Chapter 7

Role of Brain Microenvironment in Brain Metastases

J. Grunfeld and V.K. Puduvalli

Department of Neuro-Oncology, University of Texas M.D. Anderson Cancer Center, Houston, TX, USA

Abstract: The development of brain metastasis portends a grave prognosis for patients with systemic cancer. Efforts to alter the course of this disease have been hampered by a poor understanding of the biology of the metastatic process. Recent insights into the biologic determinants of this process aided by advances in molecular biology and biotechnology have altered the basic concepts of our understanding of how cancer cells metastasize to distant organs. These findings have validated and extended the “seed and soil” hypothesis emphasizing a critical role for the microenvironment of the target organ in the development of metastatic lesions. The brain microenvironment has unique characteristics that distinguish it from other organs of the body. Hence, therapeutic strategies to target the interaction between the metastatic tumor cell and the brain require a clear understanding of the molecular and anatomic features that influence this process. Recent studies have revealed an intricate and often facilitatory interaction between these elements of the brain metastatic process. These findings may allow the development of targeted therapies that in combination with therapeutic strategies against systemic malignancies hold promise to improve the prognosis of patients with brain metastases.

Key words: Brain, metastasis, microenvironment, molecular mediators

1. INTRODUCTION

Brain metastases are the most common malignancies affecting the nervous system, and their incidence far outnumbers the incidence of primary brain tumors (1). In autopsy series, intracranial metastases (symptomatic or undetected) have been demonstrated in 24% of all cancer patients examined (2). The disease confers significant mortality and morbidity. Median survival from the time of detection is 4 weeks in the absence of therapeutic intervention(s), with death resulting from intracranial disease progression. (3, 4) Even with advances in current treatments, the overall median survival remains in the range of 3-6 months. (5-7) The morbidity associated with brain metastases results from the progressive development of neurologic and systemic symptoms (8). Many therapeutic approaches have attempted to alter the course of the disease, but they have only minimally affected the overall course of the malignancy and the prognosis of the patient. The privileged status of the brain created by the blood–brain barrier (BBB), the co-existence of progressive systemic and intracranial disease that can obscure morbidity due to brain disease, and the limited understanding of the biology of metastatic disease processes have hindered the development of meaningful therapeutic advances. Understanding the biology of the metastatic process has in part been limited by difficulties in obtaining brain metastatic tumor tissue, which would enable researchers to study the determinants underlying the biologic behavior of brain metastases. There is also a paucity of investigators whose preclinical and translational studies are predominantly focused on understanding the brain metastatic process. In
addition, most clinical trials of new anticancer agents in humans exclude from enrollment patients with brain metastases, which precludes appreciation of the effects of the agents being assessed against this disease process. Although in some malignancies the occurrence of brain metastasis is an early event, possibly due to intrinsic biologic characteristics of the primary tumor, in most cases, the appearance of metastatic lesions in the brain occurs only in the late stages of disease. The progressive increase in overall tumor burden overwhelms natural biologic boundaries that normally insulate the brain from such events. Because of the overlapping effects of systemic and intracranial disease, clinical trial designs are required to be increasingly complex and the outcomes are difficult to measure. Furthermore, recent advances in molecular pharmacotherapeutics and biotechnology have been translated into improved control of the underlying systemic disease, making it increasingly likely that disease sheltered in protected sites such as the brain could become a more relevant determinant of patient prognosis than the primary disease. It is thus imperative to gain insights into the biology of brain metastasis so that new and rational therapeutic approaches can be developed for controlling this disease.

2. EVOLUTION IN THE CONCEPTS OF THE METASTATIC PROCESS

The initial concept was that metastasis develops from tumor cells that are shed from a primary lesion into the circulation, followed by passive transfer of the cells until they are arrested in the capillaries of target organs where they establish new disease foci (9). It is possible that in the past the lack of effective treatments resulted in uncontrolled disease progression, which rapidly increased the overall disease burden. In such a setting, widespread metastases are common and organ selectivity may be less apparent. Generally, these lesions localize to the gray-white matter junction, most frequently in watershed regions of the brain’s blood supply (10, 11). This pathologic pattern of distribution is invoked to support the common notion that the spread of brain metastases is primarily hematogenic. However, more than a century ago, it was observed that the occurrence of metastases did not follow simple rules based on anatomy or blood supply. The inference was that factors critical to the development of metastases were related to the tissue of origin as well as to the target tissue (12). For brain metastases, this idea evolved into the intriguing theory that not only are specific cells in the primary tumor primed to metastasize to the brain but that there may also be cooperation between metastatic tumor cells and the brain microenvironment that helps to establish metastatic tumor foci in the brain. This concept has been strengthened by the observation that some malignancies have a higher predilection than others to metastasize to the brain. It is now well accepted that brain metastatic disease is the result of several combined factors, including the tissue of origin of the primary tumor, biologic factors related to the phenotype of the involved tumor cells, and the brain microenvironment. Together, these factors strongly influence host tissue-tumor cell interactions, and anatomic and physiologic mediators that regulate the transport and physical arrest of metastatic cells. A better understanding of the biology of this process has opened the door for developing targeted therapeutic interventions, an area of interest that has been intensively investigated in recent years. This chapter is an overview of some of the recent advances in the field of brain tumor metastasis, with reference to the various molecular factors relevant to this process, and it also examines how a better understanding of these factors is helping in the effort to conceptualize and develop novel therapeutic approaches for more effectively managing brain metastases.

3. THE BRAIN MICROENVIRONMENT – RELEVANCE TO METASTASIS

Based on the concept that “the distribution of the secondary growths is not a matter of chance”, Stephen Paget proposed a “seed and soil” hypothesis, which suggested that intrinsic characteristics of both the metastasizing cells and the host tissue were critical to the establishment and advancement of metastatic disease (12). Clinical