The Pathogenesis of Neoplastic Meningitis

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Neoplastic meningitis (NM) is a dreaded metastatic complication occurring in 5% to 10% of cancer patients. Survival is limited, usually ranging from 4 to 16 weeks. The pathogenesis of NM has not been extensively investigated but can be considered from the anatomic and molecular biologic standpoints. Malignant cells reach the cerebrospinal fluid (CSF) and meninges by direct invasion from tumors located near or within the central nervous system (CNS), or via the bloodstream or other pathways that contact the CNS. Symptoms of NM are caused by malignant cells invading and damaging nervous tissue, obstructing the vascular supply to nervous tissue, or obstructing CSF pathways. The molecular changes responsible for the development of NM are not well delineated, but it is likely that they involve changes in molecules responsible for tumor cell adhesion, migration, and proliferation. An understanding of the pathogenesis of NM will allow for its earliest possible diagnosis and ultimately lead to therapies targeted at the underlying molecular causes of this devastating condition.

Introduction

Neoplastic meningitis (NM) is a relatively uncommon metastatic manifestation of cancer, occurring in 5% to 10% of common solid tumors, usually late in the course of disease [1]. NM rarely occurs as the sole focus of metastasis (1%–2.3% of autopsies) [2,3], which is consistent with its chronologically late development and suggests its development as a metastasis from a metastasis. A substantial amount of literature concerns the pathogenesis of metastases in general, but relatively little focuses on NM. Metastases outside the central nervous system (CNS) are vexing and usually incurable. Similarly, outcomes in patients with NM have not significantly improved since the early description of this complication; survival usually ranges from 4 to 16 weeks after diagnosis [1]. As cancer treatments improve, the frequency of NM may increase because of the relative sanctuary from systemic therapies offered by the blood–brain barrier.

For the purpose of discussion, the pathogenesis of NM can be conceptualized in two ways. The first involves consideration of the anatomic migration pathways of tumor cells reaching the cerebrospinal fluid (CSF) and meninges. A thorough understanding of these pathways should allow the earliest possible detection of NM, and therefore the earliest intervention and best outcome. The second involves an understanding of NM at the molecular level. What genetic and molecular changes allow tumor cells to gain access to the meninges and CSF and then to proliferate there? An understanding of this process on the molecular level will further the development of therapies that target specific molecular changes in NM.

Anatomic Concepts Relevant to Pathogenesis of Neoplastic Meningitis

Physical proximity

The pathogenesis of NM must be considered in the context of the pathogenesis of both systemic and parenchymal CNS metastases. Brain metastases occur synchronously in 28% to 75% of patients with NM [4,5], suggesting that many of the same factors predispose to both. Similarly, intramedullary spinal cord metastases often occur concurrently with NM [6]. For NM to occur, tumor cells must gain access to the meninges and CSF. The number of tumor cells necessary to reach the CSF and result in clinically relevant NM is unknown. However, in a rabbit model of NM, as few as 3000 tumor cells injected into the lateral ventricle will result in death from the consequences of NM in 21 days [7]. Theoretically, a single malignant cell within the CSF could develop into full-blown NM. The closer a tumor focus is to the meninges, the less distance tumor cells must travel and the higher the likelihood that an adequate number of cells will reach the target. In breast and lung cancer, and probably in other solid tumors, tumor foci located near the CNS are most often responsible for dissemination to the meninges [8]. In a study of 28 patients with NM, 22 (79%) had parameningeal tumor foci. Several other patients had spread to the CNS from metastases in the head and neck. Additionally, areas where the most intense NM was found were located adjacent to parameningeal bony disease, even in the setting of diffuse NM.

The concept of physical proximity is evident when primary CNS tumors growing near the CSF spaces seed the CSF. Medulloblastomas (located in or near the 4th ventricle) and pineoblastoma (located in the pineal gland) are particularly notable examples of this principle [9]. Astrocytomas are less common as a cause for clinically significant NM. Lack of an invasive phenotype may be the reason for the rare occurrence of extra-CNS metastases from glioblastoma multiforme (GBM), as shown in a rat C6 glioma model in which GBM cells were unable to penetrate the basement membrane of intracerebral vessels [10]. Leptomeningeal cells may also provide a relative barrier to the migration of GBM cells, as demonstrated in an in vitro model using glioma spheroids, and separate metastatic, leptomeningeal, and glial cell aggregates. The glioma spheroids could not invade the leptomeningeal cell aggregates, whereas the metastatic cell aggregates could. Conversely, whereas the glioma spheroids could invade the glial cell aggregates, the metastatic cell aggregates could not. This finding is consistent with the clinical behavior of these tumors [11].

A useful way to organize one's thinking about the paths tumor cells take to reach the meninges and CSF is to consider the phenomenon in patients with obvious CNS metastases (to the brain, spinal cord, or dura mater) and compare them to those without obvious CNS metastases. Figure 1 depicts several potential anatomic paths that tumor cells can take to reach the leptomeninges and CSF.

Patients with neuroimaging evidence of central nervous system metastases

Parenchymal central nervous system metastases

Parenchymal CNS metastases usually arise due to vascular seeding. NM could develop from parenchymal lesions in the following way: Tumor cells in the blood stream become lodged in a small-caliber CNS vessel, resulting in ischemia distal to the vessel and degradation of the vessel endothelium and surrounding basement membranes. This would allow for the entry of tumor cells into the space around the damaged vessel (the Virchow-Robin space, which is believed to be contiguous with the subarachnoid space [SAS]) [12•]. One can envision occasional cells becoming unattached from the growing metastasis and traveling in the CSF or migrating along the periarteriolar surface to reach the more superficial SAS (the perivascular space appears not to surround the venules as it does the arterioles) [13]. In this scenario, the NM does not become clinically or radiographically evident until tumor cells reach the SAS distal from the parenchymal tumor nidus (Fig. 1A). A caveat concerns cases where a small "parenchymal" brain metastasis is identified on neuroimaging, especially if it is located deep in brain sulci. What appears to be a "parenchymal" brain metastasis could actually be a tumor focus originating in the SAS. CNS parenchymal metastases may invade the SAS directly without traveling through the Virchow-Robin space. For this to occur, cells need the ability to migrate through neural and leptomeningeal tissue into the SAS. Experimental models have demonstrated that systemic tumor cells metastatic to the brain have a greater ability than glioma cells to migrate through leptomeningeal tissue (Fig. 1B) [11].

The risk of NM appears to be higher if the intracranial parenchymal metastases are located in the posterior fossa. In one study of 160 patients with lung cancer, the 1-year actuarial risk of NM was 21% in patients with posterior fossa metastases (n=55). No occurrences were reported in 105 patients with supratentorial metastases [14]. In another study, among 104 patients with posterior fossa brain metastases, 10 developed NM, with a 1-year actuarial risk of 25% [15].

Postoperative NM, presumably caused by intraoperative tumor cell seeding of the CSF, has been reported in 5% to 40% of patients after craniotomy. The risk is higher in patients undergoing craniotomy for posterior fossa metastases, compared with supratentorial metastases (33%–40% vs 2%–4%, respectively) [16]. This difference could result from a higher incidence of subtle NM (undetected on neuroimaging) occurring with posterior fossa metastases as compared with supratentorial metastases.

Dural metastases

The dura, adjacent to the arachnoid membrane, may contain malignant cells that can reach the SAS via direct extension through the subdural space (Fig. 1C). Bridging veins between the dura and arachnoid may provide a path between these two adjacent structures. Alternatively, malignant cells may move within the dura to reach the saggital sinus and penetrate the sinus endothelium to enter the arachnoid granulations and then the SAS, although there is no clinical report of such an occurrence.

Vascular routes in patients without neuroimaging evidence of central nervous system metastases

Arterial route

The leptomeninges derive most of their nutrition from the CSF or adjacent cortex, are relatively avascular, and are not generally believed to be the direct arterial recipients of metastatic tumors that evolve into clinically significant NM [17,18]. That being said, the meninges contain blood vessels within which tumor cells can become lodged and later extravasate into the meninges and CSF. This route of entry of malignant cells into the CSF has been described [19]. The radicular arteries traveling through the intervertebral foramina may provide access of tumor cells from the systemic circulation to the meninges of the spinal cord (Fig. 1D).

The choroid plexus, formed by the invagination of the ependyma and pial blood vessels into the ventricular cavities, is responsible for the formation of most of the CSF volume. The blood supply of the choroid plexus in the lateral, 3rd, and 4th ventricles comes from the anterior and posterior choroidal arteries, the choroidal branches of the posterior cerebral artery, and the posterior inferior cerebellar artery, respectively. Hematogenously seeded tumor cells may become lodged in the choroid plexus and later penetrate this structure into the CSF space (Fig. 1E). A number

of cases have been reported in which choroid plexus foci of tumor were believed to be responsible for seeding of the CSF [5,18]. The choroid plexus should be considered as a site of tumor cell entry into the SAS in those patients presenting with prominent 3rd and lateral ventricular hydrocephalus. Malignant cells collecting within the Sylvian aqueduct could result in this clinical presentation. The importance of the choroid plexus in the dissemination of NM has been debated. In a study in which 10 of 11 patients had tumor cells in the choroid plexus, the cells were located at the base of the plexus and around large choroidal vessels without involvement of the vascular plexus, and no tumor cells were found in the vascular lumen [2]. The authors suggested that the choroid was a recipient of hematogenously seeded cells and not a source of seeding for the CSF. Akin to the scenario described in the previous section for patients with metastases that are visible on neuroimaging, it is likely that some patients have tiny brain metastases not visible on brain imaging that occlude arterioles, penetrate vessel walls, and reach the SAS. These patients may later develop clinically evident NM.

Venous route

Within the spinal canal, the vertebral venous system (VVS) runs parallel with and provides a bypass route for the portal, pulmonary, superficial thoracic, and caval venous systems. This valveless system runs the entire length of the thorax, connecting the VVS with the intracranial venous sinuses [20]. Animal studies have demonstrated that blood that normally flows through the caval system is rerouted through the VVS when pressures in the abdominal or thoracic cavities are increased. Retrograde venous flow through the valveless VVS during periods of increased intrathoracic or intra-abdominal pressure could allow tumor cells floating within the systemic venous system to enter the VVS. Movement of tumor cells through the loose endothelial connections of the VVS is easily conceivable (Fig. 1F).

Arachnoidal veins have been shown both clinically and experimentally to provide a route of entry for leukemia cells into the CSF [21,22]. In an autopsy study of the brains of childhood leukemia patients, leukemic cells were not seen within arteries but were found, at their earliest stages of involvement, in the walls of the superficial arachnoid veins. This finding suggests that circulating malignant cells can migrate through the venous endothelium but are prevented from doing this in the more organized arterial system. Surface markers on venous endothelial cells may also play a role in adhesion and penetration of the leukemic cells.

Arachnoid granulations exist in the spinal nerve dural sheaths and empty into the spinal radicular veins. Theoretically, tumor cells can reach these vessels by way of the anastamotic VVS. Cells floating in these small vessels could access the CSF by attaching to and penetrating the arachnoid granulations (Fig. 1G).

Malignant cells within the vertebral bodies may gain access to the draining basivertebral veins and subsequently to the VVS. The VVS is valveless, which allows tumor cells access to tissues above and below their sites of entry.

Nonvascular routes in patients without neuroimaging evidence of central nervous system metastases

Parameningeal foci of tumor cells can cross basement membranes directly and invade the dura and leptomeninges. In patients with vertebral body metastases, evidence suggests that the arachnoid can be preferentially involved more than the pia, so that the malignant cells may move from an outside-in direction [8].

Malignant cells can gain access to the meninges and CSF along neural or perineural tracts or via lymphatics that accompany those tracts (Fig. 1H) [5]. Endoneural, perineural, and perivascular lymphatic spread has been proposed in a few patients with gastric cancer [2,18]. Migration of malignant cells along the spinal or cranial nerve epineurium–paraneurium has been demonstrated in patients with squamous cell carcinoma and lymphoma who have developed NM [5,23]. Once in the nerve, malignant cells can travel in the subpial space and extend along blood vessels into the endoneurial space. Malignant cells can invade the nerve parenchyma as well. The reaction of the nerve to tumor cell invasion varies from an unaffected appearance, to myelin loss with axonal preservation, to complete neural destruction and axonal degeneration [24]. Focal ischemic changes can be found in nerve specimens from patients with NM and perineural deposits of tumor [5].

Mareel *et al*. [25] suggested that subclinical bacterial meningitis may open a doorway into the CSF spaces for malignant cells to enter. They noted that the bacteria attract cytokine-releasing leukocytes, causing endothelial damage and opening a passageway through which malignant cells can travel. They also reasoned that treatment with antibiotics, causing bacterial killing, could enhance this process by increasing the amount of breakdown products in the vicinity of the meninges and creating more damage.

Once tumor cells reach the CSF or meninges, they can migrate along the meningeal surface or float in the CSF and become reattached at distant locations. Once in the CSF, malignant cells can directly traverse the pial membrane into the spinal cord or into the nerves [5]. Malignant cells commonly accumulate in the cisterns of the skull base, the posterior fossa, the posterior surface of the spinal cord, and the lumbosacral thecal sac, all of which suggests that gravity is important in the development of the progressive symptoms of NM [18].

The previous sections raise important questions: What are the molecular reasons some tumor cells gain access and thrive in the meninges and CSF? What molecular changes allow tumor cells to survive in the CSF, an environment with lower levels than the serum of potassium, calcium, oxygen, glucose, and other substances? Because parenchymal brain metastases and NM often coexist, many of their molecular determinants are likely to be the same. As reviewed by Puduvalli [26], numerous molecular changes have been identified

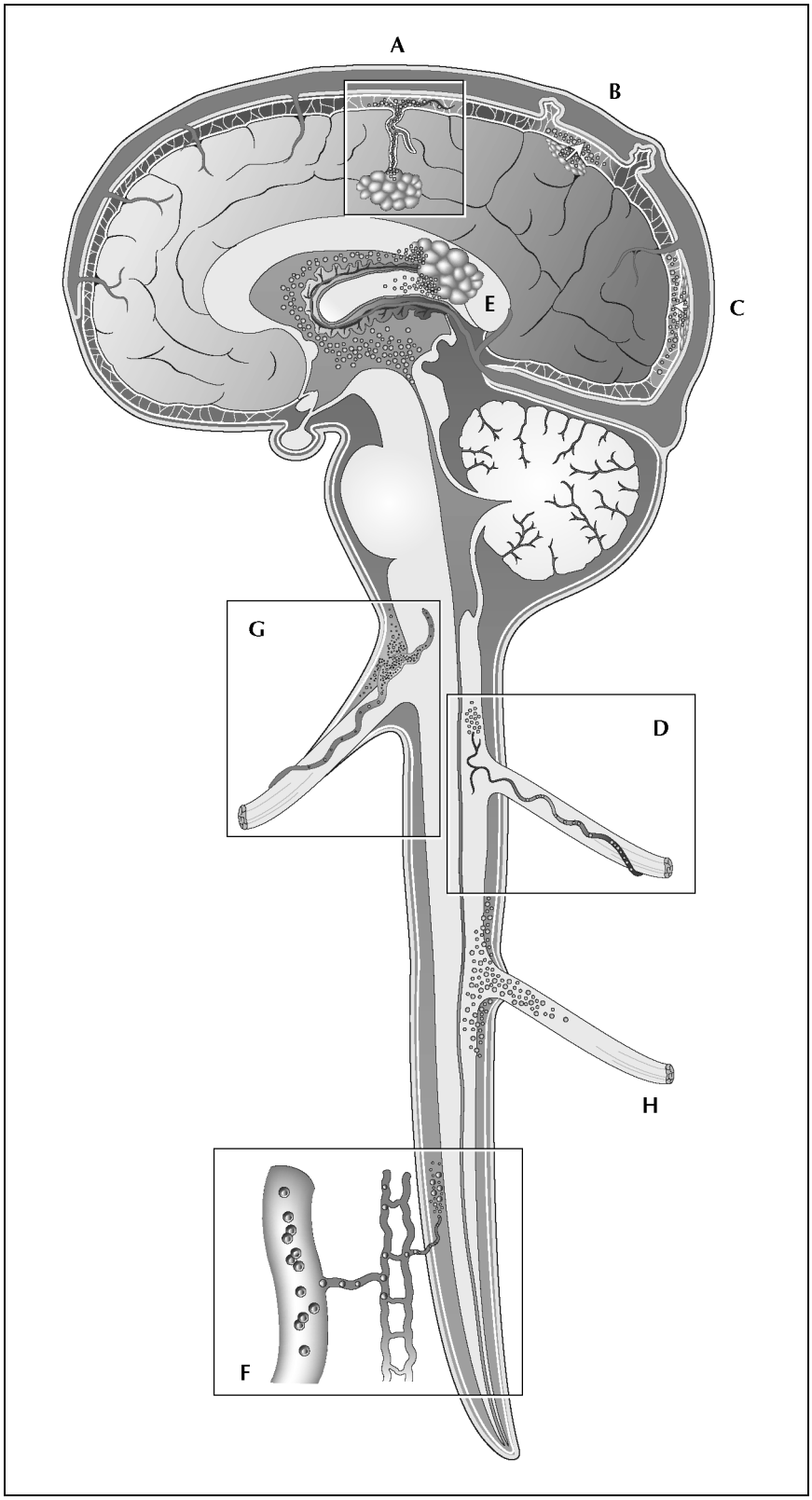

Figure 1. Various potential anatomic routes by which malignant cells may reach the leptomeninges and cerebrospinal fluid (CSF) are depicted. **A**, Path that tumor cells may take when exiting from a metastatic brain tumor into the Virchow-Robin space and moving into the subarachnoid space (SAS), where wider subarachnoid dissemination may proceed. **B**, Path that brain metastasis cells may take through brain parenchyma through the leptomeninges and into the SAS. The leptomeningeal basement membrane would be penetrated in this scenario. **C**, Path from dura to SAS. Direct extension may occur, or bridging of veins may provide a migratory scaffold for tumor cells to follow. **D**, Potential arterial route of neuromeningeal seeding through the radicular arteries. As with brain arterioles, cells must be arrested in the vessel and extravasate through its wall. **E**, Choroid plexus may be a nidus through which tumor cells seed the CSF. **F**, Tumor cells from the systemic venous system may enter the vertebral venous system at times of increased intrathoracic or intra-abdominal pressure. These cells can move in a retrograde fashion through the valveless system. Cells are shown extravasating through the loosely connected venous endothelial cells. **G**, Tumor cells from the radicular veins may reach the CSF through the arachnoid granulations in the nerve root dural sleeves. **H**, Tumor cells may invade spinal or cranial nerves and migrate centrally through the nerve itself.
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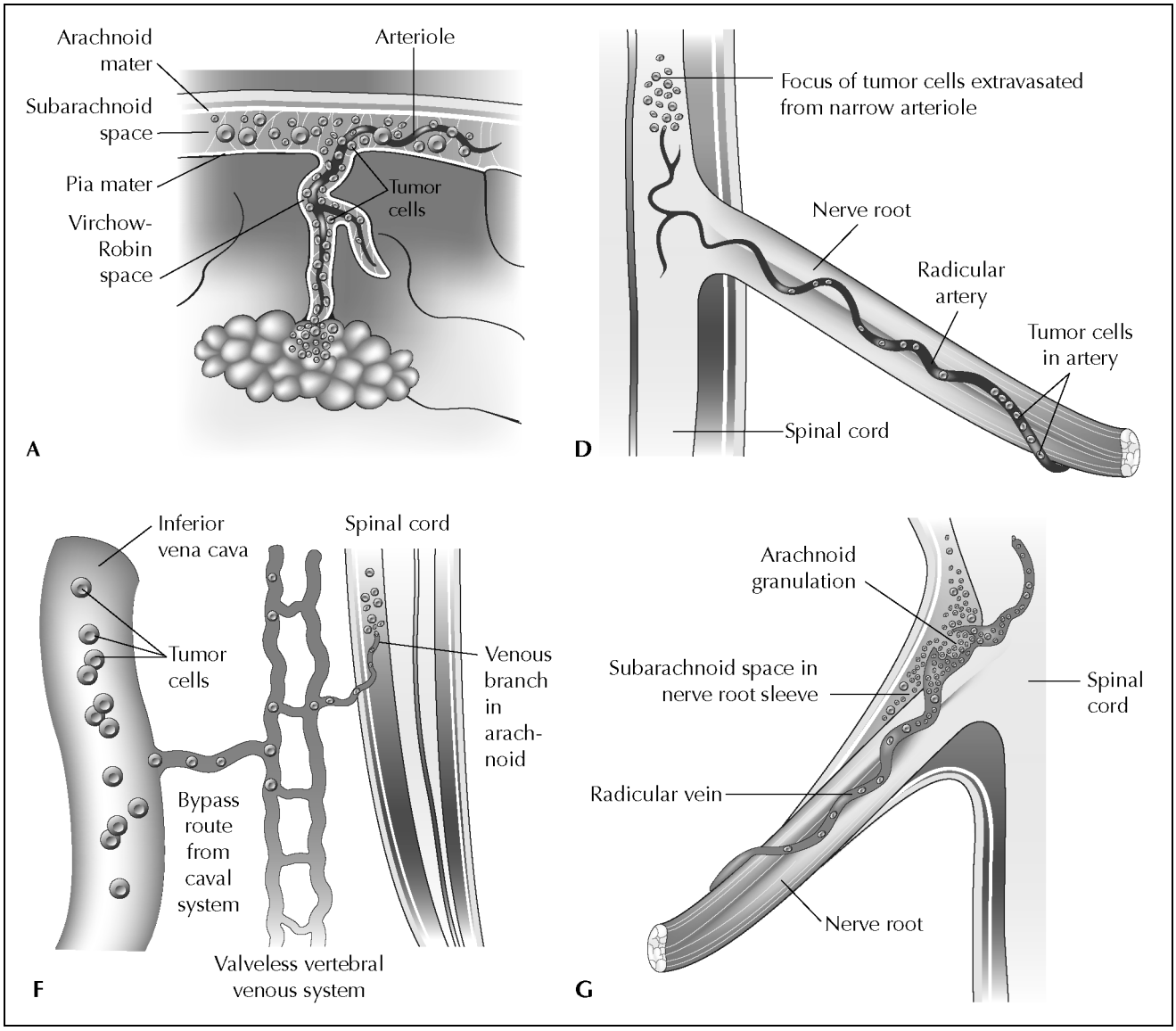

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that predispose to the development of metastases, and some have shown importance in formation of brain metastases. Candidate genes that promote metastasis formation include those associated with cell adhesion to extracellular matrix (ECM) components, proteases, motility factors, angiogenic factors, and growth regulators. Categories of molecular mediators believed to be important in the development of metastases include matrix metalloproteinases (MMP), serine proteases, integrins, and angiogenesis factors.

Molecular Pathogenesis of Metastasis with Special Attention to Central Nervous System Metastases and Neoplastic Meningitis

The biology of metastasis development is the focus of many cancer research laboratories around the world. Although little of this research has been translated into clinical improvement of metastasis control, the molecular underpinnings of metastasis development are being slowly unraveled. A recent review summarizes a number of metastasis-suppressor genes and their reported mechanisms [27•]. Broadly, the in vitro phenotypic activity of metastasis-suppressor genes includes inhibition of motility, invasiveness, colony formation, growth arrest, differentiation, proliferation, adhesion to ECM components, enhancement of cell–cell adhesion and aggregation, and immunosensitivity. The timing of all of these activities is critical and is mediated through a wide range of cellular functions. These functions include signal transduction, transcriptional activation, integrin expression and signaling, cell adhesion and motility, cell communication, cytokine–stress-induced signal transduction, serine protease expression, and nucleotide diphosphate kinase activity, some of which are discussed in later sections of this review.

Table 1. Molecular mediators of metastasis with possible relevance to brain metastases and neoplastic meningitis

Disattachment, motility, and invasion
Focal adhesion kinase (FAK)
Hyaluronidase
Tumor cell survival during migration
P-selectin
Adhesion
Selectins (*E*-selectin, *P*-selectin)
FAK
Tropism
Neurotrophins (nerve growth factor [NGF])
Heparanase
Transforming growth factor (TGF)-β
Chemokines and chemokine receptors (CXCR4, CXCL12/SDF-1)
Extravasation, intravasation, invasion, and penetration
Heparanase
NGF
Urokinase (uPA), uPA receptor (uPAR)
Matrix metalloproteinases (MMP-2, MMP-9)
Angiogenesis
Heparanase
Vascular endothelial growth factor (VEGF)

Regardless of the anatomic path to the leptomeninges, the concept of the metastatic cascade can be used as a framework within which to organize one's thinking about its pathogenesis [28]. The metastatic cascade is a sequence of events that includes cellular disattachment, invasion and intravasation, cell survival during migration, adherence, tropism, extravasation and invasion, recruitment of blood supply, avoidance of host immunologic and defense mechanisms, and proliferation, leading to a distant focus of tumor. Table 1 lists some mediators of metastasis that have been shown or that may be relevant to brain metastases and NM.

Disattachment, motility, and invasion

Cells from the primary tumor develop motility and invasive potential, allowing invasion of the ECM and penetration into capillaries, venules, and lymphatic channels [29•]. In general, this is accomplished by downregulation of cell–cell adhesion molecules, alteration of integrin expression profiles, and cellular proteolytic activity affecting the matrix around the tumor. Specifically, in some human carcinoma cells that overexpress epidermal growth factor receptor (EGFR), exposure to EGF downregulates focal adhesion kinase (FAK) activity, which allows increased cellular morphologic changes, detachment, invasion, and metastasis [30]. Hyaluronidase activity has been shown to be as much as 100- to 1000-fold greater in metastatic brain tumors compared with gliomas, suggesting that it is directly or indirectly involved in the brain metastasis phenotype [31]. In NM, tumor cells form nodules in the leptomeninges but can also be found floating in the CSF. The molecular changes that must occur to allow cell disattachment and reattachment in NM have not been investigated. Inhibition of these actions may be a reasonable therapeutic target in NM.

Tumor cell survival during migration in the vascular stream

Once tumor cells invade the vascular pathways, they must be able to survive unattached to the ECM and resist the turbulence and immunologic challenges presented within the blood stream. Tumor cells usually form multicellular aggregates with platelets and lymphocytes and can embolize to distant targets. Tumor cell–platelet interactions facilitated by *P*-selectin may "cloak" the tumor cells in platelets and assist in the avoidance of host immune response to the tumor cells [32•]. If cell-ECM interactions are disrupted, anoikis, or integrin disruption–mediated apoptosis, usually occurs. Tumor cells that are metastatic to the CSF must have the ability to avoid anoikis.

Adherence

Tumor emboli are arrested in target organ capillary beds, either becoming trapped in microscopic, narrowing blood vessels or adhering to endothelial cells or exposed basement membrane. Experimental models of cancer cells arrested in microscopic vessels show that activated vessel endothelium can cause adherence of tumor cells in vessels larger than the tumor cell [33]. This suggests that organ-specific signaling can result in tumor cell arrest in some situations. The endothelial adhesion molecules *E*-selectin, VCAM-1/α4β1, and vitronectin have been shown to mediate cancer cell attachment to activated endothelial cells in experimental models [34,35]. *P*-selectin, expressed on activated endothelial cells, contributes to leukocyte rolling and adhesion and may also be involved in tumor cell–platelet complexes that promote metastasis development [32•]. In carcinoma cell lines where FAK is downregulated to allow motility, it later becomes activated through integrin signaling, consistent with the phenotypic cellular behavior of attachment and decreasing invasiveness [30]. In breast cancer, the cell surface receptor integrin αvβ3, when activated through interaction with platelets, supports tumor cell arrest and adhesion in the vasculature and probably plays a large part in endothelial attachment of breast cancer cells [36].

Tropism

Closely related to adherence, tropism refers to the affinity of a tumor cell for coming to rest in a particular organ, which involves genetic alterations in the tumor cells as well as a receptive target organ. The metastatic process is inefficient; millions of cancer cells are shed into the vascular system on a given day, and only approximately 0.01% of shed cells form identifiable tumor rests [37,38]. This inefficiency led to the concept of "seed and soil," which refers to the propensity of a particular cancer to metastasize to and proliferate in a particular organ. Reasons for tumor tropism are being slowly unraveled [39••,40]. Both positive and negative factors in the host organ affect the ability of a metastasis to proliferate.

Support for this concept appeared in one study demonstrating that 66% of tumor metastases could be explained by blood flow patterns, whereas negative interactions inhibit tumor growth in target organs 14% of the time and positive interactions support tumor growth in target organs 20% of the time [41]. In a nude mouse metastatic breast cancer model, cells that metastasized to the brain, when harvested and reinjected, exclusively metastasized to the brain and not to bone, and vice versa for cells that metastasized to bone. Transforming growth factor (TGF)-β inhibited the growth of the breast cancer cells with predisposition to go to the brain, and insulin-like growth factor (IGF)-1 marginally stimulated anchorage-independent growth of these cells [42]. Thus, tumor cells that come to rest in a particular organ show repeated tropism for that organ.

Evidence suggests that chemokines (known to allow for "homing" of lymphocytes to specific organs) and their receptors may play a role in homing tumor cells to specific target organs. It was recently demonstrated that breast cancer cells express the chemokine receptors CXCR4 and CCR7. Common metastatic target organs of breast cancer have elevated levels of CXCL12 and CCL21, the ligands for these receptors [39••]. Recent investigations into neuronal migration in mice have shown that the ligand SDF-1 (CXCL12) is expressed in the meninges covering the entire CNS. SDF-1 attracts external germinal layer cells in the cerebellum toward the meninges [43••]. If the meninges in humans also produce SDF-1, targeting the breast cancer cell chemokine receptor CXCR4 with small molecule antagonists may provide a novel and focused treatment for brest cancer patients with NM. Activation of chemokine signaling pathways can have other effects, including activation of downstream RAS/MAPK pathways, inducement of cytoskeletal changes, and increased cell motility.

Melanoma brain metastasis cells produce heparanase, which is regulated by nerve growth factor (NGF) produced by astrocytes. Melanoma cells also produce TGF-β1, interleukin (IL)-1β, and basic fibroblast growth factor (bFGF), which stimulate astrocyte NGF synthesis. Astrocytes produce heparanase, which potentiates tumor cell invasion [44••]. These interactions provide reciprocal feedback for the development of brain metastases. Tumor cell tropism has been explored further in studies of syngeneic mice, in which a particular strain of melanoma cells injected into the internal or external carotid arteries was found to be more likely to grow in the meninges and less likely to grow in the brain parenchyma. These cells did not produce measurable gelatinase A (MMP-2), in contrast to those cells that were more likely to grow in the brain. In addition, the cells that proliferated in the meninges were highly sensitive to growth inhibition by TGF-β, which is at high levels in the brain [45].

Extravasation, intravasation, invasion, and penetration

Tumor cells extravasate into the target organ parenchyma. Cells must leave their vascular pathways and migrate through endothelial or other basement membranes to reach the CSF and meninges. Urokinase (uPA), a serine protease associated with invasion, activates plasminogen to plasmin and indirectly activates MMPs. The uPA receptor (uPAR) on the cell membrane promotes tumor cell invasion by focusing proteolysis of urokinase to the cell surface. In some pathologic conditions, soluble forms of uPAR (suPAR), are at elevated levels in the serum and CSF. Specifically, suPAR is elevated in the serum and CSF of patients with NM, paraneoplastic syndromes, and CNS infections [46]. Whether the elevation causes tumor cell migration into the CSF, or is simply due to leakage across the disrupted blood–brain barrier, is unknown, but suPAR bears further investigation as a potential mediator or marker of NM. Heparanase is an enzyme that degrades the heparan sulfate chains of heparan sulfate proteoglycans, essential components of the cell surface, endothelial basement membrane, and ECM. Heparanase is associated with invasion of melanoma tumor cells into the brain. NGF, produced by normal astrocytes, induces the production of heparanase and is produced by normal brain at the invasion front of melanoma growing in the brain [44••]. Whether NGF is involved in the pathogenesis of NM is unknown. The active, but not the inactive forms, of MMP-2 and MMP-9 (collagenases known for their ability to degrade the basement membrane) are strongly correlated with the presence of malignant cells in the CSF [47]. This may be relevant to the pathogenesis of NM and deserves further study as a potential therapeutic target and disease marker.

Angiogenesis

Evidence suggests that tumor cells must recruit additional blood supply to grow larger than 0.125 mm^2 [48]. Vascular recruitment allows further growth and later increases the probability of metastatic development [49].

Angiogenesis has not been established as important for progression of NM (Personal communication, Fuller GN, Aldape K). The lesions evident on gadolinium-enhanced magnetic resonance imaging scans of patients with NM suggest an alteration of the blood–brain barrier. Whether this alteration actually represents newly formed blood vessels is not clear, though levels of proangiogenic factors are found in the CSF of patients with NM. Recent evidence shows that CSF levels of vascular endothelial growth factor (VEGF) are more indicative of NM than of other potential diagnoses [50]. This may be due to the elaboration of VEGF from the malignant cells in the CSF and meninges and could be useful as a marker of NM or in the estimation of response to treatment, but it may not be directly relevant to the pathogenesis or progression of NM. The recent focus on antiangiogenic approaches to therapy in cancer is exciting and offers hope, but it could unwittingly increase the number of difficult-to-treat patients with NM because of the possible lack of dependence of NM on angiogenesis for its progression.

Evasion of host defenses

New tumor deposits must evade host immune responses to stay viable. This principle may not be as important in the

CNS as it is in other metastatic sites in the body, however, because the CNS is considered relatively privileged from exposure to the immune response.

Proliferation in hostile cerebrospinal fluid–meningeal environment

In studies of metastases from various organs, cells from brain metastases showed a slower growth rate and lower metastatic potential than tumor cells from non-CNS metastatic sites. These findings suggest that brain metastases may not represent the end stage of the metastatic cascade but may originate from a unique subpopulation within the primary tumor [45].

Conclusions

An understanding of the pathogenesis of neoplastic meningitis provides clinicians with the opportunity for early detection and treatment of NM and better outcomes. Even with the limited interventions currently available, with early diagnosis we can delay the progressive symptoms of NM and improve quality of life for patients by preventing neurologic disability. This approach will also decrease the cost of care because neurologic disabilities are among the most expensive to treat. As the understanding of the molecular causes of NM grows, therapies can be developed that target these causes more precisely. Some promising potential targets for NM therapy include molecular changes responsible for cellular invasion, migration, and attachment. The future application of targeted therapies is likely to present special challenges in treatment of patients with NM, considering the unique anatomy of the CNS and CSF pathways.

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- •• Of major importance

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