Chapter 10
Cross-Talk Between MSCs and Their Environments

Thomas P. Lozito and Rocky S. Tuan

Abstract The mesenchymal stromal/stem cell (MSC) has garnered attention as a promising candidate cell type for cell-based therapeutics, partly, by virtue of its ability to differentiate into a variety of cell types. However, the true therapeutic potential of MSCs may lie in the regulatory influences they exert on their environments. Indeed, as a result of their natural homing response to wound sites, MSCs come into contact with a variety of environments and cell types as they leave their perivascular niches. This chapter describes the interactions between MSCs and four such environmental signals, specifically the vasculature, the extracellular matrix, the immune system, and cancer. In vivo and in vitro studies detailing the effects of MSCs on each are presented, with special attention paid to cases of cross-talk in which MSCs alter the very environmental signals acting upon them. Finally, MSC performance in clinical trials is discussed and compared to expectations based on basic science findings. This chapter also identifies gaps in knowledge and current understandings where future research will prove most effective.

Introduction

Adult mesenchymal stromal/stem cells (MSCs) were first discovered in bone marrow and described as mononuclear cells that culture ex vivo as adherent colony-forming unit fibroblasts (CFU-F) [1–3]. In the decades since, MSCs have been

T.P. Lozito • R.S. Tuan (✉)
Department of Orthopaedic Surgery, Center for Cellular and Molecular Engineering, University of Pittsburgh School of Medicine, Pittsburgh, PA 15219, USA
e-mail: rst13@pitt.edu

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identified from mesoderm-, endoderm-, and ectoderm-derived tissues, including mesodermal (trabecular bone [4], synovium [5, 6], cartilage [7], fat [8, 9], muscle [10, 11], blood vessels, and tonsil [12]), endodermal (e.g., thymus [13]), ectodermal (e.g., skin [14], hair follicle [15], dura mater [16], and dental pulp [17]), and prenatal and perinatal tissues (umbilical cord [18], umbilical cord blood [19], and placenta [20]). Because they have been isolated from a wide range of tissues, MSCs are known by many different names in addition to the original "mesenchymal stem cells" coined by Arnold Caplan [21], including mesenchymal stromal cells [22], bone marrow stromal cells [23], marrow-isolated adult multipotent inducible cells [24], and multipotent adult progenitor cells [25]. MSCs have traditionally been thought of in terms of their multi-lineage differentiation potential, including osteogenesis, chondrogenesis, and adipogenesis [26]. Since their initial description, however, the inherent cell biology of MSCs has come into focus due to their emerging roles in a variety of physiological and pathological processes, and these will be the focus of this chapter.

Interactions Between MSCs and the Vasculature

There is strong evidence to suggest that MSCs occupy a perivascular niche in a variety of vascularized tissues, affording them a prime location for regulating vascular events such as angiogenesis [27–31]. Furthermore, numerous similarities have been described between MSCs and pericytes, a microvascular cell type analogous to the smooth muscle cells (SMCs) of macrovessels [31, 32]. For example, MSCs express pericyte markers and vice versa; cultured bovine pericytes are positive for STRO-1, an MSC marker [27], and MSCs from the bone marrow express the pericyte markers CD106 (vascular cell adhesion molecule-1(VCAM-1)), CD146 (melanoma cell adhesion molecule), and smooth muscle α-actin [27, 28]. Dental pulp MSCs express the pericyte marker 3G5 [27], and murine MSCs are positive for two perivascular markers, SAB-1 and SAB-2 [27]. Also, like pericytes, MSCs enhance vessel formation and stabilization through paracrine interactions [29, 30], and both cell types display similar differentiation capabilities [31–34].

However, interactions between MSCs and endothelial cells (ECs), the primary cell type of the vasculature, have implications beyond basic biology. Due to their natural abilities to home to wound sites, suppress inflammation, and support local cells and tissue healing, MSCs show a great promise for inclusion in cell-based therapies. Since the majority of these therapies involve intravenous (IV) or intra-arterial (IA) injection of MSCs into patients, the need to understand the interactions between MSCs and the vasculature becomes apparent. Indeed, current studies suggest that, while the therapeutic potential of MSCs to positively benefit the wound environment is strong, difficulties arise in physically delivering IV- or IA-delivered MSCs to the sites of injury. These difficulties are due to the fact that the vast majority of IV-injected MSCs embolize in the capillaries of the lungs [35, 36]. This passive arrestment of MSCs appears to be due to the large size of MSCs relative to the

small diameter of microvessels [35, 36]. Many of the trapped MSCs die, while a small number first spread out on the lumenal sides of microvessels before extravasating to the perivascular niche [35]. However, substantial evidence exists that not all exogenous MSCs embolize at the precapillary level and that some actively home to sites of injury. For example, MSC homing to organs other than the lungs increased significantly in a mouse injury model, suggesting that MSCs exhibit higher engraftment efficiencies within sites of inflammation or injury [37]. These results also suggest that MSC engraftment to damaged tissues is an active process, while the presence of MSCs in the lungs is due to passive entrapment. These in vivo findings are linked to in vitro studies in which MSCs demonstrate increased adhesiveness for damaged ECs treated with proinflammatory cytokines and proapoptotic agents [38]. However, the most convincing evidence that MSCs actively home to injured tissues comes from studies employing receptor blocking/knockout methodologies. For example, MSC interactions with ECs under shear flow were shown to be dependent upon EC-expressed P-selectin and VCAM-1 and MSC very late antigen-4 (VLA-4) [39, 40]. Prestimulating either MSCs or ECs with proinflammatory cytokines enhanced these interactions. On the other hand, blocking integrin β1 specifically was shown to interfere with MSC myocardial engraftment [41]. Such studies provide information on the identity and mechanisms of action of the receptors involved in MSC homing to various organs and tissues. A summary of these interactions is provided in Table 10.1.

Interactions Between MSCs and the Extracellular Matrix

Tightly wrapped around the vessels, pericytic MSCs also interact with another critical regulator of the vascular environment, the vascular basement membrane (VBM). The VBM is a specialized extracellular matrix (ECM) that surrounds the blood vessels of the body and is regulated through a control system involving proteases, which alter and degrade the matrix, and protease inhibitors, which maintain and protect the VBM from disruption [51]. This interplay between proteases and protease inhibitors and its effects on the VBM profoundly influences vessel stability and, hence, many physiological and pathological processes. For example, disruption of the VBM is an early step in angiogenesis [51–57]. During tumor growth and metastasis, cancer cells secrete proteases that degrade the VBM, allowing new blood vessels to sprout and nourish the growing tumor [51, 55, 58]. These extrinsic factors potentially tip the balance between proteases and protease inhibitors toward vascular disruption. As residents of the perivascular niche, MSCs are in a prime location to alter their local environment by affecting this balance.

As stem cells multipotent for lineages of the musculoskeletal system, MSCs are profoundly influenced by signals originating from their local environments, particularly when it comes to differentiation. Effects on MSC differentiation are often tissue dependent [59]. There is evidence to suggest that this tissue-instructive differentiation is actually supported by the tissue-specific composition of the

Table 10.1 Interactions between MSCs and the vasculature

Effects of MSC-produced factors on vasculature			
Vascular cell type	Factor	Effect	References
ECs	Cysteine-rich protein 61 (Cyr61)	Induces EC chord formation on Matrigel in vitro, induces Matrigel plug neovascularization in athymic mice in vivo	[42]
Apoptotic ECs	Unknown	ECs treated with proinflammatory cytokines and proapoptotic agents exhibited increases adhesion for MSCs in vitro	[38]
ECs	Unknown	MSCs enhance and stabilize EC tubes on HFF feeder layers and on Matrigel in vitro	[43]
ECs	MMPs	Enhance tube formation through high-density fibrin gels in vitro	[44]
ECs	P-selectin, VCAM-1/VLA-4	Mediate rolling and adhesion between MSCs and ECs under shear flow. Adhesion increased when ECs were prestimulated with TNF-α	[39]
ECs	VCAM-1 (NOT ICAM-1)	MSCs injected intraventrically adhered to ECs. Pre-activation of MSCs with TNF-α enhanced cardiac homing in a VCAM-dependent process	[40]
Heart	Unknown	MSCs promote wound repair and regeneration in damaged hearts	[45–50]

extracellular matrix [60–68]. Indeed, interactions with various matrix molecules, including those derived from ECs, modulate MSC behavior and differentiation [61–76]. As part of the perivascular niche, MSCs are subjected to various signals originating from the vascular environment and the VBM. For example, proteolytic degradation alters the biological activity of a variety of these matrix molecules by revealing cryptic domains [77–81], releasing bioactive fragments [51, 72–74, 79, 82–92], and liberating stores of matrix-bound and matrix-regulated growth factors [51, 83, 89, 93–102]. Interestingly, MSCs secrete a variety of molecules that regulate matrix remodeling [29, 52, 55, 56, 67, 68, 103–105].

A specific class of extracellular matrix-degrading metalloenzymes, the matrix metalloproteinases (MMPs), and their endogenous inhibitors, the tissue inhibitors of metalloproteinases (TIMP), are specifically linked with VBM remodeling [106]. Of the approximately 26 currently recognized MMPs, several are of particular relevance to the perivascular environment [106]. For example, MMP-2 and MMP-9 are unique among MMPs in that they contain type II fibronectin domains, allowing them to bind gelatin, collagens, and laminin [107]. This allows MMP-2 and MMP-9 to bind intact matrix,

where they degrade gelatin as well as laminins and collagen type IV, the main matrix components of the VBM [56]. Furthermore, membrane type 1-MMP (MT1-MMP), working pericellularly, degrades a wide range of matrix molecules, including those of the VBM [107]. The TIMPs are the main MMP inhibitors, binding 1:1 stoichiometrically with the MMP active-site cleft [107]. Four TIMPS (TIMP-1, TIMP-2, TIMP-3, and TIMP-4) have been identified [107], and each TIMP is composed of distinct N- and C-terminal domains [108]. The N-terminal domains take part in the inhibitory actions, while the C-terminal domains mediate non-inhibitory complexes with MMPs. While the TIMPs as a group are largely specific in their inhibition for MMPs over other proteases, each of the four TIMPs exhibit important differences among their binding properties for specific MMPs. For example, the N-terminal domains of TIMP-2, TIMP-3, and TIMP-4, but not TIMP-1, are potent inhibitors of MT1-MMP [108, 109]. Furthermore, the C-terminal domains of TIMP-2 and TIMP-4 bind the hemopexin domain of MMP-2, while TIMP-1 and TIMP-3 do not [54, 108, 109]. All MMPs are initially expressed as inactive zymogens and require proteolytic removal of N-terminal inhibitory pro-peptides for activation [56]. For example, proMMP-2 activation occurs at the cell surface in a process that requires TIMP-2 and active MT1-MMP [110]. The N-terminal domain of TIMP-2 binds to the active cleft of MT1-MMP on the surface of the cell, while the C-terminal domain binds to the proMMP-2 hemopexin domain [54]. ProMMP-2 is then activated though proteolytic processing by other, noncomplexed MT1-MMP. Only TIMP-2 is able to mediate the ternary complex proMMP-2/TIMP-2/MT1-MMP. TIMP-4, which binds the hemopexin domain of proMMP-2 and potently inhibits MT1-MMP but does not support the ternary complex, competes with TIMP-2 for proMMP-2 and MT1-MMP binding.

MSCs secrete high levels of TIMPs that stabilize vessels and protect the VBM from MMP-induced degradation [105]. MSC secretion of TIMPs and the consequent vessel-protective properties of MSCs were sustained even under simulated disease conditions. This last feature was not exhibited by ECs, suggesting that MSCs, acting as robust sources of TIMP-1 and TIMP-2, are an important protective element of the perivascular niche from protease-mediated degradation.

Interactions Between MSCs and Immune System

Perhaps one of the most significant discoveries involving MSCs concerns their abilities to suppress the immune system. The first such findings concerned the ability of MSCs to suppress T cell proliferation [111, 112]. While the exact mechanisms remain only partially known, cell-cell contact and soluble factors are thought to support various levels of MSC suppression of T cells. For example, cell-cell signaling involving programmed death-1 (PD-1) has been found to mediate contact-driven MSC/T cell interactions [113], while other studies have traced MSC immunosuppressive abilities to MSC-secreted factors, including transforming growth factor-β1 (TGF-β1), hepatocyte growth factor (HGF), soluble isoform of histocompatibility antigen, class I, G (HLA-G5), and indoleamine-pyrrole 2,3-dioxygenase (IDO) [112, 114–117]. Still

other studies have focused on the involvement of proteases such as MMP-2 and MMP-9, which cleave interleukin-2 receptors on the surface of T cells, in MSC modulation of T cell biology [118]. Importantly, the effects of MSCs on T cell proliferation do not appear to involve apoptosis, instead, MSCs promote T cell survival in a quiescent state [119]. The effects of MSCs on other types of T cells have also been investigated. For example, MSCs were found to decrease interferon-gamma (IFN-γ) production in type 1 helper T cells (T_H1 cells) and increase interleukin-4 (IL-4) secretion in type 2 helper T cells (T_H2 cells), indicating a shift from a pro- to an anti-inflammatory state [120–122]. MSCs have also been shown to downregulate cell killing of cytotoxic T lymphocytes (CTLs) and to induce expansion of regulatory T cells (T_{Reg} cells), both of which act to suppress immune system activity [114, 117, 123].

Whatever the mechanism, the influence of MSCs on the immune system is not restricted to T cells. Acting as links between the innate and adaptive immune systems, dendritic cells represent an important target of MSC modulation. MSCs have been shown to inhibit myeloid dendritic cell (DC) differentiation and impair the critical antigen-presenting functions of DCs [121, 124–129]. MSCs also increase IL-10 secretion by plasmacytoid dendritic cells (pDCs), which ultimately promotes T_{Reg} cell proliferation and immune system suppression [121, 128].

Interactions between MSCs and natural killer (NK) cells is complicated by the findings that NK cells effectively lyse MSCs [130]. On the other hand, MSCs decrease NK cell cytokine secretion and interfere with the ability of NK cells to kill other cells. The susceptibility of MSCs to NK cell-mediated cytotoxicity is dependent upon the naturally low levels of major histocompatibility complex (MHC) class I expression in MSCs, and treatment with factors, such as IFN-γ, that increase expression of MHC class I work to partially protect MSCs from NK cell-targeted killing. The relationship between MSCs and B cells is also difficult to interpret due to conflicting reports on the effects of their interactions. Most studies have found that MSCs, either through soluble factor or cell-cell contact, inhibit B cell proliferation and antibody production [113, 131, 132], while others have demonstrated MSC support of B cell survival, proliferation, and differentiation. In the end, however, the interactions between MSCs and B cells may be secondary to the primary roles T cells play in the regulation of B cell activity. Indeed, several in vivo studies have detected reduced levels of antibodies and T cell activity, indicating that MSCs may modulate B cell antibody production in vivo via reduced proliferation of T cells [133].

Perhaps one of the most interesting aspects of MSC interactions with the immune system is the high degree of back-and-forth cross-talk between them and other cells; often stimulation by immune cells is involved in activating MSC modulation of the same or different cells of the immune system. For example, IFN-γ released by immune cells triggers MSCs to release nitric oxide (NO) and IDO, which in turn inhibit immune cell activity and proliferation [122, 134, 135]. Similarly, IFN-γ and other cytokines stimulate MSC production of T cell-attracting chemokines and inducible nitric oxide synthase (iNOS), which inhibits T cell activation via NO [120, 122, 134, 136, 137].

These interactions between MSCs and the immune system are summarized in Table 10.2.

Table 10.2 Interactions between MSCs and the immune system

Effects of MSC-produced factors on immune system			
Target cell type	Factor	Effect	References
T cells	Cell-cell contact: PD-1	Suppress T cell proliferation	[113]
T cells	Secreted factors: TGF-β1, HGF, HLA-G5, IDO	Suppress T cell proliferation	[112, 114–117]
T cells	Secreted proteases: MMP-2, MMP-9	Reduced T cell proliferation and expression of CD25 in vitro; reduced hypersensitivity responses to allogenic antigens and prolonged survival of allogenic islet grafts in vivo	[118]
T cells	unknown	Promote T cell survival in a quiescent state, decrease IFN-γ production in vitro and in vivo	[119]
T cells	iNOS and NO	Inhibit T cell activation	[120]
T_H1 cells	IDO?, PGE_2?	Decrease IFN-γ production	[121, 122]
T_H2 cells	PGE_2?	Increase IL-4 secretion	[121]
$CD^4CD25^{high}FOXP3^+$ T_{reg} cells	HLA-G5	Induce expansion	[114]
CTL	HLA-G5?	Downregulate CTL-mediated cytotoxicity	[117, 123]
DCs	IL-6?, M-CSF?, TGF-β1?, Notch?, others?	Inhibit progenitor cell differentiation into DCs, impair antigen-presenting function of DCs	[121, 124–129]
DCs	PGE_2?	Inhibit production of TNF-α, induce production of IL-10	[121]
pDCs		Induce pDC production of IL-10, which goes on to promote T_{Reg} Cell expansion	[121, 128]
NK cells	IDO, PGE_2, HLA-G5, cell-cell contact?	Decrease IFN-γ secretion, inhibit proliferation in resting NK cells, inhibit NK cell cytotoxic activity by downregulating receptors involved in NK cell activation	[121] [114, 130, 135, 138]

(continued)

Table 10.2 (continued)

Effects of MSC-produced factors on immune system			
Target cell type	Factor	Effect	References
Neutrophils	IL-6	Delay apoptosis	[139]
B cells	soluble factors?, cell-cell contact?: PD-1?	Inhibit proliferation in vitro	[113, 131, 132]
B cells	unknown	Support B cell survival, proliferation, and differentiation to antibody-secreting cells	[140, 141]

Effects of immune system-produced factors on MSCs			
Source cell type	Factor	Effect	References
Immune cells/wound environment	TNF-α, LPS, hypoxia	Increased MSC production of VEGF, FGF2, HGF, and IGF	[142]
NK cells	NKp30, NKG2D, DNAM-1	Lyse autologous and allogeneic MSCs	[130]
Various immune Cells	IFN-γ	Low levels of IFN-γ induce MHC class II expression in MSCs, allowing them to act as APCs	[136, 137]
Immune cells	IFN-γ	Trigger release of IDO and NO in MSCs	[122, 134]
Immune cells	IFN-γ, TNF, IL-1α, IL-1β	Increase MSC production of T cell-attracting chemokines and iNOS	[120]
Immune cells	TNF, IFN-γ	Increase MSC production of PGE_2	[121]
T cells	Cell-cell contact + IL-10	Stimulate HLA-G secretion by MSCs	[114]

Table 10.3 Interactions between MSCs and cancer cells

Effects of MSC-produced factors on cancer			
Cancer type	Factor	Effect	References
Breast cancer cells	CCL5 (RANTES)	Increase motility, invasion, and metastasis	[143]
Renca adenocarcinoma or the B16 melanoma cell lines	unknown	Low numbers of MSCs induced tumor rejection; higher numbers enhanced tumor progression	[144]
Kaposi's sarcoma	Cell-cell contact? (E-cadherin/Akt?)	MSCs inhibit tumor growth and AKT activation	[145]
Adenocarcinoma	IL-6	Promote tumor growth	[146]

Effects of cancer-produced factors on MSCs			
Cancer type	Factor	Effect	References
U87 and LN229 glioma cells	PDGF-BB	Mediates MSC tropism for gliomas	[147]
Breast cancer cells	MCP-1	Responsible for MSC homing to tumors	[148]
Ovarian tumors	LL-37	Recruit MSCs to tumors and induce MSC secretion of proangiogenic factors	[149]
Adenocarcinomas	unknown	Convert MSCs to TAFs	[146]

Interactions Between MSCs and Cancer

The topic of MSCs and cancer offers a good review of the various facets of MSC environmental interactions due to the wide range of physiologic and pathologic processes that underlies cancer progression (see Table [10.3] for a summary of these interactions). MSCs naturally home to sites of injury as part of the body's natural wound healing response through their interactions with immune cells and the vasculature [31, 150]. These cellular activities are hijacked by cancer cells, which create local environments that share many similarities with chronic, unresolved wounds. The abilities of MSCs to leave their perivascular niche and migrate toward tumors and sites of injury and metastasis have been well established [148, 150–155]. Even exogenous MSCs injected into the circulation of animals with breast cancer tumors exhibit highly specific migration to the tumor microenvironment [143]. This strong chemotactic response has been attributed to tumor-produced and tumor-induced inflammatory cytokines, such as platelet-derived growth factor (PDGF-BB),

monocyte chemotactic protein-1 (MCP-1), and the N-terminal peptide of human cationic antimicrobial protein 18 (LL-37) [147–150]. Upon integrating with the tumor microenvironment, MSCs modulate tumor growth and metastasis, but the precise mechanisms remain unclear [156]. Most studies conclude that MSCs are overall pro-tumorigenic and promote cancer metastasis, but again the specifics remain unresolved. For example, the MSC-secreted chemokine (C-C motif) ligand 5 (CCL5) is reported to directly increase cancer cell motility, invasion, and metastasis [143], while other studies suggest MSCs play more indirect tumor-supporting roles by suppressing the immune system and promoting angiogenesis [144]. However, like the other areas of study concerning MSC environmental interactions, there exists a large degree of controversy. For example, several studies suggested that MSCs inhibit tumor growth through direct cell-cell contact [145], while others found a biphasic response of MSCs on tumor progression, wherein MSCs either promoted or inhibited tumor development depending on the number of cells involved in the experiment and independent of direct contact between MSCs and tumor cells [144]. In another similarity to the trends seen in the other avenues of MSC interactions, there also appears to be a great deal of back-and-forth cross-talk between MSCs and tumors. For example, exposure to cancer-secreted factors is reported to convert MSCs to tumor-associated fibroblasts (TAFs). These TAFs act to promote tumor progression through secretion of IL-6 [146]. Similarly, tumors produce LL-37, which recruits MSCs and induces their expression of pro-tumor and proangiogenic factors, including interleukin (IL)-6, IL-10, CCL5, vascular endothelial growth factor (VEGF), and MMP-2 [149]

Filling in the Gaps: Areas for Potential Future Work

The vast majority of interactions between MSCs and their microenvironment remain largely unstudied and poorly characterized. Among these areas of future study, several connections have been outlined in separate studies, and future work needs only connect the dots. In the most common examples, a group of studies describe MSC production of a particular factor, while a distinct pool of findings describes the response to the same factor in some other cell type. Connecting these two seemingly unrelated areas of study would surely yield some interesting findings. Table 10.4 summarizes a number of possible considerations. For example, the antiangiogenic properties described for the TIMPs are noteworthy. Several independent research groups have found that TIMP-1, TIMP-2, and TIMP-3 inhibit angiogenesis [157–161]. At least in the cases of TIMP-2 and TIMP-3, these antiangiogenic properties appear to result from inhibition of signaling between receptor tyrosine kinases (RTKs) and growth factors, either by competing with the growth factors for receptor binding [160] or through interactions with third-party cell surface receptors [158, 159]. Angiogenesis is an important step in cancer development, and at least TIMP-1 has been shown to slow tumor development through interfering with angiogenesis [157]. When one considers the fact that MSCs secrete high levels of functionally

Table 10.4 Potential areas of future study

Factors produced by MSCs		
Factor	Effect	Proposed connection
TIMP-1	Inhibits tumor growth and angiogenesis [157]	Does MSC-secreted TIMP-1 affect tumor progression?
TIMP-2	Interacts with integrin α3β1 and inhibits RTK-growth factor signaling, including angiogenic FGF and VEGF signaling in endothelial cells [158, 159]	Is MSC-secreted TIMP-2 an autocrine and/or paracrine inhibitor of growth factor signaling?
TIMP-3	Blocks VEGF binding to KDR and inhibits downstream signaling and angiogenesis [160]. Inhibits VEGF- and FGF-induced chemotaxis and FGF-induced angiogenesis [161]	Does MSC-secreted TIMP-3 inhibit angiogenesis?
MMP-3, MMP-7	Induce cancer cell metastasis by degrading E-cadherin	Do MSC-secreted MMPs promote cancer development?

Factors produced by other cells		
Factor	Effect	Proposed connection
Exosomes	Discharge of β-catenin and suppression of β-catenin-mediated Wnt signaling [162]	Could MSCs receive/lose β-catenin via exosomes?
Exosomes	Transfer mRNAs and microRNAs between cells [163]	Could MSCs receive/send RNA from/to other cells via exosomes?
EC- and cancer cell-derived microparticles	Bind proteases, including plasmin and MMPs, at their surfaces [164–167]	Could microparticles transfer MMPs from cancer cells to MSCs?
Immune cell-derived microparticles	Induced expression of select MMPs and cytokines in synovial fibroblasts [168]	Do microparticles affect MSC MMP/cytokine production?

activeTIMP-1 and TIMP-2 [105], it begs investigating whether MSCs affect angiogenesis and cancer development via TIMPs.

MSCs are also known to secrete proteases with demonstrated regulatory roles in breast cancer tumor progression [51, 56, 152]. For example, proteases facilitate the changes in cell-cell contacts exhibited by breast cancer cells as they transform from normal breast epithelial cells to malignant migratory cells. This epithelial to mesenchymal transition is highly regulated by E-cadherin, a homotypic cell-cell adhesion molecule that facilitates normal epithelial cell contacts and whose continued expression inhibits breast cancer metastasis [169]. As breast cancer cells become malignant, E-cadherin is degraded by proteases, weakening interactions between cancer cells and the surrounding tissue and releasing E-cadherin fragments that signal breast cancer cells to migrate [170]. MMP-7 and MMP-3, proteases secreted by MSCs, are known to degrade E-cadherin [106]. Thus, the effects of MSCs on cancer

metastasis through degradation of E-cadherin contacts remain a potential topic of study.

One of the most interesting, and often overlooked, areas of study involving interactions between cells and their environment centers on microparticles and exosomes. Both microparticles and exosomes are membrane vesicles that are released into the extracellular environment by a variety of cell types [171–177]. Microparticles and exosomes differ in size (50–1,000 nm in diameter for microparticles [171, 178], 50–100 nm for exosomes [179]) and in composition and origin. Exosomes are enriched in tetraspanins, milk fat globule-EGF factor 8 (MFG-E8), and MHC class II molecules [180], while microparticles are associated with their own set of markers, including MMPs [164, 181]). Microparticles, also known as ectosomes, are formed directly by ectocytosis [171, 177, 181], whereas exosomes originate from multivesicular bodies (MVBs) that result when endosomes bud inwardly into their lumens [182–184]. Exosomes are released as MVBs fuse with the plasma membrane and release their intraluminal vesicles. Both are distinct from apoptotic bodies, which are larger (1–4 μm), formed at the end of apoptosis, and are usually immediately taken up by macrophages [185, 186].

Both microparticles and exosomes contain membrane and cytosolic components that can be transferred from one cell to another as the particles are released and fuse with neighboring cells. For example, exosomes released by human mast cell lines are capable of transferring mRNAs and microRNAs to other mast cells. Once inside the recipient cell, this "exosomal shuttle RNA" (esRNA) is functional and affects cell behavior [163]. While the effects of esRNA on MSCs have yet to be considered, given the various cell types that MSCs interact with, the implications of MSCs receiving functional RNA from neighboring cells are very interesting.

Exosomes have also been shown to discard membrane and cytosolic proteins [162, 176]. For example, release of β-catenin from cells via exosomes has been shown to suppress β-catenin-mediated Wnt signaling. While this study did not consider intercellular transfer of β-catenin via exosomes, the notion is intriguing considering the importance of Wnt/β-catenin signaling in MSC biology; activation of canonical Wnt signaling in MSCs, which is mediated via β-catenin, is reported to keep the stem cells in a self-renewing and undifferentiated state and suppress adipogenesis and early osteogenesis and late chondrogenesis [187–190]. However, other reports describe activation of myogenesis and late-stage osteogenesis by canonical Wnt signaling in MSCs [191–193], and effects on chondrogenesis appear to be largely dependent on the specific Wnt ligand and the developmental state when Wnt is engaged [194–198]. Clearly, Wnt signaling is closely regulated in MSCs, and the shuttling of β-catenin via exosomes may represent a previously unexplored avenue by which MSC Wnt/β-catenin signaling is influenced by surrounding cells.

Formed by budding of the plasma membranes, microparticles contain a wide range of membrane-associated proteins. For example, microparticles have been shown to mediate the intracellular transfer of the chemokine receptor CCR5. While no study has focused on the transfer of membrane proteins to MSCs as of yet, the possibility is intriguing. For example, transfer of exogenous receptors to MSCs by microparticles could influence how MSCs respond to both autocrine and paracrine factors.

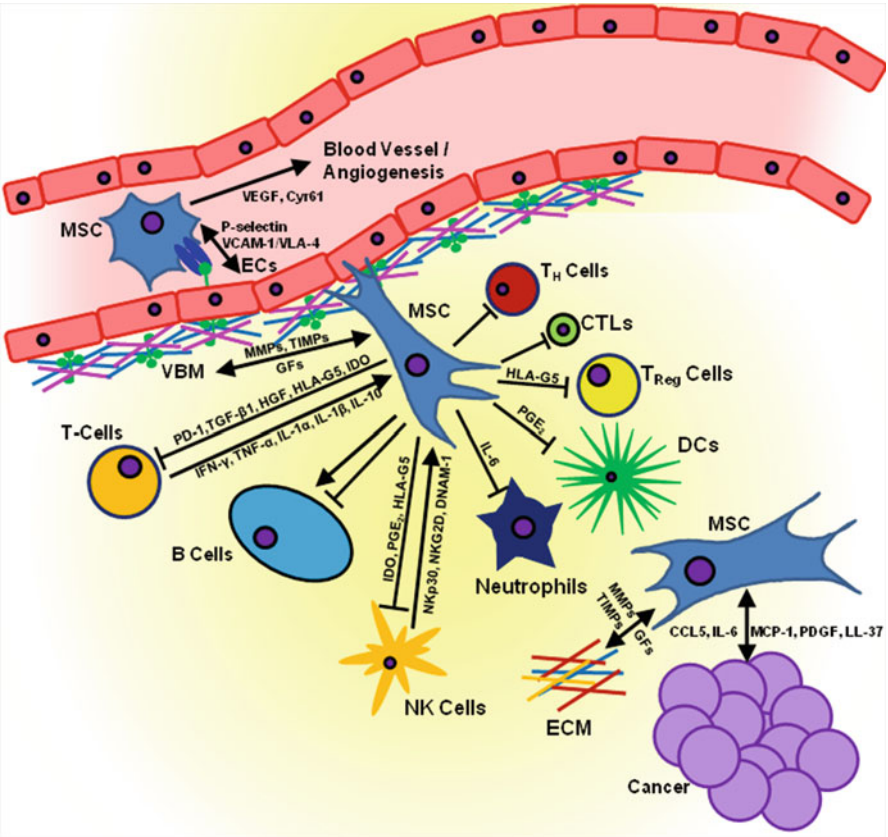

Fig. 10.1 MSC environmental interactions. MSCs influence, and are influenced by, a variety of cells, matrix molecules, and cytokines as they home to wound sites. Within the vasculature, MSCs interact with ECs, particularly those activated by the wound environment. MSCs also secrete factors that affect blood vessel structure and promote angiogenesis by regulating the extracellular matrix of the VBM. At the wound site, MSCs suppress the immune system by regulating the proliferation and activation of various immune cells. If cancer is present at the wound site, cross-talk between cancer cells and MSCs may potentiate tumor growth and metastasis (see text for abbreviations and detailed descriptions)

Furthermore, microparticles derived from cancer cells and ECs contain proteases [164–167], and EC microparticles have been shown to bind MSC-secreted MMPs [164]. Transfer of these proteases to the surfaces of MSCs could have profound effects on MSC migration and tissue invasion. Microparticles have also been shown to signal changes in cell behavior, such as induction of MMPs and cytokine expression in synovial fibroblasts [168]. This brings up the interesting possibility of microparticles and exosomes mediating long-range cell-cell interactions. Both microparticles and exosomes have been shown to display cell adhesion molecules, including E-, N-, and VE-cadherin; P-selectin; and integrins [162, 164, 180, 199]. Signaling through such

molecules are usually restricted to cells in direct physical contact with one another, but perhaps microparticles/exosomes provide a means for MSCs to interact with the surface receptors shed from other cells over longer distances.

Conclusion

The current understanding of the interactions between MSCs and their environment strongly suggests a dynamic relationship in which cells alter their surroundings and vice versa (Fig. 10.1). Studying these interactions has demonstrated unique attributes in MSCs that threaten to overshadow their differentiation capabilities as their most therapeutically important characteristics. Indeed, two of the most exciting properties of MSCs were discovered by considering their interactions with other cell types. These include the abilities of MSCs to home to sites of injury and to suppress the immune system. Several clinical trials involving MSCs that exploit the potential benefits of these properties have already concluded. These studies showed that IV delivery or direct injection of MSCs into patients with hematological pathologies, heart diseases, or cancer/chemotherapy represents a viable form of therapy with reduced chances of toxicity and adverse reactions. Furthermore, many studies observed improved healing in patients, with a variety of disorders, that were treated with MSCs. Taking into consideration that the majority of infused MSCs embolize in the lungs, these results suggest that lung-engrafted MSCs are still able to effect systemic healing in remote tissues. Perhaps the most interesting clinical results involving MSC-based therapies to promote wound repair and tissue regeneration concern cardiovascular diseases of the heart. Given the results of such studies demonstrating the proangiogenic capabilities of MSCs, the exact mechanism by which therapeutic MSCs effect improvements in impaired hearts and other wounded tissues is probably multipronged. Future research will be needed to tease apart the intricacies of these specific interactions and also to address potential side effects of MSC-based therapies, particularly those related to cancer and immunosuppression. The study of MSC and their environmental interactions thus holds the promise of generating therapies virtually impossible by any other means.

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