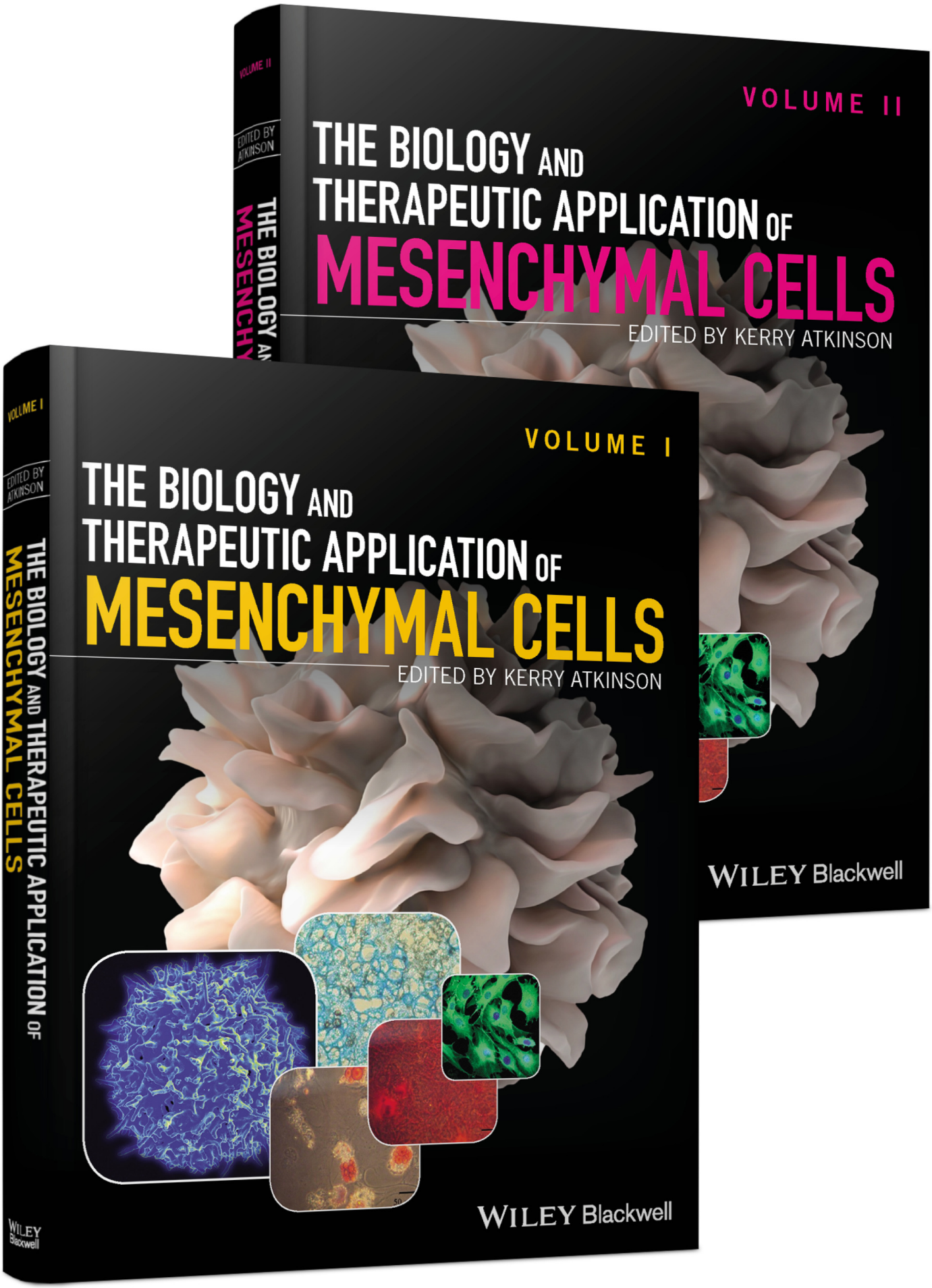
VOLUME II
THE BIOLOGY AND THERAPEUTIC APPLICATION OF
MESENCHYMAL CELLS
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The biology and therapeutic application of mesenchymal cells

Volume I and II

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Contents

Section III: The cellular and molecular biology of mesenchymal stromal cells

Section IV: The role of bioengineering in the therapeutic applications of mesenchymal stromal cells

Section V: GMP manufacturing of mesenchymal stromal cells for clinical use

Section VI: The therapeutic application of mesenchymal stromal cells

Section VII: Mesenchymal stromal cells as delivery vehicles for therapeutic agents

Section VIII: The present and the future

CHAPTER 28

The implications of multipotent mesenchymal stromal cells in tumor biology and therapy

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Chapter menu

28.1 Introduction

Multipotent mesenchymal stromal cells (MSCs) are able to differentiate *in vitro* into adipocytes, osteoblasts and chondrocytes [1] and into bone *in vivo*. MSCs have now been isolated from multiple organs and they form part of the endothelial wall of blood vessels [2,3]. In addition, they are a key component of tumor stroma and have been found to play important roles in various cancers [4]. Tumors, having many of the characteristics of injured tissue, may attract MSCs from their local tissue or from the circulation. The tumor tropism property of MSCs has suggested the possibility of their use as vehicles to deliver anticancer drugs or genes. However, extensive experimental research has demonstrated both anti- and procancer roles of MSCs in a context-dependent manner. It is now generally assumed that within this microenvironment reciprocal tumor–stroma crosstalk influences the phenotype of tumor cells, their progression, and their metastasis [5]. Various studies have reported the tumor-promoting effects of MSCs [6–8]. Others have provided evidence for an anti-oncogenic role of these cells [9–12]. MSCs are emerging as vehicles for anticancer drug/gene delivery [7]. This chapter aims to dissect this observed discrepancy in different experimental settings of human cancer so as to provide possible guidance to the appropriateness of clinical applications.

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28.2 Origin and identification of mesenchymal stromal cells in the tumor microenvironment

MSCs were initially identified by placing whole bone marrow cells in plastic culture dishes and observing the subsequent

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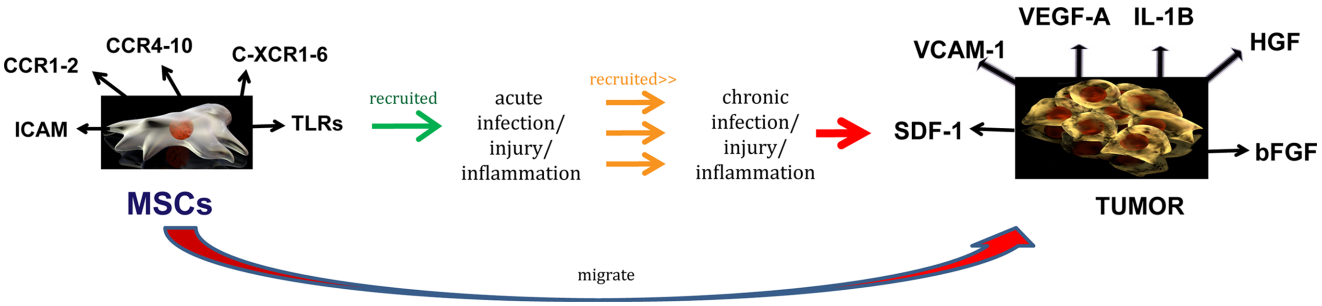

Figure 28.1 Mechanisms for the recruitment of MSCs into tumors. MSCs express chemokine receptors, intercellular adhesion molecule (ICAM), C–C motif chemokine receptor (CCR)1–2, CCR4–10, C–X–C motif chemokine receptor (CXCR)1–6, and toll-like receptors (TLRs). Tumors release various cytokines, chemokines, and growth factors, including basic fibroblast growth factor (bFGF), stromal cell-derived factor 1 (SDF-1), hepatocyte growth factor (HGF), interleukin (IL)-1β, vascular cell adhesion molecule 1 (VCAM-1), and vascular endothelial growth factor (VEGF)-A, acting as chemoattractants for MSCs. MSCs in the local organ or tissue or circulating MSCs may be recruited into the tumor. MSCs may be constantly recruited in different stages from chronic infection, injury, and inflammation to cancer development.

expansion of a rare population of plastic-adherent cells [13,14]. The spatial distribution and properties of MSCs within their organ/tissue *in vivo* are relatively unclear [15]. MSCs have been isolated from most organs, including kidney, umbilical cord, brain, liver, lung, and bone marrow [16–18], and may have unique properties depending on their source. Recruited by the inflammatory milieu, MSCs migrate to the microenvironment of tumors and orchestrate the hallmarks of cancer cells [19]. The enrichment of MSCs in the tumor environment has been reported in both primary human cancers [20,21] and in metastases [22–24]. A resident population of MSCs has also been identified in the human adult liver and express a unique gene signature [25]. Additionally, MSCs share a molecular signature with mesenchymal tumor cells and favor early tumor growth in mice [26].

In response to injury or infection, MSCs can be released from the bone marrow and migrate toward sites of injury to promote tissue regeneration [27]. High frequencies of MSCs have been found in tumors with extensive inflammation, suggesting the recruitment of MSCs in response to inflammation [20]. Additionally, high circulating levels of endothelial progenitor cells have been observed in many cancer patients, which might also home to the site of tumors and promote tumor growth [28–30]. MSCs may be recruited locally and/or from the circulation to tumor sites (Figure 28.1). Future studies using somatic genomic signatures may provide a definite answer.

28.3 The migratory capacity of mesenchymal stromal cells

MSCs tend to be recruited by injured tissue, where they are thought to contribute to tissue repair and wound healing [31]. As tumors are often considered to have many characteristics of injured tissues, it is not surprising to find MSCs enriched within tumors. Various preclinical models have confirmed that MSCs can migrate to certain types of tumors, and this is one of the rationales of using MSCs as vehicles for anticancer drug/gene delivery [7,32]. MSCs are also relatively resistant to ischemia, because in the absence of oxygen they can survive by anaerobic adenosine triphosphate production [33], which may give them a competitive advantage in a tumor microenvironment. The tumor-tropic migratory property of MSCs is attributed to two main mechanisms [34,35].

28.3.1 Intrinsic migratory properties of mesenchymal stromal cells

Activated human MSCs express adhesion molecules such as integrins, ICAM-1, ICAM-2, and VCAM-1, which enable these cells to migrate [36]. MSCs also express chemokine receptors, including CCR1, CCR2, CCR4, CCR6, CCR7, CCR8, CCR9, CCR10, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, CXCR6, and CX3CR [31]. Production of their respective ligands is a characteristic of inflamed tissue and malignant tissue, and thus these receptors are likely involved in the specific accumulation of MSCs in both processes. Thus, the cognate ligands of these receptors are efficient chemotactic stimuli for MSCs. Additional receptors implicated in MSC migration are the TLRs. TLR1–6 have been identified in human MSCs and it has been reported that TLR stimulation enhanced the migratory function of MSCs [37].

28.3.2 Stimuli produced by the tumor

Malignant cells have been shown to produce relatively high amounts of MSC chemoattractants, including HGF, SDF-1 (also known as CXCL12), bFGF, VEGF-A, and VCAM-1 [38,39]. Tumor-derived IL-1β has been found to be a mediator of the proinflammatory response in MSCs exposed to tumor conditioned media, a mechanism that is regulated by focal adhesion kinase and mitogen-activated protein kinase signaling [40].

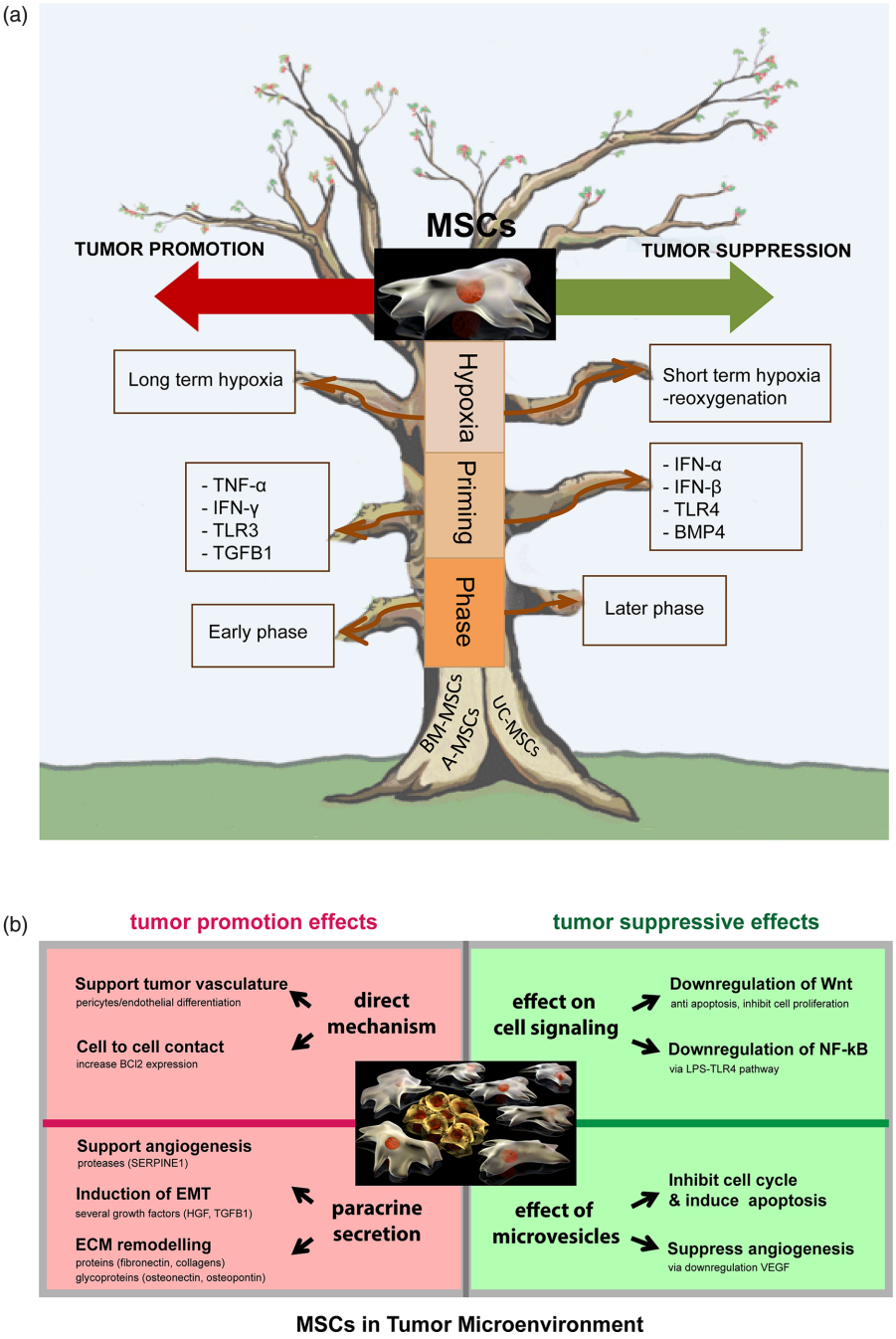

Figure 28.2 Context-dependent role of MSCs in the tumor microenvironment. MSCs can exert tumor-promoting or tumor-limiting effects, which depend on the context in which the MSCs are present. (a) Different sources of MSCs, the presence of ligands, cytokine-primed MSCs, and the hypoxic microenvironment may lead to different effects of MSCs in the tumor microenvironment. The properties of the MSCs and the particular tumor microenvironment may result in dual roles for MSCs that can either suppress or promote tumor progression. (b) The tumor-suppressive mechanisms are mainly mediated by MSC microvesicles and downregulation of the Wnt and nuclear factor kappa light chain-enhancer of activated B cells (NF-κB) pathway. The tumor-promoting mechanisms are mainly attributed to factors secreted by MSCs and direct effects such as support of tumor vasculature, epithelial to mesenchymal transition (EMT) transition, and extracellular matrix (ECM) remodeling. BM-MSCs,: bone-marrow-derived MSCs; A-MSCs: adipose-derived MSCs; UC-MSCs: umbilical-cord-derived MSCs; BMP4: bone morphogenetic protein 4; IFN: interferon; LPS: lipopolysaccharide; TNF-α: tumor necrosis factor-α.

28.4 Context-dependent role of mesenchymal stromal cells in the tumor microenvironment

The tumor microenviroment is substantially different from that of normal organs and this is a mechanism in cancer development [41]. Depending on the experimental conditions, MSCs can exert tumor-promoting [20,24,42,43] or tumor-limiting effects [9,11,12,44,45]. Various hypotheses have been postulated to explain the context-dependent role of MSCs in cancer (Figure 28.2a).

28.4.1 Hypotheses on context-dependent roles of mesenchymal stromal cells in cancer

28.4.1.1 Phase-dependent hypothesis

MSCs appear to promote tumor growth when co-injected with tumor cells, but inhibit tumor progression when administered into established tumors [4]. Thus, the presence of MSCs during

the early phase of tumorigenesis may contribute to angiogenesis that is required for tumor initiation. An increase in blood vessel density was observed when MSCs were co-injected with tumor cell lines [8,46].

28.4.1.2 Priming-dependent hypothesis

MSCs express several TLRs, and their ability to migrate, invade, and secrete immune modulating factors is tightly regulated by specific TLR-agonist engagement [47]. TLR4-primed MSCs are polarized into a proinflammatory MSC type 1 (MSC1) phenotype, whereas TLR3-primed MSCs are polarized into the classical immunosuppressive MSC2 phenotype [47]. MSC1-based treatment of established tumors in an immune competent model attenuated tumor growth and metastasis, but MSC2-treated animals displayed increased tumor growth and metastasis [48]. The priming of all MSC types with inflammatory cytokines such as IFN-γ and TNF-α results in higher levels of VEGF [19] and induction of inhibition of runt-related transcription factor 2, one of the pivotal factors driving osteoblast differentiation [49]. These effects, in turn, can enhance tumor progression. However, stimulation of MSCs with IFN-α and IFN-β decreased tumor cell proliferation and induced tumor cell apoptosis in a mouse model of melanoma [50,51]. BMP4-differentiated bone marrow MSCs became less suppressive of T cell and natural killer (NK) cell proliferation and switched on their suppressive machinery by activating both indolamine 2,3-dioxygenase (IDO) and cyclooxygenase 2 (COX-2), promoting the differentiation of neighboring MSCs and triggering the anti-inflammatory effect [52]. In contrast, preconditioning of MSCs with TGF-β1 resulted in proinvasive MSCs in the progression of colon cancer [53].

28.4.1.3 Hypoxic-dependent hypothesis

A long-term hypoxic microenvironment may lead to undifferentiated tumor cells and stromal cells, providing essential cellular interactions accompanied by the upregulation of the stemness genes [54,55]. Permanent hypoxia-stimulated MSCs proliferated and reduced their capacity to differentiate [56,57]. However, short-term oxygen limitation increased the number of apoptotic MSCs after 3–24 h of hypoxic treatment [58,59]. Moreover, oxygen limitation in hypoxia–reoxygenation-induced cell apoptosis was mediated in part by the reduction of phosphorylation of Akt and extracellular signal-regulated kinase 1/2 (ERK1/2) in MSCs [60]. ERK1/2 belongs to the class of protein kinase signal transduction pathways that are used to relay numerous extracellular signals within cells and have been reported to be involved in various cellular functions, including apoptosis and proliferation [61]. Hypoxia switches on various signaling pathways, and its context dependency determines the overall cell response and alterations in MSC functions.

Collectively, tumor cells and the tumor microenvironment will affect the ultimate function of recruited MSCs. However, there are some factors that drive MSCs to suppress or promote tumor growth (Figure 28.2b).

28.4.2 The tumor-suppressing roles of mesenchymal stromal cells

Extensive studies have reported tumor-suppressing effects of MSCs in various experimental cancer models. A variety of processes and mechanisms possibly implicated in MSC-dependent tumor suppression have been studied.

28.4.2.1 Effect on cell signaling

Several signaling pathways have been reported to be associated with MSC suppression of tumor growth. Wnt signaling is aberrantly activated in many types of tumors. In chemically induced murine liver tumors the administration of MSCs has been demonstrated to have tumor suppressive effects associated with Wnt signaling. Its target genes were downregulated, especially those related to antiapoptosis, mitogenesis, cell proliferation, and cell cycle regulation [62]. MSCs can secrete Wnt inhibitors, such as Dickkopf-1 [52,63]. MSC-dependent inhibition of NF-κB signaling in cancer cells also occurs [64]. In addition, TLR signals can stimulate downstream effectors that may interfere with the LPS–TLR4 pathway and inhibit NF-κB activation during liver fibrosis [65].

28.4.2.2 Effects of mesenchymal stromal cell microvesicles

Microvesicles are fragments of plasma membrane ranging from 100 to 1000 nm secreted by many cell types. They play an important role in intercellular communication and are capable of modifying the activity of target cells through surface receptor interactions and the transfer of proteins, mRNA, and microRNA (miRNA). Microvesicles have been implicated in tumor–stroma interactions [66]. Microvesicles released by MSCs have been associated with tumor inhibition in several preclinical studies [67] and have been shown to inhibit cell cycling and induce apoptosis or necrosis *in vitro* and to inhibit growth of established tumors *in vivo* [66,68,69], providing a further antioncogenic effect. Exosomes, a smaller type of intracellular vesicle derived from MSCs, suppress angiogenesis by downregulating VEGF expression in breast cancer cells [70], and MSCs pulsed with tumor-derived microvesicles exert an enhanced antitumor activity against hepatocellular cancer [71]. Thus, the secretome of MSCs appears to play an important role in their tumor suppressive function.

28.4.3 The tumor-promoting roles of mesenchymal stromal cells

The tumor-promoting role of MSCs has been attributed to direct mechanisms and paracrine secretion, including modulation of the immune response.

28.4.3.1 Direct mechanisms

MSCs have been shown to directly differentiate into pericytes or possibly endothelial cells [72], thus supporting tumor angiogenesis, which in turn can promote tumor growth. MSC and

tumor cell contact is another important direct mechanism. In lymphoma models, direct cell–cell contact was the major mechanism of promoting tumor cell proliferation and survival rather than secretion of soluble factors by MSCs [73]. It is well recognized that adhesion to the bone marrow of the malignant cells of the B cell neoplasm, multiple myeloma, provides the myeloma cells with protection against chemotherapy. Bortezomib is a proteasome inhibitor used in the treatment of multiple myeloma and mantle cell lymphoma. MSCs can suppress bortezomib-induced multiple myeloma cell growth inhibition in a cell–cell contact-dependent manner by increasing Bcl2 expression in the myeloma cells [74]. Cell–cell contact with MSCs was reported to protect chronic lymphocytic leukemia cells, another B cell neoplasm, from spontaneous and drug-induced apoptosis [75]. Bone-marrow-derived MSCs have been reported to fuse with non-small cell lung cancer cells, resulting in highly malignant subpopulations with stem-cell-like properties [76].

28.4.3.2 Paracrine mechanisms

MSC promotion of tumor growth via paracrine mechanisms is mainly attributed to supporting angiogenesis, promoting tumor growth, and metastasis. Secreted factors from patient tumor-derived MSCs have been shown to promote tumor growth in a xenograft mouse model associated with upregulation of cell growth and proliferation-related processes and downregulation of cell-death-related pathways in tumor cells [20]. Several growth factors secreted by MSCs, including HGF and TGF-β1, induce proinvasive signals in cancer [77,78]. A large number of proteases that have proangiogenic properties secreted by MSCs may inhibit apoptosis in vascular smooth muscle cells and endothelial cells [79]. The protease named serpin e1, a member of the serine proteinase inhibitor superfamily, is abundantly secreted by MSCs and has been shown to regulate proliferation, migration, and apoptosis of vascular smooth muscle cells and endothelial cells [80]. Transplantation of MSCs promoted microvascular growth in a mouse model [46,81], suggesting that angiogenesis plays an important role in support of tumor growth by MSCs.

A tumor-promoting effect attributed to remodeling of ECM via a paracrine secretion of MSCs also occurs. The ECM is a major component of the cellular microenvironment and is composed of diverse proteins such as collagens, elastins, fibronectin, proteoglycans, and glycoproteins [82]. Glycoproteins, such as osteonectin (also known as secreted protein acidic and rich in cysteine, SPARC), are highly expressed in stromal fibroblast cells that have been reported to promote tumor progression in several cancers [83–86]. Abundantly produced soluble fibronectin [83,87] by MSCs also plays an active role in the invasive process of human colon and liver cancer [88]. Matrix metalloproteinase proteases and hyaluronan, as well as various others factors secreted by MSCs, are capable of remodeling the ECM and facilitating tumor progression [20,89–91].

In contrast, human MSC-secreted microvesicles have been reported to have a striking antitumor effect in cancer [92] and tumor immune suppression [93], in which they transport mRNA, miRNA, and proteins between cells.

A functional role in neoplastic development and metastases has been attributed to the presence of miRNAs, small non-coding RNA molecules composed of approximately 22 nucleotides. They participate in RNA silencing and gene regulation [94]. In breast cancer, miR-21 and miR-205 were associated with tumor development, while miR-126 and miR-335 were related to metastases [37,95]. The promotion of progression of hepatocellular cancer by MSCs was attributed to miR-155 [89].

The effect of MSCs on tumor cells has also been reported to be associated with the induction of EMT [96], an effect that is further enhanced by the inflammatory milieu that characterizes many cancers. Initiation of metastasis requires invasion, and this is enabled by EMT: carcinoma cells in the primary tumor lose cell–cell adhesion mediated by repression of E-cadherin and break through the basement membrane with increased invasive properties and enter the bloodstream by intravasation. Later, when these circulating tumor cells exit the bloodstream to form micrometastases, they undergo the reverse process – mesothelial to epithelial transition. Evidence of a role for MSCs in EMT is the observation of increased expression of cancer-associated fibroblast and EMT markers in a co-culture model of hepatoma cells and MSCs [97]. There is also evidence that there are intricate links between EMT-type cells and drug resistance in tumors [98]. MSC-dependent EMT induction has been associated with shorter tumor-free survival and poorer overall survival, demonstrating the clinical relevance of this effect [96,99]. MSCs might also promote tumor progression or invasion via inducing regulation of secretion of IL-6 and secretion of SDF-1α in EMT [53,100].

28.5 The potential immunomodulation by mesenchymal stromal cells in the tumor microenvironment

MSCs can influence both the innate and adaptive immune systems, including the function of antigen-presenting cells [79,101], natural killer cells [102], B cells, and T cells [103,104] (and see Chapters 33 and 34). Immune suppressive cells accumulate in some tumors, which can impede immune surveillance and facilitate tumor growth [105]. The number and function of anti-tumor immune cells are decreased [54,106].

28.5.1 Mesenchymal stromal cells inhibit natural killer cells and macrophages

MSCs can modulate the function of NK cells [107] and macrophages [108]. NK cells are a type of lymphocyte that plays a role in the rejection of both tumors and virally infected cells. MSCs can inhibit the proliferation, cytotoxity, and cytokine production of NK cells through secretion of IDO and prostaglandin E_2 (PGE_2) [107,109]. In addition to IDO and PGE_2, cancer-

associated stromal cells produce other soluble factors, such as VEGF and platelet-derived growth factor, which enhance tumor progression by promoting or attracting M2 macrophages, which are characterized by their production of high levels of the suppressive cytokine IL-10 and low levels of the proinflammatory cytokines IFN-γ and TNF-α [110]. M2 macrophages activate T helper 2 cell activity and also promote angiogenesis, tissue remodeling, and repair. Proinflammatory stimulation by IFN-γ, TNF-α, or LPS increases the expression of COX-2 and IDO in MSCs and these enzymes promote further M2 macrophage polarization [108]. Macrophages also play an important role in the innate immune response to virus infections. Innate immune responses, including TLRs, are important for viral clearance [111].

28.5.2 Mesenchymal stromal cells inhibit T cell proliferation

T cells are the major player of the adaptive immune response and are important in controlling malignant disease, mediating both cytotoxicity of cancer cells and releasing anti-oncogenic cytokines [112,113]. MSCs can inhibit T cell function through multiple pathways [114,115]. MSC suppression of T cell responses can be mediated by cell contact and soluble factors, including TGF-β, HGF, PGE_2, soluble human leukocyte antigen (HLA)-G5, IDO, and inducible nitric oxide synthetase [112,113,116–118]. Inhibition of T cell function by MSCs affects T cell proliferation and IFN-γ production and induces the production of IL-4, resulting in a shift from a proinflammatory T cells to anti-inflammatory T cells [114,115]. Cell–cell contact T cell inhibition by MSCs can be mediated by surface expression of HLA-G [119], a nonclassical major histocompatibility complex class I molecule with tolerogenic functions that contribute to fetal graft tolerance and human allograft acceptance [120]. Fas ligand and programmed death-ligand 1 also play significant roles in immunomodulation mediated by MSCs [121].

28.5.3 Mesenchymal stromal cells promote the expansion and function of regulatory T cells

Regulatory T cells (Tregs) are a subset of T cells that suppress activation of the immune system to maintain homeostasis and tolerance to self-antigens. An increased number of highly activated Tregs were found to infiltrate the tumor milieu of liver tumors in which they were mainly localized in the stromal compartment of the tumors [106]. The frequency of Tregs has been associated with poor prognosis [122–124]. MSCs can induce the generation and expansion of Tregs by the secretion of TGF-β [125], IDO [126] and the release of soluble HLA-G5 [113]. In contrast to their suppression of cytotoxic T cells, MSCs can induce the generation and expansion of Tregs [127]. Additionally, MSCs have been reported to induce the production of IL-10 by plasmacytoid dendritic cells (DCs), which in turn triggered the generation of Tregs [114].

28.5.4 Mesenchymal stromal cells inhibit the function of dendritic cells

It has been found that MSCs also display immunosuppressive potential through inhibiting the differentiation of DCs. DCs are the most efficient cells in presenting antigen to T cells. They play a key role in the initiation of the primary immune responses and in tolerance, depending on their activation and maturation status [128]. MSCs are capable of modulating the differentiation, activation, and function of DCs [129]. MSCs reduce the production of several cytokines by DCs, including IL-12 and TNF-α [130]. MSCs isolated from different tissue sources present distinct immunomodulatory profiles [131], so it will be important to more closely study MSCs present in tumors.

28.6 Therapeutic application of mesenchymal stromal cells in cancer

28.6.1 Potential therapeutic application

Several studies have demonstrated that MSCs have the capacity to reverse acute and chronic injury in different experimental settings [132–135]. MSCs have been reported to attenuate inflammation [136–138] and ameliorate autoimmune diseases [10,139–141]. The fact that MSCs can migrate into certain types of tumors has led to their use as vehicles for tumor-specific delivery of anticancer drugs or genes.

Genetically modified MSCs have been used to deliver anticancer genes and inhibit cancer cell proliferation *in vitro* and *in vivo* [95,142–144]; and see Chapter 62. Several studies have demonstrated that MSCs have anticancer effects in different experimental settings [62,96,145–147]. MSCs have been extensively investigated in clinical trials as potential therapy in a number of different diseases [148,149]. Approximately 18 trials have been registered at ClinicalTrials.gov involving the use of MSCs in various cancers. These include ovarian cancer (NCT02068794), prostate cancer (NCT01983709), and hematologic malignancy (NCT01854567).

28.6.2 Reasons for caution

Given the context-dependent role of MSCs, it appears possible that MSCs in the tumor microenvironment could promote tumor growth [150]. MSCs may facilitate malignant development in patients at high risk of developing cancer, such as those with chronic hepatitis B or C patients or recipients of organ transplants [19,151,152]. In addition, MSCs have the potential for malignant transformation during *ex vivo* expansion [153].

Furthermore, although MSCs can be detected by magnetic resonance imaging or radioactive labeling [154] for up to 25 days [25], the cellular fate and distribution *in vivo* of transplanted MSCs remain unclear because techniques for tracking infused MSCs have low sensitivity [155]. Because of unclear clinical benefits of MSCs in patients with cancer [156–158] and because of the role of MSCs in the tumor microenvironment, it would be

wise to be cautious in the use of MSCs in patients with malignant diseases.

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