Review Article

Stem Cell INVESTIGATION

Cancer stem cells and exosome signaling

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Abstract: Exosomes have been recognized as mediators of intercellular communication among different cell populations in various biological model systems. By transfer of signaling molecules such as proteins, lipids, and RNAs between different cell types, exosomes are implicated in both physiological and pathological processes. The tumor microenvironment consists of multiple types of cells including adult stem cells, cancer stem cells, and stromal cells. These cells are known to intercommunicate with each other thereby modulating tumor progression. Recent studies have provided evidence demonstrating that exosomes mediate the interactions among different types of cells within the tumor microenvironment, providing new insight into how these cells interact with each other through exosome signaling. This review is focused on recent studies that have examined exosome-mediated intercommunication among cancer stem cells, adult stem cells, cancer cells, and stromal cells within the tumor microenvironment. Based on the current literature, it seems clear that adult stem cells and cancer stem cells secret exosomes that can be transferred to their surrounding cells thereby modulating cancer progression. Likewise, cancer cells and stromal cells also release exosomes that can be taken up by cancer stem cells or adult stem cells, leading to alterations to their phenotype. The molecular mechanisms and biological consequences of the exosome-mediated interactions of these cells remain to be further elucidated. A better understanding of how exosomes mediate intercellular communication in the tumor microenvironment and the specific biological consequences of these interactions will likely offer new opportunities in the development of diagnostic or therapeutic strategies against cancer.

Keywords: Cancer stem cells; adult stem cells; exosome signaling; tumor microenvironment

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Stem cells are characterized as unspecialized cells, including embryonic stem cells (1) and adult stem cells (2), capable of self-renewal and can be stimulated to become tissue specific cells. The concept of a cancer stem cell population present in a tumor has been frequently described in the recent literature (3). These cells are usually resistant to anticancer drug therapy and contribute to tumor recurrence (4). The interaction of cancer stem cells with their microenvironment has proved to be critical for cancer progression (5,6). While the cellular and molecular mechanisms of how cancer stem cells interact with their surrounding cells thereby facilitating tumor angiogenesis and metastasis remain to be further elucidated, the current literature has provided evidence indicating that extracellular microvesicles, especially exosomes, are transferred between cancer stem cells, adult stem cells and their surrounding cancer cells or stromal cells, which constitutes another layer of complexity in cancer stem cell biology relevant to the tumor microenvironment and tumor progression. This review is intended to summarize recent findings and conjecture future directions in this interesting and viable research area. In particular, we will focus on several basic questions about how exosomes might be involved in the interaction of cancer stem cells, adult stem cells with their surrounding cells within the tumor microenvironment, including: (I) Do cancer stem cells or adult stem cells secrete exosomes thereby affecting stromal cell function? (II) Are cancer stem cells or adult stem cells modified

by exosomes released from the surrounding cancer cells and stromal cells? (III) What are the potential molecular mechanisms and biological consequences of the exosome-mediated interactions between cancer stem cells, adult stem cells and their surrounding cells?

It has been established that cancer stem cells/adult stem cells secrete exosomes that interact with surrounding cancer cells and stromal cells. Exosomes are small endosomal pathway-derived membrane vesicles (40-100 nm) containing lipids, proteins, small RNAs, and are enriched in membrane-spanning tetraspanins (7). Exosomes are secreted by virtually all cell types (8) and can transfer their molecular contents between different types of cells (5). It is established that the intercellular transfer of molecules via exosome cargo has significant functional consequences implicated in developmental biology (9), tumor progression (5,10), immune response (11), and other pathological processes (12). Cancer stem cells are currently defined as cancer cells possessing characteristics of self-renewal, proliferation, tumor initiation and propagation (3). Recent studies have demonstrated a connection of cancer stem cells with tumor metastasis (13,14) and therapeutic resistance (15,16). The "stemness" of cancer cells seems to be associated with factors within the tumor microenvironment, such as cancer-associated fibroblasts (17,18) and exosomes secreted by various stromal cell types (19,20). Cancer stem cells are thought to secret microvesicles and exosomes into their microenvironment that interact with surrounding stromal cells (21). Direct evidence has shown that breast cancer stem cells secrete exosomes with characteristics of cancer cell derived exosomes (22). Molecular analysis of exosomes released from prostate and breast cancer stem cells has indicated the presence of several exosome markers such as CD9, CD63, CD81, Alix and TSG101 in these exosomes, although no unique features of cancer stem cell exosomes were described (22). More evidence has been provided in recent years showing that exosomes released by cancer stem cells mediate cancer progression in different model systems. In a renal cancer model, microvesicles released from human renal cancer stem cells were reported to stimulate angiogenesis and formation of a premetastatic niche in the lungs (23). A study on glioma stem cells reported that glioma-associated stem cells increase the biological aggressiveness of glioma-initiating cells through the release of exosomes (24). Furthermore, extracellular vesicles released by cancer stem-like glioblastoma cells were also shown to promote glioblastoma invasion, neurosphere growth, and endothelial tube formation (25). In a model of basal-like ductal carcinoma *in situ* (DCIS), it was found that a subpopulation of breast cancer stem-like cells release exosomes that impact signaling in nearby breast cancer cells (26). Results from these studies clearly show that cancer stem cells release exosomes that interact with surrounding cells thereby mediating cancer progression.

In addition to the interaction of cancer stem cells with surrounding cells through exosomes, studies have also revealed that interactions with adult stem cells are often involved in cancer progression via exosome signaling. Ratajczak *et al.* reported that exosomes derived from embryonic stem cells could reprogram hematopoietic progenitors by transferring exosome mRNAs and proteins, such as Wnt-3 and Oct-4 (27), which is the first report indicating the interaction of embryonic stem cells and adult stem cells via exosome signaling. In the context of cancer, exosomes from human adipose-derived mesenchymal stem cells promoted breast cancer cell migration through the Wnt-signaling pathway (28), indicating that mesenchymal stem cell exosomes facilitate tumor migration and metastasis. Similarly, a recent report indicated that exosomes derived from bone marrow mesenchymal stem cells promote dormancy in metastatic breast cancer cells (29). On the other hand, however, exosomes derived from mesenchymal stem cells suppressed angiogenesis by down-regulating VEGF expression in breast cancer cells (30). These seemingly contradictory findings may be attributed to the use of different model systems and suggest that more investigations are needed in this research area. In an effort to understand the interaction of mesenchymal stem cells with cancer cells, Yang *et al.* revealed that mesenchymal stem cells exchange membrane proteins with various human cancer cells likely through exosomes, resulting in functional alterations in both stem and cancer cells (31). Using an *in vivo* model system, exosomes derived from human bone marrow mesenchymal stem cells were shown to promote cancer progression (32). These results clearly demonstrate that adult stem cells secrete exosomes and can transfer cancer-promoting factors to surrounding cells thereby altering the tumor microenvironment and modulating tumor progression.

Initial studies indicate that cancer stem cells and adult stem cells are modified by exosomes released from surrounding cancer cells or stromal cells. One might imagine that the intercommunication between cancer stem cells and surrounding cells is not unidirectional, rather it must be bidirectional, meaning that not only cancer stem cells secrete exosomes that are absorbed by surrounding

cells, but that cancer cells and stromal cells will also release exosomes that can be transferred to cancer stem cells. However, because this field is still in its infancy, studies on cancer stem cells receiving exosomes derived from surrounding cells are relatively rare. Nonetheless, Ye *et al.* has recently pointed out that a cross-talk exists between cancer stem cells and their surrounding microenvironment and that the microenvironment supports cancer stem cell self-renewal, in part through exosomal signaling (33). A bidirectional interaction between stem cells and epithelial cells via exosomes has also been proposed (34). Furthermore, exosomes were found to mediate population equilibrium of lymphoma stem like cells and non-stem cells (35). In a breast cancer model, exosomes derived from fibroblasts were transferred to breast cancer cells where they activated Notch signaling and increased aldehyde dehydrogenase expression (a cancer stem cell marker), suggesting that fibroblast-derived exosomes increase the "stemness" of breast cancer cells (36). It is apparent that more studies are required to determine whether the bidirectional transfer of exosomes from stromal cells or cancer cells might alter cancer stem cell signaling and their "stemness" in the tumor microenvironment.

In addition to investigations of how cancer cell or stromal cell exosomes might affect cancer stem cell fate, several studies have been reported how cancer cells might affect adult stem cell function through exosome signaling. Cho *et al.* reported that exosomes derived from ovarian cancer cells induce a myofibroblastic phenotype and functionality of adipose tissue-derived mesenchymal stem cells through activating an intracellular signaling pathway (37). The same was found to be true with breast cancer-derived exosomes that can convert adipose tissue-derived mesenchymal stem cells into myofibroblast-like cells (38), which contributed to tumor progression. Aimed at exploring the function of melanoma-derived exosomes in tumor formation and metastasis, Peinado *et al.* demonstrated that exosomes derived from melanoma cells can be transferred to bone marrow progenitor cells, leading to the promotion of tumor growth and metastasis (39), clearly implicating stem cells at the receiving end of exosome-mediated intercommunication that modulates tumor proliferation and metastasis. In a separate study, exosomes derived from prostate cancer cells were shown to neoplastically reprogram patient-derived adipose stem cells (40), indicating that the exosome-mediated intercommunication between prostate cancer cells and adult stem cells contribute to tumor clonal expansion. Furthermore, prostate cancer-exosomes were able to trigger mesenchymal stem cell differentiation to pro-angiogenic and pro-invasive myofibroblasts, a functional consequence consistent with their tumor promoting effects (41). These reports provide ample evidence indicating that adult stem cells are modified by exosomes derived from cancer cells, resulting in functional alterations that favor tumor progression.

The mechanism of exosome-mediated intercommunication between cancer stem cells, adult stem cells and the tumor microenvironment remain to be further explored. Exosomes mediate intercellular communication primarily through the exchange of lipids, proteins, and mRNA/microRNAs between the cells involved (7). Current literatures suggest that this seems to be the case for cancer stem cells and their surrounding cancer and stromal cells within the tumor microenvironment. As to the involvement of exosome cargo proteins in the intercellular communication of cancer stem cells with other cell types, exosomes containing Wnt proteins were reported to mediate these events. For instance, the interaction of embryonic stem cells with hematopoietic progenitors was mediated by exosomes enriched in Wnt-3 proteins. The transfer of Wnt-3 proteins from embryonic stem cells to hematopoietic progenitors resulted in an increase in their pluripotency (27). Wnt-3 proteins were also detected in exosomes derived from lymphoma cells that could modulate the population equilibrium (stem-like cells versus non-stem cells) during tumor progression of diffuse large B-cell lymphoma (35). The Wnt-11 protein contained in fibroblast-derived exosomes was shown to mobilize autocrine Wnt-PCP signaling that drives breast cancer invasion (42). In a breast cancer model, exosomes derived from human adipose mesenchymal stem cells promoted breast cancer cell migration through the Wnt-signaling pathway (28), suggesting the presence of Wnt ligands in the exosomes. In this context, Wnt proteins were identified in exosomes derived from human cell lines and can be delivered to recipient cells (43). In addition to Wnt proteins, TGFβ present in exosomes derived from prostate cancer cells was reported to mediate mesenchymal stem cell differentiation, leading to a phenotype of pro-angiogenic and pro-invasive myofibroblasts (41). Likewise, TGFβ proteins present in breast cancer exosomes stimulated the TGFβ receptor mediated signaling pathway in adipose mesenchymal stem cells, resulting in a myofibroblast-like phenotype (38). By co-culturing breast cancer cells and mesenchymal stromal/stem cells, Yang *et al.* revealed that membrane proteins such as CD105 and CD90 were exchanged between cells that contributed to functional

alterations in both of the cell populations (31). Exosome proteins such as TYRP2, VLA-4, HSP70, HSP90, and MET constituted an exosome-specific melanoma signature that signaled to bone marrow progenitor cells to undergo a pro-metastatic phenotype (39). Interestingly, microvesicles derived from B-cell chronic lymphocytic leukemia were shown to stimulate the AKT/mTOR pathway in bone marrow stromal cells by directly delivering the phosphor-receptor tyrosine kinase Axl, indicating the important role of microvesicles in the progression of this malignancy (44).

Several recent studies have shown that exosome microRNA cargos are also involved in the intercellular communication of adult stem cells and cancer cells. Lee *et al.* demonstrated that exosomes derived from mesenchymal stem cells are enriched in miR-16 that can be transferred to breast cancer cells and suppresses VEGF expression, leading to inhibition of tumor angiogenesis *in vitro* and *in vivo* (30). miR-16 has been previously demonstrated to control the expression of VEGF and regulate angiogenesis in other model systems (45-47). Oncogenic microRNAs, such as miR-125b, miR-130b and miR-155, were identified in exosomes derived from prostate cancer cells, which promoted a neoplastic reprogramming of patient-derived adipose stem cells (40). In addition, miR-1 was reported to be associated with extracellular vesicles released by cancer stem-like glioblastoma cells (25), and miR-140 contained in exosomes derived from a stem-like subpopulation of basal-like ductal carcinoma cells was found to influence nearby breast cancer signaling (26). We expect more publications to be available regarding the involvement of microRNAs in the intercommunication of cancer stem cells, adult stem cells and other cell types in the tumor microenvironment, given the fact that microRNAs are tiny, able to regulate multiple target genes (48) and heavily involved in cancer progression (49).

Summary and future directions

Accumulating evidence has demonstrated that exosome signaling is involved in intercellular communication in various biological systems (5,7). Recent literature indicates that exosome signaling mediates the interaction of cancer stem cells and adult stem cells with other cell types in the tumor microenvironment thereby modulating tumor progression (5). Cancer stem cells and adult stem cells release exosomes that can be taken up by cancer cells and stromal cells, a process likely favoring tumor progression. Meanwhile, cancer stem cells and adult stem cells also receive exosomes released from cancer cells or stromal cells resulting in alterations of stem cell phenotype or functionality, a process capable of promoting cancer development. Whereas both exosome protein and microRNA cargos are known to be involved in intercellular communication of cancer stem cells, adult stem cells and cells in the tumor microenvironment, limited literature is currently available on this topic and we are only at the beginning of understanding these processes at the molecular level. Since exosome-mediated intercommunication in the cancer microenvironment may hold great potential for developing new therapeutic and diagnostic strategies (5), further elucidation of the molecular details of the exosome-mediated interaction among cancer stem cells, adult stem cells, cancer cells and stromal cells is necessary to facilitate this process. Several basic questions remain to be answered which may guide future studies in this field. First, are there any unique features of exosomes derived from cancer stem cells compared to those released from cancer cells or normal cells? A full characterization and comparison of exosome contents (proteins, microRNAs, and lipids) will provide important information as to whether cancer stem cell exosomes differ from others. In this regard, one would expect that cancer stem cell exosomes from different types of cancers are likely to have different molecular signatures, though experimental evidence is needed to support this assumption. Second, how does the exosome-mediated interaction of cancer stem cells with cancer cells or stromal cells modulate tumor progression? This may involve in the identification of signaling pathways or microRNA transcript targets affected by the transfer of specific exosome molecules to recipient cells that contribute to the modulation of tumor angiogenesis, metastasis, and proliferation. And finally, does the exosome-mediated interaction of adult stem cells and cancer cells or stromal cells contribute to tumor progression? As discussed, conflicting results have been reported, which need to be clarified. It is particularly interesting to see how adult stem cells respond to exosome signaling initiated by cancer cells or stromal cells thereby modulating tumor progression, a process which may be critical for cancer development and targeted for cancer therapy.

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Footnote

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