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REVIEW

Mesenchymal stem cell subpopulations: phenotype, property and therapeutic potential

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Abstract Mesenchymal stem cells (MSC) are capable of differentiating into cells of multiple cell lineages and have potent paracrine effects. Due to their easy preparation and low immunogenicity, MSC have emerged as an extremely promising therapeutic agent in regenerative medicine for diverse diseases. However, MSC are heterogeneous with respect to phenotype and function in current isolation and cultivation regimes, which often lead to incomparable experimental results. In addition, there may be specific stem cell subpopulations with definite differentiation capacity toward certain lineages in addition to stem cells with multi-differentiation potential. Recent studies have identified several subsets of MSC which exhibit distinct features and biological activities, and enhanced therapeutic potentials for certain diseases. In this review, we give an overview of these subsets for their phenotypic, biological and functional properties.

Keywords Stromal cells · Heterogeneity · Cell surface markers · PDGFR · CD146

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Introduction

Mesenchymal stem cells (MSC) have been considered as an ideal source for cell and gene therapy strategies. MSC were first isolated from the bone marrow (BM) by Friedenstein and colleagues in 1970 [1]. As a rare population (1 in 10,000 nucleated cells) in the BM, they were initially referred to as marrow stromal cells. Subsequently, MSC have been found in almost all tissues such as adipose tissue (AT) [2] and extra embryonic tissues including the amniotic membrane [3], placenta [4] and umbilical cord [5]. MSC possess the ability of self-renewal and multilineage differentiation in vitro and in vivo [6, 7]. For examples, MSC can be induced to differentiate into cells of mesenchymal lineage and form bone, cartilage and fat [6, 8, 9]; they have also been demonstrated to generate certain cell types that normally derived from the endoderm and ectoderm in vivo and contribute to tissue repair, despite at low frequencies [7, 10–13].

MSC have demonstrated profound therapeutic potential in promoting the repair and regeneration of damaged tissues in major organs such as the heart, brain, liver, lung, kidney, and skin, and may provide effective treatments for a range of degenerative and inflammatory diseases including diabetes, neurological disorders and osteochondral defects [11, 14–16].

The lack of a specific cell surface marker for prospective isolation of MSC makes the isolation and identification of the cells difficult and inconsistent. Diverse antigens have been found on the surface of MSC [17, 18], but none of them is unique to the cells. To facilitate a more uniform characterization of MSC, the International Society for Cellular Therapy (ISCT) has formulated minimal criteria for MSC: (1) MSC adhere to uncoated plastic culture dish under the standard culture conditions; (2) MSC must

simultaneously express CD105, CD73 and CD90, but not lineage markers such as CD45, CD34, CD14 or CD11b, CD79alpha or CD19 and HLA-DR; (3) MSC must differentiate into osteoblasts, adipocytes and chondrocytes in vitro [19]. The ISCT criteria for MSC are based on the features of MSC that have been culture expanded in vitro, and may not well reflect the property of MSC in vivo. In many studies, MSC that have been used meet two ISCT criteria (tri-lineage differentiation potential in vitro and attachment to uncoated tissue culture dishes) but not the requirement for surface markers, particularly positively expressed proteins.

MSC met with the above basic criteria, however, often represent a mixture of phenotypically, functionally and biochemically diverse cells [20, 21]. In many studies, MSC with morphologic homogeneity and uniform expression of certain surface antigens are obtained by high density culture for several passages [7, 19, 22]. Unfortunately, this procedure is likely to deplete MSC with valuable properties. Several studies have shown that single-cell-derived colonies of human MSC contain at least three morphologically disparate cell types: the extremely small and rapidly self-renewing cells, the elongated spindle shaped fibroblast-like cells, and the slowly replicating, large, cuboidal or flattened cells [23, 24]. The small-sized MSC derived from human BM which can be distinguished from the other cell types in the same culture exhibit rapid rate of replication and enhanced potential for multilineage differentiation, migration and tissue engraftment [23–25]. However, the fraction of small-sized MSC decreased in culture with successive expansion and lost multipotency [23]. In addition to differences in cell morphology, many proteins are not uniformly expressed in MSC even at early passages. For example, many receptors crucial for cell activities such as C-X-C chemokine receptor type 4 (CXCR4), platelet-derived growth factor receptor (PDGFR), vascular cell adhesion protein (VCAM)-1 (CD106) are restricted to certain subpopulations [26–28]. Notably, colonies formed by single MSC show different differentiation potency, with varying capacity for differentiation [29], suggesting the existence of asymmetrical division and differentiation of the stem cells in replication. The differences in isolation and culture procedures further contribute to the difference in differentiation potential of MSC [29–31]. It has been known that culture conditions affect the epigenetic state of genes involved in pluripotency and differentiation. We and others have shown that MSC tend to differentiate spontaneously toward osteoblast lineage in current adherent culture regime with decreasing expression of pluripotent genes upon passaging [32, 33]. Taken together, these findings reflect the fact that MSC are a heterogenous population consisting of cells with distinct morphologic and functional characteristics.

The heterogeneity of MSC may impair their therapeutic efficacy and introduce variations between studies [20]. The use of specific subpopulations of MSC may eliminate some interfering cells so as to enhance their particular capability for certain conditions and design more effective therapies. Therefore, it is important to further subfractionate MSC and characterize their differences with respects to differentiation potency, proliferative rate, immunosuppressive capability and other biological functions to compare studies and standardize therapies.

Surface proteins are ideal parameters for cell identification and characterization. MSC express a variety of surface antigens [11, 17, 18]. Accumulating studies have indicated that certain MSC subpopulations with distinctive surface proteins display different biological activities and corresponding therapeutic effects (Table 1). This review mainly focuses on studies involving surface proteins-based MSC subpopulations, and their biological activities and therapeutic potentials, aiming to delineate MSC subpopulations for specific therapeutic purposes.

Stro-1$^+$ MSC

Stro-1 antigen is probably the first marker used to identify MSC in the BM. Stro-1, which is a 75 kDa protein [34], was localized to the endothelium of some arterioles and capillaries in some tissues tested such as the adipose, muscle, liver, lungs and kidneys [34, 35]. A previous study showed that $\sim$8.7 % of CD34-expressing BM nucleated cells expressed Stro-1 [35]. However, its relationship with endothelial cells needs further studies to clarify.

Stro-1 has been used to identify MSC with high colony-forming unit-fibroblast (CFU-F) efficiency and multipotency. In human BM, Stro-1 antigen was expressed on the surface of $\sim$11.2 % of unfractionated mononuclear cells (MNC) [36]; in primary adherent culture of BM cells, about 6 % cells expressed Stro-1 [37]. Stro-1 were highly expressed on high-growth capacity MSC and proposed as a critical marker to assess MSC functional potency [38]. Stro-1 is also expressed in nucleated erythroid precursors. Thus, multipotent MSC can be enriched by sorting for the Stro-1^{bright}/CD34$^-$/CD45$^-$/glycophorin-A$^-$ fraction of human BM-MNC [39, 40].

Previous studies suggest that Stro-1$^+$ MSC exhibit enhanced trafficking and tissue repair abilities. After intravenous injection, higher amounts of Stro-1$^+$ cells were detected in the spleen, muscles, BM, liver and kidneys, but fewer cells were entrapped in the lungs compared to Stro-1$^-$ cells, suggesting superior trafficking ability and tissue engraftment of Stro-1$^+$ cells [37]. Additionally, intramyocardial injection of Stro-1$^+$ human BM-MNC resulted in

Table 1 Summary of biological functions and therapeutic efficacy of MSC subpopulations

MSC subpopulations	Tissue sources	Biological functions	Therapeutic efficacy
Bone repair/regeneration			
$CD146^+$ MSC [79]; $LepR^+$ MSC [121]	hBM [79] mBM [121]	Express higher osteo-related genes and show enhanced osteogenic differentiation [79, 121]	Enhance bone regeneration in irradiated or fractured bone in mice [121]
Cartilage repair/regeneration			
$CD271^+$ MSC [22, 49]	hSM [22] hBM [49]	Express higher chondrogenic genes and exhibit greater chondrogenic potential [22, 49]	Enhance chondrogenic differentiation and repair to cartilage defects in rats [49]
Myocardial repair/regeneration			
$CD105^+$ MSC [56, 60, 61]	hBM [61] hUCB [56] hWJ [60]	Enhance myogenic differentiation potential [56, 60, 61]	Reduce infarct size and improve cardiac function [56]
Stro-1^+ MSC [36, 37, 41]	hBM [36, 37, 41]	Promote angiogenesis likely through expressing high levels of pro-angiogenic factors [36, 37, 41]	Improve myocardial contractility and increase vascular density in rats [41]
$CD146^+$ MSC [86, 87]	hSMP [87] placenta [86]	Differentiate into cardiomyocytes and express higher levels of pro-angiogenic factors [86, 87]	Attenuate left ventricular dilatation and significantly improve cardiac contractility [87]
Skin repair/regeneration			
PDGFRα^+ MSC [13, 26];	mBM [13, 26]	Enhanced migration into skin lesions and differentiation into kerationcytes [13, 26]	Enhanced skin repair/regeneration and therapeutic potential to skin diseases [13, 26]
Immunoregulation			
$CD106^+$MSC [4]; $CD271^+$ MSC [50]	placenta [4] hBM [50]	Express higher levels of immunosuppressive cytokines and exhibit superior immunosuppressive effect [4, 50]	Suggest enhanced therapeutic potential in treating immune diseases [4, 50]
Migration and homing			
$CD44^+$ MSC [119]	mBM [119]	Enhance proliferation rate and homing capacity [119]	Increase recruitment of MSC into injured renal tissue, resulting in enhanced repair/regeneration [119]
$CXCR4^+$ MSC [111, 112, 114, 115]	BM [111, 112, 114, 115]	Enhance migration and engraftment to injured tissues [111, 112, 114, 115]	Promote LV function recovery [112]; promote the early regeneration of the remnant liver of rats [115]; improve renal function [111] and brain lesion [114]
As niche cells			
$Nestin^+$ MSC [85, 91, 92, 103–105]; $CD146^+$ MSC [79, 84, 85, 103]; PDGFRα^+Sca-1^+MSC [91]; PDGFR$\alpha^+$$CD51^+$MSC [92]	hBM [79, 84, 103–105] mBM [91, 92] hSVF [85]	Constitute hematopoietic niche, support HSC ex vivo expansion [79, 84, 85, 91, 92, 103–105]	Suggest therapeutic potential in enhancing hematopoiesis [79, 84, 85, 91, 92, 103–105]
Other potential applications			
$Nestin^+$ MSC [107]	hBM [107]	Produce coagulation factor FVIII [107]	Therapeutic potential in treating hemophilia [107]

MSC mesenchymal stem cells, *LepR* leptin receptor, *h* human, *m* mouse, *BM* bone marrow, *SM* synovium membrane, *UCB* umbilical cord blood, *WJ* Wharton's jelly, *SMP* skeletal muscle pericytes, *CXCR4* C-X-C chemokine receptor type 4, *LV* left ventricular, *SVF* stromal vascular fraction, *HSC* hematopoietic stem cells

improved myocardial contractility and increased vascular density in rats with myocardial infarction compared to Stro-1^- BM-MNC [41], probably through enhanced paracrine effect [36]. Impressively, human BM-MSC from Stro-$1^+$$CD45^-$Glycophorin-$A^-$ fraction showed potent differentiation into hepatocytes after intrahepatic delivery in fetal sheep [12], suggesting a valuable source of cells for liver repair and regeneration.

Stro-1 has been detected in diverse tissues, but appears not to be restricted to MSC. In the adipose tissue, for instance, putative MSC ($CD34^-CD31^-$) did not express Stro-1 initially, but turned to express the marker after being cultured in endothelial growth medium [34, 35], implying its limitation as a marker for prospective isolation of MSC from tissues.

$CD271^+$ MSC

CD271, also known as the low-affinity nerve growth factor receptor or p75 neurotrophin receptor [42], is expressed in MSC derived from different tissue sources with 2–30 % positive rates [3, 22, 43]. Basic fibroblast growth factor (bFGF) was found to decrease the expression of CD271 in BM-MSC in culture [44]. Notably, CD271 is expressed at low levels ($CD271^{dim}$) by other cells such as HSC in the BM [45, 46], and therefore, sorting for the $CD271^{bright}$ subset is necessary to avoid HSC contamination in MSC purification.

CD271 has been used as a marker to label primitive MSC. $CD271^+$ BM-MNC generate more CFU-F with stronger capability for tri-lineage differentiation and lower hematopoietic contamination, compared to those isolated by plastic adherence (PA-MSC) or BM cells negative for CD45 and glycophorin-A [43, 44, 47]. In addition, CD271 was found to define a subpopulation adipose tissue derived MSC (AT-MSC) with high proliferative and clonogenic capacity [43]. Notably, $CD271^+$ BM-MSC appear to have enhanced osteogenic and chondrogenic differentiation capacity compared to unsorted MSC [43, 47–49]. Moreover, $CD271^+$ BM-MSC have been shown to have superior paracrine effect in inhibiting the proliferation of allogeneic T lymphocytes (largely through prostaglandin E2), and in supporting the engraftment of hematopoietic stem/progenitor cells (HSC) compared to PA-MSC [50].

Recent studies suggest that $CD271^+$ MSC are not uniform in composition. MSC subpopulation based on single marker CD271 selection remain heterogeneous and maybe contaminated by other cell types such as neutrophils, endothelial cells or hematopoietic progenitors [43, 47]. In addition, colonies formed by purified single BM $CD271^+$ cells showed considerable variation in differentiation into the three cell lineages [48]. Moreover, $CD271^+CD140a^-$ but not $CD271^+CD140a^+$ BM cells exhibited capacity to support the ex vivo expansion of HSC [51]. $CD271^{bright}$-$CD56^+$ BM-MSC showed approximately threefold and 180-fold increases in cloning efficiency in comparison with $CD271^{bright}CD56^-$ cells and unfractionated BM cells, respectively [52].

$CD271^+$ MSC have shown enhanced therapeutic efficacy in many conditions. $CD271^+$ BM-MSC demonstrated enhanced effect in chondral repair and healing in rats with chondral injury compared to PA-MSC [49]. $CD271^+$ BM-MSC from humans or pigs significantly improved cardiac function and attenuated adverse remodeling in infarcted murine heart [53]. Moreover, an in vitro study suggests that $CD271^+$ BM-MSC maybe more effective in wound healing [54].

$CD105^+$ MSC

CD105 (Endoglin, SH2) is a part of the transforming growth factor (TGF)-β receptor complex and plays a vital role in vascular development and remodeling [55]. The expression of CD105 varies considerably in MSC derived from different tissue sources, from over 90 % in human BM-MSC and AT-MSC to 20–30 % in MSC derived from human synovial membranes [22, 56]. It is of note that CD105 is also expressed by other cell lineages such as endothelial cells [55] and HSC [57].

Several studies suggest that $CD105^+$ MSC have superior myogenic potential. Unfractionated MSC have been shown to promote the repair of the infarcted myocardium in numerous studies; however, the incidence of differentiation of MSC into cardiomyocytes is very low [58, 59]. To achieve enhanced regeneration of the infarcted heart, subpopulations of MSC with enhanced myogenic differentiation capacity are desirable. $CD105^+$ human MSC showed enhanced differentiation into myoblast-like cells after myogenic induction in vitro and differentiated into muscle cells upon transplantation into damaged skeletal muscles in rats [60, 61]. Similarly, $CD105^+$ human MSC showed better survival in the infarcted murine heart resulting in enhanced repair [56]. As cardiomyocytes derived from MSC have been shown in low numbers and are unlikely to cause a significant improvement in myocardial regeneration, it is likely that $CD105^+$ MSC promotes myocardial repair though an enhanced paracrine effect [62–64].

Of note, a very recent clinical study showed that disc injections of autologous BM concentrate which contained a considerable fraction of $Lin^-/CD105^+$ cells in patients with degenerative disc disease significantly reduced lumbar discogenic pain [65].

$CD106^+$ MSC

CD106 (VCAM-1) is a cell surface protein known to be involved in the adhesion of leukocytes to vascular endothelium [66]. CD106 is expressed in a fraction of MSC, varying from 30 to 75 % in human BM-MSC and placental MSC, and lower expression in cord MSC and

AT-MSC [4, 22, 67]. But the surface expression of the protein appears to decrease with extended passaging of MSC or differentiation [4, 68].

Previous studies suggest that CD106 represents MSC with enhanced multipotency. $CD106^{+}$/Stro-1^{+} human BM-MSC showed higher clonogenic capacity and tri-lineage differentiation potential [69]. A recent study found that $CD106^{hi}CD271^{+}CD90^{+}$ human BM-MSC consistently exhibited faster growth rate, robust multilineage differentiation and enhanced trafficking capacity with lower vascular obstructions in the lungs following infusion, compared to $CD271^{+}CD90^{+}CD106^{-}$ and $CD271^{+}CD90^{+}$ MSC [27]. Moreover, abundant engraftment of endogenous $Lin^{-}/CD106^{+}/CD44^{+}$ BM-MSC were found in damaged muscles in mice with muscular dystrophy [70].

A growing body of studies suggests that $CD106^{+}$ MSC have enhanced immunosuppressive activity. CD106 on the surface of MSC appears to play a critical role for mediating cell–cell contact with immune cells, a step necessary for the immunosuppressive effect of MSC to immune cells. When CD106 in MSC was genetically deleted or functionally blocked, MSC-mediated immunosuppression was significantly reversed [71, 72]. In addition, $CD106^{+}$ MSC from human placenta showed stronger immune regulatory activity that may largely be due to higher expression of immune-associated cytokines including COX-2, IL-1a, IL-1b, IL-6 and IL-8. These studies suggest that $CD106^{+}$ MSC may promise enhanced therapeutic potential for immune diseases [4].

$CD146^{+}$ MSC

CD146, also known as Mel-CAM, MUC18, A32 antigen, and S-Endo-1, is a membrane glycoprotein which functions as a Ca^{2+}-independent cell adhesion molecule involved in heterophilic cell–cell interactions [73]. The fraction of $CD146^{+}$ MSC varies from tissue to tissue and is affected by tissue culture conditions. It accounts for 40–70 % of BM-MSC [74, 75], 16–40 % of umbilical cord-derived MSC [74, 76], and about 20 % of AT-MSC [75]. The expression level of CD146 in BM-MSC was up-regulated under normoxia or after TGF-β1 treatment and down-regulated under hypoxia or being treated with bFGF [77]. CD146 is localized as pericytes, which are located immediately outside of capillaries and microvessels in various tissues such as the muscle, adipose, BM and placenta and co-express CD73, CD90, CD105 and CD44 [78]. In addition, perivascular CD146-expressing MSC are also positive for NG2 and PDGF receptor (PDGFR)β [78, 79]. $CD146^{high}CD34^{-}CD45^{-}CD56^{-}$ perivascular cells isolated from human muscle and several other tissues showed characteristic differentiation into adipoctyes, chondrocytes and osteoblasts, in addition to their myogenic potentials [78]. These findings suggest a perivascular origin of MSC. Certain pericytes that are characterized as $CD146^{high}$-$CD34^{-}CD45^{-}CD56^{-}$ appear to represent a subpopulation of MSC [78, 80, 81]. In human BM, $CD146^{+}$ MSC reside on the sinusoidal wall as subendothelial stromal cells. As clonogenic skeletal progenitors in the BM, $CD146^{+}$ MSC are capable of regenerating the bone, stroma, and maintaining the hematopoietic microenvironment by producing angiopoietin-1 (Ang-1), a pivotal molecule of the HSC niche [79]. Several studies indicated that CD146 identified MSC with multilineage differentiation potential. When $CD146^{+}$ and $CD146^{-}$ cells were separated from human umbilical cord perivascular cells, $CD146^{+}$ cells showed differentiation into adipocytes, chondrocytes and osteoblasts, but $CD146^{-}$ cells did not [82]. Consistently, MSC clones with tri-lineage differentiation potential exhibited higher CD146 expression compared to unipotent clones [83]. Moreover, the expression of CD146 decreases in culture, which is associated with the reduction of CFU-F frequency [2].

Moreover, $CD146^{+}$ MSC in the BM support HSC self-renewal likely through the release of paracrine factors such as vascular endothelial growth factor (VEGF), stem cell factor (SCF), Ang-1 and stromal cell-derived factor (SDF)-1 [84] and cell-to-cell contact such as Notch signaling [85].

Several studies indicate that $CD146^{+}$ MSC are myogenic and are capable of regenerating muscle cells. $CD146^{+}CD34^{-}CD45^{-}CD56^{-}$ MSC expressed genes typical for muscle cells in culture [78, 86] and differentiated into dystrophin-expressing muscle cells when injected into gastrocnemius muscles in mice [86]. Impressively, injection of $CD146^{+}CD34^{-}CD45^{-}CD56^{-}$ MSC purified from human skeletal muscles into the infarcted myocardium in mice attenuated left ventricular dilatation and significantly improved cardiac contractility, with detection of cardiomycytes derived from the transplanted cells [87]. Of note, pericytes have demonstrated a potent pro-angiogenic effect through release of pro-angiogenic factors such as VEGF-A, PDGF and TGF-β1 [86, 87], suggesting that the paracrine effect is also likely attribute to the enhanced effect of $CD146^{+}$ MSC in myocardial repair [87].

$PDGFR\alpha^{+}$ MSC

PDGFRα (CD140α), is a cell surface tyrosine kinase receptor for members of the PDGF family. In human BM-MSC acquired by plastic adherence, the percentage of PDGFRα-expressing cells varies from 10 to 90 %, and appears to be affected by the age of donors; with aging, the percentage of $PDGFR\alpha^{+}$ MSC declines [38].

Accumulating evidence shows that PDGFRα$^+$ cells reside in the perivascular location of many adult tissues, with robust CFU-F forming ability and tri-lineage differentiation potential [88–91]. BM-derived non-hematopoietic PDGFRα$^+$ cells have been shown to differentiate into ectodermal keratinocytes and mesenchymal dermal fibroblasts, particularly in the setting of wound with allogeneic skin grafts [13].

MSC in the BM are of central importance for the hematopoietic microenvironment. Recent studies have made significant advances toward the understanding of the phenotypic definition of these cells. PDGFRα$^+$Sca-1$^+$ cells can function as hematopoietic niche cells, and migrate to appropriate sites and differentiate into bone, cartilage, fat and endothelium after systemic infusion [88, 91]. PDGFRα$^+$CD51$^+$ MSC form self-renewing clonal mesenspheres capable of transferring hematopoietic niche activity in vivo and expressing high levels of HSC regulatory genes supporting the ex vivo maintenance and expansion of human HSC [92]. A recent study, however, showed that the expression of PDGFRα decreased progressively in postnatal humans and mice, and in adult human BM, PDGFRα was no longer expressed on the surface of MSC with potent hematopoiesis-supporting capacity [51]. Conversely, Lin$^-$CD45$^-$CD271^{+-} PDGFRα$^{low/-}$ BM cells exhibited higher proliferation potential and efficiently induced ex vivo expansion of transplantable CD34$^+$ HSC in addition to their tri-lineage differentiation potential, compared to Lin$^-$CD45^{--} CD271$^+$PDGFRα$^+$ BM cells which could not be passaged in culture [51].

BM-derived cells have long been reported to contribute to keratinocytes in vivo [93]. We and others observed that a proportion of BM-MSC transplanted into fresh wounds in mice engrafted into the tissue and some of them further differentiated into keratinocytes in the newly formed epidermis [10, 11], although these cells were not long lasting. The results suggest that there might be a special subpopulation of MSC which is prone to differentiate into epidermal cells. A recent study supports this speculation. The study showed that Lin$^-$ PDGFRα$^+$ non-hematopoietic cells in the BM were mobilized into the peripheral blood, and recruited into the allogeneic skin graft, where they differentiated into keratinocytes which accounted for a significant fraction of cells in the newly formed epidermis [13]. In a more recent study, BM-derived PDGFRα$^+$ MSC was shown to migrate to the skin graft and expressed collagen VII, leading to the amelioration of blistering lesion after transplantation into the mice with dystrophic epidermolysis bullosa (Col7-null) [26]. These results suggest that PDGFRα may serve as a marker to purify MSC for enhanced the repair/regeneration of skin injuries.

In addition, PDGFRα$^+$ MSC derived from human lungs showed greater effects in repairing elastase-injured lungs compared to unfractionated BM-MSC [89], and Nestin$^+$ PDGFRα$^+$ MSC derived from kidneys were effective in reducing renal ischemic injury in mice [90].

PDGFR-β$^+$ MSC

PDGFR-β (CD140b), as a receptor tyrosine kinase, plays a critical role in blood vessel formation and early hematopoiesis. It is expressed in vascular smooth muscle cells and pericytes [78, 94, 95]. PDGFR-β signaling is essential for the recruitment and differentiation of vascular smooth muscle/pericyte progenitors during vascular development [94, 95]. Several studies indicate that MSC derived from the BM and adipose express abundant PDGFR-β [96, 97].

Previous studies indicate that PDGFR-β signaling has a key role in vascular mural cell formation, and exerts a neuroprotective effect in adult mice. Lack of PDGFR-β leads to reduced vascular smooth muscle cell/pericyte proliferation and migration, and affects embryonic blood vessels formation in mice [95]. In addition, studies demonstrate that PDGFR-β is of significance in the recruitment, proliferation, and functional activity of pericytes during the remodeling phase of wound healing [98]. Recent studies suggest that PDGFR-β mediated signaling is a potent regulator of MSC function, which appears to promote the proliferation and migration but suppresses osteogenic differentiation of the cells [99]. In addition, sorted PDGFR-β$^+$ MSC expressed some genes normally expressed in smooth muscle cells such as α-SMA, SM22, MYH11 [9], but direct contribution of MSC to vascular smooth muscle cells has been barely detected.

Previous studies show that the contractile phenotype of MSC is regulated by PDGFRs, and PDGFR-β strongly promotes smooth muscle α-actin filament depolymerization. Therefore, PDGFR-β signaling is likely to be crucial for contractile MSC in vascular repair and tissue engineering applications [96]. Via BM transplantation and ex vivo artery culture approaches, a recent study showed that adventitial pericytes, which highly expressed PDGFR-β, CD146 and NG2, contributed to arterial restenosis following injury [100]. Notably, recent studies suggest that PDGF signaling may be involved in MSC potency; PDGFR inhibitor induced MSC towards a more round shape with increased expression of Oct4 and Nanog [97, 101], suggestive of an increase in "stemness".

PDGFR-β represents an important target for guiding tissue regeneration or tissue engineering, but limited information has been obtained regarding to the therapeutic application of PDGFR-β-expressing MSC.

Nestin$^+$ MSC

Nestin is an intermediate filament protein involved in the development of central nervous system and neural differentiation [102]. In the BM of human and mice, Nestin$^+$CD146$^+$ MSC are localized to the perivascular site. Nestin$^+$ MSC could be expanded in suspension culture as mesenspheres, which expressed high levels of alkaline phosphatase, a signature of stem cell potency. Impressively, paracrine factors of Nestin$^+$ mesenspheres supported culture expansion of HSC [92, 103, 104].

As Nestin is an intracellular protein, Nestin$^+$ MSC have recently been isolated by sorting for cells expressing a combination of certain surface markers. A large portion of Nestin$^+$ murine and human fetal MSC expressed PDGFRα and CD51 [92]. A fraction of Nestin$^+$ adult human BM-MSC also expressed CD105 and CD146, which were capable of forming mesenspheres, while CD105$^-$CD146$^-$ or CD105$^+$CD146$^-$ cells did not generate any progeny [104].

Recent studies suggest that Nestin$^+$ MSC are involved in the formation of fibrotic lesions. After arterial injury in mice and rats, activated TGF-β1 recruited circulating MSC (defined as Sca1$^+$CD29$^+$CD11b$^-$CD45$^-$, of them 91 % were Nestin$^+$) to the site of injury, where they gave rise to both endothelial cells for reendothelialization and myofibroblastic cells to form thick neointima [105]. In line with this work, a recent study suggest that Nestin$^+$ MSC in the BM is involved in the development of osteoarthritis. High levels of TGF-β1 caused the proliferation of Nestin$^+$ MSC leading to the formation of marrow osteoid islets accompanied by high levels of angiogenesis [106].

Interestingly, Nestin$^+$ BM-MSC expressed coagulation factor FVIII. Intravenous injection of Nestin$^+$ MSC into hemophilia mice corrected hemophilia and survived bleeding challenge [107].

CXCR4$^+$ MSC

CXCR-4, is an alpha-chemokine receptor specific for SDF-1. Previous studies have indicated that a fraction (0.5–96 %) of MSC in the initial culture express CXCR4 on the surface, but lose their surface expression after four to five passages [11, 108]. The expression of intracellular CXCR4, however, is maintained even after several passages [11]. Of note, some methods have been reported to increase the expression of CXCR4. Short-term exposure of human Flk1$^+$ BM-MSC to a cocktail of cytokines consisting of Flt-3 ligand, SCF, IL-6, hepatocyte growth factor (HGF) and IL-3 induced a significant up-regulation of both cell surface and intracellular CXCR4 [109]. In addition, culturing of human MSC as three-dimensional aggregates (spheroids) has been reported to restore functional expression of CXCR4 [110]. Moreover, short-term exposure of MSC to hypoxia could upregulate CXCR4 expression [111].

Previous studies suggest that CXCR4$^+$ MSC are more effective in repairing ischemic injuries. CXCR4$^+$ cells sorted from BM-MNC exhibited an increased effect in blood flow recovery after acute ischemia, probably due to their enhanced migratory capacities and increased releases of paracrine factors such as VEGF, HGF and PDGF-BB [28]. Consistently, CXCR4$^+$ MSC showed profound tissue repair advantages in many tissue injury models such as myocardial infarction [112], strokes [113, 114], acute kidney injury [111] and early liver regeneration [115]. CXCR4$^+$ MSC exhibited increased migration capacity to SDF-1 and homing to the BM [111, 114]. However, local injection of SDF-1 to the uninjured tissue failed to recruit MSC to the injection site, and blockade of CXCR4 in murine BM-MSC did not affect their intramyocardial migration to ischemic areas in mice [108], suggesting that other mediators are required for the recruitment of MSC to the site of injury. In addition to the potential involvement of CXCR4 in MSC migration, CXCR4$^+$ MSC showed enhanced secretion of several growth factors including bFGF, VEGF and insulin like growth factor (IGF) [111, 113].

Other MSC subpopulations

Several other cell surface markers including SSEA-4 [18, 116], Stro-3 [117], neural ganglioside GD2 [5], MSCA-1 [43, 52], IL-1 receptor antagonist (IL1RN) [118], CD44 [119], integrin-α6 [120], and leptin receptor (LepR) [121] have been reported to be used alone or in combination with other surface markers to subfractionate MSC with certain advantages in CFU-F formation, differentiation toward a specific lineage, and/or trafficking in blood circulation and engraftment to damaged tissues. While these findings are encouraging toward the identification of MSC subsets with enhanced tissue-specific repair/regeneration properties, more studies are required to establish their technical consistency in cell isolation and therapeutic advantages.

Conclusion

Growing evidence suggests that MSC isolated and cultured in current regimes contain multiple tissue-specific subsets. In the clinical setting, transplantation of a pure MSC subpopulation with specific biological characteristics is likely to be more advantageous and effective. Although the concept of MSC is becoming increasingly obscure due to

recent findings about their heterogeneities, further work should be carried out to fully understand the biological differences between diverse MSC subpopulations and to evaluate their therapeutic benefits in treating specific diseases.

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