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Low concentration microenvironments enhance the migration of neonatal cells of glial lineage

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Migration and Invasion of Brain Tumors

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1. Introduction

Recent advances in molecular biology have led to new insights in the development, growth and infiltrative behaviors of primary brain tumors (Demuth and Berens, 2004; Huse and Holland, 2010; Johnson et al., 2009; Kanu et al., 2009). These tumors are derived from various brain cell lineages and have been historically classified on the basis of morphological and, more recently, immunohistochemical features with less emphasis on their underlying molecular pathogenesis (Huse and Holland, 2010). The detailed molecular characterization of brain tumors has laid the groundwork for augmentation of standard treatment with patient-specific designed targeted therapies (Johnson et al., 2009; Kanu et al., 2009). Nevertheless, these tumors are extremely aggressive in their infiltration of brain tissue (Altman et al., 2007; Hensel et al., 1998; Yamahara et al., 2010), as well as in their metastasis outside of brain (Algra et al., 1992). Further, it now appears that the physiological conditions of the normal brain itself constitute a biological environment conducive to the uncontrolled dissemination of primary tumors (Bellail et al., 2004; Sontheimer, 2004). This review surveys the latest research on the invasive behavior of two major types of primary brain tumors: gliomas and medulloblastomas - the most common tumors diagnosed within adult and pediatric brain, respectively (Rickert and Paulus, 2001). The material has been divided into five sections: i) Characteristics of malignant brain tumors; ii) Mechanisms of tumor cell migration; iii) Models for the study of brain tumor invasion *in vivo* and *ex vivo*; iv) Models for the study of brain tumor invasion *in vitro*; and v) Future prospects of anti-invasive brain tumor therapy.

2. Characteristics of malignant brain tumors

Gliomas, commonly found in the anterior cerebral hemisphere, are a group of tumors derived from glial cells - the most abundant cells in the brain (Larjavaara et al., 2007; Lim et al., 2007; Louis et al., 2007). They are classified based on well-characterized histological features (Louis, 2006; Scheithauer, 2009; Trembath et al., 2008). The World Health Organization (WHO) defines gliomas by cell type, location and grade, and categorizes them into four classes (Lassman, 2004): i) Grade I tumors, or pilocytic astrocytomas; ii) Grade II tumors, also called low-grade astrocytomas; iii) Grade III tumors, or anaplastic astrocytomas; and iv) Grade IV tumors, also known as glioblastoma multiforme (GBM).

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Grade I tumors typically do not invade surrounding brain and are often curable with surgery, while tumors of grades II to IV are diffuse and invade normal brain, with grade III and IV tumors being most aggressive. Grade III and IV tumors are called “high-grade” or “malignant” tumors although they almost never metastasize to other tissues of the body (Lassman, 2004).

The etiological events causing glioma formation have not been clearly defined, but are thought to involve genetic alterations (Figure 1A). Such alterations disrupt cell cycle arrest pathways (Zhou et al., 2005; Zhou et al., 2010), and cause aberrant receptor tyrosine kinase activity in the brain cells (Dai et al., 2001). For instance, activation of receptors such as Hepatocyte Growth Factor Receptor (HGF) c-Met (Gentile et al., 2008), Platelet-Derived Growth Factor Receptor (PDGFR) (Cattaneo et al., 2006; Natarajan et al., 2006), and Epidermal Growth Factor Receptor (EGFR) (Chicoine and Silbergeld, 1997) is now well-known to stimulate glioma motility. Additionally, marker specific glial progenitor populations, neural stem cells and cancer stem cells are being investigated for their roles as possible initiators of gliomagenesis (Briancon-Marjollet et al., 2010).

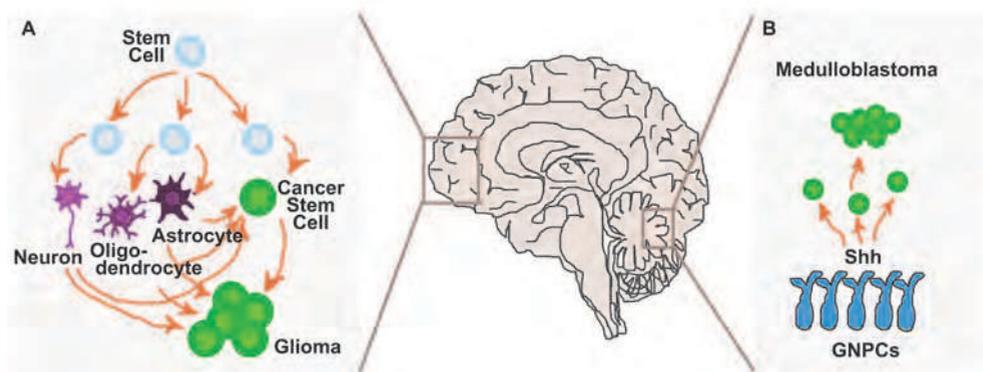


Fig. 1. Origin of brain tumors: development gone wrong. (A) During normal brain development, neural stem cells give rise to three main adult cell types: neurons, oligodendrocytes and astrocytes. Genetic alterations occur within these differentiated cells that can lead to the rise of malignant tumors. Alternatively, immature stem cells may serve as cancer stem cells that confer both radio- and chemoresistance phenotypes to gliomas. (B) Medulloblastomas originate in the cerebellum, from granule neuron precursor cells (GNPCs), upon un-controlled activation of Sonic Hedgehog (Shh) signaling pathway.

The current standard of care for gliomas is surgical removal of the tumor followed by post-operative radio- and chemotherapy (Stupp and Weber, 2005). However, due to their diffusely invasive properties, gliomas are one of the most difficult tumors to isolate or treat (Burger et al., 1985). Furthermore, while cell migration is fundamental to normal brain development and homeostasis, unconstrained migration of pathological and diseased cells makes the complete resection of tumor lesions, often performed for other types of tumors, an ineffective clinical treatment in brain. Prior to the advance of high-throughput genetic screening techniques clinicians depended primarily on glioma recurrence for prognosis of patient survival. Later, the generation of models that combined gene expression and molecular markers made it possible to subcategorize gliomas, enabling the increase in

grade-specific predictability (Zhou et al., 2010). Recent findings suggest the possibility that the recurrent growth of glioma is derived from chemo- and radio-resistant cancer stem cell renewal and/or growth of diffusively invasive cells (Hadjipanayis and Van Meir, 2009). Evidence emerging over the past decade has suggested the existence of stem-like cells within brain tumors, which are currently examined as potential sources of tumor resistance and recurrence (Galli et al., 2004; Lenkiewicz et al., 2009; Singh and Dirks, 2007). The inability to remove high-grade gliomas in their entirety, or to prohibit their migration to other parts of the brain has led to low survival rates among brain cancer patients (Demuth and Berens, 2004). Patients with GBM have a median survival of about 1 year, while patients with anaplastic gliomas can survive 2-3 years, and those with grade II gliomas often survive 10-15 years (Louis et al., 2007).

Medulloblastomas (MBs) encompass a collection of clinically and molecularly diverse tumor subtypes, and are characterized by high tumor invasiveness to extraneural tissues and reoccurrence in the cerebellum after total resection (Dhall, 2009). Four different MB subtypes have been included in the current WHO classification (Louis et al., 2007): i) Classic MB; ii) Desmoplastic/nodular MB; iii) MB with extensive nodularity; and iv) Anaplastic or large cell MB. Two other variants, medulloblastoma and melanotic MB, are much more rare. MBs are overwhelmingly found in pediatric patients, but can rarely occur within adult brain, where the tumor characteristics become very atypical. Adult MB is arguably a biologically distinct challenge in that it exhibits a higher proportion of desmoplastic histological characteristics, shows more proclivity toward cerebellar hemispheric origin, possesses different proliferative and apoptotic indices, and demonstrates a notorious tendency for late relapse with respect to the pediatric variants (Chan et al., 2000; Sarkar et al., 2002).

MBs are thought to arise within the cerebellum, with approximately 25% originating from granule neuron precursor cells (GNPCs) (Gibson et al., 2010) after aberrant activation of the Sonic Hedgehog (Shh) pathway (Figure 1B). A number of genetic alterations have been associated with MB (Biegel et al., 1997; Bigner et al., 1997; Herms et al., 2000; Yin et al., 2002). Studies of the receptors and intracellular signaling pathways that support proliferation and survival of GNPCs have shown a dysregulation of the Shh pathway, the canonical Wnt pathway, or the ERB-B pathway in both familiar and sporadic MBs (Gilbertson, 2004). A recent study showed that Wnt-subtype tumors infiltrate the dorsal brainstem, whereas Shh-subtype tumors are located within the cerebellar hemispheres (Gibson et al., 2010). These results have profound implications for future research and treatment of this childhood cancer, because to date, few data link such genetic alterations to metastasis in MB.

The treatment of patients with standard risk tumors, i.e. those who had tumors completely resected and with no evidence of dissemination to any other part of the body (Nishikawa, 2010), has been partially successful with survival rates of up to 40% for gliomas over the last five years (Van Meir et al., 2010) and 78% for MBs (Gajjar et al., 2006). In contrast, the cure of metastatic disease has been limited until recently to single cases (Fruhwald and Plass, 2002). Even though promising, the current treatment options for high-risk brain tumors are associated with neural and neuroendocrine side effects, with a tremendous decline in quality of life among survivors (Edelstein et al., 2011; Palmer et al., 2001), as well as growth reoccurrence and aggressive brain infiltration (Farin et al., 2006).

In the cases of both gliomas and MBs, the migration of cells from primary tumors to other locations, within brain or otherwise, has been one of the most clinically challenging and poorly understood processes that contributes to the poor life prognosis of patients. The

following sections will discuss the fundamental mechanisms of cellular migration, the common *in vivo* models used to examine tumor cell migration within brain, and current *in vitro* technologies used to characterize and better understand the migration of cells derived from gliomas and MBs.

3. Mechanisms of tumor cell migration

The migration of brain cancer cells is highly complex, involving interactions with extracellular matrix (ECM), and chemoattractants that either diffuse from blood vessels and/or are produced by neighboring cells (Condeelis and Segall, 2003; Sahai, 2005). As a consequence of such complexity, the molecular mechanisms of primary brain tumor migration and metastasis are poorly understood. Over the last several years, a group of critical growth factors has been the topic of research for their role as regulators of tumor biology and chemotaxis (Hamel and Westphal, 2000). It is believed that over time secreted cytokines diffuse and generate concentration gradients that are sensed by glioma and MB-derived cells, leading to the detachment and migration of these cells away from the primary tumor (Chicoine and Silbergeld, 1997; Piperi et al., 2005). Therefore, brain tumor invasion is believed to be induced by soluble cytokines that stimulate directional and/or random tumor cell motility (Brockmann et al., 2003). Alternatively, cancer cells may communicate with specific distant targets through secreted microvesicles that contain growth factors and receptors, functional mRNAs, and miRNAs (Cocucci et al., 2009; Skog et al., 2008; Valadi et al., 2007). Such microvesicles are shed by most cell types, including cancer cells, and have been found in sera from numerous cancer patients (Cocucci et al., 2009; Skog et al., 2008).

While the effects of mitogens on the *in vitro* motility and invasion of glioma cells have been well documented using conventional assays, such as transwell chambers and spheroid models (discussed later in this chapter), the ability of soluble cytokines to drive various cellular functions (i.e. migration and/or proliferative growth) has been shown to depend upon several determinant factors. Some of these factors have been addressed in the literature, such as dosage-dependence (Gonzalez-Perez and Quinones-Hinojosa, 2010; Shih et al., 2004), contact inhibition (Weidner et al., 1990), as well as autocrine and paracrine signaling-driven tumor growth via extensive proliferation and aggressive recruitment of surrounding cells to the tumor (Betsholtz et al., 1984; Fomchenko and Holland, 2005; Hermansson et al., 1988; Rood et al., 2004). The diligent study of Central Nervous System tumor cell (CNSTC) invasion has identified four commonly overexpressed receptor tyrosine kinases as targets for anti-invasive therapies (EGFR, c-MET, PDGFR, and Vascular Epidermal Growth Factor Receptor (VEGFR)) (Abounader, 2009; Arora and Scholar, 2005; Huang et al., 2009; Zwick et al., 2001).

Cancer cell locomotion is highly sensitive to stimuli from the ECM as well as from the surrounding media. Receptors on the plasma membrane can activate cellular signaling pathways that alter the mechanotransduction of a cell via reorganization of motility-related organelles and cellular compartments. As an example, tumor-derived cells are known to increase cell motility in response to protease inhibitors and adhesion inhibitors (Sahai, 2005). The modes of cancer cell migration vary according to whether the cells undergo single cell chain, or collective migration. Tumor-derived cells disseminate from the bulk tumor mass individually via mesenchymal or amoeboid movement. However, in many tumors both single cell and collective cell migration may be present depending on the molecular cues dictating migration (Friedl and Wolf, 2003).

During the mesenchymal-type migration often observed in gliomas, cells exhibit a highly polarized and fibroblastic morphology. Cells undergo the classical, overlapping processes generally exhibited during mammalian cell migration: cell polarization, protrusion of leading edge, traction at the trailing edge, and detachment (Lauffenburger and Horwitz, 1996). First, cells become highly fibroblast-like, with bipolar opposites. Second, a growing number of actin filaments begin to push the cell membrane outwards on the leading edge via the formation of lamellipodia or filopodia. Actin polymerization then initiates signal transduction pathways along the leading edge. Next, cell integrins come into contact with ECM ligands and cluster to recruit intracellular signaling proteins that induce phosphorylation signaling, or so-called “outside in” signaling (Hynes, 2002; Miyamoto et al., 1995) via focal adhesion kinases. Afterwards, surface proteases act to cleave ECM molecules via production of soluble matrix metalloproteases (MMPs) in order to degrade surrounding ECM. Finally, cell contraction occurs via myosin that leads to focal contact disassembly at the trailing edge and actin cleavage and filament turnover (Wear et al., 2000).

Contrarily, during amoeboid movement, cells utilize a “fast gliding” mechanism driven by weak interactions with the substrate. As such, cells like neutrophils and lymphocytes exhibit a shape-driven migration with appreciable lack of focal adhesions that allows them to circumnavigate rather than degrade surrounding ECM during migration (Friedl et al., 2001). The result is an increased cell motility, as well as cell ability to undergo early detachment and metastatic spread from primary tumors. Cancer cells may undergo conversion from mesenchymal to amoeboid type migration in order to alter integrin distribution and actin cytoskeleton organization for increased dissemination (Wolf et al., 2003).

Collective migration is a well-studied phenomenon that is characteristic of embryological development, such as during the migration of cell clusters or sheets in the ectoderm following closure of the neural tube (Davidson and Keller, 1999). *In vitro* studies (Friedl et al., 1995; Nabeshima et al., 1995) showed that cells can migrate as a functional unit, and that in contrast to single motile cells, cell-cell adhesion can lead to a particular form of cortical actin filament present along cell junctions. This enables formation of a larger, multicellular contractile body. Here, a select group of highly motile cells are designated as so-called “path-generating” cells that create migratory traction via pseudopod activity (Friedl et al., 1995; Hegerfeldt et al., 2002; Nabeshima et al., 1995). It is then believed that cells located in the inner and trailing regions are passively dragged behind during dissemination. In tumors, collective migration has been observed as protruding sheets that maintain contact with the primary site, or as cell clusters that detach from their origin and extend along paths of least resistance (Byers et al., 1995; Hashizume et al., 1996; Madhavan et al., 2001). Collective migration offers the advantage of protection from immunological response. Further, heterogeneous sets of cells that move as one functional unit can work together to promote the invasion of less motile, but potentially apoptosis-resistant, sub-populations that increase tumor survival. To complicate matters, cells may transition between collective and individual cell migration with dedifferentiated cells to increase dissemination and metastatic spread (Friedl and Wolf, 2003).

4. Models for the study of brain tumor invasion *in vivo* and *ex vivo*

Glioma and MB models have been largely developed by studying altered oncogene expression through retroviral transfection of murine neural tissue of genetically engineered mouse models (GEMMs) (Fisher et al., 1999; Hatton et al., 2008; Heyer et al., 2010; Huse and

Holland, 2010; Pazzaglia et al., 2002; Pazzaglia et al., 2006; Romer and Curran, 2004). Via this powerful methodology, diverse tumor types with distinct histological features have been generated dependent upon the specific genetic background of the cell of tumor origin and the disease location of interest (Furnari et al., 2007). In particular, the histological features of GEMM and implanted xenograph derived tumors have been shown to be similar to human brain tumors presented in identical CNS locations, and have shed light on the diverse nature of human gliomas found clinically (Candolfi et al., 2007).

Historically, it has been suggested that glioma cell infiltration throughout the brain primarily utilizes mechanisms of migration innately patterned by neural progenitors during normal brain development (Cayre et al., 2009; Kakita and Goldman, 1999; Scherer, 1940). Confirmation of this similarity has been accomplished *in vivo* via implanted xenographs that result in spontaneous intracranial GBMs in six different animal model variations that show reproducible invasion of tumor cells into non-neoplastic brain regions (Figure 2) (Candolfi et al., 2007). More recently, several labs began utilizing GEMMs to specifically examine glial progenitor recruitment *in vivo* (Assanah et al., 2006; Masui et al., 2010). For instance, Assanah and colleagues have demonstrated via histological analysis of cortical sections from GEMMs that overexpression of tumor inducing proteins like PDGF can induce malignant glioma cells to invade across the corpus callosum into the contralateral hemisphere and overlying cortex (Assanah et al., 2006; Assanah et al., 2009).

The diffusive invasion and increased recurrence of gliomas post-operatively have been attributed to the same therapies used to treat the disease. Narayana and colleagues reported clinical results of 61 high-grade GBM patients treated with an anti-angiogenesis drug, bevacizumab. Their results showed that 82% of the patients treated with bevacizumab suffer from tumor regrowth and 70% died from the disease within 19 months (Narayana et al., 2009). Pàez-Ribes and colleagues reported similar results showing that although the use of angiogenesis inhibitors, such as Sunitinib and SU10944, extend that survival time of treated mice to an additional 7 weeks versus non-treated mice, the kinase inhibitors tend to also evoke an increase in glioma cell invasion as well as to promote tumor progression (Pàez-Ribes et al., 2009). A closer examination using xenographs of human tumor spheroid implanted into rat brains, and further treated with the bevacizumab, led to a reduction in contrast enhancement in magnetic resonance imaging (MRI) analysis while enhancing glioma cell diffusion by 68% versus non-treated rats (Figure 3) (Keunen et al., 2011).

Characterization of MB migration *in vivo* has yet to be analyzed at large, as most of the reports to-date focused on tumor growth and not its dissemination. Nevertheless, a select number of *in vivo* studies examined tumor cell migration and invasion. Hatton and colleagues illustrated in a GEMM for MB that 94% of the mice developed MB by 2 months of age, and that these tumors frequently exhibited leptomeningeal spread, a common feature of the human disease (Hatton et al., 2008). MacDonald and colleagues implanted human MB cells in the brain of nude mice, and thereafter followed them *in vivo* at single-cell level via fluorescence microscopy (MacDonald et al., 1998). These MB cells were shown to invade the brain and to form distant micro-metastases. In another study, MB cells were engineered to overexpress HGF and were implanted subcutaneously and intra-cranially (Li et al., 2005). The study reported activated c-Met that strongly increased MB xenograft growth and invasive characteristics with finger-like protrusions, metastatic growth, and leptomeningeal spread. Such findings illustrate that the HGF/c-Met pathway is one of the mediators of MB malignancy.

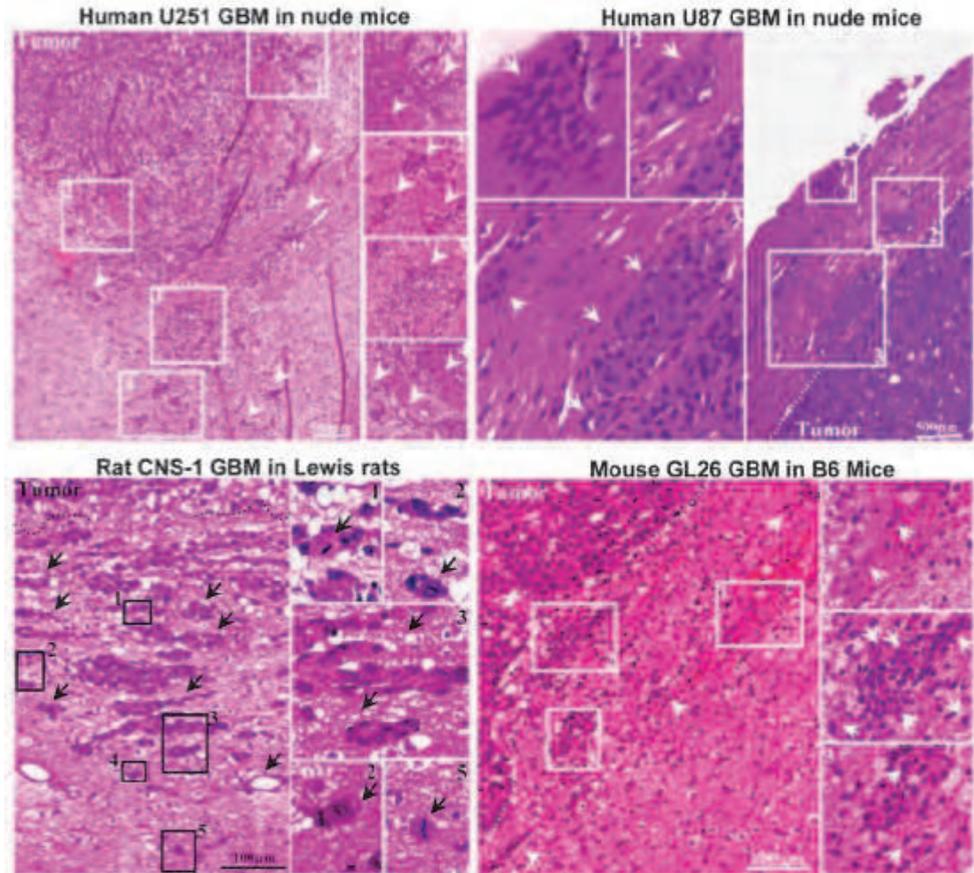


Fig. 2. Neoplastic cellular infiltration into surrounding non-neoplastic brain tissue in syngeneic rat (CNS-1) and mouse (GL26) GBM models and human glioma xenografts in nude mice (U251 and U87). Paraffin sections (5 μm) from GBM were stained with hematoxylin and eosin for evaluating neoplastic invasion. The numbers in low-magnification microphotographs depict areas magnified in the microphotographs on the right. *Arrows* indicate malignant cells, clusters of GBM cells, and tumoral blood vessels infiltrating surrounding brain parenchyma. The indistinct tumor borders and the malignant cells clearly entering the non-neoplastic brain tissue suggest an invasive phenotype. (Courtesy of Candolfi et al., 2007)

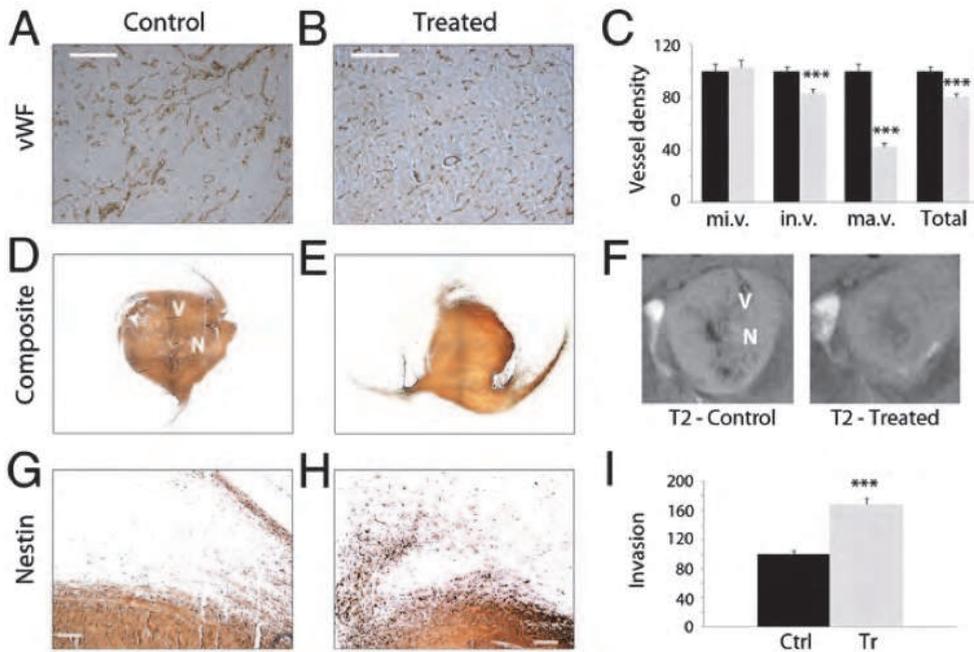


Fig. 3. Changes in blood vessel morphology and tumor cell invasion after bev treatment. Immunostaining for von Willebrand factor (vWF) (A and B) and quantification thereof (C), indicating a significant reduction in the density of medium and large blood vessels and in total vessel number after bev treatment. (Scale bar: 200 μm .) Nestin-stained composite images (D and E) reveal a more homogeneous appearance of the treated compared with untreated tumors, also reflected in corresponding T2-weighted MRI images (F). Large vessels ("V") appear as dark tortuous lines in nestin and T2-weighted images and necrotic areas ("N") as brighter spots. Quantification of the nestin-positive cells outside the tumor core (G and H) shows a 68% increase in cell invasion after treatment (I). mi.v: microvessels; in.v: intermediate-sized vessels; ma.v: macrovessels; Ctrl: controls; Tr: treated. (Scale bars: \pm SE.) *** $P < 0.001$. (Courtesy of Keunen et al., 2011)

The ability to visualize brain tumor invasion in direct response to specific genetic aberrations and alterations made to the immediate environment has been critical in understanding the characteristics of this process. An advance made in this direction was accomplished via the detection of specific biomarkers involved in the progression or migration of CNSTCs, such as Receptor Tyrosine Kinases (RTKs), using conjugated antibodies that enabled *in vivo* monitoring via MRI (Towner et al., 2008). Alternatively, to *in vivo* imaging procedures, *ex vivo* brain tumor invasion assays that enable the study of tissue outside of the living system have had a tremendous impact in the field. Brain slices from mice and rats have been used to quantify the invasion of human gliomas (Nakada et al., 2004), and have demonstrated suppressed invasion on 2D surfaces, suggesting that the brain environment alone is capable of regulating protein function and, consequentially, the pattern and directionality of glioma migration (Beadle et al., 2008). Additionally, not only have *ex vivo* cell cultures been used to study the invasive properties of CNS tumors, but also

to characterize the expression molecular markers (Riffkin et al., 2001), and to evaluate the therapeutic potential of co-cultured T-cells for anti-tumor activity (Ahmed et al., 2007).

By reducing the incidence of recurrent growth, clinicians envision the possibility of detecting and directly tracking migratory tumor cells *in vivo*, and therefore enabling operative procedures limited to a single total resection surgery. In order to accomplish this goal, there is a stringent need for development of enhanced imaging tools to allow visualization of migrating tumor cells. Meanwhile, the most successful quantitative assessment of CNSTCs migration has been accomplished outside of the brain itself, in engineered systems redesigned to mimic specific *in vivo* conditions. We will discuss these *in vitro* assays further, which have been utilized to evaluate a variety of cellular functions, from growth patterns and rates, to invasive motility of cells derived from highly malignant brain tumors.

5. Models for the study of brain tumor invasion *in vitro*

Tumor cells of the brain have been characterized as having a highly infiltrative phenotype for spreading into the healthy surrounding parenchyma. This malignant property is arguably the principle reason for tumor recurrence and high mortality rates (Lim et al., 2007). The interaction of integrins, membrane anchored heterodimeric proteins, with various ECM proteins has been explored extensively, as it is one of the key events that occurs during the invasion of tumor cells within their local microenvironments (Teodorczyk and Martin-Villalba, 2010). Another key process of tumor invasion is the cellular secretion/production of proteases that degrade ECM proteins in order to create pores through which the cells may migrate; such proteases include serine proteases, various MMPs, and cathepsins (Rao, 2003). In addition to stimulating tumor invasion via degradation of ECM protein components, it is assumed that MMPs are capable of enhancing tumor growth by indirectly triggering the release of growth factors trapped within the basement membrane itself (Mott and Werb, 2004). Lastly, another key aspect of tumor dissemination is played by the activation of RTK signaling pathways. During the destruction of the basement membrane by MMPs, soluble growth factors are sequestered from the ECM and bind to their cognate cellular receptors to trigger a cascade of events that enhance cellular migration (Zucker et al., 2000).

In vitro invasion assays are important tools for investigating the tumor-matrix interactions and the effects of extracellular macromolecules on these interactions. While not entirely identical to *in vivo* behavior, the study of tumor cell migration *in vitro* is advantageous due to the tightly-controlled experimental conditions, higher experimental throughput, and lower costs. The following section discusses the most commonly used *in vitro* assays, in the order of increased complexity.

5.1 Culture dish assays

Culture dish assays have the advantage of design simplicity and execution, while providing insightful information pertaining to cell-to-cell and cell-to-environment interactions. Coated culture dishes have been widely used to examine the roles played by specific ECM proteins, integrins, MMPs, and RTKs in stimulating the migration of brain tumor-derived cells, as detailed here.

Integrins are membrane heterodimeric proteins that mediate cell-environment attachment (Hynes, 1987; Tucker, 2006). In addition to anchoring cells to their environment, integrins

have been shown to serve as signal mediators for ECM proteins that were found to stimulate tumor migration *in vitro* (Ohnishi et al., 1997; Tysnes et al., 1996). The most abundant ECM proteins found to interact with integrins in the brain are fibronectin, laminin, fibrinogen, tenascin-C, thrombospondin, neuron-glia cell adhesion molecules (Ng-CAMs), and collagens IV and V (Rutka et al., 1988). Giese and colleagues evaluated astrocytoma migration as a function of integrin adhesiveness on various ECM proteins (collagen IV, fibronectin, laminin and vitronectin) (Giese et al., 1994). Based on the examination of eight different astrocytoma cell lines, the group concluded that the migration of glioma cells was subject to alteration depending on tumor expressed integrins and the availability of complementary matrix proteins. Furthermore, even though laminin frequently enabled tumor cells to adhere and migrate with increased adhesion, overall it was stated that there was no specific ECM protein that would always result in increased astrocytoma binding (Giese et al., 1994).

Friedlander and colleagues examined the migration trends of twenty-four excised human astrocytomas, ten GBM cell lines, and three MB cell lines on nine different ECM protein coated culture dishes (Friedlander et al., 1996). The comparative migration of astrocytomas (grades I, II and III), GBMs and MBs demonstrated that most tumor cells, regardless of their grade, were capable of migrating on fibronectin and laminin at rates exceeding 30 μm over a 16 hour period. A closer comparison between low-grade and high-grade tumor migration on all tested substrates revealed that, on average, high-grade tumors migrated approximately 14 μm more than low-grade tumor cells under similar conditions. Specifically, type IV collagen substrates induced a 4-fold increase in distances traveled by high-grade tumor cells over low-grade cells. Collagen IV coated substrates also stimulated approximately 100 μm migration over 16 hours of thirteen excised GBMs and eight well studied GBMs cell lines, with cell lines being more motile than the excised tumors (Friedlander et al., 1996). Finally, monoclonal antibodies specific for the α_v and β_1 integrins were used to reduce the migration of four GBMs cell lines (U-373 MG, U-118 MG, U-251 MG and U-87 MG) on several migration enhancing ECM substrates, including collagen IV (Friedlander et al., 1996). These results illustrate that brain tumor-derived cells can migrate remarkably large distances within the brain, often to varied regions of the brain. However, tumor cell populations are very diverse, and such studies have not identified the lineage of motile cells, or whether certain sub-populations of cells could migrate farther than others within brain.

MB samples revealed type I collagen present in the leptomeninges, and in the ECM surrounding blood vessels and tumor cells (Liang et al., 2008). Expression of both type I collagen and β_1 integrin, a subunit of a known type I collagen receptor, localized to the same area of MB. The same study showed that the adherence of MB cells to type I collagen matrix *in vitro* depends on the presence of β_1 integrin (Liang et al., 2008).

A study by Corcoran and Del Maestro revealed that MB cell lines do not defer cell proliferation for migration across an uncoated surface or invasion of a type I collagen matrix, contrary to the “Go or Grow” hypothesis (Corcoran and Del Maestro, 2003). The “Go or Grow” hypothesis proposes that cell division and cell migration are temporally exclusive events, and that tumor cells defer cell division to migrate (Giese et al., 1996). Migrating and invading MBs continued to proliferate and migrate/invade, irrespective of the number of divisions that took place (Corcoran and Del Maestro, 2003). These findings emphasize the need to evaluate the effect of future therapies on both biological events and, if possible, to

identify intracellular signaling proteins that negatively regulate MB migration/invasion and proliferation.

Matrix-degrading proteases are involved in the hydrolytic breakdown of ECM proteins and have been shown to regulate tumor cell progression and invasion (Levicar et al., 2003; Rao, 2003; Rooprai and McCormick, 1997). Additionally, proteases have been well-studied and shown to display differential expression and activation patterns, correlated to their invasion-associated effects, i.e. angiogenesis (Forsyth et al., 1999; Thorns et al., 2003). These proteases are either located in the membrane of the cell or secreted into its surroundings, respectively denoted as MT-MMP and MMP. Diffusely invasive glioma cells express MMPs that enable them to catabolize ECM proteins that have been shown to prohibit the migration of other cells that lack these MMPs. For instance, specific membrane proteins expressed by CNS myelin have been shown to have anti-spreading functionality on neurite outgrowth, astrocytes and fibroblasts (Schwab and Caroni, 1988; Spillmann et al., 1998).

The migration of glioma-, MB- and meningioma- cell lines on CNS myelin was found to be tumor grade-dependent and to involve active unspecified MMPs (Amberger et al., 1998). Culture dishes were coated with 15 µg/dish rat spinal cord myelin, a concentration shown to reduce by 80% the fibroblast migration, followed by the seeding with various cell lines and the recording of cell ability to adhere and spread (Amberger et al., 1998). The results conclude that high grade GBMs, like U-251 MG, were able to strongly attach and spread, while low grade gliomas and MBs exhibited poor attachment and inhibited spreading (Amberger et al., 1998). Additionally, spreading of GBM and anaplastic astrocytomas cells on CNS myelin was strongly blocked when cells were treated with the MMP blocker O-phenanthroline (Felber et al., 1962), and temporarily inhibited with carbobenzoxy-Phe-Ala-Phe-Tyr-amide (Amberger et al., 1997) confirming the role played by MMPs in ECM modification as a precursory for migration.

Belien and colleagues studied the role of MT1-MMP in enhanced spreading and migration of gliomas (Belien et al., 1999). As a substrate, they utilized myelin-coated culture dishes, since it was previously shown that invasion of gliomas predominantly occurs along the white matter of the CNS (Giese et al., 1996; Pedersen et al., 1995), which is heavily composed of myelin (Baumann and Pham-Dinh, 2001; McLaurin and Yong, 1995), to seed both gliomas and MT1-MMP-transfected fibroblasts. In this case, MT1-MMP was shown to be responsible for altering the cellular environment to enable migration of both gliomas and the transfected fibroblasts (Belien et al., 1999).

When the invasiveness of five MB cell lines within a 3D *in vitro* collagen I or IV-based model was studied, the data showed that within hours of implantation, individual cells readily detached from the surface of the cell aggregates and invaded the collagen matrix, to distances of up to 1,200 µm and at rates of up to 300 µm per day (Ranger et al., 2010). Furthermore, MB invasiveness within this 3D model appears to depend upon a combination of metalloproteinase (MMP-1 and -2, TIMP-1 and -2) and cysteine protease activity (Ranger et al., 2010).

The RTKs, like integrins, function as signal mediators of extracellular proteins yet in a different way. Integrins, as mentioned above, interact primarily with static, structural ECM proteins that are the composite materials of the cellular environment (Tucker, 2006). Meanwhile, RTKs interact with soluble macromolecules present in the environment, e.g. growth factors, that trigger a cascade of events in the cells, spanning from the extracellular surface of the plasma membrane to the nucleus, to elicit various cellular responses (Konopka and Bonni, 2003; Mueller et al., 2003; Teodorczyk and Martin-Villalba, 2010). Additionally,

genetically modified and overexpressed RTKs are capable of eliciting cellular signals in the absence of ligand binding, thus bypassing the need for an extracellular trigger (Akbasak and Sunar-Akbasak, 1992; Dong et al., 2011; Strommer et al., 1990; Torp et al., 2007). Ding and colleagues employed U-87 MG cells grown on coated cultured dishes to demonstrate a strong adhesion to vitronectin, as opposed to collagen or laminin, which was mediated through the $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrins (Ding et al., 2003). Additionally, the group was able to link the specific cooperative interaction between the RTK PDGFR β and the $\alpha_v\beta_3$ integrin to induce migration of U-87 MG cells into the wounded area in a scratch-wound assay after stimulation of the culture with PDGF (Ding et al., 2003). Therefore, these results suggest the direct correlation between the ability of RTKs to transmit extracellular signals into the cell and to convert these signals into direct and measurable cellular response.

As an improvement upon the simple use of cell culture dishes for study of tumor cell migration, micropipette turning assays have been used to create gradients within culture dishes that enable changes in cell migration with micropipette position. Gradients, defined as fields where biochemical concentrations are varied along a specific distance, are generated via simple diffusion of biological molecules from the micropipette into the culture medium. Gradient formation and stability are functions of the molecular properties of the stimulant being used (i.e. diffusivity constant and molecular weight), as well as pipette mechanics (i.e. dimensions and flow rates) (Lohof et al., 1992), and for these reasons make gradient measurement difficult. Wyckoff and colleagues used the micropipette method to collect subpopulations of motile mammary carcinoma and macrophage cells into microneedles filled with MatrigelTM and a range of EGF concentrations from confluent culture dishes (Wyckoff et al., 2000). The MatrigelTM matrix is a solubilized basement membrane preparation extracted from Engelbreth-Holm-Swarm mouse sarcoma (Ohashi et al., 2006; Reed et al., 2009), commonly used in cell-matrix interaction studies. The contents of the microneedles were then emptied into new culture dishes and allowed to grow for at least 6 days before quantifying cell populations. A bell-shaped curve of normalized cell numbers was reported and had the maximal number of collected cells for 25 nM EGF, 8-fold greater than controls (Wyckoff et al., 2000). Such results illustrate that growth factor concentration gradients, or differences in concentrations along given distances, stimulate brain tumor cell migration.

5.2 Spheroids

A key question regarding cancer cell migration and invasion is based on determining the reason why tumor cells detach from the bulk tumor mass. Some studies have suggested that lack of contact-inhibition may be responsible for cell migration away from the bulk (Pedersen et al., 1995). While normal cells go into a quiescent state that allows apoptosis during nutrient depleted states, cancer cells do not rely on contact-dependent growth and therefore can detach and venture out to diffusely invade the parenchyma. The Spheroid Model utilizes the natural tendency of cancer cells to form colonies and to grow into localized spheres (Santini and Rainaldi, 1999; Zhang et al., 2005). This model mimics the 3D characteristics of cell migration, while culture dish experiments described in the previous subsection provide important data on 2D cell migration. As a result, the spheroid model has been used to study the directional migration of tumor cells from the bulk spheroid mass in response to specific motogens and chemotherapeutic agents, as well as to measure the penetration of various molecules into the tumor (Carlsson and Nederman, 1983; Nederman et al., 1983).

Spheroids grown from several different GBM cell lines were placed on uncoated 24-well dishes and treated with EGF, which triggered a strong stimulation of cellular invasion and increased growth (Lund-Johansen et al., 1990). Similarly, spheroids grown from several human glioma cell lines exhibited enhanced growth and directional migration when cultured in 10 ng/ml EGF or 10 ng/ml bFGF concentrations, compared to control and other growth factors, such as PDGFBB (Engebraaten et al., 1993). When MB cultures were induced to generate spheroids, gene expression of CD133 (a hallmark of the brain cancer stem cells and radioresistant tumors), MT1-MMP, and MMP-9 were induced and correlated with increased invasiveness of the spheroid cells (Annabi et al., 2008). Additionally, Corcoran and Del Maestro revealed that MB cells from an established cell line, UW228-13, could exhibit elevated levels of invasion into a 3D matrix of type 1 collagen compared to biopsied DAOY cells (Figure 4) (Corcoran and Del Maestro, 2003).

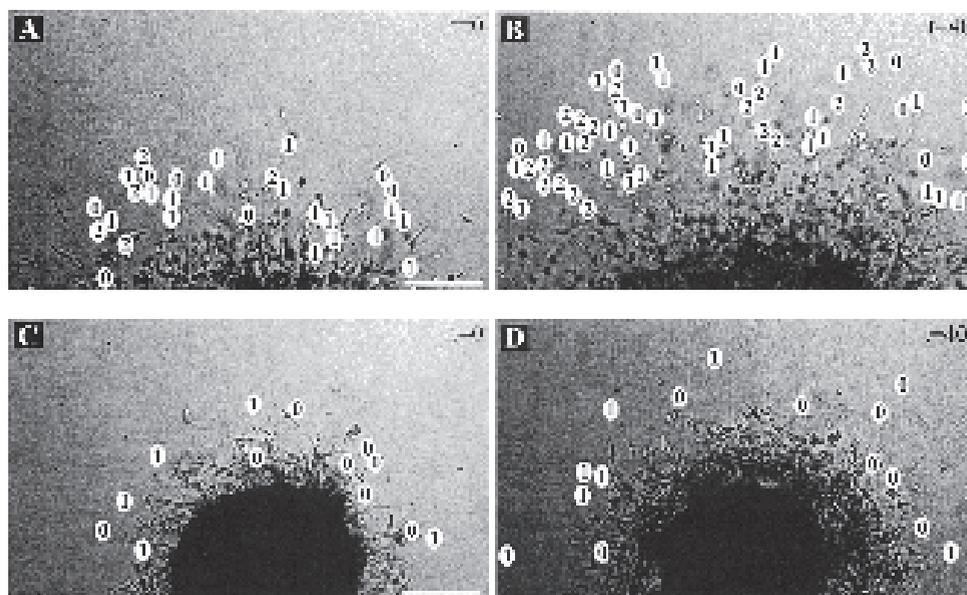


Fig. 4. First and last images extracted from time-lapse videos of DAOY (A and B) and UW228-3 (C and D) spheroids invading Type I collagen matrices. Spheroids were recorded 48 hours after implantation. The numbers identify cells that divided zero, one, or two times in 40 hours; parent cells are labeled in A and C and daughter cells in B and D. The number of hours elapsed from the start time of the videos (t) are indicated at the top right corner of images. Scale bars, 250 μm . (Courtesy of Corcoran and DelMaestro, 2003)

Wild-Bode and colleagues grew glioma spheroids on agar base-coated culture flasks until they were $\sim 200 \mu\text{m}$ in diameter, followed by their transfer to 96-well plates. In order to examine the cause of glioma relapse in close proximity to the excised lesion, they measured the radial distance of migration as function of irradiation at 3 Gy. Irradiation led to increased migration of all cell lines, compared to non-irradiated cells, a phenomenon which was linked to increased expression and activation of MMP-2, MMP-9 and MT1-MMP (Wild-Bode et al., 2001).

Just as the spheroid model employs a 3D environment in order to better mimic *in vivo* conditions, other *in vitro* technologies were developed to imitate the biochemical environment of the brain. In particular, transwell assays were developed in order to expose tumor-derived cells to different concentration gradients of cytokines present within brain.

5.3 Transwell migration assays

The transwell migration assay is a commonly-used test to study the migratory response of cells to inducers or inhibitors. This assay is also known as the Boyden or modified Boyden chamber assay, and was originally used to evaluate leukocyte chemotaxis (Boyden, 1962). In this assay, a chamber that is separated into two compartments by a polyethylene terephthalate filter (Figure 5A) and the cells placed into the upper compartment are allowed to settle, while the solution being tested for chemotactic activity is placed in the lower compartment. The membrane contains randomly distributed pores through which the cells migrate (Figure 5B), in response to the chemoattractant from the bottom compartment. Invasive cells migrated to the underside of the filter can be stained and quantified (Figure 5C).

Different ECM components can be used to coat the filter in order to mimic the basement membrane that cells must penetrate while invading *in vivo*, while exposing the cells to various chemicals for different time lengths. The main advantage of this assay is its detection sensitivity. Migration through the permeable membrane can be caused by very low levels of chemoattractants (Kreutzer et al., 1978). Prolonged studies are difficult, due to the fact that the chemoattractant concentration will quickly equalize between the compartment below the membrane and the compartment above the membrane. Another disadvantage is the relative difficulty in setting up the transwells. Despite these disadvantages, transwell assays are commonly the test of choice for migration and invasion studies *in vitro*.

Over the last 50-years, several modifications have been implemented to this technology by various research groups in order to circumvent difficulties encountered with its use. For instance, upon crossing the membrane and reaching the lower surface of the chamber, cells may detach from the filter, thus resulting in an underestimate of transmigrated cells (Li and Zhu, 1999). Albin and colleagues were among the first researchers to use filters coated with ECM. They used radiolabeled proteins to demonstrate an 8-10 hour gradient stabilization period within the Boyden chamber, and showed that cell invasion time was very much dependent on the volume of the coated matrix barrier (Albin et al., 1987). Li and Zhu pioneered the use of different cell populations to attract other cells, by growing a monolayer of bovine aortic endothelial cells on filters, and investigating the transendothelial migration of six cell lines of different human tumors (Li and Zhu, 1999).

Chemotactic migration of GMB cells in response to several growth factors, predominately PDGF, EGF, and HGF, has been extensively studied (Hoelzinger et al., 2007). These studies have demonstrated dosage-dependent mitogenic responses to various concentrations and combinations of these cytokines (Brockmann et al., 2003). For example, Moriyama and colleagues demonstrated, through a checkerboard analysis of various HGF concentrations, that a dose-dependent response to HGF induces both chemotaxis and chemokinesis of U-251 MG cells (Moriyama et al., 1996). In this study the concept of an “optimal concentration” was introduced, and the authors reported a decline in the chemotactic activity of U-251 MG cells at concentrations exceeding the reported optimal concentration of 50 ng/ml (Moriyama et al., 1996). Similarly, Koochekpour and colleagues used transwell assays to show dose-

dependent migration and invasion of five different human glioma cell lines toward various concentrations of HGF, in addition to reducing basal migration of these cells using an anti-HGF neutralizing antibody (Koochekpour et al., 1997). Brockmann and colleagues reported increases in U-87 MG migration, as high as 33-fold greater than controls, in the presence of 100 pM HGF concentrations. In the same study, 1 nM TGF α and 50 nM FGF1 stimulated U-87 MG migration 17- and 4-fold, respectively (Brockmann et al., 2003). Transwell assays were used to demonstrate the chemotaxis of metastatic breast adenocarcinomas toward bone and brain extracts, rather than extracts from liver or lung (Hujanen and Terranova, 1985). Interestingly, it was found that C6-GFP rat glioma cells could extend their leading cytoplasmic processes through membrane pores, as a function of actin dynamics alone, but they required myosin IIA/B to generate additional cytoplasmic contractile forces to push the nucleus through pores having a smaller diameter (Beadle et al., 2008).

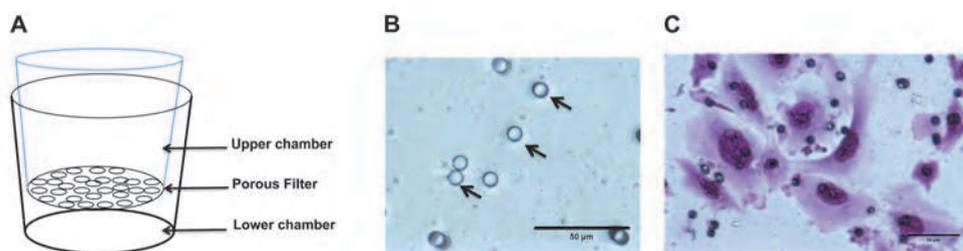


Fig. 5. Boyden chamber assay. (A) Transwell migration assays are composed of a well insert with a porous filter bottom that temporarily separates the cell solution from the test solution. (B) The filter has randomly distributed microscale diameter pores as shown by arrows. (C) Invasive Daoy cells on the underside of the filter stained and imaged for migration analysis. Scale bar = 50 μm .

A study that looked at the inhibitory effect of dietary-derived flavonols on the HGF receptor c-Met activity suggests that such an effect may contribute to the chemopreventive properties of these molecules (Labbe et al., 2009). The authors showed that the flavonols quercetin, kaempferol, and myricetin inhibited HGF/c-Met signaling in MB, preventing the formation of actin-rich membrane ruffles and resulting in the inhibition of c-Met-induced cell migration in Boyden chambers (Labbe et al., 2009). Furthermore, quercetin and kaempferol also strongly diminished HGF-mediated Akt activation (Labbe et al., 2009).

While investigating the effect of ionizing irradiation on the invasiveness of glioma cells via transwell assays, Park and colleagues reported increased Matrigel™ invasion of PTEN null gliomas, U-251 MG and U-373 MG, as a result of elevated levels irradiation treatment, which the group suggested correlates with increases in MMP-2 secretion (Park et al., 2006). Similarly, Wild-Bode and colleagues found that the sublethal irradiation doses of 1, 3, and 6 Gy increased the chemotactic migration and invasion of three different human glioma cell lines with increasing dosage (Wild-Bode et al., 2001). Similarly to glioma, radiation enhanced invasion and migration of 7 Gy irradiated MB compared to non-irradiated MB cells, as assessed via Boyden chamber assays (Nalla et al., 2010). Increased expression of urokinase-type plasminogen activator (uPA) and its receptor (uPAR), focal adhesion kinase (FAK), N-cadherin and integrin subunits (e.g., α_3 , α_5 and β_1) was detected in irradiated cells.

Conversely, down-regulation of uPAR reduced the radiation-induced adhesion, migration and invasion of the irradiated cells, primarily by inhibiting phosphorylation of FAK, Paxillin and Rac-1/Cdc42 (Nalla et al., 2010).

Transwell assays were also used to study the activated RTK-dependent MB migration. These studies have shown that MB migration is dependent on estrogen-receptor (Belcher et al., 2009), c-Met (Guessous et al., 2010), and PDGFR- β activation (Yuan et al., 2010). Via a combination of wound-healing assays and modified Boyden chamber assays, two groups showed that PDGF-induced overexpression of Rac1, a Rho GTPase, is involved in MB cell migration and invasion, whereas knockdown of Rac1 expression dramatically inhibited migration and invasion of MBs (Chen et al., 2011; Yuan et al., 2010). These findings may promote the evaluation of Rac1 as a novel therapeutic agent impairing medulloblastoma PDGF-induced migration/invasion. Additional work has demonstrated that PDGFR- β activity may guide the migration of MB by transactivating EGFR (Abouantoun and MacDonald, 2009). These results are of particular interest, since EGFR is known to be expressed in GNPCs of the human cerebellum, participating in its normal development and function (Seroogy et al., 1995). Recently, the multifunctional signaling protein neurotrophin receptor p75^{NTR} was shown to be a central regulator for GBM (Johnston et al., 2007) and MB spinal invasion while γ -secretase inhibitor, which blocks p75^{NTR} proteolytic processing, significantly abrogates p75^{NTR} induced MB migration and invasion *in vitro* and *in vivo* (Wang et al., 2010).

The transwell assays, even though used commonly for cell migration experiments, often yield inconsistent results across research groups due to the experimental individual assay modifications made by each group. For example, the ECM component used for filter coating can serve as a chemoattractant via integrin signaling (triggered by the interaction with laminin contained in the matrix), or via the release of growth factors embedded in the matrix itself. Although a reduced-growth factor form of MatrigelTM is generally used (i.e. reduced amounts of the above mentioned molecules are present in the matrix), there are a plethora of ECM proteins and growth factors, reconstituted along with MatrigelTM, whose concentrations may vary with each batch purchased, and cause variations in the results. Yet, perhaps the largest shortcoming of transwell assays with respect to quantifying migration is that the cytokine microenvironments they create are very complex to model mathematically. Diffusion gradients of molecules across the membrane pores are difficult to measure or predict analytically, with or without matrix coating. Among *in vitro* approaches, microfluidics has proven to be a powerful technology to study cell migration over the past few years, due to the ability to generate a precise cell microenvironment that can be both predicted by analytical models and validated experimentally (Kong et al., 2010), as summarized further on.

5.4 Microdevices

Advances in microfabrication have made microfluidics systems easier to design and manufacture. Currently, the majority of devices are constructed of polydimethylsiloxane (PDMS) via soft lithography pioneered by the Whitesides group (McDonald and Whitesides, 2002). The polymer allows the construction of systems with high transparency and low thickness that are highly-compatible with biological microscopy. As dissemination of glioma or MB cells can often follow the path of white matter tracks or other heterogeneous structures, mechanical properties of the microenvironment play significant roles in tumor

cell locomotion (Guck et al., 2010). PDMS microsystems pre-define the cell migratory path within microsized channels that mimic *in vivo* conditions. As such, cell motility and directionality can be examined and measured via conventional time-lapse imaging. Pioneering applications of microdevices for cancer cell study utilized microchannels coated and filled with various extracellular matrixes in 2D and 3D (Schoen et al., 2010; Sung et al., 2009) to illustrate the selectivity of cancer cell migration on distinct ECM, as well as to measure traction forces and leading edge protrusions of a variety of cancer cell types (Li et al., 2009). More recently, biomedical engineers have begun to develop systems that generate linear and non-linear cytokine gradients in order to more accurately investigate the chemotactic behavior of cells derived from primary tumors.

Establishment of steady-state gradient profiles has been examined using flow-based gradient generators, diffusion-based gradient generators, as well as hybrid generators (mixture of convection and diffusion). One of the original microdesigns for migration study was developed by Li Jeon and colleagues, in a gradient mixer design initially used for neutrophil chemotaxis (Li Jeon et al., 2002). This device contains multiple inlets that enable the loading of different ligand solutions that are then mixed in channels perpendicular to the flow direction (Figure 6A). Subsequently, a variety of system designs have been developed to generate alternative gradient shapes for further chemotaxis study (Kim et al., 2010). In such flow-based designs, two concentrations of biomolecules flow separately into a network of microchannels, where mixers are patterned to combine adjacent streams via convection in order to generate a chemical gradient. While flow-based devices are able to finely control the spatiotemporal resolution of the gradient, they require constant flow rates of reagents that remove molecules secreted from cells that are critical to regulation of tumor cell migration (Huang et al., 2011).

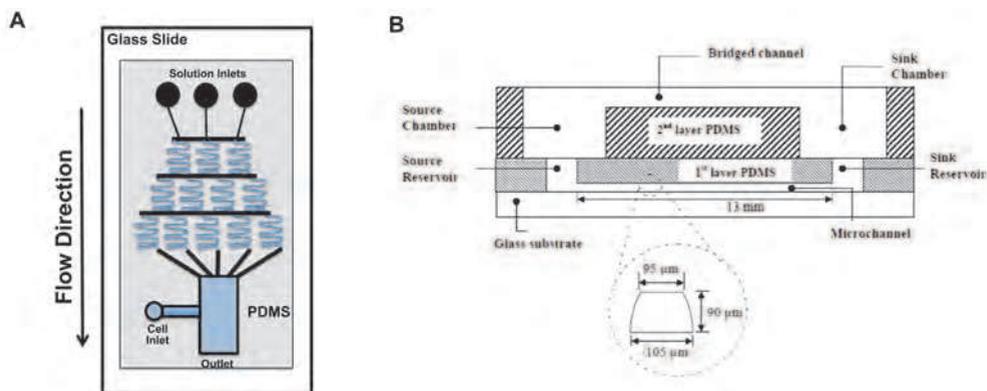


Fig. 6. Schematics of microdevices currently used to generate concentration gradients (not to scale). The flow mixer device was first proposed by Li Jeon and colleagues to create highly controllable concentrations along specific distances via continuous convective flow. (A) Schematic representation of a premixing gradient generating device pioneered by Li Jeon and colleagues. (B) A hybrid microlane system uses interconnected reservoirs to create concentration gradients via both convection and diffusion. The microchannel approximately measures 13 mm in length, 90 μm in depth and 100 μm in width (averaged with the upper side of 95 μm and the lower side of 105 μm), as its semi-hemispherical cross-section shown in inset. (Courtesy of Kong et al., 2010)

Subsequent microdevice designs now often generate soluble gradients by using passive diffusion. These systems can eliminate fluid flow near the surroundings of cells by using 3D hydrogels or high resistance channels so that transport occurs predominantly via diffusion (Beebe et al., 2002). In this configuration, two reservoirs are typically used to maintain given chemical concentration in a specified sink and source. Diffusion along adjoining microchannels then facilitates the formation of a concentration gradient between the reservoirs that enables cells to migrate along the defined gradient (Paguirigan and Beebe, 2008). While these systems eliminate the flow stresses imposed upon cells in flow-based devices, they require several hours to generate desired gradients, and rapid adjustment to the gradient profile is often difficult if not impractical. As a result, hybrid microsystems have been developed to enable the use diffusion with a minute level of convection to bolster formation of a desired gradient. For example, our group was able to generate steady-state gradients that were stable for 2-3 days using a bridge design and by exploiting the ultra-low bulk velocities generated by density differences between the reagents used (Figure 6B) (Kong et al., 2010).

The development of microfluidic platforms that incorporate real-time control of cell imaging and measurement of chemotactic concentration gradients is highly needed for understanding the dynamics of brain tumor interactions, an area which remains relatively unexplored when the majority of microfluidic studies focus on measurement of end-point cellular responses.

6. Future prospects of anti-invasive brain tumor therapy

The impetus for the development of anti-migratory therapeutic agents for brain tumors has been the desire to ease the manageability of the disease, by arresting tumor cells to their primary local environment. Such strategies can reduce the need to utilize the so-called "Search and Destroy" approach that is the currently suggested clinical necessity. Elucidation of possible mechanisms used by diffusely infiltrative glioma and MB cells will enable a better understanding of how to render these cells static, while providing targets for the development of pharmacological products capable of such a task.

More recently it has been suggested that enhancing the recruitment of endogenous progenitors toward tumor masses will aid in restoring the brain regions that have been resected or lost via necrosis (Cayre et al., 2009). Neural stem cells (NSCs) have aroused attention in the field of neurooncology as delivery vehicles of therapeutic genes. In addition to their multipotential capabilities that allow them to differentiate into neurons, astrocytes and oligodendrocytes, NSCs are also characterized by their remarkable capability to migrate through the brain (Gage, 2000; Yandava et al., 1999). The ability of implanted NSCs to distribute themselves throughout the tumors and follow invasive glioma cells has raised the idea of their therapeutic potential in targeting invasive glioma cells *in vivo* (Aboody et al., 2000; Staflin et al., 2009). Shimato and colleagues demonstrated *in vitro* that human NSCs exhibited extensive tropism for MB cells (Shimato et al., 2007). Using leptomeningeal dissemination mouse models, they confirmed *in vivo* that NSCs were able to distribute diffusely to MB cells that had spread throughout the entire spinal cord after implantation in the cisterna magna, and that genetically transformed NSCs functioned effectively in killing MB cells (Shimato et al., 2007). Similarly, genetically-modified NSCs were delivered intracranially and shown to target MBs (Kim et al., 2006). Recently, it was shown that human

umbilical cord blood-derived stem cells can integrate into human MB after local delivery, and that MMP-2 expression by the tumor cells mediates this response through the SDF1/CXCR4 pathway (Bhoopathi et al., 2011). These results offer a new promising therapeutic modality that uses human stem cells for targeting intra-cranial as well as leptomeningeal dissemination of MBs.

Although significant results are being generated from the stem cell community, brain tumor researchers have only recently begun to reflect on the specifics of glial progenitor recruitment as a form of treatment for the disease. Glial progenitor cells have shown increased healing potential after supplementing the cultures with exogenous concentrations of VEGF D when compared to controls (Kranich et al., 2009). Using transwell assays, a dose dependent invasive response of murine neural stem cells towards human glioma conditioned media (Heese et al., 2005) and bi-potential O-2A progenitors toward PDGF (Gallo et al., 1996) has been displayed.

Ideally, as has been the case in previous years, the focus should be to target cytokines and their cognate receptors involved in glioma and MB chemotaxis signaling events. Moving forward, the community is in great need of technologies and strategies that can both approximate the chemical microenvironment present in the *in vivo* brain, and replicate these environments *in vitro*. In so doing, migration strategies can be developed that examine how combinations of cytokine and/or pharmacological cocktails can be used to limit the diffusive migration of tumor-derived cells into healthy brain.

7. Conclusion

The migration of glioma and medulloblastoma tumor cells into healthy brain tissue is a critical, yet poorly-understood, component of the tumor invasion and metastasis that contributes to poor patient prognosis. Extensive *in vivo* studies of brain tumors have generated invaluable data to elucidate the molecular alterations and genetic backgrounds present in diseased cells, the signaling mechanisms cells use to communicate with their surrounding microenvironment, and the characteristic patterns of dissemination used by specific tumor cell types. Additionally, *in vitro* studies of brain tumor-derived cells have established the chemotactic potential of various cytokines and extracellular matrixes, evaluated the effectiveness of pharmaceutical cocktails on tumor growth, as well as enabled fundamental measurement of motility and directionality in tumor cell samples. While the majority of research efforts to date have focused on the origin and nature of tumorigenesis in glioma and medulloblastoma, the community is now beginning to examine the integrated role of cell migration in tumor growth and dissemination. Future research is needed to examine the existence and characteristics of tumor cell populations with highly motile phenotypes in order to establish cell migration as a viable therapeutic target, and start designing treatment regimens based on cell migratory behaviors.

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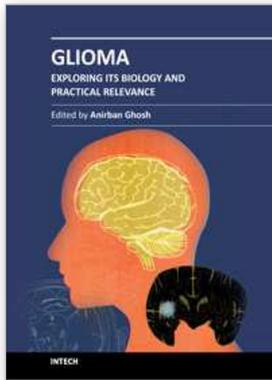
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The title 'Glioma - Exploring Its Biology and Practical Relevance' is indicative of its content. This volume contains 21 chapters basically intended to explore glioma biology and discussing the experimental model systems for the purpose. It is hoped that the present volume will provide supportive and relevant awareness and understanding on the fundamental advances of the subject to the professionals from any sphere interested about glioma.

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