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Review

Brain metastasis: New opportunities to tackle therapeutic resistance

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ABSTRACT

Brain metastasis is a devastating complication of cancer with unmet therapeutic needs. The incidence of brain metastasis has been rising in cancer patients and its response to treatment is limited due to the singular characteristics of brain metastasis (i.e., blood–brain-barrier, immune system, stroma). Despite improvements in the treatment and control of extracranial disease, the outcomes of patients with brain metastasis remain dismal. The mechanisms that allow tumor cells to promulgate metastases to the brain remain poorly understood. Further work is required to identify the molecular alterations inherent to brain metastasis in order to identify novel therapeutic targets and explicate the mechanisms of resistance to systemic therapeutics. In this article, we review current knowledge of the unique characteristics of brain metastasis, implications in therapeutic resistance, and the possibility of developing biomarkers to rationally guide the use of targeted agents.

1. Introduction

Brain metastasis is a dismal disease with still few therapeutic options. It is estimated that brain metastasis occurs in 20%–40% of advanced stage cancers (Barnholtz-Sloan et al., 2004; Gavrilovic and Posner, 2005) and surpasses primary brain tumors in frequency (Maher et al., 2009). The annual incidence of brain metastasis in the United States is estimated to be around 200,000 cases (Barnholtz-Sloan et al., 2004; Gavrilovic and Posner, 2005) and population-based studies have predicted the diagnosis of 7–14 new brain metastases cases per 100,000 persons (Smedby et al., 2009). The rise in the incidence may be in part as a consequence of improved control of primary cancers and superior imaging methods (Frisk et al., 2012; Tabouret et al., 2012). Brain metastasis mainly occurs in patients with lung cancer, breast cancer and melanoma with frequencies of 40–50%, 20% and 10–20%, respectively (Barnholtz-Sloan et al., 2004; Gavrilovic and Posner, 2005). Other primary solid tumors (e.g., colorectal cancer, bladder cancer, prostate cancer) do not tend to disseminate to the brain and maintain low frequencies.

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The development of brain metastasis is an important clinical challenge associated with poor prognosis, neurological deterioration, and reduced quality of life (Gavrilovic and Posner, 2005; Stelzer, 2013). Despite the recent success of some therapies in the treatment of extracranial diseases, the outcome of patients developing brain metastasis has not been altered. Treatment of this fatal complication relies on palliative measures involving tumor resection and radiotherapy (i.e., stereotactic radiosurgery or whole brain radiotherapy) and survival is usually less than 12 months even with aggressive treatment (Gavrilovic and Posner, 2005; Stelzer, 2013).

Brain metastasis differs in many aspects from metastatic deposits originating from other organs. Several characteristics of the brain metastatic process (i.e., blood–brain barrier, immune system, stroma) and drug-associated hurdles (i.e., intrinsic or secondary resistance) play important roles in the complex pathogenesis of brain metastasis and in the sensitivity and resistance to systemic therapeutics. Systemic therapeutic agents (either cytotoxic or targeted therapeutic agents) with confirmed clinical activity in extracranial disease may not be efficient against established brain metastases. In this manuscript, we discuss how understanding the singularities of brain metastases may offer opportunities to tackle their therapeutic resistance and develop novel biomarkers to rationally guide the use of targeted agents. The use of surgery and radiotherapy in the management of brain metastasis, as well as leptomeningeal disease, which may occur concomitantly with brain metastasis have been reviewed elsewhere (Ellis et al., 2012; Owonikoko et al., 2014; Scott and Kesari, 2013).

2. Brain metastasis constitutes a singular challenge

Metastasis is a multistage process in which malignant cells spread from the tumor of origin to colonize distant organs, following a sequence of steps (i.e., local invasion, intravasation, survival in circulation, extravasation and tissue colonization)(Chiang and Massague, 2008; Weigelt et al., 2005; Weil et al., 2005) (Figure 1). The mechanisms that allow tumor cells to colonize the brain are still not fully understood. Several molecular mechanisms contributing to brain metastasis have being revealed, as well as different classes of 'metastasis-related genes' implicated in the development of brain secondary tumors (Bos et al., 2009; Grinberg-Rashi et al., 2009; Nguyen et al., 2009; Salhia et al., 2014; Valiente et al., 2014). For example, in lung cancer the expression of HOXB9, LEF1, BPTF, CDH2, KIFC1 (Bos et al., 2009; Grinberg-Rashi et al., 2009; Nguyen et al., 2009; Valiente et al., 2014) are associated with brain metastasis, and in breast cancer, the Notch pathway, expression of FOXC1, integrin alpha(v)beta(3) ($\alpha v\beta 3$), and IGF1R are related to brain metastasis in preclinical models (Lorger et al., 2009; Nam et al., 2008; Ray et al., 2010; Saldana et al., 2013).

Metastasis is an inefficient process. Most of the cancer cells that escape from solid tumors eventually die in the process of moving from the primary site to distant organs. The cells that survive may proliferate in the new microenvironment after periods of latency (Luzzi et al., 1998). In the case of brain colonization, cells encounter an additional hurdle since they have to cross the blood–brain barrier. Moreover, once in the brain parenchyma, tumor cells have to evade the brain immune system, invade through the brain stroma, degrading extracellular matrix components, and obtain blood supply through angiogenesis.

2.1. *Blood–brain barrier*

Brain metastasis may occur as a result of the hematogenous dissemination of tumor cells, either from a primary tumor or a metastatic deposit (Chiang and Massague, 2008). To seed the brain, tumor cells have to access the arterial circulation and bypass the blood–brain barrier, which is part of the neurovascular unit (Neuwelt et al., 2011). The blood–brain barrier forms a dynamic unit with different permeability ranges controlled by intracellular and intercellular signaling events (Neuwelt et al., 2011). Once the brain metastasis is established the blood–brain barrier is usually compromised, as can be observed by gadolinium enhancement of magnetic resonance imaging. The extent to which the blood–brain barrier is disrupted influences drug penetration in metastasis (Donelli et al., 1992). For example, the center of a metastatic lesion may present a disrupted blood–brain barrier, which is accessible to optimal drug concentration, whereas the periphery of a metastatic lesion may receive subtherapeutic dose concentrations leading to early development of resistance to treatment. Importantly and in addition, evidence suggests that systemic corticosteroids, which are used to treat peritumoral edema in patients with brain metastasis, can reestablish a disrupted blood–brain barrier, thereby preventing drug delivery and response to therapy (Posner, 1995).

The blood–brain barrier contributes to the inefficient process of metastasis (Lockman et al., 2010), but also provides a shelter for metastatic cells, protecting them from the immune response and systemic treatment (Luzzi et al., 1998). Hence on the one side the blood–brain barrier prevents the initiation of metastasis, but when the metastasis is established it facilitates the metastatic growth. The blood–brain barrier restricts delivery of therapeutic compounds (i.e., large molecules and hydrophilic drugs) to specific areas of the brain (Stewart, 1994); the exact extent to which this influences chemotherapeutic delivery and therapeutic intratumoral concentrations is unknown in many cases (Lockman et al., 2010).

2.2. *Brain stroma and immune system*

The brain has a distinct immune system (Hamilton and Sibson, 2013). The inflammatory cells of the brain involve perivascular mast cells and macrophages, microglia (which are believed to be the 'brain-resident' macrophages) and astrocytes. The inflammatory response to brain metastasis consists primarily of the activation of microglial cells, which are the principal immune effectors and the main cell type of the innate immune system of the central nervous system (CNS) (Graeber, 2010; Noda et al., 2009). Metastatic tumor cells in the perivascular area or the brain parenchyma permit differential recruitment of circulating systemic immune cells to the metastatic site, though there is no systematic pattern (Blond et al., 2002; Campbell et al., 2002).