

REVIEW

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# Interaction of MSC with tumor cells

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## Abstract

Tumor development and tumor progression is not only determined by the corresponding tumor cells but also by the tumor microenvironment. This includes an orchestrated network of interacting cell types (e.g. immune cells, endothelial cells, fibroblasts, and mesenchymal stroma/stem cells (MSC)) via the extracellular matrix and soluble factors such as cytokines, chemokines, growth factors and various metabolites. Cell populations of the tumor microenvironment can interact directly and indirectly with cancer cells by mutually altering properties and functions of the involved partners. Particularly, mesenchymal stroma/stem cells (MSC) play an important role during carcinogenesis exhibiting different types of intercellular communication. Accordingly, this work focusses on diverse mechanisms of interaction between MSC and cancer cells. Moreover, some functional changes and consequences for both cell types are summarized which can eventually result in the establishment of a carcinoma stem cell niche (CSCN) or the generation of new tumor cell populations by MSC-tumor cell fusion.

**Keywords:** MSC, Mesenchymal stroma/stem cells, Tumor cell signaling, Tumor microenvironment, Cellular interaction, Cell fusion

**Abbreviations:** CAF, Carcinoma-associated fibroblast; cAMP, Cyclic adenosine monophosphate; CCL5, CC-chemokine ligand 5; CSC, Cancer stem cells; CSCN, Cancer stem cell niche; DAPT, N-[N-(3,5-difluorophenacetyl-lalanyl)]-S-phenylglycine t-butyl ester; ECM, Extracellular matrix; EMT, Epithelial-mesenchymal transition; EMT-TF, EMT transcription factors; GJIC, Gap junctional intercellular communication; HMEC, Human mammary epithelial cells;IDO, Indoleamine 2,3-dioxygenase; miRs, microRNAs; MSC, Mesenchymal stroma/stem cells; OXPHOS, oxidative phosphorylation; PKA, protein kinase A; RANTES, regulated on activation, normal T cell expressed and secreted; SCCOHT-1, primary small cell hypercalcemic ovarian carcinoma cells; TIC, tumor-initiating cells; TME, tumor microenvironment

## Background

### Tumor microenvironment and associated cell populations

Solid tumors can be regarded as a complex organ with tumor cells and a variety of differentially organized cell types, establishing a certain immune status, contributing to blood vessel formation and neovascularization, and building an extracellular matrix which enables the associated cell populations to communicate within this tumor microenvironment (TME) [1, 2]. For further insights in tumor development and chemotherapeutic approaches, it is indispensable to understand the interplay of specific components of the TME, the occurring cellular communication processes and the resulting functions

of this network between cancer cells and the various tumor-associated cell populations.

Predominant cell types within the TME are represented by immune cells, fibroblasts, pericytes, endothelial cells, mesenchymal stroma/stem cells and sometimes adipocytes [3]. Immune cells present in the TME involve cells from both, the innate and adaptive immune system whereby lymphocytes represent the majority of tumor-infiltrating immune cells [4]. It is not surprising that immune responses inhibit tumor development but recent studies have also proposed that immune cells can promote cancer growth. CD8<sup>+</sup> T cells and CD4 T<sub>H</sub>1 T cells mainly exhibit anti-cancer effects since strong infiltration of tumor tissue by these cell types is associated with favorable prognosis in many solid tumors including breast, ovarian, cervical, lung and colorectal cancer [5]. In contrast, other T lymphocyte populations such as T<sub>H</sub>2 and T<sub>reg</sub> cells have been correlated with poor

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clinical outcome in several cancer types [5]. Likewise, B lymphocytes are attributed a dual role in tumorigenesis. Whereas high numbers of B cells in the tumor stroma are linked to favorable prognosis in breast cancer, mouse models revealed opposite results assigning a tumor promoting role for B lymphocytes [6, 7]. Moreover, natural killer and natural killer T cells also found in the TME are proposed to support favorable clinical outcome [3, 8]. Tumor-associated macrophages and myeloid suppressive cells represent tumor-promoting immune cells together with their derived cytokines IL-6, IL1 $\beta$ , IL23 and TNF $\alpha$  [9]. For instance, tumor-associated macrophages can interact with metastasizing breast cancer cells in the lung via VCAM-1 and promote tumor cell survival. Furthermore, released pro-inflammatory cytokines such as TNF $\alpha$  contribute to increased migration and invasiveness of breast and ovarian cancer cells [10].

In perivascular niches of tumor blood vessels pericytes are predominantly present and can associate with vascular endothelial cells by contributing to the formation of blood capillaries [11]. In contrast to normal healthy vasculature, tumor vessels display an abnormal physiology due to aberrant pericyte coverage and leaky endothelial layers upon increasing hypoxia [11]. Thus, normalization of tumor vasculature to enhance drug delivery and to reduce hypoxia in the tumor stroma might be a promising therapeutic approach since low pericyte coverage is associated with poor prognosis and pericyte depletion has been correlated with enhanced hypoxia and metastasis [12].

Further cell populations are represented by stromal cells or fibroblasts within the TME. The so-called cancer- or carcinoma-associated fibroblasts (CAFs) which are derived from various precursors like aberrant mesenchymal stroma/stem cells (MSC) or endothelial cells secrete a plethora of growth factors, cytokines, chemokines, structural protein components, and metabolites that communicate with tumor cells and promote oncogenesis by activating cell proliferation, tumor angiogenesis and invasive properties [3]. Thus, aberrant tumor-associated MSC can acquire different functions following interaction with tumor cells including enhanced secretion of TGF- $\beta$  to contribute to epithelial-to-mesenchymal transition (EMT) and immune-suppressive activities. Moreover, these aberrant MSC release VEGF for neo-vascularization within the TME and they produce CXCL12 (=SDF1 (stromal cell-derived factor 1)) to support tumor cell growth and survival [3].

Likewise, MSC are one of the key players within the TME and can either inhibit or promote tumor cell growth by distinct types of cellular interaction [13]. Reduction of tumor growth by MSC can be mediated via inhibited angiogenesis, suppressed Wnt and AKT signaling, or induction of cell cycle arrest and apoptosis [14, 15].

MSC are recruited to tumor sites and can be activated by certain stimuli such as TGF- $\beta$ 1 to develop a CAF-like phenotype [16].

In addition to a variety of different cell populations in the tumor microenvironment, the extracellular matrix (ECM) also plays an important role in the regulation of tumor development and progression. The ECM does not only provide a structural scaffold for the tumor stroma with fibrous proteins such as elastin, collagen and fibronectin, and proteoglycans like chondroitin sulfate and hyaluronic acid, but in addition, ECM is abundant source of soluble factors including growth factors, angiogenic factors, cytokines and chemokines. This dynamic and complex network contributes to the inter-cellular cross-talk with cancer cells. During tumor development the ECM is usually dysregulated, remodeled and appears disorganized [17, 18]. Collagens are the most abundant fibrous proteins in the extracellular matrix. Nevertheless, collagen deposition and cross-linking or tight association with other structural matrix proteins such as elastins, laminins or fibronectin has been associated with cancer invasion and metastasis [19]. Cross-linking of collagen by modifying enzymes such as lysyl oxidases leads to a more rigid phenotype of the whole tumor [20]. Stiffness of the tumor stroma causes intracellular contraction and a more rigid cytoskeleton which in turn leads to a higher migratory capacity [17].

Taken together, the tumor microenvironment contains a variety of initially non-malignant cell types (immune cells, endothelial cells, fibroblasts, MSC) which develop tumor-associated functionalities together with soluble factors and ECM components that all communicate with cancer cells thereby inhibiting and promoting tumorigenesis. Nonetheless, it is important to strengthen that the TME is a dynamic and heterogeneous environment whose total composition varies between tumors and patients. However, the tumor stroma exhibits common features of these distinct cell types which may serve as interesting therapeutic targets [18].

#### **Role of mesenchymal stroma/stem cells and possible interactions**

MSC are multipotent cells that preferentially reside in perivascular niches of nearly all human tissues and organs like bone marrow, adipose tissue, heart or lung and neonatal tissues including placenta, amniotic membranes or umbilical cord [21–24].

Apart from various sources and heterogeneous populations, MSC exhibit certain common properties ranging from the expression of surface markers (CD73, CD90, CD105) to the differentiation along the adipogenic, chondrogenic and osteogenic lineage [25]. Their functions are extremely diverse and depend on the tissue-specific origins and the special microenvironment in

which MSC are embedded. Accordingly, in vitro cultured MSC can develop different morphologies and properties whereby long-term stemness can be maintained which includes MSC cultures for up to 10 passages without loss of proliferative capacity, telomerase activity or differentiation capacity [26–28].

In addition to the MSC heterogeneity, subpopulations are characterized with altered proliferative capacity and aging properties [29] which may also include epigenetic changes. Selective MSC subtypes carry additional surface markers such as Stro-1 [30], CD146 [31], the chemokine receptors VCAM-1 (CD106) and ICAM-1 (CD54) [32] predominantly found in bone marrow-derived MSC, CD271 [33], or the more embryonic like stem cell markers Oct-4 and Sox2 [34], which accompany the multi-faceted MSC functionalities and affect interactions with other cell types.

MSC are recruited to sites of injury to support tissue repair, stem cell homeostasis and immunomodulation. Similar functions are displayed by MSC during tumor development, whereby permanently proliferating and invasively growing tumor cells create an inflammatory microenvironment displaying a certain kind of “wound that never heals” [35]. Thereby, MSC exhibit tissue repair functions and support angiogenesis which simultaneously contributes to promote the growth of cancer cells [35, 36]. Migration of MSC towards the inflammation site leads to cellular interactions that occur both directly via gap junctions, membrane receptors and nanotubes and indirectly via soluble structures and factors. Through releasing of different endocrine and paracrine signals, MSC stimulate neighbored cells with pro- and/or anti-tumorigenic activities. In turn, MSC can be stimulated by tumor cells to develop an aberrant tumor-associated phenotype [14].

#### **Direct and indirect interaction of MSC with tumor cells**

Different types of cross-talk between MSC and cancer cells both directly and indirectly are illustrated in Figs. 1 and 2, respectively. Several direct and/or indirect mechanisms of interaction contribute to MSC-mediated stimulation of cancer cell growth including Notch signaling, nanotube formation, gap junctional intercellular communication, and/or the exchange of cytokines/chemokines, extracellular vesicles and exosomes [36–38]. It is thus important to emphasize that these different types of indirect and direct interactions are always multidirectional, therefore affecting and altering both, the tumor cells as well as the MSC or other cellular partners.

#### **Indirect interaction of MSC with tumor cells**

##### ***Cytokines, chemokines and growth factors***

Indirect communication proceeds via secretion of soluble molecules (e.g. growth factors, cytokines, and chemokines) that might function as substrates for specific

receptors of neighboring cells to activate intracellular signaling pathways. Activated MSC produce and secrete a large variety of bioactive molecules suggesting MSC as Medicinal Signaling Cells [39]. MSC-mediated release of these biological compounds can affect adjacent populations like tumor cells as cellular modulators. For instance, previous studies revealed that secretion of the CC-chemokine ligand 5 (CCL5) by MSC also known as RANTES (regulated on activation, normal T cell expressed and secreted) can interact with appropriate chemotactic cytokine receptors such as CCR1, CCR3 or CCR5 [35]. Moreover, CCL5 can activate the G-protein coupled receptor GPR75 in breast cancer cells in a paracrine manner. Such CCL5 signaling among further stimuli resulted in acceleration of migratory, invasive and metastatic capacity of the breast cancer cells [35] (Fig. 1).

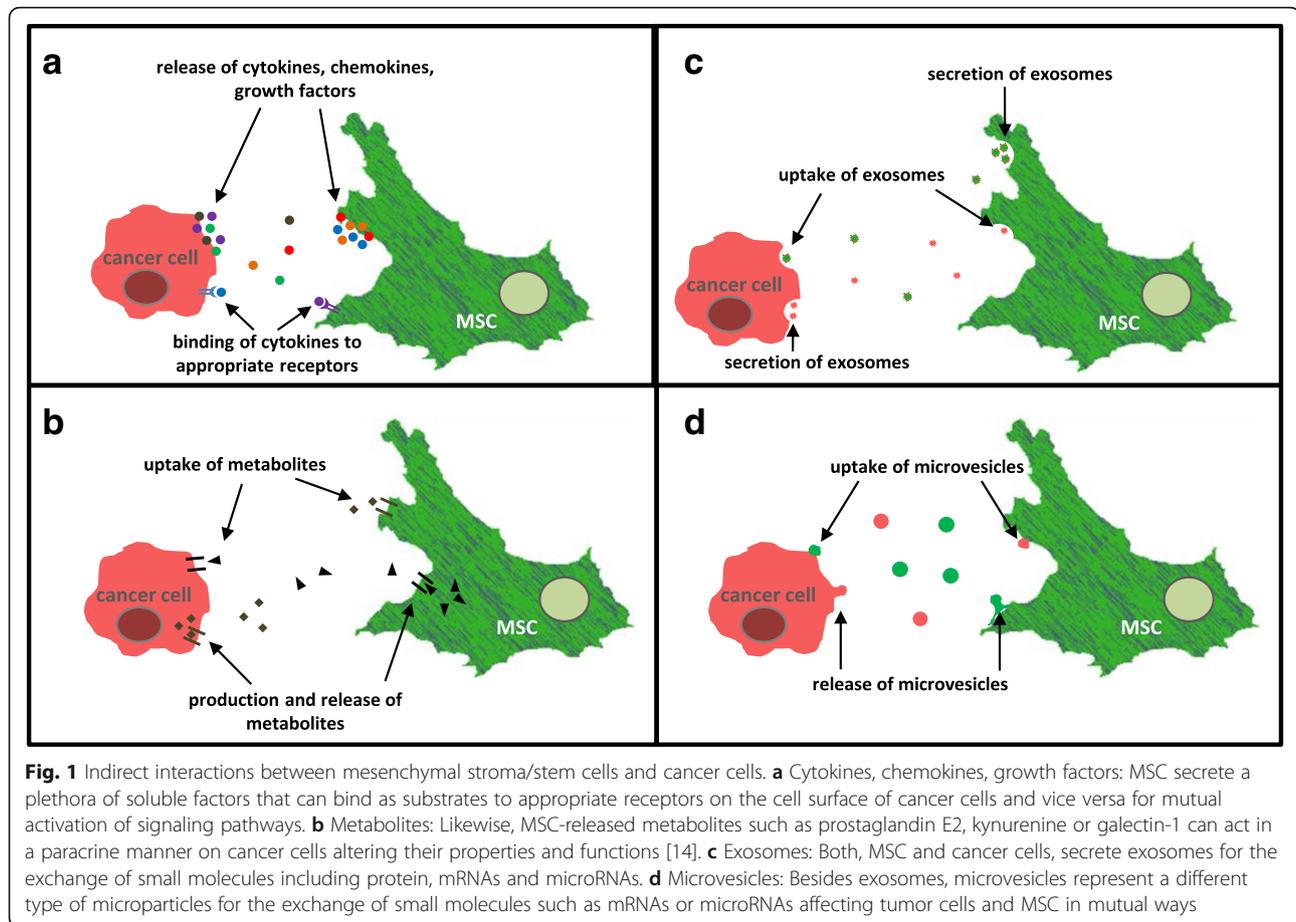
#### **Metabolites**

Various metabolites within the TME released and exchanged by the different interacting cell populations strongly affect the progress of malignancy and contribute to alter tumor cell properties such as motility, survival and self-renewal. These effects are relayed in part by altered energy turnover and consumption whereby lactate, glutamine and keton bodies contribute to a functional change of cancer cells toward an OXPHOS addicted phenotype [40].

Besides the secretion of cytokines and chemokines into the tumor stroma, several metabolites such as prostaglandins or indoleamine 2,3-dioxygenase (IDO) represent further released soluble factors stimulating cells in a paracrine manner and contributing to the interaction network of the TME [41, 42].

Previous studies observed that cyclic adenosine monophosphate (cAMP) can inhibit DNA damage-induced p53 accumulation via activation of protein kinase A (PKA) resulting in increased survival of lymphoblastic leukemia cells [43, 44]. In this context, MSC-derived prostaglandin E2 contributed to protect lymphoblastic leukemia cells from DNA-damage induced p53 accumulation and cell death via PKA supporting a tumor promoting role of MSC in the TME [45, 46].

A close metabolic coupling of MSC was demonstrated with osteosarcoma cells whereby tumor cell-induced oxidative stress in MSC was associated with higher levels of lactate and lactate efflux receptors. Consequently, osteosarcoma cells increased expression of lactate influx receptors whereby lactate secreted by MSC and incorporated by osteosarcoma cells elevated ATP production and increased migratory capacity of the cancer cells [47]. In general, metabolic modifications within the TME including osmolarity, hypoxia or acidification influence tumor cell growth and appropriate malignancy [48].



### Microparticles

Another indirect interplay between MSC and cancer cells is represented by the exchange of microparticles including exosomes and microvesicles. Whereas exosomes are defined as small homogeneous membrane particles of endocytic origin ranging in size from 40 to 100 nm, microvesicles are directly shed from the plasma membrane into the extracellular environment representing a larger and heterogeneous population with 50 to 1000 nm in diameter [49]. Although both types of microparticles differ in size, origin and releasing mechanism, exosomes and microvesicles contain a large panel of proteins, functional mRNAs and regulatory microRNAs (miRs) which contribute to the cellular interplay between MSC and cancer cells within the tumor microenvironment and thereby altering the functionality of recipient cells [37].

Previous results demonstrated that MSC-derived exosomes can modulate the function of tumor cells by induction of MMP-2 and ecto-5'-nucleotidase activity resulting in a more complex tumor microenvironment with higher tumor heterogeneity [37, 50]. Alternatively, MSC-derived exosomes also contain tumor supportive miRs which enhance tumor growth in vivo [51]. Vice

versa, cancer cells secrete exosomes as well and recent work demonstrated that prostate cancer cell-derived exosomes stimulate the differentiation of bone marrow-derived MSC into pro-angiogenic myofibroblasts with tumor growth promoting functions [52].

Anti-tumor effects have been also observed with microvesicles derived from human umbilical cord Wharton's jelly MSC which inhibit bladder tumor cell growth via cell cycle arrest and induction of apoptosis, both in vitro and in vivo [53].

Although functional mechanisms for these controversial observations of tumor promoting versus tumor inhibiting roles of MSC-derived microvesicles and exosomes remain to be elucidated, it appears conceivable that the cargo of these microparticles which depends on the activation status and state of development of the originating MSC is primarily responsible for the type of action on tumor cells.

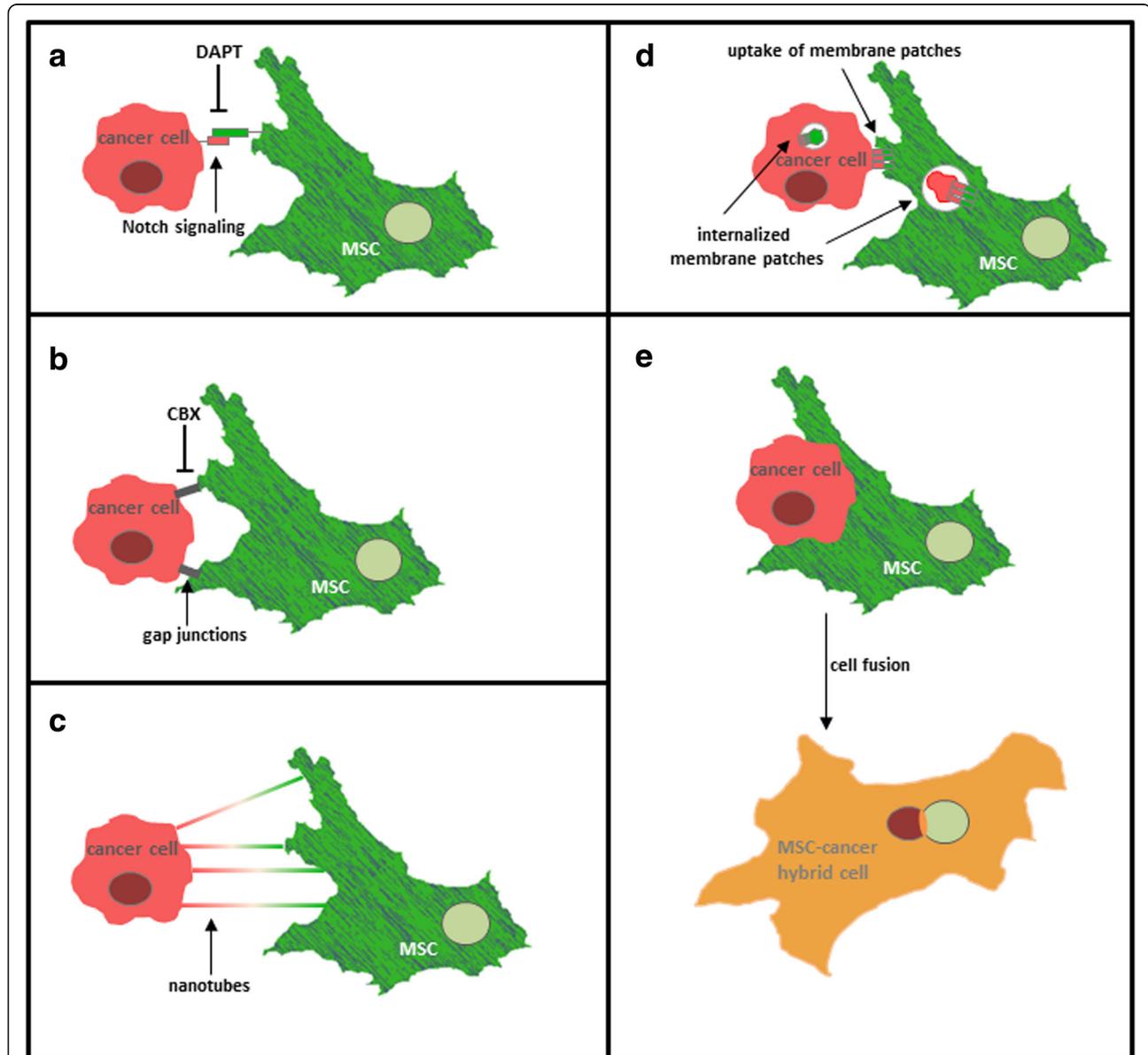
### Direct interaction of MSC with tumor cells

#### Notch signaling

Notch signaling plays an important role in fundamental processes such as support of tissue repair or regulation of various immune cell functions [54].

Activation of notch signaling involves ligand binding to the notch receptor, cleavage of the intracellular domain of the notch receptor by a presenilin- $\gamma$ -secretase and translocation of this cleavage domain into the nucleus thereby resulting in trans-activation of downstream target genes [55] (Fig. 2).

Previous experiments indicated a functional involvement of the notch pathway during the interaction between MSC and breast cancer cells [36]. Inhibition of notch signaling via N-[N-(3,5-difluorophenacetyl-lalanyl)]-S-phenylglycine t-butyl ester (DAPT), a  $\gamma$ -secretase inhibitor, reduces MSC-mediated CD90 expression and



**Fig. 2** Direct interactions between mesenchymal stroma/stem cells and cancer cells. **a** Notch signaling: A prominent example for direct cell-to-cell interaction is represented by Notch signaling. DAPT, a Notch signaling inhibitor, was shown to decrease functional alterations of breast cancer cells after co-culture with MSC underlining the involvement of Notch signaling in MSC-cancer cell interactions. **b** GJIC: Both MSC and cancer cells build gap junctions for intercellular communication. Gap junctional intercellular communication (GJIC) can be inhibited by gap junction inhibitor carbenoxolone (CBX) resulting in lesser interactions and functional alterations of cancer cells and MSC. **c** Nanotube formation: Long and thin plasma membrane structures formed between MSC and cancer cells allow the transport of small molecules and organelles for cellular cross-talk leading to altered functions and phenotype. **d** Trogocytosis: An exchange of whole plasma membrane fragments via an active transfer outlines a further possible interaction type between MSC and cancer cells resulting in structural and functional alterations of the recipient cell. **e** Cell fusion: In rare cases, mesenchymal stem cells have the capacity to fuse with various cancer cell types such as breast, ovarian, lung and gastric cancer cells. The molecular mechanism about the formation of such cancer hybrid cells is still unknown

growth of breast cancer cells in co-culture experiments [36, 56]. Moreover, DAPT could partially reduce MSC-induced EMT in pancreatic cancer cells emphasizing the involvement of notch signaling during MSC-cancer cell interactions [57].

#### **Gap junctional intercellular communication (GJIC)**

Gap junctions connect adjacent cells for intercellular, direct communication called gap junctional intercellular communication (GJIC) which can regulate cell growth and differentiation or maintain tissue homeostasis. One gap junction channel is composed of two hemi-channels from each interacting cell. One hemi-channel is formed by 6 connexin protein subunits and each connexin in turn features four transmembrane domains. Typically small molecules and second messenger such as cAMP and  $Ca^{2+}$ -ions are transported through gap junctions [58].

Acquisition of CD90 by breast cancer cells after co-culture with MSC is associated with GJIC signaling since carbenoxolone, a gap junction inhibitor, reduces MSC-mediated CD90 expression of breast cancer cells [36].

#### **Nanotubes**

Nanotubes represent thin, dynamic cytoplasmic protrusions which connect two cells enabling the exchange of a variety of biological cargo ranging from organelles such as mitochondria to small molecules including calcium ions and glycoproteins over longer distances [59].

Besides exchange of cargo between tumor cells themselves [60], cancer cells have been reported to form nanotubes with MSC as well [61]. In particular, breast cancer cells MDA-MB-231 acquire mitochondria from bone-marrow derived MSC via nanotubes resulting in altered metabolic activity and increased proliferative and invasive capacity [61].

#### **Trogocytosis**

A further mechanism for direct cross-talk between MSC and cancer cells is displayed by trogocytosis. This type of direct cellular interaction was firstly described between immune cells for the transfer of surface molecules from antigen-presenting cells to lymphocytes as an active mechanism [62]. Likewise, trogocytosis has been observed between MSC and cancer cells. Thus, ovarian cancer cells captured stromal membrane patches resulting in chemoresistance [63]. Moreover, trogocytosis has been suggested during interaction of MSC with a variety of tumor cells including ovarian cancer and breast cancer cells [38].

#### **Cell fusion**

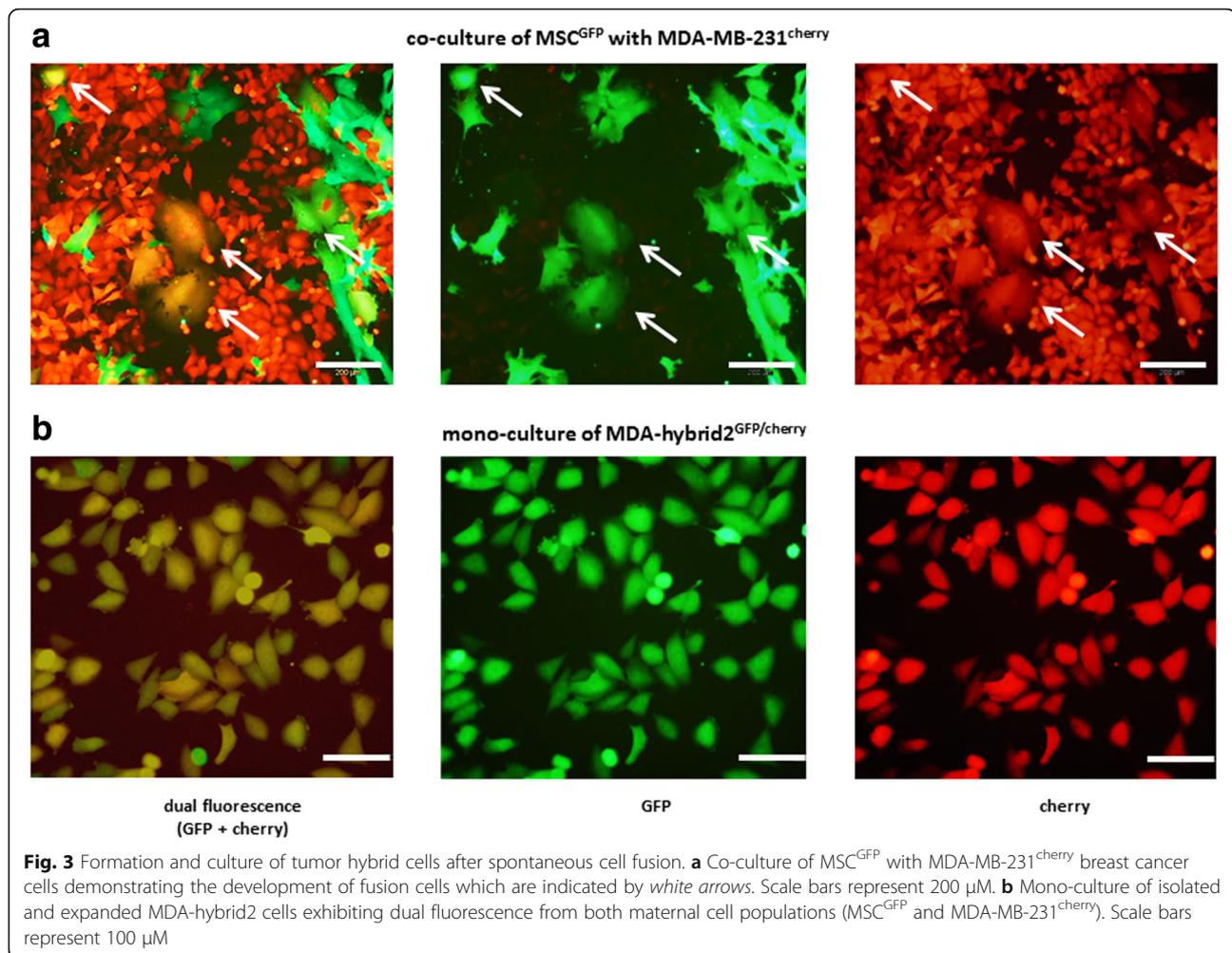
The closest/strongest and most complex interaction between MSC and cancer cells is the formation of fusion

or hybrid cells which also represents a very rare event whereby underlying molecular mechanisms are still not fully understood. Co-culture of MSC with cancer cells like breast or ovarian cancer at certain conditions in vitro can lead to the development of hybrid cells by fusion of the two parental cell lines [38]. Potential fusion events depend on the cell density, the cell ratio of the parental populations, the medium components and culture conditions (ionic strength, pH, hypoxia) among others. However, the associated signaling pathways and the precise requirements either favoring or inhibiting such hybrid cell formations remain unclear. Intercellular fusion in general represents an intricate and highly regulated event which plays an important role in fundamental processes during development, for instance during fertilization between sperm and egg [64]. Although various studies suggest a contribution of tumor cell hybrids to cancer metastasis, there is still little known about cell fusion in pathophysiological processes like cancer and the role of cell-fusion tumor products.

Nevertheless, hybrid cells from human breast cancer and breast epithelial cells are well characterized [65] and spontaneously fused hybrid cells have been reported in several co-cultures between MSC and various cancer cell lines including breast, ovarian, lung and gastric cancer [36, 38, 66–68]. Figure 3a exemplarily outlines a co-culture of primary human umbilical cord-derived MSC and the breast cancer cell line MDA-MB-231. In order to distinguish both populations, MSC and tumor cells were stably transduced with a lentiviral vector carrying either the eGFP or the mCherry gene, respectively, resulting in green-fluorescing MSC<sup>GFP</sup> and red-fluorescing MDA-MB-231<sup>cherry</sup>. In such a co-culture system with MSC and cancer cells, yellow-fluorescing hybrid cells are spontaneously formed within 3 to 6 days whereby the cell size and shape varies depending on the culture conditions and the contribution of parental cell populations [36].

Besides the labeling of both parental cell lines with fluorescent lentiviral vectors, another system has been applied to clearly identify hybrid cells in a co-culture. The so-called bimolecular fluorescence complementation involves a lentiviral transduction of both parental cells as well whereby the eGFP gene is separated into two non-fluorescent halves and each cell type is transfected with one of these halves. Consequently, only a fusion between a mesenchymal stem cell and a cancer cell can bring these two different halves together resulting in a functional GFP fluorescence after expression that is detectable via fluorescence microscopy or flow cytometry [66].

Fused hybrid cells generated in a labeled co-culture can be isolated by FACS and subsequent single cell cloning [68]. A successful isolation and expansion of one



single cell clone derived from a co-culture between MSC<sup>GFP</sup> and MDA-MB-231<sup>cherry</sup> is displayed in Fig. 3b.

Whereas knowledge about tumor cell fusion remains scarce, certain characteristics of properties and functions are available about MSC-cancer hybrid cells.

Formation of hybrid populations was reported in various studies between MSC and breast cancer as well as ovarian cancer cells [14, 36, 38]. Moreover, in vitro fusion was documented in MSC which were derived from human embryonic stem cells and fused with various breast cancer cell lines including MDA-MB-231, T47D, MCF7 and MCF10A. These hybrids acquired characteristics from both parental cell types (MSC and breast cancer cell) such as enhanced migratory capacity and expressed high motility like MSC, but their migration movement was nondirectional similar to the breast cancer cells [66]. Likewise, a higher migration rate and concomitant acquisition of distinct MSC-like characteristics was assigned to breast cancer hybrids [69]. The acquisition of some stemness properties was suggested in hybrid cells generated from MSC with gastric cancer

cells including increased expression of Oct4, Nanog, Sox2 and Lin28. Moreover, expression of CD44 and CD133 on hybrid cells was elevated compared to parental gastric cancer cells. In addition, gastric cancer fusion cells featured a higher proliferative capacity as compared to the parental cell lines [68].

A variety of important questions concerning tumor hybrid cells remain to be elucidated with respect to the existence, frequency and mechanisms of formation in vivo as well as to the role of these fused cell types in tumorigenesis and initiation of metastasis. At least breast and gastric cancer hybrids provide evidence for enhanced tumorigenic and metastatic properties [68, 69]. Nonetheless, several further questions include cell biological properties, chemosensitivities and -resistance and a possible relationship to cancer stem cells [70].

#### Molecular and functional consequences during interaction of MSC with tumor cells

During the multistep procedure of tumorigenesis, intercellular communication of diverse cell types within the

TME contributes to the malignancy of primary tumor cells as well as their metastatic ability [71]. In co-culture models of MSC populations together with different kinds of breast and ovarian tumor cells, MSC increase the proliferation of cancer cells [38]. Multiple cellular interactions between MSC and breast cancer cells are accompanied by increased growth of breast cancer both in vitro and in vivo [72] including MSC-mediated induction of CD90 expression in the tumor cells. This transient CD90 expression in breast cancer cells results from different kinds of interactions during co-culture with MSC such as microparticles, notch signaling, GJIC or nanotube formation [36–38]. Of interest, MSC functionality can alter during chemotherapy displaying different effects on breast cancer cells [73]. Whereas MSC exhibit close vicinity to breast cancer cells within the tumor microenvironment, there are also cellular interactions observed between MSC and normal human mammary epithelial cells (HMEC) which are usually localized in the normal fibroglandular breast tissue [38].

In ovarian cancer cells, MSC can induce further surface markers besides expression of CD90 such as functional CD73 and CD105. Thus, primary small cell hypercalcemic ovarian carcinoma cells (SCCOHT-1) acquired the capability to metabolize cyclic adenosine 3', 5'-monophosphate (cAMP) underlining the bidirectional molecular exchange between tumor cells and MSC [38].

Moreover, up-regulated mitotic spindle-associated factors (MZT2A) and epithelial mitogens (EPGN) suggested the promotion of proliferative capacity in ovarian cancer cells. In parallel, a down-modulation of transcription factors like TAL1, transcripts of the basic helix-loop-helix family FOS and FOSB, HES1 and HES5 are also related to the promotion of cancer development. In addition, growth factors of the bone morphogenetic protein family were acquired by ovarian cancer cells in the presence of MSC [38], whereby overactivation of BMP signaling contributes to the development of certain adenocarcinoma. Together, gene inductions during MSC and cancer cell co-culture demonstrated that MSC not only support ovarian cancer cell proliferation capacity but also induce pro-metastatic properties of ovarian cancer cells [74]. Vice versa by looking at MSC, mutual functional alteration during co-culture with tumor cells also include a variety of different gene transcripts which are up- or down-regulated in these stroma/stem cells as analyzed by RNA microarrays [38, 74]. Of interest, MSC expressed increasing levels of epithelial cell-specific transcripts including a group of KRT family genes, which are involved in the production of keratins for supporting the structural framework requirements of epithelial cells. Also certain cell-to-cell interaction related genes, intercellular junction *DSP* gene, the cell-cell adhesion-related genes *MPZL2* and *SCEL*, and the calcium-dependent

cell-cell adhesion glycoprotein gene *CDHI* are all up-regulated in MSC after co-culture with ovarian cancer cells. Conversely, a variety of cytokine mRNAs such as CSF3, IL1A, CCL20, LIF, TNF, CXCL1, CXCL2, CXCL3, and CXCL12 are down-regulated in MSC in the presence of ovarian cancer cells [38].

Furthermore, undetectable expression of the epithelial cell adhesion molecule (EpCAM) in normal MSC significantly increased both, at the mRNA and protein level after co-culture with different ovarian cancer cell lines such as SK-OV-3 or NIH:OVCAR-3 [38]. Together these findings substantiate that MSC gain certain epithelial-like cell functionalities during interaction with ovarian cancer cells and may therefore develop an aberrant and more tumor-associated phenotype. Therefore, the mutual bidirectional interactions further suggest a more epithelial-type conversion of MSC compared to transitional properties of mesenchymal characteristics in the ovarian cancer cells.

#### **MSC and cancer stem cells**

Previous work presented evidence for tumor-initiating cells (TIC) in mammary carcinoma also termed cancer stem cells (CSC) with increased expression of mesenchymal characteristics including vimentin, fibronectin and N-cadherin instead of E-cadherin [75]. Moreover, low expression of GPI-anchored sialoglycoprotein cell adhesion molecule CD24 paralleled by high expression of the hyaluronan receptor CD44 as well as expression of aldehyde dehydrogenase 1 are attributed with CSC. Further studies in mammary tumors revealed that IL6 produced by cancer cells interacts with IL6 receptor on aldehyde dehydrogenase 1-positive mesenchymal cells, whereby this IL6 signaling-mediated chemotaxis may facilitate recruitment of further MSC to the tumor microenvironment and induction of CXCL7 production by these cells. Vice versa, MSC-derived CXCL7 stimulates the cancer cells via activation of the CXCR2 receptor and induces the synthesis of additional cytokines such as IL6 and IL8 to generate a positive feedback loop which contributes to increased MSC attraction and enhanced interactions with tumor cells [76].

Following continuous mutual interaction within the TME, cytokines and particularly IL1 released by tumor cells can stimulate arachidonic acid metabolism and subsequent PGE2 production in MSC. Vice versa, released cytokines and PGE2 together can induce  $\beta$ -catenin signaling in the neoplastic cells which contributes to the development of more immature stem cell-like properties [41].

During these interactions characteristics of a mesenchymal phenotype are progressively acquired by the cancer cells [36–38] which may include a MSC-mediated epithelial-to-mesenchymal transition (EMT) in the cancer cells. This suggests a retrodifferentiation process of

cancer cells into a stem cell-like phenotype [77, 78] which involves a potential carcinoma stem cell niche (CSCN) [41] provided by interaction of MSC with cancer cells. A corresponding niche-forming property has been assigned to MSC by displaying the capacity to organize the hematopoietic stem cell niche [79, 80]. Alternatively, during cellular interactions or reprogramming MSC can acquire functional properties from the cancer cells which are displayed in an altered tumor-associated mesenchymal stem cell phenotype. Such oncogenic reprogramming can transform MSC into aggressive sarcoma cells [81] and may also play a role in tumors with mesenchymal characteristics such as desmoid tumor [82].

Consequently, the newly arising cancer cell populations after EMT and interaction display an enhanced phenotypic plasticity including metastatic potential and altered responsiveness/resistance to therapeutic approaches.

#### **MSC interactions and epithelial-mesenchymal transition (EMT)**

Conversion of epithelial cells into a mesenchymal phenotype termed as EMT is a prerequisite in physiological processes during early stages of embryonic development including gastrulation and myogenesis [83]. However, EMT is also involved in pathological events such as fibrosis, tumor development and metastasis whereby TGF- $\beta$  signaling plays an important role [84–86]. EMT as a biological process allows an epithelial cell to undergo complex multiple changes of its cell pattern and morphology which leads to a mesenchymal cell phenotype. This transition is generally delineated by changes of epithelial-like cell properties, for instance 1) down-modulation of E-cadherin for loss apico-basal polarity and cell-cell adhesion, 2) secretion of enzymes such as matrix metalloproteinases to degrade the ECM, and 3) upregulation of mesenchymal markers, e.g. vimentin, N-cadherin and fibronectin, all of which are paralleled by elevated migration, acquired invasiveness and increased resistance to apoptosis [83, 85, 87].

EMT has been implicated in several tumors including breast, ovarian and colon cancer [88–91]. In previous studies, a plethora of oncogenic EMT inducers have been characterized which comprise the EMT transcription factors (EMT-TF) Snail1/2, Slug, Twist1 and Zeb1/2 and signaling pathways such as TGF $\beta$  and Wnt [92]. Besides the overall common function of the EMT-TF in repressing E-cadherin for loss of cell adhesion, Snail and Slug also regulate tight junction stability and protease expression while Twist1 induces mesenchymal gene expression [83, 93].

Recently, it has been demonstrated that colon cancer cells increased expression of EMT-TF such as Zeb1/2, Slug, Snail and Twist which was paralleled by a down-regulation of E-cadherin expression. Moreover, these

colon cancer cells acquired the expression of stemness genes including Oct4 and Sox2 after co-culture with adipose tissue-derived MSC. Additionally, the morphology of colon cancer cells was altered to an elongated, fibroblast-like cell shape underlying the conversion to a mesenchymal phenotype. Vice versa, colon cancer cells were able to induce secretion of cytokines (TNF $\alpha$ , IL10, IFN $\gamma$ ) and metastasis-related factors (VEGFC, MMPs) in MSC via activation of Wnt signaling which in turn resulted in activation of Wnt pathways in colon cancer cells. Of interest, inhibition of Wnt signaling reduced the invasiveness and tumorigenicity of cancer cells both in vitro and in vivo [94].

Besides these direct interactions between MSC and colon cancer cells leading to induction of EMT and higher invasiveness, indirect interactions also resulted in EMT induction. Adipose tissue-derived MSC can alter cell confluence and migration of SKBR3 breast cancer cells, increase mammosphere formation, induce EMT, and alter tumor cell morphology [95]. These features were attributed to molecular changes induced by MSC-secreted cytokines and chemokines in breast cancer cells.

Nasopharyngeal carcinoma (NPC) cells exhibited a higher proliferation and migration capacity after uptake of MSC-derived exosomes. Moreover, EMT markers were significantly altered after uptake of exosomes including down-modulation of E-cadherin and upregulation of vimentin and N-cadherin. This indirect communication between MSC-derived exosomes and cancer cells induced EMT, promoted tumor growth in vitro and in vivo and metastasis [96].

Further studies substantiate the occurrence of direct and indirect MSC-cancer cell interactions leading to induction of EMT, thereby altering the cell pattern and morphology of cancer cells to a mesenchymal phenotype which facilitates metastasis to distant tumor sites [38, 41, 97–99].

#### **Conclusions**

Different types of intercellular communication both, indirect and/or direct between MSC and tumor cells (from solid cancers of the breast, ovar, colon, etc.) involve mutual functional alterations whereby the tumor cells acquire certain mesenchymal properties. Depending on the type and the extent of cellular interaction, even completely new tumor cell populations can be formed in the rare event of a MSC and tumor cell fusion. In addition, MSC which are recruited to the invasive tumor sites to initiate regenerative potential are progressively altered into an aberrant MSC phenotype to functionally support tumor cell survival. Therefore, tumor-associated aberrant MSC are involved in tumor cell protection and consequently, contribute to certain effects of chemotherapeutic resistance either directly by

expression of protective extracellular matrix proteins as a drug barrier and/or indirectly by promoting EMT of tumor cells and participating in a carcinoma stem cell niche. Such development includes the interplay with various other tumor-associated cell populations and restructure of the ECM, furthermore highlighting the tumor microenvironment as potential therapeutic anti-tumor target.

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#### Authors' contributions

CM, YY and RH drafted the manuscript. Figures were designed by CM and YY and finalized by RH. The manuscript was structured by RH. All authors read and approved the final manuscript.

#### Competing interests

The authors declare that they have no competing interests.

#### Consent for publication

All authors have critically read and approved this work.

#### Ethical approval and consent to participate

Not applicable.

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