Review

The role of exosomes in breast cancer invasion and metastasis

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Background

Within the UK, breast cancer is one of the top ten causes of female deaths. The metastasis of breast cancer into the circulatory system and, consequently, to organs, has made it increasingly difficult to treat. There has been growing evidence to suggest that exosomes (extracellular organelles) contribute to breast cancer invasion and metastasis. These nanosized vesicles can carry and release a wide range of metastatic-stimulating components, including microRNAs (miRNAs) and other tumour-promoting factors. This article will explore the way in which exosomes contribute to the journey of breast cancer in situ to secondary metastasis.

Introduction

Breast cancer is a heterogeneous disease that primarily affects female individuals. It can present in various ways, from a raised lump to a peau d'orange appearance. There are several subtypes of breast cancer that are categorised based upon the presence/absence of oestrogen receptors and progesterone receptors and amplification of human epithelial growth factor receptor 2. These receptors are all found on the epithelial cell surface of breast tumours.[1] Triple negative breast cancer, which lacks all of these receptors, particularly contributes to the growing health concern regarding metastatic breast cancer due to its resistance to current therapeutics, such as tamoxifen and herceptin.[2] Gaining insight into the establishment of the tumour microenvironment (defined as the environment permitting migration and invasion of tumour-initiating cells)[3] and the consequent metastatic cascade of breast cancer (outlined in **Figure 1**) could help determine targets for new therapy.

Exosomes derived from breast cancer cells and formed from the fusion of multivesicular bodies with the plasma membrane[4] contain increased levels of cargo involved in the metastatic cascade.[5] Such cargo includes miRNAs,[6-11] catalytic and extracellular matrix (ECM) proteins,[12] and hypoxia inducible factors.[13] The significance of exosomes in breast cancer metastasis is explored in this article, identifying potential therapeutic targets for the future.

Literature search

Initial data collection focused on obtaining an understanding of the steps involved in breast cancer metastasis. The topics presented below were chosen based on the volume and breadth of information found for both the metastatic cascade and the exosome's involvement. The search engines Ovid, PubMed and Google Scholar were used for data collection. Use of up-to-date and relevant information was key for the analysis and write-up; thus, only research spanning from 2000 to 2018 was included.

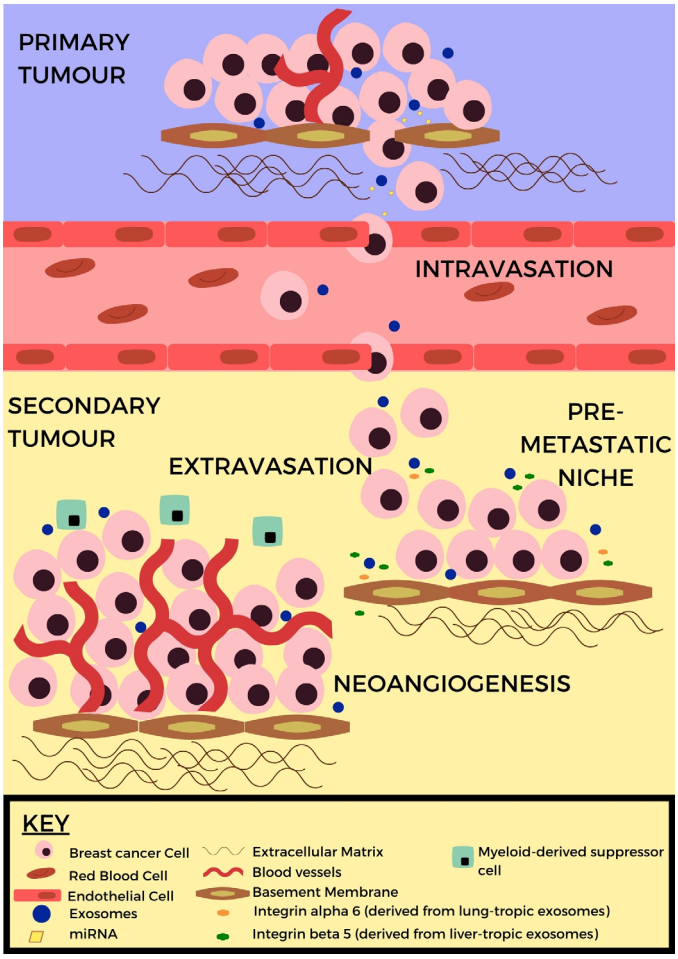

Figure 1. Metastatic cascade of breast cancer. This is a schematic diagram outlining the key steps and contributing factors to breast cancer metastasis.

Processes involved in breast cancer metastasis

Epithelial mesenchymal transition and migration In breast cancer, cell composition is altered by a process known as epithelial mesenchymal transition (EMT). Molecules that form cell–cell adhesion junctions, such as E-cadherin and N-cadherin, are downregulated and upregulated in breast cancer, respectively. This contributes to the migration of tumour initiating cells from the basement membrane to the neighbouring stroma.[14] Proteolytic factors, such as matrix metalloproteinases and urokinase plasminogen activators, also aid in ECM degradation, further contributing to breast cancer cell migration.[15]

With regard to exosomes, their carrying capability contributes to cancer cell migration. Research has shown that a specific miRNA, miR-105, derived from the breast cancer cell line MDA-MB-231, is contained within exosomes. miR-105 reduces the expression of another known adhesion cell molecule, tight junction protein 1, which may be suggestive of exosome involvement in cell migration.[10]

Organotropic metastasis Once cell migration and consequent intravasation occurs, organotropic metastasis proceeds. This involves the establishment of migrating cancer cells to another site known as the pre-metastatic niche[16] (see **Figure 1**). Current research demonstrates that integrins that promote cancer cell adhesion to parenchyma are contained and released by breast cancer-derived exosomes. For example, integrin alpha 5 has been linked to higher risk of lung metastases in breast cancer,[17] demonstrating exosome involvement in determining the metastatic site.

Neoangiogenesis promotion As metastasis occurs, neoangiogenesis (the formation of a vascular system) is required[18] (see **Figure 1**). The hypoxic environment of tumours has been shown to initiate an 'angiogenic switch',[19] resulting in neoangiogenesis. Evidence has also shown an increase in exosomes, as well as factors that promote angiogenesis activity. For example, miRNA-201 has been shown to be upregulated during hypoxia. miRNA-201 is involved in endothelial cell tubulogenesis,[20] a process whereby pre-endothelial cells transform from cuboidal to squamous cells and translocate to the periphery, lining the vessel lumen.[21]

Escape of immune response Avoiding the immune response is important for tumour progression.[22] The neoantigens present on a cancer cell's surface make it an immune target; however, exosomes have been shown to prevent cancer cell destruction by immune cells.[23] The increased number and frequency of myeloid-derived suppressor cells in metastatic breast cancer, responsible for premetastatic niche formation and T cell inhibition, are as a result of exosomes.[24] Additionally, the downregulation of NKG2D, a natural killer cell lectin receptor, from breast cancer-derived exosomes (vs exosomes not derived from breast cancer) has been shown to permit further tumour progression.[25]

Conclusion

In summary, exosomes play a role in breast cancer metastasis. The research discussed in this review, which used highly metastatic cell lines, are hugely insightful. Nonetheless, there are a few gaps that were evident in the data included. For example, stages in the metastatic cascade, such as intravasation, were not mentioned in this review due to insufficient data on the exosome's contribution. Although this may suggest that exosomes do not play a role in intravasation, further research is required to determine this. Additionally, although research has identified relevant carrier proteins involved in breast cancer metastasis, knowledge on the mechanisms regarding the specific trigger factors, exosomal transport and cargo release is scarce. This was evident in the literature surrounding neoangiogenesis, a new and emerging topic in the field of breast cancer metastasis. This highlights the need for further research in this area.

Excitingly, it is important to note that research into the use of exosomes as drug carriers is being investigated. Due to their nanoscale, endogenous and easily fusible structure, exosomes could be useful in future breast cancer management, particularly for patients with triple negative breast cancer in whom current treatment is ineffective.[26]

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