Multifactor Analysis of the Peculiar Connections Between Alzheimer's Disease and Glioblastoma - An Immunological, Metabolic, Molecular, and Gut Floral Perspective

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Alzheimer's disease (AD) and glioblastoma (GBM) are neurological diseases that result in cognitive decline and ultimately death. Although AD is characterized by excessive cell death and GBM is characterized by excessive cell proliferation, there are many commonalities in the cellular and molecular mechanisms underlying the progression of both diseases. From an immunological perspective, malfunctioning microglia and brain blood barrier (BBB) impairment are involved in both AD and GBM pathology. Metabolically, both degenerating neurons in AD and proliferating tumor cells in GMB exhibit the Warburg effect and undergo metabolic changes that lead to increased oxidative stress. AD and GBM also share common genetic risk factors, with FYN upregulation and the APOE e4 allele increasing risk for either disease. However, other studies suggest an inverse relationship between AD and GBM, including striking differences in the gut flora of AD and GBM patients. The plausible connections could reveal early diagnostic tools such as potential biomarkers and therapeutic targets through both the similar abnormalities and the inversely related pathways. By better understanding the mechanisms and pathways involved in each disease, further research can be conducted to attempt to find better treatment options respectively. In this review, we discuss the connections between AD and GBM pathology and how progression of one disease can potentially affect the onset of the other.

Keywords: *Alzheimer's Disease, Glioblastoma, microglia, cytokines, Warburg effect, pentose phosphate pathway, Blood-Brain Barrier*

Introduction

Neurodegenerative diseases are a type of disease where neurons of the central nervous system (CNS) or peripheral nervous system are damaged, malfunctioning, or dying due to apoptosis and necrosis. Various factors such as sleep deprivation, stress, tumors, and stroke contribute to the development of neurodegenerative diseases. In most cases, patients suffering from neurodegeneration experience symptoms such as memory loss, agitation, depression, and anxiety due to neuronal loss in areas of the brain that control memory formation and emotion regulation.

In the United States, approximately 6.7 million people age 65 and older live with Alzheimer's disease (AD) in 2023. After COVID-19 became one of the leading causes of death, AD was ranked as the seventh leading cause of death. Amongst those age 65 and older, AD continues to be the fifth leading cause of death. In 2022, approximately 18 billion hours of care for people living with AD or other dementias was provided by more than 11 million family members and other unpaid caregivers. However, due to the pandemic, the emotional distress and negative mental and physical health of family caregivers was exacerbated. The value of unpaid dementia caregiving in 2022 was about $339.5 billion [1].

AD is a neurodegenerative disease perpetuated by a cycle of neurotoxicity and neuronal death and is characterized by the accumulation of beta-amyloid (Aβ)plaques and tau tangles. Typically, Aβ serves as a crucial player in neural growth and repair, but in AD, Aβ aggregates can end up killing neurons [2].Tau normally binds to and stabilizes the microtubules in the neuronal cytoskeleton, but in AD, abnormal chemical changes can cause tau to detach from the microtubules that bind to other tau molecules. This leads to the formation of neurofibrillary tangles (NFTs) that can accumulate and lead to neuronal membrane degeneration and damage. Tau can be intracellular or extracellular, with neuronal death resulting in the release of intracellular NFTs and neurotoxic cytokines that further drive the neurodegenerative cycle [3].Intracellular tau can aggregate into NFTs, causing neuronal dysfunction and synaptic impairment [4]. Extracellular tau has been found to perform a crucial role in the synaptic activities in the neuron [5].

As a result of neuronal death in the hippocampus, an area of the brain that controls long-term memory formation, AD

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patients can lose the ability to generate new memories. Aβ and tau aggregates attract and activate microglia, the resident macrophages of the CNS. Microglia mainly express two phenotypes, M1 and M2. The M1 phenotype, or "classically activated" phenotype, is known to generate an excessive proinflammatory immune response in AD, whereas the M2 phenotype, or "alternatively activated" phenotype, is known to induce a reparative, healing, anti-inflammatory response[6]. Chronic activation of microglia in the M2 phase due to failure to remove a pathogen from the neural environment can result in a switch back to the M1 phase. In AD, the proinflammatory response initiated by the M1 microglia often results in cognitive decline and the exacerbation of neurotoxicity.

Cancer is the uncontrollable growth of cells that can occur nearly anywhere within the body. Cancers that affect the brain include breast cancer, lung cancer, melanoma, lymphoma, and glioblastoma. Glioblastoma (GBM) is a category of astrocytoma that is the most common malignant primary brain cancer type and is implicated in cognitive impairment[7]. In the United States, the incident rate for GBM is 3.19 per 100,000 persons[8]. Even though GBM can occur in any age range, the average age of primary GBM presentation is 62 years and the median prognosis for survival is 14 months despite the modern therapies[9,10]. The current standard of care includes radiotherapy and chemotherapy with temozolomide (TMZ). The estimated direct medical cost of newly diagnosed, TMZ-treated GBM was $268,031 per patient[11]. Even prior to confirmed diagnosis, patients experienced social, physical, psychological, and existential distress. Social and physical function consistently declined, whereas psychological and existential distress exacerbated acutely during the diagnosis and initial treatment[12]. GBM not only affects the patients but also impacts the caregivers. It has been shown that the level of perceived control over the care by family caregivers greatly influences the experienced emotional distress and burden[13].

In order for tumor cells to grow uncontrollably, the body's innate immune response is suppressed. GBM proliferates with the help of special immune cells. Some cell types involved in the tumor microenvironment include tumor-associated macrophages (TAMs) and microglia, which congregate around the tumor mass. Similarly, in AD, microglia have been found to surround neurons with Aβ and tau aggregates. TAMs are involved in the progression of both AD and GBM and originate from monocytes. For example, in GBM, TAMs start off as bone-marrow-derived macrophages (BMDMs) in the peripheral circulation and are exposed to tumor antigens upon infiltrating through the blood-brain barrier (BBB) into the brain parenchyma[14]. Uptake of tumor antigens can cause BMDMs to differentiate into TAMs, which can secrete immunosuppressive cytokines that aid tumor proliferation[15]. Not only can TAMs recruit microglia to the tumor environment, but they can also differentiate the microglia and transform them into more TAMs[16]. Some other immunosuppressive cells include myeloid-derived suppressor cells (MDSCs), tumor-associated neutrophils (TANs), regulatory T (Treg) cells, and regulatory B (Breg) cells.

Currently, there is not a lot of research looking into the relationship between neurodegenerative diseases and brain tumors compared to the vast amount of research done on the individual diseases respectively. The few papers exploring the connection do not go in depth due to the lack of research available. The clinical studies often have a small sample size, and the results cannot be generalized. However, majority of the individual studies indicated a negative correlation. Larger clinical studies and further research needs to be conducted to confirm the inverse relationship.

Immunological changes in AD and GBM

Alzheimer's disease (AD) is a neurodegenerative disease with Aβ plaques and tau tangles as its main distinguishing hallmarks. Recent research highlights the crucial role of neuroinflammation in the development of AD. Some key players in the immune response include microglia, the resident macrophages of the CNS, and astrocytes, which release cytokines such as tumor necrosis factor alpha (TNF-α) in response to neural insults. Typically, all of these cell types work together to maintain homeostasis in the CNS, but in neurodegenerative diseases, they undergo changes that prevent proper immune responses and neural functions.

Microglia have two phenotypes; M1 is known as the "classically activated" proinflammatory phenotype, whereas M2 is known as the "alternatively activated" anti-inflammatory phenotype[6]. Both phenotypes have their own purpose within the innate immune system of the CNS. M1 is most likely known as the classically activated because it is the phenotype initially activated upon detection of pathogens. It has been shown that a second wave of anti-inflammatory cytokines are released into the neural environment some time after the proinflammatory response is triggered to repair the damage via M2 microglia. However, the persistent presence of pathogens leads to chronic inflammation, overactivation, and prolonged toxicity. In AD, malfunctioning M1 microglia exacerbate the perpetual cycle of neurotoxicity by expressing an excessive inflammatory response that ends up killing neurons. It is also shown that M1 microglia can strongly activate resting natural killer (NK) cells. The activated NK cells secrete cytotoxic molecules that can kill M2 microglia[17]. The depletion of M2 microglia through their interactions with NK cells promotes a proinflammatory environment in AD patients. A 2020 study on 3xTg-AD mice reveals that the depletion of NK cells via anti-NK1.1 antibodies reduces inflammation, enhances neurogenesis, and improves cognitive function significantly[18].

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AD patients have higher levels of proinflammatory cytokines than anti-inflammatory cytokines due to chronic activation of M1 microglia and NK cells. M1 microglia and NK cells secrete proinflammatory cytokines such as interleukin-3 (IL-3), interleukin-5 (IL-5), interleukin-10 (IL-10), interleukin-12 (IL-12), interleukin-13 (IL-13), and interferon gamma (IFN-γ)[19]. In normal individuals, NK cells have a surveillance function by detecting protein aggregates and destroying them in the brain via neurotoxicity. Once the NK cells malfunction due to chronic inflammation, they fail to remove the protein aggregates and also fail to release anti-inflammatory cytokines such as vascular endothelial growth factor (VEGF) that polarizes the microglia into the M2 phase[20]. The microglial M2 phase is reparative and heals surrounding cells and tissues via growth factors and various anti-inflammatory cytokines such as IL-10 and TGF-β[21]. The M2 phase promotes anti-inflammatory action and neuroprotection. Generally, the M2 phase would suffice to clear away most of the Aβ aggregates via phagocytosis, but chronic activation of microglia results in the constant release of proinflammatory cytokines, which can be detrimental to the health of the CNS, thus becoming incapable of removing Aβ[22–24].

Furthermore, the inflammatory insults can lead to a switch from M2 back to M1 phenotypes, which further increases the release of proinflammatory cytokines. In addition, the presence of NOD-like receptor (NLR) family pyrin domain containing 3 (NLRP3) inflammasome and caspase-1 can polarize microglia into the M1 phenotype. The M1 phenotype can often have an excessive response in AD. By overreacting, the microglia accidentally kills the neuron it is attempting to save, releasing even more tau aggregates as a result[3,25,26]. The release of protein aggregates and cytotoxic molecules results in the activation of more microglial cells, driving the self-perpetuating cycle of neurotoxicity.

There are several types of brain cancers, the most common malignant form being glioblastoma (GBM), which is a severe astrocytoma in the CNS caused by glial tumorigenesis. The major cell types involved in GBM progression include microglia and tumor-associated macrophages (TAMs). Tumor-supportive phenotypes of microglia promote tumor proliferation in the tumor microenvironment[27]. The tumor recruits microglia by suppressing caspase-3, a protein that regulates cell apoptosis and ubiquitination of the oncogene cyclin E. The inhibition of caspase-3 in microglia promotes the uncontrollable growth of gliomas. The tumor itself is comprised of cancerous astrocytes and is surrounded by masses of conglomerated microglia/macrophages. GBM utilizes the M2 microglia to proliferate, metastasize, stimulate angiogenesis, and suppress the immune system's natural antitumor response. In addition, TAMs play a significant role in GBM progression by influencing other immune cells in the tumor microenvironment. TAMs originate from monocytes that are activated in the tumor region. They also have two phenotypes, M1 and M2. TAMs are typically activated into the M2 phase but have the capability to fluidly switch between phenotypes to adapt to its environment, complicating treatment options. The TAMs release growth factors, cytokines, chemokines, and can inhibit T cells' functions. TAMs play a crucial role in promoting the proliferation and sustentation of the tumor by aiding in the manipulation of other cells. TAMs can inhibit the functions of T cells to protect glioma growth by increasing the secretion of immune checkpoint proteins. One of the immune checkpoint proteins is programmed cell death protein 1 (PD-1) and its ligand programmed death ligand 1 (PD-L1). PD-L1 was observed to be highly expressed by glioma cells and played a crucial role in immunosuppression by binding to the PD-1 on the membrane of neighboring T-cells, thus suppressing T-cell activation[28]. High PD-L1 expression was seen to be an indicator of a poor prognosis for GBM patients. This may be due to the positive correlation found between PD-L1 expression and M2-polarization and infiltration of TAMs. There are also ongoing trials attempting to target PD-L1 as a possible therapy for GBM. PD-L1 inhibition resulted in increased survival, replication, and activation of macrophages. So far, preclinical studies have shown significant anti-GBM effects with the combined antibodies of PD-1 and PD-L1[29]. Not only can TAMs inhibit T cells, but they can also recruit other macrophages or microglia via cytokine and chemokine release. Cytokines and chemokines attract microglia to the tumor's location, creating a ring of microglia surrounding the tumor mass. This protects the tumor from the body's innate immune response. Due to the crucial role TAMs play in the tumor microenvironment, there have been attempts to develop TAM-targeting therapies. Currently, there are different ongoing trials for medications aiming to reduce TAM viability, polarize TAMs to the M1 phenotype, or promote phagocytosis and their antigen presenting ability[30].

In AD, the extremely proinflammatory environment induced by the expression of M1-polarized immune cells results in inhibited M2 polarization via proinflammatory cytokines. Thus, the inflammatory response elicited by the neural insults will not be cleared by M2 polarized immune cells, resulting in sustained chronic inflammation. On the other hand, GBM would benefit from proinflammatory activation since M2 polarized immune cells aid in immune evasion by secreting immune checkpoint proteins, anti-inflammatory cytokines, and deactivating proinflammatory cells such as T cells. TAMs especially suppress the innate immune response, promote tumor proliferation, angiogenesis, and metastasis.

For both AD and GBM, impairment of the Brain-Blood Barrier (BBB) can contribute to the cause or development of the disease. Although the BBB is impermeable to large molecules, cytokines can cross via residual leakiness, diapedesis, membrane diffusion, cerebral spinal fluid reabsorp-

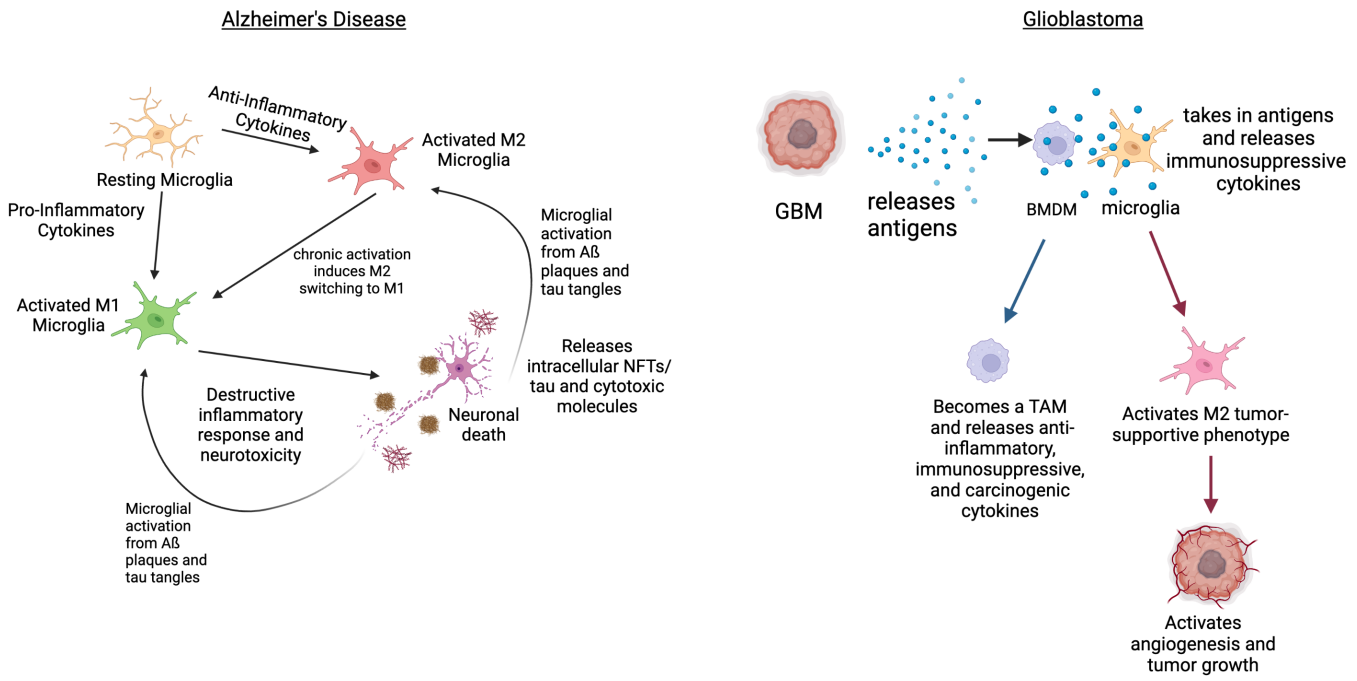

Fig. 1 The mechanisms of Alzheimer's disease (AD) and glioblastoma (GBM) both involve microglia, but the different phenotypes play different roles in AD and GBM. In AD, the M2 phenotype malfunctions and fails to clear amyloid (Aß) and tau aggregates. Thus, activating M1 microglia that excessively reacts and kills neurons. The death of the neurons releases intracellular neurofibrillary tangles (NFTs) and other cytotoxic molecules that perpetuate the cycle. In GBM, the tumor releases antigens that activate a tumor-supportive phenotype in M2 microglia, and in turn, stimulates angiogenesis and tumor proliferation.

tion, or saturable transport systems. In the neural environment, inflammatory cytokines can activate microglia in various ways, leading to an excessive immune response that kills neurons in AD and the promotion of tumor proliferation in GBM. Proinflammatory cytokines such as TNF- α, interleukin-6 (IL-6), and interleukin-1 beta (IL-1 β) can contribute to the impairment of the BBB, which can lead to an increased influx of peripheral immune cells that can contribute to this state of chronic neuroinflammation. Systemic inflammation may also promote both neurodegenerative diseases and gliomas by impairing the BBB as well. A compromised BBB can permit proinflammatory cytokine and NK cell infiltration for AD and bone-marrow derived macrophage (BMDM) infiltration from the peripheral immune system and activate an inflammatory response in the brain.

Metabolic Changes in AD and GBM

Metabolism is greatly altered in AD and GBM due to the substantial increase in energy required by the affected cells, neurons, and tumors respectively. In mild AD, majority of the neurons utilize glycolysis as the main method of energy production rather than oxidative phosphorylation (OXPHOS), despite the presence of oxygen. This shift toward glycolysis utilization is called the Warburg effect. The typical neuron undergoes OXPHOS, which produces substantially more ATP than using glycolysis as its sole method of cellular respiration. By utilizing glycolysis as the main method of ATP production, neurons are able to become temporarily Aß-resistant, but chronic exposure to lactate, a byproduct of glycolysis, consequently damages neuronal mitochondria[31,32]. However, as the disease progresses, the Warburg effect becomes more detrimental and accelerates disease progression. Neurons require OXPHOS due to the continuously high demand for energy for neuronal functions, but the damaged mitochondria are unable to continue supporting neurons through OXPHOS, leading to neuronal death.

The Warburg effect has been found in cancer as well. Even though glycolysis yields less ATP, it is faster and consumes more glucose[33]. It is imperative for the cancerous cells to switch from OXPHOS to glycolysis to maintain the high amount of energy and biomass required for the tumor to thrive[34,35]. This switch in cellular respiration is a hallmark of cancer. The Warburg effect causes permanent damage to the mitochondria which may contribute to promoting the progres-

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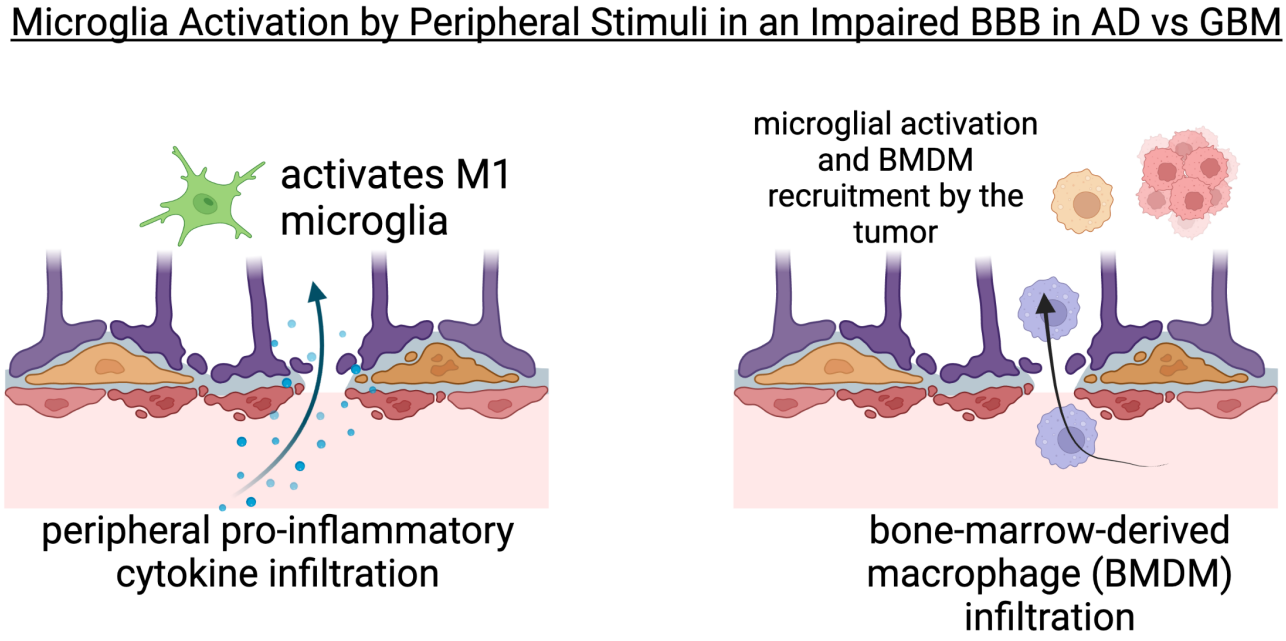

Fig. 2 In Alzheimer's disease, pro-inflammatory cytokines from peripheral circulation infiltrate the blood-brain barrier, whereas in glioblastoma, bone-marrow-derived macrophages infiltrate the blood-brain barrier.

sion of cancer.

Branching from glycolysis is the pentose phosphate pathway (PPP), an anaerobic metabolism process that produces ribose-5-phophate sugar (R5P) and nicotinamide adenine dinucleotide phosphate (NADPH) instead of ATP. In normal individuals, glucose-6-phosphate and 6-phosphogluconate inhibit H_2O_2-induced lipid peroxidation in a concentration dependent method. In the PPP of AD patients, glucose-6-phophate dehydrogenase (G6PD) and 6-phosphonogluconate dehydrogenase (6PGDH) are selectively increased in the inferior temporal cortex of AD patients. This leads to a decrease of glucose-6-phosphate and 6-phosphogluconate, which results in an increase in H_2O_2-induced lipid peroxidation, leading to cell death. The upregulation of the dehydrogenases is most likely to respond to the increase in prooxidant activity, which leads to increased oxidative stress. These facts suggest that increased oxidative stress in AD is not caused by a reduced level of antioxidants, but rather is a result of increased prooxidant activity[36]. Oxidative stress can also induce mutations and damage to the genome and excessive cell proliferation[37].

In GBM, hypoxia has been shown to result in metastasis and angiogenesis[38]. Due to the hypoxic conditions and high metabolic demand, GBM cells exhibit high levels of reactive oxygen species (ROS)[39].Oxidative stress has been shown to alter DNA, signaling pathways, and cancer progression[40]. Studies have revealed the dichotomy that cancer cells can only either proliferate or migrate and cannot do both simultaneously. The type of cancer cell is also location dependent. Glioblastomas were observed to have metastatic cells at the edge of the tumor mass and proliferating cells in the core[41]. PPP enzyme expression is upregulated by oxygenation and downregulated in hypoxic environments, whereas glycolysis enzymes are inversely altered. In a tumor friendly environment, such as oxygenation, rapidly proliferating GBM cells elevate PPP enzymes and inhibit glycolysis enzyme expression to minimize oxidative stress and increase its chances of surival[42]. It has been observed that a decreased activation of the PPP led to decreased proliferation. This is most likely because NADPH and R5P are both essential for the survival and proliferation of the tumor[43]. A hypoxic environment triggers a significant decrease in PPP enzymes and increases glycolysis enzymes in metastatic cells[44]. Due to the harsh conditions, the tumor becomes extremely malignant to enhance its survival. One study explores the specific aspects of malignancy, proliferation vs metastasis, in relation to the elevated cell turnover rate or cell apoptotic index. It is shown that the relatively high apoptotic index favors cancer cell proliferation. Interestingly, the relatively low apoptotic index is associated with cancer cell metastasis[41]. However, studies have also shown that the overall apoptosis index is still higher in malignant tumors than be-

nign tumors[45]. Further research is required to understand the exact mechanism and pathways involved. Regardless, in both AD and GBM, oxidative stress plays a crucial role in disease progression.

Molecular

In GBM patients, the oncogene FYN is upregulated. Fyn kinase has been shown to promote tumor proliferation and metastasis. In a study with human-derived glioma cell lines U251 and U343, it is found that an FYN inhibitor, rosmarinic acid (RA), significantly reduces proliferation rates, decreases the expression of other invasion-related factors, and inhibits metastasis. RA treatment also increases pro-apoptotic proteins, cleaved caspase-3 and Bax, and decreases levels of Bcl-2, an apoptosis suppressor protein[46]. RA has also been shown to have the ability to polarize microglia expressing the M1 phenotype to the M2 phenotype, to suppress tau phosphorylation by downregulating the JNK signaling pathway, to decrease Aß aggregation, and to reduce tumor proliferation and metabolism by inhibiting PI3K/Akt/NF-kB[21,47–49]. So, in GBM patients, RA reduces tumor proliferation by polarizing M1 microglia. In AD patients, that function would be detrimental due to the neurotoxic environment. However, RA has also been found to potentially suppress amyloid aggregation and tau phosphorylation, which could be a potential treatment for AD.

In both AD and cancers such as GBM, there is high expression of the APOE gene, with the E4 allele being present at higher frequencies in both diseases. ApoE protein is involved in lipoprotein metabolism, lipid transport, and regulating the distribution and redistribution of lipids in tissues and cells[50,51]. ApoE4 is highly proinflammatory and can lead to increased BBB permeability by activating a cyclophilin A-MMP9 pathway in endothelial cells and pericytes[52]. Additionally, in AD, ApoE4 is known to aid the accumulation of A β and tau and the degradation of the BBB. However, intracellular ApoE is typically responsible for lipid transport in astrocytes and may be able to regulate immune function, inflammation, and promote the repairment of neural tissue under normal circumstances.

Since astrocytes are the main cells that secrete ApoE, there is significant ApoE expression in GBM[53]. In the tumor microenvironments of certain cancers such as GBM and thyroid cancer, ApoE can mediate inflammation, promote tumor growth, metastasis, proliferation, and stimulate angiogenesis[54,55]. In contrast, in some other cancers such as melanoma and ovarian cancer, the high frequency of ApoE has protective effects. Past research has suggested that ApoE can regulate tumor inflammation and promote M1 microglia polarization via VLDL-R or apoeER2 signaling[56]. Further research is required to determine the specific mechanisms of the ApoE function in the context of cancers. However, in both AD and GBM, the expression of ApoE4 has been proven to exacerbate the condition of the patient.

Gut Flora

In recent years, researchers have explored how the gut flora impacts neurodegenerative diseases and cancers. Studies have shown that the gut flora of AD patients have an abundance of bacteria that can exacerbate AD, such as *Blautia*. However, *Blautia* is found to improve the state of cancer patients. The AD patients have a deficiency of *Ruminococcaceae* and *Prevotella*[57]. *Ruminococcaceae* was shown to induce immune tolerance through Treg cells. The deficiency of *Ruminococcaceae* also leads to decreased production of tryptamine, which is needed to produce serotonin. In AD, serotonin deficiencies have been observed. Due to the serotonergic alterations and its relationship with the gut, it may be a potential biomarker for AD progression[58]. These connections are further proof of the relationship between the gut and brain. *Ruminococcaceae* and *Prevotella* have both been shown to improve the condition of AD patients but can promote the growth of tumors such as GBM. In contrast, cancer patients have higher levels of bacteria that both promote cancerous growth and improve the condition of AD overall compared to patients who lack this bacterial strain. For example, GBM patients have been observed to have elevated levels of *Ruminococcaceae* and overexpression of the serotonin 7 receptor[59]. After being treated with TMZ, *Ruminococcaceae* levels were seen to decrease[60]. The immune tolerance induced by the *Ruminococcaceae* also further promotes tumor pathogenesis. In addition, it is found that cancer patients have lower levels of *Blautia*, resulting in tumor growth. The reduced levels of *Blautia* are shown to benefit AD patients. The contrasting gut micro bacteria populations in AD and cancer patients indicate that patients with AD would be less likely to develop cancer such as GBM and vice versa[57]. It suggests that the body, already susceptible to an illness, built up defenses against other conditions.

Discussion

AD and GBM share many pathways, and in doing so, reduce the risk of a patient developing both a neurodegenerative disease and cancer within their lifetime. Both AD and GBM involve malfunctioning microglia/macrophages, BBB impairment, exhibit the Warburg effect, and elevated levels of APOE4 in astrocytes, yet when the intestinal flora of the respective patients were compared, an inverse correlation was revealed. Most of the observational studies further supported the revelation. Most likely, patients with a cancer history have

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a decreased risk of developing AD since GBM increases M2 microglia in the tumor environment and M2 clears away protein aggregates in AD and vice versa. Patients with AD have a decreased risk of developing GBM since there is an increase of NK cells in AD and the NK cells have been shown to kill M2 microglia and tumor cells. While both diseases impact common pathways, their pathology appears to veer towards opposite sides of the spectrum.

Due to the adaptive nature of GBM and the neurotoxic cycle in AD, finding effective treatments has been difficult. However, there have been some promising trials regarding inflammatory regulation. While neuroinflammation, or the lack thereof, may not be the underlying cause of neurodegenerative diseases or glioblastoma respectively, the inflammatory environment is crucial to their progression. In AD, promoting an anti-inflammatory environment should slow down the self-perpetuated, neurotoxic cycle of cell death. In GBM, activating the proinflammatory responses should aid the immune system in fighting back against the immunosuppressive effects of the tumor. In fact, recent pharmacological trials have shown a failed promising drug for AD be repurposed to treat GBM. This drug was a beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) inhibitor. BACE1 is responsible for producing Aß plaques, but the inhibitor was seen to exacerbate cognition and increase adverse effects in the phase 3 clinical trials[61]. BACE1 is also highly expressed on TAMs. By inhibiting BACE1, reprogramming of tumor supportive TAMs to a proinflammatory phenotype was seen and significantly reduced tumor growth[62]. This is another example of how AD and GBM are on different ends of a spectrum. The specific methods as to how to achieve those goals are still unclear. Further research and clinical trials need to be conducted to confirm this connection in regards to the inflammatory processes.

Conclusion

Many studies support this hypothesis that there may be an inverse relationship between AD and GBM, though the specifics of the findings are still being debated. One nationwide cohort study suggested that the inverse associations between cancers and AD risk were minimal and diminished over time, indicating a limited association[63]. Some studies did not discern an inverse relationship when observing less aggressive cancers, so the inverse correlation may only pertain to the more malignant tumor types like GBM[64]. However, significant positive correlations between AD and malignant brain tumor mortality rates have been found as well. They even share some common risk factors such as exposure to electromagnetic radiation, smoking, and occupational exposure to pesticides[65]. Further research needs to be conducted to explore how common risk factors affect the intricate relationship between the two diseases. Some have also found that cancer therapies such as radiation, chemotherapy, and immunotherapy can consequently lead to cognitive impairment. However, others suspect that cancer treatments may be associated with a decreased risk of AD[66–71]. This peculiar relationship between neurodegenerative diseases and brain tumors is quite interesting, yet still unclear. Further research is required to explore the inverse relationship and the similarities between the two diseases. The various connections could yield potential therapeutic targets and biomarkers that could be used as tools for early diagnosis.

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