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REVIEW ARTICLE

How desirable and undesirable features of naïve or genetically reengineered mesenchymal stem cells are being considered in preclinical or clinical assays

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Summary

The implantation of adult mesenchymal stem cells (MSCs) has become a promising alternative in cancer treatments. Accordingly, in this article we revised the ultimate advances in the knowledge on the MSC-homing mechanism, the cancer cell and MSCs interactions and the microvesicles and exosomes used by malignant cells to transport and deliver pro-cancer cytokines or microRNA (miRNA), or by MSCs to favor or fight cancer progression. In addition, we analyzed the current knowledge generated by ongoing or terminated preclinical and clinical trials, using naïve MSCs as natural anti-cancer living factors or gene-engineered MSCs as cytokine delivering vehicles, where anti-cancer cytokines were chosen and the pro- cancer factors were avoided. Finally, we present some concerns about the implantation of MSCs and anti-cancer therapies and hypothesize the MSC implantation combines with conventional or new therapies to treat cancer.

Key words: *anti-cancer factors, anti-cancer treatments, cell therapy, cytokines, gene- engineered MSCs, microRNA*

Introduction

In 2012, there were 14.1 million new cancer cases and 8.2 million deaths due to cancer worldwide [1]. Furthermore, the World Health Organization (WHO) predicts that the global cancer rates could increase to 15 million by 2020 [2].

Standard therapies share the common purpose of producing a deadly effect on malignant cells [3]. Nevertheless, surgery, radiotherapy, and chemotherapy are neither totally efficacious nor specific. Moreover, conventional therapy methods produce serious iatrogenic effects [4]. Therefore, these limitations must be overcome. As an alternative, transplantation of adult MSCs as a cancer treatment is currently in accelerated progress. In this review, we present a landscape of cell and molecular characteristics of MSCs and cancer cells, their interactions and the main molecular factors involved in cancer progression and MSC´s defense response. We also discuss the function of pro- and anti-cancer factors and the way in which MSCs are reengineered, using appropriate transgenes to avoid undesirable pro-cancer effects of MSCs, and how reengineered MSCs are being used as molecular vehicles to fight cancer. We also analyze the way in which reengineered and naïve MSCs are used in preclinical and clinical studies and their results.

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Primary characteristics of cancer and new approaches to fight it

Solid tumors are composed of malignant cells plus their stroma [5,6]. All cancers have the ability to survive and invade tissues. In these abilities involved are the production of cytokines and protumoral elements that recruit tumor-associated cells. Furthermore, malignant cells exhibit self-sufficient growth signals, and they demonstrate a certain level of insensitivity to signals of growth inhibition and evasion to programmed cell death, as well as the potential to replicate in an unlimited manner, the ability to induce and cause angiogenesis, and the ability to metastasize [7]. Therefore, the approaches that have been suggested to fight cancer are as follows [3,8]: disrupt uncontrolled growth (invasion of nearby tissues and metastasis formation); disable malignant cells' ability to evade the immune system; inhibit angiogenesis led by malignant cells; disrupt the metabolic pathways used by malignant cells to obtain energy; inhibit proliferative signals; and activate apoptosis. Implementing any of these strategies involves the following three prerequisites: 1) identifying a key target molecule that forms part of the molecular mechanism of any of the aforementioned specific biological characteristics of malignant cells, and to disable its function using a specific neutralizing factor; 2) finding a specific way to deliver that neutralizing factor to every malignant cell and to any place within the organism where these cells are located; and 3) developing an ideal vehicle that specifically targets cancer cells. One strategy based on these principles includes: a) using implanted adult MSCs to take advantage of several of their outstanding natural properties; b) identifying the responsible factors and circumstances that induce MSCs to act against tumors; and c) identifying and characterizing the causes and factors responsible for the undesirable behavior of MSCs, such as cytokines, chemokines and microRNA (miR or miRNA) produced by unmodified MSCs, as well as miR and cytokines produced by tumors. One strategy that can be used to direct the MSCs to act as a specific anti-cancer weapon is by transducing or transfecting (reengineering) them with anti-cancer genes. Conversely, to avoid or minimize undesirable MSC behavior is to use complementary anti-cancer therapies and complicated-management treatments.

The role of MSCs in tumors has garnered much interest, because MSCs can find and attack cancer cells, and they can also be used as delivery vehicles for anti-cancer molecules. Adult MSCs are multipotent progenitors with a fibroblast-like morphology [9]. Due to their ability to repair organs and tissues, MSCs have been studied and introduced as therapeutic factors in regenerative medicine and cancer treatments [10]. Several biological characteristics of MSCs make of them promising tools to fight cancer. These are as follows : 1) adult MSC are relatively easy to procure, since these are present in diverse tissues and organs [10]. The most abundant, easy-to-culture, and best able to differentiate are the MSCs from adipose tissue, followed by the MSCs derived from bone marrow (BM) [11]; 2) MSCs can adhere to the culture plate, facilitating the separation of MSCs from non-MSCs [12]. In addition, MSCs are sorted by means of flow cytometry [13] or with immunobead columns [14]; 3) MSCs possess the remarkable ability known as homing, where they exhibit immunomodulatory properties; 4) MSCs exert paracrine and autocrine activities; and 5) when MSCs are implanted in the same subject from whom these cells were obtained (homologous implant), implant rejection or ethical restrictions are nonexistent [15].

Homing

Homing implies that there is a tropism to the injured site, engrafting at this site, and the subsequent secretion of cytokines [16-18]. Like injury sites, developing tumors recruit MSCs via the release of endocrine and paracrine signals, which serve as MSC chemoattractants [19]. The exact mechanism governing MSC migration – in response to an injury or oncogenesis – is still not fully characterized. One of the difficulties in studying the migratory properties of MSCs may stem from the fact that *ex vivo*-cultured MSCs often lose their abilities to express chemokine receptors (CCRs) and to respond to chemokines. In contrast, it has been observed that MSCs, which have a few numbers of reseeds, express a broad range of CCRs [20]. Figure 1 illustrates MSC homing, the chemokines secreted by tumors, and the receptors expressed by MSCs.

To reach the targeted site of injury, MSCs pass through the blood vessel endothelium. Selectins and integrins are involved in both MSC and leukocyte migration [21,22] (Figure 2).

One of the greatest challenges in cell therapy is to deliver a large quantity of viable cells to the tissue of interest in a minimally invasive manner, and with high engraftment efficiency [23]. The low and inefficient homing of delivered MSCs is thought to be a major limitation of existing MSC-based therapeutic approaches, caused predominantly by the inadequate expression of cell-surface adhesion receptors. Genetically engineered MSCs,

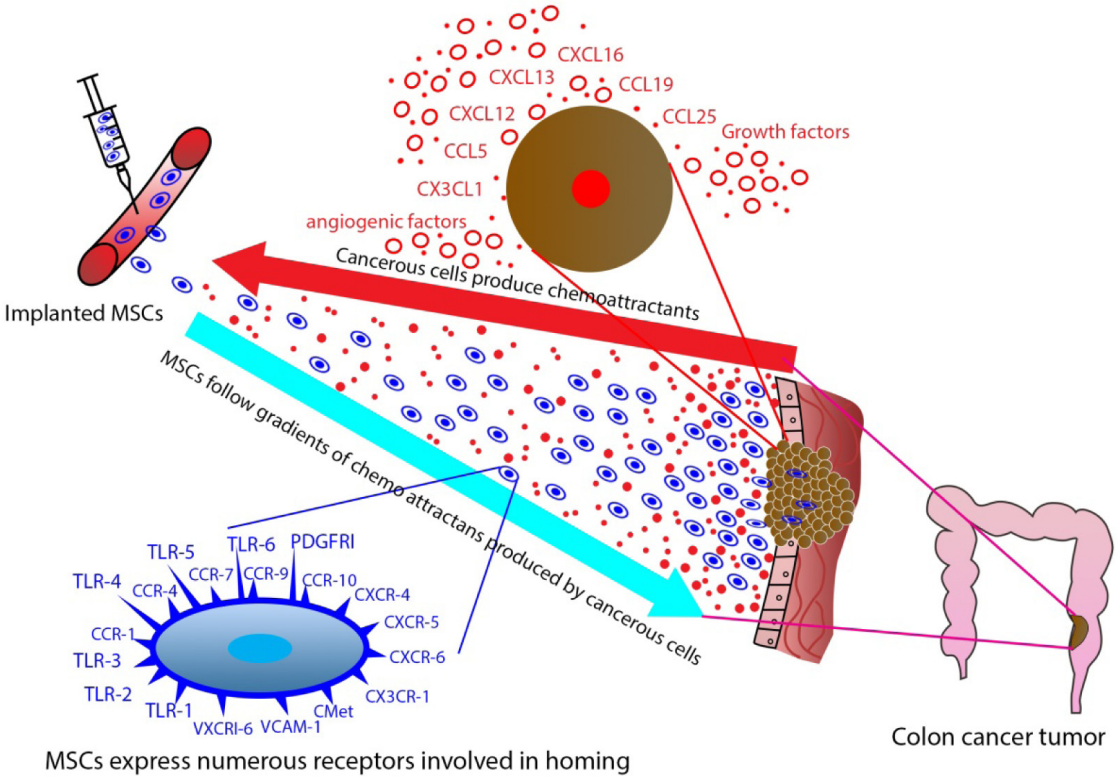

Figure 1. Schematic representation of homing [16-18]. Mesenchymal stem cells (MSCs; represented in sky blue color) are infused through a peripheral vein and homing is initiated; this is followed by concentrated gradients of cytokines, growth factors and angiogenic factors produced by cancer cells (yellow spheres [18,19]. Cytokines and the other factors are exported by cancer cells in soluble form (red points) or packaged in exosomes (EXOs) and microvesicles (tiny red circles [24-27]. On the other hand, MSCs express a broad number of receptors on their surface (for the attractant factors produced by tumors) [20].
The example in this graphic is a colon cancer tumor (yellow, bottom right). "CCR" refers to the chemokine receptor and the acronym "CXC" represents chemokines with two N-terminal cysteines that are separated by one amino acid, which is represented by the "X" in its name. "CL" is the chemokine ligand. On the other hand, c-Met is also called MET or hepatocyte growth factor receptor (HGFR). "TLR" means toll-like receptor. "VCAM-1" is the acronym for the vascular cell adhesion molecule 1.

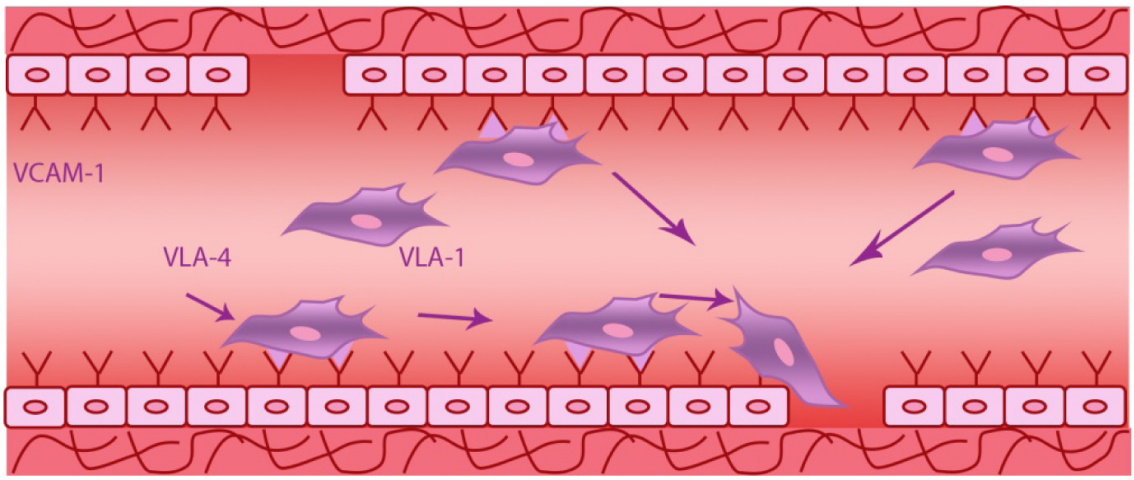

Figure 2. Rolling mechanism employed by MSCs throughout the blood vessels. Mesenchymal stem cells (MSCs) are represented by purple-colored cells being into the light of a blood-capillary segment. In this drawing, the light of the capillary endothelium appears framed by two lines of square-pale-pink cells exposing selectins in their surface (red Ys), for instance, vascular cell adhesion protein 1 [VCAM-1]. MSCs bind the endothelium-selectins through a series of molecules, as very late antigens (VLA), like VLA-1 and VLA-4 – showed in the drawing as pink triangles filling the open arms of "Ys". Once MSCs are bound to the endothelium, they roll on through the endothelium until finding a gap, from which they abandon the blood-circulatory system and arrive to a close-placed injured site. MSCs movements are represented by arrows. In cancer, the injured site is a tumor [21].

combined with the proper transgenes, can resolve this problem. Nevertheless, cancer therapies employing genetically engineered MSCs that overexpress cell-surface receptors, and which can be directed toward a particular tumor/metastasis, are still needed.

MSCs can act to favor or fight malignant cells

The current knowledge about mutual MSC/cancer interactions consists of proteins having diverse functions and miRs that act as pro- or anti-cancer factors; even some cytokines and miRs have been identified to hold dual functions as both pro- and anti-cancer factors. Nevertheless, the exact circumstances in which specific engrafted MSCs either secret pro- cancer or produce anti-cancer factors are not fully understood, and this knowledge is fundamental for improving the actual achievements of cancer cytotherapy, particularly since knowing how to properly modify MSCs can help avoid the undesirable pro-cancer effects and direct MSCs against specific kinds of cancer. Despite the above-said, considerable related information has been accumulated on the ways in which MSCs and malignant cells interact and how they then use cytokines and miRNAs, soluble or packaged into extracellular vehicles (EVs) or exosomes (EXOs). In this section, we will analyze the currently available information on cytokines and miRNAs produced by MSCs, with emphasis in the following six important matters: 1) how malignant cells, tumor microenvironment and MSCs interact with each other. 2) anti-cancer factors secreted by MSCs; 3) IL-1β, acting as a corner stone for activate pro-cancer MSCs 4) pro-cancer proteins and miRs produced by MSCs; 5) miRs and cytokines showing both pro- and anti-cancer effects, and 6) malignant cells having the capacity of make MSCs become malignant, via cytokines and miRs, soluble or packed into EVs or Exos.

How malignant cells, microenvironment and MSCs interact with each other

EVs and EXOs: conveyors of interleukins, and miRNAs

Cell–cell communication is mediated by a complex network that includes soluble factors such as cytokines, enzymes and metabolites exported from cells, membrane-bound receptors and their ligands [24], as well as various nucleic acids, like RNA messengers (mRNAs), miRs, and other non-coding RNAs (ncRNAs) [24,25]. Cell–cell communication is also mediated by EVs and EXOs, which are either shed by distant cells or exchanged by cells that make direct contact [25]. MVs and EXOs are the two classes of EVs, having interest in this review. Practically all eukaryotic cells, including MSCs [26], release MVs and EXOs [27,28]. EXOs arise from endosomes [28]. MVs, like EXOs, are released into the extracellular environment [29] by outward budding and fission of the plasma membrane [30,31]. MSC-MVs mimic the MSCs phenotype, because MSC-EVs contain membranes and cytoplasmic constituents from the original MSCs. Among these elements, a great number of proteins, mRNAs and miRs have been indentified. MSC-EVs transfer these bioactive molecules to recipient cells, exerting various effects on them like growth modulation, metastasis, and drug-response [32,33].

MSCs-derived anti-cancer factors

Knowledge on the anti-cancer role of MSCs-EVs if growing rapidly. Nevertheless, the mechanisms by means these particles inhibit tumor growth and metastasis are still uncertain; although, a considerable advance has been reached about this matter, as we will discuss below.

The MSCs' ability to induce anti-tumor activity in cancer cells has been studied in a variety of human cancer cell lines [35-39]. By using these *in vitro* models, it has been shown that MSC - EVs can block cell-cycle progression, inhibit proliferation of many cell lines; like those derived from hepatoma, Kaposi's sarcoma and ovarian cancer. These effects are mainly due to up-regulated genes related to anti-proliferative pathways [34]. As we have commented before, MSCs produce and export proteins and miRs, in a soluble form or compartmentalized into EVs [35].

Anti-cancer proteins

Examples of proteins secreted by MSCs and their functions are as follows: ribonucleoproteins, which functions include DNA replication, regulation of gene expression and metabolism of RNA; proteins, which are implicated in the transport and stability of mRNA; angiogenin, which promotes vascularization; growth factors, like, basic fibroblast growth factors (BFGF), vascular endothelial growth factor (VEGF), monocyte chemotactic protein-1 (MCP-1), receptor-2 for vascular endothelial growth factor (VEGF R2), insulin like growth factor I (IGF-I), receptor of tyrosine kinase TIE-2/TEK, interleukin 6 IL-6 [34], maintaining, in this way, intercellular communication within tumors [24].

Anti-cancer miRs

miRs are small non-coding RNAs molecules, which regulate gene expression at a post- tran-

scriptional level, by means of complementary base-pairing with countless mRNAs [40]. The discovery of the miRNA's function in the genetic exchange between cells has brought increasing attention to EXOs [41] and MVs [42]. Recently, miRNAs have been identified in EXOs, which can be taken up by neighboring or distant cells and subsequently modulate recipient cells [41]. There exists a class of miRNAs that are preferentially sorted in the EXOs, such as miR-320 and miR-150. Members of the miR-320 family are widely distributed in EXOs derived from normal tissue and tumors [43-46]. These types of molecules regulate the expression of genes that control the development, proliferation, apoptosis, and stress response [47]. On the other hand, after internalization within target cells, MVs may also deliver genetic information. MVs contain ribonucleoproteins involved in the intracellular traffic of RNA and in a select pattern of miRs [42]. Human BM-derived MSCs and liver resident stem cells (HLSCs) release MVs which shut functional miRs. Table 1 describes some examples of anti- cancer cytokines and miRs produced by MSCs.

Other MSCs-derived anti-cancer factors

Besides those mentioned in Table 1, MSCs produce many other factors, which also participate in cancer progression. Most molecules responsible of the above have not been identified, although their biological effects are well known. Some examples are as follows: bone marrow-derived MSCs inhibit human glioma growth by secreting antiangiogenic factors [58]. Bone marrow (BM)-MSCs reduce proliferation, viability and migration of non-small cell lung cancer (CSC-LC) by down-regulating translation initiation factors; like eif4e and eIF4Gi and mitogen-activated protein kinases (MAPK) signaling [59]. On the other hand, Khakoo et al. [60] showed that MSCs disable AKT activity in cancer cells, exerting anti-tumorigenic and pro-apoptotic effects on Kaposi

Table 1. Cytokines and miRs secreted by mesenchymal stem cells

Cytokines	*Biological role*	*Ref.*[1]
p38 MAPK[2]	Contributes to growth inhibition of leukemic tumor cells mediated by human umbilical cord MSCs.	[48]
IGFBPS[3]	Inhibits hepatocellular carcinoma cell proliferation via cell cycle arrest, by sequestering IGFS[4].	[49]
DKK-1[5]	Depresses WNT[6] signaling and β-catenin levels in breast cancer cells, inhibiting their growth.	[50]
(P53)[7]/BAX[8]	MCDs exported p53/BAX and induced apoptosis in lymphoblastic leukemia cells. showing that human MSCs have inhibitory effect on their neighboring malignant leukemia cells.	[51]
AKT[9]	When this was up-regulated enzyme and exported by MSCs from human umbilical cord Wharton's jelly, being packed into MVs, inhibited growth of bladder tumor T24 cells.	[52]
DIRAS3[10]	A putative tumor suppressor gene, whose function is abrogated in ovarian and breast cancer.	[33,53]
RBL-1[11]	A gene that appears to be involved in cell cycle regulation.	[33,54]
CDKN2b[12]	It is a protein encoded by the CDKN2b gene in humans, also known as multiple tumor suppressor 2 (MTS-2).	[33,55]
(MSC)[13]-(EXOs)[14]	Suppresses angiogenesis by down-regulating VEGF expression in breast cancer cells.	[56]
(IL)[15]-1β	In glioma, MSCs inhibit IL-1β, impairing tumor angiogenesis throughout antiangiogenic factors.	[58]
VEGF[16]	Exosomes derived from MSCs suppress angiogenesis by down-regulating VEGF. VEGF´s normal function is to create new blood vessels during embryonic development, new blood vessels after injury, muscle following exercise, and new blood vessels. Cancers that can express VEGF are able to grow and metastasize.	[84]
miRNAs[17]		
MSC-EXOs miR-16	Suppresses angiogenesis in breast cancer by downregulating VEGF[11]	[56]
MSC-EXOs miR-122	Delivered by EXOs. Renders hepatocellular carcinoma cells sensitive to chemotherapy.	[57]

[1]Ref., references; [2]p38 MAPK, are mitogen-activated protein kinases. [3]IGFBPS, insulin growth factor binding proteins; [4]IGFS, insulin-like growth factors: [5]DKK-1, Dickkopf-related protein 1; [6]WNT, a group of signal transduction pathways made of proteins that pass signals into a cell through cell surface receptors; [7]p53, a tumor suppressor protein; [8]BAX, a gene codifying for a Bcl-2 associated X protein (an apoptosis regulator). [9]AKT, is also called protein kinase B, [10]DIRAS3, GTP-binding RAS-like 3; [11]RBL-1, retinoblastoma-like; [12]CDKN2b, cyclin-dependent kinase inhibitor 2b transcript; [13]MSC, mesenchymal stem cells; [14]EXOs, exosomes, [15]IL, interleukin, [16]VEFG, vascular endothelial growth factor; [17]miR, microRNA

sarcoma. AKY is a gene family formed by AKT1, AKT2 AND AKT3, codifying for protein kinase B family.

It is interesting to note, from the available information, that many MSCs-derived cytokines or miRs, form part of signalization pathways, which control inflammation, cell growth or apoptosis. Therefore, it is not hard to imagine that up- or under-regulation of these gene expression, or mutations experimented by them, can result in pro-cancer instead of anti-cancer factors.

The dark side of MSCS

Pro-cancer cytokines secreted by MSCs in conditioned culture medium

MSCs can produce pro-cancer cytokines, depending on their environment. For instance, Al-Toub et al. [61] proposed that MSCs could promote cancer progression by becoming pro-inflammatory cells within the cancer stroma. Lam [62] pointed out that IL-1β is one of the mediators of the pro-inflammatory phenotype observed in MSCs exposed

Table 2. Pro-cancer cytokines produced by MSCs stimulated by IL-β1[1]

Factor	*Biological effect*	*Ref.*[2]
Chemokines		
(CCL)[3]5/CCR-5	Hematological malignancies, lymphomas, and solid tumors, favors cancer cell proliferation, metastasis, and the formation of an immuno-suppressive microenvironment.	[66]
CCL20/CCR-6	Ovarian, colorectal and pancreatic cancers. attracts tumor-promoting immuno-suppressive cells to the tumor microenvironment.	[67]
(CXCL)[4]1/CXCR2	Disregulated CXCL-1 participates in cellular transformation, tumor growth, homing, and metastasis; possible due to a constitutive activation of NF-κβ[5], which is associated to breast-, colon-, pancreatic- and ovarian-cancer and melanoma.	[68]
CXCL3/CXCR2	This axis overexpressed in prostate cancer cells, prostate epithelial cells and prostate cancer tissues may play multiple roles in prostate cancer progression and metastasis.	[69]
CXCL5/CXCR2	Increases progression of breast cancer. cxcl5 is associated with increased RAF/MEK/ERK[6] activation, and mitogen- and stress-activated protein kinase 1 (msk1) and elk-1 phosphorylation, as well as snail upregulation.	[70]
CXCL6[7]/CXCR1 or CXCR2	It is a promotor of tumor progression in vivo, under unfavorable conditions.	[71]
CXCL10 /CXCR 3	It is involved in chemotaxis, induction of apoptosis, regulation of cell growth and mediation of angiostatic effects; as well as with cancer development and metastasis.	[72]
CXCL11/CXCR3	This axis promotes growth and metastasis of human ovarian cancer.	[73]
CX3CL1/ CX3CR1	This axis has complicated functions in breast carcinogenesis and its biological role is controversial. Recently was suggested that CX3CL1 could have a pro-tumor role in breast cancer, despite its previously suggested role in enhancing anti-tumor immunity.	[74]
Interleukins		
IL-6	In head and neck squamous carcinoma a direct correlation between il-6 levels in tumor-associated endothelial cells and tumorigenicity of cancer stem cells was observed.	[75]
IL-8	IL-8 promotes angiogenic responses in endothelial cells, increases proliferation and survival of endothelial and cancer cells, and potentiates the migration of cancer cells, endothelial cells, and infiltrating neutrophils at the tumor site.	[76]
IL-23	This interleukin is an important molecular link between tumor-promoting pro-inflammatory processes and the failure of the adaptive immune surveillance to infiltrate tumors.	[77]
IL-32	Increases the proliferation of cancer cells, decreases the rate of apoptosis and enhances the growth of tumor xenografts in vivo.	[78]
TLR[8]		
TLR2, -4 AND -9	It has been suggested that pancreatic cancer cells use TLR2, -4 and-9-signaling to promote tumor cell proliferation.	[79]
CLDN[9]		
CLDN1[10]	Over-expression of CLD1 promotes colon tumorigenesis.	[80]

[1]Pro-cancer cytokines included in this table (but not receptors) were identified in MSCs by Carrero et al [38]; [2]Ref., reference; [3]CCL, ligand having a C-C motif. All CCL and CXCL work together with a receptor. In this table, we are mentioning every axis as CCL or CXCL/receptor; [4]CXCL are ligands having a C-X-C motif. [5]NF-κβ, nuclear factor KAPPA-light-chain-enhancer of activated B cells ; [6]RAF/MEK/ERK, a chain of proteins in the cell that communicates a signal from a receptor on the surface; [7]CXCL-6 is also known as granulocyte chemotactic protein-2 (GCP-2); [8]TLR, Toll-likr receptor; [9]CLDN, claudin; [10]CLDN1, integral membrane protein and a component of tight junction strands.

to tumor-derived conditioned media. MSCs from BM, which infiltrate prostate cancer, demonstrated metastatic ability by secreting cytokines, which suppress androgen receptor signaling [63,64].

IL-1β is a cornerstone for activate pro-cancer MSCs

It is known that all those factors produced by MSCs, in a soluble form or packed into MVs. nevertheless, still is very little known about those factors which induce MSCs to produce and export anti-cancer molecules. Although, some of them, like IL-1β are well known as strong stimulators to produce a variety of pro-cancer factors. furthermore, it is well known that IL-1β increases the migration and adhesion of MSCs and promotes leukocyte chemotaxis through soluble factors secreted by MSCs. Carrero et al. [65] showed that IL-1β can activates a set of MSC-genes related to biological processes, such as cell survival, cell migration, cell adhesion, chemokine production, induction of angiogenesis and modulation of the immune response. Some of these genes codify for a series of chemokines, interleukins, and Toll-like receptors, which functions in cancer have been published, by others, in an independent manner. Table 2 briefly describes the effects of cytokines and miRs secreted by MSCs stimulated by IL-1β on tumors or cancer cell lines.

Other pro-cancer cytokines and miRs produced by MSCs

MSCs may interact with tumor cells directly or indirectly through the secretion of paracrine factors [58]. This means that MSCs can favor tumor/metastasis development throughout the cytokines secreted by MSCs themselves. In addition, MSCs can become malignant under the influence of cytokines secreted by cancer cells [62]. Table 3 shows some examples of factors inducing MSCs to favor cancer progression.

miRs and metastasis

miRs are also involved in tumor metastasis when the target genes are related to the metastatic phenotypes of cancer cells. Nevertheless, research has been focused on cancer setem cells (CSCs) and malignant cells, rather than on MSCs. Thus, very few is known on the role of bioactive molecules and miRs exported by MSC-MVs, it is widely recognized the great importance that MSCs-MVs miRNAs, cytokines, and other bioactive molecules have in the pathogenesis of many kinds of cancer. Therefore, it has been pointed out that soon, all these factors will produce a great benefic impact in clinic [24].

Cytokines exported by MSCs holding controversial roles

Table 4 shows some cytokines, which can favor or fight cancer. From this table, it can be observed that cytokines dysregulation occurs widely in different types of cancer, and there is mounting evidence demonstrating several misguided mechanisms that cause cytokines and miRs dysregulation [68].

Table 3. Factors inducing MSCs[1] to favor cancer progression

Inducing factor[2]	*Effect of MSCs*	*Ref.*[3]
MDA-MB-231 BREAST cancer cells[1]	De novo secretion of the chemokine CCL5 (also known as RANTES), making breast cancer cells to enhance their motility, invasion and metastasis.	[81]
MDA-MB-231 BREAST cancer cells[1]	MSCs cultivated in MDA-MB-231 cells were differentiated into malignant carcinoma-associated fibroblasts.	[82]
Carcinoma-associated fibroblasts derived from MSCs	These fibroblasts Increased their secretion of cytokines, which suppressed the androgen receptor signaling. It is thought that these cells regulate the epithelial–mesenchymal transition and tumor-initiating stem cells in tumors. These differentiated MSCs facilitated growth of human breast and ovarian cancers as a result of being inhibited tumor cell apoptosis, enhanced cell proliferation and promoted angiogenesis.	[63,83]
Tumor micro-environment	MSCs were differentiated into endothelial-like cells or pericytes and secret VEGF, platelet-derived growth factor. In this way differentiated MSCs promoted tumor angiogenesis.	[83,84]
Activation of extracellular signal regulated kinase ½ (ERK1/2) and p38 MAPK pathway	MSC-EVs could increase tumor growth in BALB/c nu/nu mice xenograft model by enhancing VEGF expression.	[85]
(WNT)[4] pathway activation	MSC-(EVs)[5] promoted proliferation, survival, and metastasis of myeloma cells.	[86]

[1]MSCs, mesenchymal stem cells; [2]Many molecules that induce MSCs to support cancer progression have not been identified; only are known the environmental conditions; [3]Ref., references; [4]WNT, a group of signal transduction pathways made of proteins that pass signals into a cell through cell surface receptors; [5]EVs, extracellular vesicles.

Table 4. Cytokines playing a double roll, fighting or favoring tumor and metastasis progression

Cytokine	*Effect of MSCs*[1]	*Ref.*[2]
(IL)[3]-4	It acts against (TNF)[4]-α and induces the most effective immune response among several cytokines. However, IL-4 is also a tumor-promoting molecule. Its effects in tumor immunity are closely related to of its sources, as well as to its molecular and cellular environments.	[87]
IL-10	It promotes tumor incidence and progression. Conversely, IL-10 directly induces the expansion of CD8-T-cells in the tumor and enhances their cytotoxic activity.	[88]
(TGF)[5]-β	It suppresses tumors. Paradoxically, TGF-β also modulates processes such as cell invasion, immune regulation, and microenvironment modification, which cancer cells may exploit to their advantage.	[89,90]
DKK1[6]	It is known as a negative regulator of the Wnt[7], which is involved in colon cancer cell lines. On the other hand, overexpression of DKK1 was described in numerous cancers.	[91,92]

[1]MSCs, mesenchymal stem cells; [2]Ref., references; [3]IL, interleukin; [4]TNF, tumor necrosis factor; [5]TGF-β, transforming growth factor beta; [6]DKK1, this gene encodes a protein that is a member of the Dikkop family. It is a secreted protein with two cysteine rich regions and is involved in embryonic development through its inhibition of the Wnt signaling pathway; [7]Wnt, this is a name given to a group of signal transduction pathways complex.

It is noticeable that many cytokines are closely related to inflammation. Thus, inflammation is a double-end sword: on one side, under appropriate conditions immune system is a very efficient anti-cancer tool. On the other side, up-regulated or under-regulated cytokines can turn the immune system into the worst enemy of the organisms. In addition, we comment below, other circumstances that can act on MSCs, induce them to act favoring or fighting cancer.

Malignant cells make MSCs transforming into malignant cells, via cytokines and miRs

MSCs-transforming cytokines produced by cancer tumor/metastasis

Conditioned media have been valuable tools when dissecting the effects and factors – or the cancer tumors/metastases – that influence normal MSCs to undergo malignant transformation. Mishra et al. [95] showed that MSCs exposed to tumor-conditioned media from the MDA- MB-231 breast tumor line could differentiate into carcinoma-associated fibroblasts and become part of the tumor microenvironment. Furthermore, tumor cells produce factors that induce BM-MSCs and adipose-derived MSCs to transform into tumor-associated fibroblasts (TAFs). McGrail et al. [96] reported that tumor-secreted soluble factors promote MSC mobility by inducing cytoskeletal changes, which is accomplished by activating the Ras homolog gene family, member A (RhoA), pathway. RhoA is a guanosine triphosphatase (GTPase) of the Ras superfamily, which is regarded as a prominent regulatory factor, as it is involved in Ras superfamily, which is regarded as a prominent regulatory factor, as it is involved in such processes such as the regulation of cytoskeletal dynamics, transcription, cell cycle progression, and cell transformation [97].

Tumors contain MSCs and cancer stem cells (CSCs), which are also influenced by the tumor microenvironment

It has been shown that the human gliomas contain both glioma stem cells (GSCS) and glioma associated mesenchymal stem cells (GA-MSCS) [19,24], and that EXOs contribute towards intercellular communication inside the tumor structure and between distant cells [24]. Nevertheless, the influence on CSCs and microenvironment on MSCs is still poorly understood. Notwithstanding, it is known that MSCs can be influenced, and even transformed, by the effect of the tumor microenvironment. It is well known that MSCs are susceptible to being transformed into TAFs [85,95,98], and that TAFs support tumor stroma growth [98]. Both, bone marrow- and adipose-derived endothelial and mesenchymal progenitor cells were isolated, cultured, and injected back into mice, showing that these cells possess both tumor tropism and tumor-promoting capacities [99]. TAFs play a critical role in tumor remodeling, tumor growth, and metastasis. Furthermore, TAFs are also implicated in structural matrix formation [36]. TAFs generally favor the transition of non-tumorigenic cells to tumorigenic clones [100,101]. Tumors contain cells that share similar characteristics to MSCs, such as self-renovation and multipotency [102]. These CSCs express typical – although not exclusive– stem cell markers (CD24 and CD44) [102]. CSCs are implicated in tumor drug resistance and metastasis formation [103]. CSCs are responsible for propagating cancer in a highly

efficient manner [104]. This malignant clonal population represents 0.1-10% of all tumor cells [105], only some of which can develop tumors [106]. Compared with normal stem cells, CSCs are thought to show no restraint with respect to cell number (i.e., proliferation). However, the CSCs slow growth rate, plays a role in treatment resistance (chemotherapy and radiotherapy) and tumor recurrence [107,108]. In addition, CSCs' ability to initiate new tumors may be of critical importance for metastatic colonization. In fact, the ability of a cancer cell to seed an entire tumor following experimental implantation, and the ability of tumor cancer cells to seed and engage in metastatic dissemination, appear to be very similar processes, leading to the notion that CSCs are the only cells to possess metastasis-forming abilities [8, 109, 110].

The interpretation of the aforementioned information is that tumor-engrafted MSCs act against tumors, because MSCs promote anti-inflammatory activity, engage in angiogenesis suppression, inhibit cell-cycle progression, or downregulate pro-tumor pathways; such as apoptosis evasion or DNA transcription, anti-cancer drug resistance and embryonic development. On the other hand, some factors secreted by tumor-engrafted MSCs exhibit supportive effects within the tumor, as they promote angiogenesis, cell proliferation, cell survival, cell motion, leukocyte infiltration, and immune response modulation. In addition, the factors secreted by tumor-engrafted MSCs show a pro- and anti-tumor ambiguity: Tumor suppressive effects, inflammation inhibition, tumor-specific CD8 T-cell expansion or invasion, or a modification of the microenvironment in favor of cancer cells. MSCs appear to represent a double-edged sword. Therefore, a prerequisite to using these cells is to understand the circumstances in which MSCs favor cancer or act against cancer. Wagner et al. proposed that both the origin of MSCs and cancer type determine whether the MSCs act against or in favor of tumors [111].

Alternatives for using MSCS against cancer

According to the current knowledge of the advantages of using MSCs in cancer therapy, Hendijani [112] hypothesized that it is possible to obtain desirable anticancer results if MSCs are procured from the correct tissue, and if these cells are used against the correct cancer type. Nevertheless, this possibility needs to be assessed in many experiments and, if possible, in a way that is tailored to each patient. Conversely, one real possibility involves using MSCs modified with genes that have already been proven to be effective weapons against malignant cells. This last possibility is being intensively explored in pre-clinical and clinical trials. Tables 5-7 summarize the preclinical assays performed with INFs, interleukins and chemokines, respectively. These tables briefly describe the ongoing or completed experiments. In addition, in the next paragraphs, more extensive comments about each of these assays are presented.

How MSCs reengineered with genes codifying for cytokines are being used in preclinical assays

A considerable number of genes codifying for cytokines has been used to reengineer MSCs. The term "cytokines" embraces a broad group of small proteins (~5–20 kDa). These proteins interconnect eukaryotic cells via signaling mechanisms; specifically, cytokines act in autocrine signaling pathways. Cytokines include IFNs, ILs, chemokines, lymphokines, and TNFs. Cytokines are produced by a broad range of cells. In general, cytokines act through receptors and modulate the balance between humoral and cell-based immune responses, while regulating the maturation, growth, and responsiveness of particular cell populations. Some cytokines enhance or inhibit the action of other cytokines in complex ways [113]. Tables 5-7 show the experimental details of 10 preclinical assays using reengineered MSCs with transgenes codifying for INFs (Table 5), interleukins (Table 6) or chemokines (Table 7). Authors of all 10 studies performed with MSCs reengineered with INFs [113-115], interleukins [16,115,116] and chemokines [117-121] reported satisfactory homing, as the anti- cancer products produced by reengineered MSCs were successfully delivered into the tumors or to targeted malignant cell cultures and no toxic effects were noted in the implanted animals. In all *in vivo* experiments, transgenic MSCs from autologous, allogeneic, or transspecies implants showed significantly higher cancer cell mortality than negative controls. This finding accentuates the importance of using genetically engineered MSCs as molecular delivery vehicles instead of naïve MSCs or pure anticancer medications. Despite the above, in all the previously noted studies, the anti-cancer efficacy of genetically engineered MSCs was only partial; the exception to this was observed in the in vivo experiment performed with interleukin (IL)-12-engineered MSCs, which acted against HCA lung metastasis loaded in BALBc mice. In this

Table 5. Preclinical assays using genetically modified MSCs with INFs

Study No.	*Transduced Gene*	*Description of the study*	*Main observations*	*Efficacy[1] (%)*	*Ref.[2]*
5-1	(h)[3]INF-γ	Purposes: 1) Determine transduction efficiency. 2) Know the effects of hIFN-γ produced by transduced BM-hMSCs[4] on cancer cell proliferation of the human leukemia cell line K562. Modality: in vitro. Target: K562 human leukemia cell line. Transduced cells: BM-hMSCs. Gene Vector: adenoviral.	1) BM-MSCs could be readily obtained, expanded, and successfully transduced with adenoviral vectors in vitro. 2) The engineered BM-hMSCs inhibited the proliferation of the human leukemia cell line K562, while inducing apoptosis.	(30.8 ± 8.5)[Δ]	[112]
5-2	(mINF)-α	Purpose: to evaluate the potential of genetically modified BM-MSCs. Modality: in vivo. Target: mouse melanoma cell line B16F10, lung metastasis. Animal model: C57BL/6 Mice. Transfected cells: autologous BM-mMSCs Gene vector: plasmid.	1) Transduced MSC reduced the growth of melanoma cells. 2) Significantly prolonged survival of melanoma-bearing mice. 3) Immunohistochemistry analysis showed an apoptosis increase of tumors in MSC–IFN-α-treated animals and a decrease in cell proliferation and blood vasculature.	(60)*	[113]
5-3	(hIFN)-β	Purposes: 1) to investigate if over-expressing IFN-β cells could integrate into the tumors. 2) to produce biological agents at tumor sites. 3) to inhibit the growth of malignant cells in vivo. Modality: In vivo. Target: human melanoma (cell line A375SM) from lung metastases. Animal model: athymic nude mice (NCr-nu). Transduced cells: BM-hMSC. Gene vector: adenoviral.	1) The tumor microenvironment promoted the engraftment of transduced MSCs. 2) Transduced MSCs inhibited the growth of malignant cells in vivo. 3) Inhibition of malignant cells required the integration of MSCs into the tumors. 4) At distant sites from tumors transduced MSCs did not inhibited malignant cells	(50)*	[40]

[1]Efficacy of MSCs in vitro was reported as percentage of cell-death or apoptosis ([Δ]) with respect to negative controls. In in vivo experiments, implanted transgenic MSCs were measured as reduction of the number of cancer metastasis (*); [2]Ref, reference; [3](h), human.

Table 6. Preclinical assays using genetically modified MSCs with interleukines

Study No.	*Transduced Gene*	*Description of the study*	*Main observations*	*Efficacy[1] (%)*	*Ref.[2]*
6-1	(IL)[3]-2	Purpose: Investigate if transduced MSCs were efficacious against glioma. Modality: in vivo. Target: 9L rat glioma. Animal model: Fisher 344 rats. Transduced cells: autologous BM-MSCs. Gene vector: adenoviral.	Transduced MSCs migrated towards 9L glioma cells through the corpus callosum.	(74.7)**	[16]
6-2	(IL)-12	Purpose: 1) Evaluate the efficacy of an integrated immunotherapy Modality: in vivo. Targets: pre-established metastases of the following cancer cell lines: 1) B16 mouse melanoma 2) 4T1 mouse breast cancer 3) Hca mouse hepatocarcinoma Animal models: C57BL/6 (loaded with B16cell line) and BALB/c mice (loaded with 4T1 or Hca) Transduced cells: allogeneic or autologous BM-mMSCs[4] Gene vector: adenoviral.	The intratumoral expression of IL-12 by gene-engineered MSCs was tenfold greater than controls. In transduced mice, the progression of metastases into multistep lymph nodes and internal organs was, markedly impeded in the midway stage and reversed in the ultimate stage.	B16: (94.3)** 4T1: (85.7)** Hca: (100.0)** Av ± SD (93.3 ± 7.2)	[116]

[1]Efficacy of MSCs in vitro was reported as percentage of cell-death with respect to negative controls. In in vivo experiments, implanted transgenic MSCs were measured as reduction of tumor size or weight (**); [2]Ref, reference; [3]IL, interleukin; [4](BM)-mMSCs (bone marrow)-mice mesenchymal stem cells.

Table 7. Preclinical assays using genetically modified MSCs with chemokines

Study No.	*Transduced Gene*	*Description of the study*	*Main observations*	*Efficacy[1] (%)*	*Ref.[2]*
7-1	CX3CL1C	Purposes: Observe: 1) tropism of MSCs to tumor cells in vitro 2) homing in multiple lung tumors 3) anti-cancer effect of gene-engineered MSCs Modality: in vivo Target: C26 colon carcinoma and B16F10 skin carcinoma lung metastases Animal model: C57BL/6 (H-2), BALB/c (H-2) and BALB/C nude mice Transduced cells: autologous BM-mMSCs from each line of mice Gene vector: adenoviral.	Engineered MSCs: 1) strongly inhibited the development of lung metastases; 2) prolonged the survival of tumor-bearing mice.	C26: (84.0)* B16F10: (71.4)* Av: (77.7)	[117]
7-2	NK4	Purposes: 4) Observe the tropism of MSCs to tumor cells in vitro and multiple tumor tissues in the lung. 5) Investigate the anti-cancer effect of gene-enginnered MSAcs Modality: in vivo Target: lung metastases of mouse C26 colon carcinoma Animal model: BALBc mice Transduced cells: autologous BM-mMSCs Gene vector: adenoviral.	MSCs expressing NK4: 1) Preferentially migrated towards multiple lung metastases; 2) strongly inhibited the development of lung metastases; 3) inhibited tumor-associated angiogenesis and lymphangiogenesis; 4) induced apoptosis of the tumor cells; 5) significantly prolonged the survival of tumor-bearing mice.	(48.7)*	[118]
7-3	TRAIL[3]	Purpose: to know whether engineered MSCs produce and deliver TRAIL, engrafted tumors and kill cancer cells Modality: in vitro and in vivo Target: in vitro: Cancer cell lines: a) Lung A549 b) Breast MDAMB231 c) Squamous H357 d) Cervical HeLa in vivo: pulmonary metastasis of metastatic human MDAMB231 breast cancer cells Animal model: NOD/SCID[10] mice Transduced cells: allogeneic hMSCs transduced full length human TRAIL Gene vector: lentiviral.	Engineered MSCs In vitro: cell apoptosis and death in coculture experiments. In vivo: 1) MSCs were localized in lung metastases; 2) Significantly reduced tumor growth; 3) Controlled local delivery of TRAIL; 4) Completely cleared the metastatic disease in 38%.	In vitro[Δ] Lung (16.5) Breast (15.4) Scamous (12.5) Cervical (42.4) Av±SD[5] (21.7±13.9) In vivo (85.5)*	[119]
7-4	TRAIL	Purpose: to investigate if engineered MSCs effectively inhibited mesothelioma growth. Modalities: in vitro and in vivo Target: Human mesothelioma cells (HMESO and YOU lines) Animal model: SCID mice loaded with mesothelioma cells. In vitro model: 9 primary human mesothelioma cell lines (HMESO and H2373, HAY, YOU, ROB, ORT, PET, PRO and HEC) Transduced cells: BM-hMSCs and BM-mMSCs transduced with full-length TRAIL Gene vector: lentivirus.	Both mouse and human engineered MSCs caused In vivo: 1) Homed at the sites of mesothelioma tumor growth; 2) Significantly reduced the inflammatory tumor environment in vivo; 3) Significantly reduced peritoneal tumor burden; In vitro: 1) reduced tumor cell migration; 2) induced apoptosis; 3) increased tumor cell apoptosis.	In vitro[Δ] hMSCs on: HMESO (68.8) YOU (40.0) Av (54.4) mMSCs on: HMESO cells (12.5) YOU cells: (120.0) Av (66.5) In vivo (29.5)**	[120]
7-5	TRAIL	Purposes: 1) to define the relative sensitivity of cancer cells to soluble or full length TRAIL 2) to compare anticancer activity of soluble and full length TRIAL. Modality: in vitro Target: 20 cancer cell lines: a) lung (A549, NCI-H460, NCI-H727, NCI-H23, H-226 and PC9) b) pleural mesothelioma (NCI-H2052, H2795, H2804, H2731, H2810, H2452, H2869) c) colon cancer (Colo205, HT29 and RKO) d) renal (RCC10 and HA7-RCC) e) oral squamous carcinoma (H357) f) human breast adenocarcinoma (MD-AMB231) Transduced cells: hMSCs transduced with full-length TRAIL Gene vector: lentiviral.	1) MSC-full length human TRAIL demonstrated high cancer cell-killing efficiency. 2) MSC-Full-length TRAIL overcome some cancer cell resistance. 3) The 20 cell lines were grouped accordingly their (r)6 TRAIL sensitivity: sensitive (≥70%; five cell lines), moderately (35%-70%; five cell lines), low (20-35%; four) and resistant (≤20%; six cell lines). 4) Both cell surface full length TRAIL and secreted full length TRAIL induced apoptosis. 5) Nevertheless, MSC delivery of full length- was superior to MSC delivery of soluble-TRAIL for cancer therapy.	In vitro apoptosis[4] Soluble TRAIL M231: (14.4) A549: (25.1) Av: (19.8) Full length TRAIL M231: (35.5) A549: (50.2) Av: (42.9)	[121]

[1]Efficacy of MSCs in vitro was reported as percentage of cell-death. In in vivo experiments, implanted transgenic MSCs were measured as reduction of the number of cancer metastasis (*) or reduction of tumor size or weight (**); [2]Ref, reference; [3]TRAIL, (TNF)-related apoptosis-inducing ligand. TNF, tumor necrosis factor; [4]Apoptosis with respect to negative controls; [5]Av± SD, average of all experiments ± standard deviation; [6](r), recombinant.

experiment, a 100% tumor reduction was observed [116]. Considering all the *in vitro* experiments, the range of cell death or cell apoptosis achieved by transduced MSCs ranged from 12.5-68.8%. This effect was produced, respectively, by mMSCs and hMSCs carrying a TRAIL transgene [120].

The average efficacy, ranging from the lowest to the highest levels of efficacy among the transgenes used to transfect MSCs, is as follows: a) *in vitro* experiments: full-length soluble TRAIL< hIFN-γ< full-length TRAIL. It is interesting to note that many different types of cancer cell lines were susceptible to the effect of the same transgene expressed by the same kind of MSCs. For instance, mice (m)MSCs transduced with TRAIL produced apoptosis rates that were 0.13 and 1.2 times higher than those observed in non-treated HMSO and YOU cells. Nevertheless, the authors did not report the apoptosis percentage regarding the total number of cells in their cultures; b) *In vivo* experiments: soluble TRAIL < NK4 < hINF-β < mINF-α < IL-2 < full-length TRAIL < IL-12.

Soluble TRAIL is a favorite transgene that is used in the development of anticancer cell therapy procedures due to their ability to reach all malignant cells within an organism [121]. Nevertheless, at least in the frame of the analyzed articles in Table 7, soluble TRAIL produced the lowest efficacy in both *in vitro* and *in vivo* experiments; this is in contrast with what was found for full-length TRAIL, which produced the highest cell death percentage *in vitro* and the second highest percentage in *in vivo* experiments. It is worth analyzing the strategies followed by researchers that produced the worst (study number 7-4), and the best results (7-3) by conducting *in vivo* experiments. The lowest reduction in tumor size was reported by Lathrop et al. (29.5% tumor reduction size [120], and the best results were documented by Loebinger et al. (85.5% reduction of cancer metastasis) [119]. The experimental strategy followed by Lathrop [121] consisted of working with SCID mice, which were loaded with human mesothelioma cells. In these experiments, transgenic BM-mMSCs and lentiviral vectors were employed as molecular vehicles, and the TRAIL transgene was of human origin. On the other hand, Loebinger et al. [119] used NOD/SCID mice loaded with human breast cancer pulmonary metastasis and treated with hMSCs, which were infected with lentiviruses bearing a full-length human TRAIL. Even though, the results obtained by Loebinger et al. [119], using full-length TRAIL were satisfactory. The results obtained by Chen et al. [116], using IL-12 transgenes were even more impressive: 100% reduction of tumor size (Table 6, study 6-2). The strategy followed by Chen et al. [116] consisted of using two mouse cancer cell lines (breast and hepatocarcinoma) loaded in BALBc (immunocompetent) mice; the molecular vehicles were autologous BM-MSCs transduced with recombinant adenoviral vectors, and the IL-12 transgene was murine. Thus, the differences in efficacy could be due to the fact that IL-12 is more efficacious than TRAIL. The second possibility (not excluding the first) is that the cancer cells used by other researchers cited here might be specifically resistant to other transgenic anti-cancer products but not to IL-12. In support of this hypothesis, all *in vitro* studies described in Table 6 (study 6-1) and Table 7 (studies 7-4 and 7-5) reported that the different cancer cell lines exhibited different susceptibility levels to the same anti-cancer transgenic products under similar experimental conditions. The third possibility to explain the efficacy differences between the 6-2, 7-3 and 7-4 studies may be related to the origin of transgenes and MSCs: while Lathorp et al. [120] and Loebinger et al. [119] used heterogeneous systems with respect to the species origin of each element of the biological system, the system employed by Chen et al. [116] was homogeneous.

Preclinical assays with engineered MSC transplantation combined with other anti-cancer therapies

Yin et al. [122] proposed a combined hyperthermia-TRAIL-MSC therapy employing a TRAIL plasmid vector with a heat shock protein 70B' promoter, as well as with magnetic core-shell nanoparticles (to achieve 41°C hyperthermia), which exhibited controlled TRAIL expression. This study was performed on an ovarian cancer xenograft model with positive results. The stem cell-based gene therapy was responsive to stimuli, and a reduction in the tumor burden was noted. Homing exhibited an increase following radiation therapy on xenograft models of irradiated glioma, breast, and colon cancers. Combined chemotherapy, radiotherapy, and MSCs have shown increased benefits against cancer.

How naïve or reengineered MSCs are used in clinical assays

Through ClinicalTrials.gov, we identified 8 clinical trials on the use of MSC implantation to treat cancer. In addition, we found a trial published by Niess et al. [123]. Thus, in total, we identified

9 clinical trials. Table 5 contains the following information about the above mentioned clinical trials. We identified 7 ongoing and 2 completed trials. It is interesting to note that in most of the clinical trials cited herein, private enterprises and academic institutions are associated with their development, which strongly suggests that in a few years, MSC implantation will be generally used to treat a great variety of diseases. Nevertheless, very few results from these clinical trials have currently been published, primarily due to the fact that most of these clinical studies are still in Phase I or II.

Preclinical studies suggest that combining genetically engineered or unmodified MSCs with chemotherapy and radiotherapy - when applied - could be safer and more efficacious than conventional or modern therapeutic schemes used separately (Tables 8 and 9). However, it should be noted that clinical trials featuring genetically engineered MSCs are still not rendering the expected results. Therefore, knowledge on the

Table 8. Human cancer therapy clinical trials using unmodified MSCs[1]

Number, Trial title and Clinical condition	*Procedure*	*City and Country*	*Location*	*Status*	*ClinicalTrials.gov identifier [119]*	***Last verified***
1. Haploidentical stem cell transplantation in neuroblastoma. Neuroblastoma	Radiation: T-cell depletion. Allogeneic transplantation: haploidentical stem cell transplantation, lymphocyte infusion	Lund, Sweden	Lund University Hospital, Department of Pediatric Oncology	Ongoing Not recruiting participants.	(NTC)[2]00790413	March 2016
2. Safety and efficacy study of umbilical cord blood-derived mesenchymal stem cells to promote engraftment of unrelated hematopoietic stem cell transplantation. Acute leukemia	Allogeneic transplantation: human umbilical cord blood-derived MSCs.	Seoul, Republic of Korea	Samsung Medical Center.	Completed Phases I and II. No study results posted	NCT00823316	April 2012
3. Mesenchymal stem cells in cisplatin-induced acute renal failure in patients with solid organ cancers. Solid tumors. Acute kidney injury	Allogeneic implantation: mesenchymal stromal cell (MSC) infusion	Bergamo, Italy	Department of Immunology and Clinical Transplantation/ Mario Negril Institute for Pharmacological Research and Ospedali Riuniti	Ongoing Phase I. This study is currently recruiting participants	NCT01275612	January 2016
4. Intra-Osseous Co-transplant of UCB[3] and (h)[4]MSCs Acute lymphoblastic leukemia, acute myelogenous leukemia, myelodysplastic syndromes, myelofibrosis, relapsed non-Hodgkin lymphoma, refractory non-Hodgkin lymphoma, lymphoma, refractory Hodgkin lymphoma, relapsed chronic lymphocytic leukemia, refractory chronic lymphocytic leukemia, lymphoid malignancies, chronic myelogenous leukemia	Allogeneic transplantation: umbilical cord blood Autologous Implantation: homologous MSCs. Chemotherapy: cyclophosphamide, fludarabine phosphate; cyclosporine, mycophenolate mofetil Radiation: total-body irradiation	Cleveland, Ohio, USA	NCI	Ongoing Phases I and II. This study is currently recruiting participants	NCT02181478	March 2016
5. Allogenic Human Bone marrow derived mesenchymal stem cells mesenchymal stem cells in localized prostate cancer Prostate cancer	Allogeneic transplantation: MSCs	Baltimore, Maryland, USA	Johns Hopkins Hospital and Sidney Kimmel Comprehensive Cancer Center	Ongoing Phase I. This study is currently recruiting participants	NCT01983709	April 2016

[1]MSCs, mesenchymal stem cells; [2]NTC, Clinical Trials.gov identifier. https://clinicaltrials.gov/ct2/results?term=Haploidentical+Stem+Cell+transplantation+in+Neuroblastoma&Search=Search; [3]UCB, umbilical cord blood; [4](h), human.

efficacy and safety of combined therapies in humans is still necessary. Hopefully, this information will be available soon. Conversely, there is currently an attractive use of unmodified MSCs as adjuvants to improve the general health status of patients with cancer, particularly as they are being treated with chemotherapy or radiotherapy.

Concerns about the generalized use of MSC implantation

Even though MSC implantation has not yet shown any major adverse events, there are still concerns surrounding the use of genetically engineered MSCs. This is due to the fact that MSCs

Table 9. Human cancer therapy clinical trials using genetically modified MSCs[1]

Number, Trial title and Clinical condition	*Procedure*	*City and Country*	*Location*	*Status*	*ClinicalTrials.gov identifier[2]*	***Last verified***
9.1. Phase 1. Study to determine the effects of mesenchymal stem cells secreting Interferon beta in patients with advanced ovarian cancer. Ovarian cancer	Allogeneic transplantation: (h)[3]MSC secreting (INF[4])-β beta (MSC-(INF-β	Houston, Texas, USA	University of Texas MS Anderson Cancer Center	Ongoing Phase 1. This study is currently recruiting participants	NCT[2]02530047	July 2016
9.2. Phase 1. Study to determine the effects of mesenchymal stem cells secreting Interferon beta in patients with advanced ovarian cancer. Ovarian cancer	Allogeneic transplantation: (h)[3]MSC secreting (INF)[4]β (MSC-INFβ)	Houston, Texas, USA	University of Texas MS Anderson Cancer Center	Ongoing Phase 1. This study is currently recruiting participants	NCT02530047	July 2016
9.3. MV-NIS[7] Infected mesenchymal stem cells in treating patients with recurrent ovarian cancer, malignant ovarian Brenner tumor, ovarian clear cell adenocarcinoma, ovarian endometrioid adenocarcinoma, ovarian mucinous adenocarcinoma, ovarian seromucinous carcinoma, ovarian serous adenocarcinoma, ovarian transitional cell carcinoma, recurrent ovarian carcinoma, recurrent primary peritoneal carcinoma, undifferentiated ovarian carcinoma	Allogeneic transplantation: MSCs infected with oncolytic measles virus encoding thyroidal sodium iodide symporter	Rochester Minnesota, USA	Mayo Clinic and NCI[5]	Ongoing Phases 1 and 2 This study is currently recruiting participants	NCT02068794	June 2016
9.4. Genetically modified Mesenchymal Stem Cells therapeutic against Head and Neck cancer (GX-051)[6] Head and Neck cancer	Allogeneic transplantation: IT[6] injection GX-0517. Stem cell based gene therapeutics	Seul, Republic of Korea	Genexine, Inc and Seoul St. Mary's Hospital of the Catholic University of Korea	Ongoing Phase 1. Recruiting participants	NCT02079324	April, 2015
9.5. Treatment of advanced gastrointestinal tumors with genetically modified autologous mesenchymal stromal cells (TREAT-ME1): study protocol of a phase I/II clinical trial [120]. Colorectal adenocarcinoma and hepatopancreatobiliary adenocarcinoma	Autologous Implantation: genetically modified MSCs with a retrovirus Chemotherapy: Gancyclovir	Munich, Germany	Department of General, Visceral, Transplantation, Vascular and Thoracic Surgery, Department of Clinical Oncology, University of Munich and the Apceth GmbH &Co. KG, based in Munich, Germany	Ongoing Phases 1 and 2. This study is currently recruiting participants.	2012-003741-15[7]	Published on April 2015. None result informed

[1]MSCs, mesenchymal stem cells; [2]NTC, clinical Trials.gov identifier. https://clinicaltrials.gov/ct2/results?term=Haploidentical+Stem+Cell+transplantation+in+Neuroblastoma&Search=Search; [3](h), human; [4]INF, interferon; [5]NCI, National Cancer Institute, [6]GX 051, is a product comprising MSC infected with a recombinant adenovirus encoding cytokine IL-12M, for the treatment of solid tumors. [7]A specific number for this clinical trial, which was registered in the EU Clinical Trials Register/European Union Drug Regulating Authorities database

have the potential to transform malignantly, as engineered MSCs can overexpress potentially hostile molecules. Moreover, there are also concerns pertaining to the lack of safety mechanisms following MSC administration [124], as well as to the senescence of MSCs *in vitro*, which could diminish their plasticity and self-division efficacy, producing undesirable effects [125]. Despite these arguments, governments from diverse countries have considered the potential benefits of using MSCs in regenerative medicine far outweigh the risks, and there is a growing number of registered (ongoing) clinical trials that are using implanted or transplanted MSCs. For example, as of August 22, 2016, the ClinicalTrials.gov identifier registered 46 clinical studies that were using MSC implantation as a unique method of treatment, or that were combining MSC implantation with other therapies. These trials are being carried out not only to treat cancer, but to treat other catastrophic diseases, including diabetes (types I and II), cystic fibrosis, epilepsy, and rheumatoid arthritis [126].

Conclusions

The inconveniences associated with conventional anti-cancer treatments include a lack of specificity against malignant cells, partial efficacy against metastatic cancer, and the high frequency of increasing resistance to chemotherapy. On the other hand, anti-cancer therapy using genetically engineered MSCs offers the possibility of attacking both the primary tumor and metastasis in a more specific and efficacious manner. With this idea in mind, several preclinical experiments have been conducted using MSCs reengineered with various genes and in diverse tumor models. In general, cell therapies using MSCs are very promising. Several research groups have shown that, because of preclinical studies, implants with genetically engineered MSCs are satisfactorily safe. In addition, it is worth noting that such results were shown in xenograft and allograft models, highlighting the low immunogenic nature of MSCs, and that cell therapy using genetically engineered MSCs is considerably more efficacious against diverse kinds of cancer when compared with naïve MSCs or pure (recombinant) anti-cancer INFs, ILs, chemokines, or TRAIL, although with a relatively low grade of success; the only exception to this includes *in vivo* experiments performed with IL-12 [116]. Despite the considerable advances reached in the field of cancer cell therapy, certain reticence still prevails regarding the use of naïve or genetically engineered MSCs. This is due to the fact that the completed studies have been performed with animal models, and very few investigations have used cell therapy on humans; as such, the results of the latter are not yet known. Considering the broad knowledge about cancer therapy, at the present time, one very advisable strategy might include combining conventional or new anti-cancer schemes with genetically engineered MSC therapy. This procedure could considerably diminish the toxicity associated with currently used therapeutic schemes, thus increasing their efficacy in both prolonging the patient survival time and quality of life. In fact, some clinical trials that are adopting this approach are currently in progress.

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Conflict of interests

The authors declare no confict of interests.

References

1. Ferlay J, Soerjomataram I, Dikshit R et al. Cancer incidence and mortality worldwide sources, methods and major patterns. GLOBOCAN 2012. Int J Cancer 2014;136:E359-86.
2. World Health Organization (WHO). Media Centre. Global cancer rates could increase by 50% to 15 million by 2020. http://www.who.int/mediacentre/news/releases/2003/pr27/en/.
3. Hanahan D. Rethinking the war on cancer. Lancet 2014;383:558-563.
4. Jaehde U, Liekweg A, Simons S, Westfeld M. Minimising treatment associated risks in systemic cancer therapy. Pharm World Sci 2008;30:161-168.
5. Dvorak HF. Tumor: Wounds that do not heal. Similarities between tumor stroma generation and wound healing. N Engl J Med 1986;315:1650-1659.

6. Bremnes RM, Dønnem T, Al-Saad S et al. The role of tumor stroma in cancer progression and prognosis: emphasis on carcinoma-associated fibroblasts and non-small cell lung cancer. J Thorac Oncol 2011;6:209-217.
7. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell 2000;100:57-70.
8. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646-674.
9. da Silva Meirelles L, Chagastelles PC, Nardi NB. Mesenchymal stem cells reside in virtually all post-natal organs and tissues. J Cell Sci 2006;119 (Pt 11):2204-2213.
10. Mafir R, Hindocha S, Mafir P, Griffin M, Khan WS. Sources of adult mesenchymal stem cells applicable for musculoskeletal applications a systematic review of the literature. Open Orthop J 2011;5(Suppl 2-M2):242-248.
11. Hass R, Kasper C, Böhm S, Jacobs R. Different populations and sources of human mesenchymal stem cells (MSC): A comparison of adult and neonatal tissue-derived MSC. Cell Common Signal 2011;9:12.
12. Marquez-Curtis LA, Janowska-Wieczorek A, McGann LE, Elliott JAW. Mesenchymal stromal cells derived from various tissues: Biological, clinical and cryopreservation aspects. Cryobiology 2015;71:181-197.
13. Van Vlasselaer P, Falla N, Snoeck H, Mathieu E. Characterization and purification of osteogenic cells from murine bone marrow by two-color cell sorting using anti-Sca-1 monoclonal antibody and wheat germ agglutinin. Blood 1994;84:753-763.
14. Odabaş S, Sayar F, Güven G, Yanikkaya-Demirel G, Pişkin E. Separation of mesenchymal stem cells with magnetic nanosorbents carrying CD105 and CD73 antibodies in flow-through and batch systems. J Chromatogr B Analyt Technol Biomed Life Sci 2008;861:74-80.
15. Gary Brooke G, Cook M, Blair C et al. Therapeutic applications of mesenchymal stromal cells. Semin Cell Dev Biol 2007;18:846-858.
16. Nakamura K, Ito Y, Kawano Y et al. Antitumor effect of genetically engineered mesenchymal stem cells in a rat glioma model. Gene Ther 2004;11:1155-1164.
17. McMahon JM, Conroy S, Lyons M et al. Gene transfer into rat mesenchymal stem cells: a comparative study of viral and nonviral vectors. Stem Cells Dev 2006. doi:10.1089/scd.2006.15.87.
18. Stagg J. Mesenchymal stem cells in cancer. Stem Cell Rev 2008;15:87-96.
19. Birnbaum T, Roider J, Schankin CJ et al. Malignant gliomas actively recruit bone marrow stromal cells by secreting angiogenic cytokines. J Neurooncol 2007;83:241-247.
20. Honczarenko M, Le Y, Swierkowski M, Ghiran I, Glodek AM, Silberstein LE. Human bone marrow stromal cells express a distinct set of biologically funct ional chemokine receptors. Stem Cells 2006;24:1030-1041.
21. Nombela-Arrieta C, Ritz J, Silberstein LE. The elusive nature and function of mesenchymal stem cells. Nat Rev Mol Cell Biol 2011;12:126-131.
22. Sohni A, Verfaillie CM. Mesenchymal stem cells migration homing and tracking. Stem Cells Int 2013; 2013 (2013), Article ID 130763, 8 pages.
23. Sarkar D, Spencer JA, Phillips JA et al. Engineered cell homing. Blood 2011. http://www.bloodjournal.org/content/bloodjournal/early/2011/10/26/blood2010-10-311464.full.pdf
24. Xu HX, Zhang K, Zong H, Shang M, Li K, He X. Exosomal communication in glioma a review. J BUON 2016;21:1368-1373.
25. Hwang I. Cell-cell communication via extracellular membrane vesicles and its role in the immune response. Mol Cells 2013;36:105-111.
26. Chen J, Chonghui Li C, Chen L. The role of microvesicles derived from mesenchymal stem cells in lung diseases. Biomed Res Int 2015:6 pages. doi.org/10.1155/2015/985814.
27. Sato-Kuwabara Y, Melo SA, Soares FA, Calin GA. The fusion of two worlds: non-coding RNAs and extracellular vesicles –diagnostic and therapeutic implications. Int J Oncol 2015;46:17-27.
28. Thery C, Zitvogel L, Amigorena S. Exosomes: composition, biogenesis and function. Nat Rev Immunol 2002. https://dx.doi.org/10.1038/nri855.
29. Piccin A, Murphy WG, Smith OP. Circulating microparticles: pathophysiology and clinical implications. Blood Rev 2007;21:157-171.
30. Van Doormaal FF, Kleinjan A, Di Nisio M, Büller HR, Nieuwland R. Cell derived microvesicles and cancer. Neth J Med 2009;67;266-273.
31. Muralidharan-Chari V, Clancy JW, Sedgwick A, D'souza-Schorey C. Microvesicles: mediators of extracellular communication during cancer progression. J Cell Sci. 2010;123:1603-1611.
32. Cocucci E, Racchetti G, Meldolesi J. Shedding microvesicles: artefacts no more. Trends Cell Biol 2009;19:43-51.
33. Zhang X, Tu H, Yang Y, Fang L, Wu Q, J ian L i J. Mesenchymal Stem Cell-derived extracellular vesicles: roles in tumor growth, progression, and drug resistance. Stem Cells Int 2017; vol 2017: 12 pages. Doi.org/10.1155/2017/1758139.
34. Bruno S, Collino F, Deregibus MC, Grange c, Tetta C, Camussi G. Microvesicles derived from human bone marrow mesenchymal stem cells inhibit tumor growth. Stem Cells Dev 2013;22:758-771.
35. Collino1 F, Deregibus MC, Bruno S, et al. Microvesicles derived from adult human bone marrow and tissue specific mesenchymal stem cells shuttle selected pattern of miRN As. PLoS One 2010;5. article id e11803, 2010.
36. Menon LG, Picinich S, Koneru R et al. Differential gene expression associated with migration of mesenchymal stem cells to conditioned medium from tumor cells or bone marrow cells. Stem Cells 2007;25:520-528.
37. Loebinger MR, Kyrtatos PG, Turmaine M et al. Magnetic resonance imaging of mesenchymal stem cells homing to pulmonary metastases using biocompatible magnetic nanoparticles. Cancer Res 2009;69:8862-8867.
38. Kidd S, Caldwell L, Dietrich M et al. Mesenchymal stromal cells alone or expressing interferon-beta

suppress pancreatic tumors in vivo, an effect countered by anti-inflammatory treatment. Cytotherapy 2010;12:615-625.

39. Sonabend AM, Ulasov IV, Tyler MA, Rivera AA, Mathis JM, Lesniak MS. Mesenchymal stem cells effectively deliver an oncolytic adenovirus to intracranial glioma. Stem Cells 2008;26:831-841.
40. Muresan M, Zaharie F, Bojan A et al. MicroRNAs in liver malignancies. Basic Science Applied in Surgery. J BUON 2015;20:361-375.
41. Zhang J, Li S, Li L et al. Exosome and exosomal microRNA: trafficking, sorting, and function. Genomics Proteomics Bioinformatics 2015;13:17-24.
42. Collino F, Deregibus MC, Bruno S et al. Microvesicles derived from adult human bone marrow and tissue specific mesenchymal stem cells shuttle selected pattern of miRNAs. PLoS One. 2010. http//dx.doi.org/10.1371/journal.pone.0011803.
43. Skog J, Wurdinger T, van Rijn S et al. Glioblastoma microvesicles transport RNA and proteins that promote tumour growth and provide diagnostic biomarkers. Nat Cell Biol 2008;10:1470-1476.
44. Liao J, Liu R, Yin L, Pu Y. Expression profiling of exosomal miRNAs derived from human esophageal cancer cells by Solexa high-throughput sequencing. Int J Mol Sci 2014;15:15530-15551.
45. Squadrito ML, Baer C, Burdet F et al. Endogenous RNAs modulate microRNA sorting to exosomes and transfer to acceptor cells. Cell Rep 2014;8:1432-1446.
46. Huang X, Yuan T, Tschannen M, Sun Z, Jacob H, Du M, Meihua Liang M, Dittmar RL, Liu Y, Liang M, Kohli M, Thibodeau SN, Boardman L, Wang L. Characterization of human plasma-derived exosomal RNAs by deep sequencing. BMC Genomics 2013;14:319. http//www.biomedcentral.com/1471-2164/14/319
47. Croce CM, Calin GA. miRNAs, cancer, and stem cell division. Cell 2005;122:6-7.
48. Tian, K , Yang S , Ren Q et al. p38 mapK contributes to the growth inhibition of leukemic tumor cells mediated by human umbilical cord mesenchymal stem cells. Cell. Physiol Biochem 2010: 26;799-808.
49. Yulyana Y, Ho Ia, Sia KC et al. Paracrine factors of human fetal MSCs inhibit liver cancer growth through reduced activation of IGF-LR/PI3K/AKT signaling. Mol Ther 2015;23:746-756.
50. Qiao L, Xu ZL, Zhao TJ et al. DKK-1 secreted by mesenchymal stem cells inhibits growth of breast cancer cells via depression of WNT signaling. Cancer Lett 2008;269:67-77.
51. Bozok CV, Aktug H, Oltulu F et al. The effects of mesenchymal stem cells on lymphoblastic leukaemia cell proliferation. J BUON 2014;19:1006-1017.
52. Shuai W, Guan-Qun J, Tao D et al. Microvesicles derived from human umbilical cord Wharton's jelly mesenchymal stem cells attenuate bladder timor cell growth in vitro and in vivo. PLoS One 2013;8:E61366. Doi: 10.1371/journal.pone. 0061366.
53. Ncithesaurus. DIRAS3 gene (code C20761). This gene plays a role in signal transduction and suppression of cell growth. Available on line: https://nciterms.nci.nih.gov/ncitbrowser/conceptreport.jsp?dictionary=NCI_thesaurus&version=17.02D&NS=NCI&CODE=C20761. Accessed 06/02/2017.
54. Entrez gene: RBL1 retinoblastoma-like L. Available online: https://en.wikipedia.org/wiki/retinoblastoma-like_protein_1A. Accessed 06/02/2017.
55. Entrez gene: CDKN2B cyclin-dependent kinase inhibitor 2B (PL5, inhibits CDK4). Available online: https://www.ncbi.nlm.nih.gov/gene?db=gene&cmd=showdetailview&termtosearch=1030. Accessed 06/02/2017.
56. Lee JK, Park SR, Jung BK et al. Exosomes derived from mesenchymal stem cells suppress angiogenesis by down-regulating VEGF expression in breast cancer cells. PLoS One 2013;8:E84256. Doi:10.1371/Journal.Pone.0084256.
57. Lou, Song X, Yang F et al. Exosomes derived from MIR-122-modified adipose tissue-derived MSCs increase chemosensitivity of hepatocellular carcinoma. J Hematol Oncol 2015;8:122. Doi: 10.1186/S13045-015-0220-7.
58. Ho IA, Toh HC, Ng WH et al. Human bone marrow-derived mesenchymal stem cells suppress human glioma growth through inhibition of angiogenesis. Stem Cells 2013;31:146-155.
59. Attar-Schneider O, Zismanov V, Drucker L, Gottfried M. Secretome of human bone marrow mesenchymal stem cells: an emerging player in lung cancer progression and mechanisms of translation initiation. Tumour Biol 2016;37:4755-4765.
60. Khakoo AY, Pati S, Anderson SA et al. Human mesenchymal stem cells exert potent antitumorigenic effects in a model of K aposi's sarcoma. J Exp Med 2006;203;1235-1247.
61. Al-Toub M, Almusa A, Almajed M et al. Pleiotrophic effects of cancer cells' secreted factors on human stromal (mesenchymal) stem cells. Stem Cell Res Ther 2013:4:114. http://stemcellres.com/content/4/5/114.
62. Lam PYP. Biological effects of cancer-secreted factors on human mesenchymal stem cells. Stem Cell Res Ther 2013;4:138. http://stemcellres.com/content/4/6/138.
63. Luo J, Ok LS, Liang L et al. Infiltrating bone marrow mesenchymal stem cells increase prostate cancer stem cell population and metastatic ability via secreting cytokines to suppress androgen receptor signaling. Oncogene 2014;33:2768-2778.
64. Klopp AH, Gupta A, Spaeth E, Andreeff M, Marini F. Concise review: Dissecting a discrepancy in the literature: Do mesenchymal stem cells support or suppress tumor growth? Stem Cell 2011;29:11-19.
65. Carrero R, Cerrada I, Lledó E et al. IL1β induces mesenchymal stem cells migration and leucocyte chemotaxis through NF-κB. Stem Cell Rev 2012;8:905-916.
66. Aldinucci D, Colombatti A. The inflammatory chemokine CCL5 and cancer progression. Mediators Inflamm 2014; vol. 2014. Article ID: 292376. 12 pages- available online: http://dx.Doi.org/10.1155/2014/292376
67. Kingsley O. Osuala KO, Sloane BF. Many roles of CCL20: emphasis on breast cancer. Postdoc J 2014;2:7-16.
68. Dhawan P, Richmond A. Role of CXCL1 in tumorigenesis of melanoma. J Leukoc Biol 2002;72:9-18.
69. Gui SL, Teng LC, Wang SQ et al. Overexpression of

XCCL3 can enhance the oncogenic potential of prostate cancer. Int Urol Nephrol 2016;48:701-709.

70. Hsu Y-L, Hou M-F, Kuo P-L, Huang Y-F, Tsai E-M. Breast tumor-associated osteoblast- derived CXCL5 increases cancer progression by erk/msk1/elk-1/snail signaling pathway. Oncogene 2013;32:4436-4447.
71. Zhu YM, Bagstaff SM, Woll LPJ. Production and upregulation of granulocyte chemotactic protein-2/cxcl6 by IL-1β and hypoxia in small cell lung cancer. Br J Cancer 2006;94:1936-1941.
72. Mingli L, Shanchun G, Jonathan KS. The emerging role of CXCL10 in cancer (review). Oncol Lett 2011;2:583-589.
73. Lau T-S, Chung Y K-H, Cheung T-H et al. Cancer cell-derived lymphotoxin mediates reciprocal tumour–stromal interactions in human ovarian cancer by inducing CXCL11 in fibroblasts. J Pathol 2014;232:43-56.
74. Ulia YS, Ni T Y-B, Chan S-K et al. CXCL3CL1 expression is associated with poor outcome in breast cancer patients. Breast Cancer Res Treat 2013;140:495-504.
75. Krishnamurthy S, Warner Ka, Dong Z et al. Endothelial Interleukin-6 defines the tumorigenic potential of primary human cancer stem cells. Stem Cells 2014;32:2845-2857.
76. David JJ, Waugh DJJ, Wilson C. The interleukin-8 pathway in cancer. Clin Cancer Res 2008;14:6735-6741.
77. Langowski JL, Zhang X, Wu L et al. IL-23 promotes tumour incidence and growth. Nature 2006;442:461-465.
78. Wang S, Chen F, Tang L. IL-32 promotes breast cancer cell growth and invasiveness. Oncol Lett 2015;9:305-307.
79. Grimmig T, Moench R, Kreckel J et al. Toll like receptor-2, -4, and -9 signaling promotes autoregulative tumor cell growth and VEGF/PDGF expression in human pancreatic cancer. Int J Mol Sci 2016:17:2060. Doi:10.3390/ijms17122060.
80. Pope JL, Ahmad R, Bhat AA, Washington MK, Singh AB, Dhawan P. Claudin-1 overexpression in intestinal epithelial cells enhances susceptibility to adenomatous polyposis coli-mediated colon tumorigenesis. Cancer 2014;13:1-13.
81. Karnoub AE, Dash AB, Vo AP et al. Mesenchymal stem cells within tumor stroma promote breast cancer metastasis. Nature 2007;449:557-563.
82. Mishra PJ, Humeniuk R, Medina DJ et al. Carcinoma-associated fibroblast-like differentiation of human mesenchymal stem cells. Cancer Res 2008;68:4331-4339.
83. Polyak K, Weinberg RA. Transitions between epithelial and mesenchymal states: acquisition of malignant and stem cell traits. Nat Rev Cancer 2009;9:265-273.
84. Bianchi G, Borgonovo G, Pistoia V, Raffaghello L. Immunosuppressive cells and tumour microenvironment: focus on mesenchymal stem cells and myeloid derived suppressor cells. Histol Histopathol 2011;26:941-951.
85. Spaeth EL, Dembinski JL, Sasser AK et al. Mesenchymal stem cell transition to tumor- associated fibroblasts contributes to fibrovascular network expansion and tumor progression. PLoS One 2009;4:e4992.86.
86. Wang J, Hendrix A, Hernot S et al. Bone marrow stromal cell-derived exosomes as communicators in drug resistance in multiple myeloma cells. Blood 2014;124:555-566.
87. Li Z, Chen L, Qin Z. Paradoxical roles of IL-4 in tumor immunity. Cell Mol Immunol 2009;6:415-422.
88. Oft M. IL-10: Master switch from tumor-promoting inflammation to antitumor immunity. Cancer Immunol Res 2014;2:194-199.
89. Massagué J. TGFβ in Cancer. Cell 2008;13:215-230.
90. Ye H, Cheng J, Tang Y, Liu Z, Xu C, Liu Y, Sun Y. Human bone marrow-derived mesenchymal stem cells produced TGF beta contributes to progression and metastasis of prostate cancer. Cancer Invest 2012;30:513-518.
91. Sato N, Yamabuki T, Takano A et al. Wnt inhibitor Dickkopf-1 as a target for passive cancer immunotherapy. Cancer Res 2010;70:5326-5336.
92. Rachner TD, Thiele S, Andy Göbel A et al. High serum levels of Dickkopf-1 are associated with a poor prognosis in prostate cancer patients. BMC Cancer 2014;14:649. http://biomedcentral.com/1471-2407/14/649.93.
93. Ma L, Weinberg RA. Micromanagers of malignancy: role of microRNAs in regulating metastasis. Trends Genet 2008;24:448-456.
94. Nicoloso MS, Spizzo R, Shimizu M, Rossi S, Calin GA. MicroRNAs–the micro steering wheel of tumour metastases. Nat Rev Cancer 2009;9:293-302.
95. Mishra PJ, Mishra PJ, Humeniuk R et al. Carcinoma-associated fibroblast-like differentiation of human mesenchymal stem cells. Cancer Res 2008;68:4331-4339.
96. McGrail DJ, Ghosh D, Quach ND, Dawson MR. Differential mechanical response of mesenchymal stem cells and fibroblasts to tumor-secreted soluble factors. PloS One 2012;7:e33248. Doi: 10.1371/journal.pone.0033248
97. Schwartz M. Rho signalling at a glance. J Cell Sci 2004;117:5457-5458.
98. Shiga K, Hara M , Nagasaki T, Sato T, Takahashi H, Takeyama H. Cancer-associated fibroblasts: their characteristics and their roles in tumor growth. Cancers 2015;7:2443-2458.
99. Kidd S, Spaeth E, Dembinski JL et al. Direct evidence of mesenchymal stem cell tropism for tumor and wounding microenvironments using in vivo bioluminescent imaging. Stem Cells 2009;27:2614-2623.
100. Grisendi G, Bussolari R, Veronesi E, Piccinno S, Burns JS, De Santis G. Understanding tumor-stroma interplays for targeted therapies by armed mesenchymal stromal progenitors: the mesenkillers. Am J Cancer Res 2011;1:787-805.
101. Liebelt BD, Shingu T, Zhou X, Ren J, Shin S, Hu J. Glioma stem cells: signaling, microenvironment, and therapy. Stem Cells Int 2016; vol. 2016, article ID 7849890, 10 pages. Doi:org/10.1155/2016/7849890
102. Garza-Treviño EN, Said-Fernández S, Martínez-Rodríguez HG. Understanding the colon cancer stem cells and perspectives on treatment. Cancer Cell Int 2015; 15:2.

103. Visvader JE, Lindeman GJ. Cancer stem cells: current status and evolving complexities. Cell Stem Cell 2012;10:717-728.

104. Puglisi MA, Tesori V, Lattanzi W, Gasbarrini GB, Gasbarrini A. Colon cancer stem cells: controversies and perspectives. World J Gastroenterol 2013;19:2997-3006.

105. Deonarain MP, Kousparou CA, Epenetos AA. Antibodies targeting cáncer cancer stem cells: a new paradigm in immunotherapy? MAbs 2009;1:12-25.

106. Nguyen LV, Vanner R, Dirks P, Eaves CJ. Cancer stem cells: an evolving concept. Nat Rev Cancer 2012;12:133-143.

107. Moore N, Lyle S. Quiescent, slow-cycling stem cell populations in cancer: a review of the evidence and discussion of significance. J Oncol 2011;2011, Article ID 396076, 11 pages.

108. Pannuti A, Foreman K, Rizzo P et al. Targeting notch to target cancer stem cells. Clin Cancer Res. 2010;16: 3141-3152.

109. Brabletz T, Jung A, Spaderna S, Hlubek F, Kirchner T. Opinion: migrating cancer stem cells - an integrated concept of malignant tumour progression. Nat Rev Cancer 2005; 5:744-749.

110. Grillet F, Bayet E, Villeronce O, Zappia L, Lagerqvist EL, Lunke S. Circulating tumour cells from patients with colorectal cancer have cancer stem cell hallmarks in ex vivo culture. Gut 2016; 0:1-9. ID: 10.1136/gutjnl-2016-311447.

111. Wagner W, Wein F, Seckinger A et al. Comparative characteristics of mesenchymal stem cells from human bone marrow, adipose tissue, and umbilical cord blood. Exp Hematol 2005;33:1402-1416.

112. Hendijani F. Human mesenchymal stromal cell therapy for prevention and recovery of chemo/radiotherapy adverse reactions. Cytotherapy 2015. doi: 10.1016/j.jcyt.2014.10.015.

113. Studeny M, Marini FC, Champlin RE et al. Bone marrow-derived mesenchymal stem cells as vehicles for interferon-beta delivery into tumors. Cancer Res 2002;62:3603-3608.

114. Lin X, Lu Y, Huang W et al. In vitro effect of adenovirus-mediated human gamma interferon gene transfer into human mesenchymal stem cells for chronic myelogenous leukemia. Hematol Oncol 2006;24:151-158.

115. Ren C, Kumar S, Chanda D, Chen J, Mountz JD, Ponnazhagan S. Therapeutic potential of mesenchymal stem cells producing interferon-alpha in a mouse melanoma lung metastasis model. Stem Cells 2008;26:2332-2338.

116. Chen X, Lin X, Zhao et al. A tumor-selective biotherapy with prolonged impact on established metastases based on cytokine gene-engineered MSCs. Mol Ther 2008;16:749-756.

117. Xin H, Kanehira M, Mizuguchi H et al. Targeted delivery of CX3CL1 to multiple lung tumors by mesenchymal stem cells. Stem Cells 2007;25:1618-1626.

118. Kanehira M, Xin H, Hoshino K et al. Targeted delivery of NK4 to multiple lung tumors by bone marrow-derived mesenchymal stem cells. Cancer Gene Ther 2007;14:894-903.

119. Loebinger MR, Eddaoudi A, Davies D, Janes SM. Mesenchymal stem cell delivery of TRAIL can eliminate metastatic cancer. Cancer Res 2009;69:4134-4142.

120. Lathrop MJ, Sage EK, Macura SL et al. Antitumor effects of TRAIL-expressing mesenchymal stromal cells in a mouse xenograft model of human mesothelioma. Cancer Gene Ther 2014;22:44-54.

121. Yuan Z, Kolluri KK, Sage EK et al. Mesenchymal stromal cell delivery of full-length tumor necrosis factor-related apoptosis-inducing ligand is superior to soluble type for cancer therapy. Cytotherapy 2015;17:885-896.

122. Yin PT, Shah S, Pasquale NJ, Garbuzenko OB, Minko T, Lee KB. Stem cell-based gene therapy activated magnetic hyperthermia to enhance the treatment of cancer. Biomaterials 2016. Doi:10.1016/J.Biomaterials.2015.11.023.

123. Niess H, von Einem JC, Thomas MN, Michl M, Angele MK, Huss R. Treatment of advanced gastrointestinal tumors with genetically modified autologous mesenchymal stromal cells (TREAT-ME1): study protocol of a phase I/II clinical trial. BMC Cancer 2015. Doi: 10.1186/s12885-015-1241-x

124. Namba H, Kawaji NH, Yamasaki T. Use of genetically engineered stem cells for glioma therapy. Oncol Lett 2016;11:9-15.

125. Turinetto V, Vitale E, Giachino C. Senescence in human mesenchymal stem cells: functional changes and implications in stem cell-based therapy. Int J Mol Sci 2016;17. Pii: e1164.

126. Clinical trials.gov identifier. https://clinical trials.gov/c12/results?term=Haploidentical+Stem+Cell+Transplantation+in+Neuroblastoma&Search=Search