

MECHANISMS OF BREAST CANCER BRAIN METASTASIS

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Brain metastases are among the most feared complications in breast cancer that currently cannot be cured. Successful prevention and treatment will require that we know which mechanisms allow breast cancer cells to enter the brain and thrive within the central nervous system.

We established new human cell models to study breast cancer brain metastasis, and we follow establishment and progression of the disease as well as response to treatment in immune deficient mice by non invasive bioluminescence imaging. Our systems allow us to analyze mechanisms that circulating breast cancer cells use to penetrate the blood brain barrier and to survive and disseminate within the brain tissue.

Functional analyses and large-scale proteomic profiling of brain homing breast cancer cells revealed that the tumor cells use distinct functional pathways to enter the brain and to grow within the brain microenvironment. For example, expression of the adhesion receptor integrin avb3 in an activated, high-affinity form promotes tumor cell brain colonization, and Her-2 strongly supports growth within the brain tissue. Importantly, breast cancer cell survival and expansion within the central nervous system is accompanied by significant changes in tumor cell metabolism characterized by oxidative pathways for energy production and simultaneous upregulation of antioxidant pathways that allow the tumor cells to detoxify reactive oxygen species generated during high-efficiency, oxidative glucose turnover. These metabolic changes reflect an adaptation of the tumor cells to metabolic energy pathways that normal brain cells use as well.

Thus, a subset of tumor cells may evolve during malignant breast cancer progression that is capable of gaining entry into the protected environment of the brain and which can differentiate along pathways that allow the tumor cells to thrive within the brain tissue. Our study raises the possibility of targeting distinct tumor cell properties for prevention and treatment of breast cancer brain metastasis.

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