ISSN: 2638-2024

Madridge Journal of Immunology

Review Article

Open Access

Glutamate Metabolism Regulates Immune Escape of Glioma

Yuqing Cai[1], Tiantian Guo[1], Yan Wang[2] and Jun Du[1]*

[1]*Department of Chemical Biology and Molecular Ministry of Education, Institute of Biotechnology, Shanxi University, China*
[2]*Department of Neurosurgery, School of Medicine Stanford University CA, USA*

Article Info

***Corresponding author:**
Jun Du
Department of Chemical Biology and Molecular Institute of Biotechnology
92 Wucheng Road, Taiyuan 030006,
Shanxi, P.R, Shanxi University, China
E-mail: dujun@sxu.edu.cn

Received: July 18, 2018
Accepted: July 25, 2018
Published: July 31, 2018

Citation: Cai Y, Guo T, Wang Y, Du J. Glutamate Metabolism Regulates Immune Escape of Glioma. *Madridge J Immunol.* 2018; 2(1): 53-57. doi: 10.18689/mjim-1000113

Published by Madridge Publishers

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 uM [1], [6]. While the levels of glutamine in cerebrospinal fluid in glioma patients can reach up to 400 uM [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 a-ketoglutarate, which enters the TCA cycle to generate ATP through production of NADH and $FADH_2$ [25]. 2) Glutathione is a tri-peptide (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- (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 a-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-carboxymethy1-4-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 uM), glutamate increase iCa^{2+} 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 uM to 1000 uM fail to increase iCa^{2+} [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 uM 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 uM inhibits T cell apoptosis and prolongs survival, while glutamate at higher concentration of 400 uM 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 in 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 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 IFNγ 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 IFNγ and IL10 secretion by CD3 activated T cells. But at even higher concentration of 5 mM, glutamate has an opposite effect and decreases IFNγ, IL10 and IL5 secretion by these T cells. NMDA at 0.5 mM also suppresses IFNγ 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 IFNγ inhibition. T cells in vivo under physiological conditions, glutamate at 1 uM may operate via mGluRs to modulate IL6 production and enhance the secretion of TNFα, IFNγ, 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 direct affects MDSCs function and infiltration in glima 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

Authours don't have any conflict of interest.

Acknowleghments

This work was supported by the National Natural Science Foundation of China (No. 31400765), Shanxi Province Science Foundation for Youths (201601D202064), and Scientific and Technological Innovation Programs of Higher Education Institutions in Shanxi (2015117).

References

1. Meldrum BS. Glutamate as a neurotransmitter in the brain: review of physiology and pathology. *Journal of Nutrition.* 2000; 130: 1007S. doi: 10.1093/jn/130.4.1007S

2. Yan W, Qin ZH. Molecular and cellular mechanisms of excitotoxic neuronal death. *Apoptosis.* 2010; 15: 1382-1402. doi: 10.1007/s10495-010-0481-0

3. Foster AC, Fagg GE. Acidic amino acid binding sites in mammalian neuronal membranes: their characteristics and relationship to synaptic receptors. *Brain Research Reviews.* 1984; **7**: 103-164. doi: 10.1016/0165-0173(84)90020-1

4. Mayer ML, Westbrook GL. The physiology of excitatory amino acids in the vertebrate central nervous system. *Progress in Neurobiology.* 1987; 28: 197-276.

5. Komuro H, Rakic P. Modulation of neuronal migration by NMDA receptors. *Science* 1993; 260: 95-97.

6. Danbolt NC. Glutamate uptake. *Progress in Neurobiology.* 2001; 65: 1-105.

7. Robert SM, Sontheimer H. Glutamate transporters in the biology of malignant gliomas. *Cellular & Molecular Life Sciences.* 2014; 71: 1839-54. doi: 10.1007/s00018-013-1521-z

8. Sattler R, Tymianski M. Molecular mechanisms of glutamate receptor-mediated excitotoxic neuronal cell death. *Molecular Neurobiology.* 2001; 24: 107-129. doi: 10.1385/MN:24:1-3:107

9. Choi DW. Glutamate neurotoxicity and diseases of the nervous system. *Neuron*. 1988; 1: 623-34.

10. Liubinas SV, O'Brien TJ, Moffat BM, Drummond KJ, Morokoff AP, Kaye AH. Tumour associated epilepsy and glutamate excitotoxicity in patients with gliomas. *Journal of Clinical Neuroscience*. 2014; 21: 899-08. doi: 10.1016/j.jocn.2014.02.012

11. He M, Luo M, Liu Q, Chen J, Li K, Zheng M, et al. Combination treatment with fasudil and clioquinol produces synergistic anti-tumor effects in U87 glioblastoma cells by activating apoptosis and autophagy. *J Neurooncol*. 2016; 127(2): 261-70. doi: 10.1007/s11060-015-2044-2

12. Lau CL, O'Shea RD, Broberg BV, Bischof L, Beart PM. The Rho kinase inhibitor Fasudil up-regulates astrocytic glutamate transport subsequent to actin remodelling in murine cultured astrocytes. *British Journal of Pharmacology*. 2011; 163(3): 533-45. doi: 10.1111/j.1476-5381.2011.01259.x

13. Nedergaard M, Takano T, Hansen AJ. Beyond the role of glutamate as a neurotransmitter. *Nature Reviews Neuroscience*. 2002; 3(9): 748-55. doi: 10.1038/nrn916

14. Gottfried E, Kreutz M, Mackensen A. Tumor metabolism as modulator of immune response and tumor progression. *Seminars in Cancer Biology*. 2012; 22: 335-41. doi: 10.1016/j.semcancer.2012.02.009

15. Yao PS, Kang DZ, Lin RY, Ye B, Wang W, Ye ZC. Glutamate/glutamine metabolism coupling between astrocytes and glioma cells: neuroprotection and inhibition of glioma growth. *Biochemical & Biophysical Research Communications*. 2014; 450: 295. doi: 10.1016/j.bbrc.2014.05.120

16. Mazurek S, Eigenbrodt E, Failing K, Steinberg P. Alterations in the glycolytic and glutaminolytic pathways after malignant transformation of rat liver oval cells. *Journal of Cellular Physiology*. 1999; 181: 136-146. doi: 10.1002/(SICI)1097-4652(199910)181:1<136::AID-JCP14>3.0.CO;2-T

17. Newsholme P. Why is L-glutamine metabolism important to cells of the immune system in health, postinjury, surgery or infection? *Journal of Nutrition*. 2001; 131: 2515S. doi: 10.1093/jn/131.9.2515S

18. Dröge W, Eck H-P, Betzler M, her HN. Elevated plasma glutamate levels in colorectal carcinoma patients and in patients with acquired immunodeficiency syndrome (AIDS). *Immunobiology*. 1987; 174: 473. doi: 10.1016/S0171-2985(87)80019-0

19. Wilmore DW, Shabert JK. Role of glutamine in immunologic responses. *Chinese Journal of Chinical Nutrition*. 1999; 14: 618.

20. Hammami I, Chen J, Bronte V, Decrescenzo G, Jolicoeur M. L-glutamine is a key parameter in the immunosuppression phenomenon. *Biochemical & Biophysical Research Communications*. 2012; 425: 724-29.

21. Xue H, Field CJ. New role of glutamate as an immunoregulator via glutamate receptors and transporters. *Frontiers in Bioscience*. 2011; 3: 1007.

22. Ganor Y, Levite M. Glutamate in the Immune System: Glutamate Receptors in Immune Cells, Potent Effects. *Endogenous Production and Involvement in Disease*. 2012.

23. Ganor Y, Levite M. The neurotransmitter glutamate and human T cells: glutamate receptors and glutamate-induced direct and potent effects on normal human T cells, cancerous human leukemia and lymphoma T cells, and autoimmune human T cells. *Journal of Neural Transmission*. 2014; 121: 983-1006. doi: 10.1007/s00702-014-1167-5

24. Aledo JC, Segura JA, Medina MA, Alonso FJ, Nãºã±Ez dCI, Mã rJ. Phosphate-activated glutaminase expression during tumor development. *Febs Letters*. 1994; 341: 39-42.

25. Moreadith RW, Lehninger AL. The pathways of glutamate and glutamine oxidation by tumor cell mitochondria. Role of mitochondrial NAD(P)+-dependent malic enzyme. *Journal of Biological Chemistry*. 1984; 259: 6215-221.

26. Welbourne TC. Ammonia production and glutamine incorporation into glutathione in the functioning rat kidney. *Can J Biochem*. 1979; 57: 233-37. doi: 10.1139/o79-029

27. Bannai S. Exchange of cystine and glutamate across plasma membrane of human fibroblasts. *Journal of Biological Chemistry*. 1986; 261: 2256-263.

28. Sato H, Tamba M, Ishii T, Bannai S. Cloning and expression of a plasma membrane cystine/glutamate exchange transporter composed of two distinct proteins. *Journal of Biological Chemistry*. 1999; 274: 11455-458.

29. Haigis MC, Mostoslavsky R, Haigis KM, Fahie K, Christodoulou DC, Murphy AJ, et al. SIRT4 inhibits glutamate dehydrogenase and opposes the effects of calorie restriction in pancreatic beta cells. *Cell*. 2006; 126: 941-54. doi: 10.1016/j.cell.2006.06.057

30. West KA, Castillo SS, Dennis PA. Activation of the PI3K/Akt pathway and chemotherapeutic resistance. *Drug Resistance Updates*. 2002; 5: 234-48.

31. Bellacosa A, Kumar CC, Di CA, Testa JR. Activation of AKT Kinases in Cancer: Implications for Therapeutic Targeting. *Advances in Cancer Research*. 2005; 94: 29-86. doi: 10.1016/S0065-230X(05)94002-5

32. Csibi A, Fendt SM, Li C, Poulogiannis G, Choo AY, Chapski DJ, et al. The mTORC1 pathway stimulates glutamine metabolism and cell proliferation by repressing SIRT4. *Cell*. 2013; 153: 840-54. doi: 10.1016/j.cell.2013.04.023

33. Zhiyun Y, Guifang X, Guangtong Z, Ye C, Guangtao Z, Guangming Y, et al. NVP-BEZ235, a novel dual PI3K-mTOR inhibitor displays anti-glioma activity and reduces chemoresistance to temozolomide in human glioma cells. *Cancer Letters* 2015; 367: 58-68. doi: 10.1016/j.canlet.2015.07.007

34. Shi F, Guo H, Zhang R, Liu H, Wu L, Wu Q, et al. The PI3K inhibitor GDC-0941 enhances radiosensitization and reduces chemoresistance to temozolomide in GBM cell lines. *Neuroscience*. 2017; 346: 298-308. doi: 10.1016/j.neuroscience.2017.01.032

35. Choi EJ, Cho BJ, Lee DJ, Hwang YH, Sun HC, Kim HH, et al. Enhanced cytotoxic effect of radiation and temozolomide in malignant glioma cells: targeting PI3K-AKT-mTOR signaling, HSP90 and histone deacetylases. *BMC Cancer*. 2014; 14: 1-12. doi: 10.1186/1471-2407-14-17

36. Du J, Wang R, Yin L, Fu Y, Cai Y, Zhang Z, et al. BmK CT enhances the sensitivity of temozolomide-induced apoptosis of malignant glioma U251 cells in vitro through blocking the AKT signaling pathway. *Oncology Letters*. 2018; 15: 1537-44. doi: 10.3892/ol.2017.7483

37. Rogawski MA. AMPA receptors as a molecular target in epilepsy therapy. *Acta Neurologica Scandinavica*. 2013; 127: 9-18. doi: 10.1111/ane.12099

38. Lerma J, Marques JM. Kainate receptors in health and disease. *Neuron*. 2013; 80: 292-311. doi: 10.1016/j.neuron.2013.09.045

39. Hollmann M, Heinemann S. Cloned glutamate receptors. *Annual Review of Neuroscience*. 1994; 17: 31-108. doi: 10.1146/annurev.ne.17.030194.000335

40. Yu LJ, Wall BA, Wangari-Talbot J, Chen S. Metabotropic Glutamate Receptors in Cancer. *Neuropharmacology*. 2017; 115. doi: 10.1016/j.neuropharm.2016.02.011

41. Hall A. Rho GTPases and the Actin Cytoskeleton. *Science*. 1998; 279: 509-14.

42. Selena V, Utzschneider DT, Matthieu P, Giuseppe P, Dietmar Z, Alexandre H. Functional Avidity: A Measure to Predict the Efficacy of Effector T Cells? *Clinical & Developmental Immunology*. 2012; 153863.

43. Mcmahan RH, Slansky JE. Mobilizing the low-avidity T cell repertoire to kill tumors. *Seminars in Cancer Biology*. 2007; 17: 317-29. doi: 10.1016/j.semcancer.2007.06.006

44. Sikalidis AK. Amino Acids and Immune Response: A Role for Cysteine, Glutamine, Phenylalanine, Tryptophan and Arginine in T-cell Function and Cancer? *Pathology & Oncology Research*. 2015; 21: 9-17. doi: 10.1007/s12253-014-9860-0

45. Kostanyan IA, Merkulova MI, Navolotskaya EV, Nurieva RI. Study of interaction between L-glutamate and human blood lymphocytes. *Immunology Letters*. 1997; 58: 177-180. doi: 10.1016/S0165-2478(97)00086-2

46. Ganor Y, Besser M, Ben-Zakay N, Unger T, Levite M. Human T cells express a functional ionotropic glutamate receptor GluR3, and glutamate by itself triggers integrin-mediated adhesion to laminin and fibronectin and chemotactic migration. *Journal of Immunology*. 2003; 170: 4362.

47. Ganor Y, Teichberg VI, Levite M. TCR activation eliminates glutamate receptor GluR3 from the cell surface of normal human T cells, via an autocrine/paracrine granzyme B-mediated proteolytic cleavage. *Journal of Immunology*. 2007; 178: 683-92.

48. Lombardi G, Dianzani C, Miglio G, Canonico P, Fantozzi R. Characterization of ionotropic glutamate receptors in human lymphocytes. *British Journal of Pharmacology*. 2001; 133: 936-44. doi: 10.1038/sj.bjp.0704134

49. Guse AH. Ca2+ signaling in T-lymphocytes. *Critical Reviews in Immunology*. 1998; 18: 419.

50. Lombardi G, Miglio G, Dianzani C, Mesturini R, Varsaldi F, Chiocchetti A, et al. Glutamate modulation of human lymphocyte growth: in vitro studies. *Biochemical & Biophysical Research Communications*. 2004; 318: 496. doi: 10.1016/j.bbrc.2004.04.053

51. Pacheco R, Ciruela F, Casadã V, Mallol J, Gallart T, Lluis C, et al. Group I metabotropic glutamate receptors mediate a dual role of glutamate in T cell activation. *Journal of Biological Chemistry*. 2004; 279: 33352-358. doi: 10.1074/jbc.M401761200

52. Miglio G, Varsaldi F, Lombardi G. Human T lymphocytes express N -methyl- d -aspartate receptors functionally active in controlling T cell activation. *Biochemical & Biophysical Research Communications*. 2005; 338: 1875-83.

53. Chiocchetti A, Miglio G, Mesturini R, Varsaldi F, Mocellin M, Orilieri E, et al. Group I mGlu receptor stimulation inhibits activation-induced cell death of human T lymphocytes. *British Journal of Pharmacology*. 2006; 148: 760-68. doi: 10.1038/sj.bjp.0706746

54. Wang R, Dillon CP, Shi LZ, Milasta S, Carter R, Finkelstein D, et al. The transcription factor Myc controls metabolic reprogramming upon T lymphocyte activation. *Immunity*. 2011; 35: 871-82. doi: 10.1016/j.immuni.2011.09.021

55. Gerriets VA, Kishton RJ, Nichols AG, Macintyre AN, Inoue M, Ilkayeva O, et al. Metabolic programming and PDHK1 control CD4+ T cell subsets and inflammation. *Journal of Clinical Investigation*. 2015; 125: 194-207. doi: 10.1172/JCI76012

56. Klysz D, Tai X, Robert PA, Craveiro M, Cretenet G, Oburoglu L, et al. Glutamine-dependent α-ketoglutarate production regulates the balance between T helper 1 cell and regulatory T cell generation. *Science Signaling*. 2015; 8: 97. doi: 10.1126/scisignal.aab2610

57. Xiang Y, Stine ZE, Xia J, Lu Y, O'Connor RS, Altman BJ, et al. Targeted inhibition of tumor-specific glutaminase diminishes cell-autonomous tumorigenesis. *Journal of Clinical Investigation*. 2015; 125: 2293-306. doi: 10.1172/JCI75836

58. Becker JC, Andersen MH, Schrama D, Thor SP. Immune-suppressive properties of the tumor microenvironment. *Cancer Immunology Immunotherapy Cii*. 2013; 62: 1137-48. doi: 10.1007/s00262-013-1434-6

59. Andersen MH, Schrama D, Thor SP, Becker JC. Cytotoxic T cells. *Journal of Investigative Dermatology*. 2006; 126: 32-41. doi: 10.1038/sj.jid.5700001

60. Mashkina AP, Tyulina OV, Solovyova TI, Kovalenko EI, Kanevski LM, Johnson P, et al. The excitotoxic effect of NMDA on human lymphocyte immune function. *Neurochemistry International*. 2007; 51: 356-60. doi: 10.1016/j.neuint.2007.04.009

61. Pacheco R, Oliva H, Martineznavío JM, Climent N, Ciruela F, Gatell JM, et al. Glutamate released by dendritic cells as a novel modulator of T cell activation. *Journal of Immunology*. 2006; 177: 6695-704.

62. Kumar V, Patel S, Tcyganov E, Gabrilovich DI. The nature of myeloid-derived suppressor cells in the tumor microenvironment. *Trends in Immunology*. 2016; 37: 208. doi: 10.1016/j.it.2016.01.004

63. Almand B, Clark JI, Nikitina E, van Beynen J, English NR, Knight SC, et al. Increased production of immature myeloid cells in cancer patients: a mechanism of immunosuppression in cancer. *J Immunol*. 2001; 166: 678-89.

64. Krystal G, Sly L, Antignano F, Ho V, Ruschmann J, Hamilton M. Re: the terminology issue for myeloid-derived suppressor cells. *Cancer Research*. 2007; 67: 425; author reply 426.

65. Gallina G, Dolcetti L, Serafini P, De SC, Marigo I, Colombo MP, et al. Tumors induce a subset of inflammatory monocytes with immunosuppressive activity on CD8+ T cells. *Journal of Clinical Investigation*. 2006; 116: 2777-790. doi: 10.1172/JCI28828

66. Yang L, Debusk LM, Fukuda K, Fingleton B, Green-Jarvis B, Yu S, et al. Expansion of myeloid immune suppressor Gr+CD11b+ cells in tumor-bearing host directly promotes tumor angiogenesis. *Cancer Cell*. 2004; 6: 409-21. doi: 10.1016/j.ccr.2004.08.031

67. Hammami I, Chen J, Bronte V, Decrescenzo G, Jolicoeur M. L-glutamine is a key parameter in the immunosuppression phenomenon. *Biochemical & Biophysical Research Communications*. 2012; 425: 724-29. doi: 10.1016/j.bbrc.2012.07.139

68. Sturgill JL, Mathews J, Scherle P, Conrad DH. Glutamate signaling through the kainate receptor enhances human immunoglobulin production. *Journal of Neuroimmunology*. 2011; 233: 80-89. doi: 10.1016/j.jneuroim.2010.11.014

69. Chiocchetti A, Miglio G, Mesturini R, Varsaldi F, Mocellin M, Orilieri E, et al. Group I mGlu receptor stimulation inhibits activation-induced cell death of human T lymphocytes. *British Journal of Pharmacology*. 2010; 148: 760-68. doi: 10.1038/sj.bjp.0706746

70. Dickman KG, Youssef JG, Mathew SM, Said SI. Ionotropic glutamate receptors in lungs and airways: molecular basis for glutamate toxicity. *American Journal of Respiratory Cell & Molecular Biology*. 2004; 30: 139-44. doi: 10.1165/rcmb.2003-0177OC

71. Rezzani R, Corsetti G, Rodella L, Angoscini P, Lonati C, Bianchi R. Cyclosporine-A treatment inhibits the expression of metabotropic glutamate receptors in rat thymus. *Acta Histochemica*. 2003; 105: 81-87. doi: 10.1078/0065-1281-00688