

# Glutamate Metabolism Regulates Immune Escape of Glioma

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## Article Info

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## Abstract

Glutamate metabolism plays critical roles in the growth and invasion of glioma, which supports the growth of tumor cells through participating in energy supply and regulates redox balance in cells. High concentration of glutamate can destroy the normal brain tissues and get invasive space. Glutamate at excess levels in the milli-molar range acts inhibition of immune response and secretes cytokines of immune negative regulation, which promotes the immune escape of tumor cells. The production of glutamate mainly depends on the rapid consumption of glutamine by glioma cells, and the depletion of glutamine is beneficial for the maturation of myeloid derived suppressor cells, further enhancing the immune suppression. In this review, we focus on immune-modulating capacities of the glutamate metabolism of glioma, and the mechanism may be helpful towards optimization of immune systems with implications for glioma treatment.

**Keywords:** glioma, glutamate metabolism, immune escape, T cells, myeloid derived suppressor cells (MDSCs)

## Introduction

Glutamate is one of the major excitatory neurotransmitters in the central nervous system (CNS) [1], [2]. Glutamate plays an important physiological role in the process of nervous system nutrition, development and neuronal information transmission [3-6]. Under normal healthy condition, the glutamate concentration in the cerebrospinal fluid and in the brain extracellular fluid is 1  $\mu\text{M}$  [1], [6]. While the levels of glutamine in cerebrospinal fluid in glioma patients can reach up to 400  $\mu\text{M}$  [7]. Importantly, this excess of glutamate is very harmful in the CNS because it leads to 'excitotoxicity', and elevated glutamate concentrations can cause excitatory neuronal death. Glutamate over-activates the excitatory amino acid transporters (EAATs) and glutamate receptors in the postsynaptic membrane, causing massive influx of calcium ions, triggering a series of enzymatic reactions that eventually lead to organelle failure, cell lysis, and death [8-10]. The expression of EAATs [11] and glutamate receptors [12] are absent or down-regulated in glioma cells. Thus, excessive glutamate in the brain extracellular fluid cannot cause excitatory toxicity damage to glioma cells.

Under physiological and pathological conditions, the sources of extracellular glutamate in the CNS are extremely different. Normally glutamate is produced by neuronal cells and released from the synaptic vesicles [13]. Glioma cells produce glutamate by depleting glutamine. The release of glutamate from glutamate transporters system Xc- is a major source of extracellular glutamate [7], [14]. During tumor development, the number of astrocytes which can utilize glutamate is reduced and its ability to take up

glutamate of glioma microenvironment is decreased. To this end, the extracellular glutamate concentration increases rapidly, and the glutamate balance of microenvironment is destructed. The increased uptake of glutamine and its flow to glutamate is an important feature of highly proliferation tumor cells [10], [14-16]. Glutamine appears to regulate T cells proliferation, the rate of IL-2 production and IL-2 receptor expression [17]. Thus, both depletion of glutamine and accumulation of glutamate generate a limited function of T cells [17-19]. Glutaminolysis also contributes to MDSCs maturation through the energy supply and metabolic intermediation [20]. Maintaining optimal glutamine or glutamate levels are critical in preventing the MDSC-mediated immuno-suppression. As glutamate receptors and transporters are described for a variety of immune cells a new role of glutamate as an immune-regulator was suggested [21-23].

## Glutamate metabolism in glioma cells

Glioma cells present an increased glutamine turnover, partly based on the higher activity and expression of glutaminase, which converts glutamine into glutamate [24]. Glutamate metabolism in glioma cells have three major pathways: 1) Glutamate can be converted to  $\alpha$ -ketoglutarate, which enters the TCA cycle to generate ATP through production of NADH and FADH<sub>2</sub> [25]. 2) Glutathione is a tripeptide (Glu-Cys-Gly) which serves to neutralize peroxide free radicals. Glutamate metabolism is critical for cellular ROS homeostasis through synthesis of glutathione [26]. 3) Glutamate transporters system Xc<sup>-</sup> (SXC) transport glutamate to the extracellular and cystine uptake into cells. Cystine is further reduced to cysteine, which is combined with glycine and glutamate to synthesize glutathione [27], [28]. Cancer cells with strong PI3K-AKT-mTOR pathway activation increase their flux of glutamate to  $\alpha$ -ketoglutarate for metabolism and biosynthesis [29-32]. Due to the overexpression of phosphory-AKT, an increasing number of chemotherapy-resistant cases have been reported clinically [33]. Inhibitors of the PI3K-AKT signaling pathway, have identified to induce apoptosis of glioma cells and enhance the cytotoxicity of chemotherapy [33-36].

Glutamate receptors include two classes: ionotropic glutamate receptors (iGluRs) and metabotropic glutamate receptors (mGluRs). The iGluRs are membrane-spanning multimeric assemblies of four subunits and subdivided into three groups according to their pharmacology, structural similarities, and the type of synthetic agonist that activates them: The N-methyl-D-aspartate (NMDA), Alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), and 2-carboxy-3-carboxymethyl-4-isopropenylpyrrolidine (Kainate; KA) iGluRs [37-39]. The mGluRs have eight subtypes. These eight mGluRs are products of different genes and also subdivided into three groups, termed group I (mGluR 1 and 5), II (mGluR 2 and 3) and III (mGluR 4, 6, 7 and 8) mGluRs, based on sequence similarity, pharmacology and intracellular signaling mechanisms [23], [40]. Glutamate can activate all its iGluRs and mGluRs. Glioma cells lack glutamate receptors to

avoid the excitatory toxicity damage of glutamate [12]. Fasudil upregulates the expression of NMDA iGluRs in glioma cells and thus plays an anti-tumor role. The anti-tumor effect of fasudil was dose-dependent with glutamate [41].

## Glutamate metabolism induced effects on T cells

Higher functional acidity CD8 T cell responses are believed to play a direct role in clearing acute viral infections and eliminating cancer cells. The effective T cell responses are evoked by high functional avidity T cells in the case of tumors. Thus, an attenuated functional avidity exhibited by T cells in cancer can partially explain why cancer cells persist and proliferate [42-44]. Glutamate concentrations in glioma microenvironments are 400 fold higher in normal brain tissue [1], [6], [7]. Which induces excitatory neuronal cells and other normal cells death. High concentrations of glutamate is secreted by tumor cells and has been shown to suppress T cell activity in vitro [18]. In this review we summarize, analyze and discuss the relationship between glutamate metabolism and T cell activation/proliferation in glioma microenvironment.

AMPA GluR3 has been shown to be expressed on the surface of naïve normal T cells [45], [46]. And sequencing showed that the T cell expressed GluR3 is identical to the brain's GluR3 [46]. Interestingly, while at low physiological concentrations glutamate directly activates naïve T cells via AMPA iGluRs [46], when glutamate's concentration raise markedly, such as in glioma microenvironment, glutamate usually does the opposite and inhibits T cell function [23]. This GluR3 degradation following T cell activation is carried out by granzyme B, a proteolytic enzyme that is produced and secreted by TCR-activated T cells [47]. Thus, at mid micromolar concentrations (1-10  $\mu$ M), glutamate increase iCa<sup>2+</sup> in activated T cells, but not in naïve T cells [48], which is essential for the subsequent proliferation of the T cells [49]. In contrast, glutamate at a higher concentration range of 400  $\mu$ M to 1000  $\mu$ M fail to increase iCa<sup>2+</sup> [48]. Therefore, high glutamate levels with glutamate secreted by glioma cells inhibit T cell proliferation.

Glutamate suppresses the proliferation of activated T cells but not affect the proliferation of normal naïve T cells [48], [50], [51] showing the marked different GluRs between naïve and activated T cells. The NMDA iGluR antagonists D-AP5 and (+)-MK801 inhibit PHA-induced but not IL-2-induced T cell proliferation [52]. The selective mGluR5 agonist CHPG also inhibites the proliferation of CD3-activated T cells [51]. Interestingly, glutamate at a broad concentration range of 10 nM to 100  $\mu$ M protect activated T cells from apoptotic Activation-Induced Cell Death (AICD) through inhibiting FasL expression of activated T cells [53]. Together, the evidences in the above parts suggest that glutamate at 1  $\mu$ M inhibits T cell apoptosis and prolongs survival, while glutamate at higher concentration of 400  $\mu$ M to 10 mM can inhibit T cell proliferation.

The rapid consumption of glutamine by glioma cells releases glutamate as a limited function of immune cells [19]. The effects of metabolic inhibitors in vivo may also broadly influence immunity. In fact, glutamine metabolism is increased in T cell activation and regulates skewing of CD4 T cells towards more inflammatory subtypes [54-56]. While in vitro experiments suggest that inhibiting the release of glutamate and depletion of glutamine can activate lymphocytes [57], the anti-tumor immunity effect of GLS inhibition requires further studies in vivo. These data suggest that inhibiting glutamate release may be helpful to immunotherapy of tumor, either through the blocking of immune checkpoints or the use of engineered chimeric antigen receptor (CAR) T cells.

## The effects of glutamate on T cell cytokine secretion

Many of the immune escape mechanisms are based on a response that is not inhibiting but maybe even promoting the tumor. One of the best explored examples is the induction of the two different effector CD4 T helper cell responses (Th1 and Th2 responses) [58]. The Th1 response is fostering cytotoxic responses by secreting IFN $\gamma$  activating the cytolytic activities of macrophages and cytotoxic T lymphocytes (CTL); Th2 cells are fostering humoral responses by production of IL4 activating B cells. Th2 response is regarded rather as a tumor-promoting as compared to a tumor-inhibiting Th1 response which could potentially lead to tumor clearance by triggering a CTL response against tumor antigens [58], [59].

It is reported that glutamate can affect cytokine secretion by T cells. Glutamate at very high concentration of 1 mM increases IFN $\gamma$  and IL10 secretion by CD3 activated T cells. But at even higher concentration of 5 mM, glutamate has an opposite effect and decreases IFN $\gamma$ , IL10 and IL5 secretion by these T cells. NMDA at 0.5 mM also suppresses IFN $\gamma$  secretion by IL2 activated T cells [60]. These evidence show that stimulation of the NMDA iGluRs in these activated T cells by excess glutamate can lead to IFN $\gamma$  inhibition. T cells in vivo under physiological conditions, glutamate at 1  $\mu$ M may operate via mGluRs to modulate IL6 production and enhance the secretion of TNF $\alpha$ , IFN $\gamma$ , IL2 and IL10 [61]. These studies show that the effects of glutamate on T cell cytokine secretion depend on many factors: glutamate's concentration, the specific GluRs involved, the activation state of the T cells being exposed to glutamate, the specific T cell subtypes, the specific cytokine involved, and whether or not the T cells are exposed to other stimuli besides glutamate at the same time [23]. However, it is agreed that controlling glutamate in a physiological concentration helps to activate T cells.

## Glutamate metabolism induced effects on other immune cells

MDSCs are generated in the bone marrow and migrate to the peripheral lymphoid organs and tumor tissues [62]. The major function of the MDSCs during tumor progression

is to inhibit T cells activity and promote tumor growth [63-66]. Increased glutamine consumption of glioma cells contributes to MDSCs maturation through the supply of energy and metabolic intermediates [67]. Glioma cells metabolize glutamine at high rate to produce glutamate. Thus, high concentration of glutamate directly affects MDSCs function and infiltration in glioma microenvironment needs further study.

The expression of KA iGluRs in B cells has been demonstrated. And the authors suggest that activation of such KA iGluRs by glutamate and KA increased IgE and IgG synthesis and cell proliferation [68]. Human monocytes-derived macrophages express both mGluR5 and mGluR1 [69], and rat alveolar macrophages express the NMDA subunits NR1 and NR2B [70]. Both medullary dendritic cells (DCs) and cortical DCs express high levels of mGluR5 and moderate levels of mGluR2, 3 and 4 [71]. While a great deal has been learned already about the effects of glutamate on T cells, the outcome of glutamate binding to other types of immune cells is to a large extent unknown [22]. Here, we hypothesize that different glutamate concentrations affect function of immune cells as well as T cells through binding GluRs.

## Conclusion

As a neurotransmitter and an immune-regulator, glutamate plays multiple roles in the microenvironment of glioma. In addition to inducing brain tissue damage and infiltration of glioma cells, high concentration of glutamate promotes immune escape of glioma through inhibiting T cell proliferation and activity. Therefore, targeted inhibition of glutamate metabolism in glioma may prove to be beneficial.

## Conflicts of interest

Authors don't have any conflict of interest.

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