Preface

Body fluid exosomes and cancer

This issue of *Translational Cancer Research* addresses the current state of knowledge regarding exosomes in body fluids and cancer. Exosomes are produced in increased numbers in cancer compared to normal cells (1). Exosomes are made by almost all cells, with the possible exception of red blood cells and are secreted into the tumor or normal cell adjacent body fluid. Cancer cell derived exosomes influence tumor growth, metastasis, evasion of the immune system and resistance to therapy (1).

Urine

Urine contains high concentrations of exosomes derived from urinary tract cells. Isabella Panfoli reviews current knowledge available using urine as a "liquid biopsy" for benign and malignant urinary tract disease. The article highlights how tumor cell derived exosomes in urine support tumor growth, as well as how the contents of exosomes are being analyzed to predict the presence of aggressive disease, such as high grade prostate cancer. The article also suggests that urine exosomes may contain biomarkers that are more indicative of the tumor microenvironment than blood-based biomarkers. Though additional research is necessary to validate exosomal biomarkers that predict the presence of disease or of disease response, urinary exosomes are potentially an ideal fluid for such assessment, as its collection is noninvasive and it is readily available.

Breast milk

Breast milk provides nutrition for a newborn but can also be a useful tool to monitor the health of a lactating breast. It is well documented that pregnancy influences a woman's risk of developing breast cancer over both the short and long term. The report reviews studies that evaluate the presence and role of breast milk exosomes in humans and other mammals. The article highlights a recent report which determined that milk exosomes from healthy women which contained high (but not low) levels of transforming growth factor β2 promoted benign breast epithelial cells toward neoplasia and well differentiated malignant breast epithelial cells toward a more invasive phenotype by inducing epithelial mesenchymal transition. Further research is necessary in order to discover if this phenomenon occurs *in vivo*.

Nipple aspirate fluid (NAF)

With practice, NAF can be reliably collected non-invasively from the breast of a woman who is not pregnant or lactating. In this report, the authors determined if exosomes are detectable in NAF, whether the exosomes contain miRNAs, and if so, could they predict the presence of breast cancer and/or response to treatment. The investigators found that exosomes are present in NAF and they contain miRNAs. They then determined the expression of 10 miRNAs in NAF, comparing samples from subjects with newly diagnosed breast cancer with those from healthy controls. The investigators found that the expression of miR-16 and -155 were increased with regional breast cancer spread to axillary lymph nodes compared to women whose disease had not spread beyond the primary tumor.

Cerebrospinal fluid (CSF)

CSF surrounds the central nervous system (CNS) and spinal cord and contains exosomes secreted from these structures. The article by Dr. Whitehead and colleagues addresses how exosomes present in the CSF can provide insight into CNS tumors. Their analysis of 62 datasets identified six exosomal markers that were differentially expressed between gliomas and normal brain tissue. They present an overview of the potential use of glioma-derived exosomes in diagnostic, prognostic, and treatment outcomes. The review concludes with a brief discussion of the advantage of CSF as a purer and more reliable source of glioma-derived exosomes relative to serum, which has exosome contributions from many organs in the body.

Bile

Bile is produced by the liver. It is transported to, concentrated and stored in the gallbladder. It is released from the gallbladder into the duodenum to aid the absorption of lipids in food. Bile is composed of water, bile salts, bilirubin, fats and inorganic salts. Bilirubin is derived from the normal breakdown of hemoglobin, as old red cells are replaced with new ones. Biliary tract

cancers are notoriously difficult to diagnose at an early stage. Most biliary tract cancers are diagnosed when they are incurable. Exosomes derived from biliary tract cells are being evaluated as potential diagnostic biomarkers. Preliminary reports suggest that the concentration of exosomes in the bile of patients with biliary tract cancer is higher than in those with benign disease, and that certain miRNAs are differentially expressed in the bile of patients with cancer compared to those with benign disease.

Pancreatic juice

Pancreatic cancer is highly lethal, with a 5-year survival rate of 8%. Early detection of the disease is uncommon. The authors provide a brief overview of what is known today regarding biomarkers in pancreatic juice. Cytologic analysis of pancreatic juice, obtained either with or without brushing of the pancreatic duct, can be performed and is helpful if positive for malignancy, but cytologic sensitivity for pancreatic cancer detection is suboptimal. miRNAs, various proteins, and altered DNA (increased methylation, mutations) have also been analyzed, again with less than optimal sensitivity and specificity. The authors discuss various exosomal compounds which show promise in the early detection of pancreatic cancer.

Semen

Exosomes within semen have sometimes been called "prostasomes", although the exosomes are derived not only from the prostate, but also from the epididymal ducts, vesicular glands, and bulbourethral glands. The authors review the findings of studies which have evaluated biomarkers in seminal exosomes and how their expression differs between men with prostate cancer *vs.* healthy individuals. Additionally, the article summarizes the immunosuppressive effects of seminal exosomes in human immunodeficiency virus and human papilloma virus transmission.

Blood

Blood is the most common body fluid collected, and the most commonly studied body fluids regarding exosomal contents are the liquid portions of the blood, plasma (blood minus platelets, red and white cells) and serum (plasma minus clotting proteins). Both serum and plasma derived exosomes contain RNAs, DNA, lipids, carbohydrates and proteins. One of the potential advantages (and disadvantages) of blood based exosomes is that the exosomes are derived from many organs in the body. Leveraging the potential advantage that blood circulates throughout the body, the article addresses how telomerase is being investigated as a possible pan-cancer marker. The article also lists websites devoted to extracellular vesicles (including exsomes), as well as websites specifically devoted to exosomes.

Lymph

Exosomes derived from tumors can enter the lymphatics, traveling to lymph nodes and to distant parts of the body. Exosomes are actively involved in immune system regulation through their uptake by various white blood cells contained within lymph nodes, and subsequent activation or suppression of these immune mediating cells. Localization of exosomes within lymph nodes appears to depend on which antigens are expressed on the exosomal surface. How lymph nodes either suppress tumor growth or promote it is also being investigated, as well as how tumor derived exosomes are involved in this important process. For example, tumor derived exosomes prepare the receiving lymph node for the regional spread of cancer cells to the lymph node.

Future perspectives, including exosome based therapy

Two articles are devoted to the future potential of exosomes in cancer diagnosis and therapy. One report provides an overview, while the second focuses specifically on exosome based therapy using miRNAs. A promising advance regarding the early detection of pancreatic cancer is the observation that exosome derived glypican-1 expression appears to be both highly sensitive and specific for the early detection of the disease. Exosomal glypican-1 expression may also be useful in the early detection of other cancers. Exosomes can be genetically altered, such as by targeting KRAS mutations, to treat cancer. Dendritic cell exosomes have been developed in the hope of increasing the body's immune response to cancer, and depletion of tumor derived exosomes is being studied to decreased tumor growth. miRNAs or anti-miRNAs can be added to exosomes to alter miRNA expression and thereby treat cancer. Challenges that exist in increasing or decreasing miRNA expression in exosomes are reviewed. Despite the challenges, the authors conclude that findings thus far support the use of exosomes and other extracellular vesicles for miRNA/anti-miRNA transfer for cancer therapy.

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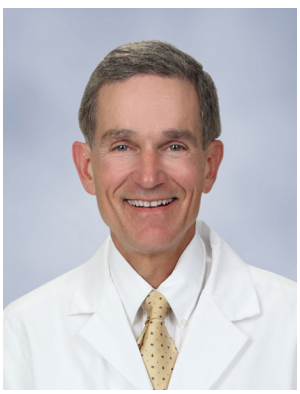

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