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Alzheimer's disease and glioblastoma: a comprehensive review of epidemiological and translational medicine

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Abstract

Alzheimer's disease (AD), neuropsychiatric disorders, and glioblastoma represent distinct yet interconnected conditions characterized by overlapping molecular, cellular, and genetic mechanisms. Epidemiological studies reveal an inverse comorbidity between AD and glioblastoma, while psychiatric disorders may influence glioblastoma susceptibility through genetic, cellular, and pharmacological factors. Consequently, numerous critical signaling pathways, such as protein kinase B/mammalian target of rapamycin (AKT/mTOR), extracellular signal-regulated kinase / mitogen-activated protein Kinase (ERK/MAPK), wingless-related integration Site/glycogen synthase kinase 3 (Wnt/GSK3), and phosphoinositide 3-kinase (PI3K), exhibit dysregulation across these conditions, affecting apoptosis, proliferation, and synaptic function. In addition, genetic risk factors, including apolipoprotein E epsilon 4 (APOE ε4) in AD and tumor protein 53 (TP53), phosphatase and tensin homolog (PTEN), and isocitrate dehydrogenase 1 and 2 (IDH1/2) in glioblastoma, play a role in shaping divergent disease trajectories. Neuroinflammatory processes, epigenetic changes, and interactions between neurons and glia further clarify susceptibility patterns. From a therapeutic perspective, repurposing psychiatric medications that target common molecular pathways and implementing epigenetic or gene-based interventions offer promising avenues for integrated treatment strategies. This review aims to synthesize the current understanding of the epidemiological, molecular, cellular, and genetic intersections among AD, psychiatric disorders, and glioblastoma.

Keywords: Alzheimer's disease (AD), Glioblastoma, Neuropsychiatric disorders, Genetic risk factors

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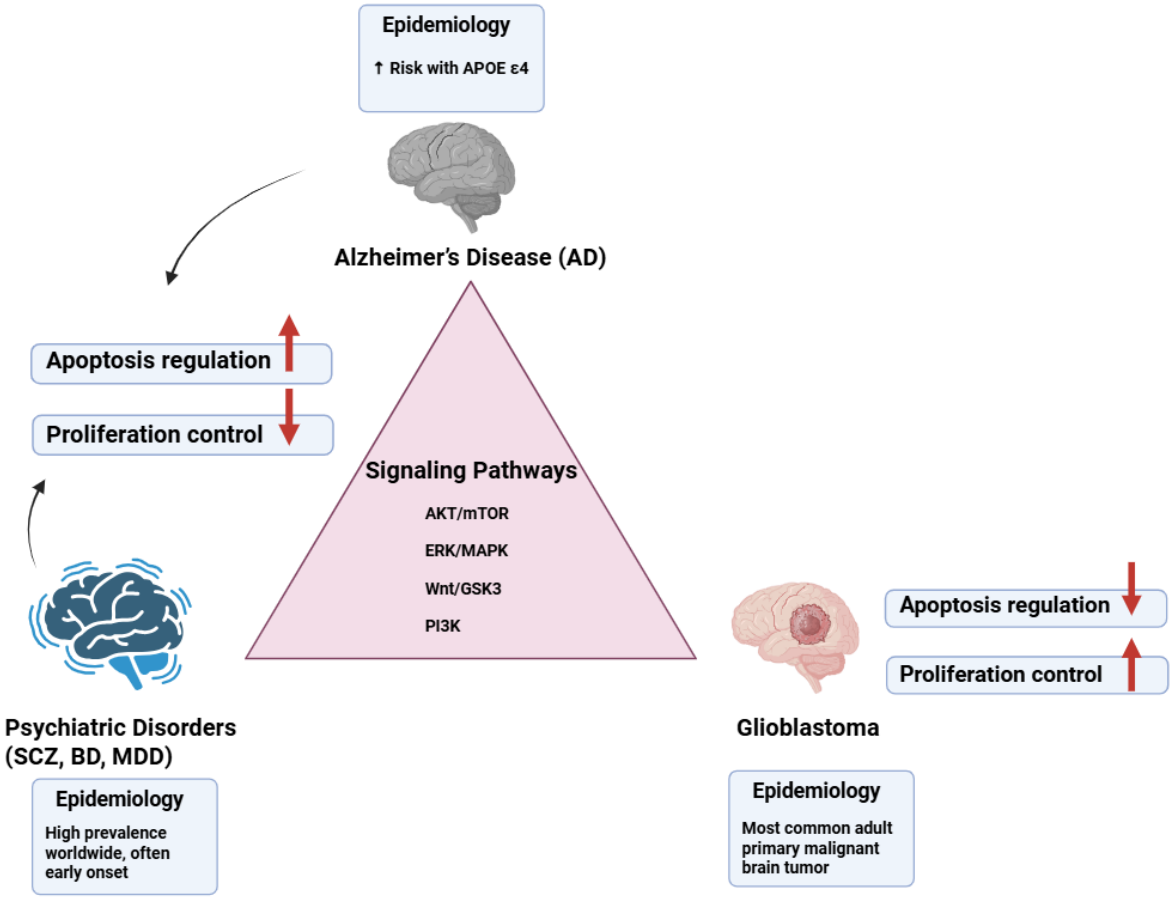
Graphical abstract



Introduction

Alzheimer's disease (AD) and glioblastoma constitute two of the most severe neurological conditions, exhibiting markedly contrasting clinical and pathological features. AD is a progressive neurodegenerative disorder marked by cognitive impairment, synaptic dysfunction, the accumulation of amyloid-β (Aβ) plaques, tau protein hyperphosphorylation, and extensive neuronal degeneration (1, 2). Glioblastoma, conversely, represents the most aggressive form of primary brain tumor found in adults, characterized by unregulated cellular growth, widespread invasion, the formation of new blood vessels, and significant resistance to standard treatment methods (3, 4). Although both conditions impact the same organ, the human brain, their pathophysiological mechanisms are remarkably distinct. AD is characterized by excessive cell death, whereas glioblastoma is marked by uncontrolled cellular survival and proliferation. The convergence of neurodegeneration and oncogenesis has garnered increasing scientific attention over the last twenty years. Epidemiological research has indicated an inverse comorbidity between AD and various cancer types, including glioblastoma, suggesting that individuals with AD may experience a lower risk of developing cancer, and conversely (5, 6). This paradox has prompted essential inquiries into the molecular and cellular mechanisms that dictate cell fate, apoptosis, proliferation, and immune surveillance within the central nervous system (CNS). Recent studies have started to investigate the molecular factors contributing to this inverse relationship. Proteins like peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 (Pin1) and p53, along with pathways such as ERK/MAPK and PI3K/AKT, seem to be inversely regulated in AD and glioblastoma (7, 8). For instance, Pin1 is reduced in

AD, which contributes to the hyperphosphorylation of tau and subsequent neurodegeneration. In contrast, it is frequently overexpressed in glioblastoma, facilitating the proliferation of tumor cells (9) . In a similar vein, the activity of p53, which is usually heightened in AD and contributes to apoptosis, is frequently rendered inactive in glioblastoma, thereby facilitating malignant proliferation. Gaining insight into these molecular interconnections not only illuminates the biological distinctions between neurodegeneration and tumorigenesis but also paves the way for potential therapeutic interventions. Furthermore, the context of cellular and microenvironmental factors is crucial in both conditions. Microglia, the CNS's resident immune cells, are involved in the pathology of AD through persistent neuroinflammation and impaired clearance of Aβ (10). In glioblastoma, microglia and tumor-associated macrophages (TAMs) may be utilized to facilitate tumor proliferation, angiogenesis, and the suppression of immune responses (11). Exploring the interplay of neuroinflammation, oxidative stress, and immune surveillance in the context of neurodegeneration and tumorigenesis is crucial for comprehending disease progression. This review seeks to deliver an in-depth examination of the relationships among AD, various neurodegenerative and psychiatric conditions, and glioblastoma. In this manner, we emphasize epidemiological data, molecular and cellular processes, genetic predispositions, and therapeutic implications.

Epidemiology: Comorbidity Patterns of AD, Neuropsychiatric Disorders, and Glioblastoma

Epidemiological studies consistently demonstrate an inverse relationship in comorbidity between AD and glioblastoma. Extensive cohort and registry-based research indicates that individuals with AD have a lower likelihood of developing glioblastoma when compared to the general population (5, 12). This inverse relationship is posited to arise from intrinsic differences in cellular destiny, like neurodegeneration, which is characterized by apoptosis, synaptic loss, and neuronal susceptibility, whereas gliomagenesis necessitates the avoidance of apoptosis and unchecked proliferation (8). Consequently, biological pathways that facilitate neurodegeneration in AD may concurrently establish an unfavorable environment for the initiation of tumors. The epidemiological context becomes increasingly intricate when psychiatric disorders are taken into account. Numerous population-based studies indicate that individuals diagnosed with schizophrenia, and to a lesser degree, bipolar disorder (BD), exhibit a lower incidence of brain tumors, such as glioblastoma (13). The protective effect has been linked to genetic variations that enhance apoptosis, modifications in cell cycle regulation, and the prolonged administration of psychotropic drugs that possess anti-proliferative characteristics (14, 15). In comparison, major depressive disorder (MDD) is more reliably linked to the risk of systemic cancer, although the evidence pertaining specifically to glioblastoma is still scarce (16). When considered collectively, these results suggest a continuum in which both neurodegenerative diseases, like AD, and specific neurodevelopmental or psychiatric conditions, such as schizophrenia, might possess shared protective molecular mechanisms against glioblastoma. In the case of AD, the excessive activation of apoptotic and degenerative pathways diminishes neuronal survival while simultaneously restricting neoplastic transformation. Likewise, in schizophrenia, impaired neurodevelopment and synaptic pruning could lead to a decrease in glial proliferative capacity. Notably, pharmacological treatments for psychiatric conditions, including lithium, antipsychotics, and selective serotonin reuptake inhibitors (SSRIs), further complicate this dynamic by providing independent anti-glioma effects (15, 17). The integration of these epidemiological insights indicates that neurodegenerative and psychiatric disorders, although clinically distinct, may intersect in their contribution to glioblastoma risk by means of a balance among genetic, cellular, and pharmacological factors.

Age and Gender Factors

Aging is the most significant risk factor for both AD and glioblastoma; however, its biological effects differ markedly. In the case of AD, aging exacerbates neuronal susceptibility due to mitochondrial dysfunction, oxidative stress, impaired autophagy, and the progressive accumulation of Aβ and hyperphosphorylated tau (18). Aging neurons and glial cells play a role in creating a persistent pro-inflammatory atmosphere, referred to as inflammaging,

which intensifies neurodegeneration and cognitive deterioration (19). In contrast, in the case of glioblastoma, the aging process makes individuals more susceptible to tumor development not by causing neuronal loss but rather by enhancing genomic instability, disrupting DNA repair mechanisms, and diminishing immune surveillance (20). Glioblastoma cells take advantage of age-related alterations by obtaining mutations in the telomerase reverse transcriptase (TERT) promoter and undergoing epigenetic reprogramming, which allows them to circumvent replicative senescence (21). Therefore, although aging promotes apoptosis and synaptic degeneration in AD, it concurrently contributes to cellular immortality and oncogenic processes in glioblastoma. Additionally, gender represents a significant factor influencing the susceptibility and progression of both AD and glioblastoma. Notably, women are disproportionately impacted by AD, comprising nearly two-thirds of the patient population, a discrepancy that cannot be fully accounted for by differences in life expectancy (22). Postmenopausal estrogen deficiency is associated with increased amyloid deposition, enhanced tau hyperphosphorylation, and diminished synaptic resilience, underscoring the neuroprotective functions of sex hormones (23). Conversely, glioblastoma demonstrates a greater prevalence and less favorable prognosis in males, with epidemiological research reporting male-to-female ratios between 1.3:1 and 1.6:1 (24). Preclinical studies indicate that androgens may facilitate the proliferation of glioma cells, whereas estrogens appear to exert protective effects by inhibiting cellular proliferation (25). Moreover, sex-specific variations in immune responses, microglial activation, and epigenetic regulation have been identified as contributing factors in the pathogenesis of both AD and glioblastoma (26). Psychiatric disorders add complexity to the relationship between aging and gender concerning the risks of AD and glioblastoma. Schizophrenia and BD generally present during early adulthood, occurring many years before the peak incidence of AD and glioblastoma. This indicates that neurodevelopmental changes occurring in early life may interact with aging processes in later stages of life (27). Interestingly, the epidemiology of mental health disorders exhibits sex-specific trends; for example, schizophrenia tends to be more frequent and severe among men, whereas mood disorders are more commonly observed in women (28). These variations may interact with the gender-specific risk profiles associated with AD and glioblastoma. For instance, the neuroprotective properties of estrogen could partly account for the reduced incidence of glioblastoma observed in females, while also modulating susceptibility to affective disorders and AD following menopause. Conversely, males diagnosed with schizophrenia might benefit from protective effects against glioblastoma attributable to genetic variants that promote apoptosis, despite their inherently higher baseline risk of glioblastoma relative to females, which is influenced by biological sex differences (14). Table 1 represents the comorbidity patterns of AD, neuropsychiatric disorders, and glioblastoma.

Table 1. Age, sex, and genetic factors influence the risk of AD, psychiatric disorders, and glioblastoma. Additionally, psychiatric conditions and treatments such as lithium or antipsychotics may reduce glioblastoma risk by promoting apoptosis.

Factor	AD	Glioblastoma	Psychiatric Disorders	Connection / Mechanism
Age	Increases neuronal vulnerability, apoptosis, oxidative stress, amyloid & tau accumulation	Increases genomic instability, TERT mutations, and immune evasion	Early-life onset (schizophrenia/bipolar) may intersect with aging pathways later	Aging drives degeneration in AD but tumorigenesis in glioblastoma
Gender	Women > Men estrogen protective	Men > Women; androgens promote proliferation	Schizophrenia: men > women mood disorders: women > men	Sex hormones modulate neurodegeneration, tumor proliferation, and psychiatric risk

AD vs Glioblastoma	Neurodegeneration	Oncogenesis	–	Inverse comorbidity: apoptotic pathways protect against glioblastoma
Schizophrenia / Bipolar	–	Reduced glioblastoma risk	Neurodevelopmental alterations, apoptosis-promoting genetic variants	Protective effect against glioblastoma despite baseline gender risk
Major Depression	–	Data limited	Higher systemic cancer risk	glioblastoma-specific link unclear
Pharmacology	–	Anti-glioma effects	Lithium, antipsychotics, SSRIs	Drugs modify glioblastoma risk independently of disease

Environmental and Lifestyle Factors

Environmental factors significantly influence the risk of developing glioblastoma. Among these, ionizing radiation is the sole environmental risk factor that has been conclusively validated through clinical and epidemiological research (29). Individuals who have undergone cranial irradiation, particularly during childhood, exhibit a significantly heightened lifetime risk of developing glioma. Additionally, occupational exposure to petrochemicals, pesticides, and heavy metals has been linked to an increased incidence of glioblastoma; however, the supporting evidence for these associations is variable and not consistently conclusive (30). Significantly, urban air pollution and fine particulate matter (PM2.5) are increasingly acknowledged as factors that contribute to oxidative DNA damage and neuroinflammation, processes that are pertinent to both neurodegeneration in Alzheimer's disease and tumorigenesis in glioblastoma (31). Lifestyle factors exert a significant impact on the risk and progression of AD. Specifically, tobacco use and excessive alcohol intake contribute to increased oxidative stress, vascular injury, and amyloid plaque accumulation, thereby hastening cognitive deterioration (32). In contrast, adherence to Mediterranean or DASH dietary patterns, which are abundant in antioxidants, omega-3 fatty acids, and polyphenols, has been associated with a decreased risk of AD and enhanced cognitive resilience (33). Engagement in physical activity facilitates neurogenesis, mitigates neuroinflammatory processes, and improves cerebral perfusion, thereby collectively contributing to the postponement of disease onset (34). These lifestyle modifications highlight the potential of non-pharmacological interventions to mitigate the risk of AD and to influence common biological pathways associated with glioblastoma. Individuals diagnosed with psychiatric disorders are disproportionately subjected to detrimental lifestyle and environmental risk factors, such as tobacco use, unhealthy dietary habits, physical inactivity, and elevated prevalence of substance abuse (35). These behaviors not only elevate the overall risk of cancer but may also contribute to gliomagenesis through mechanisms such as the induction of DNA damage, the promotion of chronic inflammation, and the disruption of immune surveillance (36). Nonetheless, individuals within psychiatric populations often undergo prolonged treatment with psychotropic medications, several of which (such as lithium, antipsychotics, and SSRIs) have demonstrated anti-glioma effects in preclinical studies (37). This interaction indicates that although lifestyle factors may elevate the risk of cancer, pharmacological interventions could mitigate these dangers, leading to the seemingly contradictory observation of a lower incidence of glioblastoma among psychiatric populations **(Figure 1)**.

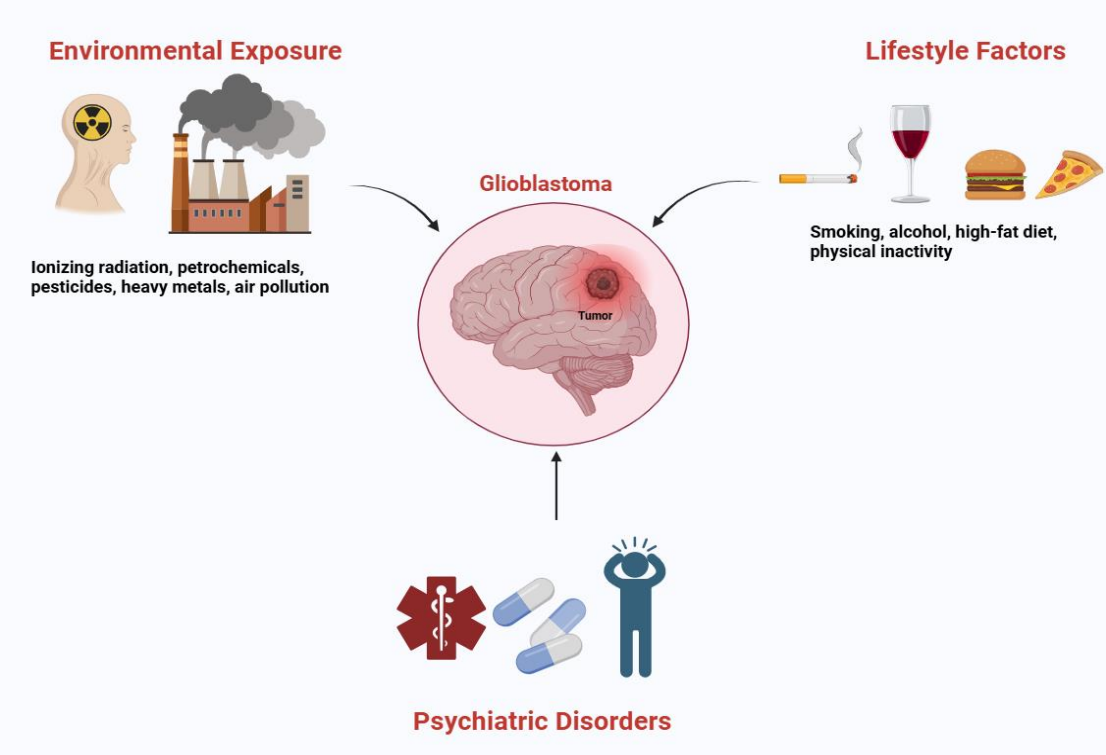


Figure 1. Environmental and lifestyle factors, including radiation, pollution, diet, and physical activity, influence Alzheimer's, psychiatric disorders, and glioblastoma, with some medications offering protective effects against tumor development.

Molecular Mechanisms: Shared and Inverse Pathways Between AD, Psychiatric Disorders, and Glioblastoma

At the molecular level, AD, psychiatric disorders, and glioblastoma demonstrate intricate interactions that could elucidate the observed patterns of comorbidity. While AD is marked by neuronal degeneration and disrupted synaptic signaling, glioblastoma is characterized by unchecked cellular growth and invasion. Psychiatric disorders, such as schizophrenia, BD, and MDD, frequently exhibit changes in neurotransmitter systems, inflammation, and regulation of the cell cycle, which may influence vulnerability to tumor development. The key molecular pathways relevant to these subjects are outlined, including Pin1 and protein folding, the p53 pathway, ERK/MAPK, PI3K/AKT, Wnt/GSK3 signaling, as well as neuroinflammation and cytokine networks, as presented in **(Table 2)**. Pin1 is a distinctive enzyme that facilitates the isomerization of phosphorylated serine/threonine-proline motifs, thereby affecting protein structure and functionality. Pin1 plays a crucial role in regulating protein conformation and signaling that is dependent on phosphorylation (38). In AD, the expression of Pin1 is reduced, resulting in the hyperphosphorylation and aggregation of tau protein. In contrast, glioblastoma often exhibits elevated levels of Pin1, which facilitates cell cycle advancement, cellular proliferation, and resistance to programmed cell death. This opposing regulation of Pin1 indicates a potential molecular mechanism that may explain the lower incidence of glioblastoma seen in patients with AD (39, 40). Furthermore, the tumor suppressor protein p53 serves as a vital regulator of the cell cycle, DNA repair mechanisms, and apoptosis, commonly known as the guardian of the genome. In AD, p53 is often upregulated in response to oxidative stress and DNA damage, which promotes neuronal apoptosis and plays a role in neurodegeneration. Increased levels of p53 can worsen synaptic dysfunction, resulting in cognitive decline. Additionally, the interaction between p53 and Aβ, as well as tau proteins, amplifies cellular stress responses, activating apoptotic pathways and causing mitochondrial dysfunction in neurons, which are fundamental to the pathology of AD (41). In glioblastoma, p53 frequently undergoes mutation or functional inactivation, enabling cells to evade apoptosis and proliferate without restraint. The loss of

p53 function in this malignancy is correlated with genomic instability, increased tumor aggressiveness, and therapeutic resistance. This differential regulation of p53 in AD versus glioblastoma may partly account for the observed inverse comorbidity: neurons in AD are susceptible to p53-mediated apoptosis, whereas glial tumor cells in glioblastoma circumvent this pathway. From a therapeutic perspective, modulation of p53 signaling is under investigation both to mitigate excessive neuronal loss in AD and to reinstate tumor suppressive mechanisms in glioblastoma, underscoring the protein's dual role in neurodegeneration and oncogenesis (42). In addition, the ERK/MAPK and PI3K/AKT pathways are central regulators of cell survival, proliferation, differentiation, and synaptic plasticity. In AD, these pathways are often disrupted: ERK/MAPK signaling shows impaired activation, which compromises synaptic function and long-term potentiation, leading to memory deficits. Similarly, PI3K/AKT activity is frequently reduced in AD neurons, favoring apoptosis through activation of pro-apoptotic proteins like Bax and inhibition of survival signals, contributing to progressive neurodegeneration. Dysregulation of these pathways also affects tau phosphorylation, enhancing the formation of neurofibrillary tangles (43). In glioblastoma, these signaling pathways are markedly hyperactivated, leading to uncontrolled tumor proliferation, increased invasiveness, and resistance to therapeutic interventions. Dysregulated ERK/MAPK and PI3K/AKT signaling pathways facilitate cell cycle progression, angiogenesis, and the avoidance of apoptosis, thereby constituting critical targets for therapeutic strategies in glioblastoma management. Similarly, psychiatric disorders exhibit differential modulation of these pathways; for instance, schizophrenia and BD frequently demonstrate altered AKT activity, which may impact neuronal survival and, notably, could influence susceptibility to tumor development. Consequently, ERK/MAPK and PI3K/AKT signaling pathways represent a molecular nexus that links neurodegenerative processes, oncogenesis, and psychiatric conditions (44). Furthermore, the tumor suppressor protein p53 serves as a vital regulator of the cell cycle, DNA repair mechanisms, and apoptosis, commonly known as the guardian of the genome. In AD, p53 is often upregulated in response to oxidative stress and DNA damage, which promotes neuronal apoptosis and plays a role in neurodegeneration. Increased levels of p53 can worsen synaptic dysfunction, resulting in cognitive decline. Additionally, the interaction between p53 and Aβ, as well as tau proteins, amplifies cellular stress responses, activating apoptotic pathways and causing mitochondrial dysfunction in neurons, which are fundamental to the pathology of AD. (45). In glioblastoma, the Wnt signaling pathway is often excessively activated, thereby facilitating the maintenance of stem cell-like properties, enhancing invasiveness, and contributing to chemoresistance within tumor cells. Dysregulated Wnt/β-catenin signaling drives cellular proliferation and migration, positioning it as a critical factor in the malignancy of glioblastoma. Notably, inhibition of GSK3 in glioblastoma has been shown to suppress tumor growth, whereas in AD, hyperactivation of GSK3 is implicated in disease pathogenesis, demonstrating an inverse molecular relationship between these conditions. Furthermore, modulation of Wnt/GSK3 signaling pathways in psychiatric disorders may affect neurodevelopmental mechanisms and cellular resilience, underscoring the role of these pathways as shared regulators in neurodegeneration, oncogenesis, and mental health disorders (46). Neuroinflammation constitutes a fundamental aspect of AD as well as numerous psychiatric disorders, predominantly mediated by microglial activation, astrocyte dysfunction, and aberrant cytokine signaling. In the context of AD, persistent microglial activation triggered by amyloid-beta plaques and tau protein aggregates results in the prolonged secretion of pro-inflammatory cytokines, including interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). This sustained inflammatory response exacerbates neuronal damage and impairs synaptic function. Concurrently, astrocytes, which typically support neuronal homeostasis, undergo a phenotypic transformation to a reactive state under inflammatory conditions, thereby intensifying neurodegenerative processes. Analogously, psychiatric conditions such as MDD and schizophrenia are frequently characterized by low-grade systemic and CNS inflammation, with dysregulated cytokine expression contributing to disturbances in mood regulation, cognitive impairments, and potentially altered cellular proliferation mechanisms. In

glioblastoma, the tumor microenvironment manipulates the immune system to facilitate tumor progression. Glioblastoma cells promote immunosuppressive phenotypes in microglia and infiltrating macrophages, concurrently secreting cytokines such as IL-6 and transforming growth factor-beta (TGF-β), which contribute to tumor proliferation, angiogenesis, and invasion. Notably, cytokines implicated in neuronal death in AD may paradoxically enhance tumor survival in glioblastoma, underscoring an inverse relationship between neurodegeneration and cancer. This dual functionality of inflammatory signaling pathways indicates that precise modulation of cytokine networks holds therapeutic promise: attenuating chronic neuroinflammation in AD and psychiatric disorders may confer neuroprotection, whereas targeting tumor-promoting inflammation in glioblastoma could inhibit tumor growth. A comprehensive understanding of the context-dependent roles of cytokines is therefore essential for the development of effective interventions addressing both neurodegenerative and oncological conditions (2).

Table 2. Key signaling pathways, including Pin1, p53, ERK/AKT, Wnt/GSK3, and neuroinflammation, show both shared and opposing dysregulation across these conditions. In AD, downregulation often drives neurodegeneration, while in glioblastoma, hyperactivation promotes proliferation and therapy resistance. Psychiatric disorders show subtler, modulatory changes affecting synaptic function and resilience. These patterns highlight how the same molecular mechanisms can lead to divergent disease outcomes depending on context.

Molecular Pathway	AD	Glioblastoma	Psychiatric Disorders
Pin1 / Protein Folding	Downregulated → tau hyperphosphorylation and aggregation	Overexpressed → proliferation, resistance to apoptosis	Limited data; possible indirect effects on synaptic regulation
p53 Pathway	Upregulated → oxidative stress response, neuronal apoptosis, cognitive decline	Mutated/inactivated → evasion of apoptosis, genomic instability, tumor aggressiveness	Altered regulation in some disorders may influence stress response and apoptosis
ERK/MAPK and PI3K/AKT	Reduced activity → impaired LTP, memory loss, increased apoptosis	Hyperactivated → tumor growth, angiogenesis, therapy resistance	Altered AKT signaling in schizophrenia/BD → impacts neuronal survival, possible tumor susceptibility
Wnt/β-catenin and GSK3	Downregulated Wnt, hyperactive GSK3 → tau pathology, neurodegeneration	Hyperactive Wnt/β-catenin → stemness, invasion, chemoresistance	Dysregulated Wnt/GSK3 → neurodevelopmental abnormalities, synaptic dysfunction
Neuroinflammation and Cytokines	Chronic microglial activation → IL-1β, IL-6, TNF-α → synaptic loss, neuronal death	Glioblastoma cells co-opt microglia/macrophages → IL-6, TGF-β → proliferation, immunosuppression	Low-grade inflammation (IL-6, TNF-α) → mood/cognitive dysfunction, altered resilience

Cellular Mechanisms: Microglia, Neuronal-Glial Interactions, and Tumorigenesis

The cellular microenvironment is critically influential in shaping the progression of neurodegenerative diseases and tumorigenic processes. In conditions such as Alzheimer's disease, psychiatric disorders, and glioblastoma, the interplay among neurons, glial cells, and immune cells constitutes a fundamental mechanism underlying disease development and may account for the epidemiologically observed inverse comorbidity patterns. Microglia, the intrinsic immune cells of the CNS, exhibit a dualistic function in the contexts of neurodegeneration and tumorigenesis. AD, persistent microglial activation contributes to chronic neuroinflammation, impaired clearance of Aβ plaques, and synaptic dysfunction. Activated microglia secrete pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α, as well as reactive oxygen species (ROS) and nitric oxide, which collectively facilitate neuronal apoptosis and exacerbate cognitive decline. This sustained inflammatory milieu disrupts neurotrophic

support and modifies neuron-glia interactions, thereby driving progressive neurodegeneration. Conversely, in glioblastoma, microglia and TAMs are co-opted into a tumor-supportive phenotype characterized by the secretion of factors that enhance cellular proliferation, angiogenesis, and immunosuppression. This tumor-promoting microglial phenotype stands in contrast to their pro-apoptotic role observed in AD. By modulating the local cytokine environment, glioblastoma cells exploit microglial plasticity to promote tumor invasion and resistance to therapy. This functional duality of microglia provides a mechanistic basis for the inverse epidemiological correlation observed between neurodegenerative disorders and gliomagenesis (47). Equally significant, astrocytes play a crucial role in maintaining synaptic homeostasis, offering metabolic support to neurons, and regulating inflammation within the CNS. In the context of AD, astrocytes exhibit a reactive state, characterized by hypertrophy and the release of inflammatory mediators that worsen neuronal damage. This reactive gliosis is implicated in the formation of plaques, loss of synapses, and disruption of neurovascular coupling. Furthermore, dysfunctional astrocytes in various psychiatric disorders, such as schizophrenia and BD, also disrupt neurotransmitter homeostasis and inflammatory responses, potentially influencing the risk of neurodegeneration or tumor development. In glioblastoma, astrocytes engage with tumor cells through gap junctions, cytokine signaling, and the remodeling of the extracellular matrix, thereby promoting tumor invasion and resistance to therapeutic interventions (48). Tumor-associated astrocytes facilitate the preservation of glioma stem cells and promote angiogenesis by releasing trophic factors and influencing immune responses. The differing functions of astrocytes, acting as pro-degenerative agents in AD compared to their pro-tumorigenic role in glioblastoma, underscore the capacity of glial plasticity to result in varied cellular consequences within the CNS (49). Besides, interactions between neurons and glia are crucial for maintaining homeostasis in the CNS, facilitating synaptic plasticity, and enabling repair mechanisms. In the context of AD, the deterioration of synaptic integrity, the reduction of neurotrophic support, and the disruption of signaling pathways involving glutamate and other neurotransmitters compromise neuron-glia communication, which in turn contributes to neurodegenerative processes. The disruption of these interactions has a detrimental impact on astrocytes, microglia, and oligodendrocytes, thereby exacerbating cognitive deficits and neuronal loss (50). Glioblastoma cells manipulate the communication between neurons and glia to facilitate tumor growth. For instance, glioma cells react to neuronal activity via neuroligin-3 signaling and utilize synaptic-like structures to boost their proliferation. This appropriation of neuronal mechanisms stands in stark contrast to the degenerative signaling seen in AD and specific psychiatric conditions, underscoring how analogous cellular signals can result in either cell death or unchecked proliferation, contingent upon the context. More importantly, Oligodendrocytes play a crucial role in providing myelin and metabolic support to axons, which is essential for the proper functioning of neurons. In AD, the dysfunction of oligodendrocytes and the resulting demyelination led to impaired axonal conduction and cognitive decline. Likewise, psychiatric conditions such as schizophrenia are linked to changes in oligodendrocyte density, abnormalities in myelin, and compromised integrity of white matter, all of which may affect neuronal vulnerability and cellular resilience. In the case of glioblastoma, tumor cells engage with oligodendrocyte progenitor cells (OPCs) to alter the extracellular matrix and establish a microenvironment that promotes invasion. This interaction underscores a context-dependent shift in which oligodendrocytes can either enhance CNS function or be repurposed to aid in tumor growth (49). Cellular senescence represents a defining characteristic of aging and plays a significant role in both neurodegeneration and the biology of cancer (51). In AD, neurons display signs of DNA damage-induced senescence and apoptotic signaling, which contribute to cell loss and cognitive deterioration. Factors associated with the senescence-associated secretory phenotype (SASP), such as pro-inflammatory cytokines, exacerbate neuroinflammation (52). In glioblastoma, tumor cells circumvent senescence by activating telomerase, inactivating p53, and increasing the levels of anti-apoptotic proteins, which allows for unrestrained proliferation. Psychiatric disorders might influence apoptotic thresholds through oxidative stress and modified signaling pathways, thereby indirectly impacting tumor vulnerability. This contrast between

cell death in neurodegeneration and the evasion of senescence in cancer elucidates the inverse epidemiological patterns observed (53).

Genetics and Risk Loci: Shared and Divergent Genetic Mechanisms in AD, Psychiatric Disorders, and Glioblastoma

Genetic elements play a crucial role in determining the vulnerability, advancement, and clinical results of AD and glioblastoma (54). Both common and distinct genetic mechanisms could elucidate epidemiological findings, including the inverse comorbidity observed between neurodegenerative diseases and specific cancers, while also offering potential molecular targets for therapeutic intervention (55). The following provides an elucidation of the risk-associated genes implicated in these disorders:

AD Risk Genes

Genetic predisposition is crucial in AD, with risk genes impacting not only neurodegeneration but also the brain's microenvironment, which may in turn influence tumor biology, including glioblastoma (56). One of the primary genetic risk factors is APOE ε4; the ε4 allele of apolipoprotein E represents the most critical risk element for late-onset AD, as it enhances Aβ aggregation, hinders its clearance, and facilitates tau hyperphosphorylation (57). In addition to amyloidopathy, APOE ε4 influences lipid metabolism, neuroinflammation, and synaptic plasticity. Microglia from individuals carrying the APOE ε4 allele display a pro-inflammatory phenotype, secreting cytokines like IL-1β and TNF-α, which promote neuronal apoptosis (58). Although this environment promotes neurodegeneration, the identical pro-apoptotic signaling may render glial progenitors less conducive to tumor initiation, which partially elucidates the noted inverse comorbidity between AD and glioblastoma. Furthermore, mutations in APP and presenilins 1 and 2 modify γ-secretase activity, leading to an increased production of the neurotoxic Aβ42 isoform (59). This disparity encourages synaptic degradation, oxidative stress, and dysfunction of mitochondria. Notably, persistent oxidative stress can initiate DNA damage responses that might inhibit unchecked proliferation in glial cells, thereby possibly restricting tumor development. Additionally, Microglial and Immune-Related Genes, such as triggering receptor expressed on myeloid cells 2 (TREM2), Clusterin (CLU), and cluster of differentiation 33 (CD33), play crucial roles in regulating microglial phagocytosis, lipid metabolism, and inflammatory signaling (60, 61). Loss-of-function mutations in TREM2 diminish the ability of microglia to clear Aβ, thereby worsening the pathology; however, they may concurrently improve glial monitoring against malignant transformation. CLU plays a role in regulating apoptosis and interactions with the extracellular matrix, which affects neuronal survival and the microenvironment conducive to glioblastoma growth. Additionally, epigenetic modulators, including genes that affect DNA methylation and histone modifications (for instance, DNA (Cytosine-5)-Methyltransferase 1 (DNMT1) and histone deacetylases (HDACs), also play a role in the risk of AD (62). Epigenetic dysregulation has the potential to modify neuronal gene expression, diminish proliferation, and sustain a cellular condition that is resistant to malignant transformation.

Glioblastoma Risk Genes

Glioblastoma represents a highly aggressive primary brain tumor influenced by a complex interaction of genetic, epigenetic, and microenvironmental elements. Gaining insight into susceptibility genes aids in clarifying the reasons certain pathways overlap with neurodegenerative and psychiatric conditions. For instance, TP53 serves as a vital tumor suppressor that governs DNA repair, apoptosis, and the regulation of cell cycle checkpoints (63). Loss-of-function mutations in TP53 frequently occur in glioblastoma, especially in secondary glioblastoma that develops from lower-grade gliomas. The presence of mutant p53 enables tumor cells to escape apoptosis even in the presence of DNA damage, which facilitates unchecked proliferation. Notably, the hyperactivation of p53 in neurons is associated with apoptosis in AD, underscoring the context-dependent duality of p53 signaling that serves a protective role against malignancy in glial cells while being pro-apoptotic in neurons (64, 65). Also, PTEN negatively regulates the PI3K/AKT pathway, a central driver of cell survival and proliferation (66). The impairment of PTEN function in glioblastoma results in the hyperactivation

of AKT, which facilitates metabolic reprogramming, angiogenesis, and therapeutic resistance. In relation to neurodegeneration, the modulation of PTEN influences neuronal survival and the guidance of axons. Consequently, the dysfunction of PTEN may play a role in tumorigenesis while also intersecting with pathways associated with neuropsychiatric disorders (67). Furthermore, the amplification of epidermal growth factor receptor (EGFR) and mutations such as EGFRvIII contribute to oncogenic signaling via the MAPK, PI3K/AKT, and signal transducer and activator of transcription 3 (STAT3) pathways (68). This facilitates cellular proliferation, migration, and resistance to programmed cell death. Notably, dysregulated EGFR signaling has been associated with psychiatric conditions such as schizophrenia and BD, potentially through its impact on neurodevelopmental mechanisms and synaptic plasticity, indicating the existence of a common molecular framework (69). An additional important aspect to highlight is that neurofibromin 1 (NF1) functions as a negative regulator of rat sarcoma (RAS) signaling. Loss-of-function mutations in the NF1 gene result in increased activity of the RAS/MAPK pathway, thereby facilitating glial cell proliferation and tumor development (70). Dysfunction of NF1 also impacts neuronal differentiation and synaptic plasticity, thereby connecting neurodevelopmental processes with an increased susceptibility to tumor formation.

Shared Molecular Pathways Between AD and Glioblastoma

AD and glioblastoma exhibit distinct pathological outcomes; they share several molecular pathways, underscoring the complexity of context-dependent effects. For example, the Pin1 pathway functions differently in these conditions: in AD, Pin1 facilitates the correction of tau protein misfolding and inhibits the formation of neurofibrillary tangles, whereas in glioblastoma, Pin1 contributes to the stabilization of oncogenic proteins such as cyclin D1 and Akt, thereby promoting cell cycle progression and cellular proliferation (71). The dual function demonstrates that pathway activity may serve a protective role in neurons while being oncogenic in glial cells. Furthermore, p53 upholds genomic integrity by triggering cell cycle arrest or apoptosis when faced with DNA damage. In the context of neurons, the activation of p53 plays a role in apoptosis and neurodegeneration associated with AD. Conversely, in glioblastoma, mutations in TP53 compromise this checkpoint, enabling cells to escape apoptosis. The shared regulation of p53 underscores a pivotal point where identical molecular mechanisms yield contrasting outcomes in various cell types (42, 72). Furthermore, the PI3K/AKT/mTOR pathway plays a crucial role. This pathway regulates cellular growth, survival, and metabolic processes. In AD, the excessive activation of mTOR leads to tau hyperphosphorylation and hinders autophagy (44). In glioblastoma, the hyperactivity of the PI3K/AKT/mTOR pathway leads to accelerated cell proliferation, metabolic alterations, and increased resistance to programmed cell death. Consequently, pharmacological agents that inhibit mTOR may possess a dual therapeutic effect: they could mitigate AD pathology while concurrently inhibiting tumor growth in glioblastoma. Additionally, the ERK/MAPK signaling pathway plays a crucial role in regulating cell proliferation, differentiation, and responses to stress. In the context of AD, its dysregulation contributes to tau phosphorylation, oxidative stress, and neuronal cell death (73). In glioblastoma, the identical pathway promotes both proliferation and invasion. Variations that depend on context, such as the availability of different cofactors and the signaling from upstream receptors, dictate whether ERK/MAPK activity results in degeneration or proliferation. Additionally, regarding oxidative stress and responses to DNA damage, both AD and glioblastoma are associated with the generation of ROS, yet the outcomes are distinct. In AD, oxidative stress triggers neuronal apoptosis and mitochondrial dysfunction. Conversely, in glioblastoma, tumor cells frequently utilize ROS signaling to facilitate DNA repair, angiogenesis, and survival in hypoxic environments (74). Furthermore, autophagy is compromised in AD, resulting in the buildup of Aβ and tau aggregates. In contrast, in glioblastoma, autophagy plays a crucial role in promoting the survival of tumor cells during metabolic stress (75). The therapeutic modulation of autophagy can thus be customized to either avert neurodegeneration or suppress tumor growth.

Neuropsychiatric Disorders and Glioblastoma: Molecular and Cellular Intersections

Neuropsychiatric disorders, such as schizophrenia, BD, and MDD, exhibit intricate associations with glioblastoma across molecular, cellular, and epidemiological dimensions. While population-based research indicates a typically reduced occurrence of glioblastoma among individuals with severe psychiatric conditions, emerging mechanistic understanding is being derived from genetic, signaling, and cellular investigations (76, 77) **(Figure 2)**. Here are some crucial examples of it:

1. Schizophrenia and Glioblastoma

Schizophrenia is associated with disturbances in dopaminergic, glutamatergic, and GABAergic signaling, along with atypical neurodevelopment and synaptic plasticity. Candidate genes like disrupted in schizophrenia 1 (DISC1), neuregulin 1 (NRG1), and AKT Serine/Threonine Kinase 1 (AKT1) are involved in the regulation of neuronal proliferation, migration, and apoptosis. The dysregulation of AKT/mTOR and ERK/MAPK pathways may diminish the proliferation of glial precursors, which could restrict the reservoir of cells that are susceptible to malignant transformation (78). Furthermore, variations in genes that control oxidative stress and DNA repair processes may provide neuroprotection while concurrently decreasing the likelihood of tumor development. In the context of schizophrenia, there are noticeable changes in neuron-glia interactions, which encompass a decrease in oligodendrocyte density, compromised myelination, and disturbances in synaptic pruning (79). These structural deficiencies may undermine the specific environment necessary for glioblastoma cell proliferation, thereby diminishing tumor initiation. Prolonged exposure to antipsychotic medications additionally influences glial function, encompassing microglial apoptosis and the proliferation of astrocytes, which contributes an extra dimension of protection (63). Antipsychotic medications, especially those that act as dopamine receptor antagonists, exhibit anti-proliferative properties in glioma cell lines, which include the suppression of cell cycle progression and the promotion of apoptosis. Consequently, prolonged treatment may provide further defense against the onset of glioblastoma. Subsequent research could aim to explore the potential of these drugs as supplementary anti-glioma treatments (37).

2. BD and Glioblastoma

BD is linked to disrupted intracellular signaling, oxidative stress, mitochondrial impairment, and neuroinflammation. Significant molecular pathways, such as glycogen synthase kinase 3 beta (GSK3β), Wnt/β-catenin, and PI3K/AKT, frequently exhibit dysregulation in both BD and glioblastoma. Lithium, a widely used mood stabilizer, acts by inhibiting GSK3β and modulating Wnt signaling, which are pathways that are excessively active in glioblastoma, consequently restricting glial proliferation and invasiveness (80). Patients with BD often display modified neuron-glia ratios, reduced oligodendrocyte density, and compromised myelination. Such cellular irregularities may restrict the assistance for tumor initiation and growth (81). Furthermore, persistent inflammation and oxidative stress can trigger DNA damage responses that encourage the apoptosis of cells that may initiate tumors. The inhibition of GSK3β by lithium also enhances neurotrophic signaling through brain-derived neurotrophic factor (BDNF), potentially safeguarding neurons while restricting the survival of glioma cells (82). Other mood stabilizers, such as valproate, modify epigenetic landscapes through histone deacetylase inhibition, which may further reduce glioblastoma susceptibility. Collectively, genetic predisposition, cellular microenvironment, and pharmacological interventions converge to reduce glioblastoma risk in BD patients (83).

3. MDD and Glioblastoma

MDD is defined by persistent systemic inflammation, dysregulation of the HPA axis, and oxidative stress. Increased levels of pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β influence microglial activation and apoptosis, which may restrict glial proliferation within the CNS (84). Genetic variants associated with apoptosis, DNA repair mechanisms, and mitochondrial function may play a role in the pathophysiology of MDD as well as in decreased susceptibility to glioblastoma. Persistent neuroinflammation observed in MDD facilitates glial cell apoptosis and disrupts astrocytic support for neuronal function (85). The altered microenvironment may exhibit decreased permissiveness for glioblastoma progression, thereby limiting the available niche for tumor initiation.

Additionally, stress-induced increases in glucocorticoid levels further regulate the functions of microglia and astrocytes, impacting the proliferation and apoptosis of pre-neoplastic glial cells (86). Antidepressant agents, such as SSRIs and SNRIs, have exhibited anti-glioma properties in vitro by promoting apoptosis, autophagy, and oxidative stress within glioma cells. The interplay between neuroinflammatory alterations associated with disease pathology and the pharmacodynamic actions of these medications may act synergistically to mitigate the risk of glioblastoma (87).

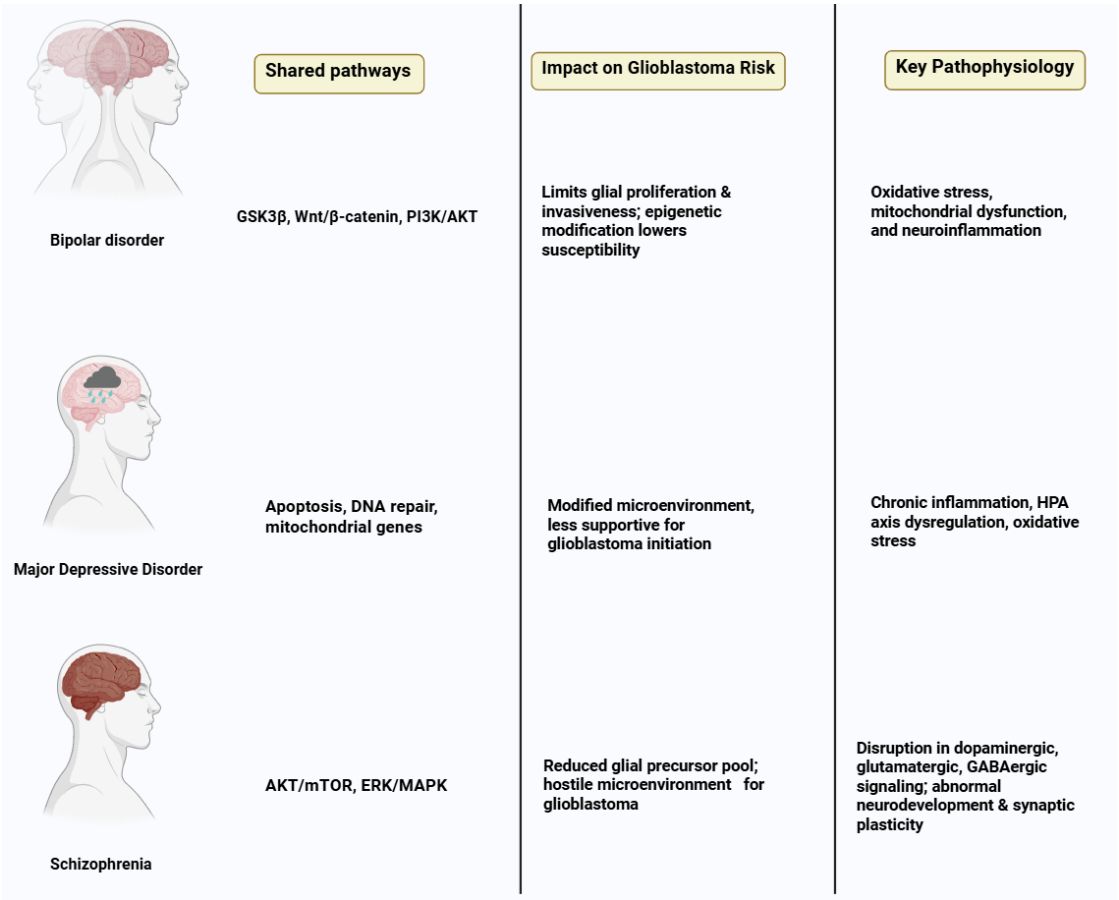


Figure 2. Shared molecular pathways, including AKT/mTOR, ERK/MAPK, GSK3β/Wnt, and PI3K/AKT, alongside alterations in oxidative stress, mitochondrial function, and neuroinflammatory signaling, collectively contribute to a neural microenvironment less permissive to glioblastoma initiation and progression. These intersecting mechanisms highlight how psychiatric pathophysiology and pharmacological modulation may influence glial proliferation and tumor susceptibility.

Implications for Therapy and Prevention

The convergence of neuropsychiatric conditions and glioblastoma opens novel avenues for developing innovative treatments and preventive strategies. These approaches seek not only to address distinct disease states but also to exploit inverse comorbidity trends to advance personalized medicine. Critical molecular pathways, including PI3K/AKT/mTOR and Wnt/β-catenin signaling, play pivotal roles in regulating cell growth, viability, and invasiveness in glioblastoma. Therapies targeting these pathways have demonstrated potential to slow tumor growth and enhance patient outcomes. For instance, lithium-mediated suppression of GSK3β has shown antitumor effects in preclinical glioblastoma studies. Repurposing established psychiatric medications offers a compelling strategy for glioblastoma management. Antipsychotic drugs, such as clozapine and aripiprazole, have been observed to curb glioma cell growth and trigger apoptosis. Likewise, SSRIs, such as sertraline, exhibit anti-glioma properties by modulating pathways associated with cell proliferation and tumor invasion. These findings suggest that prolonged use of psychiatric medications

may impact glioblastoma risk and provide new therapeutic possibilities.

Conclusion

AD, psychiatric conditions, and glioblastoma are distinct disorders with unique symptoms, yet they share underlying molecular, cellular, and genetic connections. Population-based studies suggest an intriguing negative correlation between AD and GBM, while psychiatric disorders may alter GBM risk through genetic, cellular, and drug-related mechanisms. At the molecular level, disrupted signaling networks, such as those involving PI3K/AKT/mTOR, ERK/MAPK, and Wnt/GSK3β, drive neurodegeneration or tumor development in contrasting ways. Proteins like Pin1 and p53, along with neuroinflammatory and synaptic processes, reveal shared regulatory frameworks that lead to either neuronal loss or excessive glial growth. Cellular interactions, including microglial responses, astrocyte functions, neuron-glia dynamics, and synaptic adaptations, help explain these differing disease outcomes. Genetic studies point to the role of risk variants, epigenetic alterations, and overlapping signaling genes in shaping disease predisposition. In AD, genes that heighten neuronal susceptibility may create a brain environment less favorable to GBM. Similarly, genes linked to psychiatric conditions influence tumor formation by modulating cell survival, apoptosis, and oxidative stress. Drugs used for psychiatric and neurodegenerative disorders, such as antipsychotics, mood stabilizers, and SSRIs, may lower GBM risk by affecting glial cell behavior. From a treatment perspective, these insights pave the way for tailored therapeutic strategies. By targeting shared signaling pathways, managing neuroinflammation, or using epigenetic and genetic approaches, new treatments could emerge. Repurposing existing medications or designing therapies that address multiple targets may benefit both brain disorders and GBM management. In conclusion, the complex interplay of neurodegenerative, psychiatric, and tumor-related processes calls for an integrated approach combining molecular science, genetics, neuroscience, and pharmacology. Future research leveraging multi-omics, long-term population studies, and experimental models will be vital to uncover the basis of these disease connections and develop precise interventions that bridge these seemingly distinct conditions.

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Author contribution

AN and **EB** authored the primary manuscript and developed the accompanying figures and tables. **ZT** revised and finalized the manuscript. **MGF** and **MM** contributed to the authorship of certain sections of the manuscript. All authors have reviewed and approved the final revised version of the manuscript.

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