Is the exosome a potential target for cancer immunotherapy?

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Exosomes are nano-sized (30–100 nm in diameter) membrane vesicles of endocytic origin, which interact with other cells by transferring proteins, lipids, DNA, mRNA, and microRNA (miRNA) (1,2). Exosomes have diverse biological functions depending on the cell type of origin, such as tumor cell invasion, intercellular communication, and antigen presentation (3,4). In 2012, Peinado *et al*. (5) revealed that highly metastatic melanomas could reprogram bone marrow progenitor cells through transferring the receptor tyrosine kinase MET via exosomes, and thus increase their metastatic ability. Subsequently, Hoshino *et al*. (6) demonstrated that tumor-derived exosomes uptaken by organ-specific cells prepare the pre-metastatic niche. Specifically, exosomal integrins α6β4 and α6β1 were associated with lung metastasis, while exosomal integrin αvβ5 was linked to liver metastasis. More recently, Nakamura *et al*. (7) reported that ovarian cancer-derived exosomes transfer CD44 to surrounding peritoneal mesothelial cells, thereby facilitating cancer invasion.

Tumor-derived exosomes are also known to exert different actions on the immune system, which affects cancer progression. Several reports have shown that tumor-derived exosomes facilitate immunosuppression and promote tumorigenesis by inhibiting the immune response (8). For instance, Zhou *et al*. (9) demonstrated that pancreatic cancer-derived exosomes down-regulate the expression of Toll-like receptor 4 in dendritic cells (DCs) via miR-203, inducing immune tolerance. Thus, they considered that tumor-derived exosomal miRNAs may down-regulate the anti-tumor activity of DC/cytokine-induced killer cells (CIKs), suggesting that the depletion of exosomal miRNA would enhance the anti-tumor activity. Recently, the same group further demonstrated that exosomal miRNAs can be removed by lysis and ultrafiltration without eliminating immune-regulating proteins, and that treatment with these miRNA-depleted exosomes could enhance the tumor cell-killing capacity of DC/CIKs (10). Thus, they suggested that miRNA depletion from tumor-derived exosomes may be a promising approach for activating DC/CIKs against cancer, opening the door toward development of a novel cancer immunotherapy.

Other researchers have also shown that tumor-derived exosomes can enhance immunostimulation and therefore serve as cancer vaccines. Chen *et al*. (11) evaluated the efficacy of exosomes derived from heat-shocked mouse B lymphoma cells (HS-Exo) in the induction of antitumor immune responses. They demonstrated that the heat-shock proteins HSP60 and HSP90 were more abundant in HS-Exo compared with control exosomes derived from the same cells, and induced significantly increased antitumor immune responses. Rao *et al*. (12) showed that hepatocellular carcinoma cell-derived exosomes (HCC TEX) serve as a carrier of tumor antigens and induce a strong DC-based antitumor immune response. In their study, HCC TEX-pulsed DCs increased the number of $CD8^+$ T lymphocytes and interferon-γ levels, and reduced the levels of immune-inhibitory interleukin-10 and transforming growth factor-beta in orthotopic HCC mice. In another study, vaccination with nanovesicle-bound antigens derived by the homogenization and sonication of primary melanoma

tissues decreased tumor growth and metastasis in mice (13).

The therapeutic benefit of exosome vaccination has not yet been verified in a clinical setting; however, some clinical trials have shown that disease progression was halted in a portion of patients in phase I clinical trials (14,15). Dai *et al*. (15) reported a phase I study in which tumor ascites-derived exosomes (Aex) were isolated and reintroduced in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF) into a total of 40 patients [HLA-A0201(+)CEA(+)] with advanced colorectal cancer. They found that Aex plus GM-CSF but not Aex alone could induce a beneficial tumor-specific antitumor cytotoxic T lymphocyte response with safe and tolerable profiles. The National Institutes of Health funds research related to extracellular RNA (exRNA) encapsulated in extracellular vesicles such as exosomes, including studies on the clinical use of exRNAs for therapy development (16). Collectively, the evidence collected to date indicates that cancer vaccine therapy targeting exosomes has potential as a novel cancer treatment in the near future.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Zhang X, Pei Z, Chen J, et al. Exosomes for Immunoregulation and Therapeutic Intervention in Cancer. J Cancer 2016;7:1081-7.
2. Azmi AS, Bao B, Sarkar FH. Exosomes in cancer development, metastasis, and drug resistance: a comprehensive review. Cancer Metastasis Rev 2013;32:623-42.
3. Fujita Y, Yoshioka Y, Ochiya T. Extracellular vesicle transfer of cancer pathogenic components. Cancer Sci 2016;107:385-90.
4. Greening DW, Gopal SK, Xu R, et al. Exosomes and their roles in immune regulation and cancer. Semin Cell Dev Biol 2015;40:72-81.
5. Peinado H, Alečković M, Lavotshkin S, et al. Melanoma exosomes educate bone marrow progenitor cells toward a pro-metastatic phenotype through MET. Nat Med 2012;18:883-91.
6. Hoshino A, Costa-Silva B, Shen TL, et al. Tumour exosome integrins determine organotropic metastasis. Nature 2015;527:329-35.
7. Nakamura K, Sawada K, Kinose Y, et al. Exosomes Promote Ovarian Cancer Cell Invasion through Transfer of CD44 to Peritoneal Mesothelial Cells. Mol Cancer Res 2017;15:78-92.
8. Filipazzi P, Bürdek M, Villa A, et al. Recent advances on the role of tumor exosomes in immunosuppression and disease progression. Semin Cancer Biol 2012;22:342-9.
9. Zhou M, Chen J, Zhou L, et al. Pancreatic cancer derived exosomes regulate the expression of TLR4 in dendritic cells via miR-203. Cell Immunol 2014;292:65-9.
10. Que RS, Lin C, Ding GP, et al. Increasing the immune activity of exosomes: the effect of miRNA-depleted exosome proteins on activating dendritic cell/cytokine-induced killer cells against pancreatic cancer. J Zhejiang Univ Sci B 2016;17:352-60.
11. Chen W, Wang J, Shao C, et al. Efficient induction of antitumor T cell immunity by exosomes derived from heat-shocked lymphoma cells. Eur J Immunol 2006;36:1598-607.
12. Rao Q, Zuo B, Lu Z, et al. Tumor-derived exosomes elicit tumor suppression in murine hepatocellular carcinoma models and humans in vitro. Hepatology 2016;64:456-72.
13. Lee EY, Park KS, Yoon YJ, et al. Therapeutic effects of autologous tumor-derived nanovesicles on melanoma growth and metastasis. PLoS One 2012;7:e33330.
14. Morse MA, Garst J, Osada T, et al. A phase I study of dexosome immunotherapy in patients with advanced non-small cell lung cancer. J Transl Med 2005;3:9.
15. Dai S, Wei D, Wu Z, et al. Phase I clinical trial of autologous ascites-derived exosomes combined with GM-CSF for colorectal cancer. Mol Ther 2008;16:782-90.
16. National Institutes of Health. Bethesda: Extracellular RNA Communication. Available online: https://commonfund.nih.gov/Exrna/index

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