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COMMENTARY

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Exosomal Lipids as Bioactive Regulators of Cell Signaling and Hypoxic Adaptation in Cancer Metastasis

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About the Study

Exosomes, which are small extracellular vesicles, have become important intercellular communication mediators, especially when considering cancer biology. These vesicles, typically ranging from 30 to 150 nm in size, are secreted by virtually all cell types and carry a diverse cargo of bioactive molecules, including proteins, lipids, Ribo Nucleic Acids (RNAs) and DNA. The composition of exosomal cargo is reflective of the cellular state and origin of the producing cells. In cancer, Exosomes are increasingly recognized as key players in tumor progression and metastasis, facilitating the dissemination of malignant cells and enabling the formation of a favorable microenvironment in distant organs. Their involvement in multiple stages of metastasis, including tumor cell invasion, immune evasion, angiogenesis, and the establishment of pre-metastatic niches, shows their profound impact on the disease's progression.

The exosomal cargo's capacity to affect recipient cells' behavior is a key factor in the spread of cancer. Proteins transported by exosomes, including growth factors, cytokines, integrins, and enzymes, contribute to alterations in signaling pathways within the recipient cells. For instance, exosomal proteins can activate pathways that promote cell proliferation, migration, and Epithelial-to-Mesenchymal Transition (EMT), which are all critical for the metastatic cascade. EMT is particularly important because it allows epithelial tumor cells to acquire mesenchymal characteristics, including enhanced motility and invasiveness, facilitating their escape from the primary tumor stage. Exosomal cargo also includes Matrix Metallo Proteinases (MMPs) and other proteolytic enzymes that degrade components of the extracellular matrix, thereby promoting tumor cell invasion into surrounding tissues and facilitating entry into the bloodstream or lymphatic system. Exosomal lipids further contribute to the metastatic process. These lipids not only stabilize the structure of exosomes but also play an active role in intercellular signaling and membrane fusion. Exosomes' lipid rafts can improve target cells' absorption of them, facilitating effective cargo distribution. Bioactive lipids such as sphingolipids and phospholipids influence cancer progression by regulating cell survival, migration, and inflammatory responses. In addition, lipid-mediated signaling pathways can facilitate tumor cell adaptation to hypoxic and nutrient-deprived conditions, both of which are common features of the tumor microenvironment.

The nucleic acid component of exosomal cargo, particularly non-coding RNAs such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), plays an important role in metastasis. Exosomal miRNAs can silence or activate target genes in recipient cells, modulating processes such as cell proliferation, apoptosis, and immune responses. Dysregulation of these miRNAs often contributes to the initiation and progression of metastasis. For example, miRNAs that suppress tumor suppressor genes or enhance oncogenic signaling pathways can allow the survival and spread of cancer cells. Similarly, lncRNAs transferred *via* exosomes have been shown to influence gene expression patterns and chromatin remodeling in target cells, supporting metastasis by fostering a pro-tumorigenic environment. Exosomal cargo also enables tumor cells to avoid immune surveillance, a critical step in successful metastasis. Cancer-derived exosomes carry immunosuppressive molecules, such as Programmed Death-Ligand 1 (PD-L1), which can inhibit the activation of T cells and other components of the immune system.

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By impairing immune responses, these exosomes allow tumor cells to evade destruction and establish themselves in distant tissues. Moreover, exosomal miRNAs and cytokines can modulate the activity of immune cells, such as macrophages and Natural Killer (NK) cells, further allowing immune evasion. The ability of exosomal cargo to reshape the immune landscape provides cancer cells with a significant advantage in the metastatic process.

The formation of pre-metastatic area is another critical aspect of cancer metastasis that is heavily influenced by exosomal cargo. Before metastatic cells arrive at distant organs, exosomes released by primary tumor cells can condition the microenvironment to create a supportive place for their colonization. This is achieved through the transfer of exosomal cargo that allow stromal cell activation, extracellular matrix remodeling, and angiogenesis. For example, exosomal proteins such as integrins and fibronectin can direct exosomes to specific organs, identifying potential metastasis places. These proteins create advantageous conditions for metastatic colonization by activating local fibroblasts, endothelial cells, and immune cells after they arrived. By reprogramming stromal and immunological cells to increase tumor cell survival and expansion, exosomal RNAs and cytokines also help in this process. Angiogenesis, the formation of new blood vessels, is another critical step in cancer metastasis that is facilitated by exosomal cargo. Exosomes derived from tumor cells often carry pro-angiogenic factors, such as Vascular Endothelial Growth Factor (VEGF) and angiopoietins, which can stimulate endothelial cells to form new blood vessels. These newly formed blood vessels provide nutrients and oxygen to growing tumor cells and serve as pathways for their dissemination to distant organs. Additionally, exosomal miRNAs and proteins can modulate the behavior of endothelial cells, enhancing their proliferation, migration, and tube formation.