Bridging the Metabolic Parallels Between Neurological Diseases and Cancer

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Glutamine · Glutamate · NAAG · GABA · GCP II · Cancer · Neurological diseases

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Abbreviations

2-MPPA	2-(3-Mercaptopropyl) pentanedioic acid
2-PMPA	2-(Phosphonomethyl) pentanedioic acid
α-KG	Alpha-ketoglutarate
AD	Alzheimer's disease
ADHD	Attention-deficit/hyperactivity disorder
ALS	Amyotrophic lateral sclerosis
AMPAR	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
Aβ	Amyloid-beta
cAMP	Cyclic adenosine monophosphate
CNS	Central nervous system
CREB	cAMP response element-binding protein
GABA	Gamma-aminobutyric acid
GABAAR	GABAA receptor
GABABR-ab	GABAB receptor antibodies
GABARAP	GABAAR-related protein
GAD	Glutamate decarboxylase
GAD-A	GAD autoantibodies
GCP II	Glutamate carboxypeptidase II
GLS	Glutaminase
GS	Glutamine synthetase
HD	Huntington's disease
KGM	Alpha-ketoglutaramate
LE	Limbic encephalitis
mGluR1	Metabotropic glutamate receptor I

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mGluR3	Group II type 3 metabotropic glutamate receptor
MMP	Matrix metalloproteinase
NAA	*N*-Acetyl-aspartate
NAAG	*N*-Acetyl-aspartyl-glutamate
NMDAR	*N*-methyl-D-aspartate receptor
NNK	4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone
NO	Nitric oxide
NOS	Nitric oxide synthase
OSCC	Oral squamous cell carcinoma
PAC	Pulmonary adenocarcinoma
PCP	Phencyclidine
PD	Parkinson's disease
PLP	Pyridoxal 5′-phosphate
PP-2A	Protein phosphatase 2A
PSMA	Prostate-specific membrane antigen
SCLC	Small cell lung cancer
SHR	Spontaneous hypertensive rat
SPS	Stiff-person syndrome

Key Points

- The elevated presence of glutamine in cancer and neurological diseases leads to two distinctive disease progressions and compromises patient survival.
- Glutamate has a prognostic role in cancer, schizophrenia, and hyperammonemia.
- Downregulation of glutamate transporters causes excessive extracellular glutamate in cancer, hyperammonemia diseases, and neurodegenerative diseases.
- NMDA receptor activation protects cancer cells as well as neurons in psychiatric disorders but results in cell deaths for neurodegenerative diseases and hyperammonemia diseases.
- AMPAR expression plays a contrasting role in disease progression of cancer and Alzheimer's disease.
- The complex relationship between glutamine metabolism and *MYC* contributes significantly to the pathophysiology of both cancer and neurodegenerative diseases.
- Elevated GAD expression is found in acute stress and contributes to oral squamous cell carcinoma invasiveness.
- GABA level is characteristic of various cancers and contributes to Alzheimer's disease and attention-deficit/hyperactivity disorder (ADHD).
- GABA receptors contribute to Alzheimer's disease pathogenesis, Parkinson's disease severity, and cancer invasiveness.
- Autoimmune disorder's attack on the GABA-ergic system correlates with neurological diseases and cancers.
- NAAG affects both cancer and neurological disease progression via glutamate.
- Targeting GCP II is a very promising strategy for cancer treatment.
- NAAG inhibits GABA release and indirectly affects both cancer and neurological diseases via GABA-ergic system.

1 Introduction

Despite the many recent breakthroughs in cancer research, oncology has traditionally been seen as a distinct field from other diseases. Recently, more attention has been paid to repurposing established therapeutic strategies and targets of other diseases towards cancer treatment, with some of these attempts generating promising outcomes [1, 2]. Recent studies using advanced metabolomics technologies [3] have shown evidence of close metabolic similarities between cancer and neurological diseases. These studies have unveiled several metabolic characteristics shared by these two categories of diseases, including metabolism of glutamine, gamma-aminobutyric acid (GABA), and *N*-acetyl-aspartyl-glutamate (NAAG) [4–6]. The striking metabolic overlap between cancer and neurological diseases sheds light on novel therapeutic strategies for cancer treatment. For example, 2-(phosphonomethyl) pentanedioic acid (2-PMPA), one of the glutamate carboxypeptidase II (GCP II) inhibitors that prevent the conversion of NAAG to glutamate, has been shown to suppress cancer growth [6, 7]. These promising results have led to an increased interest in integrating this metabolic overlap between cancer and neurological diseases into the study of cancer metabolism. The advantages of studying this metabolic overlap include not only drug repurposing but also translating existing knowledge from neurological diseases to the field of

cancer research. This chapter discusses the specific overlapping metabolic features between cancer and neurological diseases, focusing on glutamine, GABA, and NAAG metabolisms. Understanding the interconnections between cancer and neurological diseases will guide researchers and clinicians to find more effective cancer treatments.

2 Glutamine Plays a Vital Role in Both Cancer Growth and Neurological Diseases

Glutamine metabolism is a vital contributor to cancer growth and is discussed thoroughly in Chap. 2 [8]. The survival of some tumors depends entirely on the presence of exogenous glutamine, a condition known as glutamine addiction [9]. In addition, the severity of glutamine addiction observed in cancer is positively associated with the degree of tumor malignancies [10]. Besides its role in cancer growth, glutamine is also a well-established precursor of neurotransmitters, glutamate, and GABA [11], and glutamate is involved in learning and memory, especially long-term potentiation [12]. A growing body of evidence has shown that abnormalities in the glutamatergic neurotransmission, including excessive glutamate release and dysfunction of glutamate receptors, play a significant role in a number of neurological diseases, such as Alzheimer's disease (AD), Huntington's disease (HD), hyperammonemic disease, schizophrenia, and other psychotic disorders [13–16]. In this section, examining the glutamine metabolism in neurological diseases may provide further understanding of glutamine's role in cancer and provide insights into glutamine-targeting cancer therapies.

2.1 The Elevated Presence of Glutamine in Cancer and Neurological Diseases Leads to Two Distinctive Disease Progressions and Compromised Patient Survival

Glutamine addiction and an elevated level of glutamine are observed in a variety of cancers and promote tumor growth by serving as a major energy source. Similarly, the high presence of glutamine was also observed in hyperammonemia diseases, where ammonia level increases abnormally in blood. Hyperammonemic diseases are associated with many brain injuries, including cerebral edema, and is believed to be the primary cause of hepatic encephalopathy [17]. Glutamine acts as an astroglial intracellular idiogenic osmole, disturbing the delicate balance between water and glutamine concentrations inside and outside of astrocytes. The result is an influx of water into the cells, causing cerebral edema. The suppression of glutamine accumulation results in reduced swelling of glial cells [13]. Thus, although the role of elevated levels of glutamine in cancer progression and aggressiveness is very different from its negative effects in edema under hyperammonemia, both impair patient survival.

Glutaminase (GLS) catalyzes the conversion of glutamine to glutamate. Because it plays a central role in the glutamine/glutamate metabolic cycle, GLS is extremely important in cancer and neurological disorders. As previously discussed in Chap. 2, inhibition of GLS suppresses the growth of various tumors [8, 18–21]. Moreover, the upregulated conversion from glutamine to glutamate as a source of cellular bioenergy is a common characteristic observed in many cancers [22]. Therefore, the activity of GLS is crucial to cancer development.

An increase in GLS enzymatic activity, as well as transcription, has also been observed in schizophrenia, though without a detailed mechanism as to how the enzyme contributes to the disease pathophysiology [16]. Nevertheless, it is fair to connect the increase of GLS to glutamate accumulation and thus to the disease symptomology. In both cancer and schizophrenia, GLS upregulation is thought to be a major factor in disease progression.

On the other hand, glutamine-fueled tricarboxylic acid cycle (TCA cycle activity) via the GLS pathway [23] has differing impacts on cancer and Alzheimer's disease. In contrast to the increased GLS activation in cancer, a downregulation in GLS has been observed in AD pathophysiology [14]. Reduced GLS activation, resulting in ham-

pered oxidative glutamine metabolism, is a potential early marker of AD pathogenesis, preceding amyloid plaque formation in mice [14]. A significant decrease in glutamine-fueled TCA cycle activity, which requires GLS activity, has been observed in early AD [14], suggesting the importance of glutamine/glutamate-derived energy against disease development. It was found that a compromise in both ATP synthesis rate and cellular energy homeostasis caused by decreased TCA cycle activity likely results in amyloid plaque deposition [14], and thus is responsible for the core progression of AD.

Opposing mechanisms involving GLS, alpha-ketoglutarate (α-KG), and TCA cycle have been observed in both cancer and AD. While a decrease in glutamine-fueled TCA cycle activity is beneficial in terms of tumor suppression, it actually promotes AD progression, causing plaque formation and leading to disease development, which may appear to be a new complication for glutamine-targeting cancer therapies.

2.2 The Prognostic Role of Glutamate in Cancer, Schizophrenia, and Hyperammonemia

In addition to the elevated presence of glutamine, excessive glutamate, a direct product of glutamine via the glutaminase I pathway, also significantly impacts cancer. Glutamate acts as an energy source for cancer cells and can be directly converted to α-KG, a TCA cycle intermediate. Glutamate concentration positively correlates with the severity of cancer, as measured by the Gleason score in prostate cancer [24]. Glutamate deprivation or blockage with antagonists of metabotropic glutamate receptor I (mGluR1) results in decreased cancer cell growth, migration, and invasion and eventually contributes to apoptotic cancer cell death [24]. With the direct correlation of glutamate concentration in serum and cancer severity, glutamate can thus serve as a prominent prognostic indicator of cancer development.

Excessive glutamate levels have also been observed in a wide range of neurological diseases. This accumulation results in neuronal cell deaths due to neuro-excitotoxicity, underlying the pathophysiology of neuronal loss in multiple neurological diseases [15, 25]. Excess glutamate amplifies and exacerbates excitotoxicity through the positive feedback mechanism involving Ca^{2+} influx [25, 26]. Moreover, recent research in schizophrenia has shown that a higher glutamate level results in more severe disease symptoms and lower remission rates after treatment [26]. Interestingly, as schizophrenia moves from onset to the chronic stage, glutamate level, especially the ratio of glutamate/glutamine, increases significantly [27, 28]. Dysfunction of glutamate neurotransmission with lower glutamate levels during the disorder's onset and with higher glutamate levels for the chronic stage suggests the facilitating role of glutamate in the course of schizophrenia progression. The relationship between glutamate elevation and disease severity is also seen in hyperammonemia diseases [17]. The increasing extracellular glutamate concentration is also observed to be in a positive feedback loop with nitric oxide (NO) [17], thus contributing to the ever-worsening progression of hyperammonemia and neuronal death from both glutamate and NO toxicity.

A higher level of glutamate contributes to increased disease severity in cancer, schizophrenia, and hyperammonemia and thus is responsible for the longitudinal development of all three diseases. It is clear that the negative impact of glutamate accumulation exacerbates a variety of diseases ranging from cancer to a multitude of neurological disorders, indicating the prognostic role of excessive glutamate in these diseases.

Glutamine synthetase (GS) transforms glutamate into glutamine, preventing excitotoxicity due to glutamate accumulation. Therefore, dysfunction in GS results in an imbalance of glutamate and glutamine, causing pathophysiology in many diseases. Due to the importance of glutamate and glutamine in cancer, GS dysfunction and its implications are widely studied. Bode et al. showed that GS contributed to cancer cell proliferation, resistance, and aggression [4]. As cancer consumed glutamine to support the TCA cycle, GS provided an alternative influx of glutamine under glutamine-depleted conditions [4]. An increase in GS/GLS ratio was observed at

both mRNA and enzymatic activity levels starting at 24 h after tumor implantation in liver and kidney tumor models [10], suggesting an elevated need for glutamine production in cancer cells.

GS dysregulation is also seen in Huntington's disease (HD). An increase in GS activity has been observed to predominate in severely affected areas of the brain [29], indicating the relation between GS upregulation and symptomology and severity in HD. Therefore, GS may be responsible for disease aggression through glutamatergic energy production in cancer as well as upregulated expression in HD. In hyperammonemia, a decrease in GS activity in non-glutamatergic areas leads to ammonia and glutamate accumulation, since GS converts glutamate and ammonia into glutamine. This inability to keep the glutamate concentration from exceeding the normal physiological limit may be the root of neuronal toxicity observed in hyperammonemia [17] (Fig. 1).

The dysregulation of GS thus exerts divergent influences on different diseases. GS activity promotes aggression in both cancer and HD. On the other hand, in hyperammonemia diseases, GS activity prevents excitotoxicity from elevated glutamate levels. As glutamine and glutamate have opposite implications in diseases under certain conditions, the proper balance of these two, regulated by GS and GLS, is a fine line to navigate.

2.3 Downregulation of Glutamate Transporters Causes Excessive Extracellular Glutamate in Cancer, Hyperammonemic Diseases, and Neurodegenerative Diseases

Given the effect of excessive glutamate, targeting the cause behind high glutamate concentration is a promising therapeutic strategy. One of the reasons for the elevated concentration of glutamate is the downregulation of glutamate transporters, which are proteins embedded in the astroglial membrane. Impaired glutamate transporters often result in glutamate accumulation in the extracellular space, which underlies a wide range of diseases discussed above. As a result, the dysfunction of glutamate transporters is a contributing factor to the pathophysiology of many diseases, including cancers and neurological diseases [30]. For example, glutamate transporters were found to support cancer cells' survival, growth, and invasion [31]. In cancer, and especially in gliomas, the downregulation of glutamate transporters resulting in a glutamate excess is associated with the extreme aggressiveness of malignant gliomas [31]. This suggests that the hypofunction of glutamate transporters plays a role in energy provision in cancer, which eventu-

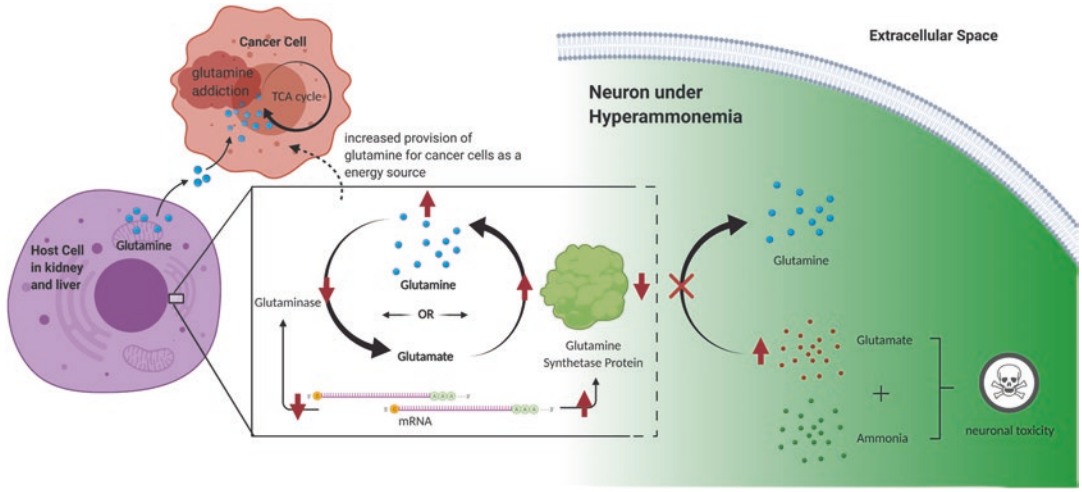

Fig. 1 The effects of glutamine synthetase dysregulation on both cancer and hyperammonemic diseases

ally results in the development of devastating tumors.

Downregulation of glutamate transporters is also observed in multiple neurological diseases [17]. Specifically, in hyperammonemia diseases, the reduced expression of astrocytic glutamate transporters possibly contributes to the delayed degeneration of a certain number of neurons as well as the increased extracellular concentrations of glutamate [15, 17], which is thought to contribute to hyperammonemia severity and other underlying abnormalities in acute liver failure [17]. In addition, neurodegenerative diseases, such as HD and AD, are also associated with excitotoxic impacts from elevated glutamate due to the downregulation of glial transporters [15]. Previous studies have shown that elicitation of glutamate transporters has neuroprotective implications, especially in AD and depression [25, 32], suggesting a direct correlation of reduced expression of glutamate transporters to disease pathophysiology.

The downregulation of glutamate transporters correlates with tumor malignancy and aggression, possibly via increasing extracellular glutamate levels. Downregulated glutamate transporters also cause neuronal deaths in hyperammonemia and neurodegenerative diseases. Despite the different effects of glutamate transporter hypofunction in cancer versus neurological diseases, they all contribute to the progression of these diseases.

2.4 NMDA Receptor Leads to Opposite Cell Fates in Cancer and Psychiatric Disorders Versus Neurodegenerative Diseases and Hyperammonemic Diseases

Although the exact mechanisms involving glutamate receptors have not yet been discovered completely in cancer, it is widely known that antagonists of the *N*-methyl-D-aspartate receptor (NMDAR), an ionotropic glutamate receptor, can decrease cancer cell viability and prevent tumor growth [33].

In schizophrenia and bipolar disorder, NMDAR activity has a neuroprotective advantage. Hypofunction of NMDAR was observed in both diseases [28, 34]. In addition, the downregulation of NMDAR induced and exacerbated schizophrenia symptoms [28]. Possible explanations for downregulated NMDAR-induced abnormalities have been suggested for schizophrenia. The receptor is likely responsible for cognitive development, axon pruning, and neuron preservation [35], which are all significantly impaired in schizophrenia symptomology [35].

Although NMDAR is essential for tumor survival and development as well as possible neuron preservation in schizophrenia, NMDAR activation is, in fact, related to cell death in neurodegenerative diseases. In neurodegenerative diseases, high Ca^{2+} permeability in NMDAR contributed to chronic neurodegeneration due to excitotoxicity [26]. Research has confirmed that neuronal survival can be maintained via NMDAR blockage [25, 26], indicating the direct causal role of NMDAR in cellular necrosis. Specifically, NMDAR activation, which reduces protein phosphatase 2A (PP-2A) activity, is a major contributor to the hyperphosphorylation of microtubule-associated protein Tau (τ) in AD [25]. In hyperammonemia diseases, NMDAR activation can result in ammonia-induced death of animals [17]. Moreover, excessive stimulation of NMDAR is also responsible for NO formation through the activation of nitric oxide synthase (NOS) [17]. NO accumulation through acute and chronic exposure is toxic to neuronal cells, which is observed in several neurological diseases, including Huntington's disease, Alzheimer's disease, and hyperammonemia [17].

It is safe to say that NMDAR is closely associated with the viability and growth of cancer cells and normal neurons in psychiatric patients' brains as well as with the toxic cellular deaths observed in neurodegenerative diseases and hyperammonemia diseases. The abundant evidence suggests that NMDAR activation leads to vastly different responses in cancer and neurological diseases. Thus, NMDAR has the potential as a drug target in cancer treatment.

2.5 AMPAR Expression Played a Contrasting Role in Disease Progression of Cancer and Alzheimer's Disease

α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), an ionotropic glutamate receptor in the central nervous system, is also a major contributor to disease development in both cancer and neurological diseases. A study by Herner et al. has shown that the inhibition of GluR1 and GluR2 subunits of AMPAR significantly decreases tumor invasion [36]. Specifically, AMPAR activation could be a switch to activate the Kras/MAPK cascade, which induces oncogenic signaling and eventually leads to tumor invasion, migration, and malignant transformation [36]. Interestingly, though both AMPAR and NMDAR are involved in neuroexcitotoxicity, the mechanism of AMPAR works opposite to that of NMDAR. In AD, a loss in GluR2 of AMPAR results in Ca^{2+}-mediated neurotoxicity and severe neuropathology [25]. Excitotoxicity could be induced by a loss of GluR2 subunit alone, and upregulation of GluR2 subunit can confer a protective advantage under increased Ca^{2+} levels [25]. Although both NMDAR and AMPAR are activated by the same neurotransmitter, glutamate, their effects on pathophysiology in cancer and AD are widely different. AMPAR expression plays a contrasting role in the two diseases' progression. While AMPAR activity in cancer is to promote tumor invasion and malignancy transformation, in AD, its role is neuroprotective against Ca^{2+}-mediated neurotoxicity and disease severity [25].

2.6 The Complex Relationship Between Glutamine Metabolism and *MYC* Contributes Significantly to the Pathophysiology of Both Cancer and Neurodegenerative Diseases

MYC is a family of regulator genes and proto-oncogenes that codes for transcription factors and plays a significant role in cancer progression [37–39]. In addition, *MYC* is also closely associated with the glutamine metabolism in both cancers and neurological diseases. *MYC* upregulates GLS expression and is primarily responsible for glutamine addiction in cancer [40–42]. The upregulation of GLS, as discussed in Sects. 2.1 and 2.2, leads to enhanced glutaminolysis and glutamate accumulation, and in turn promotes cancer growth [24]. Therefore, it is not surprising that an overexpression of *MYC* is associated with tumorigenesis [43]. Across various cancer types, *MYC* suppression results in reduced cancer cell growth, impaired colony formation, decreased tumor progression, and even induced cancer cell apoptosis [44–46]. In a recent study, new light has been shone on what was originally considered to be a one-way effect on glutamine metabolism by *MYC*. There actually exists a reciprocal regulation between *MYC* and glutamine metabolism, meaning that suppression of glutamine metabolism can prevent *MYC* transcription [47]. This mutual balance and regulation between the oncogene and the amino acid cause significant pathophysiological impacts when they affect each other, which can be a new research target for cancer treatment.

Interestingly, *MYC*, a proto-oncogene, is also closely involved in neurodegenerative diseases, especially HD and AD, via glutamine metabolism. The excitotoxic pathway through NMDAR activation in HD involves the induction of MYC and other pro-apoptotic proteins that eventually result in neuronal deaths, significant underlying pathophysiology in neurodegenerative diseases [48]. More specifically, *MYC* induces significant cognitive deficits and cell cycle reentry, which is believed to be responsible for neuronal cell death through loss of trophic support during development, thus leading to neurodegeneration in AD [43] (Fig. 2).

MYC and glutamine pathways are therefore clearly associated with each other and also with the pathophysiology of both cancer and neurodegenerative diseases. This is another indication of the close interplay between the metabolisms of cancer and neurological diseases, which also confirms glutamine as being a very promising drug target for cancer treatment.

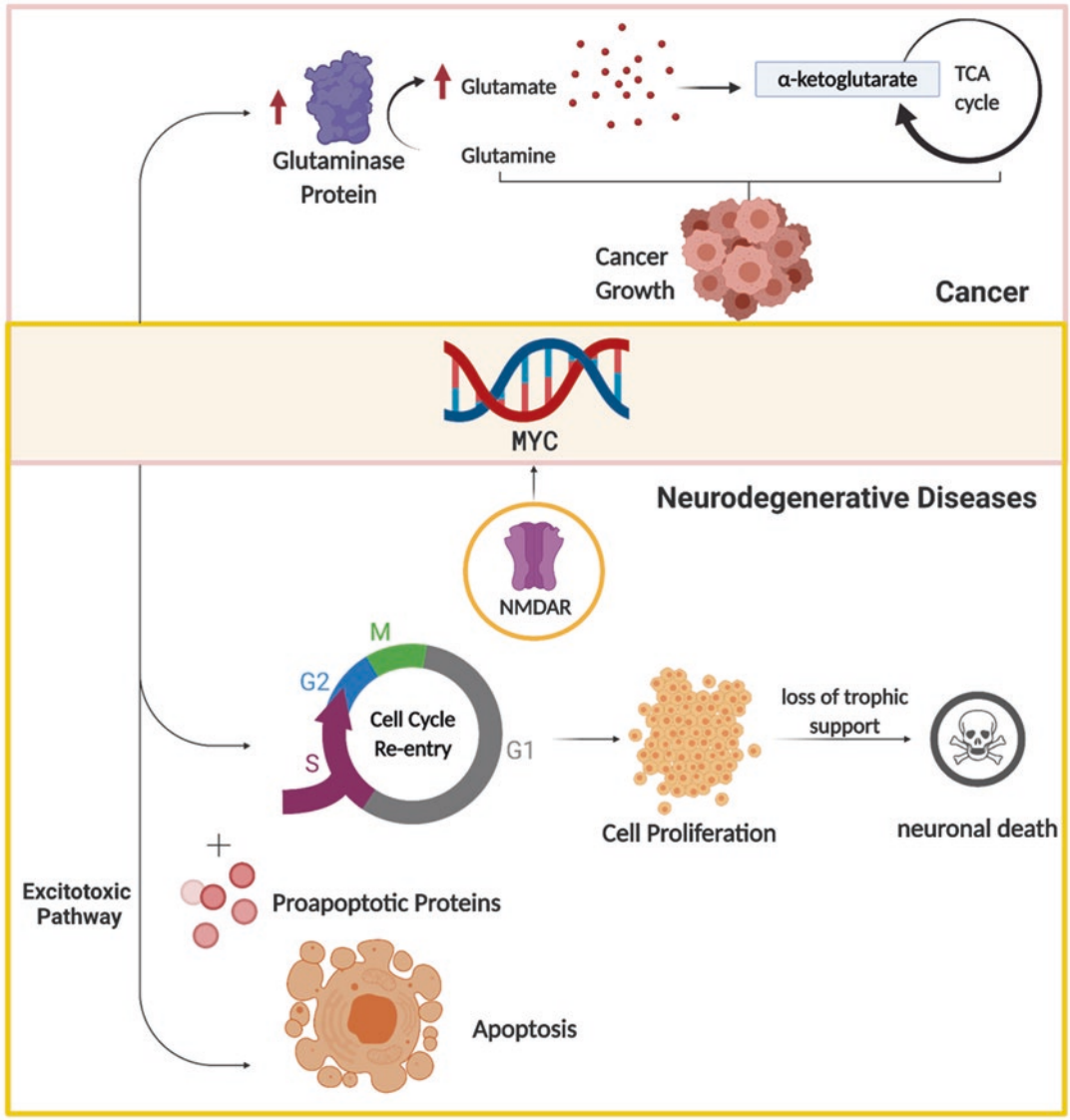

Fig. 2 MYC and its contributions in cancer and neurodegenerative diseases. *NMDAR N*-methyl-D-aspartate receptor

2.7 Alpha-ketoglutaramate and Its Shared Pathway in Cancer and Hyperammonemic Diseases

Recent study revealed that alpha-ketoglutaramate (KGM) is a significant component in glutamine addiction, connecting glutamine to the TCA cycle via the glutaminase II pathway, in which glutamine is converted to KGM by transamination with a suitable α-keto acid. KGM is then hydrolyzed to α-KG, an intermediate metabolite within the TCA cycle, by an enzyme known as ω-amidase [49]. The presence of glutamine, KGM, and α-KG, therefore, promotes tumor growth. In addition, the blockage of glutamine's conversion to KGM in the glutaminase II pathway results in the complete inhibition of pancreatic tumorigenesis in vivo, suggesting the important role KGM plays in tumor progression [2, 22]. A recently publicized study correlates increasing prostate cancer cell aggressiveness with an upregulation of the glutaminase II pathway [50].

KGM is a major contributor not only in cancer but also in hyperammonemia diseases. It is a biomarker for both primary and secondary hyperammonemia diseases, including hepatic encephalopathy [49]. KGM concentration was shown to be correlated with the degree of encephalopathy. Although the specific mechanisms are still unknown, the study indicated a direct relationship between KGM and hyperammonemia disease progression [51].

This association of hyperammonemia and cancer involving KGM is a significant discovery in the metabolic interplay between cancer and neurological diseases. KGM not only promotes tumor growth through the glutaminase II pathway [50], but also serves as an excellent biomarker for hyperammonemia diseases and an indicator for encephalopathy severity.

3 GABA and Its Multiple Functions in Neurological Diseases and Cancer

Gamma-aminobutyric acid (GABA) serves as an inhibitory neurotransmitter in the central nervous system, and can also be detected in peripheral tissues. Dysregulation of the GABAergic system and related metabolisms are observed in various cancers and neurological diseases. In neurological diseases, GABA works through the neural networks and mainly serves as an inhibitory neurotransmitter [52], whereas in cancer, GABA is found in peripheral tissues, serving as an onco-metabolite [53] by affecting multiple cell functions, including cell proliferation and mobility (Fig. 3).

3.1 Elevated GAD Expression Is Found in Acute Stress and Contributes to Oral Squamous Cell Carcinoma Invasiveness

Glutamate decarboxylase (GAD) is a rate-limiting enzyme that catalyzes the production of GABA from glutamate [54]. GAD has two enzymes: GAD65 and GAD67. The two enzymes have different subcellular locations and interact differently with the cofactor pyridoxal 5′-phosphate (PLP) [55]. GAD65 and GAD67 are encoded by genes GAD2 and GAD1, respectively. In both acute stress and oral squamous cell carcinoma (OSCC), the upregulation of GAD67 is observed [56].

Acute stress primarily affects GAD67: increased GAD67 mRNA level is observed in various brain regions, including the arcuate nucleus, dorsomedial hypothalamic nucleus, and hippocampus [57]. Increased GAD67 mRNA is preferentially induced in acute stress, compared to chronic stress, possibly due to GAD67's potentiality of rapid activation as almost all GAD67 is bounded to its cofactor in the CNS [57].

In the case of OSCC, overexpression of GAD1 is found to be a characteristic event. The knockout of GAD1 in OSCC-derived cell lines interfered with the invasive ability. It is hypothesized that the process is completed through GAD1 regulation of β-catenin, which leads to the activation of MMP7, a gene found to be expressed in many cancers, including breast cancer, lung cancer, and prostate cancer, that contributes to tumor invasiveness and metastasis [58].

Although the underlying mechanisms are different, the upregulation of GAD67 is observed in both acute stress and OSCC. Hence, GAD1 and GAD67 mRNA might be possible targets in the treatment of OSCC.

3.2 GABA Levels Are Characteristic of Various Cancers and Contribute to Alzheimer's Disease and Attention-Deficit/Hyperactivity Disorder (ADHD)

Dysregulation of GABA metabolism is observed in many CNS disorders and various types of cancers. For instance, elevated GABA levels are characteristic of both AD and gastric cancer [5]. In AD patients, astrocytes in the dentate gyrus exhibit increased GAD activation, leading to an elevated level of GABA [59]. One direct result of the increased GABA level is enhanced tonic neural inhibition, one of the major symptoms in AD [59]. In gastric cancer, evaluation of gastric neoplastic tissue revealed that GAD activity is sig-

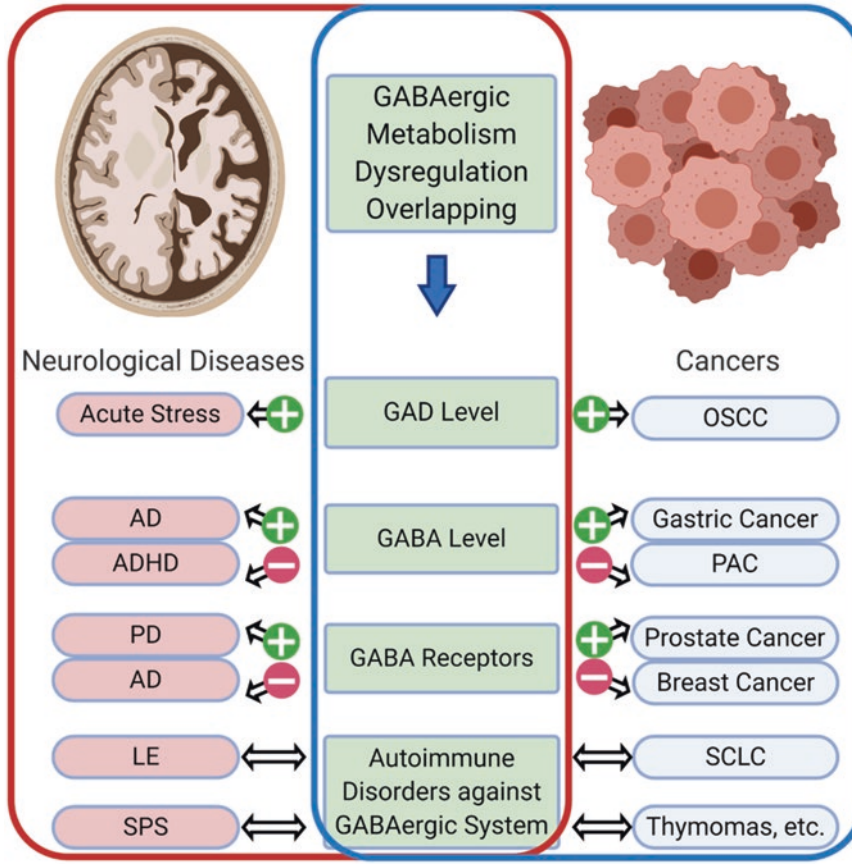

Fig. 3 A general view of GABA-ergic system-related metabolism with corresponding cancers and neurological diseases. *GAD* glutamate decarboxylase, *AD* Alzheimer's disease, *ADHD* attention-deficit/hyperactivity disorder, *PD* Parkinson's disease, *LE* limbic encephalitis, *SPS* stiff-person syndrome, *OSCC* oral squamous cell carcinoma, *PAC* pulmonary adenocarcinoma, *SCLC* small cell lung cancer

nificantly higher than in surrounding normal tissue and that GABA content increases above normal levels [5]. Similar results have also been obtained with other cancers, including breast cancer, colon cancer, and prostate cancer [5]. The exact underlying mechanism of the abnormal GABA metabolism in cancer remains unclear. It is still practical, however, to deem an elevated GABA level as a good indicator of both AD and various cancers.

Not all the neurological diseases and cancers have upregulated levels of GABA. For example, GABA downregulation is observed in ADHD and pulmonary adenocarcinoma (PAC). ADHD is the most diagnosed psychiatric disorder in children and adolescents. Recent research based on the spontaneous hypertensive rat (SHR) models suggested that a decrease in the extracellular concentration of GABA in the SHR hippocampus may be the underlying reason for the ADHD-like behaviors [60]. A decreased GABA level was also observed in PAC. It was found that tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) can significantly reduce GABA in the lungs and that NNK-induced PAC expresses particularly low levels of GABA. Data showed that GABA could limit PAC cell proliferation and migration through the inhibition of cAMP signaling, suggesting that PAC cells downregulate GABA to promote tumor growth and invasion [61]. The underlying mechanism for how NNK suppresses GABA level remains unclear, however.

3.3 GABA Receptors Contribute to Alzheimer's Disease Pathogenesis, Parkinson's Disease Severity, and Cancer Invasiveness

GABA receptors can be divided into two classes: GABAA receptors and GABAB receptors. Downregulation of ionotropic GABAA receptor (GABAAR) is observed in both AD [62] and breast cancer [63]. A recent study of AD explored amyloid beta's (Aβ) ability to weaken synaptic inhibition through the downregulation of GABAAR, indicating that such regulation is achieved through induced endocytosis of GABAAR [62]. Impaired inhibitory circuits, coupled with neuronal hyperexcitability [62], might contribute to the characteristic formation of amyloid plaque in AD [64].

In breast cancer, downregulation of GABAAR is achieved through decreased expression of GABAAR-related protein (GABARAP). In invasive ductal and invasive lobular carcinomas, GABARAP mRNA and GABARAP expression were all found to be significantly downregulated [63]. GABARAP was suggested to be a tumor suppressor, but how GABARAP is suppressed and overcome by the tumor cells is yet to be determined. Although the underlying mechanisms are different, downregulation of the GABAAR was observed in both breast cancer and AD [63]. Moreover, understanding the mechanism behind GABARAP suppression in cancer and restoring its function could be a possible strategy for cancer treatment. In the case of prostate cancer, the GABAAR plays an important role in the proliferation of prostate cancer cells. Non-cancer prostate epithelial tissues showed no GABAAR expression, whereas 15% of prostate cancer epithelial tissue samples showed GABAAR expression to various extents [1]. Applying antagonists of various receptors, including GABAAR antagonist, picrotoxin, inhibited the proliferation of prostate cancer cells. Moreover, applying a GABAAR agonist stimulates the proliferation of several prostate cancer cell lines [1]. Therefore, GABAAR is shown to significantly promote prostate cancer growth, and inhibiting GABAAR becomes a potential strategy in prostate cancer treatment.

Just like the opposite trends of GABA concentration between different neurological diseases and cancers, besides its downregulation, GABAAR upregulation is also observed in Parkinson's disease (PD). PD is the second most common neurodegenerative disease. In patients with PD, the concentration of GABAAR, especially those containing the α4 subunit, is increased approximately 22-fold in the caudate nucleus in basal ganglia [65]. Increased GABAAR levels also strengthened the tonic inhibition by astrocytes, indicating a direct relationship between increased GABAAR and PD severity [65].

Given the malignant effect that GABAAR has on both PD and prostate cancer, it is worth exploring whether reducing GABAAR expression or suppressing GABAAR function could help mitigate prostate cancer. This is another excellent example of how the overlap between neurological diseases and cancer sheds light on cancer treatment.

Besides its role in a variety of cancers, GABABR is also a possible target for the treatment of various types of cancers and neurological diseases. Specifically, baclofen, an agonist of GABABR, has been shown to be effective in inhibiting tumor growth in rat models, which further exemplifies the suppressive role of GABABR activation in tumor development [66]. Of particular note, clinical data also suggest that baclofen can be used to reduce certain types of drug addiction, including cocaine, alcohol, nicotine, and heroin [52]. Positive modulation of GABABR was also shown to be effective in treating anxiety in rat models. Rats with no GABABR were more anxious, whereas acute and chronic treatments with positive GABABR modulator CG39783 decreased anxiety levels generated in rats [67].

Research on the influence of GABA on human prostate cancer cells in vitro suggests that matrix metalloproteinase (MMP) induced by GABA greatly promotes the invasive ability of the cells [68]. Applying GABABR antagonists significantly reduced MMP production as well as prostate cancer cell invasiveness, whereas applying

GABABR agonists induced the opposite effect [68]. The overall result suggests that positive modulation of GABABR is implicated in the invasive ability of prostate cancer cells.

A blockade of GABABR using GABABR antagonist or GABABR knockout was found to produce an antidepressant-like phenotype in rat models. One hypothesis suggests that the antidepressant function is based on the interaction between the GABABR and the serotonergic system and neurotrophic factors [69].

Although GABABR function is distinctly different in cancers and neurological diseases, significant effects in cancers are observed with both the upregulation and downregulation of the receptors. Therefore, it is still very promising to develop treatments based on GABAB receptor modulators after taking cancer type-specific effects into consideration.

3.4 Autoimmune Disorders' Attack on the GABA-ergic System Correlates with Neurological Diseases and Cancers

Autoimmune disorders are observed to attack the GABA-ergic system, and two of these disorders are closely intertwined with specific types of neurological diseases and cancers.

The first disease is limbic encephalitis (LE), which is frequently related to small cell lung cancer (SCLC). LE mainly affects the medial temporal lobes and patients exhibit symptoms including seizures, short-term memory impairment, and anxiety [70]. In a study of 20 patients who have GABAB receptor antibodies (GABABR-ab), 19 (95%) patients eventually developed LE. 10 of these 19 patients developed SCLC [71]. The specific relationship between LE and SCLC is not yet clear, but the close correlation between the two could still provide valuable insights toward treatment, with GABABR-ab serving as a practical diagnostic factor.

The second disease is stiff-person syndrome (SPS), often seen accompanied by thymomas and breast cancer. SPS is a rare neurological disease with 1–2 cases/million [72, 73], and is characterized by rigidity and spasm of skeletal muscles in limbs and trunks. Patients showed increased sensitivity to stimuli, such as noise and emotional perturbation [74]. The majority of SPS patients exhibited an increased concentration of autoantibodies against both forms of GADs in cerebral fluids [75]. Additionally, 83% of sera from SPS patients with positive GAD autoantibodies (GAD-A) decreased GABA production in brain extracts of rats [75]. As a direct consequence of GAD malfunctioning, GABA synthesis is interrupted, and magnetic resonance spectroscopy revealed a reduced level of GABA in the motor cortices of people with SPS [76]. In the case of paraneoplastic SPS, research showed that 53% of the tumors in patients with SPS are thymomas and breast cancer [72]. Given that GADs are expressed in breast cancer, and the overall GABA metabolism mediates breast cancer metastasis, the association may be caused by the cancer-induced autoimmune disorder [53]. Thus, an increased GAD level might trigger an autoimmune response, leading to the production of GAD-A [72].

Although the underlying mechanisms of the interplay between autoimmune system disorders, neurological diseases, and cancers have yet to be identified, the altered metabolic signatures could serve as a prognostic indicator of cancers and neurological disease progression.

4 NAAG and Its Versatile Role in Neurological Diseases and Cancer

As one of the most prevalent and widely distributed neuropeptides found in the mammalian nervous system, *N*-acetyl-aspartyl-glutamate (NAAG) was not initially considered a neurotransmitter when it was first discovered in 1965, due to its abundance and identity as a peptide. It was not tested against neurotransmitter criteria until the 1980s, and only then was it formally established as a new neurotransmitter. Its

role in the neurological system was later found to be more versatile than simply being the precursor of glutamate, since it also functions as an agonist of group II metabotropic glutamate receptor (mGluR3), synaptic GABA release inhibitor, and cyclic AMP inhibitor [77].

The recognition of NAAG's role in cancer growth was even more delayed. Only recently a study by Nguyen et al. revealed that NAAG plays an important role as a glutamate reservoir for cancer growth via GCP II [6]. Moreover, NAAG can also serve as an indicator of cancer progression as increases in NAAG concentrations were observed in higher grade lymphoma, ovarian cancers, and gliomas compared to their lower grade counterparts [6, 78, 79]. Therefore, the direct conversion of NAAG to glutamate established NAAG as a juncture between the fields of cancer and neurological disease and became a shared characteristic pathway and a drug target for the two disease groups. Despite its positive correlation with cancer progression, the correlation between NAAG concentration and neurological disease progression varies depending on the type of neurological disease. In general, NAAG is established as a neuroprotective neurotransmitter in the neurological system, where a decreased level of NAAG is correlated with neuronal loss [80]. Besides serving as a neurotransmitter in neurological diseases, NAAG can also reduce other synaptic neurotransmitter levels, namely GABA [81] and glutamate, by activating a group II G protein-coupled metabotropic glutamate (mGlu) receptor, mGluR3, to achieve neuroprotective effects and reduce neurotoxicity caused by glutamate accumulation [82]. Meanwhile, mGluR3 is also known to promote cancer growth [83–90]. Previous studies have shown that mGluR3 expression is associated with glioma growth and poor GBM survival rates [85]. In GCP II-negative glioblastoma, it is suspected that NAAG could be taking on another role to promote cell growth through an alternative pathway by acting as an agonist to mGluR3, thereby precluding the role of NAAG as a glutamate provider.

4.1 NAAG Affects Both Cancer and Neurological Disease Progression via Glutamate

As a cancer metabolite and a neurotransmitter, NAAG has an effect on cancer metabolism and neurological diseases, which largely relies on its ability to regulate and be directly converted to another cancer metabolite/neurotransmitter, glutamate. Via hydrolysis by GCP II, NAAG can be catabolized into *N*-Acetyl-aspartate (NAA) and glutamate. This process has proven to be a crucial glutamate production pathway in cancer [6], and the produced glutamate can serve as a source of carbon and nitrogen to support the elevated need of energy, nucleotides, and protein of the cancer cells [91]. Specifically, the resulting glutamate can be further converted to α-KG and it participates in the TCA cycle for energy production in cancer cells. Therefore, NAAG promotes cancer growth by playing the role of a glutamate reservoir [6].

The conversion of NAAG to glutamate also plays an important role in neurological diseases. Glutamate has long been recognized as a neurodegenerative neurotransmitter, and its excessive release leads to neuronal loss and neural excitotoxicity. The excitotoxicity caused by glutamate is very complicated, and is promoted by extracellular $Ca2^{+}$, mediated by NO, and involves synaptic free radicals and zinc accumulation [92]. In the neurodegenerative disorder, amyotrophic lateral sclerosis (ALS), increased GCP II activity is observed, which further supports NAAG's role as a major source of extracellular glutamate [93]. Thus, this conversion of NAAG to glutamate contributes not only to cancer growth but also to a wide range of neurological diseases. This points to the significance of the NAAG-glutamate pathway as a very promising potential target in cancer therapy. Inhibition of the conversion of NAAG to NAA and glutamate has been the focus of researchers working with neurological diseases for years [94]. As we begin to uncover the valuable interplay between cancer and neurological disease, previous and ongoing research may serve to catalyze potential developments for cancer therapies.

Due to the diverse nature of different neurological diseases, the direct relationships between NAAG and these diseases are not consistent. As an established neuroprotective neurotransmitter, NAAG typically reduces neurotoxicity caused by excitatory neuroactivity, and suppresses and reverses the effect of neurodegenerative neurotransmitters like glutamate [77]. The decrease of NAAG levels in most cases is related to neuronal loss and consequent neurodegenerative disorders. In a study of HD and AD, researchers observed a decrease in NAAG level and GCP II activity and its correlation with the neuronal loss [80]. A similar trend was also observed in another neurodegenerative disease, ALS, where decreased NAAG levels in all regions of the spinal cord, except for the posterior column, were observed in ALS patients. However, in this case, GCP II activity was found to be increased, which led to excessive hydrolysis of GCP II and to a subsequent decrease in the NAAG levels [93]. Therefore, decreased NAAG level reflects the pathogenesis and progression of neurodegenerative diseases.

A reverse relationship between NAAG and disease progression, however, was observed in cancer. A recent study showed that NAAG has great potential as a noninvasive cancer-monitoring biomarker. Moreover, the NAAG concentration in plasma reflects its concentration in tumors, which indicates a higher translational value of NAAG as a cancer biomarker [6]. Another translational aspect of NAAG concentration is in monitoring cancer growth as a NAAG concentration spike could be detected prior to tumor growth surge and thus allow for the monitoring of tumor growth in a timely fashion [6, 95]. Therefore, considering the ability of NAAG concentration to reflect cancer grade, the mirror relationship between plasma NAAG concentration and tumor NAAG concentration, and its predictive time point of occurrence, NAAG shows great potential as a real-time tumor growth monitor.

Few studies have been conducted on the role of NAAG in another major neurological disease category, psychiatric disorders, and the results are more controversial. In one study of the effect of NAAG on schizophrenia, an increase in brain NAAG level and decreases in GCP II and glutamate levels were observed, which indicates a completely reverse relationship between NAAG and psychiatric disorders compared with its relationship with neurodegenerative disorders [96]. However, in another study, brain NAAG was found to be higher in younger schizophrenia subjects compared to control counterparts, while a reverse relationship was observed in the older groups [97]. Therefore, possibly due to the complex nature and disease dynamics of psychiatric disorders and their reduced reliance on neuron loss, NAAG does not completely reflect the disease progression in this category of neurological disorders compared to cancer and neurodegenerative disorders.

4.2 Targeting GCP II Is a Promising Strategy for Cancer Treatment

After recognizing the crucial role of NAAG in both cancer growth and neurological disease progression via its catabolism to NAA and glutamate, we can shift our attention from NAAG itself to its conversion process. As mentioned in Sect. 4.1, a very promising strategy for both neurological disease and cancer treatment would be shutting down the hydrolysis of NAAG to glutamate. GCP II, also known as *N*-acetyl-L-aspartyl-L-glutamate peptidase (NAALADase), is the key enzyme in NAAG's hydrolysis to glutamate and NAA [98]. Due to its dominant role in this process, GCP II has long been in consideration as a drug target. Generations of GCP II inhibitors have been developed to treat cancer and neurological diseases, including 2-(phosphonomethyl) pentanedioic acid (2-PMPA), thiol and indole thiol derivatives, and NAAG analogs. Among these, 2-(3-mercaptopropyl) pentanedioic acid (2-MPPA) showed great tolerance in a Phase I clinical trial, and a Phase II clinical trial has been initiated [94].

The use of GCP II inhibitors on a variety of neurological diseases has been proven to be effective. The GCP II inhibitors (2-PMPA, thiol-based 2-MPPA, and urea-based ZJ43) reduce

inflammatory pain and neuronal loss in rat models, and another GCP II inhibitor, GPI5232, greatly reduces the number of seizures in a rat stroke model compared to vehicle control [94]. Besides these acute neurological diseases, the effect of GCP II inhibitors was also shown in chronic neurological disorders. ZJ43 was shown to reduce dissociative anesthetic phencyclidine (PCP)-induced motor activation, falling, stereotypic circling behavior, and head movements in schizophrenia patients. In addition, GPI5332 reduces diabetic neuropathy, and 2-PMPA and 2-MPPA delay mortality and pathological abnormalities of ALS in vitro and in vivo, respectively [94]. All the above positive effects of GCP II inhibitors over neurological diseases are driven by a two-faceted mechanism. Firstly, GCP II inhibition cuts off the supply of glutamate from NAAG hydrolysis and results in a direct decrease of glutamate level. Secondly, although GCP II inhibition reduces extracellular glutamate directly, its therapeutic effects seem to primarily rely on inhibition of the synaptic release of glutamate [94]. An observation in a rat stroke model showed that after GCP II inhibition, the decrease in extracellular glutamate level exceeded extracellular NAAG levels. Via this two-faceted mechanism, GCP II exhibits great potential and effectiveness as a treatment for neurological diseases (Fig. 4). The success of the use of GCP II inhibitors in neurological diseases and the development of reliable GCP II inhibitors provides further evidence for this strategy's potential in cancer treatment and it exhibits great translational value due to the shared metabolic pathway. Likewise, GCP II inhibitors have gained interest in cancer treatment. A study by Nguyen et al. showed that the use of 2-PMPA reduces both tumor growth and glutamate concentration in vivo [6]. This was further supported by the finding that the combination use of 2-PMPA and glutaminase inhibition accentuated the effects by further cutting off glutamate supply [95]. Therefore, inhibiting GCP II and in turn shutting down the hydrolysis of NAAG to glutamate have proven to be effective in cancer treatment, and thus GCP II has become a very promising drug target.

Besides its function in hydrolyzing NAAG, GCP II is also connected with cancer from other aspects. In prostate cancer, GCP II is also known as prostate-specific membrane antigen (PSMA), which serves as a biomarker that serves to cleave terminal carboxyl glutamate from NAAG [99]. In prostate cancer, its concentration greatly increases. A study by Evans et al. has shown that reducing GCP II expression led to cell cycle arrest, decreased cell proliferation, and diminished invasiveness in prostate cancer. This trait makes GCP II a tool for prostate cancer imaging and treatment [100]. The strategy of targeting GCP II in cancer treatment, therefore, becomes more promising by the addition of this connection between GCP II and prostate cancer.

4.3 NAAG Inhibits GABA Release and Indirectly Affects Both Cancer and Neurological Diseases via the GABA-ergic System

Besides its direct effect on cancer and neurological diseases, NAAG also interacts with other molecules to indirectly influence the two disease groups. The activation of mGluR3 and the decrease of the cAMP level induced by NAAG inhibit the calcium-dependent, KCl-induced GABA release [81]. As discussed in Sect. 3, GABA is found to contribute to the TCA cycle and cancer energy supply by its conversion to succinate. The inhibition of GABA release is observed when either NAAG or DCG-IV, another mGluR3 agonist, is applied. The addition of forskolin, which leads to forskolin-induced cAMP synthesis, reverses the inhibition of GABA release caused by NAAG [81]. Therefore, NAAG potentially inhibits GABA release by mGluR3 activation and consequent cAMP decrease, and in turn downregulates the GABA-ergic system. As discussed in Sect. 3 of this chapter, this downregulation could have multifaceted effects on cancer and neurological diseases, including relieving AD and deducing the invasiveness of prostate cancer.

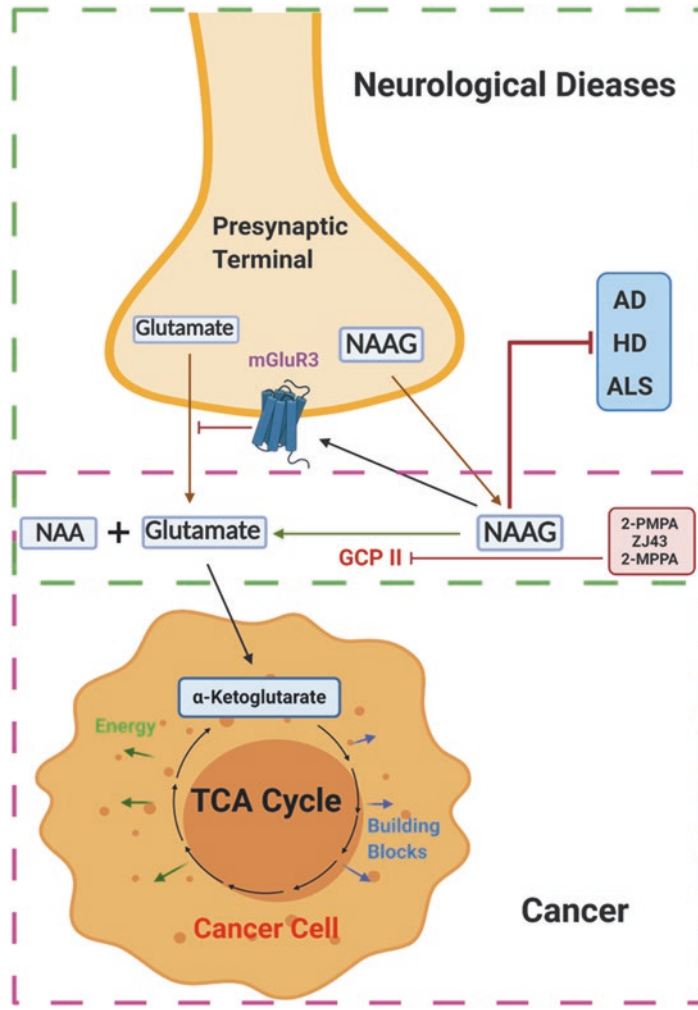

Fig. 4 Regulation of NAAG metabolism and its contribution to cancer. *AD* Alzheimer's disease, *HD* Huntington's disease, *ALS* amyotrophic lateral sclerosis, *GCP II* glutamate carboxypeptidase II

5 Conclusion

Glutamine/glutamate, GABA, and NAAG metabolism are closely involved in both cancer and neurological diseases. As important factors in neurotransmission in neurological diseases and as significant components in cancer metabolism and energy supply, glutamine/glutamate, GABA, and NAAG introduce considerable overlaps between the two categories of diseases. Possibly due to the complex nature of the neurological system and the divergent causes of different neurological disorders, the effect and correlation of one neurotransmitter are very specific to that disease type, sometimes even opposite to its effect on other diseases. However, these neurotransmitters, as cancer metabolites and signaling molecules, affect cancer development in unique ways. Glutamine and glutamate, in general, serve as cancer cell energy sources, while GABA and NAAG both have more versatile roles serving as signaling factors, metabolic reservoirs, and prognostic indicators for cancer. Therefore, taking insights gleaned from the metabolic interplay between neurological diseases and cancer and applying them to the field of oncology may not only provide further understanding of the mechanisms by which these metabolites affect cancer growth but also allow established therapeutic strategies in neurological diseases to be repur-

posed for cancer treatment and even shed light on novel drug targets. As discussed in this chapter, the regulation of these four metabolites/neurotransmitters and their related enzymes and receptors greatly impacts diagnosis, monitoring, and treatments for cancer, with some already in the process of being translated into cancer clinical trials. The future direction includes investigating potential therapeutic methods involving intertwining glutamine metabolism, GABA regulation, and GCP II/GLS/GS inhibition, which can eventually be utilized for cancer and neurological disease treatment.

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