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Editorial

Exosomes in breast cancer

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Introduction

Exosomes in microenvironment, invasion and metastasis of Breast Cancer are extracellular signalosomes that facilitate eukaryotic intercellular communication using multiple physiological contexts. In malignancies, this regulatory circuit promotes cancer cell survival and outgrowth. Tumor-derived exosomes (TDEs) carry a pro-EMT (epithelial-mesenchymal transition) programme that enhances the invasive and migratory capabilities of recipient cells, and contributes to stromal remodelling and premetastatic niche formation. The integrin expression patterns on TDEs appear to dictate their preferential uptake by organ-specific cells, implying a crucial role of this pathway in organotropic metastasis. Through the expression of immunomodulatory molecules such as CD39 and CD73, TDEs modifythe immune texture of the tumor microenvironment, which could have implications for immunotherapy. Thus, targeting TDE dysregulation pathways could represent novel therapeutic strategies to conquer cancer.

Exosomes in the development of breast cancer

Transport through the cell membrane can be divided into active, passive and vesicular types (exosomes). Exosomes are nano-sized vesicles released by a variety of cells. Emerging evidence shows that exosomes play a critical role in cancers. Cell-secreted exosomes communicate with the microenvironment through the delivery of proteins, nucleic acid and other substances. Deregulation of exosome-mediated transport leads to disease development.

Over the last decade, growing attention has been paid to the role of exosomes in the development of breast cancer. Breast cancer could induce salivary glands to secrete specific exosomes, which could be used as biomarkers in the diagnosis of early breast cancer. Exosomes function as promoters in the tumorigenesis, metastasis and drug resistance of breast cancer.

Role of exosomes in the diagnosis of breast cancer

Diagnosis of breast cancer depends on imaging, biomarkers and pathology. Biomarkers are major method for breast cancer screening and early diagnosis. Molecular markers of breast cancer are classified into tissue, genetic and serum markers. Current tissue and serum markers cannot be used in the diagnosis of breast cancer at an early stage. Saliva is used as a noninvasive method to detect cancers at an early stage, including breast, pancreatic and oral cancers. Salivary biomarkers (transcriptomic and proteomic signatures) are high-specificity and high-sensitivity discriminators for detection of early breast cancer. Exosomes derived from breast cancer (exo-BCa) can interact with salivary gland cells. In addition, the salivary biomarkers partly result from the exo-BCa-delivered proteins and mRNA. Monitoring the mRNA and protein expressions of salivary biomarkers among persons at high risk of breast cancer serves as a new efficient way for detection of breast cancer.

Exosomes in breast cancer tumorigenesis

Exosomes stimulated by hypoxia, heparanase and other factors are associated with angiogenesis of breast cancer, which is the most significant part of breast cancer tumorigenesis. Exo-BCa can restrain immunological responses through regulating the expression of the NKG2D receptor by effector cells, which promotes breast cancer immune evasion. Exosomes derived from heparanase-high breast cancer cells could enhance the spread of cancer cells. Heparanase-regulated exo-BCa is associated with enhanced tumor growth and angiogenesis. Exosomes-transported miRNA and proteins could promote neoplastic transformation and widely participate in different stages of breast cancer development. One way by which exosomes promote tumorigenesis is to convert tumor microenvironment to permissive niches.

Exosomes in microenvironment. Invasion and metastasis of breast cancer

The tumor microenvironment is comprised of stromal cells, soluble factors, extracellular matrix, signaling molecules, hypoxia and mechanical cues (e.g. exosomes). Combinations of tumor microenvironment factors can support tumor progression by helping tumor cells to escape from host immunity and drug treatments, and offer niches for metastasis. Hypoxia facilitates the release of exosomes by breast cancer cells. The consequential transformation of microenvironment is more suitable for cancer survival, high invasiveness and distant metastasis of breast cancer. The roles of exosomes in invasion and metastasis of breast cancer are gradually being clarified.

Exosomes in breast cancer resistance

New and acquired resistances to radiation, chemotherapy or targeted therapies are significant challenges in the treatment of breast cancer. Various factors participate in development of breast cancer resistance. Exosomes transfer RNA and proteins to mediate the communication between stromal cells and cancer cells, which can influence treatment response. Exosomes transferred from stromal to breast cancer cells contribute to chemotherapy and radiation resistance through antiviral and NOTCH3 pathways. Release of exosomes can be promoted by hypoxia and exosomes that are associated with the radiation

resistance of tumor cells under hypoxic conditions. Exosomes from drug-resistant breast cancer cells transmit chemoresistance through the delivery of p-gp and miRNA. Accumulation of anticancer drugs in exosomes/vesicles that shed out of cancer cells is a drug efflux mechanism involved in drug resistance; however, this hypothesis, true for Docetaxel in a prostate cancer model, has not been proven in any breast cancer model, and should be verified through further studies.

Exosomes in breast cancer therapeutics

Exosomes that are endogenous nano-sized membrane vesicles can be used to carry drugs with low immunogenicity and toxicity. Exosomes have the potential to worsen the tumor microenvironment for cancer growth. Exosomes are able to transmit anti-tumor substances to recover the surveillance of immune system. There are also some unsolved problems in the clinical application of exosomes; researchers must seek better methods to produce plenty of exosomes without great cost; the way in which exosomes should enter the body is also controversial.

Conclusion

Exosomes are nano-sized vesicles that mediate inter-cellular and intra-cellular communication. There is growing evidence that exosomes play an essential role in the process of pathological states. Exosomes could function as biomarkers of various cancers, including breast cancer. Dysregulation of exosomes in body fluid indicates that diseases may lack sensitivity and specificity. Exosomes are potential carriers of drugs targeting breast cancer cells. Further studies are required to better understand the role of exosomes in the occurrence of breast cancer and before exosomes can be utilized to establish a drug delivery system in vivo.

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Conflicts of interest

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