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Neural–Tumor and Microenvironmental Interactions in Brain Metastases from Lung Cancer: From Blood–Brain Barrier Traversal to Adaptation within the Brain

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Abstract: ***Brain metastases from lung cancer do not merely reflect passive tumor growth after entry into the central nervous system. Rather, their development is a dynamic process involving transvascular entry into the brain, remodeling of the intracranial microenvironment, metabolic adaptation, and changes in neural function. Advances in single-cell and spatial omics, electrophysiology, and functional models have increasingly clarified the interactions between lung cancer cells and host cells in the brain. Current evidence indicates that brain metastasis is associated with the selection of specific malignant cell states and is shaped by the brain vascular endothelium and blood–brain barrier integrity. Once within the brain, astrocytes, microglia, oligodendrocytes, and adaptive immune cells collectively shape the metastatic niche through signaling, metabolic exchange, and spatial organization. Local nutrient availability and metabolites such as lactate, cholesterol, and other lipids further influence tumor cell survival and growth. Neural adaptation differs markedly across lung cancer subtypes. In small-cell lung cancer (SCLC), more direct evidence supports intrinsic electrical excitability and functional neuron–tumor interactions, whereas evidence in non-small-cell lung cancer (NSCLC) remains centered on neural-like transcriptional states and neurotransmitter-related signaling; whether comparable functional neural connections are a general feature of NSCLC remains unclear. Overall, lung cancer brain metastasis is best viewed as a multilayered adaptive process involving tumor cell states, the brain vasculature, glial and immune microenvironments, metabolism, and neural signaling. Future studies should define the temporal and causal relationships among these mechanisms and establish their generalizability and translational relevance across lung cancer subtypes and patient populations.***

Keywords: Cancer neuroscience, Lung cancer, Brain metastasis, Neuron–tumor interaction, Brain microenvironment, Glial cells, Metabolic adaptation.

1. Introduction

Brain metastases are among the most common intracranial malignancies in adults, and lung cancer is one of the leading primary malignancies giving rise to brain metastases. Their development is not simply a continuation of tumor growth after dissemination to the brain; rather, it is shaped jointly by metastatic cell-intrinsic properties and the distinctive host environment of the brain. The classic “seed and soil” concept emphasizes organ selectivity in metastasis. More recently, cancer neuroscience has broadened this view: the brain is not a passive metastatic “soil.” Neurons, glial cells, the brain vasculature, and the local metabolic environment can all influence metastatic cell survival and adaptation, while tumor cells can in turn reshape local neural and microenvironmental states [1]. Brain metastasis is therefore better understood as a dynamic process of reciprocal interaction between tumor cells and the brain microenvironment.

Brain metastases from lung cancer provide an important model for studying organ-specific adaptation. To establish brain metastases, lung cancer cells must disseminate from the primary tumor, interact with the cerebral vasculature, cross the blood–brain barrier, and then adapt to cellular and metabolic conditions that differ markedly from those at the primary site. In recent years, studies using single-cell and spatial omics, organoid models, electrophysiological approaches, and animal models have increasingly revealed links among tumor cell states, glial and immune responses, metabolic reprogramming, and neural signaling. However, the strength and type of evidence vary considerably across studies, and important differences also exist among histological subtypes of lung cancer. This is particularly evident for neural mechanisms. More direct evidence supports electrical excitability and functional neuron–tumor interactions in SCLC, whereas evidence in NSCLC is currently derived mainly from neural-like transcriptional states and neurotransmitter-related signaling. Grouping these molecular, omics-based, and functional findings under a single framework of “neuralization” may therefore obscure important differences among lung cancer subtypes and experimental systems.

Based on the available evidence, this review focuses on the processes by which lung cancer cells enter and adapt to the brain environment. We first summarize malignant cell states associated with brain metastasis and their interactions with the neurovascular unit, and then discuss the roles of astrocytes, microglia, oligodendrocytes, adaptive immunity, and the local metabolic environment in the establishment and maintenance of brain metastases. We further review current evidence regarding neurotransmitters, electrical activity, and functional neuron–tumor interactions. On this basis, we distinguish among different lung cancer subtypes and levels of evidence and integrate findings related to the brain vasculature, glial and immune microenvironments, metabolism, and neural

signaling, with the aim of providing a more systematic understanding of brain adaptation in lung cancer and its potential translational implications.

2. Organ-Specific Entry and Adaptation of Lung Cancer Brain Metastases

2.1 Blood–Brain Barrier Traversal and the Premetastatic Niche

The entry of lung cancer cells into the brain does not depend solely on structural disruption of the blood–brain barrier (BBB), but also involves interactions between specific tumor cell states and the neurovascular unit. Studies have shown that CD44+ lung adenocarcinoma stem cells can differentiate into pericyte-like cells and activate Wnt7-β-catenin signaling through GPR124, thereby enhancing transendothelial migration across the brain endothelium. After entering the brain parenchyma, these pericyte-like cells can reacquire tumor-initiating characteristics. Targeting the pericyte-like cells, GPR124, or related signaling pathways can reduce the formation of brain metastases [2]. These findings suggest that specific tumor cell states may contribute both to transvascular entry into the brain and to subsequent intracranial adaptation.

Other mechanisms involved in tumor–brain endothelial interactions have also been identified under different tumor cell states. MSLN can promote MET expression and activation through JNK signaling, disrupt endothelial tight junctions, and enhance the transendothelial extravasation of NSCLC cells. In animal models, targeting MSLN or MET reduced brain metastasis and prolonged survival [3]. In cisplatin-resistant NSCLC cells, RGS2 is upregulated and enhances tumor cell adhesion to the brain endothelium and BBB traversal through caspase-1/IL-1β signaling, accompanied by increased endothelial VCAM-1 expression and reduced Claudin-5 expression. Genetic or pharmacological inhibition of caspase-1 can reverse these phenotypes [4]. These findings further indicate that different tumor cell states and treatment backgrounds may influence tumor–brain endothelial interactions through distinct mechanisms.

Studies of S100A9 provide another perspective on the relationship between tumor cell states and alterations in the brain microvascular barrier. USP33 increases S100A9 stability by inhibiting its K48-linked ubiquitination and degradation and further promotes vimentin expression and extracellular secretion. Lung adenocarcinoma cells with high S100A9 expression are associated with decreased levels of ZO-1, Occludin, and Claudin-5 in brain microvascular endothelial cells, together with increased oxidative stress, endothelial-to-mesenchymal transition, and impaired barrier function [5]. These findings further link the USP33-S100A9-associated tumor cell state to functional alterations in the brain microvascular endothelium.

In addition to direct interactions between tumor cells and the neurovascular unit, remodeling of the brain microenvironment may begin before tumor cells actually reach the brain. In vitro studies have shown that exosomes derived from H1299 lung cancer cells can induce astrocyte apoptosis and alter the expression profiles of cytokine- and metabolism-related proteins [6]. These findings suggest that tumor-derived exosomes may contribute to the formation of a premetastatic niche in the brain. However, current evidence is derived mainly from in vitro studies, and the temporal sequence of this process during brain metastasis in vivo, as well as its relevance in patients, remains to be clarified.

Successful brain colonization also requires metastatic cells to survive after extravasation and exploit the local vasculature. Brain-metastatic cells from lung and breast cancer can express plasminogen activator (PA)-inhibitory serpins, including SERPINB2 and SERPINI1, which reduce plasmin generation. By limiting plasmin-mediated death signaling and preserving L1CAM, these serpins facilitate vascular co-option along pre-existing brain capillaries and support early metastatic outgrowth [7].

2.2 Single-Cell and Spatial Omics Reveal Cellular States and Microenvironmental Heterogeneity

Single-cell and spatial omics studies have revealed substantial heterogeneity in both malignant cells and the host microenvironment of lung cancer brain metastases. Cross-organ single-cell analyses have shown that, compared with primary tumors, metastatic lung adenocarcinoma exhibits altered malignant cell differentiation states, together with an increased proportion of monocyte-derived myeloid cells, a reduction in tissue-resident cells, and features of T-cell exhaustion [8]. Spatial transcriptomic studies have further demonstrated marked spatial differences among the tumor core, tumor immune microenvironment, and adjacent brain tissue in NSCLC brain metastases. These differences include reduced antigen-presentation and B/T-cell-related functions, as well as increased M2-like macrophages, neutrophils, immature microglia, and reactive astrocytes [9]. These findings indicate that lung cancer brain metastasis involves not only changes in malignant cell states but also extensive remodeling of multiple host and immune cell populations within the brain.

With respect to tumor cell states, Tagore et al. performed single-nucleus RNA sequencing, T-cell receptor sequencing, single-cell spatial analysis, and whole-genome sequencing on untreated primary NSCLC tumors and brain metastases. Chromosomal instability emerged as a prominent feature of brain metastasis samples, and a recurrent CIN-high neural-like malignant cell subpopulation was identified. This subpopulation was already detectable in primary tumors but was markedly enriched in brain metastases [10]. Clonal and pseudotime analyses have also identified a brain metastasis-associated epithelial cell population with high S100A9 expression in lung adenocarcinoma, leading to the development of a BM-index to characterize cell states associated with brain metastasis [11]. These studies suggest that lung adenocarcinoma brain metastasis may involve the selective enrichment of distinct malignant cell states. However, the CIN-high neural-like state is currently supported mainly by transcriptional and spatial omics evidence and should not be equated with the functional neuron–tumor interactions demonstrated by electrophysiological and other functional experiments in SCLC. Likewise, the CIN-high state, the S100A9-high state, and the USP33-S100A9-related mechanism were identified in

different studies and experimental systems and therefore cannot currently be regarded as consecutive events within a single validated cellular lineage.

Beyond malignant cells, other single-cell studies have further demonstrated differences in myeloid, lymphoid, stromal, and vascular components of the brain metastatic microenvironment. A direct comparison between gliomas and lung cancer brain metastases showed that microglia, macrophages, endothelial cells, and CD8+ T cells in lung cancer brain metastases can display varying degrees of immunosuppressive states. The study also identified macrophage subpopulations associated with poor prognosis, epithelial cell populations with high chromosomal instability, and cellular interactions related to angiogenesis [12]. Another single-cell study comparing primary lung adenocarcinoma with brain metastases found reduced T/NK cells and mast cells in brain metastatic lesions, together with enrichment of macrophage subpopulations with prometastatic features, myofibroblast-like cancer-associated fibroblasts, and angiogenesis-related characteristics. The study further suggested that DDIT4 may participate in remodeling of the brain metastatic microenvironment [13]. However, some of these conclusions were derived primarily from transcriptional features and bioinformatic inference, and the specific role of DDIT4, as well as the functional interactions among different cell populations, requires further experimental validation.

The molecular background of the tumor may also be associated with differences in the immune microenvironment of brain metastases. Comparisons among lung adenocarcinoma brain metastases with different driver alterations have shown that EGFR- or ALK-positive brain metastases generally exhibit lower levels of CD8+ T-cell infiltration. EGFR-positive tumors tend to be associated with increased Treg infiltration, whereas ALK-positive tumors are more frequently associated with increased M2-like macrophages [14]. These findings indicate that the cellular and immune states of lung cancer brain metastases are not uniform but may instead be jointly shaped by tumor-intrinsic characteristics and the local brain microenvironment.

These changes in cellular states and the microenvironment do not occur in isolation. Existing evidence suggests that alterations in cholesterol metabolism may simultaneously affect EGFR stability in tumor cells, BBB integrity, and microglial states [15], indicating that adaptive processes involving tumor cells, the brain vasculature, and host cells may be metabolically interconnected. Therefore, the cellular heterogeneity revealed by single-cell and spatial omics should be interpreted in the broader context of vascular interactions, metabolism, and intercellular communication. The relevant metabolic mechanisms are discussed further below.

3. Astrocytes and the Brain Metastatic Microenvironment: Functional Heterogeneity and Intercellular Crosstalk

Once tumor cells enter the brain, astrocytes become a major host-cell component of the metastatic microenvironment. Current evidence suggests that astrocytes do not exert uniformly tumor-promoting or tumor-suppressive effects; rather, their functions vary with activation state and local context. Studies have implicated astrocytes in blood–brain barrier regulation, formation of the metastatic niche, immune and metabolic remodeling, tumor cell protection, and treatment resistance, and have further suggested that pSTAT3+, Jagged1+, and PDGFRβ+ reactive astrocytes may represent functionally distinct states [16]. The role of astrocytes in brain metastasis should therefore be interpreted in relation to their specific phenotype, disease stage, and interactions with tumor cells, immune cells, and the brain vasculature.

3.1 Bidirectional Tumor–Astrocyte Interactions Mediated by Inflammatory Factors

Early co-culture studies showed that lung cancer cells can release factors such as MIF, IL-8, and PAI-1 to activate astrocytes. In turn, activated astrocytes can secrete IL-6, TNF-α, and IL-1β and promote the proliferation of multiple lung cancer cell lines [17]. These findings demonstrate that lung cancer cells and astrocytes can engage in bidirectional signaling through inflammatory mediators and also indicate that the presence of reactive astrocytes should not be interpreted simply as a host antitumor response.

3.2 Reactive Astrocyte States and Their Interactions with Tumor Cells

In brain metastases arising from multiple primary tumor types, pSTAT3+ reactive astrocytes can be observed around metastatic lesions. Genetic or pharmacological inhibition of STAT3 activity in astrocytes reduces established brain metastases and is accompanied by changes in the local innate and adaptive immune microenvironment. In patient samples, higher astrocytic STAT3 activity is also associated with poorer clinical outcomes [18]. These findings suggest that specific reactive astrocyte states may contribute to the maintenance of established brain metastases and remodeling of the local microenvironment.

Direct intercellular communication provides another mechanism by which astrocytes support brain metastasis. Breast and lung cancer cells can use PCDH7 to promote the formation of Cx43-containing gap junctions with astrocytes, allowing transfer of cGAMP into astrocytes and activation of STING-dependent inflammatory signaling. Astrocyte-derived paracrine factors then activate STAT1 and NF-κB signaling in metastatic tumor cells, promoting tumor growth and chemoresistance [19].

In SCLC brain metastasis, astrocytes can also support tumor growth through a distinct mechanism. Tumor-derived Reelin recruits astrocytes, which subsequently secrete SERPINE1 and other factors associated with neuronal survival, thereby promoting SCLC growth. Human cortical organoid–SCLC assembloids and animal models both provide experimental support for this intercellular interaction [20]. This suggests that SCLC may exploit cell–cell signaling programs related to brain development to adapt to the intracranial environment.

3.3 Neurotransmitter-Related Signaling and Astrocyte Interactions

Astrocytes may also link neurotransmitter signaling in the

brain to tumor cell adaptation. Astrocyte-derived Wnt-5a can induce mGluR1 expression in lung cancer cells through the PRICKLE1/REST axis. Under glutamate-dependent conditions, mGluR1 interacts with EGFR and maintains its stability, subsequently activating ERK signaling and rendering brain-metastatic cells dependent on mGluR1 signaling [21]. These findings suggest that astrocytes can connect glutamatergic signaling in the brain with receptor remodeling in lung cancer cells, thereby promoting adaptation to the brain microenvironment.

In NSCLC, downregulation of FOXA2 and ABAT is associated with GABA accumulation, which can further activate NF-κB and alter astrocyte states, thereby creating a microenvironment favorable for brain colonization [22]. This finding further indicates that neurotransmitter signaling, metabolic reprogramming of tumor cells, and astrocyte responses may be interconnected.

3.4 Lactate-Mediated Metabolic Sensing and Extracellular Vesicle Feedback

Astrocytes can also sense metabolites released by tumor cells and subsequently influence tumor cells through extracellular vesicles. In a cohort of 66 patients with NSCLC brain metastases, greater astrocytic infiltration was associated with shorter overall survival. Mechanistic studies showed that tumor-derived lactate can be taken up by astrocytes through MCT1-mediated transport and induce changes in astrocyte state. These astrocytes then release extracellular vesicles enriched in miR-8085, which enter tumor cells, downregulate TRIM67, stabilize ELK1, and enhance tumor stemness. In patient samples, low TRIM67 and high ELK1 expression were likewise associated with poorer survival outcomes [23]. These findings reveal a bidirectional communication loop initiated by a tumor-derived metabolite and propagated through astrocyte-derived extracellular vesicles, providing a mechanistic basis for metabolic crosstalk within the brain metastatic microenvironment.

3.5 GAS6/AXL-Related Signaling and Interactions with the Vascular Microenvironment

The role of astrocytes can also extend to the vascular microenvironment associated with brain metastasis. Studies have shown that reactive astrocytes secrete GAS6 and activate AXL in tumor cells, inducing brain metastatic stem cells to acquire a CD146+ pericyte-like phenotype. CD146 can increase VEGF transcription in tumor cells and can also serve as a coreceptor for VEGFR2 on endothelial cells, thereby enhancing VEGFR2 stability and sensitivity. This establishes a cross-cellular interaction among astrocytes, tumor cells with pericyte-like properties, and endothelial cells. In animal models, targeting CD146 or AXL produced stronger antiangiogenic effects than VEGF blockade alone [24]. These findings suggest that astrocytes may contribute to vascular alterations in lung cancer brain metastases through interactions with both tumor cells and endothelial cells.

4. Microglia, Adaptive Immunity, and Oligodendrocytes: Immune Heterogeneity and Metabolic Crosstalk

4.1 Functional Heterogeneity and Immunometabolic Features of Microglia

Similar to astrocytes, microglia do not play a uniform role in lung cancer brain metastasis. Early pathological and in vitro studies showed marked activation and accumulation of microglia around lung cancer brain metastatic lesions, whereas their effects on tumor cells varied under different experimental conditions. Higher concentrations of microglia-conditioned medium could induce tumor cell apoptosis, while lower concentrations could instead promote tumor cell survival or growth. In addition, TNF-α was shown to promote the proliferation of some lung cancer cells [25]. These findings indicate that the degree of microglial activation alone cannot be directly interpreted as either antitumor or protumor activity; rather, its specific effects may depend on cellular state, the composition of secreted factors, and the local microenvironment.

In established brain metastatic lesions, single-cell and spatial omics studies have revealed substantial changes in both myeloid and adaptive immune cells, including increased M2-like macrophages, reduced antigen-presentation programs, reduced CD8+ T-cell abundance, and features of T-cell exhaustion. At the microglial level, mechanistic studies have shown that lung cancer cells can activate STAT3 signaling, induce SCD1 expression and lipid droplet accumulation, and reduce microglial responsiveness to inflammatory stimulation. In mouse models, combined treatment with an SCD1 inhibitor and a CSF1R inhibitor reduced brain metastasis [26]. Another study further showed that alterations in cholesterol metabolism can affect the localization of microglial IL-4Rα within lipid rafts and its downstream JAK1/STAT6 signaling. These findings suggest that functional changes in microglia involve not only conventional cytokine and signaling-pathway regulation but are also closely linked to lipid metabolism, membrane receptor localization, and downstream signal transduction.

Overall, current evidence supports interpreting the role of microglia in brain metastasis on the basis of functional state rather than cell number alone. Different driver alterations in lung adenocarcinoma may be associated with distinct T-cell and myeloid-cell compositions[14], indicating that the immune state is not fixed but may be jointly shaped by tumor-intrinsic molecular features and the local brain microenvironment.

4.2 Spatial Heterogeneity of Adaptive and Myeloid Immunity and TLS-Related Features

Building on the functional heterogeneity of microglia, recent single-cell and spatial studies have further shown that immune heterogeneity in lung cancer brain metastases is reflected in distinct immune cell subpopulations and their spatial organization. Single-cell analysis of 101,959 tumor-infiltrating immune cells showed that HSP70-high stress-response T cells and PLTP+ tumor-associated macrophages were relatively enriched in NSCLC brain metastases, whereas memory T cells and cDC2-like dendritic cells were reduced. These immune cell states were associated with poorer responses to immune checkpoint inhibitors (ICIs). The study further developed a seven-gene brain metastasis

immune signature (BMIS), which showed additional predictive value independent of tumor mutational burden across multiple cohorts [27]. These findings indicate that immune heterogeneity in NSCLC brain metastases involves multiple components, including T-cell states, macrophage subpopulations, and dendritic cells, and therefore cannot be adequately summarized simply as increased M2-like macrophages or CD8+ T-cell exhaustion.

At the same time, NSCLC brain metastases may exhibit distinct forms of spatial immune organization with different clinical implications. In 120 surgically resected NSCLC brain metastases, a higher intratumoral tertiary lymphoid structure (TLS) score was independently associated with longer overall survival and intracranial progression-free survival and was also associated with greater benefit from postoperative ICI therapy. The study further observed colocalization of TCF1+CD4+ T cells and microglia within TLS regions and suggested that LTβ/LTβR signaling may contribute to TLS formation. In mouse models, recombinant murine CXCL12 combined with anti-PD-1 therapy enhanced TLS formation and intracranial tumor control in an LTβR-dependent manner [28]. These findings further suggest that the immune microenvironment of brain metastases should not be regarded as uniformly immunosuppressive, as the roles of microglia and other immune cells may also depend on their spatial location and the context of their intercellular interactions.

4.3 Oligodendrocyte Lipid Metabolism and Microenvironmental Crosstalk

In addition to astrocytes and microglia, recent studies suggest that oligodendrocytes may also participate in the metabolic and immune microenvironment of lung cancer brain metastases. Single-cell and spatial transcriptomic analyses have shown changes in fatty acid synthesis-related programs in oligodendrocytes within lung cancer brain metastases. Under hypoxic conditions and after co-culture with metastatic cells, oligodendrocyte fatty acid synthase expression was further increased. The study also found that fatty acids derived from oligodendrocytes could be taken up by tumor cells and macrophages. Oligodendrocyte-conditioned medium increased fatty acid uptake in both tumor cells and macrophages and was accompanied by enhanced tumor cell proliferation and a shift of macrophages toward a FABP4-associated immunosuppressive state [29]. These findings suggest that oligodendrocytes may participate in tumor cell–myeloid cell interactions through lipid metabolism, thereby broadening our understanding of the contribution of glial cells to the brain metastatic microenvironment.

5. Metabolic Adaptation: The Brain Nutrient Environment, Intercellular Crosstalk, and Systemic Metabolic Factors

The glial-cell studies discussed above indicate that metabolic alterations in lung cancer brain metastasis are not restricted to tumor cells themselves. The distinct nutrient availability and metabolic conditions of the brain may also shape the metabolic dependencies of metastatic cells. Studies have shown that serine and glycine are relatively limited in the brain, and brain-metastatic cells may therefore become dependent on PHGDH-mediated de novo serine synthesis to sustain nucleotide synthesis and proliferation. Genetic or pharmacological inhibition of PHGDH selectively suppresses brain metastasis in multiple tumor models while exerting relatively limited effects on extracranial tumors [30]. These findings suggest that nutrient availability at the metastatic site may influence both tumor-cell metabolic dependencies and sensitivity to metabolic intervention.

In addition to nutrient availability, metabolic adaptation in the brain also involves the exchange of metabolites and signals between tumor cells and the host microenvironment. As discussed above, alterations in cholesterol metabolism can simultaneously affect EGFR stability in tumor cells, BBB integrity, and microglial states; tumor-derived lactate can induce astrocytes to further influence tumor cells through extracellular vesicles; and fatty acids derived from oligodendrocytes can be taken up by both tumor cells and macrophages. Together, these findings indicate that metabolic adaptation in brain metastases involves not only tumor-intrinsic metabolic changes, but also metabolic crosstalk with glial cells, myeloid cells, and the brain vascular microenvironment.

Tumor-intrinsic metabolic regulation is also associated with brain metastasis of lung adenocarcinoma. LPCAT1 upregulation has been linked to activation of the PI3K/AKT/MYC pathway, enhanced tumor cell proliferation and invasion, increased brain metastatic potential, and poorer clinical outcomes [31]. In NSCLC, IGF2BP3 stabilizes FASN mRNA, enhances lipogenesis and neutral lipid accumulation, and promotes brain colonization [32]. HMGB3 can recruit SSBP1 and promote its nuclear translocation, accompanied by mitochondrial metabolic remodeling, increased cytoplasmic reactive oxygen species, changes in PTEN/PI3K-AKT signaling, and enhanced epithelial-mesenchymal transition and brain metastasis-associated phenotypes [33]. More recently, brain-derived signals were shown to induce VGF expression in lung adenocarcinoma cells; the VGF-ABHD12B-cardiolipin axis supports mitochondrial fusion, oxidative phosphorylation, and ATP production, thereby facilitating metabolic adaptation and brain colonization [34]. Together, these findings indicate that lipid synthesis and mitochondrial remodeling represent distinct but potentially complementary tumor-intrinsic adaptations to the brain environment.

In addition to the local brain microenvironment, systemic nutritional status may also be associated with lung cancer brain metastasis. In a cohort of 7,628 patients, low body mass index (BMI) was associated with an increased risk of brain metastasis from lung cancer. Mechanistic studies further suggested that a low-BMI state may be accompanied by enhanced ghrelin-GHSR signaling and increased neuronal secretion of neuropeptide Y (NPY). NPY can act through Y5R expressed on tumor cells to alter their metabolic state and promote brain colonization. In experimental models, blockade of Y5R or related interventions suppressed brain metastasis [35]. However, BMI is also influenced by cancer-related wasting, treatment status, and other clinical factors; therefore, the association observed in patient cohorts does not establish a direct causal relationship between low BMI and brain metastasis, and its clinical significance requires further validation.

Overall, evidence from multiple levels, including nutrient availability in the brain, tumor-intrinsic metabolism, glial-cell-associated metabolic crosstalk, and systemic nutritional status, suggests that metabolic factors contribute to the adaptation of lung cancer cells to the brain. However, because these findings are derived from different tumor types, experimental models, and clinical settings, they cannot yet be integrated into a single, sequentially validated metabolic pathway.

6. Neuron–Tumor Interactions: Neural Activity and Bidirectional Functional Communication

The studies discussed above mainly describe transvascular entry, glial and immune microenvironments, and metabolic adaptation in lung cancer brain metastasis. For neural mechanisms, the strength of evidence differs substantially among lung cancer subtypes. Compared with NSCLC, in which neural-like states are currently supported mainly by transcriptional and spatial omics data, more direct electrophysiological and functional evidence is available for SCLC. Importantly, current evidence in SCLC comes from several experimental settings, including primary lung tumors, neuron co-culture systems, and intracranial tumor models. The degree to which individual studies directly support brain metastasis-specific neuron–tumor interactions therefore varies. The following section focuses on functional relationships between neural activity and SCLC cells while preserving these differences in evidentiary strength and experimental context.

6.1 Intrinsic Electrical Excitability of SCLC

Studies of SCLC provide functional evidence linking neural activity to tumor behavior. Neuroendocrine SCLC cells are capable of generating action potentials, and their electrical activity is associated with clonogenic growth, malignant progression, and metastatic potential. These electrically excitable tumor cells also show increased energy demands and greater dependence on oxidative phosphorylation. Non-neuroendocrine SCLC cells can further provide metabolic support to electrically excitable tumor cells [36]. These findings indicate that the neural-like features of SCLC are not limited to neural-associated molecular markers but also include measurable electrophysiological properties, providing a functional basis for investigating the contribution of neural activity to SCLC progression.

6.2 Functional Neuron–Tumor Communication and Neural Activity-Dependent Growth

Further studies have shown that SCLC cells can receive functional neuronal input. SCLC cells respond to NMDA receptor- and GABA_A receptor-mediated signals and exhibit a proliferative advantage when co-cultured with vagal sensory neurons or cortical neurons. In spontaneous SCLC models, inhibition of glutamatergic signaling exerts antitumor effects [37]. Another study showed that vagotomy markedly suppresses the formation and progression of pulmonary SCLC. Within the brain, glutamatergic and GABAergic neural activity can promote SCLC proliferation through both paracrine and synaptic mechanisms, while neural activity-associated membrane depolarization and Ca^{2+} transients are also linked to intracranial tumor growth [38].

The effects of neurotransmitters on SCLC cannot be inferred simply from whether they are considered “excitatory” or “inhibitory” in the mature nervous system. Current evidence indicates that both glutamatergic and GABAergic signaling can contribute to SCLC cell proliferation and tumor growth. This suggests that the effects of neural signaling on tumor cells may depend on receptor type, tumor cell state, and the anatomical context in which the interaction occurs.

6.3 Reciprocal Effects of Tumor Cells on Neuronal Excitability

Neuron–tumor interactions are not unidirectional. Co-culture of SCLC cells with human neurons can enhance neuronal synaptic activity and increase neuronal excitability. Some of the synaptic activity observed in these co-culture systems is sensitive to blockade of AMPA receptors or GABA_A receptors, whereas the NMDA receptor antagonist memantine can attenuate the associated neuronal hyperexcitability [39]. These findings suggest that SCLC cells not only receive neuronal signals but may also alter neuronal synaptic activity and excitability, further supporting bidirectional functional interactions between tumors and the nervous system.

At present, evidence for these reciprocal effects is derived mainly from in vitro neuron co-culture systems. Therefore, these electrophysiological changes cannot yet be directly interpreted as causally related to clinical manifestations such as seizures or cognitive impairment in patients with brain metastases. Their roles in the in vivo brain metastatic environment and their potential clinical significance require further investigation.

7. An Integrated Framework of Neural and Microenvironmental Adaptation in Lung Cancer Brain Metastases

Taken together, current evidence suggests that lung cancer brain metastasis can be understood at several interconnected levels, including tumor cell states, interactions with the brain vasculature, the local host microenvironment, metabolic adaptation, and neural functions. Because these findings are derived from different lung cancer subtypes, experimental models, and research systems, the framework presented below is intended to summarize the major biological dimensions of intracranial adaptation rather than to imply that all brain metastases undergo the same sequence of molecular events.

Lung cancer brain metastasis may involve the selection of specific malignant cell states as well as interactions with the neurovascular unit. The CIN-high neural-like state, the S100A9-high state, and CD44+-associated cell states identified in lung adenocarcinoma studies suggest, from different perspectives, that primary tumors contain heterogeneous tumor cell populations associated with brain metastatic potential. Meanwhile, mechanisms involving GPR124/Wnt7-β-catenin, MSLN/JNK/MET, RGS2/caspase-1/IL-1β, and USP33-S100A9 provide experimental evidence for interactions between tumor cells and brain vascular endothelial cells and for alterations in BBB

integrity. Collectively, these studies indicate that brain metastasis depends not only on the ability of tumor cells to disseminate but also on the compatibility between specific tumor cell states and the brain vascular environment. After entering the brain parenchyma, metastatic cells can also express plasminogen activator (PA)-inhibitory serpins such as SERPINB2 and SERPINI1, thereby suppressing plasmin-related host defenses and preserving L1CAM-mediated vascular co-option, which supports tumor-cell survival and expansion within the brain [7]. Alterations in cholesterol metabolism are also associated with EGFR stability in tumor cells, BBB integrity, and microglial states, further suggesting that adaptation among tumor cells, the brain vasculature, and local host cells may be interconnected.

After entering the brain, tumor cells encounter a complex microenvironment composed of glial cells, immune cells, blood vessels, and local metabolic conditions. Astrocytes participate in processes involving STAT3, Reelin-SERPINE1, GAS6/AXL, and lactate-associated extracellular vesicles. In addition, brain-metastatic cancer cells, including those derived from lung cancer, can use PCDH7 to promote the formation of Cx43-containing gap junctions with astrocytes and transfer cGAMP into astrocytes, thereby activating STING-dependent inflammatory signaling. Astrocyte-derived paracrine factors can subsequently promote tumor growth and chemoresistance [19]. Microglia are involved in SCD1-associated immunometabolic alterations, whereas oligodendrocytes can influence tumor cells and myeloid cells through fatty acid metabolism. Adaptive immune and myeloid cells also display marked functional and spatial heterogeneity. HSP70-high T cells, PLTP+ tumor-associated macrophages, and reduced cDC2 populations are associated with poorer responses to ICIs, whereas intratumoral TLSs characterized by the colocalization of TCF1+CD4+ T cells and microglia are associated with more favorable clinical outcomes and greater benefit from ICI therapy. The brain metastatic microenvironment should therefore not be viewed as uniformly immunosuppressive but interpreted according to specific cellular states and patterns of spatial organization.

Metabolic factors further connect tumor-intrinsic states with the host environment of the brain. Current studies have identified several forms of metabolic adaptation associated with lung cancer brain metastasis, including PHGDH-mediated nutrient dependence; tumor-intrinsic metabolic regulation involving LPCAT1, IGF2BP3-FASN, and HMGB3/SSBP1; and microenvironmental interactions mediated by GABA, NPY, cholesterol, and glial-cell-derived lipids. IGF2BP3 can stabilize FASN mRNA, thereby promoting lipogenesis and neutral lipid accumulation and enhancing the ability of NSCLC cells to colonize the brain [32]. Brain-derived signals can also induce VGF expression in lung adenocarcinoma cells and enhance oxidative phosphorylation and energy production through VGF-ABHD12B-cardiolipin-associated mitochondrial remodeling, suggesting that adaptation to the brain may involve coordinated regulation of mitochondrial structure and energy metabolism [34]. Because these mechanisms have been identified in different experimental systems, they cannot yet be considered components of a single unified metabolic pathway. Nevertheless, they collectively indicate that the metabolic environment of the brain helps shape conditions that support metastatic cell survival and growth.

Neural adaptation differs markedly among lung cancer subtypes. Current studies support the intrinsic electrical excitability of SCLC cells and their ability to receive functional neural input mediated by NMDA and GABA_A receptors. Neural activity-associated membrane depolarization and Ca^{2+} signaling are also linked to tumor growth. However, some of this evidence is derived from primary pulmonary tumors or in vitro co-culture systems, and the extent to which individual findings directly support brain metastasis-specific neural interactions should therefore be interpreted in light of the experimental model. In contrast, current evidence in NSCLC mainly includes CIN-high neural-like transcriptional states and neural signals involving glutamate, GABA, and NPY; this is not yet sufficient to support the widespread formation of functional neuron–tumor synapses comparable to those observed in SCLC. Neural-like transcriptional states, neurotransmitter utilization, and neuron–tumor interactions validated by functional experiments should therefore be regarded as distinct levels of evidence.

Overall, current evidence supports a multilayered view of lung cancer brain metastasis encompassing tumor cell states, brain vascular interactions, glial and immune microenvironments, metabolic adaptation, and neural functions. These levels may intersect and influence one another, but their precise temporal relationships, causal links, and generalizability across patients and lung cancer subtypes remain to be established.

8. Translational Implications and Future Perspectives

8.1 Therapeutic Targets and Biomarkers

Potential therapeutic targets in lung cancer brain metastasis span BBB traversal, metabolic dependencies, glial and immune interactions, and neural signaling. However, most remain supported mainly by mechanistic or preclinical evidence, and their relevance may vary across lung cancer subtypes and experimental models. Candidate biomarkers, including tumor cell states, glial and immune features, metabolic dependencies, and neural-associated signals, likewise require validation in independent and prospective cohorts before clinical application.

8.2 Limitations and Future Directions

Current evidence is limited by the widespread use of cell lines, immunodeficient animals, intracranial implantation models, and surgically selected patient samples, as well as by the scarcity of paired and longitudinal specimens. Evidence for functional neuron–tumor interactions still derives mainly from experimental studies. Future work should combine more physiologically relevant models and longitudinal patient samples with single-cell and spatial omics, electrophysiology, metabolic analyses, and imaging to establish causal mechanisms. Because many candidate targets also contribute to normal brain function, neurological safety, BBB integrity, and cognitive outcomes should be evaluated alongside

antitumor efficacy.

9. Conclusion

Brain metastasis from lung cancer is not a passive process in which tumor cells simply continue to grow after entering the brain. Instead, it is a dynamic process involving tumor cell states, interactions with the brain vasculature, glial and immune microenvironments, metabolic adaptation, and neural functions. Single-cell and spatial omics studies have revealed substantial heterogeneity in both tumor and host cell states, while functional studies further indicate that neurotransmitters, metabolites, and intercellular signals participate in interactions between tumor cells and the brain microenvironment. The strength of evidence for neural mechanisms differs markedly among lung cancer subtypes. In SCLC, more direct evidence supports intrinsic electrical excitability and functional neuron–tumor interactions, although some of this evidence derives from primary pulmonary tumors or in vitro models. In contrast, current evidence in NSCLC remains focused mainly on neural-like transcriptional states and neurotransmitter-related signaling. Neural-like molecular features, neurotransmitter utilization, and neuron–tumor interactions validated by electrophysiological or other functional approaches should therefore not be treated as equivalent or directly extrapolated across lung cancer subtypes.

Overall, current evidence supports viewing lung cancer brain metastasis as a multilayered adaptive process involving continuous interactions among tumor cells, the brain vasculature, glial cells, the immune system, the metabolic environment, and neural signaling rather than as an event driven by a single molecular pathway. Because many proposed mechanisms have been identified in different experimental models and research systems, their temporal relationships, causal links, and generalizability across patients remain incompletely defined. Future studies that combine models more closely reproducing the natural metastatic process, longitudinal paired patient samples, and spatial omics with functional analyses may help identify key mechanisms with robust causal support and translational potential.

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