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Mini Review

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Regional Differences in Brain Tumors: Genetic Drivers and Spatial Molecular Ecology

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Abstract
The human brain exhibits marked regional specialization in cellular composition, gene expression, and tissue architecture. Growing evidence suggests that these spatial differences influence both the anatomical distribution of brain tumors and their subsequent progression. Across tumor types such as gliomas, meningiomas, and brain metastases, specific molecular subtypes frequently show characteristic anatomical distributions, suggesting a functional coupling between tumor genetics and regional brain microenvironments. In this mini review, we summarize recent advances in understanding how regional brain biology shapes the molecular, cellular, and microenvironmental landscapes of brain tumors. This study examines evidence linking anatomical location to tumor genotype, cellular states, and microenvironmental interactions. The study also highlights the emerging concept of "region-aware oncology", in which tumor behavior is interpreted within the anatomical, cellular, and molecular context of the surrounding brain tissue. A deeper understanding of this spatial coupling may improve tumor classification and support the development of region-informed diagnostic and therapeutic strategies.

Keywords:
regional heterogeneity; glioma; brain metastasis; meningiomas; brain tumor

1. Introduction

The human brain is a highly heterogeneous organ composed of numerous anatomically and functionally distinct regions that differ in developmental origin, cellular composition, and regulatory architecture. This regional heterogeneity forms the molecular and cellular basis of diverse neural functions. Recent advances in multi-omics and spatial transcriptomics have begun to define the region-specific molecular architecture of the normal brain, revealing that each brain region has distinct gene-expression profiles, co-expression networks, and signaling environments [1–3].

Mounting evidence suggests that this intrinsic regional diversity may influence brain tumor initiation, evolution, and therapeutic response. Gliomas, meningiomas, and brain metastases exhibit clear spatial preferences: specific mutations and transcriptional programs are enriched in particular anatomical locations. For example, IDH-mutant gliomas frequently arise in the frontal and temporal lobes [4], whereas H3K27M-mutant diffuse midline gliomas commonly arise in midline structures such as the thalamus and brainstem [5]. Similarly, *NF2*-driven meningiomas predominate in the convexity, while *TRAF7–, KLF4–, AKT1–*, and *SMO-altered* variants localize mainly to the skull base [6–8]. These spatial–genetic patterns suggest that tumor genotypes and anatomical environments may be functionally coupled, reflecting possible co-evolution between oncogenic programs and regional brain ecology [9,10].

However, despite increasing recognition of these relationships, a systematic understanding of region-specific tumor biology remains limited. Most studies have focused on individual tumor types or specific brain regions, whereas integrative analyses incorporating developmental lineage, epigenetic regulation, and microenvironmental context remain scarce. Understanding how the regional molecular baseline of the human brain constrains or per-

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mits specific oncogenic pathways could provide new insights into tumor heterogeneity, regional vulnerability, and therapeutic vulnerabilities.

This review summarizes current progress in understanding regional molecular heterogeneity in the normal brain and discusses how these intrinsic differences may shape the genetic, transcriptomic, and microenvironmental landscapes of gliomas, meningiomas, and brain metastases. This study further proposes a "region-aware" framework for oncology, defined by the integration of genetic, spatial, and anatomical information to improve understanding of tumor biology and guide the development of more precise therapeutic strategies. Together, these observations support the concept that brain tumors arise within regionally defined molecular ecosystems, in which anatomical context and oncogenic mutations interact to shape tumor behavior.

2. Literature Search Strategy

Relevant English-language studies were identified through searches of PubMed and Web of Science. Search terms included "brain tumor," "glioma," "meningioma," "brain metastasis," "spatial heterogeneity," and "brain region." Priority was given to recent studies investigating regional molecular characteristics and interactions between brain tumors and their microenvironment.

3. The Molecular Landscape of Normal Brain Regions

3.1. Regional Cellular Composition and Molecular Heterogeneity in the Normal Brain

Understanding the intrinsic molecular organization of the normal brain is essential for interpreting the regional heterogeneity observed in brain tumors. The adult human brain exhibits a high degree of regional specialization at both the molecular and cellular levels. This diversity is reflected not only in cell-type composition and relative abundance but also in region-specific gene-expression patterns, co-expression networks and regulatory programs. In a landmark study, Siletti et al. generated a single-nucleus atlas comprising approximately three million cells from nearly 100 anatomically defined regions across the forebrain, midbrain, and hindbrain, revealing systematic variation in both neuronal and glial populations. The cerebral cortex exhibits a characteristic laminar architecture composed of upper- and deep-layer excitatory neuronal populations, including intratelencephalic, near-projecting, and corticothalamic subtypes, as well as inhibitory neurons derived from distinct developmental lineages. By contrast, the midbrain, brainstem, and hypothalamus contain highly heterogeneous neuronal populations that frequently co-express multiple neurotransmitters and neuropeptides, suggesting more complex and multimodal functional organization than that observed in the cerebral cortex. Regional specialization is also evident among glial cells. Astrocytes and oligodendrocyte progenitor cells (OPCs) in telencephalic regions differ markedly from their counterparts in non-telencephalic areas in both molecular signatures and relative abundance. These differences suggest that even cells derived from shared lineages may follow distinct differentiation trajectories and perform region-specific functions depending on their anatomical milieu [1].

3.2. Cross-Regional Single-Cell Atlases Reveal Region-Specific Cellular Ecosystems

Extending these efforts, Chen et al. integrated 70 single-cell and single-nucleus transcriptomic datasets comprising approximately 11.3 million cells to construct a Brain Cell Atlas encompassing 14 major brain regions and 30 subregions. This integrative analysis characterized region-specific cellular landscapes and identified the gene-regulatory networks associated with each region. Within this atlas, the cerebral cortex is predominantly composed of upper- and deep-layer intratelencephalic neuronal populations, whereas the hippocampus contains distinct neuronal populations associated with the CA1–CA4 subfields and dentate gyrus. By contrast, the thalamus and amygdala are distinguished by excitatory nuclear neurons and specialized regulatory glial subsets. Regional specialization is also apparent at the levels of cell–cell communication and transcriptional control, rather than only in cell-type composition. Microglia, for example, exhibit distinct transcriptional states and ligand–receptor interaction profiles between the prefrontal cortex and hippocampus, consistent with region-specific mechanisms of immune surveillance and metabolic support. Collectively, these integrative atlases indicate that brain regional specialization is shaped not only by the distribution of developmental lineages but also by continuous functional adaptation to local microenvironmental cues [2].

3.3. Gene Co-Expression Networks and Functional Modularization Across Brain Regions

From a systems-level perspective, analysis of GTEx RNA-seq data from 13 normal brain regions enabled construction of a genome-wide gene co-expression network (GCN), revealing distinct co-expression modules and associated functional enrichment patterns. Genes characteristic of the

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cerebral cortex is primarily enriched in pathways related to synaptic transmission and neuronal signaling, whereas genes characteristic of the basal ganglia is associated with motor control and neurotransmitter metabolism. Cerebellar modules are enriched in genes involved in ion homeostasis and neurodevelopment, whereas the spinal cord exhibits a distinct co-expression pattern, forming a separate cluster in dimensionality-reduction analyses. The number of eQTLs and the degree of gene connectivity differ substantially across regions, suggesting hierarchical variation in the complexity and robustness of regional gene-regulatory networks. These differences align closely with functional compartmentalization. The prefrontal and parietal cortices, which are involved in cognition and perception, are enriched in genes related to synaptic signaling and plasticity, whereas the basal ganglia, hypothalamus, and brainstem—regions associated with motor and autonomic regulation—predominantly express genes involved in energy metabolism and neurotransmitter pathways [3].

Taken together, molecular distinctions among brain regions appear to be shaped by developmental origins and organizational hierarchies. According to Siletti et al., telencephalon-derived structures such as the cortex, hippocampus, and striatum exhibit lineage-specific repertoires of excitatory neuron, whereas the midbrain and hindbrain contain a higher proportion of mixed-neurotransmitter cell types. This pattern may contribute to the pronounced cellular heterogeneity observed in non-cortical brain regions [1]. Chen et al. further highlighted locally driven variations in cell–cell communication—such as divergent microglial signaling networks between the hippocampus and prefrontal cortex [2]. Moreover, key genes within region-specific co-expression modules show higher mutation frequencies in various neurological disorders and brain tumors, suggesting that these baseline regional molecular differences might represent a foundational layer predisposing certain areas to disease vulnerability [3]. Overall, these studies demonstrate that the human brain is organized into region-specific molecular ecosystems characterized by distinct cellular compositions, regulatory networks, and intercellular signaling patterns. These intrinsic differences may establish regionally permissive microenvironments that favor the emergence and progression of specific brain tumor types.

4. Regional Differences and Molecular Mechanisms in Brain Tumors

4.1. Regional Features of Gliomas

Among primary brain tumors, gliomas represent one of the clearest examples of spatially structured molecular heterogeneity. Extensive evidence indicates that glioma anatomical location is closely associated with molecular profiles, cellular states, and clinical outcomes. Distinct neurodevelopmental backgrounds, lineage compositions, and epigenetic landscapes across brain regions shape tumor mutational spectra and biological behavior. Clear spatial preferences have been observed across brain regions, ranging from the frontal and temporal lobes to the thalamus, brainstem, spinal cord, and cerebellum.

For instance, Qi et al. reported in 2014 that IDH-mutant gliomas predominantly occur in the frontal or temporal lobes [4], while Vuong et al. demonstrated that H3K27M-mutant diffuse midline gliomas (DMG) are concentrated in the brainstem, thalamus, and spinal cord [5]. In contrast, Dandapath et al. found that low-grade BRAF-fusion tumors are mainly located in the cerebellum and posterior fossa. Collectively, these findings support the paradigm that "anatomical location influences tumor biology"—a central principle underlying the spatial heterogeneity of gliomas [9] (Table 1).

4.1.1. Supratentorial Regions: Molecular Distribution Across Frontal, Temporal, Parietal, and Occipital Lobes

Within the supratentorial compartment, gliomas arising in different cortical lobes exhibit distinct molecular characteristics and clinical behaviors.

Frontal lobe: The frontal lobe represents the most frequent site of adult gliomas. Qi et al. reported that IDH1/2-mutant tumors are significantly enriched in this region and typically exhibit well-demarcated margins, homogeneous MRI signal characteristics, and minimal contrast enhancement, features consistent with lower invasiveness and a more favorable prognosis [4]. Integrated radiomic analyses further indicate that frontal tumors often display *MGMT* promoter methylation and *1p/19q* codeletion, predicting better chemotherapy response [11]. Functionally, Qi et al. reported that patients with left frontal IDH-mutant tumors exhibit enhanced contralesional frontoparietal network activity, suggesting an interaction between molecular subtype and neural plasticity [12].

Temporal lobe: Temporal gliomas frequently exhibit *EGFR* amplification and enrichment of RTK II subtypes, which are associated with increased invasiveness and angiogenic activity [13]. Spatial transcriptomics has revealed that in temporal-lobe GBM, perivascular and neuron-interaction layers are especially prominent, suggesting that the local microenvironment might play a key role in shaping tumor multilayered architecture [14].

Parietal lobe: Glioblastomas in the parietal region tend to have the poorest survival. Multimodal analyses indicate enrichment of *PTEN* mutations and *FGFR3-TACC3*

fusions, along with pronounced radiographic texture heterogeneity and aggressive imaging features, reflecting greater spatial heterogeneity and more unfavorable biological behavior [11].

Occipital lobe: Occipital gliomas are relatively rare. Cini et al. noted that their mutational spectra are not distinctive and that many lesions likely represent secondary infiltration or dissemination from parietal or temporal tumors, implying a lower intrinsic tendency for primary tumorigenesis in this area [15].

4.1.2. Insular and Lateralization Effects: Structural Connectivity and Hemispheric Differences

Yang et al. demonstrated pronounced hemispheric asymmetry in insular gliomas [16]. In the left hemisphere, *MGMT* methylation levels positively correlated with damage to the IFOF tract, whereas the opposite pattern was observed on the right. This finding suggests that gliomas may remodel white matter connectivity in a hemisphere-specific manner. Systematic reviews further noted higher frequencies of *TP53* mutations and *MGMT* methylation in left-sided gliomas, often associated with poorer prognosis, implying that molecular features could be intricately linked to functional hemispheric lateralization [15].

4.1.3. Midline Regions: Spatial Stratification of the Thalamus, Brainstem, and Spinal Cord

Thalamus and Pulvinar subregion: Pediatric thalamic gliomas account for approximately 5% of CNS tumors. Chiba et al. found that lesions in the Pulvinar (posterior thalamic nucleus) display higher malignancy, enrichment of H3K27M mutations, and early ventricular dissemination [17]. The aggressiveness of Pulvinar tumors suggests that biological stratification might exist even within thalamic subregions.

Diffuse midline glioma (DMG): An integrated analysis of 804 cases revealed region-specific distinctions: brainstem DMGs occur at younger ages, show the highest Ki-67 index, and have the poorest prognosis; thalamic DMGs fare somewhat better; spinal DMGs occur mainly in adults and often harbor TERT-promoter mutations; whereas brainstem DMGs are enriched for HIST1H3B/C and ACVR1 mutations. Thus, despite a shared H3K27M background, the anatomical location and accompanying mutational landscape may determine tumor evolution and survival outcomes [5]. These findings suggest that even within the midline compartment, anatomical subregions correspond to biologically distinct tumor states.

Single-cell multi-omics analyses further revealed that H3K27M DMGs share an OPC-like stem-cell state, but differentiation trajectories and immune microenvironments vary by site: pontine lesions contain more hypoxic, stem-like populations; thalamic lesions exhibit more mature glial lineages; and adult-type DMGs show enrichment of MES-like states, suggesting that location, age, and immune milieu jointly shape the tumor's spatial and cellular architecture [18].

4.1.4. Infratentorial Regions: Distinct Subtype Signatures of the Cerebellum and Posterior Fossa

Dandapath et al. reported that 91% of pilocytic astrocytomas (PAs) carry *BRAF* fusions and almost all are located in the cerebellum or posterior fossa. These pediatric, developmentally driven tumors are associated with an excellent prognosis and represent a MAPK-activated benign lineage [9].

In contrast, Oki et al. described that cerebellar GBMs, though rare, constitute a biologically distinct subgroup—lacking *IDH*, *H3F3A*, and *TERT* mutations but showing a strong tendency for distant dissemination and ventricular invasion. This suggests that the infratentorial region might constitute an independent tumor ecosystem [19].

Overall, these findings indicate that glioma molecular subtypes are not randomly distributed across the brain but instead show clear anatomical predilections. Recognition of these spatial patterns may help refine diagnostic stratification and guide region-adapted therapeutic strategies.

4.2. Coupling Between Anatomical Location and Molecular Subtypes in Meningiomas

Meningiomas provide another clear example of tight coupling between tumor genotype and anatomical location. As the most common primary intracranial tumor type in adults, meningiomas exhibit clear location-specific molecular and clinical differences, with biological behavior closely correlated with their anatomical origin. Tumors driven by *NF2* mutations and *22q* loss predominantly arise on the cerebral convexity or supratentorial compartments and tend to recur more frequently, whereas non-NF2 variants, including *TRAF7, KLF4, AKT1, SMO, and POLR2A*) are enriched at the skull base and posterior fossa, typically presenting as benign, stable WHO grade I tumors [6]. This position-genotype coupling suggests that the cell of origin, developmental lineage, and the local microenvironment collectively shape meningioma biology (Table 2).

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Table 1: Molecular landscape of gliomas across main brain regions.

Brain Region	Representative Subtype/Mutation	Molecular/Genetic Features	Microenvironmental & Functional Traits	Clinical/Prognostic Implications
Frontal lobe	IDH1/2-mutant glioma	MGMT methylation, 1p/19q codeletion	Lower invasiveness and weak contrast enhancement, preserved network plasticity	Favorable prognosis, good chemotherapeutic response
Temporal lobe	RTK II subtype GBM	EGFR amplification	Perivascular & neuron-interaction layers enriched	Highly invasive, angiogenic
Parietal lobe	GBM with PTEN mutation, FGFR3-TACC3 fusion	High texture heterogeneity	Aggressive phenotype	Poor survival
Occipital lobe	Secondary infiltration from parietal/temporal	No distinctive mutations	Low intrinsic tumorigenesis	Rare primary lesions
Insula/Left vs. Right Hemisphere	IDH-mutant glioma (lateralized)	Left: ↑TP53 mutation, ↑MGMT methylation	White-matter remodeling (IFOF asymmetry)	Left-sided → poorer outcome
Thalamus/Pulvinar	Pediatric H3K27M-mutant glioma	H3 K27M mutation, ventricular spread	High malignancy in Pulvinar subregion	Poor prognosis
Brainstem (DMG)	H3 K27M-mutant DMG	HIST1H3B/C, ACVR1	Hypoxic, OPC-like stem states	Worst prognosis
Spinal cord (DMG)	Adult DMG	TERT-promoter mutation	MES-like enrichment	Intermediate prognosis
Cerebellum/Posterior fossa	BRAF-fusion PA; rare cerebellar GBM	BRAF fusion (MAPK activation); IDH/H3F3A-negative GBM	Developmental benign lineage (PA); invasive GBM niche	PA: excellent prognosis; cerebellar GBM: high dissemination

Table 2: Regional–molecular coupling in meningiomas.

Anatomical Region	Dominant Molecular Subtype(s)	Key Genetic Alterations	Biological/Pathway Features	Clinical/Prognostic Traits
Cerebral Convexity/Supratentorial	NF2-driven meningioma	NF2 mutation, 22q loss	NF2–YAP signaling activation; genomic instability	High-grade (II–III), aggressive, recurrent
Skull Base (Sphenoid ridge, Olfactory groove, Sellar region)	Non-NF2 lineage: TRAF7, KLF4, AKT1, SMO	TRAF7 ± KLF4 (K409Q), AKT1 (E17K), SMO mutation	PI3K–AKT–mTOR and Hedgehog pathway activation	WHO grade I, benign, chromosomally stable, low recurrence
Posterior Fossa (Tentorial notch, Clivus, Foramen magnum)	Group A–C stratification	NF2-intact (A), NF2/22q loss (B), 1p/14q loss, 9p loss, TERT/CDKN2A (C)	Gradual increase in genomic instability from lateral → midline	Group C (midline): worst prognosis, rapid recurrence
Cerebellopontine Angle (CPA)	POLR2A-mutant subtype	POLR2A mutation (female-predominant)	Altered transcriptional regulation, meningothelial histology	Grade I but higher recurrence risk

Table 2: *Cont.*

Anatomical Region	Dominant Molecular Subtype(s)	Key Genetic Alterations	Biological/Pathway Features	Clinical/Prognostic Traits
Posterior Skull Base (Petrous apex, Petroclival junction)	TRAF7–KLF4–AKT1 lineage overlap	TRAF7, AKT1 E17K	PI3K–AKT signaling	Benign, stable
Overall Pattern	NF2 vs. non-NF2 dichotomy	NF2–YAP vs. PI3K–AKT–mTOR pathways	Location-dependent developmental lineage	"Position–Genotype Coupling" defines biology

4.2.1. Supratentorial Meningiomas: NF2-Driven, Convexity-Dominant, and Aggressive

Whole-exome sequencing of 300 cases revealed *NF2* mutations in about 36% of patients, primarily located on the cerebral convexity and supratentorial tentorium. These tumors frequently exhibit *22q* deletion, genomic instability, and higher histologic grade, indicative of increased invasiveness and recurrence potential. In contrast, *TRAF7/KLF4/AKT1/SMO* mutations are largely restricted to skull-base tumors, showing mutual exclusivity with NF2-driven lesions [7]. The biology of supratentorial meningiomas thus appears to depend on the NF2–YAP signaling axis, which could represent a key driver pathway for high-risk subtypes [6].

4.2.2. Skull-Base Meningiomas: The TRAF7–KLF4–AKT1–SMO Benign Lineage

Arising from the sphenoid ridge, olfactory groove, petrous apex, and sellar region, skull-base meningiomas represent approximately one-quarter of all cases. These "non-NF2" tumors are typically driven by TRAF7 mutations (~24%), which often co-occur with *KLF4 K409Q* or *AKT1 E17K* alterations. Nearly all are located in the medial skull base or sphenoid region, characterized by chromosomal stability and benign histology. *SMO-mutant* meningiomas cluster in the olfactory groove and anterior cranial fossa, suggesting activation of the Hedgehog pathway [6]. Collectively, this group appears to represent a developmentally stable, low-invasive, and anatomically confined lineage, primarily driven by PI3K–AKT–mTOR signaling rather than NF2–YAP pathway activation [8].

4.2.3. Posterior-Fossa Meningiomas: Anatomical Sub-Regions and Chromosomal Instability

Comprehensive genomic profiling of 132 posterior-fossa meningiomas identified three molecular subtypes: Group A: NF2-intact tumors without Merlin-pathway abnormalities, typically located in lateral infratentorial or petrous areas. Group B: NF2-mutant or *22q-deleted* tumors without high-risk CNAs, showing broad distribution. Group C: Genomically unstable tumors with multiple high-risk CNAs (*1p/14q* co-deletion, *9p* loss, *TERT/CDKN2A* mutations), 81% of which occur in midline structures (tentorial notch, clivus, foramen magnum). Group C meningiomas are associated with the poorest prognosis, demonstrating significantly shorter progression-free survival even following gross-total resection [10]. These results suggest that proximity to midline structures might correlate with greater genomic instability and malignant potential, reflecting a developmental lineage-linked risk gradient.

4.2.4. Cerebellopontine-Angle (CPA) Meningiomas: Prognostic Implications of POLR2A Mutation

In a cohort of 70 WHO grade I cerebellopontine angle (CPA)meningiomas, *POLR2A* mutations were found in 17% of cases—all in women and predominantly of the meningothelial subtype. The mutation significantly increased recurrence risk, particularly in patients undergoing subtotal resection. These tumors were most frequently located at the petroclival junction and posterior petrous ridge [20]. Thus, *POLR2A* might serve as a skull-base–specific molecular biomarker, potentially influencing transcriptional regulation and cellular differentiation in region-defined contexts.

Collectively, these studies highlight a strong position–genotype coupling in meningiomas, suggesting that developmental lineage and local microenvironment jointly shape tumor biology.

4.3. Regional Adaptation of Brain Metastases

Brain metastasis (BrM) are the most common intracranial malignancies in adults and show a cortical predilection, frequently involving the frontal and parietal lobes as well as the cerebellar hemispheres, whereas deep structures such as the thalamus, basal ganglia, and brainstem are less commonly affected. At the systems level, BrM formation is not merely determined by vascular perfusion patterns but may reflect a coevolution between metastatic cells and

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regional brain microenvironments. Differences in vascular architecture, glial composition, and immune–stromal context across brain regions likely influence metastatic susceptibility.

In the study by Gonzalez et al., 15 parenchymal brain metastases from diverse primaries (breast, lung, melanoma, ovarian, colorectal, renal, etc.) were analyzed, and nearly all were located in the cerebral cortex, indicating a preference for vascular-rich cortical territories [21]. Single-cell transcriptomics and mass cytometry revealed that cortical metastases are characterized by complex vascular networks enriched for arteriovenous-transition endothelial clusters (*APLNR*$^{+}$, *EFNB2*$^{+}$, *NR2F2*$^{+}$), abundant pericytes and MSC-like cells expressing ECM-remodeling genes (*COL1A1, TINAGL1, TGFB3*), and scarcity of astrocytes, implying local breakdown of the glial barrier during cortical invasion.

Cross-tissue transcriptome-wide association analysis (TWAS) further identified CASP8 as a key driver gene in breast cancer brain metastasis, with specific overexpression in the cerebellar hemispheres and frontal cortex [22]. This finding suggests that breast-cancer cells may preferentially colonize the cerebellar–frontal axis, where distinct metabolic and immune properties, together with vascular permeability and glial fiber density, may create a favorable niche for metastatic colonization.

Together, these observations indicate that metastatic tumor cells adapt to region-specific vascular and glial niches, supporting the idea that the brain microenvironment plays a decisive role in shaping metastatic colonization patterns.

5. Discussion

Growing evidence from these studies indicates that region-specific molecular baselines exert a profound influence on brain tumor biology. Across gliomas (Figure 1), meningiomas, and brain metastases, each tumor type shows characteristic anatomical predilections and molecular features that track with its site of origin, underscoring the importance of the local host microenvironment in tumor initiation and subsequent evolution. From a translational standpoint, the spatial molecular ecology of brain tumors is likely to be a major determinant of clinical course and treatment sensitivity. Integrating anatomical localization with single-cell, spatial transcriptomic, and imaging-based omics data could enable a more nuanced, region-oriented classification framework that better supports precision neurosurgery and region-adapted adjuvant therapies. Looking ahead, it will be important to elucidate how developmental patterning cues, intercellular signaling circuits, and metabolic microenvironments jointly confer regional vulnerability or resistance to oncogenesis, thereby clarifying the intrinsic links between brain regionality and tumor behavior.

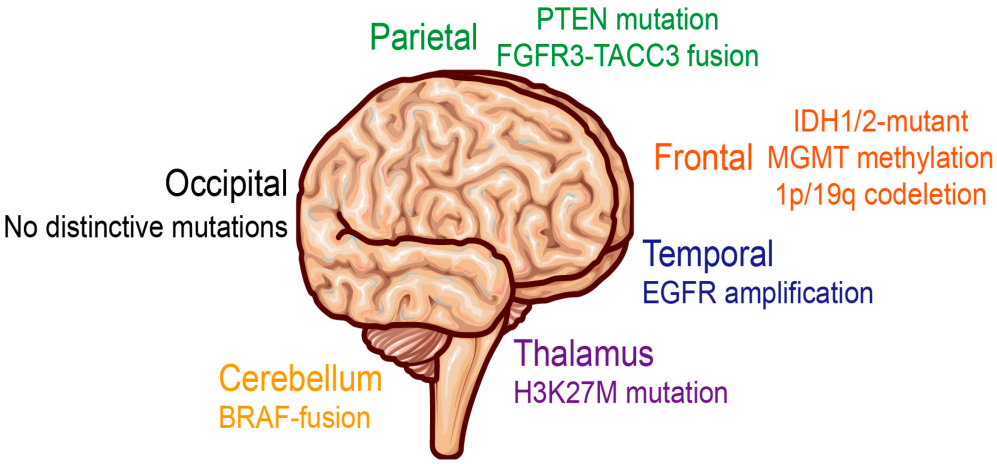

Figure 1: Molecular landscape of gliomas across main brain regions.

Despite these advances, our understanding of region-specific mechanisms in brain tumors remains limited. Although the regional molecular features of gliomas have been partially characterized, integrative studies combining developmental lineage, epigenetic regulation, and microenvironmental signaling remain limited. In meningiomas, the coupling between location and genotype has been well established, yet the developmental and biomechanical underpinnings of this relationship remain poorly characterized. In contrast, research on regional hetero-

geneity in brain metastases remains relatively underdeveloped.

Future studies should focus on integrating spatial omics with neuroimaging and radiomic analyses to better characterize region-specific tumor ecosystems. In addition, integrating anatomical location with molecular features may facilitate the development of region-informed risk stratification models, while clinical studies stratified by both tumor genotype and anatomical site may further clarify therapeutic responses across distinct brain regions. Such efforts may advance the emerging concept of "region-aware oncology" and support more precise diagnostic and therapeutic strategies for brain tumors.

6. Conclusions

In summary, growing evidence indicates that brain tumors are shaped not only by intrinsic genetic alterations but also by the region-specific molecular and cellular context of the host brain. Across gliomas, meningiomas, and brain metastases, distinct anatomical locations are associated with characteristic molecular features, tumor behaviors, and microenvironmental interactions, supporting the concept of region-aware oncology. A deeper understanding of this spatial coupling may improve brain tumor classification and provide a foundation for more precise diagnostic and therapeutic strategies.

List of Abbreviations

APLNR, apelin receptor; ACVR1, activin A receptor type 1; AKT1, AKT serine/threonine kinase 1; BrM, brain metastasis; CNS, central nervous system; COL1A1, collagen type I alpha 1 chain; CPA, cerebellopontine angle; DMG, diffuse midline glioma; ECM, extracellular matrix; EGFR, epidermal growth factor receptor; EFNB2, ephrin B2; eQTL, expression quantitative trait locus; FGFR3–TACC3, fibroblast growth factor receptor 3–transforming acidic coiled-coil containing protein 3 fusion; GBM, glioblastoma; GCN, gene co-expression network; GTEx, Genotype-Tissue Expression Project; H3 K27M, lysine-to-methionine substitution at position 27 of histone H3; H3F3A, H3 histone family member 3A; HIST1H3B/C, histone cluster 1 H3 family member B/C; IDH, isocitrate dehydrogenase; IFOF, inferior fronto-occipital fasciculus; KLF4, Krüppel-like factor 4; MES, mesenchymal; MGMT, O6-methylguanine-DNA methyltransferase; MRI, magnetic resonance imaging; MSC, mesenchymal stromal cell; NF2, neurofibromatosis type 2; NR2F2, nuclear receptor subfamily 2 group F member 2; OPC, oligodendrocyte progenitor cell; PA, pilocytic astrocytoma; PI3K, phosphoinositide 3-kinase; POLR2A, RNA polymerase II subunit A; RTK, receptor tyrosine kinase; SMO, Smoothened frizzled class receptor; TERT, telomerase reverse transcriptase; TGFB3, transforming growth factor beta 3; TINAGL1, tubulointerstitial nephritis antigen-like 1; TWAS, transcriptome-wide association study; WHO, World Health Organization; YAP, Yes-associated protein.

Author Contributions

Conceptualization, resources, data curation, writing—original draft preparation: Y.Z; Supervision, conceptualization, writing—review & editing: R.X; Methodology, visualization, validation, writing—review & editing: J.Z. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

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AI Declaration

During manuscript preparation, the authors used ChatGPT only for language polishing and improving readability. All scientific content, interpretation of the literature, and final conclusions were reviewed and approved by the authors.

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