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Pancreatic Cancer Exosomes: Shedding Off for a Meaningful Journey

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Editorial

This year, pancreatic ductal adenocarcinoma (PDAC) is expected to overtake breast cancer to become the third leading cause of cancer-related death in the United States [1]. Nearly 50,416 new cases and 41,780 deaths are estimated to occur in 2016. PDACs carry a notoriously poor prognosis due to advanced stage presentation in most patients and lack of effective therapies. Early diagnosis of PDAC continues to be a challenge in clinics along with early metastasis and resistance to available chemotherapy that together contributes to the poor prognosis [2]. These challenges have motivated researchers to define novel, reliable, and non-invasive or minimally invasive biomarkers for early detection, and understand the process of early metastasis and chemo resistance.

Exosomes are predominant extracellular vesicles of endocytic origin that are found in all body fluids. They are membrane-bound nanovesicles (30-150 nm) possessing various bioactive molecules. Exosomal membrane is enriched in endosome-specific tetraspanins (CD9, CD63, CD81), membrane transport and fusion proteins (flotillin, GTPase) and multiple vesicular bodies biogenesis-related proteins (Alix, TSG101). Molecular components and cargos of exosomes are well documented in the online database ExoCarta [3]. Exosome contains nucleic acids, lipids and proteins, which can be transferred to other cells upon fusion, macropinocytosis or caveolin-mediated endocytosis. Studies have shown that exosomes are secreted from cancer cells at higher rates compared to healthy cells and play important roles in cancer progression and metastasis via facilitating interactions between tumor-tumor and tumor-non-tumor cells [4].

Since PDAC is highly metastatic in nature, it is important that we understand how these cancerous cells adapt themselves to survive and proliferate at secondary sites. PDAC cell-derived exosomes are reported to have pro-metastatic effect [5]. It is shown that they induce pre-metastatic niche formation to promote the liver metastasis in a complex fashion. The macrophage migration inhibitory factor (MIF)-enriched exosomes are secreted by the PDAC cells into the extracellular space, which reach to the liver through blood circulation. These exosomes are preferentially taken up by Kupffer cells and the exosomes-derived MIF induces expression of fibrosis-related genes. Among these, TGFβ is reported to be significantly upregulated and secreted as a soluble factor. TGFβ activates the hepatic stellate cells, which then secrete fibronectin in the extracellular spaces. This fibronectin helps in the arrest of bone marrow-derived macrophages and neutrophils producing pro-tumorigenic cytokines and elastase, respectively, and thus promote tumor growth and immunosuppression of T cells [5-7]. PDAC cells-derived exosomes are also reported to inhibit RFXAP (transcription factor) expression, via miR-212-3p, which leads to downregulation of MHC II and induce immune tolerance of dendritic cells [8]. Thus, the exosomes facilitate the disseminated cells to survive and proliferate at secondary sites.

Although the role of secreted soluble factors and hypoxic condition enhance the ability of metastasis but how these cells are guided preferentially to a specific organ in PDAC is not well known. An extensive study on PDAC clinical data and experimental research has now proven the Stephen Paget's "seed and soil" hypothesis of organ-specific metastasis [9]. The proteomic profiling of PDAC-derived exosomes revealed the presence of distinct integrin isoforms on exosomal surface that regulate organ specific fusion and leads to organotropic metastasis. In case of PDAC, the αvβ5 was identified that specially binds to Kuffer cell and thus responsible for the liver-specific metastasis niche formation, while α6β1 and α6β4 bind with lung-resident fibroblast and epithelial cells and facilitate the lung metastasis [10].

In PDAC, weight loss is quite common. The high mortality rate in PDAC is correlated well with rapid weight loss of adipose tissue and skeletal muscles. Exosomal adrenomedullin (ADM), a lipolysis factor induces lipolysis in adipose tissue by signaling through the adrenomedullin receptor (ADMR). ADM-ADMR signaling activates ERK1/2 and p38 MAP kinase pathways that phosphorylate hormone-sensitive lipase thus promoting lipolysis which results early weight loss in PDAC patients [11]. Another study demonstrated that the PDAC cell-derived exosomes containing ADM interact with ADMR present on β-cells surface and cause paraneoplastic dysfunction of β-cells through up regulation of endoplasmic reticulum-stress genes i.e. Bip (chaperon protein) and Chop (apoptosis inducer). Bip protein interacts and binds with pro-insulin, which finally leads to impaired insulin secretion [12]. Taking together, these finding suggested the role of exosomes in weight loss and early onset of diabetes in PDAC patients.

The concentration and composition of exosomes get altered in blood with different pathophysiological conditions, therefore, they may have potential clinical implications. In a recent report, PDAC patients' serum-derived exosomes were shown to possess significantly higher glypican-1(GPC1) in 100% cases as compared to the exosomes from healthy donors [13]. Hence, differential presence of GPC1 on exosomal surface can be used as a potential diagnostic marker in early detection of PDAC with absolute sensitivity and specificity. In addition, GPC1 is found to be equally sensitive for all stages of the disease as compared to the classical CA19-9 marker [14], which mostly shows increased levels in advance stages and thus fails to discriminate the pancreatic cancer precursor lesions from benign pancreatic disease. The overexpression of survivin in pancreatic cancer cells-

exosomes that provides resistance against apoptosis was also suggested to be useful for early detection of PDAC [15].

Exosomal micro-RNAs have also gained substantial attention in recent past years. Their abilities have been identified in modulating cellular processes, disease progression and drug resistance in PDAC patients. MicroRNAs are small (~20nt) noncoding RNA molecules, which regulate the gene expression by binding at the 3'UTR of one or more m-RNAs either by translation inhibition or target degradation. In PDAC, role of different microRNAs including miR-10a, miR-21, miR-34a miR-150, miR-155, miR-203, miR-210, miR-212-3p let-7, miR-744, miR-1246 and others are well documented [16,17]. Exosomal microRNA such as miR-212-3p, miR-203, miR-21 have been shown to induce a number of biological responses such as enhancement of invasive potential, modulation of immune response, PDAC cell and pancreatic stellate cells cross-talk, and drug resistance [8,18,19]. The plasma levels of the some of the microRNA get altered along with disease progression and also in response to a specific therapy. Therefore, these properties of exosomes can be availed for the prediction and prognosis of the disease.

In spite of significant advances in chemotherapy, drug resistance remains a major obstacle in successful treatment and leads to poor prognosis in PDAC. The drug resistance in PDAC is a result of different factors such as mutational change in tumor suppressor genes, less drug accumulation due to desmoplastic microenvironment, drug expulsion, presence of tumor stem cells with higher potential for epithelial to mesenchymal transition (EMT), hypoxic tumor environment and cross-talk between tumor and surrounding cells [18]. Recently, our group demonstrated that chemotherapeutic induced exosomes potentiate the PDAC cells against further exposure with drug (unpublished data).

The stability, targeted delivery and undesirous side effects of chemotherapeutic agents are major limitations to cure the disease. The exosome-based therapy may provide an attractive strategy for targeted drug delivery. Exosomes can be loaded with drug, protein, microRNA or other therapeutic entity and its surface molecules can be engineered for specific target recognition. This will not only enhance the stability and specificity of therapeutic agents, but also reduce the side effects and immunogenic response. In order to achieve specificity and efficacy, different components of exosome-based drug delivery system should be chosen carefully e.g. exosome donor cells, loading methods, and administration routes [20]. A number of other strategies can also be applied to harness the potential of these exosomes to control drug release at the diseased sites according to the tumor microenvironment.

In conclusion, the study of PDAC-derived exosomes may provide greater understanding of the different mechanisms in cancer biology. Therefore, careful isolation, purification and characterization of exosomes are necessary to reveal the unadulterated results. The combined "omics" data sets are necessary to define the role of exosomes and their validation. The knowledge gained regarding the role of PDAC exosomes could hold significant clinical importance in early detection, disease prevention as well as improved prognostic measurement and development of effective therapies. In sum, improved understanding and characterization of pancreatic cancer exosomes may open up new avenues for designing of exosomes-based clinical management of pancreatic cancer.

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References

1. Siegel RL, Miller KD, Jemal A (2016) Cancer statistics, 2016. CA Cancer J Clin 66: 7-30.
2. Zheng X, Carstens JL, Kim J, Scheible M, Kaye J, et al. (2015) Epithelial-to-mesenchymal transition is dispensable for metastasis but induces chemoresistance in pancreatic cancer. Nature 527: 525-530.
3. Mathivanan S, Fahner CJ, Reid GE, Simpson RJ (2012) ExoCarta 2012: database of exosomal proteins, RNA and lipids. Nucleic Acids Res 40: D1241-1244.
4. Théry C, Zitvogel L, Amigorena S (2002) Exosomes: composition, biogenesis and function. Nat Rev Immunol 2: 569-579.
5. Costa-Silva B, Aiello NM, Ocean AJ, Singh S, Zhang H, et al. (2015) Pancreatic cancer exosomes initiate pre-metastatic niche formation in the liver. Nat Cell Biol 17: 816-826.
6. Sionov RV, Fridlender ZG, Granot Z (2015) The Multifaceted Roles Neutrophils Play in the Tumor Microenvironment. Cancer Microenviron 8: 125-158.
7. Fridlender ZG, Albelda SM, Granot Z (2015) Promoting metastasis: neutrophils and T cells join forces. Cell Res 25: 765-766.
8. Ding G, Zhou L, Qian Y, Fu M, Chen J, et al. (2015) Pancreatic cancer-derived exosomes transfer miRNAs to dendritic cells and inhibit RFXAP expression via miR-212-3p. Oncotarget 6: 29877-29888.
9. Paget S (1989) The distribution of secondary growths in cancer of the breast. 1889. Cancer Metastasis Rev 8: 98-101.
10. Hoshino A, Costa-Silva B, Shen TL, Rodrigues G, et al. (2015) Tumour exosome integrins determine organotropic metastasis. Nature 527: 329-335.
11. Sagar G, Sah RP, Javeed N, Dutta SK, Smyrk TC, et al. (2015) Pathogenesis of pancreatic cancer exosome-induced lipolysis in adipose tissue. Gut .
12. Javeed N, Sagar G, Dutta SK, Smyrk TC, Lau JS, et al. (2015) Pancreatic Cancer-Derived Exosomes Cause Paraneoplastic Î²-cell Dysfunction. Clin Cancer Res 21: 1722-1733.
13. Melo SA, Luecke LB, Kahlert C, Fernandez AF, Gammon ST, et al. (2015) Glypican-1 identifies cancer exosomes and detects early pancreatic cancer. Nature 523: 177-182.
14. Del Villano BC, Brennan S, Brock P, Bucher C, Liu V, et al. (1983) Radioimmunometric assay for a monoclonal antibody-defined tumor marker, CA 19-9. Clin Chem 29: 549-552.
15. Khan S, Jutzy JM, Aspe JR, Wall NR (2012) Exosomal survivin, a potential tool for early detection of pancreatic cancer health disparity Proceedings of the AACR Special Conference on Pancreatic Cancer: Progress and Challenges Cancer Research 72: 97.
16. Bhardwaj A, Arora S, Prajapati VK, Singh S, Singh AP (2013) Cancer "stemness"- regulating microRNAs: role, mechanisms and therapeutic potential. Curr Drug Targets 14: 1175-1184.
17. Srivastava SK, Arora S, Singh S, Bhardwaj A, Averett C, et al. (2014) MicroRNAs in pancreatic malignancy: progress and promises. Cancer Lett 347: 167-174.
18. Charrier A, Chen R, Chen L, Kemper S, Hattori T (2014) Connective tissue growth factor (CCN2) and microRNA-21 are components of a positive feedback loop in pancreatic stellate cells (PSC) during chronic pancreatitis and are exported in PSC-derived exosomes. Journal of Cell Communication and Signaling 8: 147-156.
19. Zhou M, Chen J, Zhou L, Chen W, Ding G, et al. (2014) Pancreatic cancer derived exosomes regulate the expression of TLR4 in dendritic cells via miR-203. Cell Immunol 292: 65-69.
20. Johnsen KB, Gudbergsson JM, Skov MN, Pilgaard L, Moos T (2014) A comprehensive overview of exosomes as drug delivery vehicles-

endogenous nanocarriers for targeted cancer therapy. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer 1846: 75-87.