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Metabolic Advantages and Vulnerabilities in Brain Metastases

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Abstract

Metabolic adaptations permit tumor cells to metastasize to and thrive in the brain. Brain metastases continue to present clinical challenges due to rising incidence and resistance to current treatments. Therefore, elucidating altered metabolic pathways in brain metastases may provide new therapeutic targets for the treatment of aggressive disease. Due to the high demand for glucose in the brain, increased glycolytic activity is favored for energy production. Primary tumors that undergo Warburg-like metabolic reprogramming become suited to growth in the brain microenvironment. Indeed, elevated metabolism is a predictor of metastasis in many cancer subtypes. Specifically, metabolic alterations are seen in primary tumors that are associated with the formation of brain metastases, namely breast cancer, lung cancer, and melanoma. Because of this selective pressure, inhibitors of key metabolic factors may reduce tumor cell viability, thus exploiting metabolic pathways for cancer therapeutics. This review summarizes the metabolic advantages and vulnerabilities of brain metastases.

Keywords

Brain metastases; metabolic adaptation; cancer metabolism

Introduction to Brain Metastases

An estimated 90% of cancer deaths are caused by metastatic disease (1). The metastasis of primary cancers to the brain remains an urgent clinical issue due to the increasing frequency of cases. The current incidence of brain metastases (BMs) ranges from 9–17% of all cancer patients, and has increased due to enhanced imaging techniques for BM diagnosis and improved treatment of primary tumors, which increases time to progression and inflicts selective pressure towards a more aggressive, brain-penetrating phenotype (2). BMs cause severe side effects, such as impaired neurological function and coma, leading to a sharp decline in quality of life. BMs are also associated with poor prognosis, as the average survival of a patient with untreated BMs is less than two months (3). Typically, BMs come

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Conflict of Interest

The authors declare that they have no conflict of interest.

from specific primary cancers, including lung cancer (39–56%), breast cancer (13–30%), melanoma (6–11%), and colorectal cancer (3–8%) (2). BMs of different primary origins exhibit various median survival times after first treatment (in months): breast cancer (13.8), renal cell carcinoma (9.63), non-small cell lung carcinoma (7.0), melanoma (6.74), GI cancer (5.36), and small cell lung carcinoma (4.9), though additional prognostic factors can be used to further stratify patients (4). Substantial heterogeneity between cases complicates the study and treatment of BMs.

Metastasis is a complex process, requiring cells to enter and travel through the bloodstream, then exit the bloodstream and colonize foreign tissues. Therefore, metastatic cells often possess advantageous adaptations that promote survival. Ongoing research seeks to identify alterations in signaling pathways, gene and protein expression levels, and metabolic phenotypes that are characteristic of metastatic cells. Identifying these pro-metastatic factors may lead to new therapeutic options to improve the survival of patients with BMs.

Tumor Metabolism and Profiling

Both cell extrinsic and intrinsic factors affect cancer metabolism and metastasis. Extrinsically, interactions with the extracellular matrix, surrounding cells, and available nutrients affect cell metabolism. For example, ~20% of the body's glucose-derived energy products are devoted to the brain (5). The brain's elevated glucose supply and demand provides an ideal, nutrient-rich environment to fuel cancer cell growth. Due to rapid proliferation, cancer cells have high energetic and biosynthetic demands; therefore, tumors often undergo metabolic reprogramming to accommodate the need for nutrients and energy (6). The shift from oxidative phosphorylation to glycolysis in cancer cells is classically known as the Warburg effect (7). An example of factors involved in metabolic reprogramming is shown in Figure 1. Intrinsically, to support this metabolic shift, mutations that cause changes in gene expression can directly alter the levels or activity of metabolic enzymes present in a cancer cell. In addition, mutations that inactivate negative regulators of glycolysis, such as p53 or its target TIGAR, allow for constitutive glycolytic activity (8). Together, these metabolic adaptations promote tumor growth in the brain.

Techniques used to establish metabolic profiles for tumors include FDG-PET imaging, metabolomics, and metabolic flux analysis. FDG-PET imaging uses the radiotracer ^{18}F-FDG to visualize tumors throughout the body, as uptake correlates with the metabolic rates of different tissues. However, restricted uptake of FDG by gray matter in the brain limits the usefulness of this technique in cases of BMs (9). An alternative metabolomics approach employs spectroscopic methods to profile the metabolites present at a point in time in specific tissues. This discovery technique can reveal the accumulation or depletion of specific metabolite pools in response to drug treatment or tumor burden. In mouse models of BMs, biofluid metabolomics using NMR spectroscopy was used to distinguish tumor burden through differential metabolic profiles (10). This approach noninvasively detects micrometastases and aims to enhance early diagnosis of BMs to allow for earlier treatment.

In contrast, metabolic flux analysis monitors whole pathway activity by examining the formation and consumption rates of many metabolites. This targeted method requires stable-

isotopes for mass spectrometry and provides a dynamic view of metabolism by quantifying the amount of specific metabolites over time (11). A metabolite with a stable isotope tracer, such as ^{13}C, is introduced into a system and this tracer is transferred as the metabolite is processed. Metabolic flux accounts for not only metabolite concentrations, but also uses stoichiometric models to calculate enzyme activity. In orthotopic mouse models of glioblastoma, tracking various ^{13}C-labeled nutrients revealed tumor accumulation of glutamine and increased mitochondrial glucose oxidation in tumor tissue compared to surrounding brain tissue (12). This analysis broadens the strict view of dependence on aerobic glycolysis into a more complex model involving glucose utilization by the citric acid cycle. Due to its targeted nature, metabolic flux is a powerful tool for scientific analysis and may uncover distinguishing metabolic characteristics that are useful for diagnostic and/or therapeutic purposes.

Signaling Pathways and Metabolism

Few cancer cells survive the journey from the primary tumor to the brain, where they can establish a metastatic lesion. The metastatic cells that inhabit the brain have a genetic predisposition for adaptability or the ability to crosstalk with host cells (13). Some common patterns of gene expression, protein levels, and signaling pathway activation have been identified in cells that colonize the brain. For example, factors involved in Notch signaling (notch1 and jagged-2) are expressed in melanoma cells with a pro-brain metastasizing phenotype (14). *Note that MDA-MB-435 cells were used in this study and erroneously classified as breast cancer cells* (15). Additionally, Il-1β is expressed in BMs from MDA-MB-231 breast cancer cells; this factor activates astrocytes to produce jagged-1, which activates Notch signaling in the tumor cells (16). Indeed, inhibition of Notch signaling in these cells reduces BMs in mice, suggesting that this may have a potential therapeutic benefit in humans (17).

In addition to its roles in cell development and communication, Notch has recently been recognized as a regulator of metabolism. Specifically, Notch regulates hepatocyte gluconeogenesis through *FOXO1*, hepatocyte lipogenesis through mTORC1 stabilization, and adipocyte thermogenesis through *HES1* activation (18). Though tissue-specific differences in metabolism must be accounted for, it would be worth investigating whether Notch plays similar metabolic roles in brain tissue. Furthermore, the influence of signal pathway crosstalk on metabolism offers potential biological insights. Studies have shown that cell cycle control genes and Wnt signaling are upregulated in BMs (19). In endothelial cells from rat brains, the Wnt/β-catenin pathway interacts with the Notch pathway to increase the amount of monocarboxylic acid transporter 1 (MCT1) protein (20). MCT1 promotes pyruvate export and cell proliferation and is upregulated in glycolytic cancer cells, therefore MCT1 inhibitors block proliferation and may be useful cancer therapeutics (21).

The propensity of a tumor cell to metastasize to the brain depends on its cancer subtype. This phenomenon is the outcome of varied molecular signatures of gene/protein/receptor expression associated with different subtypes. For example, normal brain cells express heregulin, which increases the migration of cells expressing human epidermal growth factor receptor 2 (HER2) and HER3, suggesting that overexpression of these receptors provides a

brain-metastatic advantage (22). Additional factors that favor metastatic colonization of the brain include amplification of epidermal growth factor receptor (EGFR), specifically in triple negative breast cancer (TNBC), HER2+ breast cancer, and *EGFR*-mutant lung cancer patients (23, 24). Amplification of EGFR is often associated with loss of phosphatase and tensin homolog (PTEN), a negative regulator of downstream EGFR effectors. Specifically, BMs are associated with downregulation of PTEN mRNA, allelic imbalance (differential expression of two alleles) at PTEN loci, and PTEN mutations (25). EGFR signaling activates the phosphoinositide 3-kinase (PI3K)/Akt pathway (Figure 1A), which promotes cell survival and proliferation and regulates c-Myc to facilitate metabolic reprogramming (26). Specifically, c-Myc activates enzymes involved in the pentose phosphate pathway, glutamine metabolism, and glycolysis, while reducing pyruvate flux into the citric acid cycle (Figure 1B). Together, these changes promote the Warburg effect, shifting cancer cells towards a more glycolytic state. Because these pathways support metabolic reprogramming and tumor growth, many involved factors are valuable therapeutic targets. Because signaling pathways are interconnected, simultaneous targeting of multiple pathways may be required for efficacious antitumor activity.

Adapting to the Brain Microenvironment

Crosstalk also occurs between cancer cells and other cells in the brain. This crosstalk can be indirect, through signaling pathways, or direct, through physical contact between cells. Both astrocytes and microglia inadvertently promote cancer growth through such interactions. For example, melanoma cells use gap junctions to hijack the neuro-protective function of reactive astrocytes to avoid chemotherapy-induced apoptosis (27). In addition, breast cancer cells secrete Il-1β, which activates nearby astrocytes (16). Once activated, astrocytes secrete factors that promote cancer cell proliferation, migration, and survival; such oncogenic signals include TGFβ, interleukins, cytokines, chemokines, MMP2, MMP9, and Wnt (28–31). Astrocytes also induce the loss of PTEN through the release of exosomes containing miRNAs that inhibit PTEN expression (32). Loss of PTEN increases the level of chemokine C-C motif ligand 2 (CCL2), which recruits myeloid cells that promote tumor outgrowth in the brain (Figure 2). Therefore, interactions between malignant and host cells in the brain perpetuate cancer growth. Blocking these interactions may inhibit brain metastasis.

In addition to signaling pathway similarities, metastatic cancer cells share certain metabolic characteristics with neuronal cells. In the brain, cancer cells adapt to utilize endogenous substrates for metabolism. For example, neurons typically catabolize gamma-aminobutyric acid (GABA) to create NADH to support biosynthetic processes. Previous studies on breast-to-brain metastases have shown that breast cancer cells with a GABAergic phenotype possess a strong growth advantage in the brain by converting GABA to succinate to augment the citric acid cycle (33). Thus, metastatic cells with neuron-like properties thrive in the brain microenvironment. Additionally, acetate is commonly metabolized by both primary brain cancers and BMs from melanoma, breast, and lung cancer (34). The ability to use acetate in addition to glucose as a carbon and energy source provides greater metabolic flexibility to these cells. Despite their origin or subtype, these common metabolic adaptations provide an advantage for rapid cancer growth in the brain.

Many metabolites and metabolic enzymes correlate with tumor invasiveness and may serve as indicators of disease progression. For example, glutamine metabolism is altered in lung cancer and in melanoma (35, 36). In addition, glutamine and lactate are associated with breast cancer proliferation and invasiveness, and enzymes involved in lipolysis support cancer growth and metastasis (37). Lipolysis creates lipid signaling messengers that affect a variety of cellular processes. In particular, oncogenic lipid signaling supports the metastasis of breast cancer cells to the brain by promoting cell survival, migration, and invasion (37). Key enzymes in lipolysis include monoacylglycerol lipase (MAGL) and alkylglyceronephosphate synthase (AGPS). Inhibition of MAGL or AGPS decreases the metastatic potential of breast cancer cells and reduces tumor growth and invasiveness (37, 38). Therefore, enzymes involved in lipid metabolism may be targeted to prevent the formation of BMs.

Breast-to-Brain Metastases

Improved treatment of primary tumors has increased the observed frequency of breast cancer metastases to secondary sites, including the brain. For example, HER2+ breast cancer patients treated with trastuzumab show a higher incidence of breast-to-brain metastasis (39). This issue is twofold: 1) primary disease is better controlled so patients are living longer, allowing time for metastasis to occur; and 2) the blood-brain barrier (BBB) protects tumor cells from most targeted therapies. Breast cancer commonly metastasizes to the bone, lung, and brain (40). Preference for metastatic sites is determined by many factors, including proximity to the primary tumor site, immune protection from the BBB, and breast cancer subtype. For example, luminal (especially ER+) and HER2+ breast cancers primarily metastasize to the bone, though 15.4% of luminal and 28.7% of HER2+ breast cancers metastasize to the brain (41). While basal subtypes prefer the lung, 10.9% of basal-like and 7.2% of TN non-basal-like breast cancers metastasize to the brain (19, 41). Thus, the subtype of the primary breast cancer affects future disease progression. This suggests an important link between gene expression patterns and metastasis of breast cancer. Further detailed examination of pro-metastatic genes in these subtypes may reveal additional metabolic mechanisms supporting breast-to-brain metastasis.

Metabolic phenotypes vary between different breast cancer subtypes. For example, luminal subtypes exhibit reverse-Warburg/null phenotypes that are metabolically inactive, while TNBC/basal-like subtypes exhibit Warburg/mixed phenotypes that are metabolically active (42). Because metabolically active tumors are typically more aggressive, metabolic status may predict disease progression and the likelihood of metastasis. Due to an elevated metabolism, TNBC and TNBC-derived BMs may benefit the most from metabolic intervention therapies.

The metabolic state of a cell is regulated by a variety of molecular mechanisms. In TNBC, metabolic dysregulation is driven by factors such as glutathione S-transferase Pi 1 (GSTP1), forkhead box O 3a (FOXO3a), and EGFR-induced c-Myc (43–45). Specifically, c-Myc represses thioredoxin-interacting protein (TXNIP), an inhibitor of glycolytic gene expression and glucose uptake (46). Recent work has identified TXNIP as a suppressor of breast cancer metastasis, which strengthens the mechanistic link between metabolism and

metastasis (47). *MYC* amplification is acquired during the metastatic process (48). Therefore, c-Myc-induced TXNIP inhibition drives glycolytic metabolism and provides a metastatic advantage to breast cancer cells (Figure 3). As certain types of TNBC are also sensitive to kinase inhibitors, a combination of kinase inhibitors with drugs targeting these metabolic differences may promote synthetic lethality (49). Due to certain molecular similarities between BMs and their tissue of origin, these therapies may also benefit TNBC-derived BMs. Cancer subtypes must be accounted for during drug development because they affect drug response and overall survival in patients.

Lung-to-Brain Metastases

Lung cancer is divided into two major groups: non-small cell lung carcinoma (NSCLC) and small cell lung carcinoma (SCLC). Around 20–40% of patients with NSCLC develop BMs, and the adenocarcinoma subtype is generally more invasive than the squamous cell carcinoma subtype (50). Despite its less metastatic nature, squamous cell carcinoma exhibits an elevated glucose metabolism due to impaired blood vessel growth and tumor hypoxia (51). Therefore, it is important to evaluate metabolic state concurrently with other phenotypic and prognostic markers when assessing metastatic potential. NSCLC often harbors mutant LKB1, a kinase that activates the energy sensor AMPK, thus rendering tumors sensitive to metabolic stress (52). Mutations in *LKB1* and *KRAS,* which are commonly associated, correlate with the formation of BMs in NSCLC patients (53). Therefore, patients with LKB1-mutant BMs may respond well to metabolic-targeted therapeutics.

SCLC is an aggressive disease that presents at advanced stages and leads to brain metastases in 80% of cases (54). In SCLC, a highly active metabolic phenotype, as assessed by volumetric metabolic parameters in FDG-PET imaging, correlates with poor prognosis (55, 56). Parameters assessed include metabolic tumor volume, total lesion glycolysis, and average standardized FDG uptake. Together, these parameters provide critical metrics for clinicians to interpret the metabolic phenotypes of tumors for the diagnosis of clinical stage and expected survival. Molecular characteristics observed in SCLC include c-Kit overexpression, EGFR mutation, VEGF overexpression, constitutively active PI3K, PTEN mutation, and Myc overexpression (57). These molecular abnormalities represent potentially actionable targets for drug development to treat aggressive SCLC.

Melanoma-to-Brain Metastases

Although melanoma accounts for a small percentage of skin cancers, it has the worst prognosis. Almost 45% of stage IV melanomas metastasize to the brain, and only 10% of these patients respond to systemic chemotherapy (58). Melanoma is often associated with *BRAF* mutations, which drive malignancy and have been targeted by successful therapeutics such as Vemurafenib and Dabrafenib (59). Melanoma cells that exhibit neuronal-like phenotypes such as glutamate and calcium signaling during early metastatic growth possess a brain-colonizing advantage (60). In addition, loss of claudin 1, a factor in tight junctions that interacts with endothelial cells in the brain, promotes melanoma-to-brain metastasis (61). Together, this suggests that both direct and indirect interactions with the

microenvironment foster colonization of metastatic melanoma in the brain. Exposure of melanoma cells to the micro-environmental factor S100A4 causes a Warburg-like shift in metabolism, which promotes an invasive, malignant phenotype (62). In addition, metastatic melanoma cells exhibit increased oxidative phosphorylation, glutaminolysis, and β-oxidation compared to non-metastatic cells (63). Upregulation of these pathways supports rapid proliferation and invasiveness, demonstrating an additional link between metabolic reprogramming and metastasis.

Implications for Therapeutics

Currently, patients with BMs are treated by surgical resection or radiation. Radiation is targeted to the entire brain (whole brain radiation therapy, WBRT) or to a specific area of the brain (stereotactic radiotherapy). Though radiation may cause potential side effects such as cognitive impairment and radionecrosis of exposed brain tissue, resection followed by WBRT offers acceptable control of local disease (64). Treatment planning depends on the size, location, and number of metastases. Systemic therapy is still beneficial to many patients because it controls primary disease. Clinical trials have shown that some agents, such as anti-HER2 therapy in breast-BMs and anti-EGFR therapy in lung-BMs, provide benefits to a small subset of patients (65–67). However, the lack of response in the majority of patients may be attributed to poor drug distribution in the brain or acquired drug resistance of BMs (68, 69). Therefore, these therapies are not sufficient to treat the majority of patients with BMs.

Metabolic alterations observed in BMs offer potential targets for new therapeutics. However, because normal brain cells use the same metabolic pathways as BMs it is important to account for the potential off-target toxicities of metabolic-targeted therapeutics. Some metabolic interventions already show minimal toxicity profiles. For example, the treatment of cancer cells with dichloroacetate, an inhibitor of mitochondrial pyruvate dehydrogenase kinase, “normalizes” glucose oxidation, making the cancer cells susceptible to apoptosis while normal cells are unaffected (70). Dichloroacetate is also well tolerated in mice and in humans (71, 72). For more hazardous compounds, toxicity may be reduced by identifying mutations or unique isoforms of receptors, enzymes, or signaling proteins that are specific to tumor cells. Such targeted therapeutics should exhibit limited off-target toxicity. In general, side effects must be minimized for treatments to be worthwhile.

Experimental drug delivery methods combined with metabolic targets may provide needed advances in the treatment of BMs. Many delivery methods take advantage of endogenous transport pathways across the BBB (Figure 4). Methods in development include drug-loaded nanoparticles and liposomes, which accumulate in areas of leaky vasculature via the enhanced permeability and retention (EPR) effect (73). In addition, upregulation of the receptors for transferrin, insulin, and folate allow for receptor-mediated transcytosis of drugs conjugated to receptor ligands (74, 75). For example, transferrin-conjugated liposomes have been use to enhance the *in vivo* uptake and efficacy of 5-fluorouracil in brain tissue (76). Instead of traditional chemotherapeutic agents, these methods could be used to deliver drugs that target specific metabolic enzymes. However, many of these new delivery methods

remain in preclinical testing and will require extensive evaluation before treatment of patients with BMs in the clinic.

Conclusion

In conclusion, brain metastasis remains a growing health concern as treatment of primary tumors improves. The seclusion of the brain behind the BBB protects cancer cells from many chemotherapeutic agents and complicates treatment options. Further analysis of the differences between primary cancer subtypes and their matched BMs is necessary to develop molecular signatures and diagnosis-specific therapeutics. Cancer cells that metastasize are highly adaptable, and those able to mimic neuronal patterns of gene and protein expression, signaling, and metabolism can survive in the brain microenvironment. New therapies are needed to target factors unique to brain metastatic cells in order to enhance the survival of cancer patients with advanced disease.

Abbreviations

AGPS	Alkylglyceronephosphate synthase
BMs	Brain metastases
BBB	Blood-brain barrier
CCL2	Chemokine C-C motif ligand 2
EGFR	Epidermal growth factor receptor
EPR	Enhanced permeability and retention
ER	Estrogen receptor
FDG	Fluorodeoxyglucose
FOXO3a	Forkhead box O 3a
GABA	Gamma-aminobutyric acid
GSTP1	Glutathione S-transferase Pi 1
HER2	Human epidermal growth factor receptor 2
MAGL	Monoacylglycerol lipase
MCT1	Monocarboxylic acid transporter 1
NMR	Nuclear magnetic resonance
NSCLC	Non-small cell lung carcinoma
PET	Positron emission tomography
PI3K	Phosphoinositide 3-kinase

PTEN	Phosphatase and tensin homolog
SCLC	Small cell lung carcinoma
TXNIP	Thioredoxin-interacting protein
TNBC	Triple negative breast cancer
WBRT	Whole brain radiation therapy
VEGF	Vascular endothelial growth factor

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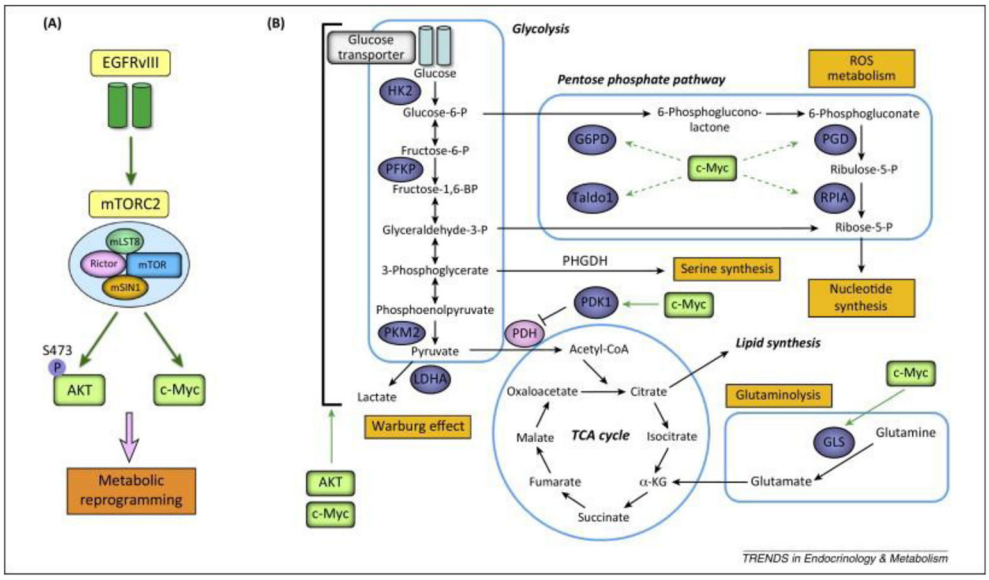

Figure 1. EGFR amplification promotes metabolic reprogramming

A) Amplification of EGFR activates mTORC2, AKT, and c-Myc to promote metabolic reprogramming. EGFR variant III is shown as a representative mutation causing EGFR activation because it is commonly found in glioblastoma and breast cancer (77, 78). B) AKT and c-Myc (in green) activate enzymes (in blue) involved in glycolysis, the pentose phosphate pathway, and glutamine catabolism to supply energy and macromolecules to rapidly proliferating cancer cells.

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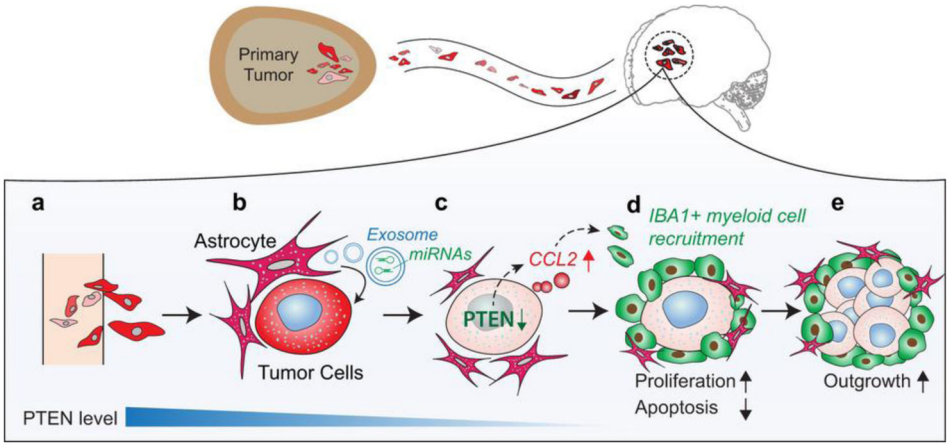

Figure 2. Interactions between astrocytes and tumor cells support tumor growth

A) Circulating tumor cells extravasate in the brain. B) Astrocytes (in pink) release exosomes containing miRNAs that reduce PTEN expression in nearby tumor cells. C) Loss of PTEN results in release of the chemoattractant CCL2. D) CCL2 recruits IBA1+ myeloid cells (in green), which promote tumor cell proliferation and reduce apoptosis. E) The myeloid cells support tumor outgrowth in the brain.

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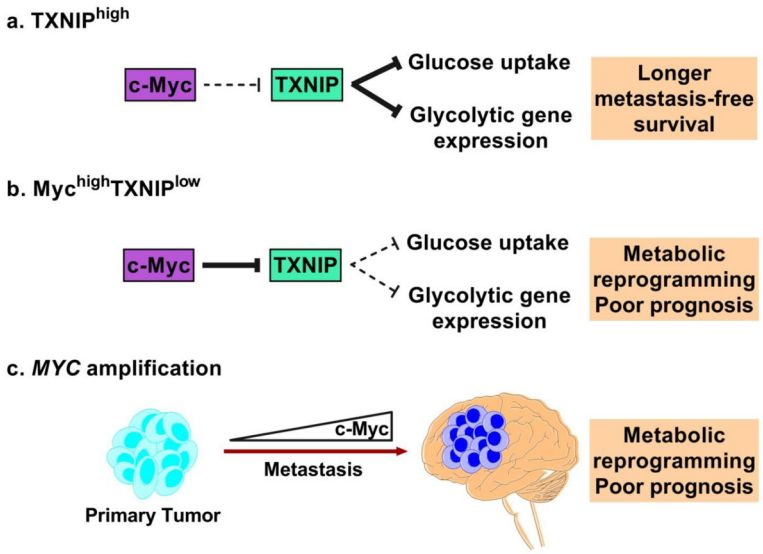

Figure 3. Potential role of c-Myc in metabolic dysregulation

A) Thioredoxin-interacting protein (TXNIP) typically inhibits glucose uptake and glycolytic gene expression. High TXNIP expression is associated with longer metastasis-free survival (46). B) $Myc^{high}TXNIP^{low}$ signature is associated with metabolic reprogramming and poor prognosis in TNBC patients through reduced glucose uptake and glycolytic gene expression. C) *MYC* amplification is acquired during the metastatic process, which supports a general mechanism of metabolic dysregulation in BMs. This results in an aggressive, glycolytic tumor with a poor prognosis.

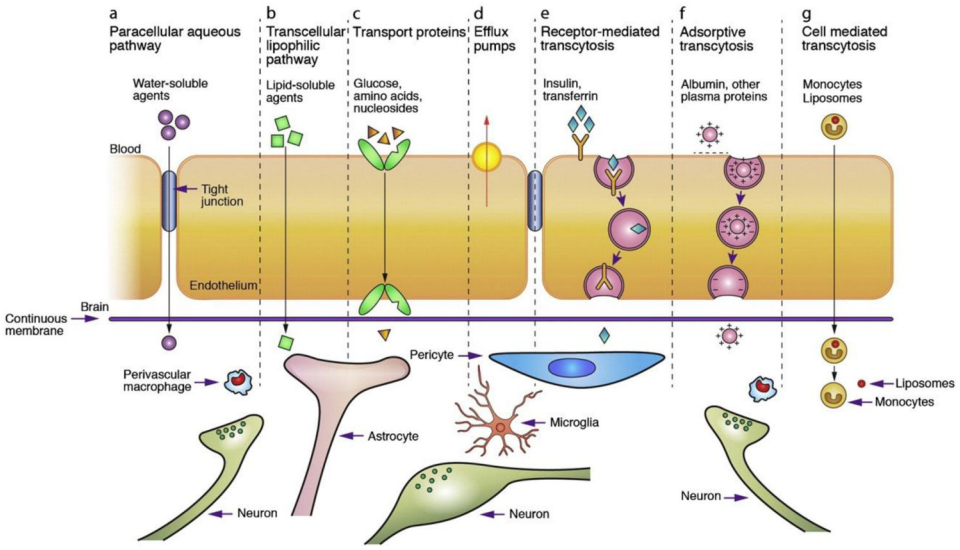

Figure 4. Methods of transport across the BBB and potential drug delivery routes

A–D) Common transport routes for solute molecules that are needed for normal brain metabolism. E–G) Transport routes that can be hijacked to deliver drugs to the brain. Drugs can be conjugated to insulin, transferrin, or albumin or loaded into liposomes, nanoparticles, or immune cells to utilize transcytosis pathways.

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