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The role of the organ microenvironment in brain metastasis.

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Abstract

More than 40% of patients with lung cancer and breast cancer develop brain metastasis. With improved local control and therapy of metastasis to visceral organs, the morbidity and mortality due to late diagnosed brain metastasis are projected to rise. The median survival for untreated patients is 1-2 months, which may be extended to 6 months with surgery, radiotherapy, and chemotherapy. The development of a relevant mouse model for the establishment and growth of brain metastasis has advanced our understanding of the biology and therapy of this most feared consequence of cancer. Injection of murine or human tumor cells into the internal carotid artery of mice produces experimental metastases in specific regions of the brain that are not due to patterns of initial cell arrest, motility, or invasiveness, but rather to the ability of metastatic tumor cells to exploit homeostatic mechanisms and proliferate. Immunohistochemical and morphometric analyses demonstrate that the density of blood vessels within experimental metastases in brains of mice or in clinical specimen of human lung cancer brain metastases is lower than that in the adjacent tumor-free brain parenchyma. However, brain metastasis-associated blood vessels are dilated and contain numerous dividing endothelial cells. Immunohistochemical analysis also reveals that tumor cells located less than 100μm from a blood vessel are viable, whereas more distant tumor cells undergo apoptosis. Tumor cells within brain metastasis produce VEGF which induces permeability in adjacent vessels. The BBB in metastases that are larger than 0.25mm in diameter is leaky. Metastases in the brain are resistant to chemotherapeutic drugs. The venerable "seed and soil" hypothesis suggests that the outcome of metastasis depends on the interaction between unique tumor cells and the specific organ microenvironment. The demonstration that activated astrocytes whose physiological role is to protect neurons from toxic substances can be exploited by tumor cells for protection from chemotherapeutic drugs suggests new approaches to the treatment of this fatal disease.

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