

Cancer Stem Cells, Together with Mesenchymal Stem Cells and Other Cooperative Cells, Govern the Initiation and Development of Cancer

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Abstract

Cancer stem cells, a family expressed by all cancers, are necessary for the origin and critical for the growth of all cancers. In the latter tissue the cancer stem cells are concentrated and operative in small areas called niches, analogous to the stromas of non-cancer tissues. In addition to cancer stem cells, the niches contain normal cancer cells and various types of cooperative non-cancer cells. Most important among the latter are the mesenchymal stem cells, analogous to those expressed by non-cancer tissues, that are important, and in some cases necessary for the development of several cancers. Various effects dependent on the already mentioned, two types of stem cells are induced not directly by them, but via their secreted extracellular vesicles, the exosomes and ectosomes. Additional cancer-cooperative cells, concentrated within the niches, include fibroblasts and immune cells that participate in the development of some cancer-relevant processes including angiogenesis. Cancer stem cells govern many critical processes of cancer life, from initiation and progression, including generation and distribution of metastases, therapy resistance, and cancer-relapse, as well as additional severe tissue problems such as efflux of anti-cancer drugs, autophagy, and evasion of immune surveillance. Without their stem cells specific cancers cannot develop. In case of defect, the cancer stem cells are induced by transformation of either normal cancer cells or mesenchymal stem cells. The present knowledge about cancer stem cells and their key effects are of critical importance in the development of therapeutic processes addressed against these cells

Keywords: Mesenchymal stem cells, Cancer stem cells, Extracellular vesicles, Niches, Cancer differentiation, Cancer initiation, Progression and relapse, Metastasis, Cancer microenvironment, Therapy targets

Introduction

Until the end of last century, the origin and development of cancers were mostly attributed to the proliferation of their active cells, operative in collaboration with non-cancer cells of the patients. In particular, an important role was attributed to cells now recognized as mesenchymal stem cells (MSCs), first considered a few decades ago. Initially, however, the role attributed to these cells was only limited. After 1990, interest about MSCs increased progressively, starting upon their discovery to induce relevant functions, including tissue regeneration and therapy of diseases. Among therapies, a growing number was recognized to depend on MSCs, first including those of bone and cartilage followed by blood,

heart, brain, liver, kidney, lung, and almost all the other organs [1-3]. Soon thereafter the effects of MSCs were found to be even larger, mediated by the secretion of their extracellular vesicles (EVs) including exosomes and ectosomes [4,5].

Based on the data summarized so far, MSCs and their EVs were considered as the cells and vesicles active in all diseases. Such definitions, however, appeared short to other major classes of cells and vesicles, those of cancer. Cells somewhat analogous to MSCs were shown to be expressed by cancers, initially by those of brain and breast [6,7]. When the interpretation of these cells was extended to other types of cancers, they were appropriately named cancer stem cells, CSCs.

Increasing studies of CSCs, carried out during the following years, lead to their functional and pathological characterization. Subpopulations of heterogeneous CSC revealed their capacity of self-renewal and aberrant differentiation for divergent lineages of cancer cells [6-8]. CSC concentrations were found to occur within small tissue volumes, the niches, analogous to the stromas of non-cancer cells [9,10]. Niches are the sites of high degree CSC plasticity dependent on transitions from slowly cycling quiescent phases to actively proliferative phenotypes [10-12]. Within niches, stem cells and their EVs are accompanied by other cells and their EVs: normal cancer cells, fibroblasts, immune (macrophages, lymphocytes) and other cells, all cooperative to cancer function (Figure 1) [12-18]. Some of the general properties of CSCs and their vesicles were found to depend on the cooperation with MSCs and the other cell types [13,14]. The tumor microenvironment (TME), different from the non-cancer microenvironments, includes in space the niches and other areas of cancer development and growth [19,20]. Finally, studies about CSCs and their associated cells/structures have been developed in areas of potential interest for therapeutic development [10]. Some of these studies have already reached the field of clinical medicine [21,22]. So far, most published reviews and articles in the field were focused on single or a few specific cancers and their peculiar properties. The authors attempt is a short presentation of general cancer developments and progress, with special interest for recently published studies and their interpretation.

MSCs and their EVs in cancer

In agreement with a general criterion anticipated in the Introduction, present Section is focused on a family of cells and their EVs present in all diseases including cancers where they interact with CSCs, however with various effects. In some cancers, such as glioma and breast cancer, their results resemble those of non-cancer diseases, i.e. they induce reductions of cell proliferations. In other cancers, such as multiple myeloma and gastric cancer MSCs induce no reduction, but stimulation of cancer proliferation. In a third type of cancer, the effects of MSCs change depending on the parental cells. For example, the MSCs and their EVs from bone marrow and umbilical cord are protective, whereas those from adipose tissue increase cell proliferation [23-26]. Another factor participating in the MSC effects are miRNAs expressed by the EVs [27]. Interestingly, in tumor-positive results obtained in the niches of the cancer body were not confirmed on the metastatic developments, where responses were all negative. In this case, therefore, the mechanisms of stem cell function evolved in distinct processes can be different [19]. Additional examples of MSC effects in favor or against cancer growth have been reported in the literature.

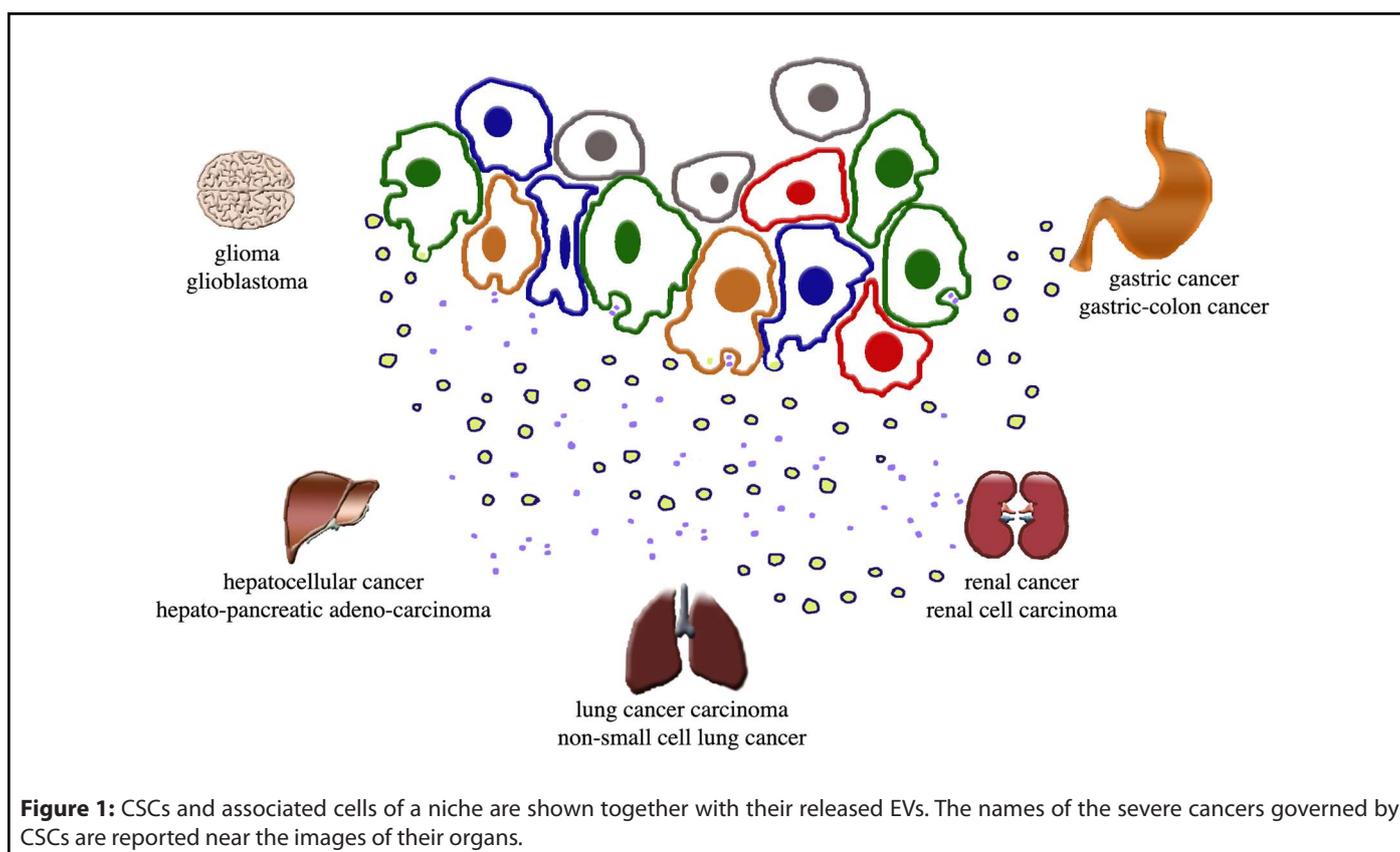
The group of cells of the center illustrates the general structure of a cancer niche that includes many types of cells

distinguished here by the color of their nucleus: green for CSCs, orange for MSCs, red for normal cancer cells, blue for examples on non-cancer cells, such as immune cells, that participate in cancer function. The dots spread below the cells are the two types of EVs secreted by all cells of the group: the small exosomes released upon exocytosis of the multi-vesicular bodies, the endocytic vacuoles that contain them; the larger ectosomes assembled at mini-rafts of the plasma membranes and then released by shedding of cell surface mini-expansions [5,10]. Various factors (interleukins, cytokines, growth factors, not shown) are secreted by all these cells. Based on the key role of CSCs in the processes governing cancer life and activity, their intense cooperation with the other cells is important for the activity of the niche.

Cancer Stem Cells: Most Important for Cancer Initiation, Specificity and Actions

CSCs, identified a few years after 2000, account for significant fractions of the cells concentrated within cancer niches together with normal cancer cells, MSCs and various other collaborative, non-cancer cells, that participate in cancer functions (Figure 1). Functionally, however, the critical properties of CSCs are original [10-13,16,28,29]. Shared with MSCs can be other properties, such as broad proliferation capacity, signaling and expression of stem cell markers. At variance to the cells cooperating with MSCs, many immune modulations of CSCs induce evasion of their surveillances. In other words, cancer growth is stimulated by the CSC resistance to immunotherapy [14,16,17]. Another property concerns differentiation. CSCs show multi-lineage differentiation properties leading to the generation of distinct cancer subtypes [12,16]. Moreover, CSCs govern many critical processes of cancer life, from initiation and progression to formation of metastases, therapy resistance, cancer-relapse [10,16,28,29]. Based on their unique support to critical cancer processes, CSCs are now recognized as potential key targets of anti-cancer therapy.

The origin of CSCs has been debated. Differentiation from normal cancer cells have been confirmed by experiments showing that, upon their elimination, CSCs are replaced by surrounding cancer cells, differentiated by changes and acquisition of peculiar properties [23,28]. Conversion into CSCs has been reported also from MSCs [28]. The sites of CSC generation and differentiation are distributed within small niches, present in all organs. The function of CSCs depends on their secretion of both soluble factors (interleukins, cytokines, growth factors) and EVs [9,23] (Figure 1). Concomitantly, CSCs receive soluble signaling factors and EVs released by cancer and other cells distributed at TMEs. Such bi-directional and also multi-directional exchanges of signals are important for preserving the activity and specificity of CSCs and other cells involved. Most important interactions, however, are mediated by their secreted EVs [12,13,29-31].



Up to now, consistent distinctions between EVs secreted by CSCs and MSCs have not been reported. Therefore, CSC-dependent vesicles are simply indicated as EVs, characterized by their interactions with cells distributed in TMEs and by their strong effects. During tumor progression the molecular profiling of circulating EVs provides non-invasive means to diagnose, monitor, and predict the course of cancers [9,23,24,30,31]. The main role of EVs is intra-tumoral cell-to-cell communication that includes fusion of the EVs from CSC and MSC with macrophages and other immune cells [15,32]. In addition, the EVs from CSCs are able to control cancer cell proliferation by proteins and miRNAs released from their luminal cargoes, believed to originate or participate in specific signaling cascades. Examples of miRNAs of CSC origin have been reported recently. Examples are the stimulation by miR-200c of metastatic traits of the colorectal cancer; the *in vitro* and *in vivo* attenuation of the human liver cancer by miR-145 and miR-200; the inhibition of lung metastasis in osteosarcoma by miR-101 [33-35].

Cancer Microenvironment

As already mentioned in previous Sections, within the niches CSCs are not distributed alone. Rather, they are co-localized and co-interactive with many normal cancer and non-cancer cells (Figure 1). In particular, the EVs secreted by the various niche cells undergo autocrine and paracrine fusions that often contribute their progress to cancer development. Both

these and other processes are all sustained by the activity of non-cancer cell, such as those active on circadian clocks [18], that participate in the regulation of many cancer processes via direct and indirect effects [36]. The latter, that occur with niches and wider TMEs, include the inhibition of immune cells from the so-called immune escape process, sustained by the CSC interaction with macrophages [37]. An ensuing effect includes the development and dissemination of tumor-associated cells, promoting the immune escape of tumors via the immunosuppressive reprogramming of lymphatic vessels [17,35].

In addition to its transition processes already mentioned, TMEs includes angiogenesis by which new blood vessels grow from pre-existing vessels of tumors. Angiogenesis depends on EVs, favoring release of positive factors, including vascular endothelial growth factors and matrix metalloproteinases together with another factor inhibiting the hypoxia-inducible factor [31]. The tumor-derived EVs activate also the proliferation of endothelial cells, necessary for the ensuing formation of new vessels [18,38].

Therapy

The therapy by MSCs and their EVs was initially discovered from their positive effects against many non-cancer diseases [1-3]. The effects of CSCs are largely opposite, inducing strengthened cancer progress by activation of events such as

efflux of anti-cancer drugs, autophagy, immunosuppression [28,32,36]. Investigation of EVs secreted by MSCs and CSCs opened possibilities against processes of cancer stimulation such as the transition from mesenchymal stromal cells into cancer-associated fibroblasts [39]. Specific therapeutic processes, aimed to eradicate tumors by preventing their main processes, such as metastases, tumor relapses and drug resistance, can be induced by reverse responses, such as increased drug efficacy [40,41]. Improved results have been obtained by new strategies of appropriate CSC lesion targeting. Nanomedicine strategies, initiated over 10 years ago, have reinforced the potential of anti-cancer drug strategies by the inclusion of various tools, such drugs and genes, qualified by specific targeting and combinational delivery. By this approach the prognosis observed in various types of cancers treated with typical drugs, potentially appropriate but little efficient, has been greatly improved [20,42]. The drugs employed in nanomedicine and EV therapy are encapsulated by an engineering technique developed according to a GMP technique [21,43]. Such encapsulation succeeds to target cancers, obtaining therapy effects much stronger than those of drugs administered alone [20,42,44-46].

Conclusions

At present, stem cells are attracting great interest, and innovative properties are reported every year about these cells. In their stroma of origin, MSCs undergo various types of differentiation that contribute peculiar properties and functions of their target cells. The various MSCs, including those employed in research, are not homogeneous. Yet, based on many common properties, most of them are indicated by the same MSC nomenclature.

This however is not the case of cancers. As emphasized in this review, the stem cell system of cancer cells is more complex with respect to the other cells. In particular, it does include not a single type but two distinct types of stem cells. Together with MSCs, all cancers express specific CSCs, known since 2005 based on their initially discovered properties [47,48]. Subsequent intense studies in recent years, reported here by two recent reviews [49,50], have led to the identification of many specific properties of CSCs and their EVs [9,12,13,28-31]. In cancer niches CSCs coexist not only with cells of the MSC family, but also with normal cancer cells and various non-cancer cells, such as fibroblasts, macrophages, and immune cells, participating in specific steps of cancer development. A main property of the cancer system is that of CSCs, cooperative however with MSCs and other types of cells.

The role of CSCs depends on critical cancer processes. CSCs show multi-lineage differentiation properties leading to distinct cancer subtypes [12,13,29]. The bidirectional exchange of signals between CSCs and the other cells of the niches protects the activity and the specificity of the various

cells involved [10-13]. The role of CSC, including events such as efflux of anticancer drugs, autophagy and immune suppressions, can be envisaged from key steps of its actions: cancer initiation, its progression up to the formation of metastatic processes; therapy resistance and cancer relapse [9,10,23]. Such steps are highly important. Without CSCs, therefore, cancer diseases would not exist. From all these properties, CSCs are expected to become targets of innovative therapies, induced not only by scientific studies but also by clinical medicine.

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