



The expanding role of exosomes in cancer biology and therapy

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Comment on: Hoshino A, Costa-Silva B, Shen TL, *et al.* Tumour exosome integrins determine organotropic metastasis. *Nature* 2015;527:329-35.

Submitted May 24, 2016. Accepted for publication Jun 01, 2016.

doi: 10.21037/tcr.2016.06.34

View this article at: <http://dx.doi.org/10.21037/tcr.2016.06.34>

The role of extracellular vesicles, of which exosomes is one type, in oncogenesis continues to be defined. Normal human blood is estimated to contain about 2,000 trillion exosomes, and the blood of cancer patients is estimated to contain about 4,000 trillion exosomes (1). Virtually all cell types appear able to produce exosomes. Exosomes are heterogeneous, and heterogeneity appears enhanced in cancer (1). Exosomes provide a means of intercellular communication for both normal and malignant cells. Since exosomes are detected in many body fluids, including urine, semen, saliva, amniotic fluid, cerebrospinal fluid, bile, ascites, tears, breast milk and blood, they have been reported as a potentially useful liquid biopsy for cancer detection (1). Tumor cells use exosomes to promote their survival and growth (2). Tumor derived exosomes can program the immune system to evade an anti-tumor response (3). Cancer exosomes have also been implicated in tumor resistance to chemotherapy. Exosomes have been reported to remove cisplatin and trastuzumab from cancer cells (4). In a hypoxic environment, tumor cells secrete exosomes with enhanced angiogenic and pro-metastatic potential (5). Tumor-derived exosomes promote the transition of cells from an epithelial to a mesenchymal phenotype through the upregulation of transforming growth factor beta (TGF β), caveolin-1, hypoxia-inducible factor 1 alpha (HIF1 α), and β -catenin, which promotes tumor invasion and metastasis (2). Hoshino *et al.* (6) provide additional clarity to how tumor derived exosomes lay the groundwork for tumor cells to spread to specific organs. The authors build on findings indicating that cancer cells from a given metastatic site have an enhanced ability to metastasize to a given organ (7). Their findings suggest that tumor-derived exosomes are at least part of how a tumor sets the stage for organ specific metastasis, based on the integrin

profile of the exosomes.

The authors evaluated tumor derived exosomes and found that integrins direct organ specific metastasis by fusing to target cells of a given tissue, which initiates an environment favorable to metastasis (6). To demonstrate this, they isolated exosomes from human breast and pancreatic cancer cell lines that metastasize primarily to the lung (MDA-MB-231), liver (BxPC-3 and HPAF-II), or both (MDA-MB-468), injected the exosomes into nude (immunodeficient) mice and quantified exosome distribution and uptake in distant organs. They observed an increase in exosomes in to the lung or liver of the mice based on where the cell lines primarily spread. This was also true for murine breast and pancreatic cancer exosomes in immunocompetent mice.

Both quantitative mass spectrometry and western blotting demonstrated that exosomes have distinct integrin expression patterns. Integrins $\alpha_6\beta_4$ and $\alpha_6\beta_1$ were associated with lung metastasis, while integrin $\alpha_v\beta_5$ was linked to liver metastasis. The authors confirmed this observation by qualitative mass spectrometry in 28 additional organ specific metastatic cell lines. Further investigation demonstrated that exosomes first induced vascular leakiness, followed by parenchymal cell uptake in the metastatic site. The specific parenchymal cell type to take up the exosomes, generally stromal cells such as fibroblasts or Kupffer cells, depended on the organ of uptake. This provided a “pre-metastatic niche” according to the authors. Targeting the integrins $\alpha_6\beta_4$ and $\alpha_v\beta_5$ decreased exosome uptake, as well as lung and liver metastasis, respectively.

Finally, they isolated exosomes from the plasma of breast cancer patients who did or did not go on to develop lung metastasis, and patients with pancreatic cancer who

did or did not go on to develop liver metastasis. Notably, the exosomes were isolated from plasma collected before clinical evidence of metastasis. Exosomes from breast cancer patients that went on to develop lung metastases expressed integrin β_4 at significantly higher levels than patients who did not, whereas integrin α_v levels were higher in patients with pancreatic cancer who developed liver metastasis than those who did not.

The authors previously reported that in patients with melanoma, exosome protein concentrations are higher in patients with stage IV than those with earlier stage disease and normal controls, and that individuals with stage IV melanoma who have protein poor exosomes have a survival advantage compared to those who have protein-rich exosomes (8). They observed that melanoma derived circulating exosomes induce vascular leakiness, a frequent precursor to tumor metastasis (9). They extended these human observations to preclinical studies, comparing highly metastatic (B16-F10, SK-Mel128 and SK-Mel1202) to poorly metastatic (B16-F1) melanoma cell lines, demonstrating that the highly metastatic cell lines had higher amounts of exosomal protein than the poorly metastatic melanoma cell line. Exosomes from B16-F10 cells injected intravenously into nude mice were found in the lung, liver, bone marrow and spleen (sites of B16-F10 metastasis) by the next day. Moreover, the B16-F10 derived exosomes increased lung vascular endothelial permeability. Mice with orthotopically injected B16-F10 cells that were also injected with B16-F10 exosomes developed lung metastases by day 19, whereas the mice with orthotopically injected cells but without the exosome injections did not develop metastases. Whereas exosome treatment had a delayed effect on primary tumor growth, the main effect was on the development of organ specific metastases.

Exosomes are also being considered as a tool to treat cancer. Exosomes appear to pass the blood-brain barrier and have been demonstrated to deliver RNAs to the brain (10). Since exosomes are non-viable, their risk is considered less than that of cellular therapies. Exosomes can be manufactured in culture to include therapeutic molecules, including chemotherapeutic agents (10). Interest in the use of exosomes to treat cancer is growing, either by downregulating gene expression or by increasing the immune system's tumor response.

Exosomes are considered as potentially ideal for the delivery of proteins, RNAs, small molecule drugs, etc., due to their biocompatibility, stability in circulation, and ability to target them to certain cell types (11). The

delivery of small interfering RNAs (siRNAs), which have great potential to decrease gene expression, microRNAs (miRNAs), which are frequently dysregulated in cancer, short hairpin RNA (shRNA) and messenger RNA (mRNA) are all being investigated. A recent report demonstrated that loading mesenchymal stem cell exosomes with miR-146b and intra-tumoral injection decreased tumor growth in an animal model of glioma (12).

Further work to determine how to optimally load RNAs (and other agents, including proteins and small molecules) into exosomes is required to optimize these strategies. Some things have already been learned. Endogenous or passive loading of RNAs can be carried out by overexpressing the RNA or other molecule of interest in the producer cells (11). Passive loading is enabled by the cell's native exosomal production mechanisms. Exogenous or active loading requires either co-incubation or electroporation of exosomes with the drug/molecule of interest (13). In theory exosomes could be loaded both endogenously and exogenously.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Jin Yan (Department of Gastroenterology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China).

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2016.06.34>). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Sauter E. The expanding role of exosomes in cancer biology and therapy. *Transl Cancer Res* 2016;5(S2):S300-S302. doi: 10.21037/tcr.2016.06.34