Use of Bone Marrow Mesenchymal Stem Cells as Tumor Specific Delivery Vehicles

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Abstract

Eradication of cancer, especially when it has metastasized is extremely difficult and conventional cancer therapies are simply unable to specifically target tumors/cancers, thus causing unwanted side effects and complications. Recently, it has been shown that bone marrow mesenchymal stem cells (MSCs) are able to migrate specifically to tumors and contribute to the formation of tumor-associated stroma. These properties make MSCs good candidates as anti-tumor agent delivery vehicles and lead to a great deal of interest in the possibility of genetically modifying MSCs to express anticancer molecules and using them as specific targeted anticancer agents. In this chapter, we will review the biological properties of MSCs and the contribution of MSCs in tumor establishment. The potential therapeutic applications of MSCs in the treatment of tumor using different MSCs-delivered anticancer agents will also be reviewed.

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Introduction

Cancer is a major public health problem throughout the world and remains one of the leading causes of mortality and morbidity. A major obstacle for the effective treatment of cancer is the invasive capacity of the tumor cells. Due to the absence of sufficient specificity to the tumor tissue, current conventional cancer therapies (surgery, chemotherapy and radiotherapy) are frequently unsuccessful

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and cause severe side effects and results in low therapeutic efficiency. Therefore, it is critical to develop remedial tumor-targeting approaches for improved efficiency and minimizing systemic toxicity. In many cases, using a gene promoter to drive specific gene expression selectively in a cancer context is the strategy for avoiding toxicity to normal cells and tissues. A gene delivery vehicle that will deliver the tumor killing factors into a majority of the cancer cell population, with the potential to be administered to patients multiple times without eliciting an immune response, represents an essential requirement for successful cancer gene therapy. Mesenchymal stem cells (MSCs) are multi-potent adult stem cells that are easy to acquire and expand *in vitro*; MSCs also have higher migration potential to the injury or tumor sites (Studeny et al. 2002). The tropism of MSCs for tumors makes MSCs uniquely destined to function as cellular delivery vehicles for antitumor agents. It is possible to genetically modify MSCs for the purpose of expressing therapeutic proteins and secreting these proteins into the tumor, such as interferon IFN -β, cytosine deaminase, tumornecrosis factor-related apoptosis-inducing ligand, and oncolyticviruses (Ren et al. 2008; Kucerova et al. 2008; Duan et al. 2009; Sasportas et al. 2009). These approaches have been demonstrated in various pre-clinical models and yielded potent antitumor effects. In the present chapter, a general description of MSCs will be described and we will also review the interactions of MSCs with cancers and therapeutic potential of genetic engineered MSCs.

Mesenchymal Stem Cells (MSCs)

MSCs are multipotent adult stem cells of mesodermal germ layer origin which were first identified in the stromal compartment of bone marrow by Friedenstein et al. in 1960s (Friedenstein et al 1968). In addition to the primary source of bone marrow, MSCs can be isolated from different tissues including adipose tissue, tendons, synovial membrane, skeletal muscle, dermis, pericytes, trabecular bone, human umbilical cord, lung, dental pulp, amniotic fluid, fetal liver, and even peripheral blood, suggesting that MSCs are diversely distributed *in vivo*. Although there is not a single cell surface marker that uniquely characterizes MSCs, a panel of specific cell surface antigens for MSCs has been identified, including expression of CD105, CD73, and CD90 in greater than 95% of the culture, and lack expression of CD45, CD34, CD14 or CD11b, CD79a, or CD19 and HLA-DR surface molecules. The immune phenotype of MSCs is widely described as MHC I+, MHC II-, CD40-, CD80- and CD86- (Loebinger and James 2010). Therefore, transplantation of MSCs into an allogenic host may not require immunosuppression, and thus, MSCs are regarded as non-immunogenic through bypassing host immune surveillance. MSCs are considered non-hematopoietic multipotent stem-like cells that possess an innate ability for self-renewal and capable of differentiating into a variety of mesodermal lineage, including chondrocytes, osteoblasts, adipocytes, muscle cells, pericytes, reticular fibroblasts under proper experimental conditions *in vitro* and *in vivo*. A growing body of evidence suggests that MSCs also have endodermic and neuroectodermic differentiation potential (Loebinger and James 2010). The multilineage potential of MSCs plays an important role in wound healing and tissue regeneration through differentiation and the release of important growth factors and cytokines (Hall et al. 2007).

Their multilineage potential as well as easy acquisition, fast *ex vivo* expansion, and the feasibility of autologous transplantation makes MSCs the ideal choice for cell therapy application in regenerative medicine. Moreover, once MSCs are intravenously or systematically delivered, they are endogenously recruited and selectively homed to sites of inflammation and injury, and improved recovery in animal models of skin wounds, stroke and myocardial infarction (Cheng et al. 2008). Tumor/cancer resemble chronic wounds and is considered as “a wound that never heals”, also tumor microenvironments share many similarities with the tissue repair processes that attract specific homing of MSCs (Hall et al. 2007). The specific tumor-oriented migration and incorporation of MSCs have been demonstrated in various preclinical models, including malignant glioma (Sasportas et al. 2009), melanoma pancreatic and

breast carcinoma (Zischek et al. 2009; Kidd et al. 2009), colon carcinoma (Mueller et al. 2011) and neuroblastoma in immuno-compromised mouse models, regardless the location of the tumors, which demonstrated the potential for MSCs to be used as ideal delivery vehicles for anticancer agents.

However, some studies reported that bone marrow-derived MSCs could increase the growth of human breast cancer, colon cancer, lymphoma, and melanoma cells *in vivo*. Once they are incorporated into the tumor mass, MSCs contribute with other cells like myofibroblasts, endothelial cells, pericytes, and inflammatory cells to create a microenvironment and influence the morphology and proliferation of cells within their vicinity through a combination of cell-to-cell interactions and the produce of tumorigenic chemokines (Direkze et al. 2004; Cogle et al. 2007). Due to the potential effects of MSCs on tumor growth, understanding the interaction between MSCs and tumor cells has become fundamental to determine whether the homing ability of MSCs can be harnessed for tumor-targeted delivery of therapeutic agents. Therefore MSCs were described as a "double-edged sword" in their interaction with tumors. However, if MSCs are suitably engineered with anticancer genes they could be employed as a valuable "single-edged sword" against cancers.

Tumor Microenvironment and Involvement of MSCs in Tumor Establishment

Malignant cells cannot survive alone but live within a complex microenvironment termed as tumor "stroma". Tumor stroma are composed of four main elements: (1) tumor vasculature, (2) cells of the immune system, (3) extra cellular matrix (ECM), and (4) fibroblastic stromal cells-also known as tumor-associated fibroblasts (TAF), carcinoma-associated fibroblasts (CAF), and reactive stroma. Most tumors have some degree of tumor stroma and the tumor viability is dependent on the nonmalignant cells of the tumor microenvironment. These stromal elements respond to signals and factors produced by the tumor cells and provide components necessary for tumor survival, including structural support, cytokines, growth factors, and removal of metabolic and biological wastes, vasculature and extracellular matrices (Hall et al. 2007).

Tumor cells need the necessary oxygen and nutrient supplies for growth and survival. Tumors can switch on angiogenesis by recruiting surrounding mature host blood vessels to sprout new capillaries which grow toward, and eventually infiltrate the tumor mass. The pro-angiogenic molecules such as basic fibroblast growth factor (bFGF) could function as a tumor-derived capillary growth factor and stimulate angiogenesis in various models and vascular endothelial growth factor (VEGF) functions as a potent pro-survival (anti-apoptotic) factor for endothelial cells in newly formed vessels. Tumor cells, tumor-associated macrophages, and TAF could produce VEGF and are involved in tumor-induced angiogenesis. Both tumor-associated macrophages and TAF could support tumor growth and are abundantly detected in tumors (Hall et al. 2007). The cellular origin of TAF remains unclear. Many studies have showed that in addition to their involvement in haematopoiesis, bone marrow is a source of myofibroblasts for many tissues including the gut, lung, and kidney and this phenomenon has been demonstrated particularly in areas of damage and repair, including simple wound healing. Actually, tumors have been compared to unresolved wounds that produce a continuous source of inflammatory mediators. Direkze et al. (2004) showed that bone marrow can contribute to myofibroblast and fibroblast populations in the stromal tissue of tumors in a mouse model of pancreatic insulinoma; they also provided much of the evidence for the participation of BMSCs in tumor tissue and demonstrated with up to 40 % of the myofibroblasts were bone marrow-derived in mouse model of bone marrow transplantation (Direkze et al. 2004). Another study by Cogle et al. (2007), showed that and up to 20 % of the neoplastic cells are bone marrow derived in a patient with lung cancer after sex-mismatched bone marrow transplantation. Tumor neovasculature is critical for tumor growth. Bexell et al. (2009), indicated that MSCs could efficiently migrate to and integrate into tumor vessels and act as pericyte-like cells for delivery

of antiangiogenic substances to vascularized tumors following intra-tumoral grafting. In addition, another research group demonstrated that MSCs are precursors of TAF-like cells in tumors and act as a component of tumor associated fibrovascular networks, including the pericytic population that contributes to the microvessels involved in the neovacularization as well as the fibroblastic population that contributes to matrix remodeling and tumor growth (Spaeth et al. 2009). However, our understanding of the fate and function of MSCs inside the tumor microenvironment is still limited, better understanding of the nature of MSCs-tumor cell interaction is needed to ensure high efficacy of MSCs-based anticancer strategies. New approaches targeting both malignant cells and tumor stromal elements may lead to advancement of anticancer therapy.

Tumor-Tropic Characteristics of MSCs

Numerous studies of various pathological conditions have demonstrated that after systemic or local infusion, MSCs could selectively migrate to sites of injury, or inflammation and to stimulate proliferation and differentiation of resident progenitor cells through growth factor secretion and matrix remodeling. Moreover, their immunomodulatory and anti-inflammatory effects may benefit wound healing. Recent studies have demonstrated that treatment of brain injury with MSCs accelerates wound healing and tissue regeneration (Hall et al. 2007). Tumors can be characterized as sites of tissue damage, or "wounds that never heal", as well as sites of potential inflammatory mediators, cytokine and chemokine production. These signals are capable of recruiting responding cell types including MSCs. The first report of the homing of MSCs to tumors was demonstrated by implantation of rat MSCs into rats bearing syngeneic gliomas, and showed that genetically modified with interleukin-2 (IL-2) had antitumor effect and prolonged the survival time of tumor-bearing rats (Nakamura et al. 2004). Since then, the innate tropism of MSCs for tumors and incorporation of MSCs into tumors have been confirmed in a number of pre-clinical studies in animal tumor models. In these animal models, intravenously delivered MSCs have been shown to selectively migrate to and survive in cancer tissues, such as breast and melanoma lung metastases, Kaposi's sarcoma, colorectal cancer, pancreatic cancer, ovarian cancer and malignant gliomas (Loebinger and James 2010). MSCs administrated by other routes have shown consistent results as intravenous administration, including intraperitoneal delivery for ovarian cancer and intracerebrally in a glioma model.

While many factors have been implicated, the exact mechanisms underlying the migration of MSCs to tumors have not been fully characterized. Secretion of chemokines/cytokines from tumor tissues stimulates the migration of MSCs. MSCs have a variety of chemokine and cytokine receptors on their surface and could respond to the ligands. Cytokines and growth factors such as VEGFs, TGFs, FGFs, PDGFs and IL-8 released from the neoplasm or inflammatory tissues are the possible factors that mediate MSCs migration toward tumors. It is known that these factors released from cancer cells promote the migration of endothelial cell and stromal progenitors from the bone marrow towards the cancer bed and participate in the formation of tumor stroma (Direkze et al. 2004). Adhesion molecules, such as integrins and L-selectin may also play roles in the mobilization and homing of MSCs to tumors. The engraftment of MSCs in tissues is likely triggered by tissue damage or tumor growth. Among the chemokines, stromal cell-derived factor-1 (SDF-1) is of particular interest. The receptor for SDF-1 is CXCR4, is expressed on MSCs. CXCR4 and SDF-1 are found to play very important roles in inflammation and tumor tropism of MSCs. The migration of BMSCs to fibrotic lung is reduced with SDF-1 neutralization. When retrovirally transduced MSCs constitutively express CXCR4, more MSCs were homed toward the infarct region of the myocardium (Cheng et al. 2008). Overexpression CXCR4 in human umbilical cord blood derived MSCs (hUCB-MSCs) also enhanced the migratory capacity of MSCs toward gliomas (Loebinger and James 2010). A better understanding of the signaling pathways associated with tropism of MSCs to tumors may permit more targeted MSCs delivery to desired sites for therapeutic purposes.

In Vivo Imaging Demonstrating MSCs Tumor-Homing Potentials

Multimodal imaging methods have been developed to monitor MSCs tracking in the past decade. *In vivo* imaging techniques help to understand the cell fate *in vivo* and design effective strategies for MSCs administration route and timing. There are optical and non-optical techniques for tracking MSCs fate *in vivo*, including fluorescent in situ hybridization (FISH), flow cytometry methods, histology, immunohistochemistry, immunofluorescence etc. FISH has been used to identify male MSCs within gliomas of female mice (Bexell et al. 2009). Flow cytometry allows for quantification of MSCs within a tumor after digesting the tumor into a single cell suspension. Histology and immunofluorescence can detect MSCs *in vivo* using specific antibodies to detect the labeled cells, such as anti-green fluorescent protein (GFP), anti-firefly luciferase, or anti-human antibodies. Histology is often used in combination with bioluminescent imaging (BLI) to validate MSCs engraftment and their spatial orientation, morphology, differentiation, and function within tumors.

BLI technology is noninvasive, nondestructive, quantitative, and commonly used in cancer studies. Real-time MSC tracking is often done in animal models employing fluorescent dyes and enzymes as cell labels. Reporter genes, such as GFP and *luciferase* are considered indirect labels and produce a signal undiminished following cell proliferation and differentiation that can be detected using *in vivo* optical imaging devices. Different cell types may be distinguished by indirect labeling with different reporter genes. Wang and colleagues have conducted study to track the distribution and differentiation of MSCs in tumor-bearing mice; the 4 T1 murine breast cancer cells were labeled with renilla luciferase-monomeric RFP reporter gene and the MSCs were labeled with firefly luciferase-enhanced GFP reporter gene; and results showed that the MSCs can selectively localize, survive, and proliferate in both subcutaneous tumors and lung metastastic tumors by bioluminescence imaging (Wang et al. 2009). BLI is ideal for longitudinal studies that will significantly reduce the number of animal used. But the BLT imaging cannot be used clinically due to the absence of inherent MSC-specific markers and FDA approved genetically modified MSCs or agents for optical imaging purposes. Non-optical methods such as magnetic resonance imaging (MRI), positron emission tomography (PET), and single photon emission computed tomographies (SPECT), which are already used clinically for cell tracking, but their sensitivity and accuracy need further important.

Evidence for Use of MSCs as Anti-tumor Agents Delivery Vehicles

Upon homing to the tumor mass, MSCs may promote tumor progression through immune response suppression, inhibition of tumor cells apoptosis, and stimulation of epithelial-to-mesenchymal transition, angiogenesis, cell proliferation and metastasis. It has been found that co-injection of mouse melanoma cells, Lewis lung carcinoma cells or colon cancer cells and MSCs into syngeneic mice led to increased tumor size compared with injection of cancer cells alone through enhanced tumor angiogenesis (Suzuki et al. 2011). In the other hand, some studies demonstrated that MSCs also display their intrinsic anticancer activities. In an *in vivo* model of Kaposi's sarcoma, intravenously injected human MSCs homed to tumor sites and potently inhibited tumor growth (Loebinger and James 2010). When mixed with tumor cells, adherent bone marrow cells inhibit primary tumor growth and metastases formation in mice transplanted with Lewis lung carcinoma or B16 melanoma due to some soluble factor(s) released by marrow stromal cells (Loebinger and James 2010). Human skin-derived MSCs also exhibited tumor targeting characteristics and significantly inhibited tumor growth when systemically injected into tumor bearing animals (Loebinger and James 2010). Therefore, the effects of MSCs on tumor growth may vary in different tumor types or at different stages of tumor development. Because MSCs can be easily acquired, culture expanded, and manipulated by viral transduction, as (Fig. 19.1) showed, genetically modified MSCs could be

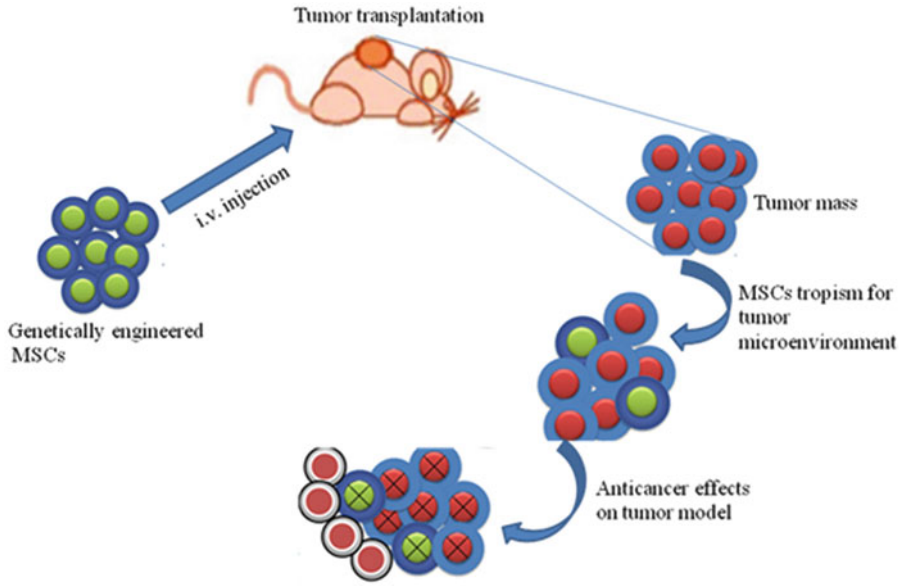

Fig. 19.1 Engraftment of MSCs within tumor xenografts. Subcutaneous tumor xenografts were established prior to intravenous injection of MSCs, which were subsequently found within the tumor stroma. The therapeutic potential of delivering agents to tumors via genetically engineered MSCs was effective in inhibiting the tumor growth

promising tools for delivery therapeutic agents such as small chemical molecules, modulators of the immune system, oncolytic and antiangiogenetic factors, as well as enzymes that can be activated by pro-drugs. As indicated in Table 19.1, a number of anticancer genes have been engineered into MSCs, resulting in anticancer effects on various carcinoma models.

We have showed that when MSCs were infected with herpes simplex virus thymidine kinase (HSV-TK) gene by lentiviral transduction, TK-BMSCs maintained their tumor tropism capabilities and significantly inhibited the growth of subcutaneous PC3 prostate cancer xenografts in nude mice, in the presence of pro-drug Ganciclovir (GCV) (Fig. 19.2a, b). Xenogenic TK-BMSCs also survived and exerted a significant anti-tumor effect in an animal model bearing metastastic RIF-1 (fibrosarcoma) tumor in the presence of pro-drug GCV. Using the TK-BMSCs alone did not cause any harmful side effects *in vivo* (Song et al. 2011). Another research group reported that engineered MSCs expressing the suicide gene cytosine deaminase::uracilphosphoribosyltransferase (CD::UPRT), which convert the relatively nontoxic 5-fluorocytosine (5-FC) into the highly toxic antitumor 5-fluorouracil (5-FU), significantly inhibited prostate cancer tumor growth following intravenous administration (Cavarretta et al. 2010). MSCs as cellular vehicles delivering prodrug-activating enzymes together with their ability to engraft into tumors make them an attractive form of tumor gene therapy. MSCs derived from adipose tissue expressing fusion yeast CD::UPRT gene in combination with prodrug 5-FC also showed potent cytotoxic effect over human colon adenocarcinoma cells HT-29 *in vitro* and *in vivo* (Kucerova et al. 2008).

Using viral-mediated transfection approach, MSCs could be genetically modified to express different kinds of interleukins and mediate efficient cytotoxic effect on target tumor cells *in vivo*. For instance, when MSCs were transfected with IL-12 gene and intravenously delivered, they induced IL-12 production in the tumors and inhibited tumor growth (Duan et al. 2009).

Table 19.1 Anticancer agents delivered by mesenchymal stem cell

Anticancer agents	Anticancer mechanism	Tumor model	Administration route	Species: MSC/ tumor hosts	Reference
CX3CL1	Activates cytotoxic lymphocytes and NK cells	Lung	iv	Mouse/mouse	Xin et al. (2007)
NK4	Inhibits angiogenesis and lymphogenesis and promote apoptosis	Colon	iv	Mouse/mouse	Kanehira et al. (2007)
CD	Pro-drug conversion	Prostate	sc/iv	Human/mouse	Cavarretta et al. (2010)
		Colon	sc/iv	Human/mouse	Kucerova et al. (2008)
HSV-tk		Pancreas	iv	Mouse/mouse	Zischek et al. (2009)
		Prostate	iv	Rat/mouse	Song et al. (2011)
		Fibrosarcoma	iv	Rat/mouse	Xiang et al. (2009)
IFNα	Immunostimulatory, apoptosis inducing and anti-angiogenic	Melanoma	iv	Mouse/mouse	Ren et al. (2008)
		Glioma	it/ic	Mouse/mouse	Sato et al. (2005)
		Glioma	it/iv	Human/mouse	Nakamizo et al. (2005)
IFNβ		Breast	sc/iv	Human/mouse	Studeny et al. (2004)
		Pancreas	ip	Human/mouse	Kidd et al. (2009)
		Melanoma	sc/iv	Human/mouse	Studeny et al. (2002)
IL2	Immunomodulatory cytokine	Glioma	it/ic	Rat/rat	Nakamura et al. (2004)
IL7	Immunostimulatory	Glioma	it	Rat/rat	Gunnarsson et al. (2010)
IL12	Activates cytotoxic lymphocyte and NK cells and produce IFNγ	Melanoma	iv	Mouse/mouse	Chen et al. (2008)
		Hepatoma	iv	Mouse/mouse	Chen et al. (2008)
		Breast	iv	Mouse/mouse	Chen et al. (2008)
		Ewing sarcoma	iv	Mouse/mouse	Duan et al. (2009)
IL18	Immunostimulatory	Glioma	it	Rat/rat	Xu et al. (2009)
TRAIL	Induce apoptosis	Glioma	it	Human/mouse	Sasportas et al. (2009)
		Glioma	ic	Human/mouse	Menon et al. (2009)
		Glioma	iv	Human/mouse	Kim et al. (2008)
		Lung	iv	Human/mouse	Loebinger et al. (2009)
		Breast, lung	sc/iv	Human/mouse	Grisendi et al. (2010)
		Colon	sc	Human/mouse	Mueller et al. (2011)
		Pancreas	iv	Human/mouse	Mohr et al. (2010)

CD Cytosine deaminase, *CX3CL1* Chemokine fractalkine, *HSV-tk* Herpes simplex virus-thymidine kinase, *ic* Intracerebral, *IFN* Interferon, *IL* Interleukin, *ip* Intraperitoneal, *it* Intratumoral, *iv* Intravenous, *NK* Natural killer, *sc* Subcutaneous, *TRAIL* Tumor necrosis factor-related apoptosis inducing ligand

In a mouse melanoma model, application of MSCs expressing IL-12 strongly reduced the formation of lung metastases through activating CD8+ T cells (Chen et al. 2008). In a mouse xenograft model of hepatocellular carcinoma, MSCs overexpressing IL-12 homed to tumors after intravenous injection and significantly reduced the tumor growth and prolonged mouse survival time (Chen et al. 2008).

Type I interferon (IFN) also displays multiple antitumor effects including inhibition of tumor cell proliferation, tumor angiogenesis, induction of tumor cell apoptosis, and activation of host immune defense against tumors. Experiments

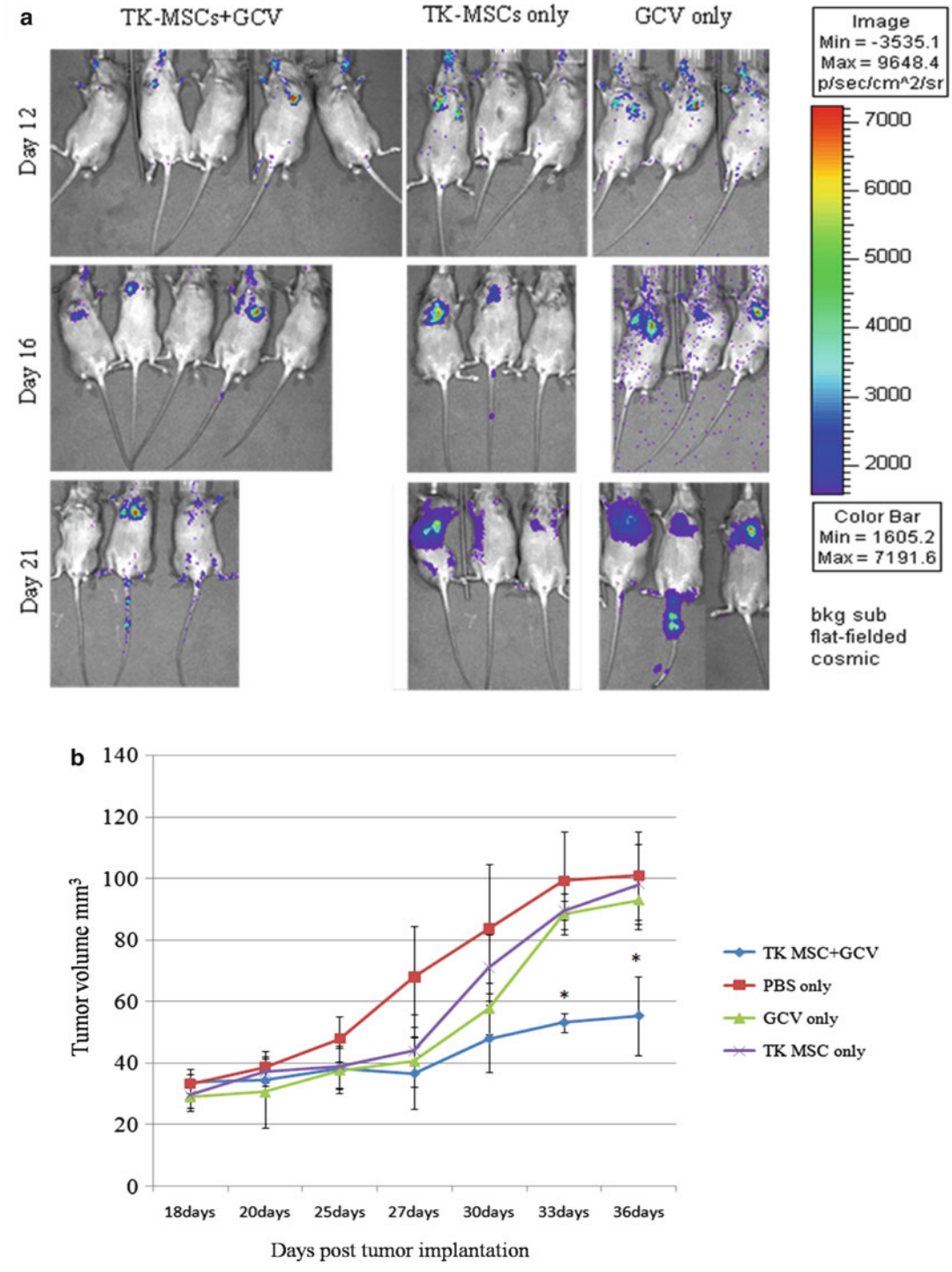

Fig. 19.2 (**a**) In the RIF-1 lung metastasis model, significant inhibition of tumor growth was found only in the TK-BMSCs + GCV group. (**b**) Anti-tumor effect of systemically administered TK-BMSCs in the presence of GCV in PC3 tumor transplant mice was confirmed. At day 33 and day 36 post tumor implantation, tumor volume was significantly smaller in the TK-BMSCs + GCV group (*p <0.05)

showed that treatment of human intracranial glioma xenografts with hMSC-IFN-β significantly increase animal survival time (Nakamizo et al. 2005). In a mouse prostate cancer lung metastasis model, MSCs producing IFN-β at tumor sites in the lungs was found to mediate natural killer (NK) cell activity and anti-tumor effects; and MSCs constitutively producing IFN-α could reduce the growth of melanoma lung metastasis (Ren et al. 2008).

Induction of tumor apoptosis by necrosis factor-related apoptosis inducing ligand (TRAIL) has also been reported. TRAIL induces apoptosis in tumor cells, but has no or minimal toxicity in normal cells. TRAIL has a short pharmacokinetic half-life *in vivo*. When TRAIL gene is stably transduced to MSCs, MSCs serve as a continuous source of TRAIL production that overcomes the problem. In a recent study, when injected i.v. or s.c. into the tumor bearing mice, MSCs overexpressing TRAIL localized into tumors and mediated tumor apoptosis without apparent toxicities to surrounding normal tissues. MSCs expressing TRAIL have also shown to target a variety of tumor cell lines *in vitro*, including human cervical carcinoma, lung cancer, breast cancer, pancreatic cancer and colon cancer (Loebinger et al. 2009; Grisendi et al. 2010). Menon et al.(2009),-demonstrated that after transduced with a lentivirus expressing secretable TRAIL (S-TRAIL), the tumor tropic ability of human bone marrow MSCs are retained and hMSC S-TRAIL together with ipsilateral significantly inhibited tumor growth in an established intracranial glioma tumor model (Menon et al. 2009).

In conclusion, in this chapter we have described the rationale for using MSCs as delivery vehicles for therapeutic agents in anti-tumor therapy. We have also discussed the mechanisms underlying the MSCs homing and killing. Because of their better accessibility, higher expansion potential, low immunogenicity and suitability for genetic manipulation, MSCs become an ideal source for transgene or drugs delivery and for anti-tumor therapy. At present it is unclear whether MSCs have positive or negative effects on tumor progression. Studies supported using genetically engineered MSCs as anticancer vehicles and efficiency of MSCs mediated anticancer therapy has been demonstrated. When genetically modified MSCs were administrated systemically, they significantly inhibited tumor growth in multiple animal models, supporting their clinical application. Issues like how long the engineered MSCs will survive *in vivo*, how specific will the MSCs target tumors as well as the optimal does and timing of MSCs delivery needed further careful investigations.

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