Cellular Oncology (2019) 42:727–738
https://doi.org/10.1007/s13402-019-00459-7

REVIEW

The therapeutic potential of mesenchymal stem cells in lung cancer: benefits, risks and challenges

Lourdes Cortes-Dericks[1] · Domenico Galetta[2]

Accepted: 3 June 2019 / Published online: 28 June 2019

Abstract

Background Lung cancer is one of the most challenging diseases to treat. In the past decades standard therapy including surgery, chemo- and radiation therapy, alone or in combination has not changed the high mortality rate and poor prognosis. In recent years, mesenchymal stem cells (MSCs) have emerged as putative therapeutic tools due to their intrinsic tumor tropism, anti-tumor and immunoregulatory properties. MSCs release biomolecules that are thought to exert the same beneficial effects as their cellular counterparts and, as such, they may offer practical possibilities of using MSC-secreted products. Owing to their innate affinity to home to tumor sites, MSCs have also gained interest as selective vehicles for the delivery of anti-cancer agents. However, MSCs are also known to confer pro-oncogenic effects, rendering them into double-sword weapons against neoplastic diseases.

Conclusions Here, we present published data on the cell- and secretome-based therapeutic competences of MSCs, as well as on their potential as engineered delivery vectors for the treatment of lung cancer. Despite the controversial role of MSCs in the context of lung cancer therapy, current findings support hopeful perspectives to harness the potential of MSC-based regimens that may augment current treatment modalities in lung cancer.

Keywords Lung cancer · Lung cancer therapy · Mesenchymal stem cells · Mesenchymal stem cell secretome · Anti−/pro-tumorigenic effect

1 Introduction

Every year, worldwide 1.8 million people are diagnosed with lung cancer and 1.6 million die because of this disease [1]. The two major subtypes of lung cancer are non-small-cell lung cancer (NSCLC), comprising ~85% of all cases, and small-cell lung cancer (SCLC), comprising ~15% of all cases. Despite advances that have been made in early detection and therapy, the prognosis for lung cancer remains poor [2]. Hence, a more effective therapeutic approach is mandatory to improve current disease management regimens.

✉ Lourdes Cortes-Dericks
cortes-dericks@gmx.de; lcortes@physnet.uni-hamburg.de

Domenico Galetta
domenico.galetta@ieo.it

[1] Department of Biology, University of Hamburg, Hamburg, Germany

[2] Division of Thoracic Surgery, European Institute of Oncology, Milan, Italy

Mesenchymal stem cells (MSCs) are non-hematopoietic stromal cells having properties of self-renewal and differentiation into mesodermal lineages, and they can be easily isolated and cultured in vitro [3]. Although originally isolated from bone marrow [4], MSCs can also be isolated from umbilical cord blood [5], adipose tissues [6], fetal liver, lungs and bone marrow [7], amniotic fluid [8], placenta [9] and peripheral blood [10]. The International Society for Cellular Therapy defines a human MSC by the following criteria: its plastic adherence, its cellular phenotype: $CD14^-$, $CD19^-$, $CD34^-$, $CD45^-$, $HLA\text{-}DR^-$, $CD73^+$, $CD90^+$, $CD105^+$, and its capacity to differentiate into three lineages: chondrocytes, osteoblasts and adipocytes [11].

Initially, it was thought that MSCs exert their beneficial effects through their ability to locally engraft and differentiate into a variety of cell types and, subsequently, replace injured tissues. Current findings advocate that most implanted cells do not survive, and that the beneficial benefits of MSC-based therapy may be accounted for by a plethora of bioactive molecules secreted by the cells that play an essential regulatory role in major biological processes [12]. These bioactive molecules, including cytokines, chemokines and growth factors,

are defined as the MSC secretome and may be collected as conditioned medium (CM) [13].

MSCs have been recognized as potential tools in cancer therapy, particularly because an anti-tumor capacity has been observed in different neoplasms, including lung cancer [14–18]. Importantly, however, MSCs have also been found to be implicated in cancer progression, and they have the ability to migrate towards primary tumors and metastatic sites, exhibiting a local tumor-sustaining capacity. Because of their innate capacity to migrate and home to tumor sites, MSCs have been engineered to deliver anti-cancer agents for the specific targeting of neoplastic cells, thereby providing a novel option of cell-mediated gene therapy [19]. MSCs are in focus of cancer research because of their multi-facetted actions in malignant settings as well as their putative therapeutic effects. Current lung cancer research is challenged to harness the unique features of MSCs to develop and augment lung cancer treatment strategies with hopeful perspectives.

2 Simultaneous pro-and anti-tumor properties of MSCs in lung cancer

MSCs have been found to exhibit diverse biological functions under in vitro and in vivo conditions. Their pro- and anti-tumor abilities may be partly explained by the type of tumor being investigated, the isolation methods used to obtain MSCs and the cell density used in experiments [20]. Indeed, some studies have reported contrasting effects of MSCs. Human umbilical cord MSC-conditioned medium (hUCMSC-CM) has, for instance, been found to be able to promote epithelial-mesenchymal transition (EMT), invasion and migration, but at the same time to inhibit proliferation and promote apoptosis of lung cancer cells [21]. According to this study, the EMT-promoting ability of MSCs was derived from MSC exosomes, which can be abrogated by the inhibition of exosome release. In addition, it was found that expression knockdown of TGF-β1 in MSCs can reverse the EMT-inducing effect to enhance the anti-proliferative and pro-apoptotic efficacies of MSCs on lung cancer cells via MSC-exosomes, suggesting a method by which MSCs may be used safely in lung cancer treatment. The team of Volcano [22] has noted that Wharton jelly-derived MSCs (WJMSCs) can exert contrasting effects on lung cancer stem cells (LCSCs) isolated from adenocarcinoma (AC) and squamous cell carcinoma (SCC). WJMSCs were found to restrict the growth of SCC-LCSCs, to increase the pre-G1 cell cycle phase indicating the induction of apoptosis and to reduce the expression of the putative cancer stem cell (CSC) markers ALDH and CD133. Conversely, they found that WJMSC-CM increased the proliferation of AC-LCSCs and the levels of ALDH and CD133 in AC- and SCC-LCSCs. Under in vivo conditions, they found that combined AC-LCSCs/WJMSCs evoked the formation of larger tumors, whereas combined SCC-LCSCs/WJMSCs had no effect on tumor size. Tian et al. [23] also noted a discrepancy in the outcome of human MSCs (hMSCs) on tumor growth. Using co-culture systems, they found that hMSCs and hMSC-CM inhibited the proliferation and invasion of human A549 lung adenocarcinoma and Eca-109 esophageal carcinoma cells, arrested the tumor cells in the G1 phase of cell cycle and induced apoptosis. Intriguingly, they found that in vivo hMSCs promoted tumor formation and growth associated with an increase in vessel formation. Human adipose tissue-derived MSCs (hATMSCs) have also manifested dual effects on A549 lung and H-29 colorectal adenocarcinoma xenograft models, i.e., hATMSCs suppressed the growth of A549 xenografts while promoting that of HT-29 xenografts. The expression of a significant number of genes was found to be altered during the observed anti-tumor effect of hATMSCs on A549 xenografts, whereas no such effect was detected after hATMSC-promoted growth of HT-29 xenografts [24].

3 Tumor-suppressing effects of MSCs and MSC-CM in lung cancer

Numerous reports have provided evidence that MSCs and/or MSC-CM may confer suppressive actions on lung cancer. Early work of Maestroni et al. [25] reported that adherent bone marrow stromal cells inhibited primary tumor growth and metastasis formation in mice inoculated with Lewis lung carcinoma or B16 melanoma cells, which was apparently caused by soluble factors(s) secreted by the stromal cells. In another study, it was found that human bone marrow-derived MSCs (hBMMSCs) restrained the proliferation of SKMES-1 and A549 lung adenocarcinoma cells under co-culture conditions, and induced apoptosis of the tumor cells via soluble factors. The authors also found that pretreatment of the tumor cells with hBMMSC-derived CM suppressed tumorigenesis and angiogenesis in a murine model, and that VEGF may be implicated in the observed decrease in tumor vessel formation, thus supporting a soluble factor-based capacity of MSCs [14]. Previously, we found that human lung mesenchymal stem cell-derived CM (hLMSC-CM) elicited significant inhibitory effects on cell proliferation and viability, as well as on the elimination of cisplatin-resistant sphere forming cells in H28 malignant pleural mesothelioma, thereby uncovering a paracrine-based response of hLMSC-CM [17]. Wang and colleagues [26] found that human bone marrow-derived MSC-CM inhibited the migration, invasion and cell cycle progression, and promoted the MET pathway in lung adenocarcinoma (LAC) cells. In this study, oncostatin M (OSM), a differentiation-promoting cytokine, was found to be elevated in MSC-CM and to exert the same effect as MSC-CM, indicating a principal role of OSM in the above-mentioned effects

on LAC cells. An additional xenograft model showed that OSM per se could suppress tumor formation and metastasis of LAC cells, thereby substantiating the notion that OSM plays a major role in MSC-dependent inhibition of tumorigenicity in LAC cells.

Co-culture studies of hBMMSC-CM and NSCCL cells have revealed deleterious effects on NSCLC cell proliferation, viability and migration. These co-cultures also reduced the levels of eukaryotic translation initiation factor 4E (elF4E) and 4G1 (elF4G1), which have been associated with tumor progression. These results thus showed that there is a direct dialogue between the BMMSC-CM secretome and NSCLC cells altering translation initiation, which markedly impinges cell fate [27]. Another co-culture and CM experiment revealed a paracrine-based inhibitory effect on NSCLC cell proliferation, apoptosis and migration by suppressing elF4E via the MAPK pathway, indicating that MSCs are able to manipulate translation initiation in NSCLC cells and, by doing so, to modify their fate [28].

Umbilical cord-derived MSCs (UCMSCs) have been found to inhibit H1299 adenocarcinoma cell invasion and to induce apoptosis, whereas no suppressive effect was observed on their proliferation and cell cycle progression [29]. The authors also found that the expression of key kinases (AKT, phosphoinositide 3-kinase [PI3K], signal transducer and activator of transcription 3 [STAT3] and target of rapamycin [TOR]) were significantly decreased in the H1299 cells, indicating that the signaling circuit of these kinases is implicated in the UCMSC-mediated regulation of H1299 cell behavior.

In a murine model of luciferase-positive mouse adenocarcinoma cells (TSA-Luc^{+}), inoculation of hMSCs resulted in decreased tumor growth owing to a decline in tumor cell proliferation, probably because of a broad modification of tumor angiogenesis. Although it was found that the hMSCs induced a significant remodeling of the tumor vasculature, no major effect was noted in the amount of hemoglobin delivered into the tumors or metastases [30]. Using a similar approach, labelled rat MSCs (rMSCs) were instilled into genotoxic-induced lung cancers in female rats to investigate the effect of MSCs on their development. It was found that 80% of the non-rMSCs treated rats developed tumors, while none of those in the rMSCs treated groups developed tumors, thereby revealing a tumor-inhibiting property of the rMSCs. Interestingly, however, no difference in cell proliferation was noted between the two groups [31].

A possible mechanism by which MSCs may evoke tumor suppressing actions has recently been reported [32]. High density (40,000 cells/cm^2) cultured adipose tissue-derived MSCs (40 K-ASCs) were found to express interferon (IFN)-ß and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). The expression of these cytokines was also found to be induced under serum-deprived cell culture conditions. The washing step required for transplantation purposes of normal-density (5000 cells/cm^2) cultured MSCs (5 K-ASCs) was also found to increase the level of IFN-ß, but not that of TRAIL. A profound death of H460 lung cancer cells was noted under co-culture conditions with 40 K-ASCs, and inoculation of 5 K-ASCs or 40 K-ASCs into a H460-derived cancer mouse model substantially reduced tumor weight, suggesting implication of IFN-ß and/or TRAIL in the execution of the tumor suppressive activity of ASCs.

In another study, MSCs were found to fuse spontaneously with lung cancer cells, after which the latter were reprogrammed to a slow growth, a stem-like phenotype and a more benign state, indicating that MSC fusion does not enhance the intrinsic malignancy of lung cancer cells [33]. An overview of the tumor-suppressing activities of MSCs is depicted in Table 1.

4 Tumor-sustaining effects of MSCs and MSC-CM in lung cancer

MSCs do not only have an intrinsic property of tropism for tumors, but they also take part in the development of neoplastic tissues. Using a Lewis lung carcinoma model (LL3), it was found that inoculation of BMMSCs with LL3 cells significantly accelerated tumor growth by inhibiting inflammation induced by adenovirus Fas ligand (Ad-FasL), thus, preventing their rejection [34]. In addition, it was found that MSCs diminished the subsequent expansion of tumor-specific T cells in the treated hosts, indicating that MSCs within the tumor environment may reduce the efficacy of immunotherapy by establishing a functional barrier that hinders inflammation, T cell priming and expansion, as well as the recruitment of effector cells.

Besides favoring tumor growth, MSCs have the capacity to foster metastasis of lung cancer cells by suppressing antitumor responses of the host cells. Gazdic et al. [35] reported that MSCs can significantly enhance lung cancer metastasis, attenuate the concentration of proinflammatory cytokines and increase the levels of immunosuppressive IL-10, nitric oxide (NO) and kynurerine. They also found that MSC-CM hampered the cytotoxicity of natural killer (NK) cells against tumor cells. Carnet and coworkers [36] demonstrated how BMMSCs can promote tumor growth and metastasis in mice. According to these authors, the pro-invasive effect of BMMSCs was conveyed by a juxtacrine action of BMMSCs, leading to trans-shedding of amphiregulin (AREG) from the tumor cell membrane by virtue of the tumor necrosis factor-α-converting enzyme released from the BMMSC plasma membrane. The soluble AREG thus generated by the tumor cells may activate and promote the invasiveness of the tumor cells. Hence, an AREG activation loop initiated by MSCs and tumor interactions may be a potential therapeutic approach to halt cancer development and invasion.

Table 1 Tumor-suppressing actions of MSCs/MSC-CM in lung cancer

Type of MSC	Experimental method	Effect	Reference
BMMSCs	LLC/B16 mouse model	Inhibit primary tumor growth and formation of metastasis	Maestroni et al. [25]
hBMMSCs	Co-culture assays	Suppress cell proliferation; induction of apoptosis in lung AC cells	Li et al. [14]
BMMSC-CM	Murine model	Suppress tumorigenesis and angiogenesis	
hBMMSC-CM	In vitro/co-culture assays	Inhibit cell migration, invasion and cell cycle progression; promote MET pathway	Wang et al. [26]
BMMSCs	Xenograft model	OSM-dependent inhibition of tumorigenesis	
hMSCs	TSA-Luc + mouse model	Decrease tumor growth	Kéramidas et al. [30]
MSCs	In vitro assays	Induce slow growth and more benign state of lung cancer cells	Wei et al. [33]
hLMSC-CM	In vitro assays	Inhibit cell proliferation and sphere formation of H28 mesothelioma cells	Cortes-Dericks et al. [17]
hBMMSC-CM	Co-culture assays	Inhibit cell proliferation, viability and migration; reduction of translation initiation factors, elF4G1 and elF4E in NSCLC cells	Attar-Schneider et al. [27]
rBMMSCs	Genotoxic-induced lung cancer rat model	Inhibit carcinogen-induced tumor formation	Liu et al. [31]
hUCMSCs	In vitro assays	Inhibit cell invasion and apoptosis; decrease expression levels of AKT, PI3K, STAT3, and TOR in H1299 lung AC cells	Chai et al. [29]
MSC-CM	Co-culture/scratch assays	Inhibit cell proliferation, apoptosis and migration of NSCLC cells	Pan et al. [28]
40K-ASCs	Co-culture assays	Increase necrotic cell death in H460 lung AC cells	Jung et al. [32]
40K-ASCs/5 K-ASCs	H460-derived mouse model	Reduce tumor weight	

Abbreviations: *hBMMSCs* human bone marrow mesenchymal stem cells, *BMMSC-CM* bone marrow mesenchymal stem cell-conditioned medium, *hMSCs* human mesenchymal stem cells, *hUCMSCs* human umbilical cord mesenchymal stem cells, *40 K-ASCs* high density (40,000 cells/cm^2) cultured adipose tissue-derived MSCs, *5 K-ASCs* normal-density (5000 cells/cm^2) cultured adipose tissue-derived MSCs, *hLMSC-CM* human lung mesenchymal stem cell-conditioned medium, *OSM* oncostatin M, *elF4G1* eukaryotic translation initiation factor 4 gamma 1, *elF4E* eukaryotic translation initiation factor 4E, *AKT* protein kinase B, *PI3K* phosphoinositide 3-kinase, *STAT3* signal transducer and activator of transcription 3, *TOR* target of rapamycin, *NSCLC* non-small cell lung cancer cell, *LLC* Lewis lung cancer (mouse), *AC* adenocarcinoma: TSA-Lu+, luciferase-positive mouse adenocarcinoma cells

Mouse adipose-derived stem cells (ADSCs) have been found to promote malignant characteristics of LLC1 cells, including their growth and cancer stem cell properties in vitro [37]. In this study, ADSCs were found to enhance tumor formation and growth in mice. The interaction between ADSCs and LLC1 cells was found to increase the secretion of interleukin-6 (IL-6) primarily from ADSCs, acting in a paracrine circuit on LLC1 cells to augment their malignant phenotype. Equally important, ADSC-induced IL-6 was found to activate the JAK2/STAT3 pathway in LLC1 cells. Hsu and colleagues [38] additionally found that MSCs can increase sphere formation, drug resistance and overexpression of pluripotency markers via activation of the IL-6/ JAK2/ STAT3 pathway in A549 and CL1–5 lung cancer cells. MSCs were also found to intensify the in vivo tumorigenicity of A549 and CL1–5 cells in immunodeficient mice.

MSCs have been shown to promote autophagy, ROS (reactive oxygen species) formation and EMT, as well as to increase invasion and migration of A549 adenocarcinoma cells [39]. The authors found that inhibition of autophagy restricted MSC co-culture-mediated EMT and reduced lung cancer cell migration and invasion, indicating that MSC-induced signaling may be a potential target for blocking these phenomena. Another study showed that MSC-derived stanniocalcin (STC1) enhanced the survival of A549 lung cancer cells by uncoupling oxidative phosphorylation, decreasing ROS and shifting metabolism towards a more glycolytic profile, suggesting that MSCs can modulate cell survival by regulating mitochondrial respiration via STC [40].

Co-culture of human ADSCs and H358 lung cancer cells has led to differentiation of ADSCs into myofibroblasts expressing α-SMA (α-smooth muscle actin) and a strong attachment of the H358 cells to ADSCs, indicating that ADSCs may differentiate into tumor stroma, which in turn may play a collateral role in tumor development [41]. An interesting study of Ampollini and co-workers [42] reported that mesenchymal stem cells derived from NSCLC (hlcMSCs) biopsies may exert a supportive role in cancer development. They found that subcutaneous injection of Calu-3 cells in the presence of hLcMSCs into BALB/nude mice doubled the size of the Calu-3 xenografts, indicating that hLcMSCs may provide an inducive microenvironment for the growth of lung cancer. Equally striking, they found that conditioned medium from A549 lung adenocarcinoma cells (A549-CM) induced the expression of periostin, an extracellular matrix protein, in human adipose-derived MSCs (hAMSCs). In a xenograft model of

A549 cells, co-injection of hAMSCs was found to promote the growth of A459 cells in vivo, and these co-transplanted hAMSCs were found to express both periostin and α-SMA, a marker of cancer-associated fibroblasts (CAFs) [43].

A recent study has shown that the property of MSC secretomes to promote lung cancer progression is largely dependent on where the MSCs were derived from [44]. It was, for instance, found that MSCs obtained from lung tumor adjacent sites (pathological niche) exerted worse effects compared to those derived from healthy lung tissues in terms of enhancing NSCLC expression of translation initiation signals, proliferation, migration, induction of EMT and autophagy. These observations underscore that MSCs derived from different tissues, such as primary (healthy) and pathological (tumor) niches, may exert different effects on the tumorigenic state. A summary of the tumor-sustaining abilities of MSCs is depicted in Table 2.

5 Engineered MSCs as drug vehicles in lung cancer therapy

The intrinsic property of MSCs to migrate to tumor sites renders these cells particularly suited for the delivery of anti-cancer molecules [45]. Since MSCs exhibit low expression levels of MHC1 and MHC11 and do not possess the co-stimulatory molecules CD80 and CD86 [46], they do not cause immunological reactions and/or rejection after inoculation into allogenic systems [47]. MSCs also have the ability to integrate into tumor niches and to track down microscopic metastases when inoculated intravenously, highlighting their ability to deliver anti-cancer agents [48].

MSCs have been found to express transgenes efficiently for a long period without alterating their stem cell properties [49]. Indeed, Sadhuka and coworkers [50] could show that incorporation of nanoparticles in MSCs did not affect their viability, differentiation and/or migration potential. They showed that human MSCs treated with drug-loaded polymeric nanoparticles elicited a dose-dependent cytotoxicity in A549 lung adenocarcinoma cells and MA 148 ovarian tumor cells. Using an orthotopic A549 tumor model, they also noted a non-specific biodistribution of nanoparticles, with a pronounced accumulation in the liver and spleen. Nano-engineered MSCs showed a selective accumulation and retention in lung tumors, indicating the utility of nano-engineered MSCs loaded with anti-cancer agents without affecting their tumor-targeting or drug resistance properties.

Layek and coworkers [51] found that nano-engineered MSCs carrying the anti-cancer drug paclitaxel (PTX) homed to tumors and generated cellular drug depots that released the drug load over several days in an A549 orthotopic lung tumor model. These nano-engineered MSCs significantly showed a good survival and inhibited tumor growth despite low doses of PTX, indicating that these MSCs can function as an efficient carrier for tumor-specific drugs that can improve the efficacy of standard chemotherapy. In another study, PTX-primed BM-MSCs were also found to markedly inhibit in vitro proliferation of NCl-H28 human mesothelioma cells, warranting further in vivo investigation of these initial findings [52].

Yao et al. [53] tested the efficacy of nano-engineered doxorubicin (DOX) MSCs for the systemic treatment of pulmonary metastasis of breast cancer cells. These DOX-loaded MSCs were found to exhibit multifunctional properties, such as stemness and migration of MSCs, stability of drug loading, acid sensitive release and cytotoxicity against 4 T1 breast cancer cells. In vivo, DOX-loaded MSCs were found to reside for a long period of time in the lungs where the foci of metastatic tumors were located, resulting in inhibition of tumor growth and metastasis in the lungs, and a prolonged life span of the tumor-bearing mice.

Under co-culture conditions, human adipose-derived MSCs (hAMSCs) transduced with IL-12 have been found to prevent the growth and invasiveness of A549 adenocarcinoma cells [54]. IL-24-transduced umbilical cord MSCs (IL-24-MSCs) also restrained the growth of A549 cells, and inoculation of IL-24 MSCs hampered xenografted tumor growth [55].

TNF-related apoptosis-inducting ligand (TRAIL) is known to exert high anti-tumor properties, particularly by inducing apoptosis in tumor cells while sparing normal cells [56]. Mohr and colleagues [57] conducted a first study to explore the potential therapeutic utility of adenoviral vector expressing TRAIL (Ad.TR)-transduced MSCs in lung cancer. They found that Ad.TR-loaded MSCs are able to block tumor growth in an A549 xenograft mouse model and to induce apoptosis in TRAIL-resistant A549 lung carcinoma cells. The Ad.TR-transduced MSCs did not induce T cell proliferation, which may have led to cytotoxic T cell-mediated apoptosis induction in the Ad.TR-transduced MSCs. Remarkably, these authors found that Ad.TR-transduced MSCs inhibited apoptosis in A549 lung cancer cells in the presence of physiological concentrations of white blood cells (WBCs), erythrocytes and sera from human donors that normally inhibit or neutralize adenovirus-mediated transgene therapy, indicating the stability of this vector in a blood environment. Another pioneering study of Loebinger and co-workers [58] demonstrated the ability of inducible TRAIL-transduced MSCs to significantly diminish metastatic tumor burden with a frequent eradication of metastasis in a murine lung metastasis model. Under co-culture conditions, these TRAIL-transduced MSCs induced apoptosis in lung (A549), squamous (H357), breast (MDA-MB-231) and cervical (Hela) cancer cells. In murine subcutaneous xenograft and pulmonary metastasis models, TRAIL-engineered MSCs were found to cause a profound reduction in tumor growth and a clearance of metastatic disease, respectively, indicating a broad therapeutic potential for both primary tumors and their metastases, and probably as an

Table 2 Tumor-sustaining properties of MSCs/MSC-CM in lung cancer

Type of MSC	Experimental method	Effect	Reference
hAMSCs	A549 lung AC xenograft model	Co-injection of hAMSCs potentiates xenograft tumor growth	Heo et al. [43]
MSCs	In vitro assays	Increase sphere formation, drug resistance and overexpression of pluripotency markers in lung cancer cells	Hsu et al. [38]
	NOD/SCID model	Intensify tumorigenicity of A549 and CL1–5 lung cancer cells	
MSCs	In vitro assays	MSC-derived stanniocalcin enhances survival of A549 lung AC cells	Ohkouchi et al. [40]
ADSCs	In vitro/co-culture assays	Induce EMT-like phenotype in H358 lung cancer cells	Park et al. [41]
hLcMSCs	Calu-3 lung AC xenograft mouse model	Co-injection of hLcMSCs increases tumor size of Calu-3 xenograft tumors	Ampollini et al. [42]
BMMSCs	In vitro	Juxtacrine action of BMMSCs leads to trans-shedding of AREG by tumor cells; AREG activates and promotes invasiveness of lung cancer cells	Carnet et al. [36]
BMMSCs	Mouse model	Accelerate tumor growth; reduce efficacy of immunotherapy	Modiano et al. [34]
ADSCs	In vitro	Promote cell growth and in vitro cancer stem cell characteristics of LLC1 cells	Lu et al. [37]
	LLC1 mouse model	Mediate tumor growth; augment the malignant phenotype of LLC1 cells via IL-6/JAK2/STAT3 pathway	
MSC-CM	In vitro assays	Hamper cytotoxicity of NK cells against tumor cells	Gazdic et al. [35]
MSCs	LLC1 mouse model	Enhance lung cancer metastasis by suppression of anti-tumor immune response	
MSCs	In vitro assays	Promote autophagy, ROS and EMT formation; increase invasion and migration of lung AC cells	Luo et al. [39]
Healthy/pathological lung-derived MSCs	In vitro assays	Pathological lung-derived MSCs exert higher tumor-promoting properties compared to healthy lung-derived MSCs	Attar-Schneider et al. [44]

Abbreviations: *BMMSCs* bone marrow mesenchymal stem cells, *mMSCs* mouse mesenchymal stem cells, *hLcMSCs* human lung cancer-derived mesenchymal stem cells, *hAMSCs* human adipose tissue-derived mesenchymal stem cells, *ADSCs* adipose-derived mesenchymal stem cells, *MSC-CM* mesenchymal stem cell-conditioned medium, *LLC1* Lewis lung carcinoma cell line (mouse), *AC* adenocarcinoma, *AREG* amphiregulin, *IL-6* interleukin 2, *JAK2* Janus kinase 2, *STAT3* signal transducer and activator of transcription protein 3, *NK* natural killer cell, *ROS* reactive oxygen species, *EMT* epithelial-mesenchymal transition

adjuvant therapy for the prevention of micro-metastatic disease following primary tumor resection. Further studies also revealed that IFN-ϒ-modified hBMMSCs expressing TRAIL induced apoptosis in H460, H1299 and A549 lung tumor cells, and in MCF-7 breast cancer cells via TRAIL-mediated caspase-3 activation within the co-cultured target cells. The IFN-ϒ-secreting hBMMSCs were also found to suppress the growth of a lung carcinoma xenograft model [59].

The combination of cytosine deaminase-uracil phosphoribosyltransferase protein (CDA/UPRT)-transfected adipose tissue-derived MSCs (ATMSCs) and lysomustine chemotherapy has shown a superior effect in a murine lung carcinoma model compared to monotherapy-based treatment with either transfected ATMSCs or lysomustine alone. As reported by Krassinova and colleagues [60], the observed effect may be caused by a synergistic effect between the CDA/UPRT-expressing ATMSCs and lysomustine.

Matsuzuka et al. [61] investigated the supposedly potent anti-tumor effect of interferon-beta (IFN-β) on bronchioloalveolar-derived cells. Co-culture of IFN–β transfected human umbilical cord-derived MSCs (hUCMSCs) and H358 or SW1573 cells attenuated the growth of both carcinoma cell types significantly. IFN-β-hUCMSC-CM also showed a profound growth-inhibiting effect on the two cells types. Systemic administration of IFN-β-hUCMSCs remarkably decreased the growth of orthotopic H358 bronchioloalveolar carcinoma xenografts in SCID mice by increasing apoptosis, indicating a potential of IFN-β-hUCMSCs as a cytotherapeutic tool for this type of carcinoma. Genetically modified BMMSCs with pigment epithelium-derived factor (PEDF) were found to reduce the growth of LLC tumors and to prolong survival in murine models. MSC-PEDF-treated tumors displayed a high degree of apoptosis and a decreased microvessel density, suggesting a potential of MSCs as effective vehicles for therapeutic gene delivery in LLC tumors [62].

The anti-oncogenic ability of apoptin, a potential tumor-selective apoptosis-inducing protein, has been tested in lung carcinoma cells by transduction of MSCs with lentiviral vectors encoding apoptin. In vitro, apoptin-modified MSCs were found to enter the target cancer cells and to mediate apoptosis via activation of caspase-3. Injection of apoptin-modified MSCs into nude mice inhibited the growth of lung carcinoma cells, showing the potential of MSCs as cellular vehicles for apoptin-based cancer therapy [63]. The immune-stimulatory

chemokine CX3CL1 (fractalkine), when transduced into mouse MSCs, has also been found to strongly inhibit the development of lung metastases and to prolong the survival of C26 and B16F10 lung metastasis-bearing mice [64]. An overview of the different actions of engineered MSCs in lung cancer is depicted in Table 3.

6 Conclusions and perspectives

6.1 MSC-based anti-tumor modalities: Benefits and drawbacks

The direct administration of anti-tumor agents may be limited due to their short half-life and their toxicity to non-cancerous cells [65]. The unique ability of MSCs to home to tumors and to directly transport anti-cancer agents to neoplastic niches renders them into potential therapeutic vehicles for lung cancer. The above reviewed studies provide compelling evidence that MSCs can be genetically engineered to deliver anti-tumor drugs (PTX, DOX) and immunomodulatory factors (IL-12, IL-24, IFN-ϒ, IFN-β, TRAIL, PEDF, apotin, CDA/UPRT and CX3CL1) to target cells, thereby conferring anti-tumor/anti-metastatic actions. In the different lung cancer models used, modified MSCs were able to home to tumors and to accumulate in neoplastic tissues, to reside for long periods in the foci of metastatic regions and, importantly, to inhibit tumor growth and metastatic disease. In vitro, engineered MSCs showed an ability to enter target cells, to provide stable drug loading and release, to inhibit cancer cell growth and to induce apoptosis. Of note, none of these studies revealed any significant adverse effects of the modified MSCs under different experimental conditions. Among the engineered MSCs, those expressing TRAIL have shown a particular anti-tumor potential in multiple pre-clinical cancer models, including metastatic lung cancer and mesothelioma [46, 58, 66, 67]. These pre-clinical findings have led to a Phase I/II clinical trial to assess the safety and anti-tumor efficacy of TRAIL-expressing MSCs in combination with cisplatin and pemetrexed in metastatic NSCLC patients (ClinicalTrial.gov Identifier: NCT03298763). This trial may provide crucial information on the clinical competence of MSCs as delivery vectors for anti-tumor agents in lung cancer (https://clinicaltrials.gov/ct).

In contrast to the anti-oncogenic actions of modified MSCs, administered MSCs have shown bi-directional effects in lung cancers. The publications reviewed above revealed an equal number of studies affirming the tumor suppressive and supporting potentials of native MSCs from different origins. MSCs are able to induce apoptosis, and to suppress tumor cell proliferation and sphere formation of putative cancer stem cells. In the murine models of lung cancer, native MSCs and MSC-CM exhibited inhibiting effects on tumorigenesis and metastasis. Conversely, it has been found that injected MSCs can also potentiate tumor growth, augment the malignant phenotype of lung cancer cells and enhance metastasis. Pro-oncogenic effects such as the promotion of drug resistance, survival of lung cancer cells and induction of cancer stem cell characteristics, including the inhibition of cytotoxicity of NK cells, have also been observed in different in vitro settings. Substantial differences may very well emerge in MSC fitness and functionality based on their tissue of origin, culture methods and expansion levels. Other variables such as handling at the point of care, thawing, route of delivery and dosing may represent critical functionalities [68]. Because no single factor can determine the fate of tumor cells exposed to MSCs due to the complex cross-talk between MSCs, stroma components and cancer cells [69], it is essential to understand the biology of every type of MSC and its potential mode of action within a given tumor environment to harness its beneficial effects.

6.2 Clinical impact

Despite the progress that has been made in lung cancer therapy, this tumor remains the leading cause of cancer-related death worldwide. NSCLC is a heterogeneous disease that requires personalized treatment depending on the clinical profile that may include (i) surgery alone in case of localized cancer [70], (ii) multimodality treatment including surgery, chemotherapy and radiotherapy in case of locally advance lung cancer without metastasis [71, 72], or (iii) definitive chemo- and/or radiotherapy, immunotherapy or molecular targeted therapy [73]. Although chemotherapy is preferentially indicated in most of the non-small cell lung cancers, molecular targeted therapy, immunotherapy and mesenchymal stem cell drug loading and delivery represent alternative options to traditional chemotherapy [74]. The main problem with current chemotherapy is its toxicity accompanied by common side effects of pronounced gastrointestinal upset, such as nausea and vomiting, as well as bone marrow suppression causing susceptibility to infection and, in some cases, even death [46]. Nanovectors of anti-cancer agents as well as mesenchymal stem cells potentially harbor and protect therapeutic compounds before they reach the target site, hence enhancing tumor drug uptake and reducing drug interactions with normal cells, thereby reducing clinical toxicity [74].

MSC-based gene treatment in conjunction with chemotherapy is currently under evaluation and, as such, it may provide a rationale for improving the efficacy of anti-tumor drugs [46, 75]. This approach has been used in a combined CDA/UPRT-transfected ATMSC and lysomustine chemotherapy regimen, resulting in a superior therapeutic effect in a murine lung carcinoma model compared to monotherapy-based treatment with either transfected ATMSCs or lysomustine alone. A synergistic effect between CDA/UPRT-transfected ATMSCs and lysomustine may have caused the improved therapeutic effect

Table 3 Engineered MSCs with anti-tumor effects

Engineered MSC	Experimental method	Effect	Reference
CX3CL1-transduced mMSCs	C26/B16F10 lung metastasis mouse model	Inhibit lung metastasis	Xin et al. [64]
Ad.TRAIL-transduced human MSCs	In-vitro assays	Induce apoptosis in A549 lung cancer cells	Mohr et al. [57]
	A549 lung AC xenograft model	Suppress tumor growth	
TRAIL-transduced human MSCs	Co-culture assays	Mediate cancer cell apoptosis and death	Loebinger et al. [58]
	MDAMB231 breast carcinoma xenograft model	Reduce tumor growth	
	Pulmonary metastasis mouse model	Localize to lung metastasis and clear metastatic disease	
IFN-β-transfected hUCMSCs /IFN-β- hUCMSCs-CM	Co-culture assays	Attenuate bronchioloalveolar cell growth	Matsuzuka et al. [61]
	Bronchioloalveolar orthotopic model	Decrease growth of orthotopic xenograft tumors	
PEDF-transduced mBMMSCs	In vitro assays	Increase apoptosis, decrease microvessel density	Chen et al. [62]
	LLC mouse model	Reduce size of LLC tumors; prolong survival of tumor-bearing mice	
IL-24-transduced hUCMSCs	In vitro assays	Inhibit A549 lung AC growth	Zhang et al. [55]
	Lung AC xenograft model	Suppress xenograft tumor growth	
MSCs containing drug-loaded polymeric nanoparticles	In vitro assays	Dose-dependent cytotoxicity in lung AC and ovarian tumor cells	Sadhukha et al. [50]
	A549 lung AC orthotopic model	Selective retention and accumulation in lung tumors	
IFN- γ-modified hBMMSCs expressing TRAIL	Co-culture assays	Induce apoptosis in lung and breast tumor cells	Yang et al. [59]
	Lung AC xenograft model	Inhibit growth and development of xenograft tumors	
Apoptin-transduced MSCs	In vitro assays	Enter target cells; mediate apoptosis; activate caspase-3	Du et al. [63]
	Mouse lung AC model	Inhibit growth of lung AC	
IL-12 transduced hMSCs	Co-culture assays	Inhibit growth and invasiveness of A549 lung AC	Li et al. [54]
CDA/UPRT- transfected ATMSCs	Murine model	CDA/UPRT-MSCs + lysomustine chemotherapy exert better effect compared to monotherapy	Krassikova et al. [60]
Nano-engineered DOX MSCs	In vitro assays	Stable drug loading and release; preserve stemness and migration of MSCs; exert cytotoxicity in breast cancer cells	Yao et al. [53]
	Lung metastasis mouse model of breast cancer	Reside in foci of metastatic tumors in the lungs; inhibit tumor growth and metastasis; prolong life span of tumor-bearing mice	
PTX-primed MSCs	In vitro	Inhibit cell proliferation of H28 malignant mesothelioma cells	Petrella et al. [52]
Nano-engineered PTX MSCs	A549 lung AC orthotopic model	Generate cellular drug depots; home to tumors; inhibit tumor growth	Layek et al. [51]

Abbreviations: *MSCs* mesenchymal stem cells, *mMSCs* mouse mesenchymal stem cells, *MSC-CM* mesenchymal stem cell-conditioned medium, *hUCMSCs* human umbilical cord mesenchymal stem cells, *hBMMSCs* human bone marrow mesenchymal stem cells, *ATMSCs* adipose tissue-derived mesenchymal stem cells, *AC* adenocarcinoma, *Ad.TRAIL* adenoviral vector-expressing TRAIL, *IFN- γ* interferon gamma, *LLC* Lewis lung carcinoma cell line (mouse), *DOX* doxorubicin, *IL-12* interleukin 12, *IL-24* interleukin 24, *IFN-β* interferon beta, *IFN- γ* interferon gamma, *PEDF* pigment epithelium-derived factor, *PTX* paclitaxel, *TRAIL* TNF-related apoptosis- inducing ligand, *CDA/UPRT* cytosine deaminase-uracil phosphoribosyltransferase protein

[60]. In line with this, an increased anti-oncogenic potential of a combination of cisplatin and TRAIL-modified MSCs relative to cisplatin or TRAIL-engineered MSCs alone has been observed in a hepatocellular carcinoma xenograft mouse model [76], an approach that may also be applicable to lung cancer. MSCs are relatively resistant to cytostatic and cytotoxic drugs [65], which facilitates a nano-engineering strategy allowing the incorporation of small molecules such as PTX [50], which is an effective anti-lung cancer agent [77, 78]. Encouraging preclinical data have shown a true active targeting potential of nano-engineered MSCs loaded with a low dosage of PTX, as these MSCs exhibited a profound effectivity in suppressing lung cancer growth compared to PTX and PTX nanoparticles alone. These PTX-loaded MSCs actively migrated to tumor sites where they remained for several days, facilitating targeted delivery of chemotherapeutic drugs and inhibition of tumor development [51].

Although a vast number of experimental studies attested the capability of modified MSCs as therapeutic vehicles to deliver anti-cancer agents to target tissues, optimizing this

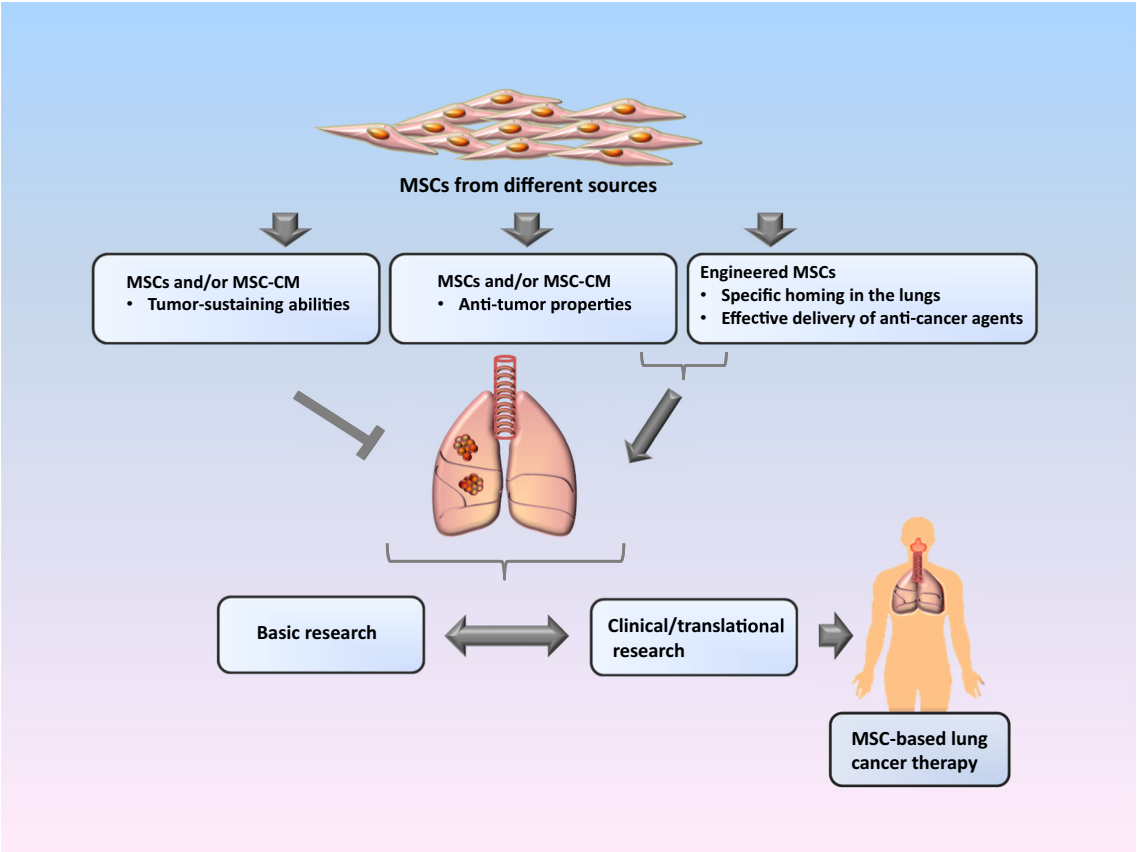

Fig. 1 Beneficial MSC properties in lung cancer therapy. MSCs and/or MSC-CM possess innate anti-oncogenic properties, and can be engineered to home and deliver specific anti-cancer agents to tumor sites. On the other hand, they are capable of promoting tumor development, which must be taken into serious consideration to avoid putative devastating effects. To harness the therapeutic potential of MSCs, a multi-functional collaboration between basic and clinical research groups is necessary to provide a deeper understanding of the "hows" and "whys" of the biological behavior of MSCs within a given tumor, which will facilitate the use of MSC-based regimens in the treatment of lung cancer

approach in combination with standard chemotherapy needs to be addressed. The deliberate use of methodologies with a standardized reporting system will promote accurate comparisons across studies and facilitate a fast and efficient translation of the platforms that will most likely bring success in the clinic [79].

Another application of MSCs may be in adjuvant settings for localized treatment of residual disease following surgery or radiotherapy. Site-directed delivery to neoplastic regions may bypass limitations implicated with homing efficiency, and the high level of safety observed in clinical trials using MSCs in other settings makes this a feasible strategy [79]. To date, no principle can be applied in deciding which MSC-based approach to choose that will assure improved lung cancer management. Although pre-clinical data provide a good understanding of MSC biology and therapeutic strategies, clinical trials need to be initiated to prove the beneficial effects and resolve all critical aspects of MSC-based therapy in lung cancer. Phase I clinical trials have already shown a safe use of MSCs in chronic lung diseases such as chronic obstructive pulmonary disease (COPD), mild to moderate idiopathic pulmonary fibrosis (IPF), acute respiratory distress syndrome (ARDS), advanced pulmonary sarcoidosis and severe emphysema (reviewed in [80]), but none yet in the setting of lung cancer.

The "hows" and "whys" of the cellular and molecular behavior of MSCs within the tumor niche are likely the key parameters to be considered to harness the potential of these cells. This knowledge may provide detailed insight into the intricate associations between MSCs and cancer cells and, consequently, pave the way for the use of MSCs in lung cancer therapy (Fig. 1).

Acknowledgements We thank Prof. Dr. Stefan Kirschner for his continuous *moral support.*

Author's contribution LCD and DG contributed equally in the conception, organization of data and writing of the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Abbreviations *hBMMSCs,* human bone marrow mesenchymal stem cells; *BMMSC-CM,* bone marrow mesenchymal stem cell-conditioned medium; *hMSCs,* human mesenchymal stem cells; *hUCMSCs,* human umbilical cord mesenchymal stem cells; *hLMSC-CM,* human lung mesenchymal stem cell-conditioned medium; *hLcMSCs,* human lung cancer-derived mesenchymal stem cells; *hAMSCs,* human adipose tissue-derived mesenchymal stem cells; *AMSCs,* adipose-derived mesenchymal stem cells; *OSM,* oncostatin M; *elF4G1,* eukaryotic translation initiation factor 4 gamma 1; *elF4E,* eukaryotic translation initiation factor 4E; *AKT,* protein kinase B; *PI3K,* phosphoinositide 3-kinase; *STAT3,* signal transducer and activator of transcription 3; *TOR,* target of rapamycin; *NSCLC,* non-small cell lung cancer cell; *LLC,* Lewis lung cancer (mouse); *AC,* adenocarcinoma TSA-Lu + luciferase-positive mouse adenocarcinoma cells.; *AREG,* amphiregulin; *IL-6,* interleukin 2; *JAK2,* Janus kinase 2; *STAT3,* signal transducer and activator of transcription protein 3; *NK,* natural killer cell; *ROS,* reactive oxygen species; *EMT,* epithelial-mesenchymal transition; *IFN- γ,* interferon gamma; *AREG,* amphiregulin; *DOX,* doxorubicin; *IL-12,* interleukin 12; *IL-24,* interleukin 24; *IFN-β,* interferon beta; *IFN- γ,* interferon gamma; *PEDF,* pigment epithelium-derived factor; *PTX,* paclitaxel; *TRAIL,* TNF-related apoptosis- inducing ligand; *CDA/UPRT,* cytosine deaminase-uracil phosphoribosyltransferase protein; *Ad.TRAIL,* adenoviral vector-expressing TRAIL

References

1. F.R. Hirsch, G.V. Scagliotti, J.L. Mulshine, R. Kwon, W.J. Curran, Y.-L. Wu, L. Paz-Ares, Lung cancer: Current therapies and new targeted treatments. Lancet **389**, 299–311 (2017). https://doi.org/10.1016/S0140-6736(16)30958-8
2. R.S. Herbst, J.V. Heymach, S.M. Lippman, Lung Cancer. N Engl J Med **359**, 1367–1380 (2008). https://doi.org/10.1056/NEJMra0802714
3. C.-L. Zhang, T. Huang, B.-L. Wu, W.-X. He, D. Liu, Stem cells in cancer therapy: Opportunities and challenges. Oncotarget **8**, 75756–75766 (2017). https://doi.org/10.18632/oncotarget.20798
4. A.J. Friedenstein, K.V. Petrakova, A.I. Kurolesova, G.P. Frolova, Heterotopic of bone marrow. Analysis of precursor cells for osteogenic and hematopoietic tissues. Transplantation **6**, 230–247 (1968)
5. A. Erices, P. Conget, J.J. Minguell, Mesenchymal progenitor cells in human umbilical cord blood. Br J Haematol **109**, 235–242 (2000)
6. S. Gronthos, D.M. Franklin, H.A. Leddy, P.G. Robey, R.W. Storms, J.M. Gimble, Surface protein characterization of human adipose tissue-derived stromal cells. J Cell Physiol **189**, 54–63 (2001)
7. C. Campagnoli, I.A. Roberts, S. Kumar, P.R. Bennett, I. Bellantuono, N.M. Fisk, Identification of mesenchymal stem/progenitor cells in human first-trimester fetal blood, liver, and bone marrow. Blood **98**, 2396–2402 (2001)
8. M.-S. Tsai, J.-L. Lee, Y.-J. Chang, S.-M. Hwang, Isolation of human multipotent mesenchymal stem cells from second-trimester amniotic fluid using a novel two-stage culture protocol. Hum Reprod Oxf Engl **19**, 1450–1456 (2004). https://doi.org/10.1093/humrep/deh279
9. K. Igura, X. Zhang, K. Takahashi, A. Mitsuru, S. Yamaguchi, T.A. Takashi, Isolation and characterization of mesenchymal progenitor cells from chorionic villi of human placenta. Cytotherapy **6**, 543–553 (2004)
10. N.J. Zvaifler, L. Marinova-Mutafchieva, G. Adams, C.J. Edwards, J. Moss, J.A. Burger, R.N. Maini, Mesenchymal precursor cells in the blood of normal individuals. Arthritis Res **2**, 477–488 (2000)
11. M. Dominici, K. Le Blanc, I. Mueller, I. Slaper-Cortenbach, F. Marini, D. Krause, R. Deans, A. Keating, D.J. Prockop, E. Horwitz, Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy **8**, 315–317 (2006)
12. F.J. Vizoso, N. Eiro, S. Cid, J. Schneider, R. Perez-Fernandez, Mesenchymal stem cell Secretome: Toward cell-free therapeutic strategies in regenerative medicine. Int J Mol Sci **18** (2017). https://doi.org/10.3390/ijms18091852
13. S.H. Ranganath, O. Levy, M.S. Inamdar, J.M. Karp, Harnessing the Mesenchymal stem cell Secretome for the treatment of cardiovascular disease. Cell Stem Cell **10**, 244–258 (2012). https://doi.org/10.1016/j.stem.2012.02.005
14. L. Li, H. Tian, Z. Chen, W. Yue, S. Li, W. Li, Inhibition of lung cancer cell proliferation mediated by human mesenchymal stem cells. Acta Biochim Biophys Sin **43**, 143–148 (2011). https://doi.org/10.1093/abbs/gmq118
15. A.Y. Khakoo, S. Pati, S.A. Anderson, W. Reid, M.F. Elshal, I.I. Rovira, A.T. Nguyen, D. Malide, C.A. Combs, G. Hall, J. Zhang, M. Raffeld, T.B. Rogers, W. Stetler-Stevenson, J.A. Frank, M. Reitz, T. Finkel, Human mesenchymal stem cells exert potent antitumorigenic effects in a model of Kaposi's sarcoma. J Exp Med **203**, 1235–1247 (2006). https://doi.org/10.1084/jem.20051921
16. K. Gauthaman, F.C. Yee, S. Cheyyatraivendran, A. Biswas, M. Choolani, A. Bongso, Human umbilical cord Wharton's jelly stem cell (hWJSC) extracts inhibit cancer cell growth in vitro. J Cell Biochem **113**, 2027–2039 (2012). https://doi.org/10.1002/jcb.24073
17. L. Cortes-Dericks, L. Froment, G. Kocher, R.A. Schmid, Human lung-derived mesenchymal stem cell-conditioned medium exerts in vitro antitumor effects in malignant pleural mesothelioma cell lines. Stem Cell Res Ther **7**, 25 (2016). https://doi.org/10.1186/s13287-016-0282-7
18. J.-O. Ahn, Y.-R. Coh, H.-W. Lee, I.-S. Shin, S.-K. Kang, H.-Y. Youn, Human adipose tissue-derived mesenchymal stem cells inhibit melanoma growth in vitro and in vivo. Anticancer Res **35**, 159–168 (2015)
19. G. Lazennec, C. Jorgensen, Concise review: Adult multipotent stromal cells and cancer: Risk or benefit? Stem Cells **26**, 1387–1394 (2008). https://doi.org/10.1634/stemcells.2007-1006
20. R. Ramasamy, Lam EW-F, Soeiro I, Tisato V, bonnet D, Dazzi , Mesenchymal stem cells inhibit proliferation and apoptosis of tumor cells: Impact on in vivo tumor growth. Leukemia **21**, 304–310 (2007)
21. X. Zhao, X. Wu, M. Qian, Y. Song, D. Wu, W. Zhang, Knockdown of TGF-β1 expression in human umbilical cord mesenchymal stem cells reverts their exosome-mediated EMT promoting effect on lung cancer cells. Cancer Lett **428**, 34–44 (2018). https://doi.org/10.1016/j.canlet.2018.04.026
22. F. Vulcano, L. Milazzo, C. Ciccarelli, A. Eramo, G. Sette, A. Mauro, G. Macioce, A. Martinelli, R. La Torre, P. Casalbore, H.J. Hassan, A. Giampaolo, Wharton's jelly mesenchymal stromal cells have contrasting effects on proliferation and phenotype of cancer stem cells from different subtypes of lung cancer. Exp Cell Res **345**, 190–198 (2016). https://doi.org/10.1016/j.yexcr.2016.06.003
23. L.L.H. Tian, W. Yue, F. Zhu, S. Li, W. Li, Human mesenchymal stem cells play a dual role on tumor cell growth in vitro and in vivo. J Cell Physiol **226**, 1860–1867 (2011). https://doi.org/10.1002/jcp.22511
24. J.J. Rhyu, J.-W. Yun, E. Kwon, J.-H. Che, B.-C. Kang, Dual effects of human adipose tissue-derived mesenchymal stem cells in human lung adenocarcinoma A549 xenografts and colorectal adenocarcinoma HT-29 xenografts in mice. Oncol Rep **34**, 1733–1744 (2015). https://doi.org/10.3892/or.2015.4185
25. G.J. Maestroni, E. Hertens, P. Galli, Factor(s) from nonmacrophage bone marrow stromal cells inhibit Lewis lung carcinoma and B16 melanoma growth in mice. Cell Mol Life Sci CMLS **55**, 663–667 (1999)
26. M.-L. Wang, C.-M. Pan, S.-H. Chiou, W.-H. Chen, H.-Y. Chang, O.K.-S. Lee, H.S. Hsu, C.W. Wu, Oncostatin m modulates the

mesenchymal-epithelial transition of lung adenocarcinoma cells by a mesenchymal stem cell-mediated paracrine effect. Cancer Res **72**, 6051–6064 (2012). https://doi.org/10.1158/0008-5472.CAN-12-1568

27. O. Attar-Schneider, V. Zismanov, L. Drucker, M. Gottfried, Secretome of human bone marrow mesenchymal stem cells: An emerging player in lung cancer progression and mechanisms of translation initiation. Tumor Biol **37**, 4755–4765 (2016). https://doi.org/10.1007/s13277-015-4304-3
28. M. Pan, L. Hou, J. Zhang, D. Zhao, J. Hua, Z. Wang, J. He, H. Jiang, H. Hu, L. Zhang, Inhibitory effect and molecular mechanism of mesenchymal stem cells on NSCLC cells. Mol Cell Biochem **441**, 63–76 (2017). https://doi.org/10.1007/s11010-017-3174-y
29. L. Chai, L. Bai, L. Li, F. Chen, J. Zhang, Biological functions of lung cancer cells are suppressed in co-culture with mesenchymal stem cells isolated from umbilical cord. Exp Ther Med **15**, 1076–1080 (2018). https://doi.org/10.3892/etm.2017.5456
30. M. Kéramidas, F. de Fraipont, A. Karageorgis, A. Moisan, V. Persoons, M.-J. Richard, J.L. Coll, C. Rome, The dual effect of mscs on tumour growth and tumour angiogenesis. Stem Cell Res Ther **4**, 41 (2013). https://doi.org/10.1186/scrt195
31. T. Liu, K. Zhu, C. Ke, S. Yang, F. Yang, Z. Li, Z. Zhang, Mesenchymal stem cells inhibited development of lung cancer induced by chemical carcinogens in a rat model. Am J Transl Res **9**, 2891–2900 (2017)
32. P.Y. Jung, H. Ryu, K.-J. Rhee, S. Hwang, C.G. Lee, S.-Y. Gwon, J. Kim, B.-S. Yoo, S.-K. Baik, K.-S. Bae, Y.-W. Eom, Adipose tissue-derived mesenchymal stem cells cultured at high density express IFN-β and TRAIL and suppress the growth of H460 human lung cancer cells. Cancer Lett **440**, 202–441, 210 (2019). https://doi.org/10.1016/j.canlet.2018.10.017
33. H.-J. Wei, W.-C. Lo, J.A. Nickoloff, W.-H. Chen, H.-Y. Liu, Y.-T. Chang, P.-C. Yang, C.-W. Wu, D.F. Williams, J.G. Gelovani, W.-P. Deng, FOXF1 mediates mesenchymal stem cell fusion-induced reprogramming of lung cancer cells. Oncotarget **5**, 9514–9529 (2014). https://doi.org/10.18632/oncotarget.2413
34. J.F. Modiano, B.A. Lindborg, R.T. McElmurry, M. Lewellen, C.L. Forster, E.A. Zamora, J. Schaack, D. Bellgrau, O'Brien TD, Tolar J, Mesenchymal stromal cells inhibit murine syngeneic anti-tumor immune responses by attenuating inflammation and reorganizing the tumor microenvironment. Cancer Immunol Immunother **64**, 1449–1460 (2015). https://doi.org/10.1007/s00262-015-1749-6
35. M. Gazdic, B. Simovic Markovic, N. Jovicic, M. Misirkic-Marjanovic, V. Djonov, V. Jakovljevic, N. Arsenijevic, M.L. Lukic, V. Volarevic, Mesenchymal stem cells promote metastasis of lung cancer cells by downregulating systemic antitumor immune response. Stem Cells Int **2017**, 1–11 (2017). https://doi.org/10.1155/2017/6294717
36. O. Carnet, J. Lecomte, A. Masset, I. Primac, T. Durré, L. Maertens, B. Detry, S. Blacher, C. Gilles, C. Pequeux, J. Paupert, J.M. Foidart, G. Jerusalem, D. Cataldo, A. Noel, Mesenchymal stem cells shed Amphiregulin at the surface of lung carcinoma cells in a Juxtacrine manner. Neoplasia **17**, 552–563 (2015). https://doi.org/10.1016/j.neo.2015.07.002
37. J.-H. Lu, H.-J. Wei, B.-Y. Peng, H.-H. Chou, W.-H. Chen, H.-Y. Liu, W.-P. Deng, Adipose-derived stem cells enhance Cancer stem cell property and tumor formation capacity in Lewis lung carcinoma cells through an Interleukin-6 paracrine circuit. Stem Cells Dev **25**, 1833–1842 (2016). https://doi.org/10.1089/scd.2016.0163
38. H.-S. Hsu, J.-H. Lin, T.-W. Hsu, K. Su, C.-W. Wang, K.-Y. Yang, S.-H. Chiou, S.-C. Hung, Mesenchymal stem cells enhance lung cancer initiation through activation of IL-6/JAK2/STAT3 pathway. Lung Cancer Amst Neth **75**, 167–177 (2012). https://doi.org/10.1016/j.lungcan.2011.07.001
39. D. Luo, S. Hu, C. Tang, G. Liu, Mesenchymal stem cells promote cell invasion and migration and autophagy-induced epithelial-mesenchymal transition in A549 lung adenocarcinoma cells. Cell Biochem Funct **36**, 88–94 (2018). https://doi.org/10.1002/cbf.3320
40. S. Ohkouchi, G.J. Block, A.M. Katsha, M. Kanehira, M. Ebina, T. Kikuchi, Y. Saijo, T. Nukiwa, D.J. Prockop, Mesenchymal stromal cells protect cancer cells from ROS-induced apoptosis and enhance the Warburg effect by secreting STC1. Mol Ther J Am Soc Gene Ther **20**, 417–423 (2012). https://doi.org/10.1038/mt.2011.259
41. Y.M. Park, S.H. Yoo, S.-H. Kim, Adipose-derived stem cells induced EMT-like changes in H358 lung cancer cells. Anticancer Res **33**, 4421–4430 (2013)
42. L. Ampollini, D. Madeddu, A. Falco, C. Frati, B. Lorusso, G. Graiani, F. Saccani, A. Gervasi, P. Rossetti, S. Bonomini, L. Gnetti, C.A. Lagrasta, E.M. Silini, E. Quaini, P. Petronini, R. Alfieri, M. Rusca, P. Carbognani, F. Quaini, Lung mesenchymal cells function as an inductive microenvironment for human lung cancer propagating cells†. Eur J Cardiothorac Surg **46**, e103–e112 (2014). https://doi.org/10.1093/ejcts/ezu359
43. S.C. Heo, K.O. Lee, S.H. Shin, Y.W. Kwon, Y.M. Kim, C.H. Lee, Y.D. Kim, M.K. Lee, J.H. Kim, Periostin mediates human adipose tissue-derived mesenchymal stem cell-stimulated tumor growth in a xenograft lung adenocarcinoma model. Biochim Biophys Acta **1813**, 2061–2070 (2011). https://doi.org/10.1016/j.bbamcr.2011.08.004
44. O. Attar-Schneider, L. Drucker, M. Gottfried, The effect of mesenchymal stem cells' secretome on lung cancer progression is contingent on their origin: Primary or metastatic niche. Lab Investig **98**, 1549–1561 (2018). https://doi.org/10.1038/s41374-018-0110-z
45. M. Studeny, F.C. Marini, R.E. Champlin, C. Zompetta, I.J. Fidler, M. Andreeff, Bone marrow-derived mesenchymal stem cells as vehicles for interferon-beta delivery into tumors. Cancer Res **62**, 3603–3608 (2002)
46. E.K. Sage, R.M. Thakrar, S.M. Janes, Genetically modified mesenchymal stromal cells in cancer therapy. Cytotherapy **18**, 1435–1445 (2016). https://doi.org/10.1016/j.jcyt.2016.09.003
47. K. Le Blanc, O. Ringdén, Immunobiology of human mesenchymal stem cells and future use in hematopoietic stem cell transplantation. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant **11**, 321–334 (2005). https://doi.org/10.1016/j.bbmt.2005.01.005
48. I.T. Cavarretta, V. Altanerova, M. Matuskova, L. Kucerova, Z. Culig, C. Altaner, Adipose tissue–derived Mesenchymal stem cells expressing Prodrug-converting enzyme inhibit human prostate tumor growth. Mol Ther **18**, 223–231 (2010). https://doi.org/10.1038/mt.2009.23
49. A.I. Caplan, S.P. Bruder, Mesenchymal stem cells: Building blocks for molecular medicine in the 21st century. Trends Mol Med **7**, 259–264 (2001)
50. T. Sadhukha, T.D. O'Brien, S. Prabha, Nano-engineered mesenchymal stem cells as targeted therapeutic carriers. J Control Release **196**, 243–251 (2014). https://doi.org/10.1016/j.jconrel.2014.10.015
51. B. Layek, T. Sadhukha, J. Panyam, S. Prabha, Nano-engineered Mesenchymal stem cells increase therapeutic efficacy of anticancer drug through true active tumor targeting. Mol Cancer Ther **17**, 1196–1206 (2018). https://doi.org/10.1158/1535-7163.MCT-17-0682
52. F. Petrella, V. Coccè, C. Masia, M. Milani, E.O. Salè, G. Alessandri, E. Parati, F. Sisto, F. Pentimalli, A.T. Brini, A. Pessina, L. Spaggiari, Paclitaxel-releasing mesenchymal stromal cells inhibit in vitro proliferation of human mesothelioma cells. Biomed Pharmacother **87**, 755–758 (2017). https://doi.org/10.1016/j.biopha.2017.01.118
53. S. Yao, X. Li, J. Liu, Y. Sun, Z. Wang, Y. Jiang, Maximized nanodrug-loaded mesenchymal stem cells by a dual drug-loaded mode for the systemic treatment of metastatic lung cancer. Drug Deliv **24**, 1372–1383 (2017). https://doi.org/10.1080/10717544.2017.1375580
54. X. Li, P. Zhang, X. Liu, P. Lv, Expression of interleukin-12 by adipose-derived mesenchymal stem cells for treatment of lung adenocarcinoma. Thorac Cancer **6**, 80–84 (2015)

55. X. Zhang, L. Zhang, W. Xu, H. Qian, S. Ye, W. Zhu, H. Cao, Y. Yan, W. Li, M. Wang, W. Wang, R. Zhang, Experimental therapy for lung cancer: Umbilical cord-derived mesenchymal stem cell-mediated interleukin-24 delivery. Curr Cancer Drug Targets **13**, 92–102 (2013)
56. M. MacFarlane, TRAIL-induced signalling and apoptosis. Toxicol Lett **139**, 89–97 (2003)
57. A. Mohr, M. Lyons, L. Deedigan, T. Harte, G. Shaw, L. Howard, F. Barry, O'Brien T, Zwacka R, Mesenchymal stem cells expressing TRAIL lead to tumour growth inhibition in an experimental lung cancer model. J Cell Mol Med **12**, 2628–2643 (2008). https://doi.org/10.1111/j.1582-4934.2008.00317.x
58. M.R. Loebinger, A. Eddaoudi, D. Davies, S.M. Janes, Mesenchymal stem cell delivery of TRAIL can eliminate metastatic cancer. Cancer Res **69**, 4134–4142 (2009). https://doi.org/10.1158/0008-5472.CAN-08-4698
59. X. Yang, J. Du, X. Xu, C. Xu, W. Song, IFN-γ-secreting-Mesenchymal stem cells exert an antitumor effect in vivo via the TRAIL pathway. J Immunol Res **2014**, 1–9 (2014). https://doi.org/10.1155/2014/318098
60. L.S. Krassikova, S.S. Karshieva, I.B. Cheglakov, A.V. Belyavsky, Combined treatment, based on lysomustine administration with mesenchymal stem cells expressing cytosine deaminase therapy, leads to pronounced murine Lewis lung carcinoma growth inhibition. J Gene Med **18**, 220–233 (2016). https://doi.org/10.1002/jgm.2894
61. T. Matsuzuka, R.S. Rachakatla, C. Doi, D.K. Maurya, N. Ohta, A. Kawabata, M.M. Pyle, L. Pickel, J. Reischman, F. Marini, D. Troyer, M. Tamura, Human umbilical cord matrix-derived stem cells expressing interferon-beta gene significantly attenuate bronchioloalveolar carcinoma xenografts in SCID mice. Lung Cancer Amst Neth **70**, 28–36 (2010). https://doi.org/10.1016/j.lungcan.2010.01.003
62. Q. Chen, P. Cheng, T. Yin, H. He, L. Yang, Y. Wei, X. Chen, Therapeutic potential of bone marrow-derived mesenchymal stem cells producing pigment epithelium-derived factor in lung carcinoma. Int J Mol Med **30**, 527–534 (2012). https://doi.org/10.3892/ijmm.2012.1015
63. J. Du, Y. Zhang, C. Xu, X. Xu, Apoptin-modified human mesenchymal stem cells inhibit growth of lung carcinoma in nude mice. Mol Med Rep **12**, 1023–1029 (2015). https://doi.org/10.3892/mmr.2015.3501
64. H. Xin, M. Kanehira, H. Mizuguchi, T. Hayakawa, T. Kikuchi, T. Nukiwa, Y. Saijo, Targeted delivery of CX3CL1 to multiple lung tumors by Mesenchymal stem cells. Stem Cells **25**, 1618–1626 (2007)
65. D.S. Chulpanova, K.V. Kitaeva, L.G. Tazetdinova, V. James, A.A. Rizvanov, V.V. Solovyeva, Application of Mesenchymal stem cells for therapeutic agent delivery in anti-tumor treatment. Front Pharmacol **9**, 259 (2018). https://doi.org/10.3389/fphar.2018.00259
66. J. Luetzkendorf, L.P. Mueller, T. Mueller, H. Caysa, K. Nerger, H.-J. Schmoll, Growth inhibition of colorectal carcinoma by lentiviral TRAIL-transgenic human mesenchymal stem cells requires their substantial intratumoral presence. J Cell Mol Med **14**, 2292–2304 (2010). https://doi.org/10.1111/j.1582-4934.2009.00794.x
67. L.S. Sasportas, R. Kasmieh, H. Wakimoto, S. Hingtgen, J.A.J.M. van de Water, G. Mohapatra, J.L. Figueiredo, R.L. Martuza, R. Weissleder, K. Shah, Assessment of therapeutic efficacy and fate of engineered human mesenchymal stem cells for cancer therapy. Proc Natl Acad Sci **106**, 4822–4827 (2009). https://doi.org/10.1073/pnas.0806647106
68. J. Galipeau, L. Sensébé, Mesenchymal stromal cells: Clinical challenges and therapeutic opportunities. Cell Stem Cell **22**, 824–833 (2018). https://doi.org/10.1016/j.stem.2018.05.004
69. C.M.F. Gomes, The dual role of mesenchymal stem cells in tumor progression. Stem Cell Res Ther **4**, 42 (2013). https://doi.org/10.1186/scrt189
70. W.J. Scott, J. Howington, S. Feigenberg, B. Movsas, K. Pisters, American College of Chest Physicians. Treatment of non-small cell lung cancer stage I and stage II: ACCP evidence-based clinical practice guidelines (2nd edition). Chest **132**, 234S–242S (2007). https://doi.org/10.1378/chest.07-1378
71. D. Galetta, A. Borri, R. Gasparri, F. Petrella, L. Spaggiari, Surgical techniques and long-term results of pulmonary artery reconstruction in patients with lung Cancer. Ann Thorac Surg **100**, 1196–1202 (2015). https://doi.org/10.1016/j.athoracsur.2015.04.124
72. D. Galetta, A. Cesario, S. Margaritora, V. Porziella, A. Piraino, R.M. D'Angelillo, M.A. Gambacorta, S. Ramella, S. Trodella, S. Valente, G.M. Corbo, G. Macis, A. Mule, V. Cardaci, S. Sterci, P. Granone, P. Russo, Multimodality treatment of unresectable stage III non-small cell lung cancer: Interim analysis of a phase II trial with preoperative gemcitabine and concurrent radiotherapy. J Thorac Cardiovasc Surg **131**, 314–321 (2006). https://doi.org/10.1016/j.jtcvs.2005.07.044
73. D. Planchard, S. Popat, K. Kerr, S. Novello, E.F. Smit, C. Faivre-Finn, T.S. Mok, M. Reck, P.E. Van Schil, M.D. Hellmann, S. Peters, Metastatic non-small cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol **29**, iv192–iv237 (2018). https://doi.org/10.1093/annonc/mdy474
74. F. Petrella, I. Rimoldi, G. Facchetti, L. Spaggiari, Novel platinum agents and mesenchymal stromal cells for thoracic malignancies: State of the art and future perspectives. Expert Opin Ther Pat **28**, 813–821 (2018). https://doi.org/10.1080/13543776.2018.1528234
75. F. Papaccio, F. Paino, T. Regad, G. Papaccio, V. Desiderio, V. Tirino, Concise review: Cancer cells, Cancer stem cells, and Mesenchymal stem cells: Influence in Cancer development: Stem cells-Cancer stem cells interplay. Stem Cells Transl Med **6**, 2115–2125 (2017). https://doi.org/10.1002/sctm.17-0138
76. B. Zhang, H. Shan, D. Li, Z.-R. Li, K.-S. Zhu, Z.-B. Jiang, The inhibitory effect of MSCs expressing TRAIL as a cellular delivery vehicle in combination with cisplatin on hepatocellular carcinoma. Cancer Biol Ther **13**, 1175–1184 (2012). https://doi.org/10.4161/cbt.21347
77. M.R. Green, G.M. Manikhas, S. Orlov, B. Afanasyev, A.M. Makhson, P. Bhar, M.J. Hawkins, Abraxane®, a novel Cremophor®-free, albumin-bound particle form of paclitaxel for the treatment of advanced non-small-cell lung cancer. Ann Oncol **17**, 1263–1268 (2006)
78. J. Hu, S. Fu, Q. Peng, Y. Han, J. Xie, N. Zan, Y. Chen, J. Fan, Paclitaxel-loaded polymeric nanoparticles combined with chronomodulated chemotherapy on lung cancer: In vitro and in vivo evaluation. Int J Pharm **516**, 313–322 (2017). https://doi.org/10.1016/j.ijpharm.2016.11.047
79. T.E.G. Krueger, D.L.J. Thorek, S.R. Denmeade, J.T. Isaacs, W.N. Brennen, Concise review: Mesenchymal stem cell-based drug delivery: The good, the bad, the ugly, and the promise: MSC-based drug delivery: Good, bad, ugly, & promise. Stem Cells Transl Med **7**, 651–663 (2018). https://doi.org/10.1002/sctm.18-0024
80. K. Antoniou, K. Karagiannis, E. Tsitoura, E. Bibaki, I. Lasithiotaki, A. Proklou, D.A. Spandidos, N. Tzanakis, Clinical applications of mesenchymal stem cells in chronic lung diseases (review). Biomed Rep (2018). https://doi.org/10.3892/br.2018.1067