MINI REVIEW

Plasticity of vascular resident mesenchymal stromal cells during vascular remodeling

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Abstract

Vascular remodeling is a complex and dynamic pathological process engaging many different cell types that reside within the vasculature. Mesenchymal stromal/stem cells (MSCs) refer to a heterogeneous cell population with the plasticity to differentiate toward multiple mesodermal lineages. Various types of MSC have been identified within the vascular wall that actively contribute to the vascular remodeling process such as atherosclerosis. With the advances of genetic mouse models, recent findings demonstrated the crucial roles of MSCs in the progression of vascular diseases. This review aims to provide an overview on the current knowledge of the characteristics and behavior of vascular resident MSCs under quiescence and remodeling conditions, which may lead to the development of novel therapeutic approaches for cardiovascular diseases.

Key Words

- mesenchymal stromal/stem cell (MSC)
- vascular resident MSC
- vascular remodeling
- MSC differentiation
- genetic lineage tracing

Introduction

Mesenchymal stromal/stem cells (MSCs) generally refer to a heterogeneous population of fibroblast-like cells with the self-renewal ability and the capacity to differentiate into cells of the mesodermal lineages including smooth muscle, bone, adipose and cartilage cells (1). MSCs isolated from multiple different organs and tissues commonly share similar features in *in vitro* settings. However, the characteristics and function of MSCs in their endogenous *in vivo* environment are still under study.

Accumulating evidence shows that MSCs primarily reside within the perivascular zone of both the adventitial layer of large vessels and the pericyte niche of microvessels in multiple organs (2, 3, 4). Many studies proposed that MSCs participate in maintaining the tissue homeostasis and contributing to the tissue regeneration in response to injury. However, there are also findings arguing against the tissue-specific differentiation ability of MSCs in their endogenous environment (5). Other comprehensive reviews discussed the differentiation of MSCs to tissue-specific cells under different conditions (6, 7). In this review, we aim to provide an overview on the contribution of large-vessel resident MSCs to vascular remodeling based on recent literatures.

Overview of vascular remodeling of large vessels

Large vessels are essentially composed of three layers: tunica intima, tunica media and tunica adventitia. The intimal layer mainly contains endothelial cells. The medial layer consists mostly of smooth muscle cells (SMCs) and a small number of MSCs. The adventitial layer hosts a heterogenous population of cells including fibroblasts, inflammatory cells, microvascular cells and a variety of MSCs (8). Vascular remodeling is a dynamic

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process involving the changes of vascular structure and vascular distribution in response to physiological or pathophysiological stimuli (9). During vascular remodeling such as atherosclerosis progression, vascular wall resident cells including MSCs undergo dynamic changes and actively contribute to the remodeling process.

Atherosclerotic vascular remodeling that underlies various cardiovascular diseases is initiated with endothelial dysfunction in response to pathogenic triggers and followed by the accumulation of SMCs, inflammatory cells and lipid to form neointimal lesions which lead to fibrous cap or plague rupture (10). SMC proliferation and accumulation is the predominant event that determines the progression and severity of vascular remodeling. A large proportion of these lesion-forming cells are derived from vascular resident SMCs that undergo phenotypic transitions. At the same time, vascular resident MSCs hold the plasticity to differentiate toward SMC and actively participate in the vascular remodeling process (Fig. 1).

Plasticity of vascular resident MSC during vascular remodeling

Since Hu *et al.* firstly reported the presence of adventitial Sca1+ MSC-like cells and their contribution to neointima formation in a vein graft atherosclerosis mouse model (11), many more studies provided evidence on the identification of resident MSCs within large vascular wall and their plasticity during vascular remodeling. Alternative names have been used to describe this population such as vascular progenitor cells, smooth muscle progenitor cells and so forth. To avoid confusion in this review, we use the name MSC for the mesenchymal cells with the plasticity to differentiate toward mesodermal lineages despite the original terms been used in previous reports. Recent advances of lineage tracing techniques allow better evaluation of the contribution of vascular resident MSCs to the progression of large vascular remodeling. Due to the lack of distinct marker that exclusively expressed by MSCs, multiple markers have been proposed to identify and trace large-vessel resident MSCs (Table 1).

Genetic lineage tracing of vascular resident MSCs in mouse

Applying a triple transgenic mouse model to map the fate of vascular SMCs, a recent study demonstrated that neointima-forming SMCs of severe arterial injury were derived from adventitial MSCs, but not from pre-existing SMCs (12). Using *Gli1-CreER*^{T2} to label Gli1+ MSCs that reside within the adventitia of large arteries and arterioles, a recent study showed that Gli1+ MSCs participate in vascular remodeling during both acute femoral artery injury and chronic atherosclerosis in *ApoE*$^{-/-}$ mice subjected to chronic kidney disease (13). Gli1+ MSCs differentiated toward SMCs and contributed to neointima formation in response to acute vascular injury. During chronic vascular injury, Gli1+ MSCs differentiated into osteoblast-like cells and accelerated vascular calcification. Inducible lineage tracing of c-Kit lineage cells labeled a subpopulation of adventitial MSCs and these c-Kit+ MSCs contributed to neointima formation in an aortic allograft mouse model of severe arteriosclerosis (14).

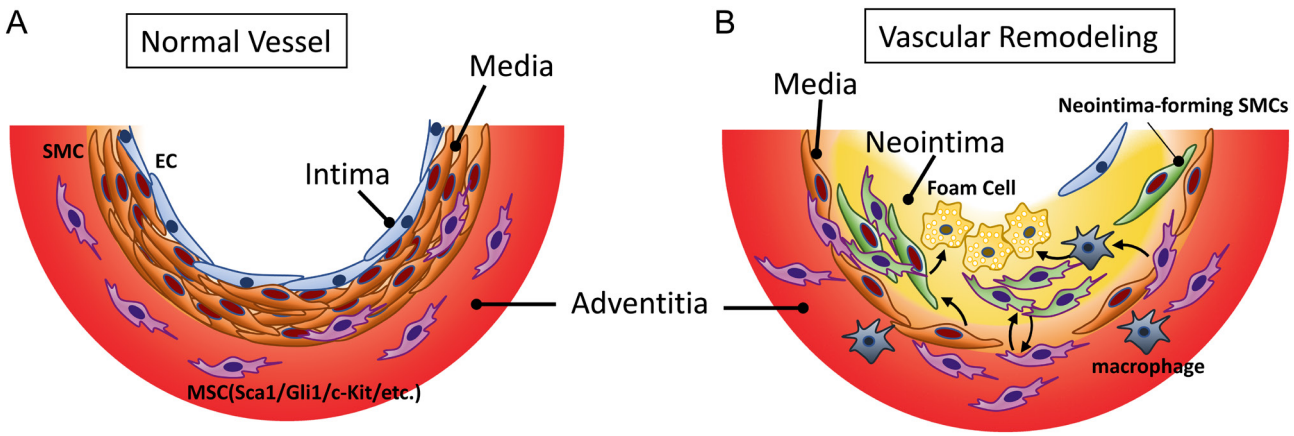

Figure 1
Plasticity of vascular resident MSC upon vascular remodeling. (A) Under normal physiological condition, majority of MSCs reside within the adventitial layer and a small population of MSCs reside within the medial layer. (B) Upon vascular remodeling, MSCs migrate and differentiate toward SMCs and contribute to neointima formation.

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Table 1 Mouse vascular resident MSCs identified in large vessels.

Main marker	Labeling tool	Location	Co-expressing markers	*In vitro* differentiation ability	*In vivo* function during vascular remodeling
Gli1 (13)	Genetic lineage tracing: *Gli1-CreER^{t2}*; *R26tdTomato*	Mouse arterial adventitia	CD34, Sca1, Pdgfrb	Toward SMCs, osteoblasts, adipocytes, chondrocytes.	• Acute arterial wire injury: differentiate toward SMCs and contribute to neointima formation. • Chronic injury during atherosclerosis: migrate and differentiate toward SMC and osteoblast-like cells during media and intimal calcification.
c-Kit (14, 15)	Genetic lineage tracing: *Kit-CreER*; *R26tdTomato/RFP*	Mouse aortic adventitia	Sca1, CD34, Pdgfra, CD45	Toward SMCs induced by TGFβ1.	• Aortic allograft model of severe arteriosclerosis: differentiate toward SMC and contribute to neointima formation. • Wire injury and carotid artery-ligation: minimal contribution. • *ApoE*$^{-/-}$ or *Ldlr*$^{-/-}$ mice on high-fat diet: give rise to SMC in the fibrous cap.
Tcf21 (16)	Genetic lineage tracing: *Tcf21-CreER*; *R26tdTomato/lacZ*	Mouse aortic and coronary arterial adventitia, aortic root media			
Sox10 (17, 18)	Genetic lineage tracing: *Sox10-Cre*; *R26RFP/lacZ*	Mouse arterial media and adventitia upon injury	S100β, Nfm	Toward SMCs, adipocytes, chondrocytes, osteoblasts.	• Carotid artery denudation injury: give rise to SMCs and contribute to neointima formation.
Sca1 (11, 27, 30)		Mouse aortic root adventitia	c-Kit, CD34, Ptc1, Ptc2	Toward SMCs induced by PDGF-BB.	• Vein graft in *ApoE*$^{-/-}$ mice: migrate and differentiate to SMCs traced by SM-lacZ. • Sca1+ cells grafting on the adventitial side of wire-injured femoral arteries: contribute to neointima formation.

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However, c-Kit+ MSCs participated minimal in the neointimal lesions in wire injury and carotid artery-ligation models (15). Nurnberg *et al.* used TCF21 to identify an adventitial MSC population that can differentiate toward SMC and contribute to fibrous cap formation during atherosclerosis in *ApoE*$^{-/-}$ or *Ldlr*$^{-/-}$ mice (16). Song Li's group proposed an MSC-like population in the arterial media and adventitia marked by Sox10 that can give rise to SMC in neointima formation upon carotid artery denudation injury (17, 18).

Collectively, above evidence using different genetic labeling tools indicates the dynamic plasticity of different subpopulations of the heterogeneous large-vessel resident MSCs during vascular remodeling. Of note, MSCs generally contribute to a greater extent in the more severe vascular remodeling models.

In addition to the process of vascular resident MSCs differentiating toward other cell types during vascular remodeling, differentiated SMCs can also give rise to MSCs. Using *Myh11-CreER*^{T2} and *SM22a-Cre* to trace SMC-derived cells, Mark Majesky *et al.* demonstrated a subpopulation of adventitial Sca1+ MSCs was generated from differentiated SMCs and they participated in the adventitial remodeling in response to vascular injury (19). Using a similar lineage tracing strategy to trace SMC-derived cells in chronic atherosclerosis model with *ApoE*$^{-/-}$ mice, Shankman *et al.* identified MSC-like cells derived from SMCs within the atherosclerotic plaques (20). Interestingly, both studies identified Klf4 as a key factor for regulating phenotypic plasticity. Combining single-cell transcriptomics with *Myh11-CreER*^{T2} to examine SMC in healthy and atherosclerotic vessels, a recent study showed that adventitial Sca1+ MSCs were rarely derived from SMCs while a subset of Sca1+ SMC within the media underwent active phenotypic transitions in response to carotid ligation injury (21). Taken together, the dynamic switching between different MSC populations and SMCs requires further clarifications to demonstrate a well-defined hierarchical structure upon vascular injury.

Identification of vascular resident MSCs in human

The identification of vascular resident MSCs in human is challenging due to the lack of proper research tools. The direct mapping of MSCs identified in mouse to human is hard to achieve. For example, a human ortholog of *Sca1* gene has not been well defined. Several studies proposed using specific markers to carefully label subsets of MSCs within human large vascular wall that play potential roles in vascular remodeling (Table 2). CD34+/CD31− cells with MSC properties were identified in the adventitia of human adult saphenous vein (22). After isolation, they could differentiate toward SMC *in vitro* and engraft and support vascular formation *in vivo* using a mouse model of hindlimb ischemia. CD90 marked a subset of mesenchymal cells within adult human healthy and atherosclerotic medium- and large-sized arterial adventitia (23). By performing RNA-Seq analysis on the CD90+ MSCs from health and diseased aortas, the study showed that CD90+ MSCs from diseased aorta exhibited altered gene expression signature related to the disease progression. CD44+ was applied to mark an MSC population isolated from human arterial adventitia that also exhibited multi-lineage differentiation ability *in vitro* (24). With the fast-evolving single-cell level analytic tools, characterization of human large-vessel resident MSCs under healthy and vascular remodeling conditions may be better understood in the near future.

Mechanisms regulating vascular resident MSC plasticity

Various mechanisms including PDGFβ (11), TGFβ1 (25), collagen IV (26) and other signaling pathways have been implicated in regulating the phenotypic changes of vascular resident MSCs in *in vitro* differentiation settings. However, mechanisms that regulate MSC plasticity upon vascular remodeling *in vivo* are not well elucidated. A few studies using different genetically engineered mouse models shed light on this issue. Using Sonic hedgehog (Shh) signaling receptor patched-1 (*Ptc1*^{lacZ}) and patched-2 (*Ptc2*^{lacZ}) reporter mice, Passman *et al.* reported that Shh signaling was activated in the adventitial layer of artery wall and might play a role in maintaining the progenitor phenotype of adventitial Sca1+ MSCs (27). Hypomorphic c-myb (*c-myb*$^{h/h}$) mice showed reduced neointimal formation in response to carotid artery denudation injury due to impaired adventitial Sca1+ MSC proliferation and differentiation (28). As mentioned in the previous session, transcription factor Klf4 is implicated in modulating the phenotypic changes between MSC and SMC upon vascular injury (19, 20). With the current progression, further work is required to better understand the comprehensive signaling network that coordinates the plasticity of vascular resident MSCs during vascular remodeling. Deciphering the regulatory mechanisms is the base to develop novel therapeutic approaches targeting selected vascular resident MSC populations.

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Table 2 Human vascular resident MSCs identified in large vessels.

Main marker	Location	Co-expressing markers	*In vitro* differentiation ability	*In vivo* function upon cell transplantation to mouse models
CD34 (22, 31)	Human saphenous vein adventitia	NG2, PDGFRβ, Desmin, Vimentin	Toward SMCs, osteoblasts, adipocytes, chondrocytes.	• Hindlimb ischemia model: incorporate with host tissue and facilitate neovascularization and blood flow recovery. • Subcutaneous Matrigel vasculogenesis assay: support vessel formation.
CD44 (24)	Human internal thoracic artery	CD90, CD73	Toward SMCs, adipocytes, chondrocytes, osteocytes.	
CD90 (23)	Human internal thoracic artery, ascending aorta	PDGFRα, CD44, CD73, CD105	Toward osteoblasts, adipocytes, chondrocytes.	• Hindlimb ischemia model: increase angiogenesis and tissue perfusion.
(32)	Human pulmonary artery adventitia	Vimentin, Col1a1, CD29, CD44, CD105	Toward SMCs, adipocytes, chondrocytes, osteocytes.	
CD34+, CD146− (33)	Human adipose tissue arteries and veins adventitia	CD44, CD73, CD105, CD90	Toward pericytes, adipocytes, chondrocytes, osteocytes.	

Summary and perspectives

Vascular wall serves as a reservoir hosting a variety of MSC populations. Upon vascular remodeling, MSCs profoundly contribute to the dynamic cell composition changes within the vasculature. The fast-evolving genetic lineage tracing and genetic engineering tools facilitate us to study the exact roles of different vascular resident MSC populations in more details. However, many of the markers that we use to label vascular resident MSCs are also shared by other cell populations. A combination of single-cell transcriptomics/proteomics and genetic lineage tracing techniques could potentially provide more insights into the different roles played by vascular resident MSCs during vascular remodeling.

With the growing knowledge of the behavior of vascular resident MSCs under pathological conditions, MSC emerges as a potential therapeutic target by manipulating their plasticity. A previous work demonstrated that overexpressing Smad7 by adenovirus around adventitia to antagonize TGFβ1 signaling led to attenuated migration of adventitial cells and reduced neointima formation after balloon injury in rat carotid arteries (29). A recent study showed improved vascular remodeling by delivering a single gene ETV2 into vascular adventitial Sca1+ cells to direct them toward the endothelial lineage (30). Gene therapy targeting the vascular resident MSC represents a promising therapeutic approach to control vascular remodeling progression and to enable endogenous vascular repair.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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