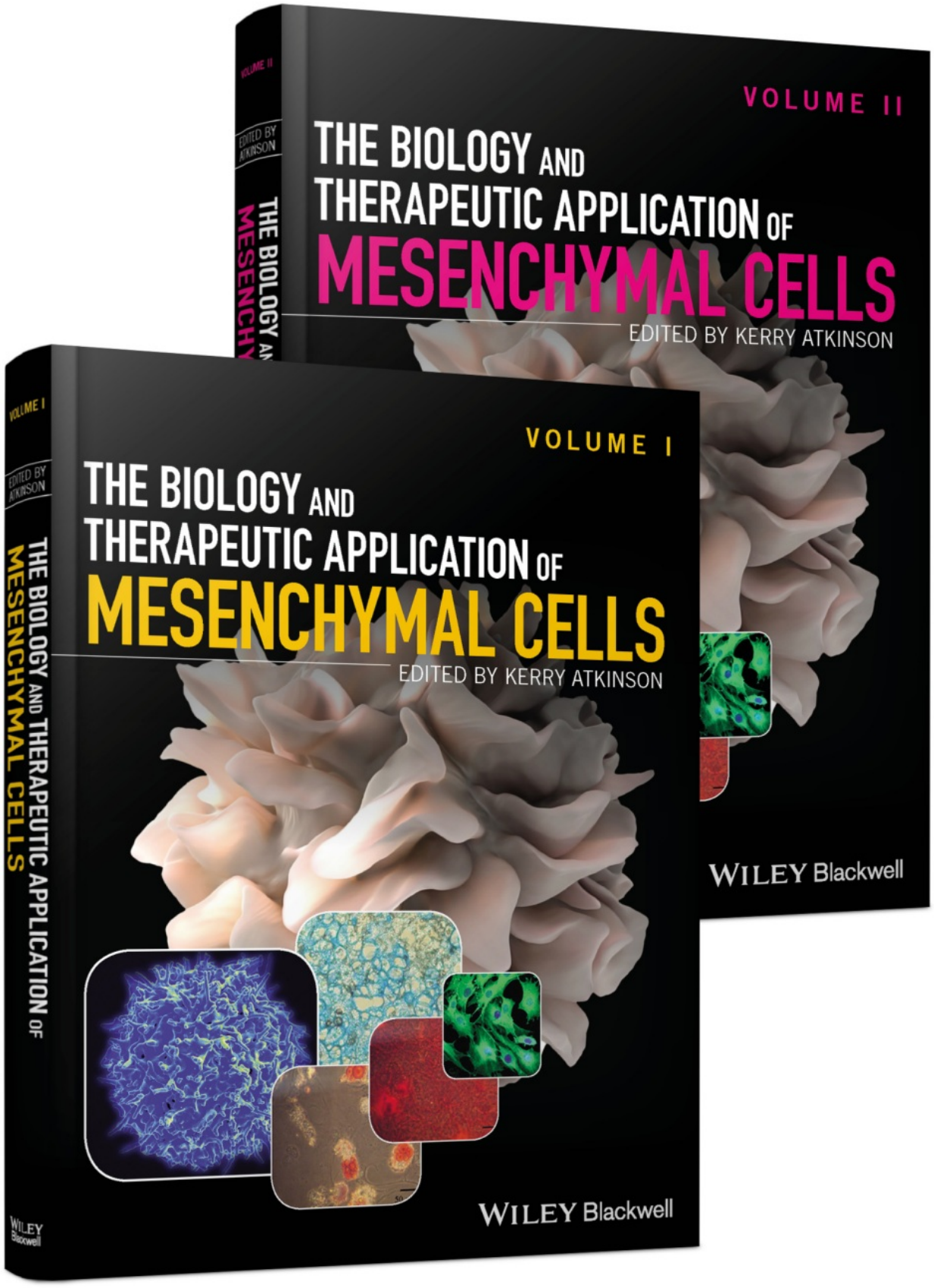
4

by Pratika Y

Submission date: 10-Jun-2020 02:29AM (UTC+0300)
Submission ID: 1340964758
File name: 1._The_implications_of_multipote.pdf (4.26M)
Word count: 18686
Character count: 102079


VOLUME II
THE BIOLOGY AND THERAPEUTIC APPLICATION OF MESENCHYMAL CELLS
EDITED BY KERRY ATKINSON
WILEY Blackwell
VOLUME I
THE BIOLOGY AND THERAPEUTIC APPLICATION OF MESENCHYMAL CELLS
EDITED BY KERRY ATKINSON
WILEY Blackwell

The biology and therapeutic application of mesenchymal cells

Volume I and II

Edited by

Kerry Atkinson

WILEY Blackwell

Contents

CHAPTER 28

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

Pratika Y. Hernanda,[a] Maikel P. Peppelenbosch,[b] and Qiuwei Pan[b,*]

[a] Medical Genetics Laboratory, Centre of Biomolecular Research, Wijaya Kusuma University Surabaya, Indonesia
[b] Department of Gastroenterology and Hepatology, Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, The Netherlands

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.

* Corresponding author: Department of Gastroenterology and Hepatology, Erasmus MC, room Na-617, 'sGravendijkwal 230, NL-3015 CE Rotterdam, The Netherlands. E-mail: q.pan@erasmusmc.nl.

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

The Biology and Therapeutic Application of Mesenchymal Cells, First Edition. Edited by Kerry Atkinson.

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].

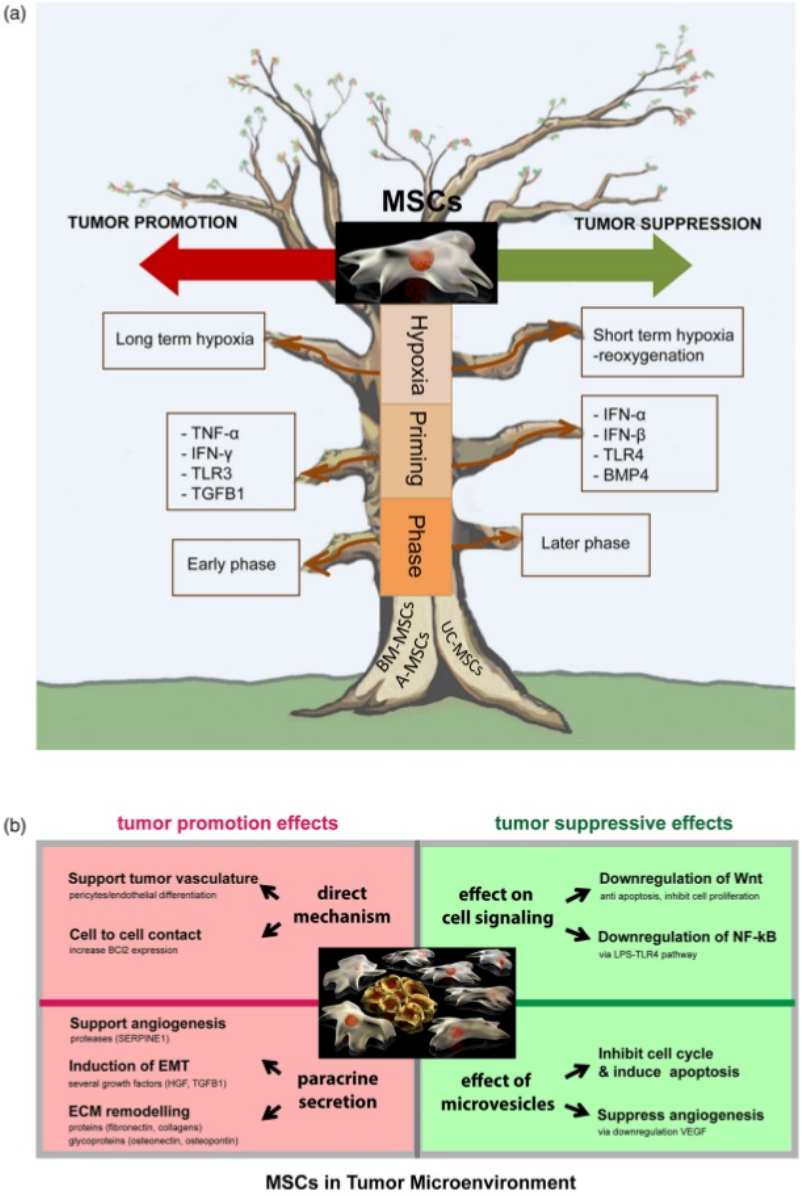


Figure 28.2 Context-dependent role of MSCs in the tumor microenvironment. MSCs can exert tumor-promoting or tumor-limiting effects, which depend on the context in which the MSCs are present. (a) Different sources of MSCs, the presence of ligands, cytokine-primed MSCs, and the hypoxic microenvironment 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.

Acknowledgments

We thank the Dutch Digestive Foundation (MLDS) for a career development grant (No. CDG 1304), the Netherlands Organization for Scientific Research (NWO/ZonMw) for a VENI grant (No. 916-13-032), and the Daniel den Hoed Foundation for a Centennial Award Fellowship to QP.

References

1 A. J. Friedenstein, S. Piatetzky, II, K. V. Petrakova. Osteogenesis in transplants of bone marrow cells. *J Embryol Exp Morphol* 1966;**16**:381–390.

2 C. M. Kolf, E. Cho, R. S. Tuan. Mesenchymal stromal cells. Biology of adult mesenchymal stem cells: regulation of niche, self-renewal and differentiation. *Arthritis Res Ther* 2007;**9**:204.

3 D. G. Phinney, D. J. Prockop. Concise review: mesenchymal stem/multipotent stromal cells: the state of transdifferentiation and modes of tissue repair – current views. *Stem Cells* 2007;**25**:2896–2902.

4 A. H. Klopp, A. Gupta, E. Spaeth, *et al.* Concise review: dissecting a discrepancy in the literature: do mesenchymal stem cells support or suppress tumor growth? *Stem Cells* 2011;**29**:11–19.

5 D. Hanahan, R. A. Weinberg. Hallmarks of cancer: the next generation. *Cell* 2011;**144**:646–674.

6 A. E. Karnoub, A. B. Dash, A. P. Vo, *et al.* Mesenchymal stem cells within tumour stroma promote breast cancer metastasis. *Nature* 2007;**449**:557–563.

7 Z. Gao, L. Zhang, J. Hu, Y. Sun. Mesenchymal stem cells: a potential targeted-delivery vehicle for anti-cancer drug, loaded nanoparticles. *Nanomedicine* 2013;**9**:174–184.

8 B. M. Beckermann, G. Kallifatidis, A. Groth, *et al.* VEGF expression by mesenchymal stem cells contributes to angiogenesis in pancreatic carcinoma. *Br J Cancer* 2008;**99**:622–631.

9 G. C. Li, Q. H. Ye, Y. H. Xue, *et al.* Human mesenchymal stem cells inhibit metastasis of a hepatocellular carcinoma model using the MHCC97-H cell line. *Cancer Sci* 2010;**101**:2546–2553.

10 J. Y. Oh, T. W. Kim, H. J. Jeong, *et al.* Intraperitoneal infusion of mesenchymal stem/stromal cells prevents experimental autoimmune uveitis in mice. *Mediators Inflamm* 2014;**2014**:624640.

11 W. Zhao, G. Ren, L. Zhang, *et al.* Efficacy of mesenchymal stem cells derived from human adipose tissue in inhibition of hepatocellular carcinoma cells *in vitro*. *Cancer Biother Radiopharm* 2012;**27**:606–613.

12 K. Takahara, M. Ii, T. Inamoto, *et al.* Adipose-derived stromal cells inhibit prostate cancer cell proliferation inducing apoptosis. *Biochem Biophys Res Commun* 2014;**446**:1102–1107.

13 A. J. Friedenstein, R. K. Chailakhjan, K. S. Lalykina. The development of fibroblast colonies in monolayer cultures of guinea-pig bone marrow and spleen cells. *Cell Tissue Kinet* 1970;**3**:393–403.

14 E. M. Horwitz, K. Le Blanc, M. Dominici, *et al.* Clarification of the nomenclature for MSC: The International Society for Cellular Therapy position statement. *Cytotherapy* 2005;**7**:393–395.

15 P. Bianco, P. G. Robey, P. J. Simmons. Mesenchymal stem cells: revisiting history, concepts, and assays. *Cell Stem Cell* 2008;**2**:313–319.

16 L. da Silva Meirelles, P. C. Chagastelles, N. B. Nardi. Mesenchymal stem cells reside in virtually all post-natal organs and tissues. *J Cell Sci* 2006;**119**:2204–2213.

17 P. A. Zuk, M. Zhu, H. Mizuno, *et al.* Multilineage cells from human adipose tissue: implications for cell-based therapies. *Tissue Eng* 2001;**7**:211–228.

18 H. Y. Choi, S. J. Moon, B. B. Ratliff, *et al.* Microparticles from kidney-derived mesenchymal stem cells act as carriers of proangiogenic signals and contribute to recovery from acute kidney injury. *PLoS ONE* 2014;**9**:e87853.

19 Y. Liu, Z. P. Han, S. S. Zhang, *et al.* Effects of inflammatory factors on mesenchymal stem cells and their role in the promotion of tumor angiogenesis in colon cancer. *J Biol Chem* 2011;**286**:25007–25015.

20 P. Y. Hernanda, A. Pedroza-Gonzalez, L. J. van der Laan, *et al.* Tumor promotion through the mesenchymal stem cell compartment in human hepatocellular carcinoma. *Carcinogenesis* 2013;**34**:2330–2340.

21 F. Huang, M. Wang, T. Yang, *et al.* Gastric cancer-derived MSC-secreted PDGF-DD promotes gastric cancer progression. *J Cancer Res Clin Oncol* 2014;**140**:1835–1848.

22 P. Hernanda, A. Pedroza-Gonzales, L. J. W. van der Laan, *et al.* Human liver carcinomas recruit mesenchymal stem/stromal cells that can promote tumor growth via paracrine signaling. *J Hepatol* 2013;**58**:S431.

23 H. Li, Z. Feng, T. C. Tsang, *et al.* Fusion of HepG2 cells with mesenchymal stem cells increases cancer-associated and malignant properties: an *in vivo* metastasis model. *Oncol Rep* 2014;**32**:539–547.

24 B. Song, B. Kim, S. H. Choi, *et al.* Mesenchymal stromal cells promote tumor progression in fibrosarcoma and gastric cancer cells. *Korean J Pathol* 2014;**48**:217–224.

25 Q. Pan, S. M. Fouraschen, F. S. Kaya, *et al.* Mobilization of hepatic mesenchymal stem cells from human liver grafts. *Liver Transpl* 2011;**17**:596–609.

26 M. Galie, G. Konstantinidou, D. Peroni, *et al.* Mesenchymal stem cells share molecular signature with mesenchymal tumor cells and favor early tumor growth in syngeneic mice. *Oncogene* 2008;**27**:2542–2551.

27 E. Mansilla, G. H. Marin, H. Drago, *et al.* Bloodstream cells phenotypically identical to human mesenchymal bone marrow stem cells circulate in large amounts under the influence of acute large skin damage: new evidence for their use in regenerative medicine. *Transplant Proc* 2006;**38**:967–969.

28 C. C. Ling, K. T. Ng, Y. Shao, *et al.* Post-transplant endothelial progenitor cell mobilization via CXCL10/CXCR3 signaling promotes liver tumor growth. *J Hepatol* 2014;**60**:103–109.

29 A. Taddeo, P. Presicce, L. Brambilla, *et al.* Circulating endothelial progenitor cells are increased in patients with classic Kaposi's sarcoma. *J Invest Dermatol* 2008;**128**:2125–2128.

30 C. F. Bellows, Y. Zhang, J. Chen, *et al.* Circulation of progenitor cells in obese and lean colorectal cancer patients. *Cancer Epidemiol Biomarkers Prev* 2011;**20**:2461–2468.

31 J. Ringe, S. Strassburg, K. Neumann, *et al.* Towards *in situ* tissue repair: human mesenchymal stem cells express chemokine

receptors CXCR1, CXCR2 and CCR2, and migrate upon stimulation with CXCL8 but not CCL2. *J Cell Biochem* 2007;**101**:135–146.
32 L. J. Dai, M. R. Moniri, Z. R. Zeng, *et al.* Potential implications of mesenchymal stem cells in cancer therapy. *Cancer Lett* 2011;**305**:8–20.
33 L. A. Mylotte, A. M. Duffy, M. Murphy, *et al.* Metabolic flexibility permits mesenchymal stem cell survival in an ischemic environment. *Stem Cells* 2008;**26**:1325–1336.
34 R. N. Kaplan, B. Psaila, D. Lyden. Niche-to-niche migration of bone-marrow-derived cells. *Trends Mol Med* 2007;**13**:72–81.
35 P. Y. Hernanda, A. Pedroza-Gonzalez, D. Sprengers, *et al.* Multipotent mesenchymal stromal cells in liver cancer: implications for tumor biology and therapy. *Biochim Biophys Acta* 2014;**1846**:439–445.
36 G. Xu, L. Zhang, G. Ren, *et al.* Immunosuppressive properties of cloned bone marrow mesenchymal stem cells. *Cell Res* 2007;**17**:240–248.
37 M. Tome, P. López-Romero, C. Albo, *et al.* miR-335 orchestrates cell proliferation, migration and differentiation in human mesenchymal stem cells. *Cell Death Differ* 2011;**18**:985–995.
38 A. Schmidt, D. Ladage, T. Schinkothe, *et al.* Basic fibroblast growth factor controls migration in human mesenchymal stem cells. *Stem Cells* 2006;**24**:1750–1758.
39 M. G. Garcia, J. Bayo, M. F. Bolontrade, *et al.* Hepatocellular carcinoma cells and their fibrotic microenvironment modulate bone marrow-derived mesenchymal stromal cell migration *in vitro* and *in vivo*. *Mol Pharm* 2011;**8**:1538–1548.
40 M. Al-toub, A. Almusa, M. Almajed, *et al.* Pleiotropic effects of cancer cells' secreted factors on human stromal (mesenchymal) stem cells. *Stem Cell Res Ther* 2013;**4**:114.
41 L. E. Holz, G. W. McCaughan, V. Benseler, *et al.* Liver tolerance and the manipulation of immune outcomes. *Inflamm Allergy Drug Targets* 2008;**7**:6–18.
42 N. Bezdenezhnykh, N. Semesiuk, O. Lykhova, *et al.* Impact of stromal cell components of tumor microenvironment on epithelial–mesenchymal transition in breast cancer cells. *Exp Oncol* 2014;**36**:72–78.
43 T. Li, B. Song, X. Du, *et al.* Effect of bone-marrow-derived mesenchymal stem cells on high-potential hepatocellular carcinoma in mouse models: an intervention study. *Eur J Med Res* 2013;**18**:34.
44 H. Ryu, J. E. Oh, K. J. Rhee, *et al.* Adipose tissue-derived mesenchymal stem cells cultured at high density express IFN-β and suppress the growth of MCF-7 human breast cancer cells. *Cancer Lett* 2014;**352**:220–227.
45 S. H. Abd-Allah, S. M. Shalaby, A. S. El-Shal, *et al.* Effect of bone marrow-derived mesenchymal stromal cells on hepatoma. *Cytotherapy* 2014;**16**:1197–1206.
46 P. Gong, Y. Wang, Y. Wang, *et al.* Effect of bone marrow mesenchymal stem cells on hepatocellular carcinoma in microcirculation. *Tumour Biol* 2013;**34**:2161–2168.
47 R. S. Waterman, S. L. Tomchuck, S. L. Henkle, A. M. Betancourt. A new mesenchymal stem cell (MSC) paradigm: polarization into a pro-inflammatory MSC1 or an immunosuppressive MSC2 phenotype. *PLoS ONE* 2010;**5**:e10088.
48 R. S. Waterman, S. L. Henkle, A. M. Betancourt. Mesenchymal stem cell 1 (MSC1)-based therapy attenuates tumor growth whereas MSC2-treatment promotes tumor growth and metastasis. *PLoS ONE* 2012;**7**:e45590.
49 J. S. Lee, J. M. Lee, G. I. Im. Electroporation-mediated transfer of Runx2 and Osterix genes to enhance osteogenesis of adipose stem cells. *Biomaterials* 2011;**32**:760–768.
50 J. Ahn, H. Lee, K. Seo, *et al.* Anti-tumor effect of adipose tissue derived-mesenchymal stem cells expressing interferon-β and treatment with cisplatin in a xenograft mouse model for canine melanoma. *PLoS ONE* 2013;**8**:e74897.
51 C. Xu, L. Lin, G. Cao, *et al.* Interferon-α-secreting mesenchymal stem cells exert potent antitumor effect *in vivo*. *Oncogene* 2014;**33**:5047–5052.
52 G. Bassi, F. Guilloton, C. Menard, *et al.* Effects of a ceramic biomaterial on immune modulatory properties and differentiation potential of human mesenchymal stromal cells of different origin. *Tissue Eng Part A* 2015;**21**(3–4):767–781.
53 A. De Boeck, A. Hendrix, D. Maynard, *et al.* Differential secretome analysis of cancer-associated fibroblasts and bone marrow-derived precursors to identify microenvironmental regulators of colon cancer progression. *Proteomics* 2013;**13**:379–388.
54 Q. Lin, Z. Yun. Impact of the hypoxic tumor microenvironment on the regulation of cancer stem cell characteristics. *Cancer Biol Ther* 2010;**9**:949–956.
55 A. Lavrentieva, I. Majore, C. Kasper, R. Hass. Effects of hypoxic culture conditions on umbilical cord-derived human mesenchymal stem cells. *Cell Commun Signal* 2010;**8**:18.
56 L. B. Buravkova, Y. V. Rylova, E. R. Andreeva, *et al.* Low ATP level is sufficient to maintain the uncommitted state of multipotent mesenchymal stem cells. *Biochim Biophys Acta* 2013;**1830**:4418–4425.
57 A. Salim, R. P. Nacamuli, E. F. Morgan, *et al.* Transient changes in oxygen tension inhibit osteogenic differentiation and Runx2 expression in osteoblasts. *J Biol Chem* 2004;**279**:40007–40016.
58 W. Zhu, J. Chen, X. Cong, *et al.* Hypoxia and serum deprivation-induced apoptosis in mesenchymal stem cells. *Stem Cells* 2006;**24**:416–425.
59 Y. Nie, B. M. Han, X. B. Liu, *et al.* Identification of microRNAs involved in hypoxia- and serum deprivation-induced apoptosis in mesenchymal stem cells. *Int J Biol Sci* 2011;**7**:762–768.
60 J. A. Wang, T. L. Chen, J. Jiang, *et al.* Hypoxic preconditioning attenuates hypoxia/reoxygenation-induced apoptosis in mesenchymal stem cells. *Acta Pharmacol Sin* 2008;**29**:74–82.
61 G. D. Dispersyn, M. Borgers. Apoptosis in the heart: about programmed cell death and survival. *News Physiol Sci* 2001;**16**:41–47.
62 M. T. Abdel aziz, M. F. El Asmar, H. M. Atta, *et al.* Efficacy of mesenchymal stem cells in suppression of hepatocarcinorigenesis in rats: possible role of Wnt signaling. *J Exp Clin Cancer Res* 2011;**30**:49.
63 L. Qiao, Z. Xu, T. Zhao, *et al.* Suppression of tumorigenesis by human mesenchymal stem cells in a hepatoma model. *Cell Res* 2008;**18**:500–507.
64 L. Qiao, T. J. Zhao, F. Z. Wang, *et al.* NF-κB downregulation may be involved the depression of tumor cell proliferation mediated by human mesenchymal stem cells. *Acta Pharmacol Sin* 2008;**29**:333–340.
65 P. P. Wang, D. Y. Xie, X. J. Liang, *et al.* HGF and direct mesenchymal stem cells contact synergize to inhibit hepatic stellate cells activation through TLR4/NF-kB pathway. *PLoS ONE* 2012;**7**:e43408.
66 S. Bruno, F. Collino, M. C. Deregibus, *et al.* Microvesicles derived from human bone marrow mesenchymal stem cells inhibit tumor growth. *Stem Cells Dev* 2013;**22**:758–771.

67 C. Akyurekli, Y. Le, R. B. Richardson, *et al.* A systematic review of preclinical studies on the therapeutic potential of mesenchymal stromal cell-derived microvesicles. *Stem Cell Rev* 2015;**11**(1): 150–160.

68 R. D. Balsara, V. A. Ploplis. Plasminogen activator inhibitor-1: the double-edged sword in apoptosis. *Thromb Haemost* 2008;**100**: 1029–1036.

69 Y. Zhang, L. Li, J. Yu, *et al.* Microvesicle-mediated delivery of transforming growth factor beta1 siRNA for the suppression of tumor growth in mice. *Biomaterials* 2014;**35**:4390–4400.

70 J. K. Lee, S. R. Park, B. K. Jung, *et al.* Exosomes derived from mesenchymal stem cells suppress angiogenesis by down-regulating VEGF expression in breast cancer cells. *PLoS ONE* 2013;**8**:e84256.

71 B. Ma, H. Jiang, J. Jia, *et al.* Murine bone marrow stromal cells pulsed with homologous tumor-derived exosomes inhibit proliferation of liver cancer cells. *Clin Transl Oncol* 2012;**14**:764–773.

72 A. Al-Khaldi, N. Eliopoulos, D. Martineau, *et al.* Postnatal bone marrow stromal cells elicit a potent VEGF-dependent neoangiogenic response *in vivo*. *Gene Ther* 2003;**10**:621–629.

73 B. D. Roorda, A. Elst, T. G. Boer, *et al.* Mesenchymal stem cells contribute to tumor cell proliferation by direct cell–cell contact interactions. *Cancer Invest* 2010;**28**:526–534.

74 M. Hao, L. Zhang, G. An, *et al.* Bone marrow stromal cells protect myeloma cells from bortezomib induced apoptosis by suppressing microRNA-15a expression. *Leuk Lymphoma* 2011;**52**:1787–1794.

75 A. V. Kurtova, K. Balakrishnan, R. Chen, *et al.* Diverse marrow stromal cells protect CLL cells from spontaneous and drug-induced apoptosis: development of a reliable and reproducible system to assess stromal cell adhesion-mediated drug resistance. *Blood* 2009;**114**:4441–4450.

76 M. H. Xu, X. Gao, D. Luo, *et al.* EMT and acquisition of stem cell-like properties are involved in spontaneous formation of tumorigenic hybrids between lung cancer and bone marrow-derived mesenchymal stem cells. *PLoS ONE* 2014;**9**:e87893.

77 O. De Wever, Q. D. Nguyen, L. Van Hoorde, *et al.* Tenascin-C and SF/HGF produced by myofibroblasts in vitro provide convergent pro-invasive signals to human colon cancer cells through RhoA and Rac. *FASEB J* 2004;**18**:1016–1018.

78 M. J. Lee, S. C. Heo, S. H. Shin, *et al.* Oncostatin M promotes mesenchymal stem cell-stimulated tumor growth through a paracrine mechanism involving periostin and TGFBI. *Int J Biochem Cell Biol* 2013;**45**:1869–1877.

79 A. Uccelli, L. Moretta, V. Pistoia. Mesenchymal stem cells in health and disease. *Nat Rev Immunol* 2008;**8**:726–736.

80 N. M. Hagan, M. R. Joyce, J. M. Murphy, *et al.* Impact of mesenchymal stem cell secreted PAI-1 on colon cancer cell migration and proliferation. *Biochem Biophys Res Commun* 2013;**435**:574–579.

81 M. S. Ko, J. Y. Jung, I. S. Shin, *et al.* Effects of expanded human adipose tissue-derived mesenchymal stem cells on the viability of cryopreserved fat grafts in the nude mouse. *Int J Med Sci* 2011;**8**:231–238.

82 W. P. Daley, S. B. Peters, M. Larsen. Extracellular matrix dynamics in development and regenerative medicine. *J Cell Sci* 2008;**121**: 255–264.

83 B. Le Bail, S. Faouzi, L. Boussarie, *et al.* Osteonectin/SPARC is overexpressed in human hepatocellular carcinoma. *J Pathol* 1999; **189**:46–52.

84 N. Yusuf, T. Inagaki, S. Kusunoki, *et al.* SPARC was overexpressed in human endometrial cancer stem-like cells and promoted migration activity. *Gynecol Oncol* 2014;**134**:356–363.

85 C. Neuzillet, A. Tijeras-Raballand, J. Cros, *et al.* Stromal expression of SPARC in pancreatic adenocarcinoma. *Cancer Metastasis Rev* 2013;**32**:585–602.

86 S. Sangaletti, C. Tripodo, P. Portararo, *et al.* Stromal niche communalities underscore the contribution of the matricellular protein SPARC to B-cell development and lymphoid malignancies. *Oncoimmunology* 2014;**3**:e28989.

87 J. Ou, Y. Peng, J. Deng, *et al.* Endothelial cell-derived fibronectin extra domain A promotes colorectal cancer metastasis via inducing epithelial–mesenchymal transition. *Carcinogenesis* 2014;**35**: 1661–1670.

88 B. Tian, Y. Li, X. N. Ji, *et al.* Basement membrane proteins play an active role in the invasive process of human hepatocellular carcinoma cells with high metastasis potential. *J Cancer Res Clin Oncol* 2005;**131**:80–86.

89 X. L. Yan, Y. L. Jia, L. Chen, *et al.* Hepatocellular carcinoma-associated mesenchymal stem cells promote hepatocarcinoma progression: role of the S100A4–miR155–SOCS1–MMP9 axis. *Hepatology* 2013;**57**:2274–2286.

90 A. Calabro, M. M. Oken, V. C. Hascall, A. M. Masellis. Characterization of hyaluronan synthase expression and hyaluronan synthesis in bone marrow mesenchymal progenitor cells: predominant expression of HAS1 mRNA and up-regulated hyaluronan synthesis in bone marrow cells derived from multiple myeloma patients. *Blood* 2002;**100**:2578–2585.

91 N. Tobar, M. C. Avalos, N. Mendez, *et al.* Soluble MMP-14 produced by bone marrow-derived stromal cells sheds epithelial endoglin modulating the migratory properties of human breast cancer cells. *Carcinogenesis* 2014;**35**:1770–1779.

92 D. Castellana, F. Zobairi, M. C. Martinez, *et al.* Membrane microvesicles as actors in the establishment of a favorable prostatic tumoral niche: a role for activated fibroblasts and CX3CL1–CX3CR1 axis. *Cancer Res* 2009;**69**:785–793.

93 P. D. Robbins, A. E. Morelli. Regulation of immune responses by extracellular vesicles. *Nat Rev Immunol* 2014;**14**:195–208.

94 D. P. Bartel. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell* 2004;**116**:281–297.

95 S. F. Tavazoie, C. Alarcón, T. Oskarsson, *et al.* Endogenous human microRNAs that suppress breast cancer metastasis. *Nature* 2008;**451**:147–152.

96 Y. Jing, Z. Han, Y. Liu, *et al.* Mesenchymal stem cells in inflammation microenvironment accelerates hepatocellular carcinoma metastasis by inducing epithelial–mesenchymal transition. *PLoS ONE* 2012;**7**:e43272.

97 S. D. Bhattacharya, Z. Mi, L. J. Talbot, *et al.* Human mesenchymal stem cell and epithelial hepatic carcinoma cell lines in admixture: concurrent stimulation of cancer-associated fibroblasts and epithelial-to-mesenchymal transition markers. *Surgery* 2012;**152**: 449–454.

98 H. Sui, L. Zhu, W. Deng, Q. Li. Epithelial–mesenchymal transition and drug resistance: role, molecular mechanisms, and therapeutic strategies. *Oncol Res Treat* 2014;**37**:584–589.

99 S. Saito, H. Okabe, M. Watanabe, *et al.* CD44v6 expression is related to mesenchymal phenotype and poor prognosis in patients with colorectal cancer. *Oncol Rep* 2013;**29**:1570–1578.

100 E. L. Spaeth, J. L. Dembinski, A. K. Sasser, *et al.* Mesenchymal stem cell transition to tumor-associated fibroblasts contributes to fibrovascular network expansion and tumor progression. *PLoS ONE* 2009;**4**:e4992.

101 X. X. Jiang, Y. Zhang, B. Liu, *et al.* Human mesenchymal stem cells inhibit differentiation and function of monocyte-derived dendritic cells. *Blood* 2005;**105**:4120–4126.

102 P. A. Sotiropoulou, S. A. Perez, A. D. Gritzapis, *et al.* Interactions between human mesenchymal stem cells and natural killer cells. *Stem Cells* 2006;**24**:74–85.

103 A. Corcione, F. Benvenuto, E. Ferretti, *et al.* Human mesenchymal stem cells modulate B-cell functions. *Blood* 2006;**107**:367–372.

104 F. Benvenuto, S. Ferrari, E. Gerdoni, *et al.* Human mesenchymal stem cells promote survival of T cells in a quiescent state. *Stem Cells* 2007;**25**:1753–1760.

105 R. Hass, A. Otte. Mesenchymal stem cells as all-round supporters in a normal and neoplastic microenvironment. *Cell Commun Signal* 2012;**10**:26.

106 A. Pedroza-Gonzalez, C. Verhoef, J. N. Ijzermans, *et al.* Activated tumor-infiltrating $CD4^+$ regulatory T cells restrain antitumor immunity in patients with primary or metastatic liver cancer. *Hepatology* 2013;**57**:183–194.

107 C. Noone, A. Kihm, K. English, *et al.* IFN-γ stimulated human umbilical-tissue-derived cells potently suppress NK activation and resist NK-mediated cytotoxicity *in vitro*. *Stem Cells Dev* 2013;**22**:3003–3014.

108 M. Francois, R. Romieu-Mourez, M. Li, L. Galipeau. Human MSC suppression correlates with cytokine induction of indoleamine 2,3-dioxygenase and bystander M2 macrophage differentiation. *Mol Ther* 2012;**20**:187–195.

109 G. M. Spaggiari, A. Capobianco, H. Abdelrazik, *et al.* Mesenchymal stem cells inhibit natural killer-cell proliferation, cytotoxicity, and cytokine production: role of indoleamine 2,3-dioxygenase and prostaglandin E2. *Blood* 2008;**111**:1327–1333.

110 J. Maggini, G. Mirkin, I. Bognanni, *et al.* Mouse bone marrow-derived mesenchymal stromal cells turn activated macrophages into a regulatory-like profile. *PLoS ONE* 2010;**5**:e9252.

111 N. Arpaia, G. M. Barton. Toll-like receptors: key players in antiviral immunity. *Curr Opin Virol* 2011;**1**:447–454.

112 M. Di Nicola, C. Carlo-Stella, M. Magni, *et al.* Human bone marrow stromal cells suppress T-lymphocyte proliferation induced by cellular or nonspecific mitogenic stimuli. *Blood* 2002;**99**:3838–3843.

113 Z. Selmani, A. Naji, I. Zidi, *et al.* Human leukocyte antigen-G5 secretion by human mesenchymal stem cells is required to suppress T lymphocyte and natural killer function and to induce $CD4^+CD25^{high}FOXP3^+$ regulatory T cells. *Stem Cells* 2008;**26**:212–222.

114 S. Aggarwal, M. F. Pittenger. Human mesenchymal stem cells modulate allogeneic immune cell responses. *Blood* 2005;**105**:1815–1822.

115 E. Zappia, S. Casazza, E. Pedemonte, *et al.* Mesenchymal stem cells ameliorate experimental autoimmune encephalomyelitis inducing T-cell anergy. *Blood* 2005;**106**:1755–1761.

116 K. Sato, K. Ozaki, I. Oh, *et al.* Nitric oxide plays a critical role in suppression of T-cell proliferation by mesenchymal stem cells. *Blood* 2007;**109**:228–234.

117 R. Meisel, A. Zibert, M. Laryea, *et al.* Human bone marrow stromal cells inhibit allogeneic T-cell responses by indoleamine 2,3-dioxygenase-mediated tryptophan degradation. *Blood* 2004;**103**:4619–4621.

118 A. Nasef, N. Mathieu, A. Chapel, *et al.* Immunosuppressive effects of mesenchymal stem cells: involvement of HLA-G. *Transplantation* 2007;**84**:231–237.

119 M. Giuliani, M. Fleury, A. Vernochet, *et al.* Long-lasting inhibitory effects of fetal liver mesenchymal stem cells on T-lymphocyte proliferation. *PLoS ONE* 2011;**6**:e19988.

120 E. D. Carosella, P. Moreau, J. Le Maoult, *et al.* HLA-G molecules: from maternal–fetal tolerance to tissue acceptance. *Adv Immunol* 2003;**81**:199–252.

121 Y. Z. Gu, Q. Xue, Y. J. Chen, *et al.* Different roles of PD-L1 and FasL in immunomodulation mediated by human placenta-derived mesenchymal stem cells. *Hum Immunol* 2013;**74**:267–276.

122 X. Shen, N. Li, H. Li, *et al.* Increased prevalence of regulatory T cells in the tumor microenvironment and its correlation with TNM stage of hepatocellular carcinoma. *J Cancer Res Clin Oncol* 2010;**136**:1745–1754.

123 K. J. Chen, S. Z. Lin, L. Zhou, *et al.* Selective recruitment of regulatory T cell through CCR6–CCL20 in hepatocellular carcinoma fosters tumor progression and predicts poor prognosis. *PLoS ONE* 2011;**6**:e24671.

124 S. Z. Lin, K. J. Chen, Z. Y. Xu, *et al.* Prediction of recurrence and survival in hepatocellular carcinoma based on two Cox models mainly determined by $FoxP3^+$ regulatory T cells. *Cancer Prev Res (Phila)* 2013;**6**:594–602.

125 S. A. Patel, J. R. Meyer, S. J. Greco, *et al.* Mesenchymal stem cells protect breast cancer cells through regulatory T cells: role of mesenchymal stem cell-derived TGF-β. *J Immunol* 2010;**184**:5885–5894.

126 W. Ge, J. Jiang, J. Arp, *et al.* Regulatory T-cell generation and kidney allograft tolerance induced by mesenchymal stem cells associated with indoleamine 2,3-dioxygenase expression. *Transplantation* 2010;**90**:1312–1320.

127 X. Xia, W. Chen, T. Ma, *et al.* Mesenchymal stem cells administered after liver transplantation prevent acute graft-versus-host disease in rats. *Liver Transpl* 2012;**18**:696–706.

128 R. M. Steinman, J. Banchereau. Taking dendritic cells into medicine. *Nature* 2007;**449**:419–426.

129 Z. Han, Y. Jing, S. Zhang, *et al.* The role of immunosuppression of mesenchymal stem cells in tissue repair and tumor growth. *Cell Biosci* 2012;**2**:8.

130 W. Zhang, W. Ge, C. Li, *et al.* Effects of mesenchymal stem cells on differentiation, maturation, and function of human monocyte-derived dendritic cells. *Stem Cells Dev* 2004;**13**:263–271.

131 M. Najar, G. Raicevic, H. Fayyad-Kazan, *et al.* Impact of different mesenchymal stromal cell types on T-cell activation, proliferation and migration. *Int Immunopharmacol* 2013;**15**:693–702.

132 A. Monsel, Y. G. Zhu, S. Gennai, *et al.* Cell-based therapy for acute organ injury: preclinical evidence and ongoing clinical trials using mesenchymal stem cells. *Anesthesiology* 2014;**121**:1099–1121.

133 V. Donega, C. H. Nijboer, L. Braccioli, *et al.* Intranasal administration of human MSC for ischemic brain injury in the mouse: *in vitro* and *in vivo* neuroregenerative functions. *PLoS ONE* 2014;**9**:e112339.

134 Y. Zhang, W. Cai, Q. Huang, *et al.* Mesenchymal stem cells alleviate bacteria-induced liver injury in mice by inducing regulatory dendritic cells. *Hepatology* 2014;**59**:671–682.

135 K. H. Jung, T. Yi, M. K. Son, *et al.* Therapeutic effect of human clonal bone marrow-derived mesenchymal stem cells in severe acute pancreatitis. *Arch Pharm Res* 2015;**38**(5):742–751.

136 K. Raza, T. Larsen, N. Samaratunga, *et al.* MSC therapy attenuates obliterative bronchiolitis after murine bone marrow transplant. *PLoS ONE* 2014;**9**:e109034.

137 N. Gu, C. Rao, Y. Tian, *et al.* Anti-inflammatory and antiapoptotic effects of mesenchymal stem cells transplantation in rat brain with cerebral ischemia. *J Stroke Cerebrovasc Dis* 2014;**23**(10):2598–2606.

138 K. S. Cho, M. K. Park, S. A. Kang, *et al.* Adipose-derived stem cells ameliorate allergic airway inflammation by inducing regulatory T cells in a mouse model of asthma. *Mediators Inflamm* 2014;**2014**:436476.

139 H. K. Lee, S. H. Lim, I. S. Chung, *et al.* Preclinical efficacy and mechanisms of mesenchymal stem cells in animal models of autoimmune diseases. *Immune Netw* 2014;**14**:81–88.

140 S. Hajizadeh-Sikaroodi, A. Hosseini, A. Fallah, *et al.* Lentiviral mediating genetic engineered mesenchymal stem cells for releasing IL-27 as a gene therapy approach for autoimmune diseases. *Cell J* 2014;**16**:255–262.

141 A. C. Bowles, B. A. Scruggs, B. A. Bunnell. Mesenchymal stem cell-based therapy in a mouse model of experimental autoimmune encephalomyelitis (EAE). *Methods Mol Biol* 2014;**1213**:313–319.

142 C. Xie, D. Y. Xie, B. L. Lin, *et al.* Interferon-β gene-modified human bone marrow mesenchymal stem cells attenuate hepatocellular carcinoma through inhibiting AKT/FOXO3a pathway. *Br J Cancer* 2013;**109**:1198–1205.

143 D. Zhang, L. Zheng, H. Shi, *et al.* Suppression of peritoneal tumorigenesis by placenta-derived mesenchymal stem cells expressing endostatin on colorectal cancer. *Int J Med Sci* 2014;**11**:870–879.

144 H. Kikuchi, H. Yagi, H. Hasegawa, *et al.* Therapeutic potential of transgenic mesenchymal stem cells engineered to mediate anti-high mobility group box 1 activity: targeting of colon cancer. *J Surg Res* 2014;**190**:134–143.

145 W. Ding, H. You, H. Dang, *et al.* Epithelial-to-mesenchymal transition of murine liver tumor cells promotes invasion. *Hepatology* 2010;**52**:945–953.

146 K. M. Akram, S. Samad, M. A. Spiteri, N. R. Forsyth. Mesenchymal stem cells promote alveolar epithelial cell wound repair *in vitro* through distinct migratory and paracrine mechanisms. *Respir Res* 2013;**14**:9.

147 X. Zhang, L. Zhang, W. Xu, *et al.* Experimental therapy for lung cancer: umbilical cord-derived mesenchymal stem cell-mediated interleukin-24 delivery. *Curr Cancer Drug Targets* 2013;**13**:92–102.

148 M. M. Lalu, L. McIntyre, C. Pugliese, *et al.* Safety of cell therapy with mesenchymal stromal cells (SafeCell): a systematic review and meta-analysis of clinical trials. *PLoS ONE* 2012;**7**:e47559.

149 M. Duijvestein, A. C. Vos, H. Roelofs, *et al.* Autologous bone marrow-derived mesenchymal stromal cell treatment for refractory luminal Crohn's disease: results of a phase I study. *Gut* 2010;**59**:1662–1669.

150 M. Abou-Shady, H. U. Baer, H. Friess, *et al.* Transforming growth factor betas and their signaling receptors in human hepatocellular carcinoma. *Am J Surg* 1999;**177**:209–215.

151 K. Chen, K. Man, H. J. Metselaar, *et al.* Rationale of personalized immunosuppressive medication for hepatocellular carcinoma patients after liver transplantation. *Liver Transpl* 2014;**20**:261–269.

152 R. Wieczorek-Godlewska, D. Miszewska-Szyszkowska, K. Slubowska, *et al.* Dramatic recurrence of cancer in a patient who underwent kidney transplantation – case report. *Transplant Proc* 2014;**46**:2897–2902.

153 Q. Pan, S. M. Fouraschen, P. E. de Ruiter, *et al.* Detection of spontaneous tumorigenic transformation during culture expansion of human mesenchymal stromal cells. *Exp Biol Med (Maywood)* 2014;**239**:105–115.

154 L. Bindslev, M. Haack-Sørensen, K. Bisgaard, *et al.* Labelling of human mesenchymal stem cells with indium-111 for SPECT imaging: effect on cell proliferation and differentiation. *Eur J Nucl Med Mol Imaging* 2006;**33**:1171–1177.

155 D. L. Kraitchman, M. Tatsumi, W. D. Gilson, *et al.* Dynamic imaging of allogeneic mesenchymal stem cells trafficking to myocardial infarction. *Circulation* 2005;**112**:1451–1461.

156 M. El-Ansary, I. Abdel-Aziz, S. Mogawer, *et al.* Phase II trial: undifferentiated versus differentiated autologous mesenchymal stem cells transplantation in Egyptian patients with HCV induced liver cirrhosis. *Stem Cell Rev* 2012;**8**:972–981.

157 S. Terai, T. Ishikawa, K. Omori, *et al.* Improved liver function in patients with liver cirrhosis after autologous bone marrow cell infusion therapy. *Stem Cells* 2006;**24**:2292–2298.

158 A. Gholamrezanezhad, S. Mirpour, M. Bagheri, *et al.* *In vivo* tracking of ^{111}In-oxine labeled mesenchymal stem cells following infusion in patients with advanced cirrhosis. *Nucl Med Biol* 2011;**38**:961–967.

4

ORIGINALITY REPORT

22%	24%	15%	0%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	repub.eur.nl Internet Source	13%
2	au.wiley.com Internet Source	9%

Exclude quotes	Off	Exclude matches	< 7%
Exclude bibliography	Off		