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COMPREHENSIVE REVIEW

Interactions of Mesenchymal Stem Cells with Endothelial Cells

Seyed Mahdi Nassiri and Reza Rahbarghazi

Recent years have witnessed the emergence of a considerable amount of data pertaining to the application of bone marrow mesenchymal stem cells (MSCs) in promoting angiogenesis in the field of regenerative medicine. Nevertheless, some authors have provided evidence that MSCs can also prevent the process of angiogenesis, which is desirable in certain pathologies such as tumor growth. Plenty of in vitro and in vivo research studies have been undertaken to illuminate the underlying mechanisms by which MSCs promote or inhibit neo-angiogenesis. To date, both secretary capacity and differentiation into endothelial-like cells have been reported in MSC-based pro-angiogenic therapies. This review seeks to shed further light on interactions between MSCs and endothelial cells in different physiopathological conditions.

Introduction

At present, stem cells and—in particular—bone marrow mesenchymal stem cells (MSCs) are heralded as a source of great promise for augmenting angiogenesis during tissue repair/regeneration [1]. However, over the years, there has been much controversy over the fundamental biology, kinetics, and therapeutic application of MSCs on different kinds of pathological conditions—especially angiogenesis-dependent illnesses. Equivocal research paradigms or inconsistent results have—to some extent—contributed to the ambiguity or uncertainty over the behavior of MSCs in cell-based therapies.

Angiogenesis is defined as the formation of new capillaries from pre-existing vessels and consists of several steps—including stimulation of endothelial cells (ECs), extracellular matrix (ECM) degradation, migration, and proliferation of ECs, capillary tube formation, and, eventually, stabilization of newly formed tubes by peri- ECs such as pericytes (PCs) [2]. The dynamic balance between pro-angiogenic and anti-angiogenic factors in milieu shifts equilibrium to vessel formation or regression. The great potency of expansion, pro/anti-angiogenic properties, and easy harvesting of MSCs render these cells a good candidate for angiogenesis-augmenting or inhibiting purposes [3,4]. There are a number of preclinical and pioneering clinical studies corroborating that MSCs can differentiate into endothelial-like cells, vascular smooth muscle cells, and PCs.

MSCs have been administrated intravenously and shown to have distributed among several tissues in animal models. Similar to leukocytes and progenitor cells, MSCs also coordinate the sequence of adhesion steps (cytoskeletal and motogenic changes) to egress from blood stream [5,6]. Moreover, a variety of pro-angiogenic factors have been elucidated in MSC secretome, which facilitate the proliferation and migration of ECs and contribute to the recruitment of endothelial progenitor cells (EPCs) into newly sprouting blood vessels [1,7–12]. In contrast, novel properties of MSCs, as anti-angiogenic/cytotoxic agents that abrogate capillary formation, have also been observed in some experiments and tumors which are thought to mediate via cell-cell contact or paracrine signaling [13,14]. Appreciable efforts have been undertaken to illuminate the mechanisms underlying the interaction between MSCs and ECs or peri-ECs in both in vivo and in vitro experiments.

This review aims at scrutinizing the interaction between MSCs and ECs or peri-ECs during neo-angiogenesis, tumor vascularization, and vascular remodeling.

Trans-Endothelial Migration of MSCs

MSC adhesion

It was demonstrated that MSCs could adhere to the endothelium and extravasate at the site of inflammation by a leukocyte-like, novel mechanism controlled by a precisely regulated interaction between stem cell and endothelium via selectin-mediated rolling, chemokine-triggered activation, and integrin-dependent arrest on the endothelium (Fig. 1) [15,16].

It was clearly demonstrated that MSCs have the extensive ability to influence the behavior of ECs and vice versa, especially via ligand–receptor interactions (Fig. 1) [17,18]. The migration and homing potential of MSCs to sites of injury as well as MSC-EC adhesion was shown to be governed by a

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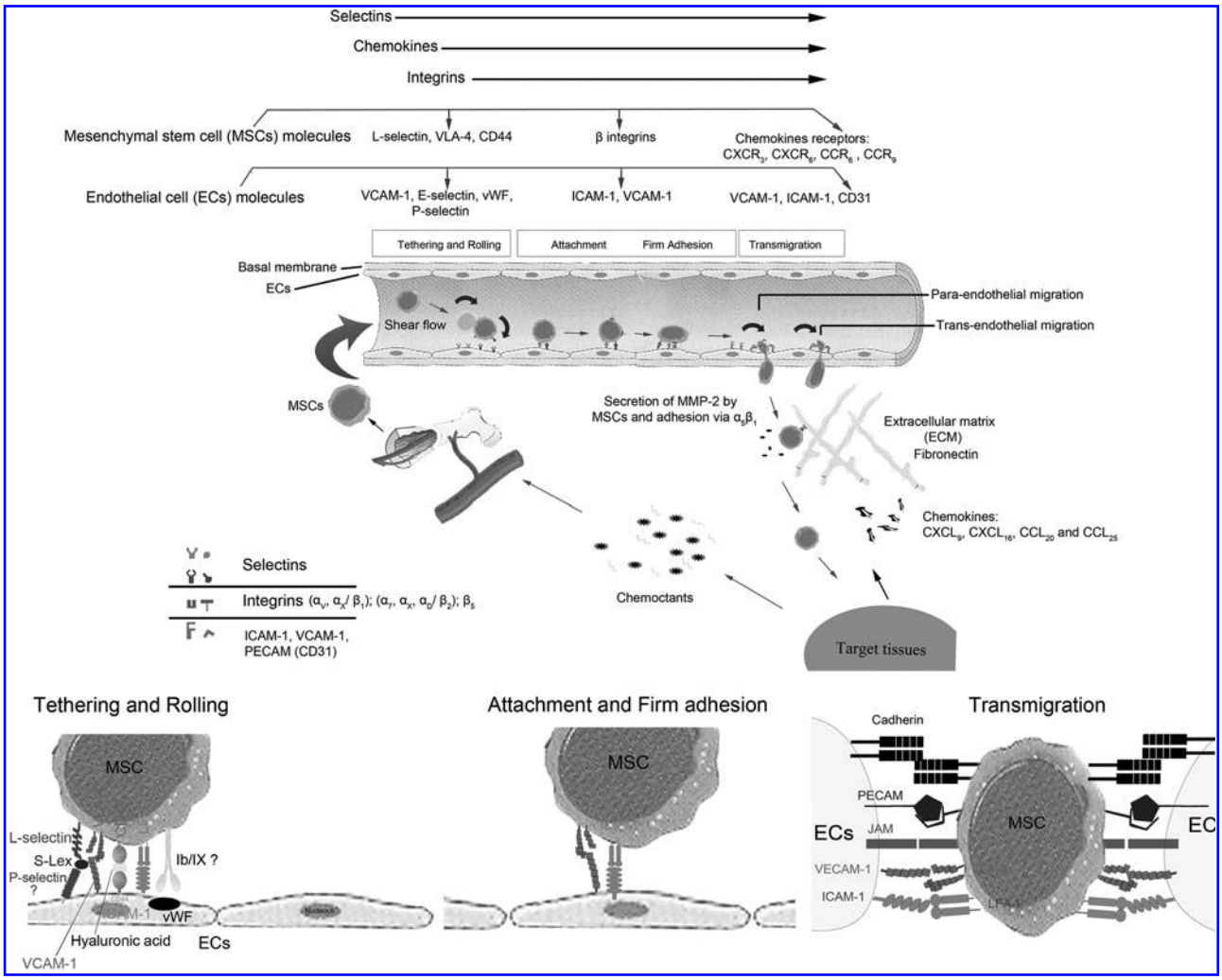

FIG. 1. This schematic illustration summarizes the stages for the recruitment and contribution of bone marrow MSCs to target tissues. Chemoattractants, released by target tissues, circulate to reach the marrow-resident MSC niche. Next, factor-activated MSCs leave the bone marrow and enter into the blood stream. Under shear flow and in the blood vessels of target tissues, MSCs are tethered by endothelial cells (ECs) and then, they start rolling on the EC-lined surface. As shown, selectins are the first adhesion molecules that mediate cell-to-cell contact. MSCs have the capability to express L-selectin, whereas ECs express P- and E-selectins on the luminal surface. Simultaneously, other adhesion or synergetic molecules are expressed on the cell membrane of MSCs (VLA-1, CD44, and LFA-1) and ECs (ICAM-1, VCAM-1, vWF, CD44, and S-Lex). Then, the attached stem cells firmly adhere to the endothelial surface through the binding of β-integrins on the MSC membrane with their receptors (VACAM-1 and ICAM-1) on ECs. It is also believed that released chemokines determine tropism to target tissues. In addition, MSCs are able to express chemokine receptors, that is, $CXCR_3$, $CXCR_6$, CCR_6, and CCR_9. There are two modes of trans-migration for MSC extravasation—including para- (inter-endothelial space migration) and trans-migration (through EC). Receptor ligands are essential for the trans-endothelial migration of MSCs. CD31 (PECAM-1), cadherins, and JAMs molecules are also exploited in this stage. Moreover, the secretary potential of MSCs facilitates extra-vascular movement. For example, secreted MMP-2 degrades endothelial basal membrane. ECs-derived MMP-9 and nitric oxide also play a role in this phenomenon. ECs, endothelial cells; ICAM-1, intercellular adhesion molecule-1; JAMs, junctional adhesion molecules; LFA-1, leukocyte function-associated antigen-1; MMP-2, -9, matrix metalloproteinase-2, -9; MSCs, mesenchymal stem cells; PECAM-1/CD31, platelet endothelial cell adhesion molecule, S-Lex, Sialyl Lewis x; VCAM-1, vascular cell adhesion molecule-1; VLA-4, very late antigen-4; vWF, von Willebrand factor.

vast array of different cell surface trans-membrane molecules such as integrins [19]. Integrins, as eukaryotic cell surface receptors, consist of heterodimers of α (α_1 to α_8) and β (β_1 to β_{16}) subunits. Each subunit contains a large extracellular and a small cytoplasmic domain [20]. MSCs, similar to other cells, express subunits β (β_1 to β_3) and α (α_1 to α_6, and α_V) in the cell culture system. On reaching confluency, the expression of β_3, α_1, α_3, α_5, and α_V integrins is increased, whereas the expression of α_6 is decreased. Specific integrins play a role in the adhesion of MSCs to a variety of human ECs such as pulmonary arteries (β_1, α_V, and α_X), cardiac-derived microvasculature (β_2, α_X, α_7, and α_D), and umbilical veins (β_1, β_2, and β_3); whereas the neutralizing antibodies against the integrins of the β_5 subclass reduce MSC adherence to all the

ECs mentioned earlier [19]. Integrin-dependent intracellular signaling is believed to be induced in leukemic cells in the MSC-leukemic cell co-culture system, which is mediated by integrin-linked kinase (ILK) that phosphorylates protein kinase B (Akt) in a phosphatidylinositol 3-kinase (PI3K)–dependent manner [21]. It was shown that the expression of VEGF in tumor cells was stimulated by ILK via stimulating HIF-1α expression, and inhibition of ILK expression or activity resulted in the inhibition of VEGF-mediated EC migration, capillary formation in vitro, and angiogenesis in vivo [22] and suppressed VEGF-induced p38 mitogen-activated protein kinase (MAPK) and Akt phosphorylation in ECs [23]; so, the integrin-dependent interaction between MSCs with ECs may trigger neo-angiogenesis in ECs.

Notch receptors, Notch-1 to 4, with five structurally similar ligands—namely Delta-like1, Delta-like3, Delta-like4 (Dll-1 to 4), Jagged-1, and Jagged-2—are other types of co-counter receptors that provoke MSC-EC interaction [24]. Notch-1, -2, and -3 receptors and Jagged 1 ligand were shown to be expressed at significant levels in MSCs [24]. Notch-1 was found to increase the proliferation as well as recruitment of MSCs (more Ki-67$^+$ proliferative and less cleaved-Caspase3$^+$ apoptotic cells) to the infarcted murine myocardium [25]. Chiming with these observations, the activation of MSCs via TNF-α and Interleukin-1 treatment before the injection significantly enhanced adhesion to the cardiac endothelium and promoted the homing of MSCs via ICAM-1/LFA-1 and G-protein-coupled receptor signaling [15,26,27]. Rυster and colleagues demonstrated that MSCs underwent coordinated rolling on and adhesion behavior to ECs under shear flow and reported that human MSCs did not express detectable levels of some adhesion molecules such as P-selectin glycoprotein ligand 1 (PSGL-1) and pre-incubation of MSCs—with the antibody against PSGL-1—did not block the binding of MSCs to the surface of ECs (Fig. 1) [5]. Meanwhile, preincubation of HUVECs with a blocking antibody against P-selectin strongly decreased MSC binding to EC, indicating that MSCs might bind to P-selectin using a fucose and sialic acid-containing ligand that is different from PSGL-1 [5]. In addition, the preincubation of ECs with anti-VCAM-1 or of MSCs with anti-VLA-4 prevented the adhesion of MSCs to ECs (Fig. 1). Finally, the authors concluded that MSCs bound to ECs in a P-selectin–dependent manner either in vitro or in vivo, and that CD44 as well as VLA-4/VCAM-1 was engaged in the rolling of MSCs on ECs [5,28].

An increase in the level of cell surface CD44 by the platelet-derived growth factor (PDGF) stimulation of MSCs facilitated cell migration through an interaction with extracellular hyaluronic acid (Fig. 1) [29]. In addition, P- or L-selectin aptamers-engineered MSCs efficiently adhered on the respective selectin surfaces of ECs and leukocytes [30]. Sackstein et al. reported that a CD44 glycoform—bearing α-2, 3-sialyl modifications—was expressed on human MSCs but they lacked E-selectin ligands and CXCR4, which limited osteo-tropism to the bone tissue. Therefore, the modification of native CD44 to convert it into E-selectin/L-selectin ligand conferred potent binding capacity and tropism to the bone tissue through specialized marrow vessels expressing E-selectin [31].

Potapova et al. demonstrated that the treatment of ECs with the von Willebrand factor (vWF) resulted in the activation of intracellular downstream ERK-1, 2, and p38 MAPK without an effect on the gene or cell surface expression of E-selectin, P-selectin, VCAM1, and ICAM1. They showed that the activation of p38 MAPK in ECs by the vWF could initiate MSC-EC adhesion (Fig. 1) [32]. Nevertheless, VCAM-1/VLA-4 as well as beta 1 integrins and matrix metalloproteinase 2 play key roles in the trans-endothelial migration of MSCs [33]. The addition of MSCs to ECs tubes on the Matrigel assay initiated MSC-EC intercalation via connexin 43-based intercellular gap junction [13]. Some MSC-derived secretary soluble factors could up-regulate connexin-43 and facilitate the functional integration of MSCs into target tissues [34].

Trans-endothelial migration

The firm adhesion of MSCs to ECs is followed by endothelial transmigration via platelet-endothelial cell adhesion molecule-1 (PECAM-1/CD31), junctional adhesion molecules (JAMs), and cadherins (Fig. 1) [15,35,36].

Similar to leukocytes, MSCs transmigrate by para- (between ECs) and trans-cellular (directly through individual ECs) diapedesis through discrete pores and gaps in the endothelial monolayer—which is associated with VCAM-1-enriched trans-migratory cups [15]. Both lamellipodia (a flattened cellular extension over surface) and invadosomes (a dot-like accumulation of the filamentous actin at the site of cell-matrix contact) [37] were observed in the trans-migratory process of MSCs; however, unlike leukocytes, nonapoptotic membrane blebbing was also evident, as was previously described for metastatic tumors [15].

Chemokine receptors are known as G-protein-coupled receptors for CXC, CC, C, or CX3C chemokines. MSCs express CCR1, CCR2, CCR4, CCR6, CCR7, CCR9, CCR10, CXCR1, CXCR2, CXCR4, CXCR5, CXCR6, and CX3CR1 receptors and secrete a variety of chemokines [38,39]. Chamberlain et al. stated that chemokine receptors and their chemokine ligands had an indispensable role in the migration of murine MSCs (mMSCs) across murine aortic endothelial cells (MAECs) and that both chemokine stimulation and shear stress enhanced the trans-endothelial migration of mMSCs across MAECs [28]. Initially, mMSCs established fine microvillous processes, namely filopodia, and then extended pseudopodia in multiple directions. Thereafter—CXCL9, CXCL16, CCL20, and CCL25 ligands improved trans-endothelial migration across MAECs, and shear forces markedly stimulated the crawling and spreading of mMSCs [28].

In addition to the direct MSC-EC cross-talk via receptor/ligand interactions, ECM also regulates MSCs migration during vascular remodeling (Fig. 1). MSC binding to matrix fibronectin induced the α5β1-integrin-dependent phosphorylation of PDGFR-β, leading to PI3K/Akt activity, actin re-organization, and MSCs migration [6]. However, in spite of the effective role of the ECs on the extravasations of MSCs, MSCs—in turn—could contribute to the growth of ECs into the EC-MSC islets by paving the way via producing proteases into the tissue [40]. During myocardial infarction and in inflammatory conditions, endothelial nitric oxide synthase (eNOS)-derived nitric oxide (NO) production, by PI3K/Akt/eNOS downstream signaling and MMP-9 activation, could trigger MSCs and EPCs migration to target tissues [41].

MSC-EC Cross-Talk in Angiogenesis

Various types of MSC-EC three-dimensional (3D) co-culture systems have revealed extensive cellular cross-talk through a variety of mechanisms. This process is exquisitely controlled by cell-cell connection, paracrine, and juxtacrine interaction—or vesicle trafficking between the MSC and EC lineage, leading to the modulation of the angiogenic response (Fig. 2A) [1,42].

Juxtacrine interactions of MSC-EC

In an in vitro Matrigel assay using rat and human MSC-EC co-culture systems, self-assembled and elongated tubes-like structures are formed by intimate MSC-EC contact soon after seeding on Matrigel, and, subsequently, EC phenotype is induced in co-aligned MSCs via VEGF-dependent downstream signaling and then activation of the Rho/ROCK pathway [1,43]. MSCs that express stemness markers such as

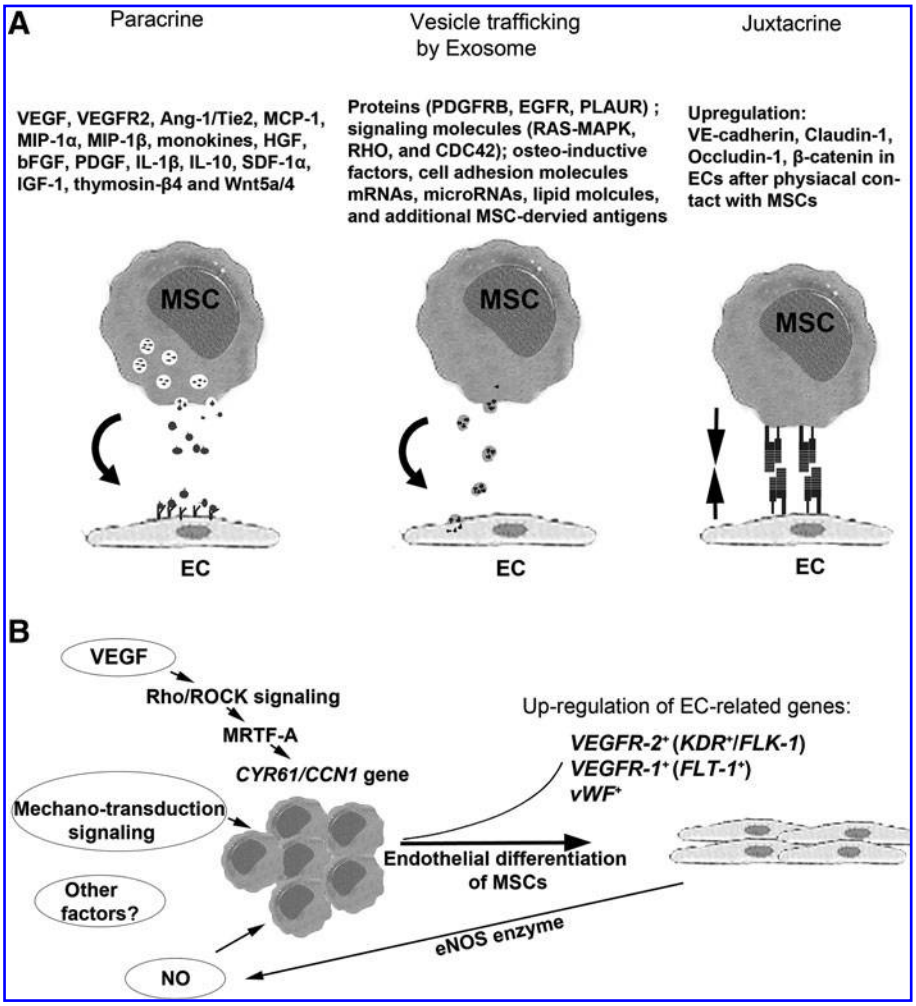

FIG. 2. This schematic illustration presents the potential effects of MSCs on ECs in angiogenesis. **(A)** MSCs interact with ECs in three different manners: paracrine; juxtacrine; and vesicle trafficking. A different panel of angiogenic growth factors, cytokines, and other signaling molecules are secreted by MSCs, which may influence ECs. MSC-derived factors are to promote the angiogenesis process after binding to the relevant receptors on the EC surface. Moreover, the intercellular trafficking of exosomes transfers various kinds of molecules—including proteins, mRNAs, microRNAs, and lipid molecules to target cells. Finally, juxtacrine interactions require cell-to-cell physical contact through ligand-receptor interactions. All these mechanisms, ultimately, induce or inhibit different intracellular signaling pathways, which, in turn, lead to the promotion of angiogenesis. **(B)** The endothelial differentiation of MSCs involves concomitant changes in the expression of EC-specific genes—including *KDR*, *FLT-1*, *vWF*, *VEGFR-1*, and *VEGFR-2*. VEGF, the most prominent EC-inductive phenotype in MSCs, acts via Rho/ROCK and MRTF-A signaling, leading to the up-regulation of *CYR61/CNN-1* gene. In addition, extracellular mechanical properties influence the trans-differentiation of MSCs through an interaction between ECM proteins and MSC surface receptors, thereby inducing mechano-transduction signaling pathways in MSCs. Also ECs, by themselves, initiate MSC differentiation into endothelial-like cells by producing NO. Ang-1/Tie-2, angiopoietin 1/Tie-2; bFGF, basic fibroblast growth factor; ECM, extracellular matrix; EGFR, epidermal growth factor receptor; FLT-1, Fms-related tyrosine kinase-1 (VEGFR-1); HGF, hepatocyte growth factor; IGF-1, insulin-like growth factor-1; IL-1β, -10, Interleukin-1β, -10; KDR, kinase insert domain receptor (VEGFR-2); MCP-1, monocyte chemoattractant protein-1; MIP-1α/β, macrophage inflammatory protein-1 alpha/beta; MRTF-A, myocardin-related transcription factor-A; PDGF, platelet-derived growth factor; PDGFRβ, platelet-derived growth factor receptor beta; PLAUR, plasminogen activator urokinase receptor; SDF-1α, stem cell-derived factor-1α; VEGF, vascular endothelial growth factor; VEGFR-2, vascular endothelial growth factor receptor-2.

CD146, Sca-1, and PDGFRα have been shown in close proximity of vessels with a tendency to express PCs-like markers, NG2, CD146, and PDGFRβ. As a matter of fact, it has recently been demonstrated that $CD146^+$ PCs represent a subpopulation of bone marrow MSCs which support neoangiogenesis [44]. $PDGFR\alpha^+$ progenitor cells also have a great potential to mimic endothelial as well as smooth muscle cell phenotypes in the heart [45]. In vivo perivascular homing of MSCs along the vascular wall was also observed after an IV injection of MSCs in a critically ischemic murine skin flap model [46]. In addition, in vivo co-implantation of MSCs isolated from four murine tissues, including bone marrow, white adipose tissue, skeletal muscle, and myocardium, with human blood-derived endothelial colony-forming cells developed a complex network of blood vessels with ECs lining the lumens and MSCs aligning the perivascular space immediately adjacent to the lumenal structures [47]. Indeed, the existence of MSCs in the peri-endothelial space highlights the notion that endothelium, as an important component of MSC niche, can regulate the functional activity of MSCs [48–50].

MSCs-derived spindle-shaped myofibroblast-like cells, containing organized smooth muscle alpha-actin filaments, were also determined in the EC-MSC co-culture [51]. With regard to intracellular signaling, HUVECs, in a 3D spheroid co-culture system, promoted endogenous Wnt as well as BMP signaling in human MSCs with an increased level of nuclear β-catenin and pSmad1/5/8 under osteogenic conditions [52]. The MSC-EC interaction enhances the expression and co-localization of VE-cadherin and β-catenin at the cell membrane, decreases vascular tube breakdown, and inhibits ECs permeability with the preservation of VE-cadherin, Claudin-1, and Occludin-1 in vivo in the pulmonary ECs in a rat model of hemorrhagic shock-induced acute lung injury [53] and in vitro in a human MSC-EC co-culture system [54,55]. Secreted frizzled-related protein-1 (sFRP-1), as the soluble modulator of Wnt signaling, up-regulated PDGF-BB in mMSCs and facilitated β-cantenin-dependent MSC-MSC, MSC-EC, and MSC-SMC adhesions in vitro [56]. This pathway, in turn, triggered MSC glycogen synthase kinase 3 beta (GSK3β)-dependent angiogenesis as well as vessel maturation and functionality after a subcutaneous injection of MSCs mixed with Matrigel in mice, although no endothelial differentiation of MSCs was evident by this pathway [56,57]. Other studies implicated sFRP-2 as a key molecule for the regenerative potential of mMSCs after transplantation into myocardial infarction [58]. Specific knockdown of sFRP-2 in mMSCs decreased the MSC engraftment and vascular density in the granulation tissue [58].

The proliferation rate of rat MSCs was reportedly reduced in the EC-MSC co-culture, which is in consequence of the down-regulation of a number of growth factors—especially TGF-β family members [1,42]. Duffy and colleagues, however, showed that human MSCs increased aortic ECs proliferation in a noncontact co-culture system using human cells [59]. Bidarra et al. reported that human MSC-EC co-culturing not only augmented the proliferation of MSCs but also triggered osteogenic differentiation by ECs-dependent BMP-2 signaling [60]. These authors used three ratios of MSC-EC, including 3:1, 1:1, and 1:3 ratios, and found that the relative number of ECs declined over time in all cell ratios with the most tremendous downward trend in the highest percentage of MSC to EC ratio. Moreover, the maximum metabolic activity of MSCs was achieved at 1:1 MSC to EC ratio. They also showed that a combined medium of M199 + DMEM provided optimal outcome on the metabolic activity and protein content of MSC compared with M199 or DMEM alone. On the other hand, when rat-derived MSCs were added to rat lung microvascular EC-derived capillaries in Matrigel at EC-MSC ratios of 1:1 or 3:1, degeneration of the capillaries was notified as a result of reactive oxygen species production by MSCs [13]. Such discrepancies seem to be partly related to culture conditions and difference in the origin of the cells employed in each of these in vitro systems. [60]. The addition of human MSCs at an increasing dose from 1:10 to 1:1 MSC-EC ratio to pre-established human aortic EC lattice at Matrigel surface after 24 h proportionally increased the thickness of vessel-like structures and junction size, whereas the addition of MSCs before EC seeding on Matrigel resulted in only EC bunching and loss of lattice formation [59]. Therefore, it seems that the addition of MSCs to the EC-derived fully formed lattice contributed, similar to PCs, to the stabilization and maturation of the vessel-like structures; whereas MSCs acted as a stimulus of EC migration and bunching at early time points during vessel formation [59,61].

Overall, it seems that the inhibitory or stimulatory effect of MSCs on co-cultured ECs is dependent not only on the MSC-EC ratio but also on the sequence of cell addition in different experiments. Since distinct signaling mechanisms can change cell-cell ratios, for example, a change in the intrathymic CD4:CD8 cell ratio from the fetal to adult thymus as a result of differential expression of Notch signaling molecules by the thymic stroma during thymus development [62], it seems that a change in cell-cell ratios might also induce distinct signaling mechanisms with different phenotypic and genotypic profiles.

MSCs also enhanced angiogenesis and vascular integrity by increased angiopoietin-1 (Ang1), Tie2 (Ang-1 receptor), VEGF/VEGFR2 (Flk1), and Occludin expressions in the murine experimental stroke [63]. Ang1/Tie-2 signaling protects MSCs, ECs, and some other cells against insulting conditions such as serum deprivation and hypoxia-induced apoptosis by Akt phosphorylation, increased Bcl-2:Bax ratio, and decreased activation of caspase-9 and -3 [64].

Paracrine interactions of MSC-EC

In addition to the physical contribution of MSCs to the microenvironment, MSCs dynamically influence the surrounding environment through the production of biomolecules (cytokines, chemokines, growth factors, and ECM molecules) in a paracrine or even autocrine manner. Of these bio-molecules, a variety of angiogenic, immunosuppressive, anti-inflammatory, and anti-fibrotic factors—along with ECM homeostasis regulators such as collagens and tissue inhibitors of MMPs—were delineated [65].

Lipid vesicles of MSCs, including micro- and nano-vesicles, contain the molecules mentioned earlier (Fig. 2A) [66]. Exosome, which is a nano-sized vesicle, serves to transfer various kinds of molecules—including proteins, mRNAs, microRNAs, and lipid molecules. The therapeutic effects of MSC-derived exosomes in cancer therapy or in regenerative medicine such as cardiovascular regeneration have been

investigated by some authors, while our information on the role of exosomes in pathophysiological processes is still in its infancy. There are some pro-angiogenic properties pertaining to MSC exosomes [67]. A number of surface proteins such as PDGFRB, EGFR, and PLAUR, some signaling molecules such as RAS-MAPK, RHO, Cdc42 cell adhesion molecules, osteo-inductive factors, and additional MSC antigens were also determined to be carried out by exosomes [68,69]. Indeed, MSC-derived exosomes have provided a fascinating insight into developing novel cell-free therapeutic approaches that may bypass the difficulties associated with stem cell therapy. The beneficial effects of MSC exosomes have been shown in various diseases, such as stroke [70,71], ischemic heart disease [72], acute lung injury [73], liver fibrosis [74], rheumatic diseases [75], and a number of malignancies, including glioma [76] and multiple myeloma [77].

Moreover, a variety of soluble factors—including VEGF, VEGFR2, Ang-1/Tie2, monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1α (MIP-1α), MIP-1β, monokine, basic fibroblast growth factor (bFGF), PDGF, IL-1β, IL-10, stem cell-derived factor (SDF)-1, hepatocyte growth factor (HGF), insulin-like growth factor-1 (IGF-1), thymosin-β4, and Wnt5a—were found to be secreted by MSCs to the conditioned medium (Fig. 2A) [1,65]. MSC-derived VEGF support the survival and functional commitment of ECs [78]. Meanwhile, it has been suggested that at the site of injury when a complex of factors is secreted by multiple stem cells, local angiogenesis might be better stimulated [79]. The soluble fragment of Tie-2, produced by proteolytic cleavage [80], has been detected in the rat MSC conditioned medium—which might participate in the angiogenic axis [1].

The suppression of Wnt-4 expression in hypoxic preconditioned mMSCs abrogated vasculogenic properties in the mouse ischemic hind limb model [81], suggesting that Wnt signaling pathway plays a key role in the paracrine pro-angiogenic properties of MSCs. Moreover, the overexpression of Wnt-4 may enhance the osteogenic differentiation of human MSCs by the activation of p38 MAPK in a novel, noncanonical signaling pathway [82].

Mechanical signals such as compressive loading could also alter the gene expression and function of MSCs. Theses stimuli are transduced by stretch-activated ion channels, cell adhesion molecules, G-protein-coupled receptors, and growth factor receptor tyrosine kinases [83]. Mechanical loading in a bioreactor system for modeling the fracture gap during the early phase of bone healing induced the up-regulation of pro-angiogenic molecules such as FGF receptor, VEGFR, TGF-β, MMP-2, MMP-9, bFGF, and Membrane Type 1- Metalloprotease (MT1-MMP or MMP-14) in human MSCs [83,84]. Taken together, it is thought that milieu-dependent conditions—including cell-cell contact, soluble factors, and mechanical stimulations—ultimately determine the behavior of MSCs.

Endothelial Differentiation of MSCs

MSCs have the potential for trans-differentiation into endothelial-like cells in both in vivo and in vitro systems [7,85,86]. Nevertheless, the precise mode of action of a wide variety of stimulatory or inhibitory factors such as intracellular signaling molecules, receptors, soluble factors, and even extracellular nanomechanical cues with a considerable influence on endothelial differentiation of MSCs is still under investigation [87,88]. Given the vital importance of neoangiogenesis in regenerative medicine and the therapeutic potential of MSCs as a promising source of restoring damaged tissue, recent efforts have been focused on employing MSCs both as a source of cells for the regeneration of injured tissues and—at the same time—as a source of ECs [89,90]. There are, however, some controversies among researchers regarding the differentiation of MSCs into ECs—with culture conditions, milieu of targeted tissues, and particular subpopulations of MSCs having been suggested as the potential effectors that regulate the fate of MSCs [87].

Differentiation of MSCs into endothelial-like cells resulted in the expression of a panel of EC-specific markers—including kinase insert domain receptor (KDR), Fms-related tyrosine kinase-1 (FLT-1), and vWF—at both gene and protein levels, which was followed by integrin modulation (Fig. 2B) [7,91,92]. On the contrary, endothelial differentiation induction of human amnion-derived MSCs resulted in the appearance of cells with some angiogenic properties, but a complete differentiation into mature ECs was not achieved because of the down-regulation of pro-angiogenic factors such as tenascin C, Tie-2, VEGF, and FGF2 and up-regulation of anti-angiogenic factors, serpinF1, sprouty1, angioarrestin, and endostatin [90]. Some specific experimental conditions, for example, hypoxic or osteogenesis-inducing conditions, may cause MSCs to secret the pro-angiogenic factor VEGF and express the endothelial marker VEGFR1 (FLT-1) [93]. Moreover, the capability of MSCs to express the EC-related markers after injection to damaged tissues has been shown by some investigations [94,95].

In addition to the juxtacrine and paracrine mechanisms behind the endothelial differentiation of MSCs, extracellular mechanical properties (as alternative differentiation inducers) influence cell fate at both genotypic and phenotypic levels. For instance, the endothelial differentiation of MSCs was guided through the contact of ECM proteins with MSC surface receptors, resulting in the induction of intracellular mechano-transduction pathways [87,96]. Mechano-sensors and mechano-transduction signaling pathways were also reported to ally MSC fate to the endothelial phenotype under shear stress [97].

VEGF stimulates the differentiation of human and rat MSCs into endothelial-like cells via Rho/myocardin-related transcription factor-A (MRTF-A) family (Fig. 2B) [43]. Further investigations revealed that the activation of the Rho/ROCK signaling pathway promoted the nuclear translocation of MRTF-A [43]. Wang et al. showed that the depletion of MRTF-A selectively ablated the VEGF-induced differentiation of MSCs into endothelial-like cells [43]. In addition, the authors demonstrated that VEGF could up-regulate the promoter activity of *CYR61/CCN1* (regulator of vascular development and angiogenesis) and that MRTF-A knockdown resulted in the reduction of the VEGF-induced activation of *CYR61/CCN1* promoter (Fig. 2B) [43]. Unlike these findings, Au and coworkers concluded that the up-regulation of the myocardin transcription factor promoted MSC differentiation into smooth muscle cells, but instead hampered the differentiation of human MSCs into other lineages—peculiarly ECs [98,99].

The effect of NO signaling in the endothelial differentiation and maturation of EPCs is well documented (Fig. 2B) [100,101]. Moreover, there is some convincing evidence that NO signaling plays a role in the differentiation of MSCs to ECs, although the exact mechanisms underlying the pro-angiogenic effects of NO remain to be clarified [102]. Gomes and colleagues demonstrated that the homozygous ablation of *S*-nitrosoglutathione reductase ($GSNOR^{-/-}$), a denitrosylase that regulates S-nitrosylation in mice MSCs, profoundly blunted the capacity for vasculogenesis in an in vitro Matrigel tube-forming assay as well as in an in vivo Matrigel plug assay in immunocompromised mice, which was related to NO/GSNOR imbalance [102]. Ahmed et al. showed that the re-programming of rat MSCs with sonic hedgehog, a morphogen during the embryonic development of MSC growth, improved the viability and angiogenic properties of these cells in hearts subjected to myocardial infarction via inducible NO synthase/netrin-1/PKC signaling [103]. In addition to the NO-mediated angiogenic potential of MSCs, NO could also provide osteogenic differentiation in physically activated rat marrow MSCs in vitro [104]. In addition, NO and prostaglandin E_2 released by mechanically stimulated MSCs stimulated osteogenic differentiation in vivo [105]. Moreover, prostaglandin E_2 secretion by implanted MSCs in mice induced a phenotypic switch in macrophages from pro-inflammatory to anti-inflammatory status, and the subsequent recruitment of EPCs and osteogenesis-promoting cells [106].

Ephrin-B2, a trans-membrane ligand for Eph receptor tyrosine kinases, also induced early EC-like phenotype in human MSCs and led to the up-regulation of vWF and VEGFR-2 (KDR/Flk-1) in MSCs under EC culture conditions (Fig. 2B) [59]. On the other hand, Notch signaling was reported to induce the expression of smooth muscle cell markers in human MSCs and embryonic stem cells along with a decrease of endothelial markers in embryonic stem cells [107]. Moreover, in vitro oxidative stress was shown to promote the cardiogenic differentiation of rat MSCs through the activation of Notch-1 signaling [108].

Role of MSCs in Tumor Angiogenesis

It is unanimously agreed that angiogenesis, as a crucial process, is employed in tumor progression and metastasis [109]. The effect of MSCs on tumor growth and angiogenesis has currently generated strong controversy [110]. Indeed, while some evidence indicates a tumor-suppressive effect, there is evidence implying a tumor-promoting effect—especially via vasculature remodeling (Fig. 3) [111]. Tumor-derived vessels usually have a distinct structure and function. Not supported by PCs, tumor-derived vessels are paved by actively dividing ECs, which are irregularly dispersed in the tumor stroma, generating an irregular structure [112]. Despite the distinct nature of the tumor-derived vessels, VEGF signaling also plays a key role in tumor angiogenesis [113,114]. Bidirectional cross-talk interactions and paracrine signaling may contribute to the recruitment of a variety of cells—including progenitor cells and MSCs—into the tumor stroma, which is important for blood vessel formation (Fig. 3) [115,116]. There is strong evidence that tumor development is associated with the continuous recruitment of MSCs, with a tendency to maintain the MSC population at a steady-state level within the tumor mass [117]. Therefore, many attempts have been made to exploit the tendency of MSCs to tumors, as a tumor-targeting strategy. For example, MSCs are widely used as the delivery vehicles for the transfer of gene constructs in cancer gene therapy [118].

Stimulatory effects of MSCs on tumor angiogenesis

The treatment of MSCs with tumor-derived conditioned media in vitro or close proximity of these cells to tumor microenvironments in vivo resulted in the up-regulation of a number of transcripts—including SDF-1α (CXCL-12), VEGF-A, PDGF/PDGFR, MIP-2, TGF-β, IL-6, HIF-1α, NF-Kβ, bFGF, HGF, angiopoietins, epithelial growth factor, keratinocyte growth factor, IGF-1, and galectin-1 in MSCs—which stimulated tumor neo-angiogenesis (Fig. 3) [10,116,117,119–123]. MSC-derived angiogenic factors induce the proliferation and survival of ECs and smooth muscle cells [124]. Huang and colleagues showed that IL-6 secretion by MSCs, subsequently, promoted endothelin-1 expression in human colorectal cancer cells and triggered Akt and ERK signaling pathways in the neighboring ECs, resulting in the positive tropism of these ECs to the tumor matrix [118]. The co-administration of MSCs and cancerous cells in nude immunocompromised mice resulted in the generation of a highly vascularized tumor mass with the differentiation of MSCs into CD31-positive cells and localization at the sites of active tumor neo-angiogenesis [125,126]. A co-injection of B16 melanoma cells or Lewis lung carcinoma cells and MSCs into syngeneic mice led to increased tumor size with increased tumor vessel area compared with an injection of cancer cells alone [127]. Increased blood vessel area in tumors outgrown from a co-injection of tumor cells with marrow MSCs decreased central tumor necrosis and increased tumor cell proliferation [120]. Localizing close to vascular walls and expressing an endothelial marker by MSCs was proposed as the underlying mechanism behind the supportive effects of MSCs on the tumor vasculature [127]. In C26 colon cancer-bearing mice, inflammatory cytokines such as IFN-γ and TNF-α in the tumor microenvironment could also stimulate MSCs to increase the expression of VEGF via activation of the HIF-1α signaling pathway, thereby augmenting tumor angiogenesis and accelerating the growth of colon cancer in the animals [128].

Recent findings revealed that MSC exosome-mediated cell-cell interactions contributed to VEGF expression in human tumor cells by activating ERK1/2 pathway [129,130]. It is becoming increasingly clear that cancer-associated fibroblast (CAFs)—which are $CD133^+$ and $CD44^+$ cells generated from the malignant transformation of MSCs recruited into the tumor stroma—contribute to tumor growth, progression, metastasis, and resistance to chemotherapy in many solid cancers such as brain, breast, and colon cancers (Fig. 3). MSC-derived CAFs are more potent than MSCs to produce cytokines, chemokines, and pro-angiogenic factors [131–134]. Recent evidence also suggested that there was a complex and close bidirectional relationship between MSC-derived CAFs and ECs insofar as ECs-derived cytokines such as NO maintained the stemness-like state of the adjacent CAFs via inducing a Notch pathway in CAFs [135–137]. Reportedly, SDF-1α produced by MSCs, CAFs, or tumor cells leads to the incorporation of EPCs into the growing tumors, thereby promoting tumor angiogenesis [138]. MSC-derived CAFs can also differentiate to endothelial-like as well as PCs-like cells

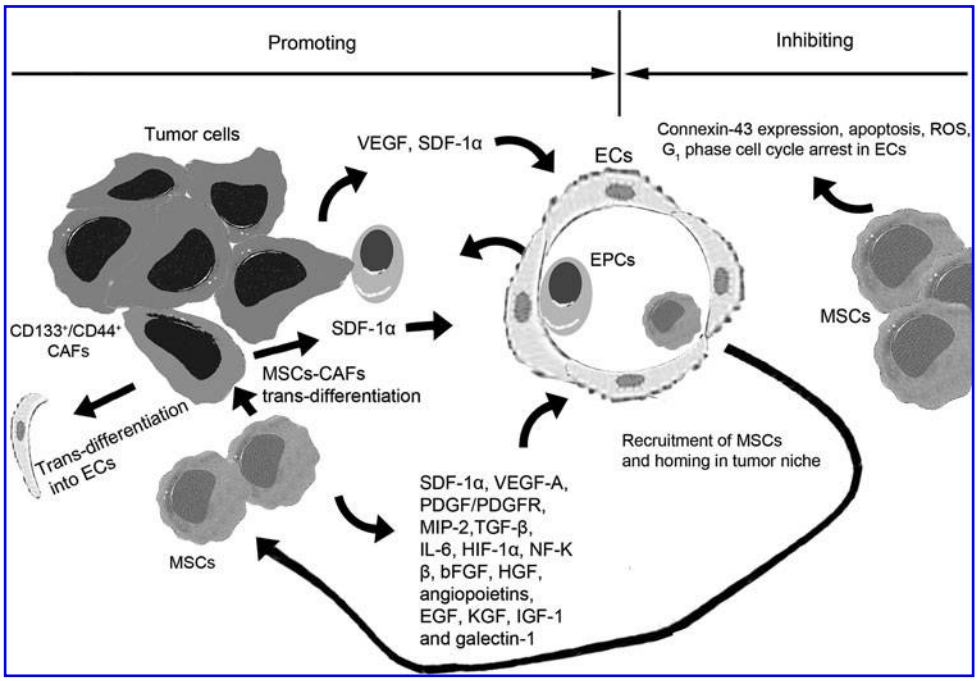

FIG. 3. This schematic depiction summarizes the MSC-derived inductive and suppressive mechanisms of tumor angiogenesis. Tumor development is associated with perpetual recruitment of MSCs, with a tendency to maintain the MSC population at a steady-state level within the tumor mass. In addition, MSCs trans-differentiate into cancer-associated fibroblasts (CAFs), which are $CD133^+/CD44^+$. The endothelial differentiation of both MSCs and CAFs could occur in a tumor microenvironment. Although tumor cells promote angiogenesis by the secretion of VEGF and SDF-1α, CAFs- and MSCs-derived factors also contribute to the induction of angiogenesis and proliferation of ECs as well as recruitment of endothelial progenitors into the tumor mass. In contrast to MSC pro-angiogenic effects, MSCs could inhibit angiogenesis by inducing cell cycle arrest at the G1 phase and apoptosis of ECs, as well as by expressing connexin-43 and producing reactive oxygen species (ROS) with potential effects on ECs. It seems that the balance between the inhibitory and stimulatory effects of MSCs on angiogenesis depends on the tumor niche. EGF, epidermal growth factor; EPCs, endothelial progenitor cells; HIF-1α, hypoxia-inducible factor 1-alpha; IL-6, interleukin-6; KGF, keratinocyte growth factor; MIP-2, macrophage inflammatory protein-2; NF-kβ, nuclear factor kappa beta; PDGF/PDGFR, platelet-derived growth factor/receptor; ROS, reactive oxygen species; TGF-β, transforming growth factor-beta; VEGF, vascular endothelial growth factor.

and, therefore, stimulate neo-angiogenesis during tumor development (Fig. 3) [139,140]. In a recent study of a KM12SM cell transplantation model of colon cancer, imatinib blockade of PDGFR signaling in CAFs prevented the increase in tumor growth and liver metastasis achieved by co-transplantation of human MSCs and KM12SM human colon cancer cells [141]. Moreover, treatment with imatinib impaired MSCs migration to tumor stroma and decreased the number of MSCs surviving in the tumor microenvironment. Interestingly, new recent studies unveiled that vessels-derived cells might undergo endothelial-to-mesenchymal trans-formation in the context of tumor development—in particular, in hemangioma [142].

Inhibitory effects of MSCs on tumor angiogenesis

Apart from the reported stimulatory effects of MSCs on tumor angiogenesis, there is, however, strong evidence that genetically manipulated or normal MSCs exert inhibitory effects on tumor angiogenesis [143–145]. Many underlying mechanisms are presumed to be responsible for this discrepancy, such as chemokine signaling, modulation of apoptosis, vascular support, and immune modulation (Fig. 3) [144]. Ramasamy and colleagues showed the anti-proliferative activity of human MSCs on the tumor cells of hematopoietic and nonhematopoietic origin in vitro with transient arrest of tumor cells in the G_1 phase of the cell cycle [145]. A co-injection of tumor cells and MSCs, however, resulted in an increased incidence of tumor growth in immunodeficient mice. Finally, the authors conculded that the discrepancy between the in vitro and in vivo findings would be due to development of a cancer stem cell niche after co-trasnplantation of MSC in which the tumorigenicity can be augmented [145].

It was demonstrated that some reactive oxygen species are produced when MSCs migrate toward ECs-derived capillaries in Matrigel, which finally led to EC apoptosis. Moreover, an ECs: MSCs ratio-dependent suppression effect on the ECs growth rate was also evident when the cells were co-injected into immunocompromised mice [13]. The mechanistic basis of the inhibitory effects of MSCs on ECs is currently under investigation. For example, human MSCs have the capability to express connexin-43, which mediated gap junctional intercellular communication and functional coupling with ECs [146]. It was shown that MSCs interfere with angiogenesis in a dose-dependent cytotoxicity manner, whereas the administration of an antagonizing peptide against connexin-43 abrogated MSC-derived cytotoxicity behavior [13]. Ho et al. found that co-administration of MSCs

and glioma cells significantly reducted tumor size and vascular density [3]. In MSCs-glioma in vitro coculture, they showed reduced expression of PDGF-BB and IL-1β, and proposed that MSC may exert its antitumor effect through down-regulation of PDGF/PDGFR axis, which is critical for glioma angiogenesis [3]. In fact, tumor cells play a decisive role in mutual cross-talks between the diverse heterogeneity of cell types in the tumor microenvironment [140], suggesting the possibility of dual, contradicting effects of MSCs in tumor neo-angiogenesis. Accordingly, the tumor milieu profoundly influences the interplay between MSCs and ECs.

Conclusion

Since the beneficial effect of MSCs in regenerative medicine was discovered, numerous researchers have sought to understand the potential underlying mechanisms—including proliferation, recruitment, extravasation, homing, and differentiation into the cellular components of damaged tissues. One of the pivotal roles of MSCs is their effect on neoangiogenesis, which may change the milieu of the targeted tissue. Interactions between MSCs and ECs tend to be quite context dependent, and sometimes completely opposite effects may be seen based on the condition of the target tissue. As a matter of fact, a large number of molecular mechanisms vis-à-vis the effect of MSCs on tissue angiogenesis and their interactions with ECs need to be addressed for the optimal application of MSCs in different therapeutic situations. Exposure of marrow-derived MSCs to chemotactic factors triggers a chain of molecular cascades, which promote MSC recruitment toward remote signaling centers. After circulating in the blood stream, MSCs—by expressing adhesion molecules—preferentially mimic inflammatory cell-like mechanisms in their interactions with ECs to transmigrate through the vessel wall. Moreover, recent studies consolidate the notion that MSCs possess juxtacrine and paracrine effects on ECs and are even capable of endothelial trans-differentiation, although the effect of ECs on MSCs should not be overlooked. In addition to the potential properties of MSCs, milieu-dependent conditions define MSC fate as well. It has also been described that MSC-derived chemotactic factors initiate the recruitment of EPCs from the bone marrow, thereby promoting angiogenesis in the target tissue. Investigations through a growing number of studies have revealed both the suppressive and promoting effects of MSCs on tumor growth via vascular remodeling. The contribution of MSCs to tumor niche and bi-directional cross-talks with ECs may affect the tumor response to anti-cancer therapeutics. Endothelial differentiation of MSCs can be induced by various intracellular signaling mechanisms. Meanwhile, controlling MSC function by ECM-mediated elements and mechanical stimulation are other influencing factors that drive MSC differentiation. Taken together, considering the paradoxical effects of MSCs on tissue angiogenesis, it seems that there are intricate mechanisms in cell-to-cell as well as in cell-to-ECM cross-talks, which finally guide stem cell fate and behavior in physiologic and pathologic tissues.

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Author Disclosure Statement

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