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Review

A Multi-Omics and Systems Biology Perspective on the Potential Inverse Association Between Alzheimer's Disease and Glioblastoma: A Hypothesis-Generating Narrative Review

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Abstract

Background: Alzheimer's disease (AD) and glioblastoma (GBM) are characterized by opposing cellular phenotypes (neurodegeneration versus uncontrolled proliferation) and have been considered for a long time as unrelated, but have been increasingly studied in the last decade because of their major individual, social, and economic burden. Several recent epidemiological studies reported an inverse association between AD and brain cancers, yet the biological basis of this relationship remains incompletely understood. ***Objective and Methods***: This work aims to synthesise current evidence on the potential inverse relationship between AD and GBM, considering shared molecular pathways and divergent regulatory mechanisms through a multi-omics and systems-biology approach. ***Results***: Multi-omics data reveal that AD and GBM share overlapping molecular pathways related to cell cycle regulation, apoptosis, metabolism, and immune responses, but exhibit opposite patterns of regulation. Transcriptomic analyses suggest inverse gene expression signatures, while proteomic and metabolomic studies highlight contrasting states of protein homeostasis and energy metabolism. Epigenetic modifications further contribute to disease-specific regulatory landscapes. Systems biology approaches identify key hub nodes, such as p53 and the PI3K/AKT/mTOR signaling pathway, that may act as molecular switches between neurodegeneration and tumorigenesis. ***Conclusions***: The potential inverse association between AD and GBM observed in epidemiological studies may reflect differential modulation of shared biological networks, although GBM-specific evidence remains limited. This multi-omics perspective is consistent with a conceptual neurodegeneration–tumorigenesis axis, proposed here as an interpretive framework rather than an experimentally validated mechanism, and suggests candidate nodes warranting functional investigation.

Keywords: Alzheimer's disease; glioblastoma; multi-omics; systems biology; p53; PI3K/AKT/mTOR pathway

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1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder and the leading cause of dementia worldwide [1], representing a major and growing public health challenge in aging populations [2]. From a pathological perspective, AD is characterized by extracellular amyloid-β (Aβ) aggregates [3] and intracellular hyperphosphorylated tau

protein forming neurofibrillary tangles [4], leading to synaptic dysfunction and progressive neuronal loss [5], ultimately resulting in cognitive decline and functional impairment [6]. Despite extensive preclinical and clinical research over the past decades [7], the molecular mechanisms underlying AD remain incompletely understood, and disease-modifying therapies remain limited [8]. Increasing evidence suggests that AD is a multifactorial disorder involving complex interactions between genetic susceptibility [9], metabolic dysregulation [10], mitochondrial dysfunction [11], and chronic neuroinflammation [12].

In contrast, glioblastoma (GBM), the most aggressive primary brain tumor in adults, represents a biologically distinct condition; GBM is characterized by rapid cellular proliferation [13], diffuse invasion [14], and increased resistance to therapy [15]. Despite advances in neurosurgery, radiotherapy, and chemotherapy, prognosis remains poor, with a median survival of approximately 15 months [16]. At the molecular level, GBM is driven by complex genomic and epigenomic alterations, including dysregulation of receptor tyrosine kinases [17], dysregulation of PI3K/AKT/mTOR signaling [18], and dysfunction of cell cycle control pathways [19]. Compared to AD, which is defined by progressive neuronal loss [20], GBM exhibits uncontrolled cell proliferation, supported by metabolic reprogramming and a sustaining immunosuppressive tumor microenvironment [21].

Although AD and GBM have traditionally been considered unrelated diseases, accumulating epidemiological evidence over the past decade has revealed an unexpected inverse association between neurodegeneration and cancer, including primary brain tumors [22]. Several population-based studies and meta-analyses have reported that patients with AD exhibit a reduced risk of developing cancer, while cancer survivors show a lower incidence of AD, suggesting the existence of shared but oppositely regulated biological mechanisms [23–25]. However, the underlying mechanisms of this relationship remain poorly defined, particularly with respect to the specific potential inverse association between AD and GBM, for which direct evidence remains limited. Recent advances in high-throughput technologies and integrative data analysis now enable a comprehensive exploration of disease biology across multiple molecular layers [26]. In this context, the present review aims to synthesize current evidence on the potential inverse association between AD and GBM from a multi-omics and systems-biology perspective. The originality of this work lies in its attempt to integrate shared molecular networks, divergent regulatory pathways, and possible therapeutic implications within a conceptual neurodegeneration–tumorigenesis framework, rather than to establish a definitive mechanistic continuum.

2. Search Methodology and Limitations

This paper was designed as a narrative review. The literature was identified through an informal, non-structured search of three databases (PubMed/MEDLINE, Scopus, Web of Science) conducted between April/2026 and August/2026, supplemented by snowballing of the reference lists of retrieved reviews and of key primary articles. Search terms combined [“Alzheimer’s disease” OR “Alzheimer disease”] and [“glioblastoma” OR “glioma” OR “brain tumour/tumor”] with terms reflecting the domains of interest, including [“multi-omics,” “transcriptomics,” “proteomics,” “epigenomics,” “metabolomics,” “systems biology,” “network analysis” and “PI3K/AKT/mTOR”]. No language or publication-date restriction was applied.

Because the objective was to integrate findings across heterogeneous omics modalities rather than to estimate a pooled effect, the review was not conducted according to a systematic protocol: no a priori eligibility criteria, formal risk-of-bias assessment, or PRISMA flow diagram were applied. Study selection was therefore purposive, prioritising studies that reported mechanistic or integrative analyses directly linking AD and GBM biology. Where

a domain was represented by a small number of studies, we prioritised those with the most directly relevant biological findings.

Several limitations of our approach should be noted. As a narrative synthesis, it did not follow a formal systematic protocol. Thus, our search was not exhaustive, and selection and publication bias cannot be excluded. The marked heterogeneity of omics platforms, cohorts, and analytical pipelines across the included studies further limits quantitative comparison, and our conclusions should be regarded as hypothesis-generating rather than definitive. This review did not involve original bioinformatic analysis. No network reconstruction, hub-identification procedure, or pathway-enrichment analysis was performed by the authors. Where network-based findings are reported (including the identification of TP53, PI3K/AKT/mTOR, MYC and NF-κB as central nodes), these reflect the reported results of previously published studies, summarized and integrated here rather than independently derived.

3. Inconclusive Epidemiological Evidence for a Specific AD–GBM Inverse Relationship

Population-based and longitudinal cohort studies have suggested an inverse association between AD and different types of cancer [27]. Large observational cohorts have shown that individuals diagnosed with AD exhibit a reduced incidence of subsequent malignancies, while cancer survivors show a lower risk of developing AD [27]. This association has been replicated across diverse populations, tumor types, and study designs, supporting its robustness [28]. One possible, although still incompletely established, explanation is that shared biological mechanisms may be differentially regulated in neurodegeneration and tumorigenesis.

Compared with the broader AD–cancer association, studies specifically addressing GBM prevalence and its correlation with dementia remain limited. Epidemiological observations suggest that AD and GBM infrequently co-occur despite sharing similar age-related incidence peaks [29]. This hypothesis is further supported by recent integrative studies using publicly available genomic datasets, which have reported opposing disease patterns between AD and GBM, including inverse gene-expression profiles and distinct regulatory pathways [30]. Genetic evidence remains more restricted. A two-sample bidirectional Mendelian randomization study reported that genetically predicted glioma, including GBM-specific analyses, was associated with reduced AD risk, although these data do not establish a causal relationship [31]. In that study, genetic liability to GBM was associated with a reduced risk of AD under the primary analysis (OR 0.93, 95% CI 0.91–0.95, $p = 5.11 \times 10^{-9}$), with a concordant MR-Egger estimate (OR 0.92, 95% CI 0.86–0.98) and no evidence of pleiotropy (intercept $p = 0.79$) or heterogeneity ($p = 0.40$). Importantly, however, the reverse direction was null: genetic liability to AD was not associated with GBM (OR 1.03, 95% CI 0.93–1.13, $p = 0.61$), all glioma (OR 1.01, 95% CI 0.94–1.09, $p = 0.75$) or non-GBM glioma (OR 1.00, 95% CI 0.91–1.09, $p = 0.96$).

Recent meta-analyses and large registry-based studies have provided more robust quantitative estimates of the inverse association between AD and cancer. A systematic review and meta-analysis published in 2020, including over 9.6 million individuals, demonstrated that cancer diagnosis is weakly associated with a reduced risk of subsequent AD, with pooled hazard ratios consistently below unity [32]. Importantly, bias-adjusted analyses indicated that this association is unlikely to be fully explained by confounding or diagnostic bias. More recent meta-analytic work has reinforced these findings, reporting that individuals with AD have a substantially lower risk of developing cancer (relative risk ~ 0.53), while cancer patients exhibit a reduced risk of AD (relative risk ~ 0.61), further supporting a bidirectional inverse relationship [33]. In parallel, registry-based and Mendelian randomization

studies published after 2020 have confirmed the inverse association at both observational and genetic levels, including evidence suggesting that glioma may be causally linked to decreased AD risk [31]. Collectively, these large-scale analyses provide epidemiological support for an inverse AD–cancer relationship. Still, when considering the narrow AD-GBM association, definitive data indicating that this pattern also applies to malignant primary brain tumors must be supplemented with more solid evidence in the future.

When considering the abovementioned epidemiological findings, summarized in Table 1, regarding the potential inverse association between AD and GBM, several methodological limitations must be considered.

Table 1. Epidemiological findings suggesting an inverse association between AD and GBM.

Evidence Level	Key Finding(s)	Study Type	Focus on the Disease	Relevant Reference
Broad/direct for cancer	Bidirectional inverse association	Population-based cohort	AD vs. cancer (general)	[27]
Broad/direct for cancer	Inverse association replicated across diverse populations, tumor types, and study designs	Cohort/multi-population studies	AD vs. multiple cancers	[28]
GBM-specific but limited	AD and GBM rarely co-occur despite similar age-related incidence peaks	Epidemiological observation	AD vs. GBM	[29]
GBM-specific molecular, not epidemiological	Opposing disease patterns with inverse gene expression profiles and distinct regulatory pathways	Integrative genomic analysis	AD vs. GBM	[30]
Glioma-level indirect evidence	Genetically predicted glioma associated with reduced AD risk (no definitive causality)	Mendelian randomization	Glioma (including GBM) vs. AD	[31]
Broad/direct for cancer	Cancer diagnosis weakly associated with reduced AD risk (HR < 1); not fully explained by bias	Meta-analysis	AD–cancer	[32]
Broad/direct for cancer	Bidirectional inverse association	Meta-analysis	AD–cancer	[33]

Survival bias represents a major concern, as patients with aggressive cancers such as GBM may not live long enough to develop clinically detectable AD, potentially exaggerating the inverse relationship. Diagnostic bias is also relevant, as cognitive impairment may be underdiagnosed in cancer patients due to competing clinical priorities or overlapping symptoms [34]. However, meta-analytic evidence suggests that diagnostic bias and confounding alone are unlikely to fully explain the observed association [35]. Treatment-related effects, including chemotherapy-induced neurotoxicity or anti-inflammatory responses, may further influence risk estimates. Additionally, heterogeneity in study design, population characteristics, and disease definitions complicates direct comparisons across studies [36]. Competing mortality is especially relevant in the AD–GBM context, since patients with

glioblastoma have a median survival of approximately 15 months and therefore cannot survive long enough to develop clinically detectable AD—a structural feature that could generate an apparent inverse association in the absence of any biological antagonism. Differences in age structure and follow-up duration between AD and cancer cohorts introduce further asymmetry, as AD cohorts are typically older and followed for longer periods during which competing outcomes accumulate. Reverse causation cannot be excluded, and the reported bidirectionality of the association may reflect ascertainment rather than biology: severe cognitive impairment may reduce the likelihood that cancer is screened for, diagnosed or recorded, while conversely, patients under active cancer care may undergo cognitive assessment less often. Diagnostic surveillance operates in both directions, since frequent neurological consultation and neuroimaging in AD patients may increase detection of incidental findings. Therefore, the inverse association should be interpreted in light of these potential biases and the need for longitudinal, well-controlled studies that integrate clinical and molecular data.

Importantly, the available epidemiological evidence should be interpreted according to disease specificity. The most robust data concern the broad AD–cancer association, derived from population-based cohorts and meta-analyses including multiple tumour types. Evidence at the glioma level is more limited and includes observational or genetic analyses in which glioma is often treated as a broad diagnostic category rather than stratified by histological and molecular subtype. Direct evidence for a specific AD-GBM inverse association remains scarce, and GBM-specific incidence estimates, effect sizes, and confidence intervals are not consistently available across existing studies.

A final relevant aspect should not be forgotten: the inverse association described above is a population-level statistical trend and should not be read as absolute biological exclusivity. Although AD and GBM co-occur rarely, cases of glioblastoma arising in patients with a clinical diagnosis of AD, and neuropathological descriptions of AD-type pathology coexisting with glioma in the same brain, have been documented [37]. Such observations constrain the interpretation of AD-GBM inverse association: the shared pathways discussed in the following sections are unlikely to behave as a binary switch, and their modulation probably depends on cell type, tissue microenvironment, and age-related context. The "neurodegeneration–tumorigenesis axis" proposed here should therefore be understood as a predisposition detectable at the population and pathway level rather than a strict antagonism.

4. The AD-GBM Link—Neurodegeneration Versus Tumorigenesis

AD and GBM represent two biologically distinct conditions that exemplify the dichotomy between neurodegeneration and tumorigenesis. At the cellular level, AD is characterized by progressive neuronal loss via apoptosis and synaptic dysfunction [38], whereas GBM is defined by uncontrolled cellular proliferation, resistance to apoptosis, and the acquisition of stem-like phenotypes that sustain tumor growth and invasion [39]. This fundamental opposition reflects divergent cellular fates: neurons in AD undergo degeneration in response to chronic stress and damage [40], while glioma cells evade regulatory checkpoints and exploit similar stress pathways to promote survival and expansion [41]. These contrasting phenotypes support the conceptualization of AD and GBM as two extremes of a biological continuum, sharing molecular systems that are differentially regulated to produce either degenerative or proliferative outcomes.

A relevant aspect for our hypothesis is that neither AD nor GBM represents a biologically uniform entity. GBM is characterized by marked inter- and intratumoral heterogeneity, with clinically and molecularly relevant differences between IDH-wild-type glioblastoma and IDH-mutant diffuse gliomas, as well as variation in transcriptomic state,

clonal architecture, microenvironmental composition, and treatment response. Similarly, AD pathology is regionally and temporally heterogeneous, with differential vulnerability of hippocampal, entorhinal, association cortical, and subcortical networks, and with variable contributions from amyloid-beta deposition, tau pathology, vascular injury, neuroinflammation, and synaptic dysfunction across disease stages. These subtype-specific and regional differences may influence whether shared pathways such as cell-cycle regulation, apoptosis, proteostasis, metabolism and immune signaling appear convergent, divergent or context-dependent. Therefore, the AD-GBM inverse association and the proposed neurodegeneration–tumorigenesis axis should be interpreted as a broad systems-level framework rather than as a single uniform mechanism operating identically across all GBM subtypes, AD-affected brain regions, or phases of disease progression.

Moreover, the degeneration–proliferation continuum proposed in this paper should be understood as a conceptual and hypothesis-generating framework rather than as an established biological mechanism or a demonstrated transition between AD and GBM. Although the two diseases share several pathway-level features, as described in this section, they arise in distinct biological contexts. Their initiating events, cellular substrates, regional vulnerability, microenvironmental pressures and disease-specific regulatory programmes therefore differ substantially. Accordingly, shared molecular pathways should be interpreted as context-dependent points of convergence or divergence, not as deterministic switches that necessarily direct tissue biology toward neurodegeneration or tumorigenesis.

At the molecular level, transcriptomic studies provide indirect support for a potential inverse association between AD and GBM. In GBM, genes driving cell cycle progression and proliferation (e.g., *CDK1*, *CCNB1*, *CCNA2*, *MKI67*) and survival pathways (*BCL2*, *MDM2*, *AKT1*) are upregulated, enabling uncontrolled growth and resistance to apoptosis [42]. In contrast, AD is characterized by suppression or aberrant reactivation of cell cycle pathways in post-mitotic neurons, leading to apoptosis, alongside increased expression of genes associated with synaptic dysfunction and neuronal stress (e.g., MAPT, APP, PSEN1, SYN1, DLG4) and pro-apoptotic mediators (BAX, CASP3) [43]. These opposing patterns extend to cellular metabolism, with AD showing impaired oxidative phosphorylation and mitochondrial dysfunction, while GBM exhibits enhanced glycolysis and metabolic reprogramming consistent with the Warburg effect [44]. However, these transcriptomic contrasts should be interpreted with caution. Apparent inverse expression of cell-cycle regulators, apoptosis-associated genes, synaptic genes, or oncogenic pathways should be regarded as a cross-study, hypothesis-generating observation unless derived from harmonized direct comparative analyses.

Central regulatory hubs further illustrate this divergence: TP53 activity promotes apoptosis in AD but is frequently inactivated in GBM [45], whereas the PI3K/AKT/mTOR pathway is downregulated in AD and hyperactivated in GBM through alterations in EGFR, PTEN, and PIK3CA [46]. Additional regulators, such as MYC and NF-κB, also exhibit opposing activity profiles [47]. Together, these findings indicate that AD and GBM arise from shared molecular frameworks that are differentially regulated, with the direction of pathway activity determining whether cells undergo neurodegeneration or malignant transformation.

Advances in single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics have further revealed pronounced cell-type-specific transcriptional heterogeneity in both diseases. In AD, these approaches have identified vulnerable neuronal subpopulations with downregulation of synaptic genes (e.g., *SYN1*, *DLG4*) and upregulation of stress-response and apoptotic pathways [48], alongside distinct glial states such as disease-associated microglia (DAM) characterized by *TREM2*, *APOE*, and *C1QA* expression, and reactive astrocytes expressing GFAP and inflammatory mediators [49]. In contrast, GBM exhibits marked intratumoral heterogeneity, driven by glioma stem-like cells (GSCs) that display

high plasticity and can transition among transcriptional states, including proneural (OLIG2, SOX2), mesenchymal (CD44, CHI3L1), and proliferative phenotypes, thereby supporting tumor growth and therapy resistance [50]. Recent single-cell atlases further reveal complex regulatory layers in GBM, including alternative splicing programs and lineage-specific gene expression patterns that modulate tumor progression and immune interactions. Notably, microglial and macrophage populations in both AD and GBM share partially overlapping transcriptional programs, yet diverge functionally, with microglial populations adopting predominantly neurotoxic, pro-inflammatory phenotypes in AD [51] and macrophages adopting immunosuppressive, tumor-supportive states in GBM [52]. These differences are underpinned by key molecular pathways acting as regulatory switches: activation of the p53 pathway in AD promotes apoptosis and limits aberrant neuronal cell cycle re-entry [53], whereas in GBM, *TP53* is frequently mutated or inhibited (e.g., via MDM2/MDM4), enabling survival and proliferation [54]. Similarly, the PI3K/AKT/mTOR axis is downregulated or dysregulated in AD [55] but hyperactivated in GBM through alterations in EGFR, PTEN, and PIK3CA [56]. In addition, stress response pathways, including oxidative stress and DNA damage signaling, drive neuronal dysfunction and cell death in AD [57] but are co-opted by GBM cells to enhance adaptability and resistance to therapy [58]. Thus, AD and GBM share transcriptomic and signaling frameworks that are differentially regulated at the single-cell level, as summarized in Table 2.

Table 2. Neurodegeneration versus Tumorigenesis explaining the AD-GBM Link.

Processes	Neurodegeneration (in AD)	Tumorigenesis (in GBM)	Key Molecules/Pathways
Cell cycle regulation	Suppressed or aberrant re-entry, leading to apoptosis	Strong activation of proliferation and mitosis	CDK1, CCNB1, CCNA2, MKI67
Synaptic/neuronal function	Synaptic loss and dysfunction	Suppressed neuronal programs	MAPT, APP, PSEN1, SYN1, DLG4
Metabolism	Hypometabolism, mitochondrial dysfunction	Glycolysis upregulation (Warburg effect)	OxPhos genes (AD); HK2, LDHA (GBM)
Growth signaling	Downregulated or dysregulated	Hyperactivated oncogenic signaling	PI3K/AKT/mTOR, EGFR, PTEN, PIK3CA
Astrocyte states	Reactive astrocytes (neurotoxic)	Tumor-supportive astrocyte-like cells	GFAP, inflammatory mediators
Other glial populations	Disease-associated microglia (pro-inflammatory)	Tumor-associated macrophages (immunosuppressive)	TREM2, APOE, C1QA (AD); CD163, ARG1 (GBM)
Transcriptional regulators	Controlled or stress-induced activation	Oncogenic activation	MYC, NF-κB

The transcriptomic patterns discussed in this section should be interpreted with caution because the underlying expression data are not always derived from directly comparable datasets. In several cases, AD-related expression changes are reported from post-mortem brain regions such as hippocampus, entorhinal cortex, or association cortex, whereas GBM-related changes are derived from tumour tissue, tumour-adjacent brain, publicly available glioma cohorts, or experimental models. These studies may differ substantially in disease stage, tissue composition, cell-type proportions, sample size, sequencing or microarray platform, preprocessing strategy, and statistical pipeline. Therefore, apparent inverse expression of cell-cycle regulators, apoptosis-associated genes, synaptic genes, or oncogenic pathways should be understood as a cross-study, hypothesis-generating observation unless

derived from a harmonized direct comparative analysis. In conclusion, these findings indicate context-dependent molecular regulation that requires confirmation in matched datasets and experimental systems.

5. Proteomics and Epigenomics of the AD–GBM Association

Proteomic and epigenomic alterations provide another relevant perspective into the divergent yet interconnected mechanisms underlying AD and GBM, as summarized in Table 3.

Table 3. Proteomic and Epigenomic Alterations in the AD-GBM Association.

Mechanism/Pathway	Alzheimer's Disease	Glioblastoma	Key Molecules
Protein aggregation	Accumulation of misfolded, aggregation-prone proteins (Aβ, hyperphosphorylated tau)	Not a defining or diagnostic feature Overexpression of oncogenic proteins	Aβ42, p-tau181, p-tau217
Synaptic proteins	Reduced synaptic protein abundance, synaptic loss	Suppressed neuronal/synaptic programs, reflecting bulk tumour tissue composition	SYP, DLG4
Proteostasis systems	Impaired UPS and autophagy–lysosomal pathways	Highly active proteostasis supporting tumor growth (may reflect the tumour cell state rather than whole-tissue composition)	UCHL1, LC3, SQSTM1/p62
Cell cycle/apoptosis proteins	Increased pro-apoptotic signaling reported in affected regions	Increased proliferation and anti-apoptotic signaling	CDK4, cyclin D1, BCL-XL
Chaperones/protein synthesis	Reduced or dysfunctional proteostasis	Increased chaperone activity and protein synthesis	HSP90, HSP70
Extracellular vesicles	Spread of toxic proteins (Aβ, tau)	Transfer of oncogenic proteins and RNAs	Aβ, tau; EGFRvIII, miRNAs
DNA methylation	Region-specific, age-associated changes; not uniform across brain regions or stages	Global hypomethylation and focal hypermethylation (pattern depends on IDH status)	ANK1, BIN1, SORL1 (AD); MGMT (GBM)
Histone alterations	Reduced acetylation (impaired plasticity), including H3K27ac, reported in affected regions and specific to disease stage and brain area	Increased repressive methylation, chromatin remodeling, EZH2 abundance elevated	H3K27ac (reduced in AD); EZH2 (increased in GBM)

Note: Findings summarized in this table represent broad, disease-associated trends and are not universal features of either disease. In particular, AD findings are region- and stage-dependent, and glioma methylation patterns differ substantially according to IDH mutation status and tumour entity. Direct, matched comparisons between AD and glioma tissue remain limited.

In AD, proteomic studies consistently highlight the accumulation of misfolded and aggregation-prone proteins, most notably Aβ derived from amyloid precursor protein (APP) and hyperphosphorylated tau encoded by *MAPT*. Large-scale proteomic analyses of AD brain tissue and cerebrospinal fluid have reported increased levels of Aβ42 peptides and phosphorylated tau species (e.g., p-tau181, p-tau217), as well as alterations in synaptic

proteins such as synaptophysin (SYP) and PSD-95 (DLG4), reflecting synaptic loss and dysfunction [59,60]. In addition, dysregulation of protein quality control systems, including the ubiquitin–proteasome system (UPS) and autophagy–lysosomal pathways, has been associated with impaired clearance of toxic aggregates [61]. Proteins such as ubiquitin carboxyl-terminal hydrolase L1 (UCHL1) and autophagy regulators (LC3, SQSTM1/p62) are reported to be depleted, further promoting proteostatic imbalance [62]. These findings concern protein abundance and post-translational state rather than functional pathway activity, and should be interpreted accordingly.

In contrast, GBM proteomics is dominated by altered abundance and post-translational modification of oncogenic signaling proteins that drive proliferation, invasion, and resistance to apoptosis. Receptor tyrosine kinases such as epidermal growth factor receptor (EGFR), including its constitutively active mutant EGFRvIII, and platelet-derived growth factor receptor alpha (PDGFRA) are frequently amplified or overexpressed, leading to activation of downstream pathways such as PI3K/AKT/mTOR and RAS/MAPK [63]. Proteomic profiling of GBM has also identified elevated levels of cell cycle regulators (CDK4, cyclin D1), anti-apoptotic proteins (BCL-XL), and invasion-associated proteins such as matrix metalloproteinases (MMP2, MMP9) [64]. Unlike AD, in which proteostasis failure leads to toxic accumulation, GBM cells maintain a highly active proteostasis network, including increased chaperone activity (e.g., HSP90, HSP70) and enhanced protein synthesis [65], thereby supporting rapid tumor growth. It should be noted that EGFRvIII is a genuine activating alteration, whereas for most other components discussed here the distinction between increased abundance and demonstrated functional activation has not been directly established.

Across both diseases, the same caution applies: abundance of a pathway component is not equivalent to pathway activation, and transcript-level or total-protein measurements cannot establish the phosphorylation state, subcellular localisation or functional output of the signalling axes discussed. Where phospho-specific or functional readouts are unavailable, the findings should be regarded as suggestive of pathway involvement rather than as evidence of a defined activation state.

Extracellular vesicles (EVs), including exosomes, represent a key point of convergence. In AD, EVs have been shown to carry Aβ and tau species, contributing to the spread of pathology across brain regions [66]. In GBM, tumor-derived EVs transport oncogenic proteins such as EGFRvIII, as well as RNA and microRNA cargo, facilitating tumor progression, angiogenesis, and immune modulation [67]. Thus, EV-mediated intercellular communication may represent a shared mechanism with disease-specific functional consequences.

Epigenetic modifications play a central role in regulating gene expression in both AD and GBM, with distinct patterns reflecting their complementary biological phenotypes. DNA methylation changes are among the most extensively studied epigenetic alterations. In AD, epigenome-wide association studies have identified differential methylation in genes related to immune response, synaptic function, and amyloid processing, including *ANK1*, *BIN1*, and *SORL1* [68]. These changes are often region-specific and associated with aging-related epigenetic drift, characterized by gradual, stochastic alterations in DNA methylation patterns that contribute to disease susceptibility.

In contrast, GBM exhibits more pronounced and structured epigenetic alterations, including global DNA hypomethylation and focal hypermethylation of tumor suppressor genes. One of the most clinically relevant epigenetic markers in GBM is methylation of the O6-methylguanine-DNA methyltransferase (MGMT) promoter, which is associated with improved response to temozolomide therapy [69]. Additionally, mutations in isocitrate dehydrogenase 1 and 2 (IDH1/2) define a distinct subset of gliomas characterized by the glioma-CpG island methylator phenotype (G-CIMP), leading to widespread DNA

hypermethylation and altered gene expression [70]. These IDH mutations result in the accumulation of the oncometabolite 2-hydroxyglutarate, which inhibits DNA and histone demethylases [71], thereby reshaping the epigenetic landscape. Importantly, the epigenetic findings discussed in this section are derived from distinct cohorts and tissue types, and while IDH-mutant and IDH-wild-type gliomas show substantially different epigenetic landscapes, the relationship of these patterns to AD-related epigenetic changes has not been directly compared in matched datasets.

Histone modifications further contribute to epigenetic regulation in both diseases. In AD, alterations in histone acetylation and methylation have been linked to impaired synaptic plasticity and memory formation, with reduced histone acetylation (e.g., H3K27ac) observed in affected brain regions [71]. In GBM, histone-modifying enzymes, such as EZH2 (a histone methyltransferase), are frequently overexpressed, and increased EZH2 abundance has been linked to transcriptional repression of tumor suppressor genes and the maintenance of stem-like states [72]. Additionally, mutations in histone genes (e.g., H3K27M in diffuse midline gliomas) further highlight the role of chromatin dysregulation in glioma biology [73].

Finally, it should be emphasized that the signaling axes and common regulators described in this section are derived from correlational analyses and identify candidate points of divergence rather than demonstrated mechanistic drivers. Proteomic and epigenomic hypotheses indicate a high degree of connectivity among the most relevant molecules of the proposed pathways and networks, but should not be considered causal control, as the direction of any relationship between the two diseases cannot be established from cross-sectional omics data alone. These findings should therefore be regarded as generating hypotheses that require functional validation, not as evidence of a deterministic switch.

6. Metabolic Reprogramming in AD and GBM

Another relevant aspect that might explain the AD-GBM inverse relation is metabolic reprogramming of the two disorders. While AD is characterized by cerebral hypometabolism and mitochondrial dysfunction, GBM exhibits enhanced glycolysis and anabolic metabolism, supporting the rapid proliferation of tumor cells. Details of these common metabolic pathways that diverge are presented in the following paragraphs.

One of the earliest and most consistent features of AD is a reduction in cerebral glucose metabolism, detectable by fluorodeoxyglucose positron emission tomography (FDG-PET) even in preclinical stages [74]. This hypometabolic state is associated with impaired mitochondrial function, decreased oxidative phosphorylation, and reduced ATP production [75]. At the molecular level, transcriptomic and proteomic studies have demonstrated downregulation of key components of the electron transport chain, including NDUFS1 (complex I), SDHB (complex II), UQCRC1 (complex III), COX4I1 (complex IV), and ATP5F1A (complex V), reflecting widespread mitochondrial dysfunction [76]. Furthermore, pathological accumulation of Aβ and hyperphosphorylated tau directly impair mitochondrial dynamics and function in AD [77]. Aβ has been shown to interact with mitochondrial proteins, including amyloid-binding alcohol dehydrogenase (ABAD) and components of the mitochondrial permeability transition pore, thereby increasing reactive oxygen species (ROS) production and oxidative stress [78]. Tau pathology disrupts mitochondrial transport along axons, impairing synaptic energy supply. Additionally, alterations in mitochondrial biogenesis regulators, including PGC-1α and NRF1, contribute to reduced mitochondrial turnover and resilience [79].

Beyond glucose metabolism, AD is associated with impaired utilization of alternative energy substrates. Dysregulation of lipid metabolism, including decreased expression of apolipoprotein E (APOE) isoforms and altered cholesterol homeostasis, further compro-

mises neuronal function [80]. Glutamate metabolism is also disrupted, contributing to excitotoxicity and neuronal damage [81]. Lipid metabolism is also dysregulated from the early phases of AD, with increased cholesteryl esters and impaired cholesterol transport contributing to amyloidosis [82]. Fatty acid imbalance, characterized by increased free fatty acids, leads to mitochondrial dysfunction and sustained neurodegeneration [83].

In contrast to AD, GBM exhibits a highly active and adaptive metabolic phenotype that supports rapid cell growth and proliferation. A hallmark of GBM metabolism is the Warburg effect, characterized by increased glycolysis and lactate production even in the presence of oxygen [84]. This metabolic shift is driven by upregulation of key glycolytic enzymes, including hexokinase 2 (HK2), phosphofructokinase (PFKFB3), pyruvate kinase M2 (PKM2), and lactate dehydrogenase A (LDHA), as well as glucose transporters such as GLUT1 (SLC2A1) [85]. Hypoxia-inducible factor 1-alpha (HIF1A) plays a central role in this process by promoting glycolytic gene expression and suppressing mitochondrial oxidative metabolism under hypoxic conditions commonly found within the tumor microenvironment. In addition to glycolysis, GBM cells rely heavily on glutamine metabolism, with increased expression of glutaminase (GLS) supporting nucleotide biosynthesis, redox balance, and anaplerotic replenishment of the tricarboxylic acid (TCA) cycle [86]. Lipid metabolism is also upregulated, with enhanced fatty acid synthesis mediated by enzymes such as fatty acid synthase (FASN) and acetyl-CoA carboxylase (ACC), providing essential components for membrane biogenesis and signaling molecules [87].

Mitochondria in GBM are not dysfunctional but rather reprogrammed to support biosynthetic and survival functions. The PI3K/AKT/mTOR pathway, frequently activated in GBM through alterations in EGFR, PTEN, and PIK3CA, enhances glucose uptake, protein synthesis, and lipid production [88]. Additionally, oncogenes such as MYC further drive metabolic reprogramming by coordinating glycolysis, glutaminolysis, and mitochondrial biogenesis [89]. This integrated metabolic network enables GBM cells to adapt to fluctuating environmental conditions and sustain tumor growth.

Despite their contrasting metabolic phenotypes, AD and GBM share alterations in several core metabolic pathways, including mitochondrial function and redox regulation. In AD, mitochondrial dysfunction leads to reduced ATP production and increased oxidative stress, with elevated ROS levels contributing to protein damage, lipid peroxidation, and DNA damage [90]. In GBM, moderate ROS production is maintained at levels that promote signaling and proliferation while being tightly regulated by antioxidant systems such as glutathione (GSH) and enzymes like superoxide dismutase (SOD) [91]. Another point of convergence is the regulation of the AMP-activated protein kinase (AMPK) and mTOR pathways, which coordinate cellular responses to energy availability. In AD, AMPK is often overactivated in response to energy stress, leading to inhibition of anabolic processes and promotion of catabolic pathways such as autophagy [92]. In contrast, GBM frequently exhibits hyperactivation of mTOR signaling, favoring anabolic growth and suppressing autophagy [93]. Additionally, metabolites such as acetyl-CoA, NAD^+, and α-ketoglutarate act as cofactors for chromatin-modifying enzymes, thereby linking metabolic state to gene expression. In GBM, accumulation of oncometabolites such as 2-hydroxyglutarate (in IDH-mutant tumors) alters epigenetic landscapes, while in AD, reduced NAD^+ levels impair sirtuin activity and mitochondrial function [94]. Table 4 synthesizes the most relevant aspects discussed in this subsection.

Table 4. Metabolic reprogramming in AD and GBM—a synthetic overview.

Shared Metabolic Pathway	Alzheimer's Disease	Glioblastoma
Glucose metabolism	Reduced glucose uptake and utilization	Increased glucose uptake and glycolysis (Warburg effect)
Mitochondrial biogenesis	Impaired (reduced PGC-1α, NRF1)	Maintained or enhanced
Mitochondrial function	Dysfunctional mitochondria, impaired oxidative phosphorylation	Functionally reprogrammed mitochondria supporting biosynthesis
Electron transport chain (ETC)	Downregulation of ETC components	Partial suppression, but compensated by glycolysis
Oxidative stress	Excess reactive oxygen species (ROS) results in cellular damage and apoptosis	Controlled ROS results in signaling and proliferation
Lipid metabolism	Dysregulated cholesterol transport, increased cholesteryl esters, APOE alterations, accumulation of free fatty acids	Increased fatty acid synthesis and lipid production
Glutamate metabolism	Dysregulated resulting excitotoxicity	Rewired for tumor metabolism
Redox systems	Impaired antioxidant defenses	Enhanced antioxidant systems (GSH, SOD)

7. Neuroinflammation, Local Microenvironment, and Systems-Level Network Integration Insights of the AD-GBM Association

Neuroinflammation is a central and shared feature of both AD and GBM, yet it yields fundamentally divergent functional outcomes shaped by the local microenvironment. In AD, chronic neuroinflammation is largely driven by activated microglia and astrocytes in response to Aβ plaques and tau pathology [95]. DAMs, characterized by the expression of TREM2, APOE, TYROBP, and complement components such as C1QA and C3, adopt a predominantly pro-inflammatory and neurotoxic phenotype. These cells contribute to synaptic pruning, release of cytokines (e.g., IL-1β, TNF-α), and propagation of neuronal damage [96]. In contrast, the tumor microenvironment of GBM is enriched with TAMs, derived from both resident microglia and infiltrating monocytes, which are reprogrammed toward an immunosuppressive, tumor-supportive phenotype. These TAMs exhibit increased expression of markers such as CD163, CD206 (MRC1), ARG1, and anti-inflammatory cytokines (e.g., IL-10, TGF-β), promoting tumor growth, angiogenesis, and immune evasion [97].

Astrocytes further contribute to the divergent inflammatory landscapes of AD and GBM. In AD, reactive astrocytes (often classified as the A1 neurotoxic phenotype) upregulate GFAP, SERPINA3, and complement cascade components, amplifying neuroinflammation and contributing to neuronal dysfunction [98]. In GBM, astrocyte-like tumor cells and tumor-associated astrocytes support tumor progression by secreting growth factors such as VEGF, EGF, and TGF-β, as well as by modulating extracellular matrix remodeling [99]. Moreover, astrocytes in the GBM microenvironment can facilitate therapeutic resistance by enhancing survival signaling and protecting tumor cells from cytotoxic stress [100].

At the molecular level, immune signaling pathways are deeply integrated across multiple omics layers, including transcriptomics, proteomics, and epigenomics. In AD, activation of innate immune pathways, particularly those mediated by NF-κB, NLRP3 inflammasome, and complement signaling, drives chronic inflammation and neuronal injury [101]. In GBM, similar pathways are activated but co-opted to promote immunosuppression and tumor progression. For example, NF-κB signaling enhances the expression of pro-survival and pro-invasive genes, while immune checkpoint molecules such as PD-L1 (CD274) are upregulated, contributing to T-cell dysfunction [102]. Multi-omics analyses have revealed that cytokine networks, chemokines (e.g., CCL2, CXCL8), and immune modulators are shared between AD and GBM but are differentially regulated, resulting in either neurotoxicity or tumor-promoting inflammation.

An additional extracerebral dimension that may be relevant to both AD and GBM is the gut–brain axis. Alterations in gut microbiota composition have been increasingly associated with AD pathophysiology, potentially through systemic inflammation, blood–brain barrier permeability, microbial metabolites, amyloid-like bacterial products, and modulation of microglial activation [103]. In parallel, emerging neuro-oncology studies suggest that gut microbiota may influence glioma biology by shaping systemic and intratumoral immune responses, regulating short-chain fatty acids and other metabolites, and potentially affecting responses to immunotherapy [104]. These observations do not establish a direct microbiome-mediated link between AD and GBM, but they suggest that extracerebral factors may modulate the inflammatory, metabolic, and immune pathways discussed above. Therefore, the gut microbiota–brain axis should be considered a potentially relevant peripheral modifier of the proposed AD-GBM framework.

From a systems biology perspective, these complex interactions can be understood through network-based approaches that integrate molecular and cellular data (see Figure 1). Protein–protein interaction (PPI) networks constructed from multi-omics datasets have identified highly interconnected modules involving inflammation, cell cycle regulation, and stress response pathways that are common to both AD and GBM. Within these networks, key hub genes are differently modulated and differ between the two diseases. Among these, TP53 plays a critical role in determining cell fate, promoting apoptosis and genomic stability in AD [105], and is frequently mutated or inactivated in GBM, thereby enabling tumor progression [106]. Similarly, the PI3K/AKT/mTOR pathway functions as a major signaling hub, integrating growth factor signaling, metabolism, and survival; it is typically downregulated or dysregulated in AD but hyperactivated in GBM due to alterations in EGFR, PTEN, and PIK3CA. Other important network hubs include MYC, which drives metabolic and proliferative programs in GBM but is tightly regulated in neurons, and NF-κB, which coordinates inflammatory responses in both diseases with divergent outcomes [107].

Still, a limitation concerns the level of causal inference supported by the available evidence. The multi-omics and systems-biology findings integrated in this review are predominantly associational: they identify statistical enrichment, correlative network structure, and candidate regulatory nodes, but they cannot establish that the shared pathways reviewed here are mechanistically sufficient to drive either disease, nor that their modulation is causal rather than consequential. Direct functional evidence remains scarce, and what exists comes largely from non-human systems and small experimental series. Testing the proposed neurodegeneration–tumorigenesis axis would require, at minimum, perturbation studies in animal models or patient-derived brain organoids to determine whether manipulating the implicated nodes, such as p53, PI3K/AKT/mTOR and related axes, shifts cellular phenotype, together with longitudinal human data integrating molecular and clinical measures. Until such evidence is available, the model advanced here should be considered hypothesis-generating, and our conclusions are framed accordingly.

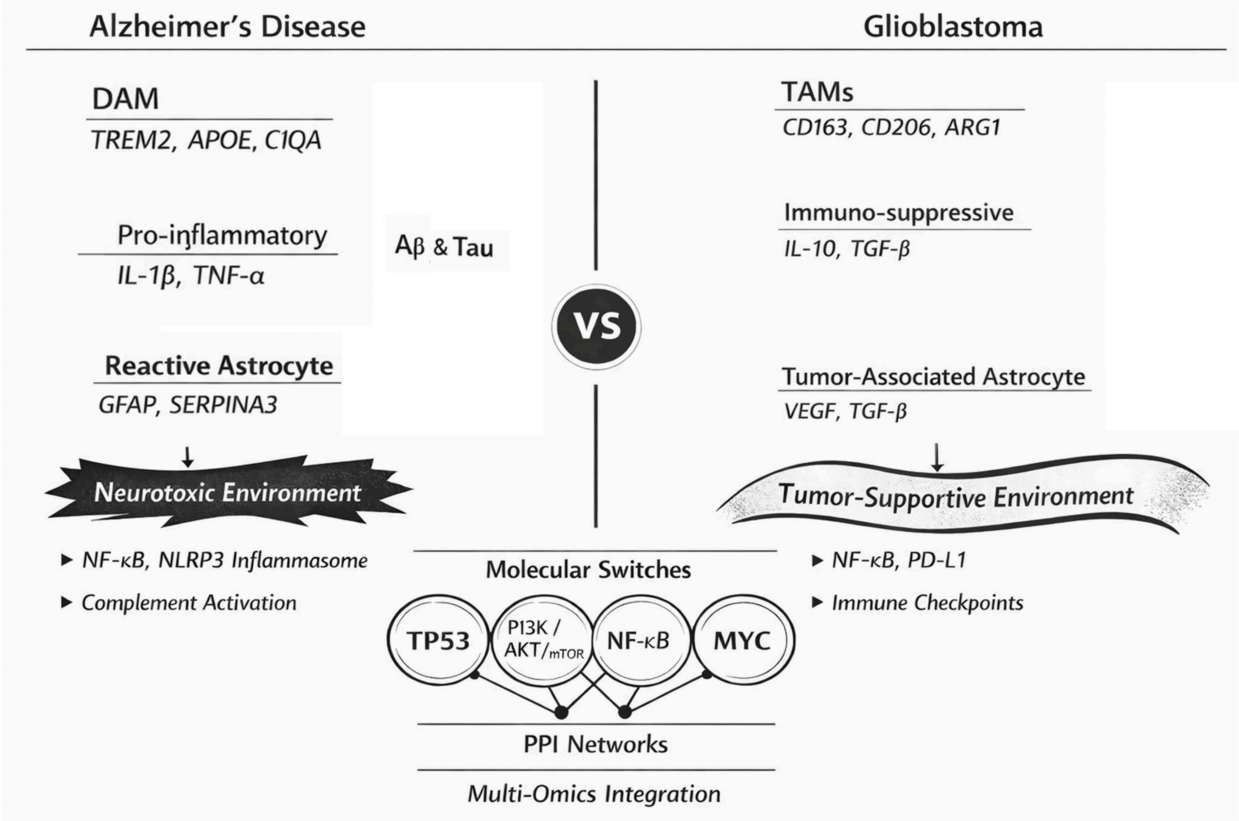


Figure 1. Systems biology perspective on neuroinflammation and tumor microenvironment related to the AD-GBM association. Abbreviations used in the figure are the same as in the main text.

8. Therapeutic Perspective: Shared Targets, Repurposing Opportunities, and Risks

The therapeutic implications discussed in this section should be interpreted according to the level of supporting evidence. Most drug-repurposing candidates proposed in the AD-GBM context are supported primarily by preclinical or indirect evidence, including cell-culture and animal model studies, computational pathway analyses, and observational associations in AD or cancer populations. By contrast, human interventional evidence directly testing these agents in relation to the AD-GBM inverse association is currently very limited or absent. Therefore, the candidates reviewed below should not be regarded as clinically validated therapies, but as hypothesis-generating leads requiring stepwise translational evaluation, including confirmation of target engagement, blood–brain barrier penetration, disease-stage specificity, safety in older and cognitively vulnerable populations, and prospective clinical testing. It is important to distinguish evidence obtained in one disease from evidence supporting use in the other: a completed oncology trial of an mTOR inhibitor establishes tolerability and activity in GBM, but provides no information about its effects on cognition, synaptic function or neuropathology, and the converse applies to agents developed for AD.

The recognition of a shared yet oppositely regulated molecular landscape between AD and GBM might have relevant therapeutic implications. Several molecular pathways implicated in both AD and GBM represent potential shared therapeutic targets. One interesting example is the PI3K/AKT/mTOR axis, a central regulator of cell growth, metabolism, and survival. Pharmacological inhibitors of this pathway, including mTOR inhibitors such as rapamycin and its analogs, have demonstrated anti-tumor activity and are being explored in GBM clinical trials [108]. Modulation of mTOR signaling has also been investigated in AD,

where excessive or dysregulated signaling contributes to impaired autophagy and accumulation of misfolded proteins. In this context, mTOR inhibition may enhance autophagic clearance of Aβ and tau aggregates, suggesting a potential therapeutic overlap [109]. This example also illustrates the central difficulty of the shared-target approach. mTOR activity is anti-proliferative and can be inhibited in GBM, but in AD it supports cap-dependent translation required for synaptic plasticity and long-term memory consolidation; sustained pharmacological suppression of the same node may therefore be desirable in one disease and detrimental in the other. The direction of the desired modulation, and not merely the identity of the target, is what distinguishes the two therapeutic contexts.

Similarly, neuroinflammatory pathways represent a convergent target. Targeting key inflammatory mediators, such as the NF-κB pathway or cytokine signaling (e.g., IL-1β, TGF-β), may therefore have dual relevance. Additionally, modulation of immune checkpoints, including PD-1/PD-L1 signaling, has shown promise in oncology [110] and is being explored for its potential role in neurodegenerative diseases, although with limited success to date [111]. Proteostasis pathways, including the ubiquitin–proteasome system and autophagy–lysosomal pathways, also represent shared therapeutic opportunities. Enhancing protein clearance mechanisms may be beneficial in AD by reducing toxic aggregates [112], while in GBM, targeting proteostasis could disrupt the high protein turnover required for tumor growth [113]. Chaperone inhibitors (e.g., HSP90 inhibitors) and autophagy modulators are currently under investigation in oncology and may have relevance across both disease contexts [114].

The overlap in molecular pathways between AD and GBM provides a rationale for drug repurposing strategies. Several anti-cancer agents have been evaluated for their potential neuroprotective effects. For example, PI3K/AKT/mTOR inhibitors and certain tyrosine kinase inhibitors (TKIs) targeting EGFR or PDGFRA may modulate signaling pathways implicated in AD pathology [115]. Conversely, drugs developed for AD, such as tau protein aggregation modulators or Aβ-targeting molecules, may influence tumor biology, although evidence remains limited [116]. Metabolic modulators represent another promising area. Agents targeting glycolysis or mitochondrial function, such as metformin, have been investigated in both cancer and neurodegeneration. Metformin activates AMP-activated protein kinase (AMPK), influencing energy metabolism and potentially exerting antitumor and neuroprotective effects [117]. Similarly, anti-inflammatory agents and antioxidants may have cross-disease applicability by modulating shared pathways of oxidative stress and inflammation, with trials in progress. However, metabolic interventions require particular caution, since the metabolic states of the two diseases are not simply reciprocal: agents that restore neuronal energy balance or mitochondrial function may equally supply substrates and survival signals to tumour cells, and the net effect is likely to depend on dose, exposure duration and disease stage.

Figure 2 illustrates the potential therapeutic modalities targeting shared mechanisms in AD and GBM.

Despite these opportunities, successful translation remains challenging due to differences in disease context, blood–brain barrier penetration, and cell-type-specific effects. These barriers warrant explicit emphasis. Blood–brain barrier penetration varies widely across the drug classes discussed. It is inadequate for many agents at systemically tolerable doses, so that several repurposing candidates are unlikely to reach the relevant central nervous system compartment at all. Selectivity is a further problem: inhibitors of PI3K/AKT/mTOR, NF-κB or the proteostasis machinery act on nodes with broad downstream effects, and the resulting pharmacological profile may differ substantially between tumour cells and post-mitotic neurons. A critical consideration in targeting shared pathways is the potential for unintended consequences arising from their opposing roles in AD and

GBM. For instance, inhibition of cell proliferation pathways may be beneficial in GBM but could exacerbate neuronal loss or impair regenerative processes in AD. Conversely, therapies aimed at enhancing neuronal survival or reducing apoptosis in AD might inadvertently promote tumorigenesis by facilitating cell survival and proliferation.

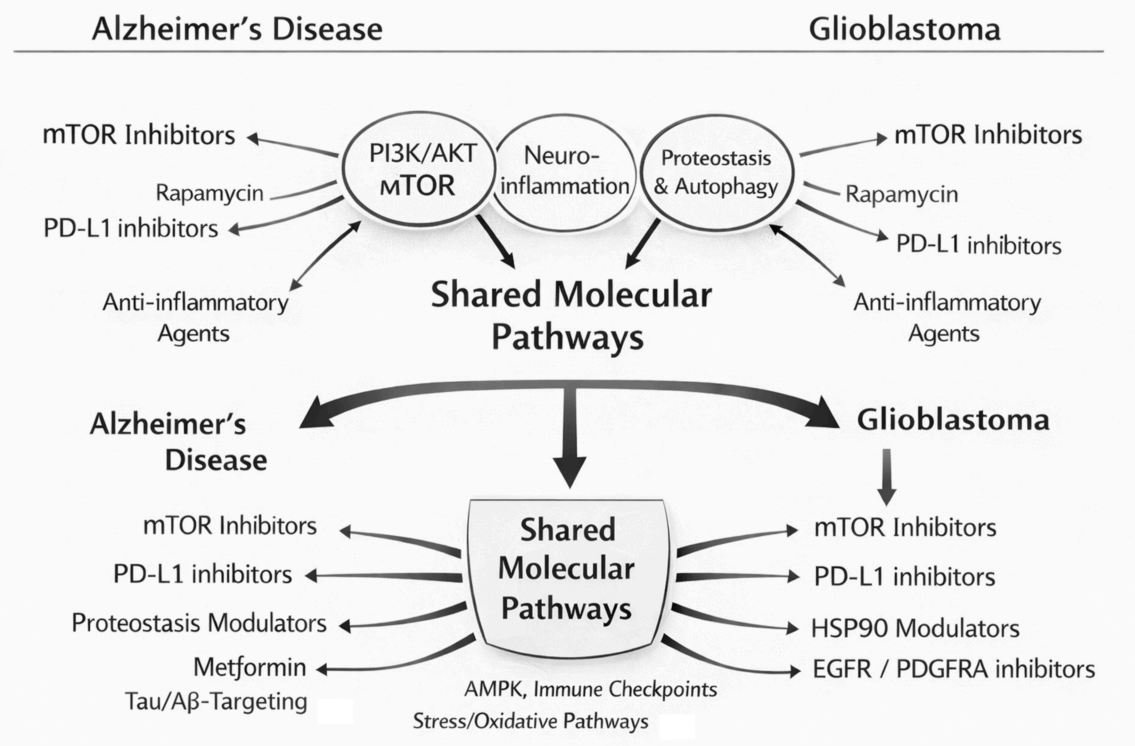


Figure 2. Potential therapeutic modalities targeting shared mechanisms in AD and GBM.

Modulation of immune responses also presents a double-edged sword. While suppressing neuroinflammation may be beneficial in AD, similar strategies could impair anti-tumor immunity in GBM [118]. Immunostimulatory approaches used in cancer therapy may increase neuroinflammation and accelerate neurodegeneration. Likewise, metabolic interventions that restore energy balance in AD could potentially support tumor growth if not carefully controlled. These risks highlight the need for a nuanced, systems-level understanding of disease biology. Therapeutic strategies should aim to selectively modulate pathway activity in a cell-type- and context-specific manner, potentially through targeted delivery systems or precision medicine approaches.

9. Conclusions and Future Directions

The evidence synthesized across epidemiological, transcriptomic, proteomic, epigenomic, metabolic, and immunological domains is consistent with a potential AD-GBM association, but does not establish a unified biological mechanism. Within this conceptual model, AD and GBM may be interpreted as contrasting disease states within a broader degeneration–proliferation framework, rather than as strict opposite extremes of a single continuum. They share several molecular networks that appear to be differentially regulated, including pathways related to cell-cycle control, apoptosis, metabolism, proteostasis, and immune signaling. However, these pathways are not uniformly or exclusively disease-specific, and their effects depend on cell type, disease stage, tissue microenvironment, genetic background, and analytical context. Central regulatory nodes such as TP53 and the PI3K/AKT/mTOR pathway should therefore be regarded as candidate context-dependent hubs, not as experimentally validated molecular switches determining cellular fate.

Advances in single-cell and spatial multi-omics technologies may further refine this model by enabling high-resolution mapping of cellular states and interactions within the brain. Single-cell RNA sequencing, combined with epigenomic and proteomic profiling, could allow the identification of transitional cell populations and dynamic regulatory states that may predispose toward either neurodegeneration or tumorigenesis. Spatial transcriptomics can add critical context by preserving tissue architecture and revealing how microenvironmental factors shape disease trajectories. These approaches, integrated through systems biology and computational modeling, may facilitate the discovery of biomarkers that predict disease directionality, identify individuals at risk of developing AD versus GBM, or even detect early shifts along the degeneration–proliferation axis.

In conclusion, the AD–GBM association provides a novel conceptual and translational framework that integrates diverse molecular and cellular findings into a coherent model of brain disease. Recognizing the shared yet oppositely regulated pathways underlying AD and GBM has important implications for understanding disease mechanisms and identifying therapeutic targets. Future research should focus on validating this inverse association through longitudinal, multi-omics studies and on developing precision medicine approaches that account for the dual nature of these pathways. Importantly, therapeutic repurposing opportunities arising from this framework remain largely preclinical and should be advanced only after rigorous functional validation, pharmacokinetic assessment, and prospective human studies.

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Abbreviations

ACC	acetyl-CoA carboxylase
AD	Alzheimer's disease
AMPK	AMP-activated protein kinase
DAM	disease-associated microglia
EGFR	epidermal growth factor receptor
FASN	fatty acid synthase
GBM	glioblastoma
GSH	glutathione
PPI	protein–protein interaction
scRNA-seq	single-cell RNA sequencing
SOD	superoxide dismutase

TKIs	tyrosine kinase inhibitors
UCHL1	ubiquitin carboxyl-terminal hydrolase L1

References

1. Safiri, S.; Ghaffari Jolfayi, A.; Fazlollahi, A.; Morsali, S.; Sarkesh, A.; Daei Sorkhabi, A.; Golabi, B.; Aletaha, R.; Motlagh Asghari, K.; Hamidi, S.; et al. Alzheimer's disease: A comprehensive review of epidemiology, risk factors, symptoms diagnosis, management, caregiving, advanced treatments and associated challenges. *Front. Med.* **2024**, *11*, 1474043. [CrossRef]
2. Liu, W.; Deng, W.; Gong, X.; Ou, J.; Yu, S.; Chen, S. Global burden of Alzheimer's disease and other dementias in adults aged 65 years and over, and health inequality related to SDI, 1990–2021: Analysis of data from GBD 2021. *BMC Public Health* **2025**, *25*, 1256. [CrossRef]
3. Ma, C.; Hong, F.; Yang, S. Amyloidosis in Alzheimer's Disease: Pathogeny, Etiology, and Related Therapeutic Directions. *Molecules* **2022**, *27*, 1210. [CrossRef]
4. Metaxas, A.; Kempf, S.J. Neurofibrillary tangles in Alzheimer's disease: Elucidation of the molecular mechanism by immunohistochemistry and tau protein phospho-proteomics. *Neural Regen. Res.* **2016**, *11*, 1579–1581. [CrossRef]
5. Chen, Y.; Fu, A.K.Y.; Ip, N.Y. Synaptic dysfunction in Alzheimer's disease: Mechanisms and therapeutic strategies. *Pharmacol. Ther.* **2019**, *195*, 186–198. [CrossRef]
6. Testo, A.A.; Roundy, G.; Dumas, J.A. Cognitive Decline in Alzheimer's Disease. *Curr. Top. Behav. Neurosci.* **2025**, *69*, 181–195. [CrossRef]
7. Ciurea, V.A.; Covache-Busuioc, R.A.; Mohan, A.G.; Costin, H.P.; Voicu, V. Alzheimer's disease: 120 years of research and progress. *J. Med. Life* **2023**, *16*, 173–177. [CrossRef]
8. Smith, B.; Ownby, R.L. Disease-Modifying Treatments and Their Future in Alzheimer's Disease Management. *Cureus* **2024**, *16*, e56105. [CrossRef]
9. Pan, Y.; Cho, H.; Lou, Q.; Zhang, W.; Asken, B.; Song, Q. Genetic risk in Alzheimer's disease. *npj Syst. Biol. Appl.* **2026**, *12*, 39. [CrossRef]
10. Christodoulou, R.C.; Eller, D.; Papageorgiou, P.S.; Angelopoulou, E.; Vassiliou, E.; Papageorgiou, S.G. Metabolic Dysfunction in Alzheimer's Disease: Brain Glucose Hypometabolism as an Early Precursor to Amyloid and Tau Pathology. *J. Clin. Med.* **2026**, *15*, 1884. [CrossRef]
11. Wang, S.; Liao, Z.; Zhang, Q.; Han, X.; Liu, C.; Wang, J. Mitochondrial dysfunction in Alzheimer's disease: A key frontier for future targeted therapies. *Front. Immunol.* **2025**, *15*, 1484373. [CrossRef]
12. Kiraly, M.; Foss, J.F.; Giordano, T. Neuroinflammation, its Role in Alzheimer's Disease and Therapeutic Strategie. *J. Prev. Alzheimer's Dis.* **2023**, *10*, 686–698. [CrossRef]
13. Zhang, Y.Y.; Ruan, L.X.; Zhang, S. Rapid progression of glioblastoma multiforme: A case report. *Oncol. Lett.* **2016**, *12*, 4803–4806. [CrossRef]
14. Doroszko, M.; Stockgard, R.; Uppman, I.; Heinold, J.; Voukelatou, F.; Mangukiya, H.B.; Millner, T.O.; Skeppås, M.; Ballester Bravo, M.; Elgendy, R.; et al. The invasion phenotypes of glioblastoma depend on plastic and reprogrammable cell states. *Nat. Commun.* **2025**, *16*, 6662. [CrossRef]
15. Yalamarty, S.S.K.; Filipczak, N.; Li, X.; Subhan, M.A.; Parveen, F.; Ataide, J.A.; Rajmalani, B.A.; Torchilin, V.P. Mechanisms of Resistance and Current Treatment Options for Glioblastoma Multiforme (GBM). *Cancers* **2023**, *15*, 2116. [CrossRef]
16. Brown, N.F.; Ottaviani, D.; Tazare, J.; Gregson, J.; Kitchen, N.; Brandner, S.; Fersht, N.; Mulholland, P. Survival Outcomes and Prognostic Factors in Glioblastoma. *Cancers* **2022**, *14*, 3161. [CrossRef]
17. Barcan, E.N.; Duta, C.; Staicu, G.A.; Artene, S.A.; Alexandru, O.; Costachi, A.; Pirvu, A.S.; Tache, D.E.; Stoian, I.; Popescu, S.O.; et al. Current Research Trends in Glioblastoma: Focus on Receptor Tyrosine Kinases. *Int. J. Mol. Sci.* **2025**, *26*, 3503. [CrossRef]
18. Pournajaf, S.; Pourgholami, M.H. The mTOR pathway in Gliomas: From molecular insights to targeted therapies. *Biomed. Pharmacother.* **2025**, *189*, 118237. [CrossRef]
19. Gousias, K.; Theocharous, T.; Simon, M. Mechanisms of Cell Cycle Arrest and Apoptosis in Glioblastoma. *Biomedicines* **2022**, *10*, 564. [CrossRef]
20. Goel, P.; Chakrabarti, S.; Goel, K.; Bhutani, K.; Chopra, T.; Bali, S. Neuronal cell death mechanisms in Alzheimer's disease: An insight. *Front. Mol. Neurosci.* **2022**, *15*, 937133. [CrossRef]
21. Lin, H.; Liu, C.; Hu, A.; Zhang, D.; Yang, H.; Mao, Y. Understanding the immunosuppressive microenvironment of glioma: Mechanistic insights and clinical perspectives. *J. Hematol. Oncol.* **2024**, *17*, 31. [CrossRef]
22. Salemi, M.; Mogavero, M.P.; Lanza, G.; Mongioì, L.M.; Calogero, A.E.; Ferri, R. Examples of Inverse Comorbidity between Cancer and Neurodegenerative Diseases: A Possible Role for Noncoding RNA. *Cells* **2022**, *11*, 1930. [CrossRef]

23. Bassil, D.T.; Zheng, B.; Su, B.; Kafetsouli, D.; Udeh-Momoh, C.; Tzoulaki, I.; Ahmadi-Abhari, S.; Muller, D.C.; Riboli, E.; Middleton, L.T. Lower Incidence of Dementia Following Cancer Diagnoses: Evidence from a Large Cohort and Mendelian Randomization Study. *J. Prev. Alzheimer's Dis.* **2024**, *11*, 1397–1405. [CrossRef]
24. Mezencev, R.; Chernoff, Y.O. Risk of Alzheimer's Disease in Cancer Patients: Analysis of Mortality Data from the US SEER Population-Based Registries. *Cancers* **2020**, *12*, 796. [CrossRef]
25. Kang, H.S.; Kim, J.H.; Lim, H.; Kim, J.-H.; Noh, H.-M.; Choi, H.G.; Min, K.-W.; Kim, N.Y.; Kwon, M.J. Alzheimer's Disease and Different Types of Cancer Likelihood: Unveiling Disparities and Potential Protective Effects in a Korean Cohort Study. *Cancers* **2023**, *15*, 4615. [CrossRef]
26. Vitorino, R. Transforming Clinical Research: The Power of High-Throughput Omics Integration. *Proteomes* **2024**, *12*, 25. [CrossRef]
27. Zabłocka, A.; Kazana, W.; Sochocka, M.; Stańczykiewicz, B.; Janusz, M.; Leszek, J.; Orzechowska, B. Inverse Correlation Between Alzheimer's Disease and Cancer: Short Overview. *Mol. Neurobiol.* **2021**, *58*, 6335–6349. [CrossRef]
28. Su, Z.; Zhang, G.; Li, X.; Zhang, H. Inverse correlation between Alzheimer's disease and cancer from the perspective of hypoxia. *Neurobiol. Aging* **2023**, *131*, 59–73. [CrossRef]
29. Xia, S.; Chen, H.; Tang, T. Risk of Death from Alzheimer's Disease Associated with Brain Tumor, Glioma, and Glioblastoma. *J. Alzheimer's Dis.* **2023**, *96*, 623–631. [CrossRef]
30. Xu, X.; Wang, J.; Chen, T.; Wang, S.; Wang, F.; He, J.; Meng, X.Y.; Shen, Y. Deciphering novel mitochondrial signatures: Multi-omics analysis uncovers cross-disease markers and oligodendrocyte pathways in Alzheimer's disease and glioblastoma. *Front. Aging Neurosci.* **2025**, *17*, 1536142. [CrossRef]
31. Liu, Y.; Chen, Y.; Gao, M.; Luo, J.; Wang, Y.; Wang, Y.; Gao, Y.; Yang, L.; Wang, J.; Wang, N. Association between glioma and neurodegenerative diseases risk: A two-sample bi-directional Mendelian randomization analysis. *Front. Neurol.* **2024**, *15*, 1413015. [CrossRef]
32. Ospina-Romero, M.; Glymour, M.M.; Hayes-Larson, E.; Mayeda, E.R.; Graff, R.E.; Brenowitz, W.D.; Ackley, S.F.; Witte, J.S.; Kobayashi, L.C. Association Between Alzheimer Disease and Cancer with Evaluation of Study Biases: A Systematic Review and Meta-analysis. *JAMA Netw. Open* **2020**, *3*, e2025515. [CrossRef]
33. Zheng, G.; Xu, M.; Dong, Z.; Abdelrahman, Z.; Wang, X. Meta-analysis reveals an inverse relationship between Alzheimer's disease and cancer. *Behav. Brain Res.* **2025**, *478*, 115327. [CrossRef]
34. Ghadimi, K.; Abbas, I.; Karandish, A.; Crisman, C.; Eskandar, E.N.; Kobets, A.J. Cognitive Decline in Glioblastoma (GB) Patients with Different Treatment Modalities and Insights on Untreated Cases. *Curr. Oncol.* **2025**, *32*, 152. [CrossRef]
35. Furukawa, T.A.; Guyatt, G.H. Sources of bias in diagnostic accuracy studies and the diagnostic process. *CMAJ* **2006**, *174*, 481–482. [CrossRef]
36. Damen, J.A.A.G.; Debray, T.P.A.; Pajouheshnia, R.; Reitsma, J.B.; Scholten, R.J.P.M.; Moons, K.G.M.; Hooft, L. Empirical evidence of the impact of study characteristics on the performance of prediction models: A meta-epidemiological study. *BMJ Open* **2019**, *9*, e026160. [CrossRef]
37. Fetcko-Fayad, K.; Batich, K.; Reitman, Z.J.; Walsh, K.M.; Chamberlin, G.; Smith, V.; Jones, K.; Cummings, T.; Peters, K.B. Coexisting Biopsy-Diagnosed Dementia and Glioblastoma. *Brain Sci.* **2024**, *14*, 143. [CrossRef]
38. Agnello, L.; Gambino, C.M.; Ciaccio, A.M.; Cacciabaudo, F.; Massa, D.; Masucci, A.; Tamburello, M.; Vassallo, R.; Midiri, M.; Scazzone, C.; et al. From Amyloid to Synaptic Dysfunction: Biomarker-Driven Insights into Alzheimer's Disease. *Curr. Issues Mol. Biol.* **2025**, *47*, 580. [CrossRef]
39. Pouyan, A.; Ghorbanlo, M.; Eslami, M.; Jahanshahi, M.; Ziaei, E.; Salami, A.; Mokhtari, K.; Shahpasand, K.; Farahani, N.; Meybodi, T.E.; et al. Glioblastoma multiforme: Insights into pathogenesis, key signaling pathways, and therapeutic strategies. *Mol. Cancer* **2025**, *24*, 58, Erratum in *Mol. Cancer* **2026**, *25*, 156. https://doi.org/10.1186/s12943-026-02717-3.. [CrossRef]
40. Lyons, C.E.; Bartolomucci, A. Stress and Alzheimer's disease: A senescence link? *Neurosci. Biobehav. Rev.* **2020**, *115*, 285–298. [CrossRef]
41. Mokhles, F.; Moosavi, M.A.; Gutierrez-Uzquiza, A.; Velasco, G.; Li, M.; Cordani, M. Unraveling stress-adaptation pathways in cancer: Functional dissection through CRISPR-based genetic screens. *Cancer Lett.* **2026**, *644*, 218246. [CrossRef]
42. Liu, B.; Peng, D.; Chen, Y.; Li, Q.; Hu, Y.; Liu, S.; Hu, H. Multi-omics analysis identifies CCNB1 as a cell cycle factor driving glioblastoma progression and its inhibition by resveratrol. *PLoS ONE* **2026**, *21*, e0344872. [CrossRef]
43. Lanza, M.; Scuruchi, M.; Saitta, A.; Basilotta, R.; Aliquò, F.; Casili, G.; Esposito, E.; Copani, A.; Oddo, S.; Caccamo, A. Aberrant Cell Cycle Gene Expression in a Transgenic Mouse Model of Alzheimer's Disease. *Cells* **2026**, *15*, 132. [CrossRef]
44. Cortes Ballen, A.I.; Amosu, M.; Ravinder, S.; Chan, J.; Derin, E.; Slika, H.; Tyler, B. Metabolic Reprogramming in Glioblastoma Multiforme: A Review of Pathways and Therapeutic Targets. *Cells* **2024**, *13*, 1574. [CrossRef]
45. Wolfrum, P.; Fietz, A.; Schnichels, S.; Hurst, J. The function of p53 and its role in Alzheimer's and Parkinson's disease compared to age-related macular degeneration. *Front. Neurosci.* **2022**, *16*, 1029473. [CrossRef]
46. Razani, E.; Pourbagheri-Sigaroodi, A.; Safaroghli-Azar, A.; Zoghi, A.; Shanaki-Bavarsad, M.; Bashash, D. The PI3K/Akt signaling axis in Alzheimer's disease: A valuable target to stimulate or suppress? *Cell Stress Chaperones* **2021**, *26*, 871–887. [CrossRef]

47. Marinkovic, T.; Marinkovic, D. Obscure Involvement of MYC in Neurodegenerative Diseases and Neuronal Repair. *Mol. Neurobiol.* **2021**, *58*, 4169–4177. [CrossRef]
48. Williams, J.B.; Cao, Q.; Yan, Z. Transcriptomic analysis of human brains with Alzheimer's disease reveals the altered expression of synaptic genes linked to cognitive deficits. *Brain Commun.* **2021**, *3*, fcab123. [CrossRef]
49. Spanos, F.; Liddelow, S.A. An Overview of Astrocyte Responses in Genetically Induced Alzheimer's Disease Mouse Models. *Cells* **2020**, *9*, 2415. [CrossRef]
50. Uribe, D.; Niechi, I.; Rackov, G.; Erices, J.I.; San Martín, R.; Quezada, C. Adapt to Persist: Glioblastoma Microenvironment and Epigenetic Regulation on Cell Plasticity. *Biology* **2022**, *11*, 313. [CrossRef]
51. Fujikawa, R.; Tsuda, M. The Functions and Phenotypes of Microglia in Alzheimer's Disease. *Cells* **2023**, *12*, 1207. [CrossRef]
52. Zhao, W.; Zhang, Z.; Xie, M.; Ding, F.; Zheng, X.; Sun, S.; Du, J. Exploring tumor-associated macrophages in glioblastoma: From diversity to therapy. *npj Precis. Oncol.* **2025**, *9*, 126. [CrossRef]
53. Abate, G.; Frisoni, G.B.; Bourdon, J.C.; Piccirella, S.; Memo, M.; Uberti, D. The pleiotropic role of p53 in functional/dysfunctional neurons: Focus on pathogenesis and diagnosis of Alzheimer's disease. *Alzheimer's Res. Ther.* **2020**, *12*, 160. [CrossRef]
54. Zhang, Y.; Dube, C.; Gibert, M., Jr.; Cruickshanks, N.; Wang, B.; Coughlan, M.; Yang, Y.; Setiady, I.; Deveau, C.; Saoud, K.; et al. The p53 Pathway in Glioblastoma. *Cancers* **2018**, *10*, 297. [CrossRef]
55. Pan, J.; Yao, Q.; Wang, Y.; Chang, S.; Li, C.; Wu, Y.; Shen, J.; Yang, R. The role of PI3K signaling pathway in Alzheimer's disease. *Front. Aging Neurosci.* **2024**, *16*, 1459025. [CrossRef]
56. Carpenter, A.B.; Sacknovitz, A.; Hanft, S.; Gandhi, C.D.; Jhanwar-Uniyal, M. Complex role of mTOR signaling pathway in glioblastoma and its stem cells. *Adv. Biol. Regul.* **2025**, *100*, 101143. [CrossRef]
57. Plascencia-Villa, G.; Perry, G. Roles of Oxidative Stress in Synaptic Dysfunction and Neuronal Cell Death in Alzheimer's Disease. *Antioxidants* **2023**, *12*, 1628. [CrossRef]
58. Nowacka, A.; Śniegocki, M.; Ziółkowska, E. Oxidative Stress and Antioxidants in Glioblastoma: Mechanisms of Action, Therapeutic Effects and Future Directions. *Antioxidants* **2025**, *14*, 1121. [CrossRef]
59. Johnson, E.C.B.; Dammer, E.B.; Duong, D.M.; Ping, L.; Zhou, M.; Yin, L.; Higginbotham, L.A.; Guajardo, A.; White, B.; Troncoso, J.C.; et al. Large-scale proteomic analysis of Alzheimer's disease brain and cerebrospinal fluid reveals early changes in energy metabolism associated with microglia and astrocyte activation. *Nat. Med.* **2020**, *26*, 769–780. [CrossRef]
60. Anschuetz, A.; Schwab, K.; Harrington, C.R.; Wischik, C.M.; Riedel, G. Proteomic and non-proteomic changes of presynaptic proteins in animal models of Alzheimer's disease: A meta-analysis 2015–2023. *J. Alzheimer's Dis.* **2025**, *107*, 452–476. [CrossRef]
61. Ihara, Y.; Morishima-Kawashima, M.; Nixon, R. The ubiquitin-proteasome system and the autophagic-lysosomal system in Alzheimer disease. *Cold Spring Harb. Perspect. Med.* **2012**, *2*, a006361. [CrossRef]
62. Mi, Z.; Graham, S.H. Role of UCHL1 in the pathogenesis of neurodegenerative diseases and brain injury. *Ageing Res. Rev.* **2023**, *86*, 101856. [CrossRef]
63. Li, X.P.; Guo, Z.Q.; Wang, B.F.; Zhao, M. EGFR alterations in glioblastoma play a role in antitumor immunity regulation. *Front. Oncol.* **2023**, *13*, 1236246. [CrossRef]
64. Han, H.; Du, A.; Li, J.; Han, H.; Feng, P.; Zhu, Y.; Li, X.; Tian, G.; Yu, H.; Zhang, B.; et al. Transitioning from molecular methods to therapeutic methods: An in-depth analysis of glioblastoma (Review). *Oncol. Rep.* **2025**, *53*, 48. [CrossRef]
65. Iglesia, R.P.; Fernandes, C.F.L.; Coelho, B.P.; Prado, M.B.; Melo Escobar, M.I.; Almeida, G.H.D.R.; Lopes, M.H. Heat Shock Proteins in Glioblastoma Biology: Where Do We Stand? *Int. J. Mol. Sci.* **2019**, *20*, 5794. [CrossRef]
66. Nannuri, V.; Ababneh, E.; El Rayes, S.; Smith, J.; Sugaya, K.; Zhao, J. Extracellular Vesicles in Tauopathies: Mechanisms and Applications. *Int. J. Mol. Sci.* **2026**, *27*, 1998. [CrossRef]
67. Chen, Y.; Jin, Y.; Wu, N. Role of Tumor-Derived Extracellular Vesicles in Glioblastoma. *Cells* **2021**, *10*, 512. [CrossRef]
68. Delgado-Morales, R.; Esteller, M. Opening up the DNA methylome of dementia. *Mol. Psychiatry* **2017**, *22*, 485–496. [CrossRef]
69. Feldheim, J.; Kessler, A.F.; Monoranu, C.M.; Ernestus, R.I.; Löhr, M.; Hagemann, C. Changes of O^6-Methylguanine DNA Methyltransferase (MGMT) Promoter Methylation in Glioblastoma Relapse-A Meta-Analysis Type Literature Review. *Cancers* **2019**, *11*, 1837. [CrossRef]
70. Liu, Y.; Lang, F.; Chou, F.J.; Zaghloul, K.A.; Yang, C. Isocitrate Dehydrogenase Mutations in Glioma: Genetics, Biochemistry, and Clinical Indications. *Biomedicines* **2020**, *8*, 294. [CrossRef]
71. Janke, R.; Iavarone, A.T.; Rine, J. Oncometabolite D-2-Hydroxyglutarate enhances gene silencing through inhibition of specific H3K36 histone demethylases. *eLife* **2017**, *6*, e22451. [CrossRef]
72. Zhang, L.; Yang, Y.; Li, Y.; Wang, C.; Bian, C.; Wang, H.; Wang, F. Epigenetic regulation of histone modifications in glioblastoma: Recent advances and therapeutic insights. *Biomark. Res.* **2025**, *13*, 80. [CrossRef]
73. Wu, W.; Chen, W.; Ma, W.; Wang, Y. Epigenetic mechanisms and therapeutic advances in diffuse midline glioma (Review). *Oncol. Rep.* **2026**, *55*, 50. [CrossRef]
74. Kumar, V.; Kim, S.H.; Bishayee, K. Dysfunctional Glucose Metabolism in Alzheimer's Disease Onset and Potential Pharmacological Interventions. *Int. J. Mol. Sci.* **2022**, *23*, 9540. [CrossRef]

75. Alkhalifa, A.E.; Alkhalifa, O.; Durdanovic, I.; Ibrahim, D.R.; Maragkou, S. Oxidative Stress and Mitochondrial Dysfunction in Alzheimer's Disease: Insights into Pathophysiology and Treatment. *J. Dement. Alzheimer's Dis.* **2025**, *2*, 17. [CrossRef]
76. D'Alessandro, M.C.B.; Kanaan, S.; Geller, M.; Praticò, D.; Daher, J.P.L. Mitochondrial dysfunction in Alzheimer's disease. *Ageing Res. Rev.* **2025**, *107*, 102713. [CrossRef]
77. Fišar, Z. Linking the Amyloid, Tau, and Mitochondrial Hypotheses of Alzheimer's Disease and Identifying Promising Drug Targets. *Biomolecules* **2022**, *12*, 1676. [CrossRef]
78. Ye, Z.; Liu, Y.; Jin, X.; Wu, Y.; Zhao, H.; Gao, T.; Deng, Q.; Cheng, J.; Lin, J.; Tong, Z. Aβ-binding with alcohol dehydrogenase drives Alzheimer's disease pathogenesis: A review. *Int. J. Biol. Macromol.* **2024**, *264*, 130580. [CrossRef]
79. Xiao, X.; Yan, X.; Liang, C.; Yang, Y. Metabolic dysfunction and mitochondrial failure in Alzheimer's disease: Integrating pathophysiology, clinical evidence and emerging interventions. *Front. Neurol.* **2026**, *17*, 1772036. [CrossRef]
80. Yang, L.G.; March, Z.M.; Stephenson, R.A.; Narayan, P.S. Apolipoprotein E in lipid metabolism and neurodegenerative disease. *Trends Endocrinol. Metab.* **2023**, *34*, 430–445. [CrossRef]
81. Bukke, V.N.; Archana, M.; Villani, R.; Romano, A.D.; Wawrzyniak, A.; Balawender, K.; Orkisz, S.; Beggiato, S.; Serviddio, G.; Cassano, T. The Dual Role of Glutamatergic Neurotransmission in Alzheimer's Disease: From Pathophysiology to Pharmacotherapy. *Int. J. Mol. Sci.* **2020**, *21*, 7452. [CrossRef]
82. Yin, F. Lipid metabolism and Alzheimer's disease: Clinical evidence, mechanistic link and therapeutic promise. *FEBS J.* **2023**, *290*, 1420–1453. [CrossRef]
83. Yang, Y.; Wang, Q.; Wang, Z.; Wang, Y.; Liu, B.; Zhang, Y.; Mao, X.; Sun, H. The role of fatty acids in neurodegenerative diseases: Mechanistic insights and therapeutic strategies. *J. Lipid Res.* **2025**, *66*, 100944. [CrossRef]
84. Jacquet, P.; Stéphanou, A. Beyond the Warburg Effect: Modeling the Dynamic and Context-Dependent Nature of Tumor Metabolism. *Cancers* **2025**, *17*, 3563. [CrossRef]
85. Kathagen-Buhmann, A.; Maire, C.L.; Weller, J.; Schulte, A.; Matschke, J.; Holz, M.; Ligon, K.L.; Glatzel, M.; Westphal, M.; Lamszus, K. The secreted glycolytic enzyme GPI/AMF stimulates glioblastoma cell migration and invasion in an autocrine fashion but can have anti-proliferative effects. *Neuro-Oncol.* **2018**, *20*, 1594–1605. [CrossRef]
86. Gokani, V.; Kotta, A.; Repaka, V.; Rauniyar, S.; Noch, E.K. Targeting Metabolic Vulnerabilities in Glioblastoma: A Framework for Multi-node Combination Therapy. *Curr. Oncol. Rep.* **2026**, *28*, 19. [CrossRef]
87. Korbecki, J.; Bosiacki, M.; Gutowska, I.; Chlubek, D.; Baranowska-Bosiacka, I. Biosynthesis and Significance of Fatty Acids, Glycerophospholipids, and Triacylglycerol in the Processes of Glioblastoma Tumorigenesis. *Cancers* **2023**, *15*, 2183. [CrossRef]
88. Barzegar Behrooz, A.; Talaie, Z.; Jusheghani, F.; Łos, M.J.; Klonisch, T.; Ghavami, S. Wnt and PI3K/Akt/mTOR Survival Pathways as Therapeutic Targets in Glioblastoma. *Int. J. Mol. Sci.* **2022**, *23*, 1353. [CrossRef]
89. Cencioni, C.; Scagnoli, F.; Spallotta, F.; Nasi, S.; Illi, B. The "Superoncogene" Myc at the Crossroad between Metabolism and Gene Expression in Glioblastoma Multiforme. *Int. J. Mol. Sci.* **2023**, *24*, 4217. [CrossRef]
90. Misrani, A.; Tabassum, S.; Yang, L. Mitochondrial Dysfunction and Oxidative Stress in Alzheimer's Disease. *Front. Aging Neurosci.* **2021**, *13*, 617588. [CrossRef]
91. Liu, S.; Dong, L.; Shi, W.; Zheng, Z.; Liu, Z.; Meng, L.; Xin, Y.; Jiang, X. Potential targets and treatments affect oxidative stress in gliomas: An overview of molecular mechanisms. *Front. Pharmacol.* **2022**, *13*, 921070. [CrossRef]
92. Xia, L.; Chen, J.; Huang, J.; Lin, X.; Jiang, J.; Liu, T.; Huang, N.; Luo, Y. The role of AMPKα subunit in Alzheimer's disease: In-depth analysis and future prospects. *Heliyon* **2024**, *10*, e34254. [CrossRef]
93. Masliah, E. Role of the Interplay Between Autophagy and Cell Senescence in the Pathogenesis and Therapeutics of Glioblastoma in the Aging Population. *Cells* **2025**, *14*, 1764. [CrossRef]
94. Reiter-Brennan, C.; Semmler, L.; Klein, A. The effects of 2-hydroxyglutarate on the tumorigenesis of gliomas. *Contemp. Oncol.* **2018**, *22*, 215–222. [CrossRef]
95. Dias, D.; Socodato, R. Beyond Amyloid and Tau: The Critical Role of Microglia in Alzheimer's Disease Therapeutics. *Biomedicines* **2025**, *13*, 279. [CrossRef]
96. Gao, C.; Jiang, J.; Tan, Y.; Chen, S. Microglia in neurodegenerative diseases: Mechanism and potential therapeutic targets. *Signal Transduct. Target Ther.* **2023**, *8*, 359. [CrossRef]
97. Pennisi, G.; Valeri, F.; Burattini, B.; Bruzzaniti, P.; Sturiale, C.L.; Talacchi, A.; Papacci, F.; Olivi, A.; Della Pepa, G.M. Targeting Macrophages in Glioblastoma: Current Therapies and Future Directions. *Cancers* **2025**, *17*, 2687. [CrossRef]
98. Stanca, S.; Rossetti, M.; Bongioanni, P. Astrocytes as Neuroimmunocytes in Alzheimer's Disease: A Biochemical Tool in the Neuron-Glia Crosstalk along the Pathogenetic Pathways. *Int. J. Mol. Sci.* **2023**, *24*, 13880. [CrossRef]
99. Tripathy, D.K.; Panda, L.P.; Biswal, S.; Barhwal, K. Insights into the glioblastoma tumor microenvironment: Current and emerging therapeutic approaches. *Front. Pharmacol.* **2024**, *15*, 1355242. [CrossRef]
100. Akl, C.F.; Andersen, B.M.; Quintana, F.J. Astrocytes in the glioblastoma tumor microenvironment. *Neuro-Oncol.* **2025**, *27*, 2749–2750. [CrossRef]

101. Zou, C.; Jiang, S.; Li, H.; Zhao, K.; Cao, D.; Yang, G. The NLRP3 Inflammasome: Mechanisms of Activation, Regulation, and Therapeutic Opportunities. *MedComm* **2026**, *7*, e70660. [CrossRef]
102. Ramar, V.; Guo, S.; Wang, G.; Liu, M. The Pivotal Role of NF-κB in Glioblastoma: Mechanisms of Activation and Therapeutic Implications. *Int. J. Mol. Sci.* **2025**, *26*, 7883. [CrossRef]
103. Hung, C.C.; Chang, C.C.; Huang, C.W.; Nouchi, R.; Cheng, C.H. Gut microbiota in patients with Alzheimer's disease spectrum: A systematic review and meta-analysis. *Aging* **2022**, *14*, 477–496. [CrossRef]
104. Dono, A.; Nickles, J.; Rodriguez-Armendariz, A.G.; McFarland, B.C.; Ajami, N.J.; Ballester, L.Y.; A Wargo, J.; Esquenazi, Y. Glioma and the gut-brain axis: Opportunities and future perspectives. *Neuro-Oncol. Adv.* **2022**, *4*, vdac054. [CrossRef]
105. Stanga, S.; Lanni, C.; Govoni, S.; Uberti, D.; D'Orazi, G.; Racchi, M. Unfolded p53 in the pathogenesis of Alzheimer's disease: Is HIPK2 the link? *Aging* **2010**, *2*, 545–554. [CrossRef]
106. Esperante, D.; Galicia, K.D.; Rivas-Cuervo, K.G.; Cacho-Díaz, B.; Trejo-Becerril, C.; Taja-Chayeb, L.; Aboud, O.; Carlos-Escalante, J.A.; Wegman-Ostrosky, T. *TP53* oncogenic variants as prognostic factors in individuals with glioblastoma: A systematic review and meta-analysis. *Front. Neurol.* **2024**, *15*, 1490246. [CrossRef]
107. Trejo-Solís, C.; Castillo-Rodríguez, R.A.; Serrano-García, N.; Silva-Adaya, D.; Vargas-Cruz, S.; Chávez-Cortéz, E.G.; Gallardo-Pérez, J.C.; Zavala-Vega, S.; Cruz-Salgado, A.; Magaña-Maldonado, R. Metabolic Roles of HIF1, c-Myc, and p53 in Glioma Cells. *Metabolites* **2024**, *14*, 249. [CrossRef]
108. Singh, S.; Barik, D.; Lawrie, K.; Mohapatra, I.; Prasad, S.; Naqvi, A.R.; Singh, A.; Singh, G. Unveiling Novel Avenues in mTOR-Targeted Therapeutics: Advancements in Glioblastoma Treatment. *Int. J. Mol. Sci.* **2023**, *24*, 14960. [CrossRef]
109. Mueed, Z.; Tandon, P.; Maurya, S.K.; Deval, R.; Kamal, M.A.; Poddar, N.K. Tau and mTOR: The Hotspots for Multifarious Diseases in Alzheimer's Development. *Front. Neurosci.* **2019**, *12*, 1017. [CrossRef]
110. Mani, M.; Park, J.W.; Martin, T.F.J. Regulatory Mechanisms and Therapeutic Targeting of PD-L1 Trafficking and Stability in Cancer Immunotherapy. *Cancers* **2025**, *17*, 1747. [CrossRef]
111. Wu, J.; Zhang, C.; Cao, Q.; Xuan, W.; Huai, X.; Zhou, J.; Tian, J. Bibliometric analysis of global research on PD-L1/PD-1 pathway and neurodegenerative diseases over the last two decades (2004–2023). *Front. Aging Neurosci.* **2025**, *17*, 1570428. [CrossRef]
112. Yoon, S.S.; Jo, S.A. Mechanisms of Amyloid-β Peptide Clearance: Potential Therapeutic Targets for Alzheimer's Disease. *Biomol. Ther.* **2012**, *20*, 245–255. [CrossRef]
113. Zhang, C.; Li, J.; Tang, Q.; Li, L.; Cao, D. Targeting proteostasis for cancer therapy: Current advances, challenges, and future perspectives. *Mol. Cancer* **2025**, *24*, 265. [CrossRef]
114. Shevtsov, M.; Multhoff, G.; Mikhaylova, E.; Shibata, A.; Guzhova, I.; Margulis, B. Combination of Anti-Cancer Drugs with Molecular Chaperone Inhibitors. *Int. J. Mol. Sci.* **2019**, *20*, 5284. [CrossRef]
115. Choi, H.J.; Jeong, Y.J.; Kim, J.; Hoe, H.S. EGFR is a potential dual molecular target for cancer and Alzheimer's disease. *Front. Pharmacol.* **2023**, *14*, 1238639. [CrossRef]
116. Hedna, R.; Kovacic, H.; Pagano, A.; Peyrot, V.; Robin, M.; Devred, F.; Breuzard, G. Tau Protein as Therapeutic Target for Cancer? Focus on Glioblastoma. *Cancers* **2022**, *14*, 5386. [CrossRef]
117. Reed, S.; Taka, E.; Darling-Reed, S.; Soliman, K.F.A. Neuroprotective Effects of Metformin Through the Modulation of Neuroinflammation and Oxidative Stress. *Cells* **2025**, *14*, 1064. [CrossRef]
118. Markopoulos, G.S.; Sioka, C.; Alexiou, G.A.; Peschos, D.; Vartholomatos, G.; Kyritsis, A.P. Natural Anti-Inflammatory Agents in the Chemoprevention of Gliomas: Targeting Neuroinflammation and the Tumor Microenvironment. *Cancers* **2025**, *17*, 3922. [CrossRef]

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