A mRNA expression level 1 wk after injection, detection of GFP-labeled MSC at aortic wall and vWF positive cells formed tubuloluminal structures within outer layer of media and throughout the adventitia	[54]

AA: Aortic aneurysm; AT II: Angiotensin II; MSC: Mesenchymal stem cell; BM-MSC: Bone marrow-derived MSC; *iv*: Intravenous; VEGF: Vascular endothelial growth factor; GFP: Green fluorescent protein; TIMP-1: Tissue inhibitor of metalloproteinase 1; MMP: Matrix metalloproteinases; MCP-1: Monocyte chemotactic protein 1; IL: Interleukin; TNF: Tumor necrosis factor; IGF: Insulin-like growth factor; INF: Interferon; ASC: Adipose tissue-derived MSC; vWF: von Willebrand factor.

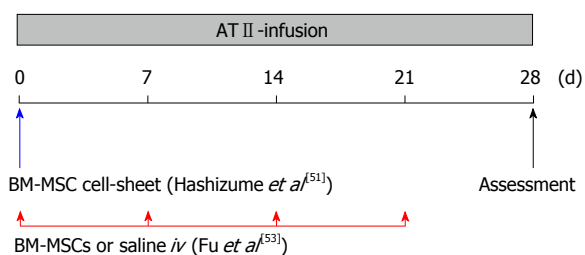


Figure 1 Diagram of bone marrow-derived mesenchymal stem cell cell-sheet implantation or bone marrow-derived mesenchymal stem cell intravenous-administration protocol. At the time of Alzet osmotic minipump implantation, the BM-MSC cell-sheet was implanted into the nearby abdominal aortic adventitia^[51], and 1 \times 10⁶ BM-MSCs (in 0.2 mL saline) or 0.2 mL saline were injected intravenously via the tail vein every week^[53]. Mice were sacrificed and assessed on day 28. AT II: Angiotensin II; *iv*: Intravenous; BM-MSC: Bone marrow-derived mesenchymal stem cell.

with BM-MSCs *in vitro* in this paper. In addition, the protein expression of tissue inhibitor of metalloproteinase

(TIMP)-1 was increased in the BM-MSC cell-sheet implanted group. The BM-MSC cell-sheet implanted group also showed decreased inflammatory cytokines including IL-6, MCP-1 and TNF- α . These results suggested that BM-MSC cell-sheet might suppress the excess inflammatory reaction which caused AT II-induced AA. On the other hand, degradation of elastin was inhibited by implantation of the BM-MSC cell-sheet compared with control. This result could be supported by the increase of the gene expression of elastin in VSMCs co-cultured with BM-MSCs *in vitro*. Moreover, the protein expression of IGF-1 and TIMP-1 in AA tissue with BM-MSC cell-sheet implantation was deemed to be in a paracrine manner, because the IGF-1 and TIMP-1 are identified to be present in the condition medium of MSCs^[46,52]. Our study showed a new approach by treating AA through implantation of BM-MSC cell-sheet. However, such implantation using laparotomy is a relatively invasive procedure, even less invasive than prosthetic graft replacement

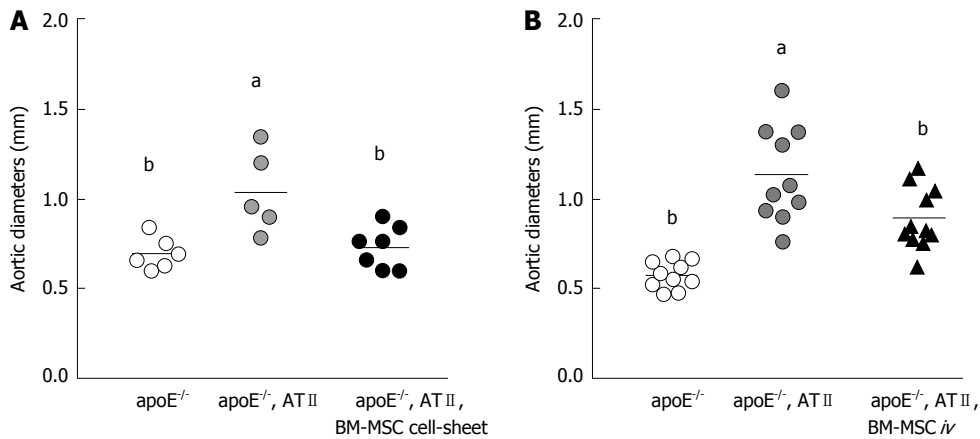


Figure 2 Bone marrow-derived mesenchymal stem cell cell-sheet implantation or bone marrow-derived mesenchymal stem cell IV-administration attenuates aortic aneurysm progression and expansion. Aortic diameter was measured at the infrarenal aorta in the bone marrow-derived mesenchymal stem cell (BM-MSC) cell-sheet (A) or the BM-MSC IV-administration. Data are assessed by one-way ANOVA with Bonferroni correction. ^aP < 0.05 vs apoE^{-/-} group, ^bP < 0.05 vs apoE^{-/-} + AT II group. Data are from Hashizume *et al.*^[51] and Fu *et al.*^[53]. AT II : Angiotensin II ; *iv* : Intravenous.

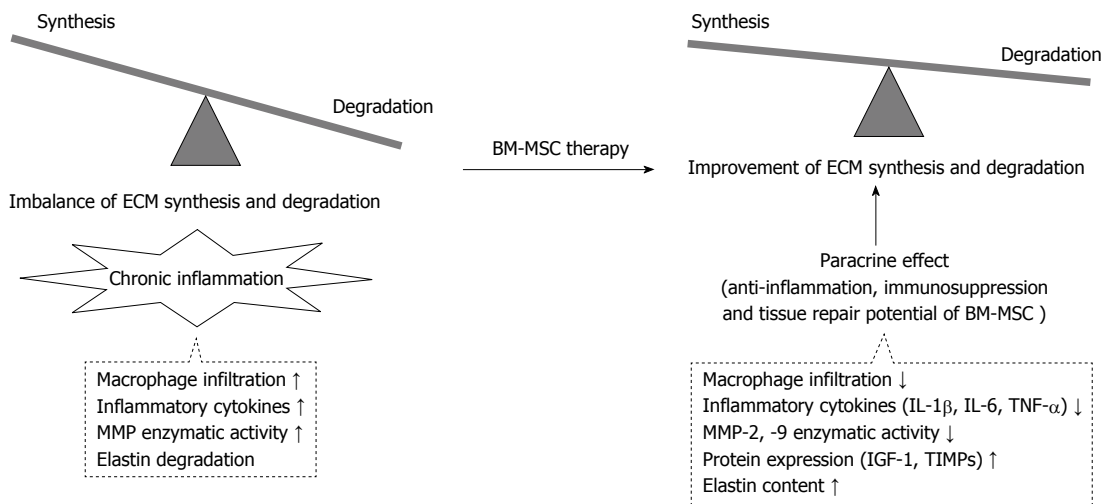


Figure 3 Attenuation of aortic aneurysm development and growth is associated with improvement of the imbalance between degradation and synthesis of extracellular matrices by bone marrow-derived mesenchymal stem cell therapy. ECM: Extracellular matrices; BM-MSC: Bone marrow-derived mesenchymal stem cell; TIMP: Tissue inhibitor of metalloproteinase; MMP: Matrix metalloproteinase; IL: Interleukin; IGF: Insulin-like growth factor.

for AA.

Intravenous administration for aortic aneurysm

To treat AA by a less-invasive BM-MSC delivery, we demonstrated multiple intravenous (*iv*) administration of BM-MSC for an AT II-infusion AA mouse model^[53]. At the time of Alzet osmotic minipump implantation, 1 × 10⁶ BM-MSCs (in 0.2 mL saline) or 0.2 mL saline were injected intravenously *via* the tail vein every week (Figure 1). After the treatment (4 wk later), the BM-MSC (*iv*)-administration group reduced the incidence of AA compared with that of the saline group, and attenuated the progression and expansion at the infrarenal levels of the aorta (Figure 2B). The BM-MSC IV-administration group also suppressed MMP-2 and MMP-9 enzymatic activity and protein expression of inflammatory cytokines including IL-1β, IL-6 and MCP-1 in the aortic tissue. In addition, the infiltration of macrophages was suppressed by BM-MSC IV-administration. Moreover, the BM-MSC

IV-administration group showed inhibition of elastin degradation, which might have been affected by the up-regulation of IGF-1 and TIMP-2 protein expression. This study showed that the multiple IV-administration of BM-MSC inhibits AA development and progression as a less-invasive procedure. Our studies suggest that the attenuation of AA development and growth is associated with improvement of the imbalance between degradation and synthesis of ECMs due to the anti-inflammation, immunosuppression and tissue repair potential of BM-MSC (Figure 3).

Sharma *et al.*^[54] reported the role of IL-17 in the elastase-perfused mouse AAA model and the effectiveness of *iv* injection of human placental-derived MSC for experimental AAA. T-cell-produced IL-17, which is known as a regulator of inflammation and VSMC apoptosis, induced the expression of various cytokines, chemokines, and MMPs^[55]. On day 1 after elastase-perfused wild-type (WT) mice, 1 × 10⁶ placental-derived MSCs were

injected intravenously *via* the tail vein. After 2 wk, the aortic diameter was attenuated in the placental-derived MSC-treated mice group compared with untreated elastase-perfused WT mice group. In histological analysis, infiltration of inflammatory cells including CD3⁺ T cells, macrophages and neutrophils was attenuated and elastic fiber disruption decreased in placental-derived MSC-treated mice group. In addition, the placental-derived MSC-treated mice group suppressed the protein production of IL-17, IL-23, IFN- γ , TNF- α , RANTES and MCP-1 in aortic tissue. The same investigators suggested that placental-derived MSC treatment attenuated AAA formation and inflammatory cytokine production including IL-17 *via* paracrine effect of soluble factors secreted from MSCs such as TGF- β , hepatocyte growth factor, or PGE₂. This suggestion was supported by co-culture of placental-derived MSCs and mononuclear cells (MNCs) in an *in vitro* experiment. The placental-derived MSCs co-cultured with MNCs suppressed the proliferation of activated MNCs and attenuated IL-17 production from MNCs.

Catheter-based MSC therapy for aortic aneurysm

Schneider *et al.*^[56] also reported that an already-formed tentative AA was stabilized by BM-MSCs using a xenograft rat AAA model. To obtain xenograft, guinea pig infrarenal aortas were decellularized using 1% sodium dodecyl sulfate. Then, the male Fischer 344 rat aorta was replaced by a decellularized xenograft. Fourteen days after xenograft implantation, 1×10^6 BM-MSCs were injected into the lumen of clamped xenograft aorta through a PE10 catheter, and allowed to attach for 8 min. The results showed down-regulation of MMP-9 mRNA, up-regulation of TIMP-1 mRNA and decrease of macrophages at the xenograft site at 1 wk, and a decrease in aortic diameter at the xenograft site 4 wk after BM-MSC injection. These results suggest that BM-MSCs inhibit xenograft aneurysmal wall injury and heal through paracrine mechanisms and induction of collagen production rather than direct differentiation. This endovascular seeding of BM-MSCs may support the development of catheter-based intervention for AA treatment in the future.

The possibility of catheter-based delivery of MSCs has also been reported by Riera Del Moral *et al.*^[57] who demonstrated adjuvant treatment with MSCs in EVAR based on clinical current treatment. They injected 1×10^7 adipose tissue-derived MSCs (ASCs) (in 1 mL fibrin sealant) inside the aneurysmal sac through a second 5F introducer using a Dacron-patched AAA pig model. This study investigated whether the MSCs induced local immunosuppression, prevention of excessive fibrosis, prevention of apoptosis and induction of intrinsic progenitor cell. The results showed that the ASC-treated group was a lower infiltration of inflammatory cells compared with the non-treated group, and green fluorescent protein (GFP)-linked ASCs were detected 3 wk after. They suggested that ASC endovascular administration into aneurysmal sac assuming common clinical treatment might stabilize AAA.

Direct Injection of MSCs to the aneurysmal aortic wall

Turnbull *et al.*^[58] reported the success of implantation of autologous BM-MSC by direct injection into the aortic wall using a porcine AAA model and the potential of cell-based therapies. The aneurysm was created by injection of type 1 collagenase and elastase solution into the aortic lumen, following dilation of the infrarenal aorta using a 12 mm noncompliant angioplasty balloon. After that, 1×10^7 BM-MSCs were directly injected into the aortic wall immediately after the injury. The GFP-labeled BM-MSCs were identified in the aortic wall 1 wk after injection. And, von willebrand factor positive cells formed tubuloluminal structures were detected within the outer layer of the media and throughout the adventitia. In addition, the mRNA level of vascular endothelial growth factor (VEGF)-A was increased at 72 h in BM-MSC-injected aortic tissue compared with non-treated control aorta. Thus, they suggested BM-MSC-enhanced wound healing and angiogenic response through paracrine factor, such as VEGF.

In these studies, MSC phenotypic characteristics have been identified by surface marker and pluripotency. Although these different positive and negative immunophenotypes are concerned with differences in animal species, they resemble human MSC immunophenotypic characteristics.

FUTURE PERSPECTIVE OF MSC THERAPY FOR AA

Unsolved issues

The efficacy of MSC for treatment of AA has been suggested in current experimental studies showing the advantages of inhibition of excess inflammation, decrease of inflammatory cells, suppression of elastic fiber disruption and increase of elastin content by MSC administration. However, some unresolved issues remain in the treatment with MSCs. First, it remains unclear whether the cell numbers, frequency and administration timing of MSCs are required for AA treatment. Thus, these optimizations warrant further investigation. Second, the delivery methods of MSC in these studies are respectively different. Investigators have performed administration using several methods involving implantation of cell-sheet, IV-administration, direct injection into aortic wall, and catheter delivery (Table 3). Among them, although IV-administration is the least invasive and simple procedure, the targeting ability is lower and injected MSCs are trapped in other tissues such as lung, spleen, liver and kidney. In contrast, the implantation of cell-sheet and the direct injection into aortic wall make it possible to target AA. However, these are relatively invasive procedures. On the other hand, endovascular delivery using a catheter is less invasive and has a high targeting ability. Third, the long-term follow-up administration of MSCs has not been reported yet. The injected MSCs may differentiate into adipocyte, osteocyte or other differentiated cells at the aortic wall site. These cells might promote harmful

Table 3 Methodology of delivery system

Delivery system	Administration site	Localization, timing	Delivery system		Ref.
			Merits	Demerits	
Cell-sheet	Adventitia of abdominal aorta	Adventitia, 4 wk after implantation	High targeting ability	Invasive procedure by laparotomy	[51]
<i>iv</i>	Tail vein	Media and/or adventitia, at 4 wk	Least invasive	Low targeting ability and trapping in other tissue	[53]
<i>iv</i>	Tail vein	Data not shown	Least invasive	Low targeting ability and trapping in other tissue	[54]
Catheter	Clamped endovascular	Intima 1 wk after injection	Less invasive and high targeting ability	Requirement of a surgical procedure or advanced catheter intervention	[56]
Catheter	Clamped endovascular	Media 3 wk after injection	Less invasive and high targeting ability	Requirement of a surgical procedure or advanced catheter intervention	[57]
Direct injection	Injured aortic wall	Aortic wall, 1 wk after injection	High targeting ability	Risk of rupture	[58]

iv: Intravenous.

effects to the aorta such as deposition of lipid or calcification. Fourth, the isolation and expansion of MSCs might become difficult with aging. Therefore, we must investigate the therapeutic effect of AA using allogeneic MSCs, not only autologous MSCs. Finally, further investigation using a large animal will be ultimately required to confirm the repeatability.

Future perspective

Meanwhile, it is important to elucidate the mechanisms by which MSCs induced negative effects for progression of AA. One of the mechanisms was suggested to be the paracrine effect of MSCs. Recently, trophic factors of MSC-conditioned medium (MSC-CM) were profiled by proteomic analysis using mass spectrometry, protein microarrays and bioinformatics; as a result, many candidates such as TGF- β , IGF-1, epidermal growth factor, fibroblast growth factor, interleukins, MMPs, or TIMPs were identified^[59]. TGF- β is an important signal that induces smooth muscle cell (SMC) differentiation and increases serum response factor (SRF) expression through an increase in transcription of the *SRF* gene^[60]. Moreover, SRF controls vasoconstriction *via* SMC phenotypic modulation^[61]. This fact might be supported by cellular activities in the treatment of AA using MSC therapy. Timmers *et al.*^[62,63] demonstrated that *iv* injection of human MSC-CM for treatment of MI in porcine model, resulted in reduced myocardial apoptosis, oxidative stress, myocardial infarct size, preserved systolic and diastolic function through reduction of TGF- β signaling including phospho-Smad2 and apoptosis including active caspase 3 following MSC-CM treatment. These studies also revealed that the fraction of the MSC-CM containing products > 1000 kDa improved cardiac function rather than the fraction of products < 1000 kDa. This result indicates that a large complex protein such as a combination of angiogenic factors rather than a single protein may be the responsible paracrine factor. Regarding MSC for AA, it is not clear which factors can induce a better effect. Although *iv* injection of MSC-CM provides easy delivery compared to direct MSC injection, the effects would be of short-term duration by degradation of molecules im-

mediately.

Study of MSC therapy for AA has only just begun, and MSCs are indeed a promising tool for AA treatment. Some studies have suggested that inflammation and ECM degradation at the AA wall site were inhibited by various anti-inflammatory cytokines, inhibitor of proteases and stimulator of ECMs synthesis which were induced by various growth factors secreted from MSCs. In addition, MSC therapy has been demonstrated to have an efficacy not only for prevention of AA development and progression but also regression of already-formed AA. These healing mechanisms remain unknown, and so further research will be warranted in the future.

CONCLUSION

Treatment of AA using MSCs has been demonstrated to be effective, and promises to be a new non-surgical therapeutic strategy. These effects might be promoted in a paracrine manner from MSCs as one possible mechanism.

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