


REVIEW

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Mesenchymal stem cells and cancer therapy: insights into targeting the tumour vasculature

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Abstract

A crosstalk established between tumor microenvironment and tumor cells leads to contribution or inhibition of tumor progression. Mesenchymal stem cells (MSCs) are critical cells that fundamentally participate in modulation of the tumor microenvironment, and have been reported to be able to regulate and determine the final destination of tumor cell. Conflicting functions have been attributed to the activity of MSCs in the tumor microenvironment; they can confer a tumorigenic or anti-tumor potential to the tumor cells. Nonetheless, MSCs have been associated with a potential to modulate the tumor microenvironment in favouring the suppression of cancer cells, and promising results have been reported from the preclinical as well as clinical studies. Among the favourable behaviours of MSCs, are releasing mediators (like exosomes) and their natural migrative potential to tumor sites, allowing efficient drug delivering and, thereby, efficient targeting of migrating tumor cells. Additionally, angiogenesis of tumor tissue has been characterized as a key feature of tumors for growth and metastasis. Upon introduction of first anti-angiogenic therapy by a monoclonal antibody, attentions have been drawn toward manipulation of angiogenesis as an attractive strategy for cancer therapy. After that, a wide effort has been put on improving the approaches for cancer therapy through interfering with tumor angiogenesis. In this article, we attempted to have an overview on recent findings with respect to promising potential of MSCs in cancer therapy and had emphasis on the implementing MSCs to improve them against the suppression of angiogenesis in tumor tissue, hence, impeding the tumor progression.

Keywords: Mesenchymal stem cells, Tumor microenvironment, Anti-angiogenesis, Tumor therapy

Introduction

Given the importance of cancer, research on timely diagnosis and effective treatment in cancer field is on the fast track [1, 2]. Old different cancer therapies, such as radiotherapy and chemotherapy are both harmful to normal cell and many other side effects [3, 4]. These limitations have led to the spread of studies on efficient therapeutic strategies specifically targeting malignancies [5, 6]. One type of stem cells for therapeutic approaches of cancer is

mesenchymal stem cells (MSCs). Numerous studies have previously demonstrated the potential of MSC therapy for various diseases [7]. MSCs have different advantages like simplicity of expression and differentiate into various cell types, which have caused widespread using MSCs for therapeutic applications to treat cancer and other disease. Some MSCs can be extracted from different types of tissues such as brain, kidney, and heart. In addition, these stem cells have the ability of development into mesenchymal lineages and self-renewal. MSC therapy is a sub-type of cell therapy and regenerative medicine. Other stem cells such as induced pluripotent stem cells (iPS) and pluripotent embryonic stem cells (ES) have some disadvantages, including teratoma formation and ethical concerns. Therefore, considering that MSCs do not have this

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limitations, they are frequently used for cancer therapy [8]. One of the important reason for tumor cells proliferation is tumor angiogenesis [9]. Therefore, given that MSCs can inhibit expression of anti-angiogenesis factors, attentions for utilization of targeted MSCs therapy of cancers by inhibition of angiogenesis have been raised [10].

This review paper endeavoured to go through the recent findings with regard to promising potential of MSCs in cancer therapy and have emphasis on the implementing MSCs to improve them against the suppression of angiogenesis in tumor tissue.

Biology of MSC and its implication in tumors

Origin and characteristics of MSCs

In addition to bone marrow, MSCs have been extracted from multiple tissues, such as adipose tissues, skeletal muscle, dental pulp, placenta, synovial membranes and umbilical cord [11]. Some important advantages of MSCs are easily accessible, self-renewable, culturally expandable in vitro, and being multipotent [12]. Some other biological characteristics, including immune regulatory, potential of differentiation, and secretion of trophic factors that help tissue remodelling have caused MSCs suitable for cancer therapy [13, 14]. MSCs operate immunomodulatory functions by different ways. They express low levels of costimulatory CD80, CD86, CD40 proteins and major histocompatibility complex (MHC) class I and no MHC class II molecules. MSCs have a role in upregulating the secretion of IL-4 and IL-10 (immune suppression cytokines). MSCs secrete different factors in site of injury that have ability in regenerative processes by inducing angiogenesis, modulating immune system, and protecting cells from apoptotic cell death [15].

Mobilization from the bone marrow and other organs is the very necessary role for MSC homing to tumors. Endogenous MSCs have been demonstrated to mobilize from the bone marrow and other tissues to the peripheral tissues through various injury conditions, such as normoxia, inflammatory conditions, and hypoxia [16]. It has been revealed that a normal role of MSC is the potential to migrate and repair wounded tissue. This factor of wound healing originates with migration toward inflammatory signals caused by the injured tissue [17]. Migration is implemented through a wide range of mediators secreted by MSCs [18]. These researches conferred a validation for the development of therapeutic approaches that have role in the tumorigenic characteristics of MSCs by engineering them as delivery vehicles of antitumor compounds.

Tumor microenvironment influences on the plasticity of MSC phenotype and responses through diverse stimuli, leading to polarization of MSCs and obtaining

specific characteristics [19]. Regarding the inflammatory settings, MSCs are phenotypically are categorized into pro-inflammatory MSC-1 cells (developed in response to priming by toll-like receptor (TLR) 4) and anti-inflammatory MSC-2 cells (developed in response to priming by TLR3) [20]. Priming with TLR4 stimulates the development of pro-inflammatory MSC-1 phenotype that is distinguished by higher production of inflammatory cytokines like interleukin (IL)-6 and IL-8 [21]. The pro-inflammatory MSC-1 phenotype was shown to be incapable of suppressing the expansion and proliferation of other cells [22]. The plasticity of MSCs influence on the released mediators by these cells and thereby their function.

MSCs and tumor microenvironment

Numerous mediators have been identified that play critical roles in the cross-talk between MSCs, tumor microenvironment, and tumor cells (Table 1). By inducing various signalling pathways, MSCs possess different functions on the cells in tumor microenvironment. Naïve MSCs can inhibit Wnt signalling pathways through modulating the Dickkopf-related protein 1 (DKK1) released by tumor cells, and subsequently downregulating c-Myc and Cyclin D2 and upregulated expression of P21CIP1 and P27KIP1, leading to tumor cells suppression [23–25]. Naïve MSCs can cause apoptosis of the vascular endothelial cells by inhibiting angiogenesis [26] (Fig. 1). MSCs have some adverse effect on tumor cells, such as differentiation of vascular endothelial cells in melanoma [27], enhancing the expansion of gastric cancer cell lines [28], inducing cancer stem cells (CSCs) that has been associated with increased metastasis, tumorigenesis, and recurrence of tumors [29]. Additionally, MSCs release chemokines, such as CXCR4 [30], CCL5, intracellular adhesion molecules (ICAMs) and vascular cell adhesion molecules (VCAMs) [31, 32]. MSCs isolated from mouse lymphomas (L-MSCs) release CCL2 and promote cancer cell proliferation and also recruitment of immunosuppressive cells, including CD11b+Ly6G+neutrophils, F4/80+ macrophages to lymphoid tissues [33]. Previous studies demonstrated that MSCs from breast cancer, when co-cultured with peripheral blood mononuclear cells (PBMC), resulted in development of regulatory T cells [34]. Moreover, MSCs derived from breast cancer tissues generate high amount of immunosuppressive mediators such as IL-4, transforming growth factor (TGF)- β and IL-10 [34]. Increased levels of bone morphogenetic proteins (BMPs), including BMP2, BMP4, and BMP6 in ovarian cancer derived-MSCs can promote the development of CSCs. BMP2 was detected to be involved in promoting the phospho-SMAD 1/5 protein levels in the SKOV3 cells (ovarian cancer cell line) and

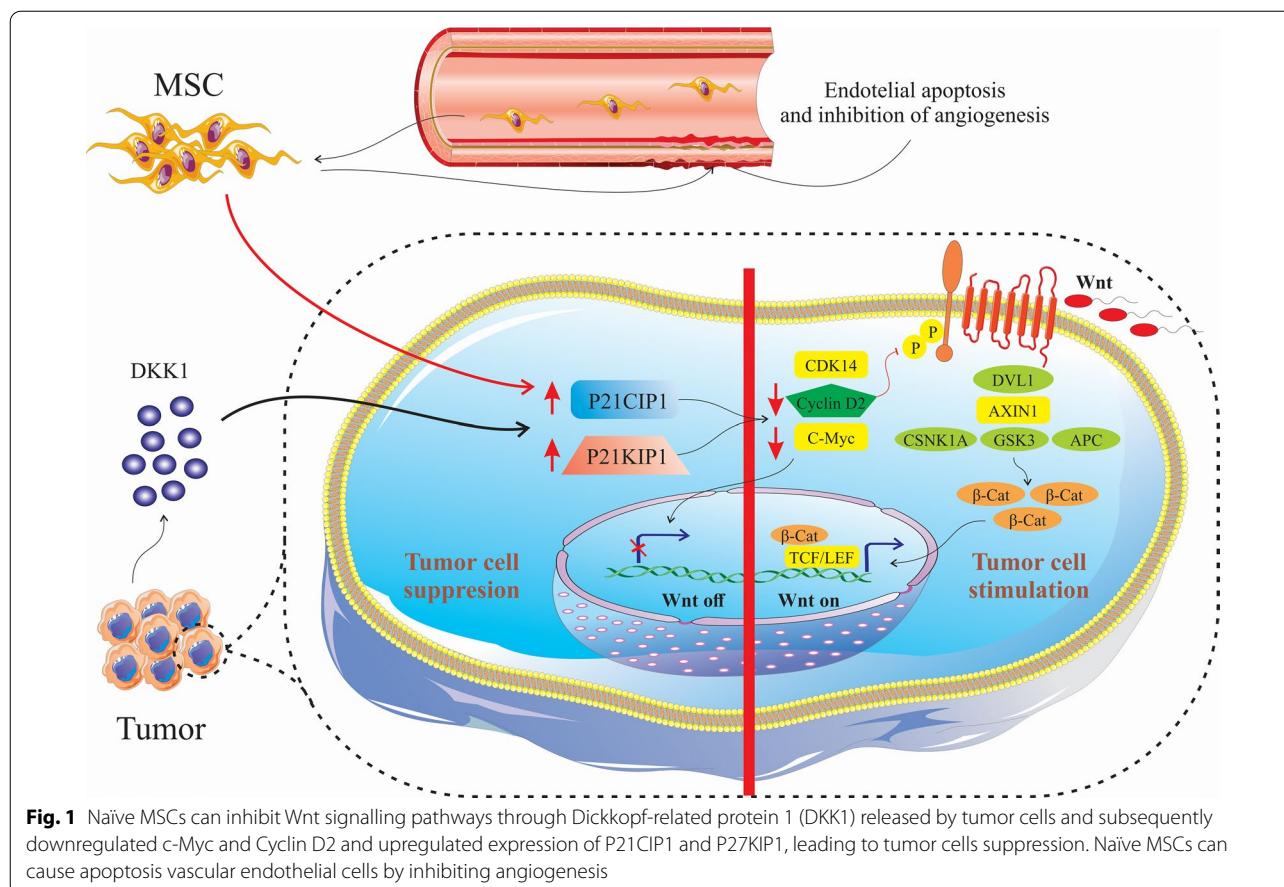
Table 1 Cytokines and mediators secreted from MSCs during cross-talk with tumor cells responsible for homing, growth, and stemness in tumor cells

Effect	Mediator type	Mediator	References	
Homing of MSC in tumor	Cytokine	TNF- α	[132, 133]	
		IFN- γ	[132]	
		IL-1 β	[132]	
		IL-6	[29]	
		IL-8	[134]	
	Chemokine	SDF-1/CXCR4	[135, 136]	
		MCP-1	[137]	
		GRO- α	[134]	
	Growth factor	TGF- β	[138]	
		PGF	[139]	
PDGF		[132]		
HGF		[132]		
MSC-mediated tumor growth (metastasis and proliferation)	Cytokine	IL-6	[38, 140]	
		IL-10	[140]	
		TNF- α	[140]	
	Chemokine	CCL5	[31, 141]	
		CXCL1	[142]	
		CXCL2	[142, 143]	
		CXCL3	[142]	
		CXCL5	[142]	
		CXCL6	[142]	
		CXCL8	[116, 142]	
		CCL2	[142]	
		CCL8	[142]	
		CCL20	[142]	
		Growth factor	IGF-1	[144]
			TGF β 1	[145]
HGF	[146]			
MSC-mediated cancer cell stemness	Cytokine	IL-1 α	[147]	
		IL-1 β	[147]	
		IL-6	[147, 148]	
	Chemokine	CXCL1	[147]	
		CXCL8	[147]	
		CXCL1	[29]	
		CXCL5	[29]	
		CXCL6	[29]	
		CXCL7	[29]	
	Growth factor	CCL5	[141]	
		BMP4	[35]	
		PGE2	[147]	

MSC Mesenchymal stem cell, TNF tumor necrosis factor, IFN interferon, IL interleukin, SDF stromal cell-derived factor, MCP monocyte chemoattractant protein, GRO growth-regulated oncogene, TGF transforming growth factor, PGF placental growth factor, PDGF platelet-derived growth factor, HGF hepatocyte growth factor, BMP4 bone morphogenetic protein, IGF-1 insulin-like growth factor-1, PGE2 prostaglandin E2

BMP2 inhibitor (Noggin) suppressed this process. [35]. In fact, BMP2 activates phospho-SMAD signalling in ovarian cancer and is involved in triggering the epithelial-to-mesenchymal transition [36] (Fig. 2).

The communication of MSCs with tumor microenvironment might either suppress or promote the tumor progression. Although most of researches aiming to exert MSCs in cancer therapy have focused on the tumor



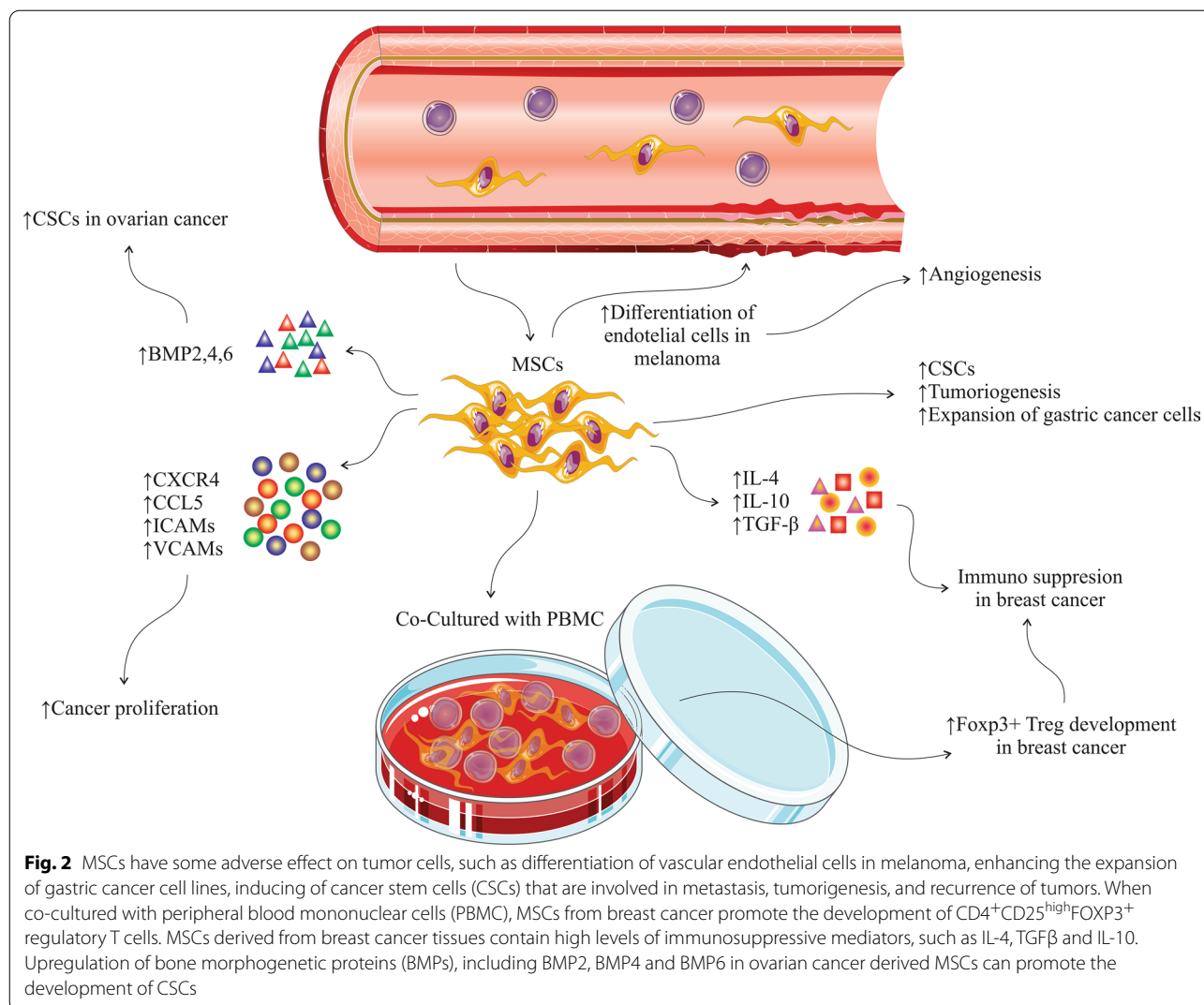
suppressor properties of MSCs, these cells may also promote tumor advancement. In vivo and in vitro experiments revealed that human MSCs were able to enhance the metastasis and growth of tumor cell in a mice model of osteosarcoma [37]. Additionally, MSCs were detected to promote the cancerous behaviour of tumor cells in ovarian cancer [38], colon cancer [39], and gastric cancer [40]. MSCs accelerate the tumor progression mainly through enhancing metastasis, contributing to epithelial–mesenchymal transition, and disturbing the immune surveillance. MSCs might show adverse effects during tumor therapy based on the number of MSCs injected, source or origin of MSC, differentiation level of MSC, and tumor type. As a consequence, limitations in MSC-based cancer therapy should be taken into account and further investigations needs to be performed to characterize the safety and efficacy of such therapeutic approach in tumor treatment.

MSCs exosomes therapy in tumors

Exosomes are extracellular vesicles (EVs) that are generated in the endosomal compartment of eukaryotic cells [41]. Exosomes and other EVs can be detected in tissues

and biological fluids, such as urine, blood, and cerebrospinal fluid. Exosomes predominantly contain microRNAs (miRs) and proteins surrounded with lipid bilayer membrane [42, 43]. Other RNA forms like nucleolar RNA, long noncoding RNA and ribosomal RNA and also fragments of DNA may be found in the exosomes [44]. Studies have demonstrated that secreted exosomes can be directed to other cells through proteins located at surface of cells such as tetraspanins [45]. MSCs produce exosomes that can regulate tumor cell angiogenesis, metastasis and proliferation by controlling a number of cellular pathways [46]. Additionally, MSC-derived exosomes can play paracrine role by transferring signalling molecules. MSC-derived exosomes have supporting or suppressing impact on the tumor development.

Prodrug suicide gene therapy by different MSCs can deliver the chemotherapeutic drug and activate the prodrug directly within the tumor to generate toxic products for tumor cells [47, 48]. Adipose tissue derived MSCs expressing thymidine kinase of Herpes simplex virus with ganciclovir as a prodrug TK HSV-MSC/ganciclovir system [49] was developed to generate MSCs that were able to act as a tumor-specific prodrug



converting cellular vehicle for targeted chemotherapy. Additionally, MSCs engineered to express fused yeast cytosine deaminase:Uracil phosphoribosyl transferase (γ CD::UPRT) with chemotherapeutic compound 5-fluorocytosine (5-FC) as a prodrug- γ CD:UPRT-MSC/5-FC system in human colon cancer [47]. This system indicated the potential of adipose tissue derived MSCs as favourable delivery vehicles for prodrug converting gene. In another study, researchers prepared MSCs from various tissues and transduced them with the γ CD:UPRT gene. γ CD::UPRT-MSCs released prodrug mRNA and exosomes that were internalized into tumor cells, and then intracellular translation of mRNA to a protein that played a role in tumor cell death [50]. Paclitaxel (PTX) is an effective antitumor agents against cancer [51]. Kolimuthu et al. [52] loaded PTX in MSCs exosome mimetics and demonstrated cytotoxicity of MDA-MB-231 breast cancer cell lines when treated

with PTX-MSC-Ems (Table 2). In a recent study, nano-sized vesicles secreted by MSC were used to encapsulate doxorubicin and determined for potential therapy in colon adenocarcinoma, resulting in introduction of MUC1 aptamer-decorated MSC-derived exosomes as a promising platform for cancer therapy [53]. Overall, such attempts to increase the efficacy of chemotherapy through employing the tumor targeting characteristic of MSCs could hopefully increase the chance of cancer therapy in different solid tumors.

The composition and biological activities as well as the therapeutic potential of MSC-derived EVs in cancer have been extensively reviewed by Xunian and Kalluri [54]. The virtual impression of MSC-derived exosomes on the tumor cells is still debating and might be tumor supporting or suppressing effects, based on different issues, like the origin of the exosomes, components of the exosomes, and tumor type.

Table 2 Strategies toward inhibition of angiogenesis to treat malignancies

Strategy	Mechanism	Therapeutic	References
Exosomal miRNAs	Exosomes can regulate tumor cell angiogenesis, metastasis and proliferation by controlling a number of cellular pathways	Exosomes have supporting or suppressing impact tumor development	[47, 48]
Inhibition of VEGF	Suppression of progression and growth of ECs	Bevacizumab, a VEGF neutralizing mAb Soluble receptor of VEGF, VEGF-TrapR1R2	[78] [81]
Inhibition of signal transduction by targeting receptor tyrosine kinases	Repression of receptor tyrosine kinases	(2-(3,4-Dihydroxyphenyl)-6,7-dimethylquinoline-HCl and (E)-3-(3,5-Diisopropyl-4-hydroxyphenyl)-2-[(3-phenyl-n-propyl) amino-carbonyl] acryl-onitrile)	[97]
MSC therapy	Regulation of pro-angiogenic and anti-angiogenic compounds	MSCs-based delivery of endostatin	[103]

VEGF vascular endothelial growth factor, ECs endothelial cell, mAb monoclonal antibody, MSC mesenchymal stem cells

Novel MSC therapy in other solid tumors

Graphene oxide (GO) is a versatile platform for bioimaging, tissue engineering, gene delivery, and drug delivery, that is functionalized with carboxylic acid [55]. The important feature of GO is large area and this feature has caused to use GO in wide range of therapeutics. Suryaprakash et al. [55] first loaded GO with two types of drugs (doxorubicin and mitoxantrone) and then loaded drug-GO complex on MSCs surface. The result of this study demonstrated MSC-GO is an useful mean to carry the drugs to the tumor cells and kill the cancer cells [55]. Human amniotic fluid mesenchymal stem cells (hAF-MSCs) obtained from second trimester or end of pregnancy by amniocentesis [56] have been used for some human life-threatening disease. Ghoizadeh et al. [57] showed that co-culture of hAF-MSCs with SKOV3 ovarian cancer cells can cause release of soluble factors and efficient anticancer effect. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) increase apoptosis in cancer cells without side effect on normal cells [58, 59]. Different histone deacetylase inhibitors (HDACi) such as valproic acid (VPA), suberanilohydroxamic acid (SAHA) and panobinostat have effect on the malignant glioma [60, 61]. hAF-MSCs expressing TRAIL have therapeutic effect against different cancers [62]. Choi et al. [63] combined treatment with hAF-MSCs expressing TRAIL and panobinostat, which increased apoptosis and suppressed viability of glioma cells. Using PTX in the treatment of

tumors has an important limitation, which is their severe dose-limiting toxicities. A study has shown that nano-engineered MSCs can be contributing in intra-tumoral distribution of the therapeutic agent [64]. Layek et al. [64] have demonstrated that combined nano-engineered MSCs with PTX anti-cancer drug can provide a better efficacy in tumor cells death than MSCs lacking nano-engineered procedures. All these investigations implicate on the application of a strengthened MSC in treatment of different tumor types.

Cancer therapy and angiogenesis

The process of tumor angiogenesis

In recent years, different treatment strategies have been proposed for the treatment of cancers. Generation of new blood vessels (neoangiogenesis) from pre-existing vasculature during the embryogenesis is characterized as a fundamental process that leads to development of concomitant vascular network [65]. Neoangiogenesis in common physiological state is considered a stable event that are rarely observed in adults. That notwithstanding, angiogenesis might be occurred in adults during pregnancy as well as the ovarian corpus luteum development [66]. In addition, neoangiogenesis is a critical key event in pathological conditions, such as tumor progression [67]. However, there is unique characteristics of tumor cells vessels compared with normal vessels with respect to architecture and structure [68]. Tumor vasculature

commonly lacks organization and is and mazy, and usually has no organized layers of venules, arterioles, and capillaries. With regard to molecular structure, ECs of tumor tissues have been reported to highly express Placental growth factor (PlGF), CD137, CD109, and CD276. That notwithstanding, the origin of ECs in tumor tissues has not been clearly revealed [69]. However, studies have established that endothelial progenitor cells (EPCs) are primarily involved in the angiogenesis of tumor tissue [69]. An imbalance between factors triggering and suppression angiogenesis in tumor microenvironment is required for initiation of angiogenesis. The most key triggering factors of angiogenesis in a tumor tissue include MMPs, vascular endothelial growth factor-A (VEGF-A), fibroblast growth factor (FGF), hepatocyte growth factor (HGF), and PlGF, [70, 71]. Conversely, the angiogenic suppressors include thrombospondins (THSBs), IL-12, endostatin, and angiostatin [72].

Anti-angiogenesis tumor therapy through inhibition of VEGF

Considering the participation of angiogenesis and vascularization the development and progression of cancers, it seems that inhibition of tumor angiogenesis confers a therapeutic strategy. Basically, inhibition of growth factors/signalling pathways necessary for progression and growth of ECs is regarded as a vital approach to supers the tumor angiogenesis [67, 73]. It has been shown that vascular endothelial growth factor (VEGF) plays a key modulatory function during the process of angiogenesis not only in the physiological conditions, but also in the pathological settings [74]. Moreover, it was reported that VEGF-null embryonic stem cells could not develop construct teratoma in a recipient after inoculation in testis capsule, suggesting that VEGF and angiogenesis are fundamentally involved in the tumor growth and development. Hypoxic conditions in different areas of cancers cause upregulation of VEGF in the tumor microenvironment, implying to the expedited growth of cancer cells and defective blood flow [75].

It was shown that treatment of mice with human tumor by an anti-VEGF neutralizing monoclonal antibody (mAb) resulted in fundamental repression of the tumor expansion in the animal [76]. Bevacizumab, a humanized variant of a VEGF neutralizing mAb [77], was approved by the Food & Drug Administration (FDA) as the first anti-angiogenic treatment for therapy with standard of care (SOC) in subjects suffering from metastatic colorectal cancer (CRC) [78]. Afterwards, bevacizumab was then approved to have positive therapeutic effects in individuals with non-small-cell lung cancer (NSCLC) [79] and metastatic breast cancer (BC) [80].

Upon successful experiences, several agents inhibiting the VEGF pathway have been developed that are in the clinical trial evaluations, which target either VEGF or the related receptor. AS a chimeric soluble receptor of VEGF, VEGF-TrapR1R2 contain functional sections of VEGFR1 and VEGFR2 [81], and thereby, cab attach to and neutralize circulating VEGF molecules. Additionally, clinical studies on animal models have reported that VEGF-TrapR1R2, in comparison to other VEGF receptor blockers such as DC101, may have better anti-tumor function.

Inhibition of VEGF signalling pathway by blocking the VEGFR has been accompanied with promising outcomes [82, 83]. For example, receptor tyrosine kinase inhibitors (RTKIs) like linifanib [84, 85], cabozantinib [86], axitinib [87], tivozanib [88], vandetanib [89], sunitinib [90], pazopanib [91], and sorafenib [92] have been assessed. Although the clinical studies establish the positive effects of these agents on tumor repression, the exact mechanism of action of them has not been divulged yet. Studies have indicated that angiogenesis inhibitors against VEGF pathway suppress tumor development by interfering the angiogenesis of tumor tissue. That notwithstanding, these agents may act by vascular normalization, through which they function on the non-functional vessels in tumors, resulting in increased blood flow and, thereby, improved delivery of cytotoxic agents to the tumor tissue for the aim of killing tumor cells [93].

Conflicting outcomes have been approached with respect to the efficacy of VEGF inhibitors between pre-clinical models and clinical trials. Through clinical trials, it has been observed that the efficacy of mAbs might be different compared with the small anti-angiogenesis blockers. Studies have revealed that bevacizumab combined with SOC had suitable results in individuals with metastatic BC [80], CRC [78], and NSCLC [79]. In general, development of VEGF blockers as well as anti-angiogenic agents have conferred a promising therapeutic tool for tumors.

Besides VEGF blockers, vascular disrupting agents (VDAs) have also been developed to inhibit angiogenesis. VDAs action in inhibition of the tumor development is through stimulation vascular collapse, leading to hypoxia and, therefore, cancer cells necrosis [94]. As a VDA, ASA404 is a flavonoid factor and stimulates apoptosis in tumor ECs, resulting in interruption of blood flow in tumor tissues. Nowadays, ASA404 is under clinical trials in NSCLC patients [95] (Table 2). Application of vascular VDAs might be promising in repressing tumor angiogenesis, but further investigations is still needed to ensure their efficacy in the clinical use during different tumor types.

Anti-angiogenesis tumor therapy through inhibition of receptor tyrosine kinases

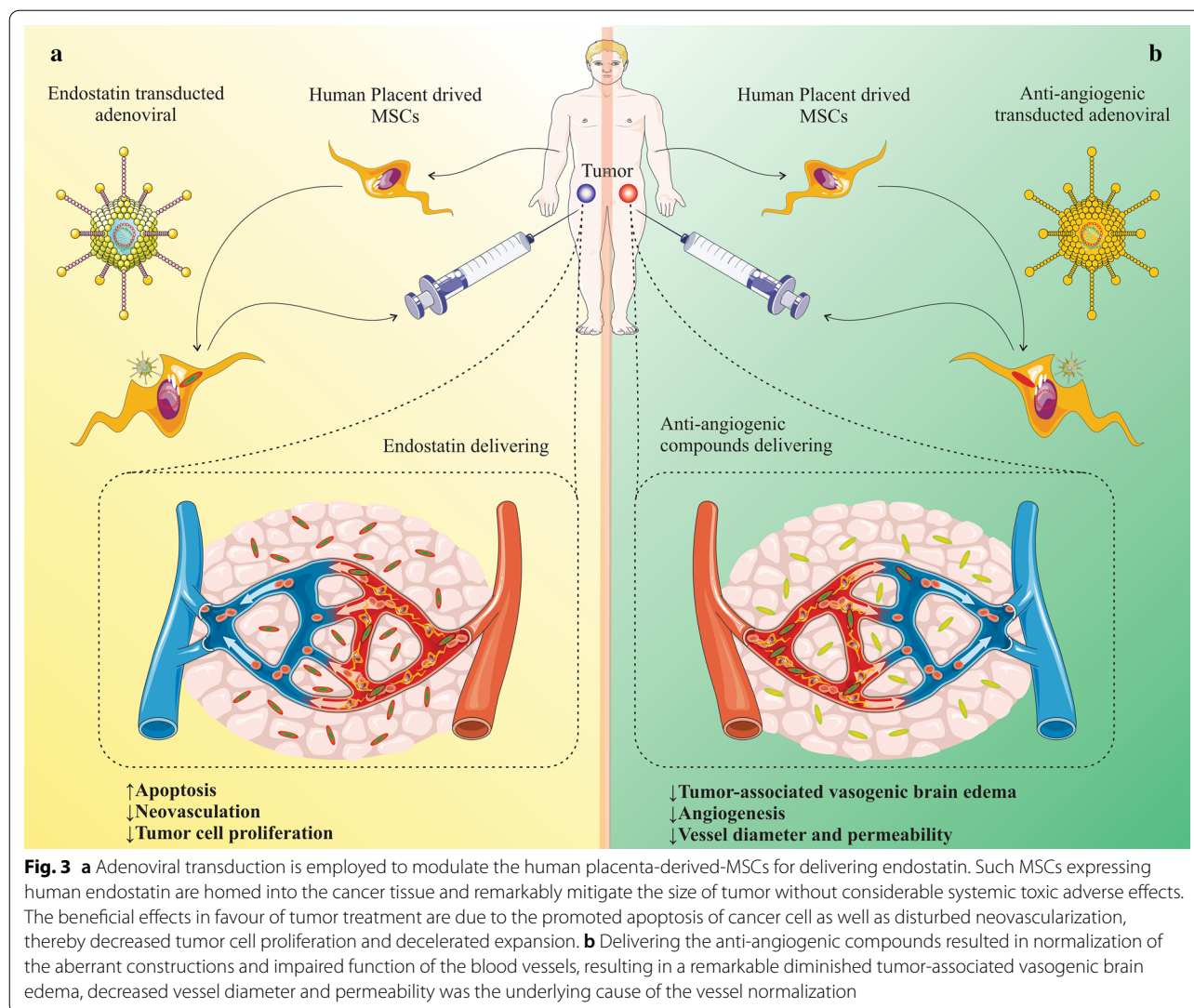
Ligation of growth factors to their corresponding receptors leads to acceleration of the process of angiogenesis, resulting in activation and signal transduction through receptor tyrosine kinases (RTKs) [96]. A number of small molecules that are involved in the prevention of the angiogenesis disturbs the phosphorylation of VEGFR-2, and thereby inhibit the expansion of ECs and development of blood vessel cells [97]. As a potential therapeutic approach, RTKs can be targeted through devising novel anti-angiogenesis factors. In this way, sorafenib, as a kinase inhibitor, are involved in prevention of tumor growth through interrupting in proliferation and antiangiogenic effects. Additionally, sorafenib has been shown to possess antitumor function according to the phase III trials in patients with hepatocellular carcinoma as well as advanced renal cell carcinoma [98]. Furthermore, sunitinib in a phase III clinical trial in gastrointestinal stromal tumor patients was accompanied with promising outcomes [99] (Table 2). Although inhibitors of RTKs have been associated with remarkable outcomes in different cancers, their general response rate is not considerably satisfying. Additionally, such agents might be toxic and accompany with resistance against the anti-angiogenic targeted agents.

MSCs-based cancer therapy by inhibition of angiogenesis

Angiogenesis is a key event involved in the perpetuation of the growth and progression of tumor cells [9]. Employing MSC vehicles can be potentially considered as one of the approaches to deliver anti-angiogenic compounds to confine the tumor expansion and metastasis. Such modified MSCs have been accompanied with a tropism to tumor tissue and can deliver antiangiogenic factors that lack unwanted adverse effects [100]. That notwithstanding, systemic and chronic delivering of the anti-angiogenic agents has been attributed with toxicity, and poor blood circulation, which reduces the delivering capacity of the chemotherapeutic drugs to the cancer cells [101]. Tumor-associated angiogenesis has been established to originate from an imbalance in the regulation of both antiangiogenic and pro-angiogenic factors along with through growth factors expressed in the tumor niche [10, 102]. As an remarkable endogenous inhibitor of the angiogenesis in the tumors, endostatin has been extensively exerted to interrupt the antiangiogenic for the aim of treating diverse malignancies [103]. In an animal study, adenoviral transduction was employed to modulate the human placenta-derived MSCs for delivering endostatin that were injected into nude mice. Such MSCs that expressed human endostatin homed

into the cancer tissue and remarkably mitigated the size of tumor without considerable systemic toxic adverse impressions. The boon effects in favour of tumor treatment underlined the promoted apoptosis of cancer cell as well as disturbed neovascularization, thereby decreased tumor cell proliferation and decelerated expansion [103] (Fig. 3a). Furthermore, delivering the anti-angiogenic compounds in a phase II clinical trial resulted in normalization of the abnormal constructions and impaired function of the blood vessels, resulting in a remarkable diminished tumor-associated vasogenic brain edema [104]. Decreased vessel diameter and permeability was the underlying cause of the vessel normalization [105, 106]. As such, promoted mural cell coating of the small vessels was another contributing issue for vessel normalization [107]. Investigations demonstrate that MSCs have the potential in localization to tumor vasculature following intratumoral injection, proposing boon features for targeted delivery of anti-angiogenic compounds, particularly in vascularized malignancies [108] (Fig. 3b).

Exosomes derived from MSCs are able to deliver miRs into the target cells with the aim of modulation of angiogenesis in tumors. Exposure of MSCs with the exosome secretion blocker GW4869 led to reduced levels of pro-angiomiRs in the MSC-derived medium [109]. These observations propose that exosomal transfer of pro-angiogenic miRs are vitally involved in MSC-associated angiogenesis and the communication between MSC and endothelial cell [109]. An anti-tumor role of intratumoral injection of MSC-derived exosomes was led to inhibition of angiogenesis in hamster buccal pouch carcinoma as a preclinical model for human oral squamous cell carcinoma [110]. It was also observed that exosome-treatment of endothelial cells resulted in promoted cytotoxicity and downmodulation of VEGF secretion and angiogenesis [110]. Other study reported that after MSCs injection, corneal neovascularization was decreased in human umbilical vein endothelial cells (HUVECs). These MSCs prevented the angiogenesis of HUVECs by upmodulating miR-211, which targeted and suppressed the expression of prospero homeobox 1 (PROX1) [111]. Other research demonstrated that MSC-derived exosomes, containing miR-16 (that target and suppress VEGF), could downmodulate the expression of VEGF in tumor cells, culminating in *in vitro* and *in vivo* suppression of angiogenesis [112]. MSC-derived exosomes may play a significant role in mediating the cell-to-cell cross-talk in the tumor microenvironment and are able to repress the angiogenesis through transferring anti-angiogenic molecules. As a result, targeted delivering of exosomes expressing miRNAs to inhibit angiogenic molecules using MSCs may provide a potential approach in hindering angiogenesis and tumor development.



The inflammatory setting of tumor microenvironment induces the local recruitment of MSCs. Pro-inflammatory mediators produced in the tumor microenvironment might influence on the phenotype and functional characteristics of MSCs that finally results in MSC-mediated angiogenesis of tumor. In vitro investigations demonstrated that tumor necrosis factor (TNF)- α , as an inflammatory cytokine, was able to stimulate the expression of VEGF in the intra-pancreatic tissue-derived (IPTD) MSCs. Moreover, the secreted VEGF was able to enhance angiogenesis in the human endothelial cells [113]. Yang et al. indicated that pro-inflammatory cytokines, such as TNF- α and interferon (IFN- γ) triggered MSCs to overexpress platelet-derived growth factor (PDGF) and VEGF,

therefore promoted angiogenic effects of MSCs on the prostate cancer in mice [114]. Additionally, both IFN- γ and TNF- α were observed to stimulate MSCs to produce higher levels of VEGF in the tumor microenvironment, leading to enhanced angiogenesis in colon cancer of mice [115]. Wang et al. reported that MSC-derived IL-8 (rather than CRC-derived IL-8) had a substantial effect on the pro-angiogenic properties of MSCs. In fact, MSC-derived IL-8 was able to induce angiogenesis through proliferation of HUVECs [116]. Moreover, MSC-derived IL-6 was shown to promote the secretion of endothelin-1 (ET-1) in the CRC cancer cells, leading to activation of Akt and ERK in the endothelial cells, hence upmodulate the angiogenesis of CRC cells [117]. All these data support the involvement of the

inflammatory mediators in promoting the pro-angiogenic effects of MSCs.

Clinical trials on cancer therapy underlying MSC application

Over the course of past decade, there has been a quick progression on the application of cells in treatment of cancers, and MSCs-based therapies has been on the fast track even further. Despite the general anti-tumor characteristics of MSCs, these cells conferred a potential for the personalized cell-based treatments due to the ease of availability with little invasive implementations on the individuals along with a great potential of expansion *in vitro* [118]. At the moment, according to the Clinical-Trials.gov records, there are 25 registered trials intending to utilize MSCs through diverse approaches for amelioration of tumors. The majority of such clinical trials are currently under implementation in the phase I or II that aimed to assess the adverse effects, safety and efficacy of MSC therapy in the individuals under study.

The 2013 phase I/II clinical trial conducted in the Hospital Universitario Niño Jesús, Madrid, Spain, evaluated the application of bone marrow-derived autologous MSCs that were transduced with the oncolytic adenovirus Celyvir for treating refractory and metastatic solid tumors both in adults and children [119]. In this trial, 20 subjects received weekly ($n=6$) intravenous infusion of Celyvir. This study assessed the side effects of infusions after 48 h and the clinical observations were monitored for up to 2 months after the last infusion. The trial indicated that multidoses of Celyvir had an acceptable safety as well as prosperous outcomes in treating the tumor [120, 121].

The Treatment of Advanced Gastrointestinal Tumors with Genetically Modified Autologous Mesenchymal Stromal Cells (TREAT-ME1) phase I/II clinical trial delivered herpes simplex virus thymidine kinase (HSV-TK) by genetically modified autologous MSCs as a delivery vehicle and monitored the safety and efficacy of the treatment [122]. A phase I clinical trial by The University of Texas M.D. Anderson Cancer Center applied the human IFN- β -transduced MSCs to determine the side effects, safety and the well-tolerable dose in patients with ovarian cancer. Additionally, the Mayo Clinic performed a phase I/II trial in order to identify the side effects as well as the optimal dose of MSCs transfected with oncolytic measles virus encoding NIS (MV-NIS) in the ovarian cancer. A phase I clinical trial in prostate cancer subjects, investigated the potential of allogeneic bone-marrow MSCs for homing in the target sites. The trial reported that MSCs were not able to home in tumor sites efficiently to modulate desired therapeutic functions [123].

Among the clinical trials, nine studies assessed the potential of MSCs in the amelioration of adverse outcomes during the conventional anti-cancer therapies, for example radiation-induced hemorrhagic cystitis (NCT02814864), radiotherapy-induced xerostomia (NCT03874572), anthracyclines-induced cardiomyopathy (NCT02509156), cisplatin-induced acute renal failure (NCT01275612). As a result, MSC-associated cell-based cancer therapy confer a therapeutic approach in the treatment of side effects by other anti-cancer therapies, along with direct application of MSCs in cancer therapy. Although a promising progression have been made with respect to exploring the potential of MSCs in cancer therapy, this therapeutic system is in its infancy and it will take a great deal of work to transform the pre-clinical and clinical findings into real clinical practice (Table 3).

Challenges and limitations of MSC-based cancer therapy

Although application of modified MSCs has conferred a novel and promising treatment option in cancer therapy, a number of challenging issues have been raised that might limit their use. As an instance, proper homing of MSCs in the target sites as well as their survival after engraftment are potential limitations. Biomaterial scaffolds may promote the suitable engraftment of the delivered MSCs in the target regions [124–126]. For treatment of postoperative brain cancer, researchers developed an approach to deliver the engendered MSCs on the biomaterials [127]. In this method, MSCs are seeded on the biodegradable fibrin scaffolds that are implanted into the region under surgery to combat the residual cancer cells, leading to promoting the potential of tumor-free survival. In acute myeloid leukemia, researchers applied cryogel-housed MSCs modulated to secrete a bispecific (anti-CD3 and anti-CD33) antibody for maximizing cancer immunotherapy [128]. Biomaterials may also be utilized to encapsulate the MSCs, resulting in protective ability within the host's body along with conferring the potential of releasing drugs and providing an MSC-nourishing microenvironment. Cellulose, alginate and agarose have shown favourable results in designing biomaterial microcapsules for MSCs [129–131]. It was reported that alginate-encapsulated cells in the glioblastoma patients had beneficial effects in preventing cancer growth [131]. As a consequence, use of biomaterials in the engineered MSCs systems for cancer therapy possess the potential to deter the limitations and improve the treatment efficacy, but needs further researches.

Table 3 Clinical trials aiming to cancer treatment using MSCs

Cancer type	Trial NCT number	Treatment approach	Phase	Country	Status	Year
Hematological malignancies	NCT01045382	MSC	II	Belgium	Recruiting	2010
Hematological malignancies	NCT01092026	Umbilical cord blood hematopoietic stem cell (UCB-HSC) transplantation with co-infusion of MSCs	I, II	Belgium	Unknown	2010
Myelodysplastic syndromes	NCT01129739	MSCs derived from human umbilical cord/placenta	II	China	Unknown	2010
Solid tumors metastases	NCT01844661	Bone marrow-derived autologous MSCs infected with ICOVIR5 (Celyvir)	I, II	Spain	Completed	2013
Prostate cancer	NCT01983709	Bone marrow-derived MSCs	I	US	Terminated (Study was Terminated by PI due to low accrual)	2013
Hematological malignancies	NCT02270307	Cyclophosphamide and MSC	II, III	Russia	Unknown	2014
Ovarian cancer	NCT02068794	Tissue-derived MSCs infected with oncolytic measles virus encoding thyroidal sodium iodide symporter (AdMSC-MV-NIS)	I, II	US	Recruiting	2014
Hematological malignancies	NCT02181478	Intra-osseous umbilical cord blood hematopoietic stem cells (UC-HSC) and MSC	I	US	Completed	2015
Ovarian cancer	NCT02530047	Bone marrow-derived MSCs expressing INF- β (BM-MS-C- β)	I	US	Completed	2016
Myelodysplastic syndromes	NCT03184935	Human umbilical cord-derived MSCs	I, II	China	Suspended	2017
Lung adenocarcinoma	NCT03298763	MSCs genetically engineered to express TRAIL (MSC-TRAIL)	I, II	UK	Recruiting	2019
Pancreatic cancer	NCT03608631	MSC-derived exosomes loaded with KrasG12D siRNA	I	US	Not yet recruiting	2019
Glioma	NCT03896568	Allogeneic bone marrow-derived MSCs loaded with the oncolytic adenovirus DNX-2401 (BM-MS-C-DNX2401)	I	US	Recruiting	2019

Conclusions and future directions

MSCs can preferentially migrate into the tumor tissues and have transactions with various cells in the tumor microenvironment. These cells are easily accessible, do not induce immunological responses, can be simply manipulated in vitro without requirement for immortalization; therefore, they are the most suitable choices for cell-based treatments in cancers. In spite of progress in obtaining sufficient amount of autologous and allogeneic MSCs from bone marrow, adipose tissue, umbilical cord blood, and local tissues, nonetheless, their regulation and kinetics requires further elucidation. Moreover, engineering the exosomes released by MSCs may offer another promising technique in MSC-based cancer therapy.

In spite of providing novel and attracting therapeutic system in cancer therapy, MSCs has been accompanied by a number of challenging issues and limitations. Efficient homing of MSCs in the target regions and their survival after engraftment seem to be challenges in the way toward MSC-based cancer therapy. Nonetheless, a number of recent studies have tried to utilize the biomaterials to come up with solutions for such setbacks. It should be noted that we just started to understand the

behaviours of MSCs and exert them in the clinical trials. We need to be armed with identification of new hypotheses in exertion of anti-angiogenic agents that have little adverse effects. Reaching to an optimal anti-angiogenic treatment strategy requires elaborated solutions. Manipulation of MSCs for precise delivering of the angiogenesis inhibitors could be still the first option. That notwithstanding, searching for novel molecular targets as well as agents with less side effects may help to improve the anti-angiogenesis therapy of tumors in the future.

Abbreviations

PTX: Paclitaxel; GO: Graphene oxide; hAFMSCs: Human amniotic fluid mesenchymal stem cells; TRAIL: Tumor necrosis factor-related apoptosis-inducing ligand; HDACi: Different histone deacetylase inhibitors; VPA: Valproic acid; SAHA: Suberanilohydroxamic acid; EPCs: Endothelial progenitor cells; MMPs: Matrix metalloproteinases; VEGF-A: Vascular endothelial growth factor-A; FGF: Fibroblast growth factor; HIF-1 α : Hypoxia inducible factor; mAb: Monoclonal antibody; FDA: Food & Drug Administration; SOC: Standard of care; CRC: Colorectal cancer; NSCLC: Non-small-cell lung cancer; BC: Breast cancer; RTKIs: Receptor tyrosine kinase inhibitors; VDAs: Vascular disrupting agents; RTKs: Receptor tyrosine kinases; AngGF: Angiogenic growth factor.

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Authors' contributions

SA and SSE drafted the article, MHL contributed to article figures design, MA contributed to study design, AVY revised the final manuscript and MA supervised the work and correspondence during the paper submission. All authors read and approved the final manuscript.

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Availability of data and materials

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Competing interests

The authors declare that they have no competing interests.

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