

Clinical Significance as Biomarkers of Exosomes in Cancer

Yoshihiro Kikuchi*

Ooki Memorial Kikuchi Cancer Center for Women, Japan

Commentary

It has been reported that exosomes contains extracellular vesicles involved in intracellular communications including cancer cells. Cancer exosomes carry malignant information in the form of proteins, lipids, and nucleic acids that can reprogram recipient cells. Such extracellular vesicles, named as exosomes, can be detected in all types of cancer patients. The intricate network mediated in exosomes seems to establish between tumor and non-tumor cells. These communications seem to be involved in every step of cancer progression, from tumor growth to cell dissemination [1]. Cancer cells seem to promote a favorable microenvironment that supports tumor growth through enhanced cell proliferation and escape to apoptosis by exosome-mediated mechanisms. The capacity of tumors to become invasive and disseminate can be done by cancer exosomes with information that contributes to extracellular matrix (ECM) remodeling, cancer cell migration, and invasion [2,3]. The tumor microenvironment corresponds to the histological components surrounding cancer cells. The components generally contain mesenchymal cells such as fibroblasts, endothelial cells, hematopoietic cells, and extracellular matrix. The bidirectional network of communication between cancer and stromal cells is based on the release of soluble compounds like growth factors or on the release of exosomes. Cancer exosomes were found to modulate the surrounding cells to support tumor growth and dissemination. Activated fibroblasts are commonly found at tumor site and are well described for their active role in tumor progression by the secretion of growth factors, chemokines, and deposition of ECM, facilitating tumor growth and invasion. Normal cell to cell cross-talk by signal-exchange through exosomes and/or unknown signal-transduction materials is of most importance for normal life-activity of cells. Such normal cell-to-cell cross talk in cancer cells is lost and abnormal cancer-cross talk by the cancer cells may result in abnormal effects on the cancer fibroblasts or stromal cells and even to the surrounding cells (Figure 1).

Generally, anticancer agents have been reported to induce hypoxia in the targeted cancer tissues and cause the killing activity. Cancer exosomes induced by hypoxia may result in malignant formation (invasion in the surrounding tissues or remote metastases). The role of cancer exosomes in metastasis was extensively addressed over the past years. Exosome factories seem to show a tight binding between exosomes secretion and cancer invasion processes. Further in vivo findings highlight exosomes as important effectors of cancer cells' ability to move in a nonstochastic fashion. Exosomes seem to be involved in

*Corresponding author: Kikuchi Y

✉ QWL04765@nifty.ne.jp,

Ooki Memorial Kikuchi Cancer Center for Women, Japan.

Tel: +74954343690

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a critical autocrine mechanism responsible for directing cell movement and influencing the migration seed of cancer cells. Therefore, cancer exosomes seem to regulate cell movement and increase cell invasion potential by promoting ECM degradation. Similarly, a recent study has demonstrated the ability of cancer exosomes to promote peritoneal metastases through the destruction of the mesothelial barrier. Recently, the relation between metastatic organotropism and cancer exosomes has

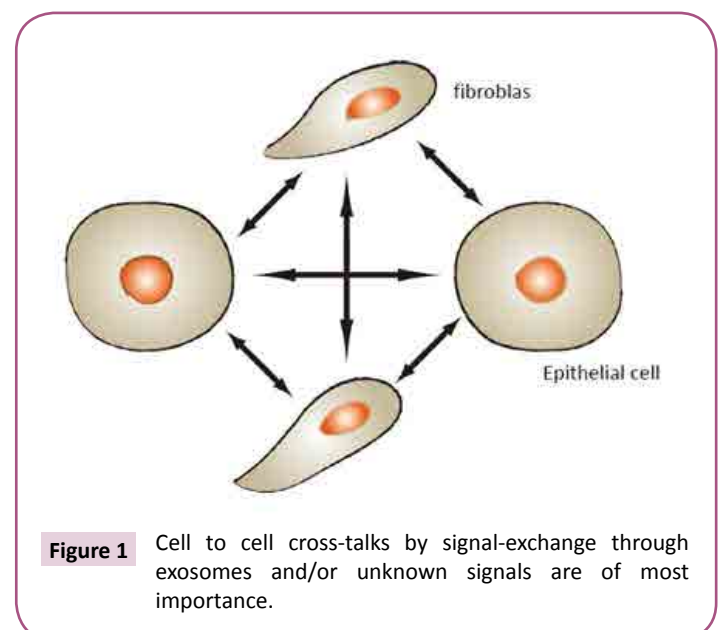


Figure 1 Cell to cell cross-talks by signal-exchange through exosomes and/or unknown signals are of most importance.

been explored. In vivo studies have shown that pancreatic cancer exosomes are preferably uptaken by lung, liver, and brain cells. It is noteworthy that metastases could be redirected using exosomes derived from cells known to metastasize to specific sites. Finally, exosomes' role in the premetastatic niche formation has also been extensively reported. The premetastatic niche describe the ability of hematopoietic precursor cells from the bone marrow to home to specific sites before the arrival of tumor niches where they can seed and proliferate. In this sense, cancer exosomes are the perfect long distant messengers due to all their known biologic features. Collectively, studies addressing exosomes biological functions, namely during metastasis formation, should be developed in biological systems that closely resemble the human disease, moving exosomes studies toward biological significant findings.

Exosomes are small nano-molecules secreted by extracellular vesicle bodies which carries various biochemical or genetic information. It plays a vital role in the maintenance of stable physiological and morphological functions. The dynamic studies elucidate the contribution of exosomes to the process of tumor-resistance by facilitating the efflux. The drug and its metabolites can be associated with the production and movement of encapsulated exosomes in the cell microenvironment. Regarding remote metastases, such abnormal signals in cancer mentioned-above stimulate the remote tissues such as the fibroblasts and stromal cells and they may make convenient environment to induce cancer metastases. In addition, regarding remote metastases exosomes carried by blood circulation may work to produce the pre-metastatic soil (**Figure 2**).

Resultantly, transition from normal cells to malignant cells and/or from malignant cells to normal cells may be commonly occurring. Exosomes are very robust due to their bilayered lipid membrane that protects the encapsulated cargo against degradation. Even a cycle of freezing and thawing of exosomes hardly affects the integrity of exosomes. Likewise, exosomes can be stored at 4°C for 48-96 hours or at -70°C for a long time without losing their biological activity. These features may also help to increase the detection rate of mutated tumor DNA from the blood. Accordingly, if such changes can be obtained in advance, new treatment strategies to malignant tumors may be born in near future [4]. In addition, exosomal induction of tumor innervation may be hallmark of cancer [5]. For example, nerve ablation has been reported to block and cancer initiation and progression. It is of much interest that chemical and physical denervation of the normal prostate results in tissue atrophy, showing direct neural contributes to tissue homeostasis [6]. In addition, embryologic prostate development requires nerves. Therefore, normal prostate development demands also neural signals. In cancer, these signals may be changed or potentiated and contribute to cancer initiation and progression. Consistent with these findings, patients with spinal cord injuries resulting in functional prostate

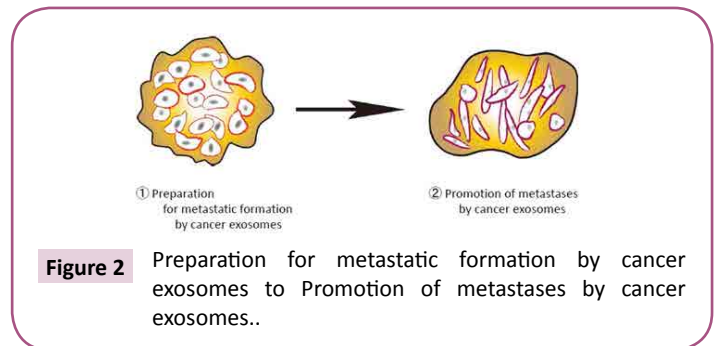


Figure 2 Preparation for metastatic formation by cancer exosomes to Promotion of metastases by cancer exosomes..

denervation have a lower prostate cancer incidence [7]. Similarly, nerves have been reported to contribute to disease in pancreatic cancer. In addition to soluble nerve recruiting and guiding factors, glial cells may also contribute to tumor innervation. While these are early data and molecular mechanisms still require refined definition, perhaps the bigger question remains. Finally, tumor-infiltrating nerves may directly synapse on tumor cells and release factors that promote proliferation, inhibit cell death, induce migration, or epithelial-mesenchymal transition.

In conclusion, for establishment of remote metastases preparation for metastatic formation by metastatic exosomes may be necessary. Few circulating tumor cells make any formation of metastases; so called "soil but not seed". Regarding metastases, invasive metastases seem to be different from remote metastases. Invasive metastases may result in tumor transformation of invasive tissues by invasive cancer exosomes. Thus, exosomes play significant roles in exchange of various cargo, not only materials but also information. If we can understand important information containing information in cancer cells to normal cells, cancer cells to stromal cells and cancer cells to surrounding cells exchanges, we will be able to get strategies to control cancer cell growth. In addition, Exosomes also represent an efficient means of local and distal communication between the tumor and potentially innervating nerves. As such, defining the critical components driving tumor innervation will identify new targets for intervention. With a deepening understanding, tumor innervation may emerge as a new hall mark of cancer. With potentially broad-ranging control over tumor biology, tumor-infiltrating nerves may well represent a new hall mark of cancer. In mechanistically defining the contribution of these to disease progression, we will gain a broader understanding of cancer not just as a disease, but as a functioning foreign organ with multiple connections to its host. Critically defining complex signals and interactions will lead to novel approaches to treat cancer, some of which, given the breadth of FDA-approved neurologically active drugs, may already be in clinical use.

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