

Trophic factors and central nervous system metastasis

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Key words: brain metastasis, melanoma, tumor progression, growth factors, neurotrophins, nerve growth factor, melanotropins, signal transduction, tyrosine receptor kinase

Abstract

To metastasize to the central nervous system (CNS) malignant cells must attach to brain microvessel endothelial cells, respond to brain endothelial cell-derived motility factors, respond to CNS-derived invasion factors and invade the blood-brain barrier (BBB), and finally, respond to CNS survival and growth factors. Trophic factors such as the neurotrophins play an important role in tumor cell invasion into the CNS and in the survival of small numbers of malignant cells under stress conditions. Trophic factors promote BBB invasion by enhancing the production of basement membrane-degrading enzymes in neurotrophin-responsive cells. The expression of certain neurotrophin receptors on brain-metastatic neuroendocrine cells occurs in relation to their invasive and survival properties. For example, CNS-metastatic melanoma cells respond to particular neurotrophins (nerve growth factor, neurotrophin-2) that can be secreted by normal cells within the CNS. In addition, a paracrine form of transferrin is important in CNS metastasis, and brain-metastatic cells respond to low levels of transferrin and express high levels of transferrin receptors. CNS-metastatic tumor cells can also produce autocrine factors and inhibitors that influence their growth, invasion and survival in the brain. Synthesis of paracrine factors and cytokines may influence the production of trophic factors by normal brain cells adjacent to tumor cells. Moreover, we found increased amounts of neurotrophins in brain tissue at the invasion front of human melanoma tumors in CNS biopsies. Thus the ability to form metastatic colonies in the CNS is dependent on tumor cell responses to trophic factors as well as autocrine and paracrine growth factors and probably other underdescribed factors.

1. Introduction-prevalence of CNS metastases

The central nervous system (CNS) is a unique organ for metastatic colonization [1–3]. It is highly sensitive to the slightest change in the local microenvironment, and it is surrounded by a formidable blood-brain barrier (BBB, Fig. 1) that must be penetrated by brain-metastatic tumor cells. Moreover, the CNS lacks lymphatic drainage and cannot remove fluid that accompanies tumor growth in the brain. This results in cerebral edema which represents a major complication resulting from CNS tu-

mors [4]. Therapy of CNS metastases is usually only palliative and is often accompanied by clinical complications. Thus CNS tumor formation and metastasis to the CNS are extremely difficult clinical problems.

Metastatic lesions in the CNS and spinal cord commonly occur in certain types of cancers, such as disseminated malignant melanoma, breast cancer, lung cancer and others. When these cancers metastasize to the CNS, they frequently result in severe and debilitating neurological complications. Even small metastasis in the CNS can cause severe symp-

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