



Mechanisms of Brain Metastasis from Lung and Breast Cancers: Crossing the Blood-Brain Barrier

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DESCRIPTION

Brain metastases present a significant clinical challenge for patients with advanced lung and breast cancers, impacting survival and quality of life. The ability of cancer cells to spread from their original sites and establish secondary tumors within the brain requires a complex series of biological events. Central to this process is the crossing of the Blood Brain Barrier (BBB), a highly selective interface that protects the brain from toxins and pathogens. Understanding the mechanisms by which cancer cells penetrate this barrier is essential for developing strategies to prevent and treat brain metastases.

The blood-brain barrier consists primarily of endothelial cells tightly connected by junctional complexes, surrounded by astrocyte end-feet and pericytes. This structure limits the passage of substances from the bloodstream into the brain, maintaining neural homeostasis. For tumor cells to invade the brain, they must first survive in the circulation, then arrest in cerebral blood vessels, adhere to the endothelial lining, and finally traverse the BBB to colonize the brain tissue.

Lung and breast cancer cells are among the most common sources of brain metastases, yet they appear to use slightly different tactics to accomplish this task. Tumor cells release factors that disrupt the integrity of the BBB. These factors include proteolytic enzymes like Matrix Metallo Proteinases (MMPs), which degrade components of the basement membrane and extracellular matrix. This degradation loosens tight junctions between endothelial cells, creating openings that allow cancer cells to migrate through.

In addition to enzymatic disruption, cancer cells secrete cytokines and growth factors that activate signaling pathways in endothelial cells, leading to changes in cell permeability. For example, Vascular Endothelial Growth Factor (VEGF) promotes angiogenesis but also increases vascular permeability, aiding in the transmigration of tumor cells.

Once cancer cells adhere to the brain endothelium, they interact with surface molecules such as integrins and selectins, which facilitate firm attachment. These adhesion molecules enable tumor cells to resist the shear forces of blood flow and initiate trans endothelial migration. The precise molecular partners differ between lung and breast cancer cells but often involve upregulation of integrins like $\alpha v \beta 3$ and $\alpha 4 \beta 1$.

Emerging research highlights the role of exosomes small extracellular vesicles released by tumor cells in preparing distant sites such as the brain for metastasis. These vesicles carry proteins, RNA, and other molecules that modulate the local microenvironment. Exosomes can alter BBB permeability and influence the behaviour of resident brain cells, such as astrocytes and microglia, facilitating tumor cell entry and survival.

Once past the barrier, cancer cells face the challenge of adapting to the brain's unique microenvironment. The brain is a nutrient-restricted, immune-specialized site, and only a subset of circulating tumor cells can thrive there. Successful metastatic cells modify their metabolism and signaling pathways to survive under these conditions. Cross-talk with brain stromal cells supports tumor growth and protects cancer cells from immune clearance.

Immune evasion within the brain is an important aspect of metastasis. The central nervous system is traditionally considered an immune-privileged site, yet immune cells like microglia and infiltrating lymphocytes still play roles in detecting and responding to abnormal cells. Cancer cells manipulate these immune components, often shifting microglia towards a tumor-supportive state through secretion of immunosuppressive molecules, thus promoting metastasis progression.

Both lung and breast cancer brain metastases share common features but also exhibit subtype-specific behaviors. For example, HER2-positive breast cancer frequently metastasizes to the brain, with cells showing enhanced abilities to cross the BBB and proliferate within the cerebral environment. Lung

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adenocarcinomas expressing certain mutations, such as EGFR or ALK alterations, demonstrate similar tendencies toward brain dissemination.

In the future, deeper understanding of the steps cancer cells use to navigate the blood-brain barrier will likely lead to improved preventative therapies and personalized treatment approaches. Identifying patients at high risk for brain metastases and intervening early could reduce neurological complications and improve overall outcomes.

In summary, lung and breast cancer cells employ a series of coordinated actions to penetrate the blood-brain barrier and establish secondary tumors within the brain. Disruption of endothelial integrity, firm adhesion to vascular surfaces, and immune modulation are essential components of this process. Continued study into these mechanisms offers hope for more effective therapies and better management of patients affected by brain metastases.