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Role of Kynurenine Pathway in Glioblastoma

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<http://dx.doi.org/10.5772/intechopen.68939>

Abstract

In brain, the tryptophan degradation products through the kynurenine pathway exhibit neuromodulatory and inflammatory effects and have been related to the progression of neurodegenerative disorders, furthermore, their protagonism on the modulation of immune response and in cancer development has been reported. The immunosuppressive role of kynurenines has been described on glioblastoma models. In patients, the elevated activity of indoleamine-2,3-dioxygenase (IDO) such as the increase of kynurenine/tryptophan ratio have been also reported, suggesting that activation of kynurenine pathway is present during glioblastoma formation and can be related with tumor progression. The importance of the kynurenine pathway during cancer development has encouraged recent studies to the use of IDO inhibitors as a therapeutic strategy for treatment of breast, lung and ovarian cancer, until to get its use in clinical trials. IDO inhibitors also have been used in in vitro and in vivo models of glioblastoma showing promising results. The effect of kynurenines on glioblastoma offer a new perspective about the tryptophan metabolism during cancer. Due to the relevance of the kynurenine pathway in brain homeostasis, immunomodulation and cancer, we discuss the relevance of the kynurenine pathway on the development of glioblastoma multiforme as well as a possible molecular target for glioblastoma treatment.

Keywords: glioblastoma, tryptophan catabolism, immune response, immunoedition

1. Introduction

Tryptophan (Trp) is considered as an essential amino acid, which is required for life and growth but is not synthesized by the organism. Although approximately 1% of tryptophan dietary intake is used for protein synthesis, the rest 99% is metabolized through the 5-hydroxyindole pathway for the production of melatonin and serotonin, decarboxylated to tryptamine, transaminated to indol-3-pyruvic acid, or oxidized by the so-named kynurenine pathway (KP), for the new synthesis of NAD⁺ and NADP⁺ (**Figure 1**) [1–3].

The KP degrades over 95% of whole tryptophan intake; its rate-limiting enzymes, tryptophan 2,3-dioxygenase (TDO), and indoleamine 2,3-dioxygenase (IDO), catalyze the cleavage of the tryptophan pyrrole ring to produce N-formylkynurenine [1, 4]. Among mammals, TDO is mainly expressed in liver and only uses L-tryptophan as a specific substrate; instead of that, IDO is expressed in extrahepatic tissues, such as brain, lung, kidney, and immune cells [1, 4]. Furthermore, IDO’s substrate span is wider than TDO’s, being D- or L-tryptophan, D- or L-hydroxytryptophan, tryptamine, serotonin, and melatonin available for the catalytic activity of IDO [5]. An IDO isoenzyme has been reported, IDO2 is expressed in the murine kidney, liver, and reproductive system, and the gene encoding IDO2 is adjacent to the IDO gene and has similar affinity for substrates than IDO [6, 7]. N-formylkynurenine is transformed

Figure 1. Tryptophan catabolism occurs by different pathways. Ninety-five percent of the dietary uptake of tryptophan is catabolized mainly by the kynurenine pathway. About 3% is decarboxylated to tryptamine or transaminated to indol-3-pyruvic acid, 1% is intended for serotonin and melatonin synthesis, and resting 1% is for protein synthesis.

Figure 2. The kynurenine pathway.

to L-kynurenine (L-kyn) by the arylformidase (AFMID); kynurenine aminotransferases (KAT I, KAT II), and kynureninase (KYNU), with pyridoxal-5'-phosphate as a cofactor, as well as kynurenine monooxygenase (KMO), which uses FAD as a cofactor, transform L-kyn into kynurenic acid (Kyna), anthranilic acid (AA), or 3-hydroxykynurenine (3-HK), respectively [8–10]. KMO is located in mitochondrial outer membrane and it has been shown to have high affinity by the substrate suggesting that KMO metabolizes more L-kyn than other enzymes [11]. KATs and KYNU can also use 3-HK as a substrate to produce xanthurenic acid (Xanth) or 3-hydroxyanthranilic acid (3HAA) [8, 12]. Oxidation of 3HAA by the 3HAA dioxygenase (3HAADO) produces 2-amino-3-carboxymuconate semialdehyde (Acms) which is transformed by non-enzymatic dehydration into quinolinic acid (Quin), or into picolinic acid (Pic) by the Acms decarboxylase (ACMSD). Finally, Quin phosphoribosyltransferase (QPRT) uses Quin as a substrate for the formation of nicotinamine-adenine-monomucleotide (NaMN), the nicotinamine-adenine-dinucleotide (NAD⁺) precursor (**Figure 2**) [13, 14]. Enzyme kinetics of the whole KP have been determined, giving a wide perspective of the kynurenine pathway and its functionality [13], enzyme kinetics data of the KP are summarized in **Table 1**.

Enzyme	Substrate	K _M (mM)	K _{cat} (s ⁻¹)	Reference
IDO	5-Hydroxytryptamine	0.02	0.043	[5, 13, 15]
	Serotonin	0.1	0.002	
	Tryptophan	0.045	1.65	
	Oxygen	0.042		
TDO	Tryptophan	0.222	1.4	[16]
	Oxygen	0.037		
AFMID	N-formylkynurenine	0.05	100	[17, 18]
KAT I	L-kynurenine	4.7	3.35	[19]
KAT II	L-kynurenine	4.7	9.76	[20]
	3-hydroxykynurenine	3.8	1.7	
KAT III	L-kynurenine	1.5	2.3	[21]
KMO	L-kynurenine	0.89	1.88	[22]
	Oxygen	0.071		
	NADPH	0.82		
KYNU	L-kynurenine	0.495	0.23	[23]
	3-hydroxykynurenine	0.028	3.5	
3HAADO	3-hydroxyanthranilic acid	0.016	64	[24]
	Oxygen	0.615		
ACMSD	2-amino-3-carboxy muconate semialdehyde	0.0065	1	[25]
QPRT	Quinolinic acid	0.022	0.05	[26]

Table 1. Enzyme kinetics parameters for the kynurenine pathway enzymes.

2. Role of kynurenine pathway in brain

Although NAD⁺ is a final product of the KP, many of the intermediary metabolites, the so-called kynurenines, have demonstrated to exert many effects on cellular homeostasis and bioenergetics resulting on changes in organism behavior or immune response. In brain, Trp is transported through the blood-brain barrier by the large neutral amino acids transporter [27]. The imbalance on the levels of its metabolites (kynurenines) has been related with the progression of neurodegenerative disorders, such as Huntington, Alzheimer, and Parkinson due to their redox nature and their capacity to exert neuromodulatory mechanisms [28].

On a redox perspective, both 3-HK and 3-HAA represent a double-edged sword. Reports show that 3-HK is able to promote cell death due to the increase in reactive oxygen species (ROS) production; also, 3-HK interaction with metallic ions promotes protein aggregation as well as cataract formation and toxicity in neuronal cultures without region selectivity [29–32] pointing this kynurenine as a pro-oxidant and cytotoxic compound. In the same way, 3-HAA is able to cause protein damage due to interaction with metals producing OH[•]; furthermore, this metabolite causes oxidative phosphorylation uncoupling and decreased oxygen consumption [31, 33]. On the other hand, there are reports pointing to the antioxidant and protective side of these molecules, demonstrating a 3-HK-induced decrease of oxidative stress parameters; also, it has been observed that 3-HK acts as a free radical scavenger of radicals like O₂^{•-} [34, 35]; the antioxidant activity of 3-HAA also has been reported showing free radical scavenging and ROS production decrease [36]. Finally, the protective effect of 3-HK and 3-HAA on the inhibited mitochondrial electron transport chain, as electron carriers, also has been reported [37].

On the other hand, Kyna is the only endogenous antagonist to N-methyl-D-aspartate (NMDA) receptors known so far, it inhibits the α7-nicotinic receptors, showing anticonvulsant effects on murine models as well as in human patients [38]. Recently, it was found that Kyna is a free radical scavenger of radicals, such as superoxide anion (O₂^{•-}), hydroxyl radical (OH[•]), and peroxynitrite (ONOO⁻), besides it is able to reduce oxidative damage caused by pro-oxidants, so it is considered an endogenous antioxidant [39]. Furthermore, it has been shown that Kyna binds selectively to GPR35 receptor [40]; Kyna-mediated activation of GPR35 leads to intracellular Ca²⁺ influx, inositol phosphate production and, attenuates LPS-induced TNF-α release and reduces acetic acid-induced pain, suggesting that GPR35 could be mediating Kyna excitatory, anti-inflammatory, and antinociceptive functions [40–42]. Contributing with the anti-inflammatory response, Kyna also has been described as an agonist of the intracellular aryl hydrocarbon receptor (AHR); AHR translocation into the nucleus modulates the production of proinflammatory mediators and, as discussed below, inhibits T immune responses [43]. Because of Kyna is unable to cross the blood-brain barrier, systemic L-kyn administration has been used to show the protective effect of Kyna in 6-hydroxidopamine-induced Parkinson disease models, hippocampal β-amyloid, and glutamate toxicity [44–46].

Contrasting with Kyna, Quin has been described as an agonist of NMDA receptors; in fact, it has been demonstrated that Quin is a pro-convulsive agent which generates mitochondrial progressive dysfunction by reducing activity of respiratory complexes II and III [47], increases ROS production and lipid peroxidation in presence of Fe²⁺ [48], induces Ca²⁺ cellular influx increase, release of glutamate, and apoptosis [49–51]. Recently, the decrease in

autophagy inhibition by Beclin-1 reported in human astrocytes and neurons has been attributed to Quin toxicity [52]. Because of the selective damage that exerts in striatal spiny neurons with γ -amino butyric acid and substance P, Quin has also been a good model to mimic early symptoms of Huntington's disease [53–55]. In addition, increases in Quin concentrations were observed in the cerebral cortex of macaques infected with retroviruses, particularly those with local inflammatory lesions [56]. Moreover, Quin levels are increased in cerebrospinal fluid in the acquired immunodeficiency syndrome and in HIV patients; also in humans, Quin levels are elevated after traumatic brain injury [57].

2.1. Inflammatory process and kynurenine pathway components

Moreover, kynurenine pathway has been related to inflammatory processes. It has been shown that IDO, KMO, and KYNU expression is strongly induced by proinflammatory cytokines, mainly interferon- γ (IFN- γ), interleukin 1 (IL1), interleukin 17 (IL17), or the tumor necrosis factor α (TNF- α) during bacterial and viral infections in immune privileged tissues, such as brain [58, 59]. Thus, activation of the KP by proinflammatory molecules inhibits bacterial proliferation through tryptophan depletion, avoids autoimmune responses by limiting T cell activation and recruiting of immune regulatory cells [60–62]. The immunoregulatory role of the KP could act as a double-edged sword, meanwhile it is inhibiting pathogen growth and regulating immune responses to avoid an autoimmune damage, the same activation during cancer supports tumor immune evasion and promotes tumor growth and invasiveness.

Beyond their role on neurodegenerative disorders, kynurenines have also been related with cancer progression in more than one way. It has been described that IDO expression is high in all thyroid carcinomas [63]. Moreover, L-kyn and Quin promote neoplastic cell proliferation *in vitro* and the formation of larger tumors *in vivo*, in a colorectal cancer model, through the Wnt/ β -catenin signaling, despite of the ablation of IDO [64]. L-kyn modulates the repairing enzyme DNA polymerase kappa, protecting tumor cells from DNA damage and propitiating genomic instability [65]. Also, Quin produced by microglial cells in glioma models confers tumor tolerance to oxidative stress due to the production of NAD⁺, promotes cell proliferation by the modulation of the fibroblast growth factor-1 (FGF-1) release, and it is elevated in children with central nervous system tumors [66–68]. Kyna also promotes glioma cell proliferation through FGF-1 release [67]. The high expression and activity of the KP in the tumor microenvironment will be reflected on the maintenance of the NAD⁺/NADH supply, NAD⁺ and its reduced form NADH participate in several metabolic, redox, and stress response signals, providing favorable growing conditions for cancer cells. Finally, IDO expression and activity as well as the kynurenines promote cancer development by affecting the host's immune responsiveness. The effects of the KP on cancer immunosuppressive mechanisms will be detailed below.

2.2. Cancer immunoedition

All the cancer cells must possess a series of characters that allow them to develop tumors, these “hallmarks” let cancer cells to rapidly grow, evade cell death, migrate through the organism and colonize new tissues, modify their metabolic program, and to avoid immune destruction [69].

Before the establishment and development of a tumor, cancer cells must overcome elements of the immune system of the organism that can recognize, induce cellular signals, and finally, destroy exogenous agents or defective cells within the organism. In the early twentieth century, Paul Ehrlich formulated the idea that the immune system of an organism is able to recognize, destroy, and then protect against tumor cells. Later in the mid-twentieth century, the “immunosurveillance” hypothesis was then postulated by Sir Macfarlane Burnet and Lewis Thomas, based on this original idea and in experimental evidence of that, mouse lacking of interferon- γ responsiveness or with adaptive immunity defects, were susceptible to develop cancer [69, 70]. More recent evidence has demonstrated that the immune system not only protects against cancer progression, immune cells, and signaling but also promotes tumor cell establishment, and furthermore, cancer cells modulate immune mechanisms favoring tumor progression, transforming the idea of “immunosurveillance” into the “cancer immunoediting” hypothesis [69–70].

The cancer immunoediting hypothesis postulates that cancer cells and immune system create a set of dynamical interactions during the formation of a tumor; these interactions are arranged in three stages of the “cancer immunoediting,” or “The three E's hypothesis” process named: elimination, equilibrium, and escape [70]. During the elimination phase, cancer cells are recognized by the immune system and cytotoxic reactions induce cancer cell death; in the equilibrium phase, the cytotoxic mechanisms of the immune system act as selective pressure on tumor cells; cancer cells that survive, remain proliferating and establishing the tumor. Finally, at the escape phase, cancer cells are able to evade and suppress the immune mechanisms leading to the formation of tumors [70–72].

Cancer immunoediting mechanisms could be given by genetic alterations, proper of the cancer cells, which induce overexpression and secretion of suppressive molecules, such as the transforming growth factor- β , the vascular endothelial growth factor, prostaglandin E2, and the soluble MHCI-related gene A; cancer cells also recruit immune regulatory cells like T regulatory cells (Tregs), myeloid-derived suppressor cells (MDSC), and tolerogenic dendritic cells (TDC); and finally, by induction of immune checkpoint, inhibitory molecules, such as PD-L1 [73]. A second type of immunoediting is carried out by cytotoxic T cells of the own adaptive immune system, while exerting their protective role against cancer, T cells release cytokines like IFN- γ which can also induce the production of immune suppressive molecules by tumor cells, during the equilibrium phase of the “cancer immunoediting” [73]. Remarkably, IFN- γ is a strong inducer of IDO expression and activity which leads tryptophan metabolism through the KP in tumor microenvironment, and then to the triggering of the kynurenines' immunosuppressive effects [73, 74]. In cultured human glioma, stimulation with IFN- γ significantly increased the expression of IDO-1, IDO-2, kynureninase, and kynurenine hydroxylase, which potentiate the KP; whereas significantly decreased 2-amino-3-carboxymuconate semialdehyde decarboxylase (ACMSD) and kynurenine aminotransferase-I (KAT-I), which reduce the neuroprotective metabolites [75].

2.2.1. *The kynurenines in cancer immunoediting*

As mentioned above, the own immune response against tumors could propitiate the formation of an immunosuppressive microenvironment, one of these mechanisms is carried out

by IFN- γ and other proinflammatory cytokines secreted by cytotoxic lymphocytes which strongly induce IDO expression. Beyond the increase of IDO levels in tumor cells, the formation and accumulation of different kynurenines have demonstrated immunosuppressive and immunoinhibitory effects [76].

Recent works have demonstrated that tryptophan starvation is able to inhibit T cell and macrophage cell viability and proliferation [77–80]. Furthermore, KP metabolites have also shown direct effects as immunosuppressive molecules. L-kyn is able to activate the aryl hydrocarbon receptor (AHR) and thus to promote the generation of Tregs from naive T cells [81]. Moreover, there are reports showing that 3-HAA, 3-HK, and Quin promote Treg generation and that 3-HAA and 3-HK block T cell activation and induce cell death of CD4⁺ T and CD8⁺ T cells as well as of natural killer cells (NK) and B lymphocytes [82–86]. All these reports settle down the idea that immunosuppressive mechanisms carried out through the KP activation may be due to tryptophan deprivation of the tumor microenvironment or secondly, by the direct effect of the kynurenines on Treg recruitment and the impact on viability of effector T cells. Finally, both tryptophan depletion and the presence of the KP intermediates could enhance an immunosuppressive environment. It has been showed that L-kyn, Pic, 3-HK, 3-HAA, and Quin reduced cell viability and induced apoptosis on CD4⁺ in absence of tryptophan [82, 83]; besides at lower concentrations were able to increase Treg-mediated immunotolerance [84].

It is relevant to note that in some cases, the kynurenines are not produced by cancer cells but by other components of the tumor microenvironment, such as dendritic cells (DCs) or mesenchymal stem cells and also by microglial cells in the case of brain tumors [83, 87, 88]. Regarding dendritic cells expressing IDO, they can suppress effective immune responses through diverse strategies: by inhibiting the proliferation and effector functions of cytotoxic cells, such as NK and CD8⁺ T lymphocytes, as well as plasma cells; by inducing of CD4⁺ CD25⁺ FOXP3⁺ regulatory T cells from naive CD4⁺ cells; and by triggering immunosuppressive activity in adjacent IDO-expressing DCs [89]. Possible implication of IDO2 in cancer immunosuppression has been suggested due to reports showing its ability to mobilize the nuclear factor interleukin 6 inhibitor, LIP [6].

Thus, locating the IDO expression and the kynurenines in the “Three E’s” context, it would be in this way: IFN γ , TNF α , and proinflammatory cytokines secreted by cytotoxic lymphocytes, while killing recognized tumor cells during Elimination and Equilibrium phases, induce IDO expression of tumor cells, those that survived to immune response, and of other infiltrating cells, such as DCs and macrophages. Tumor cells expressing IDO, deplete tryptophan from the tumor microenvironment and begin to produce kynurenines and NAD⁺; tryptophan depletion from, and release of kynurenines to the tumor microenvironment, inhibit T cells and NK proliferation; induce apoptosis, while promote differentiation and proliferation of Tregs, and recruiting of DCs and macrophages. NAD⁺ production allows cancer cells to overcome DNA damage and oxidative stresses, promoting their proliferation during the Escape phase.

Because of the importance of the KP in brain and the relationship of tryptophan catabolism with immune modulation during cancer, researchers have begun to clarify the role of the activation of this pathway on glioblastoma progression for further development of new strategies to treat this illness.

2.3. The glioblastoma multiforme

Astrocytes are non-excitabile nervous cells of great importance for the physiological maintenance that exert on neurons, by regulating ions and excitatory amino-acids concentrations on synaptic regions, forming the brain-blood-barrier (BBB)-mediating neuron-blood stream signaling and regulating the transport of nutrients into and out of the brain [90, 91]. Beyond this, astrocytes can be differentiated on a wide span of morphological, physiological, and genomic subtypes [90–91].

Deregulation of cell proliferation and uncontrolled proliferation caused by mutations of certain genes lead astrocytes to transform into astrocytomas. Astrocytomas have been classified into four subtypes depending on the rate of proliferation and the grade of malignancy: grade I pilocytic astrocytomas are non-invasive tumors, they represent the less malignant of astrocytomas; diffuse astrocytomas are grade II tumors that tend to invade peripheral tissues but their growth rate is slow; anaplastic astrocytomas grow faster than diffuse astrocytomas and tend to form tentacle-like projections into surrounding tissues, instead of grade III anaplastic astrocytomas, their frequency is low; finally, glioblastomas (GBM), also known as glioblastoma multiforme, are grade IV tumors, these are the most malignant of astrocytomas [92]. GBM can be originated *de novo* from mature astrocytes, primary GBM, or from a less malignant astrocytoma, secondary GBM; they represent 15.1% of all brain primary tumors and 55.1% of all gliomas [93].

Incidence rate of GBM is 3.19 per 100,000 people with a median age at diagnosis of 64 years old for primary GBM, and 45 years old for secondary GBM, the median survival overall for diagnosed and treated GBM ranges between 12 and 14 months [94, 95]. Furthermore, GBM represent 2.8% of brain tumors during childhood [96]; however, its frequency is lower in adults, high-grade astrocytic tumor incidence rate is 0.85 per 100,000 people being more frequent in children between 5 and 9 years old, also, the median survival overall is over 43 months [97–99]. The most common treatment for GBM is surgical resection of the tumor, followed by temozolomide-based chemotherapy, and 5000–6000 Gy radiotherapy which prolongs the lifespan 202 weeks [100–102]. Despite the treatment, the survival of afflicted patients is no longer than 14 months and only 5% of the patients have a survival rate of 5 years. It is believed that the lack of response of GBM to the multimodal treatment is due to multiple factors that combined, make GBM resistance and aggressiveness.

A major character among GBM is a loss-of-function mutation of Retinoblastoma (Rb) gene, a cell cycle regulator protein at the phase G to phase S checkpoint, that also regulates apoptosis and differentiation, which occurs on 77% of GBM [103, 104]. Instead of that, another genetic mutations and genomic expression patterns differ among GBM, integrated genomic analysis originated four types of GBM named: proneural, associated with PDGFRA, IDH1, and TP53 mutations; neural, expressing neuronal markers, such as NEFL, GABRA1, SYT1, and SLC12A5; classical, showing amplifications on EGFR expression and deletions of Ink4a/ARF locus; and mesenchymal, characterized by overexpression of CHI3L1 and MET so as deletion of NF1 [103]. Several other mutations in key oncogenic signaling pathways, such as the receptor tyrosine kinase (RTK)/RAS/PI3K, p53 pathways, lead to uncontrolled tumor cell proliferation, genomic instability, and resistance to therapeutic strategies.

GBM may have a wide cellular diversity, more than tumor cells which are polygonal or spindled small sized with big nuclei, GBM-initiating cells (also called glioma stem cells) are responsible for cell proliferation and renewal of GBM cells, also confer chemo- and radioresistance; infiltrating multinucleated cells, such as lymphocytes, macrophages, and neutrophils, and cells with lipid vacuoles are present in these tumors [105]. Because GBM are highly angiogenic tumors, blood vessels surrounded by pericytes are also present in tumors. GBM also show necrotic regions among the central body tumor and some other necrotic foci in outer regions of the tumor [105, 106]. In addition to all these mechanisms, the GBM has the ability to create an immunosuppressive environment that prevents the response lead by the immune system against GBM.

2.3.1. Immunosuppressive environment in GBM

Historically, the brain has been considered an immune privileged organ due to the inability of reject exo-grafts and the lack of response in case of infection [107], as well as, absence of a normal response of the lymphatic system and the extremely distinctiveness of antigen-presenting cells (APCs) in brain tissue [108, 109]. However, diverse studies have recently found that there is not an absolute isolation of the rest of the organism; moreover, within the dural sinuses is located a lymphatic system that connect with the deep cervical lymph nodes, able of taking immune cells and macromolecules into the CNS [108].

Even with this lymphatic system, the access to CNS is highly regulated, mostly by the BBB [110]. The BBB is a highly selective layer composed of basement membranes, brain pericytes, astrocytes, and neurons, which have the ability to reject more than the 90% of small molecules, allowing the entrance just to certain lipophilic molecules [111]. However, it has been observed that when a GBM appears, this tumor easily disrupts the BBB due to this abnormal structure, which has as consequence the free-crossing of a more varied group of substances into the CNS [111] and also cells of the immune system.

GBM is infiltrated by several cell types, such as monocyte-derived cells, microglia, and activated T cells. These immune cells are recruited by chemotaxis to the tumor and together with molecules secreted by GBM itself, such as IL-10, prostaglandins, and TGF- β 1 (**Table 2**), playing a major role in the immunosuppression of the tumor [112–113]. Specifically, several studies have found that the infiltration of T cells subtypes is higher in GBM than any other CNS tumor [114], comprising between 10 and 30% of cells within the tumor mass [115–116]. Due to the production of immunosuppressive cytokines, inhibition of T cell proliferation, activation of Tregs and hypoxia, an immunosuppressive environment, is made in GBM, which can be enhanced by the activation of the KP.

Because of the high immunosuppressive conditions in the GBM, new therapies have begun to being developed, focusing on antitumoral immune response for improvement of GBM patients. Thus, epidermal growth factor receptor (EGFR) variant III-specific peptide vaccination and autologous tumor lysate-DC vaccination have been tested with successful results on phase I and phase II clinical trials [117–120]. However, a better understanding of the immunosuppressive mechanisms occurring during GBM development, including those carried out by IDO activity and the kynurenines, could impulse the furtherance of new tools and strategies for GBM treatment.

Molecule	Effect	Mechanism
Interleukin-10 (IL-10)	Induce apoptosis in T cells, possibly through the expression of Fas-ligand	[121–123]
Tumor-promoting cytokines	Dampen the antitumor immune response	[124, 125]
Interleukin-6 (IL-6)	Shifting adaptive immunity to humoral response (TH2)	[124, 126]
Prostaglandin E2 (PGE2)	Dampen the antitumor immune response suppressing lymphocyte proliferation	[124, 125, 127–129]
TGF- β 1	Ability to polarize TAMs toward M2 phenotype	
CD70 and ganglioside	Promotion of T cells apoptosis	[130, 131]
Colony stimulating factor-1 (CSF-1)	Stimulating of monocytic cells	[124, 126]
	Ability to polarize TAMs toward M2 phenotype	
Basic fibroblast growth factor (BFGF),	Dampen the antitumor immune response	[124, 125]
Vascular endothelial growth factor (VEGF)	Proangiogenic factor. Support of vascularity and tumor growth	[132]
Factor-1 α (HIF-1 α)	Activation of Tregs and production of vascular endothelial growth factor (VEGF)	[133]
Transcription 3 (STAT3)	Synthesis of hypoxia-inducible factor -1 α (HIF-1 α) that subsequently induces activation of Tregs and production of vascular endothelial growth factor (VEGF). Promotion of angiogenesis	[133]

Table 2. Molecules implicated in the immunosuppression of GBM.

2.3.2. Implications of kynurenine pathway in GBM development

Kynurenine pathway enzymes are overexpressed in GBM. Upregulated expression of these enzymes has been related to severity of gliomas and patient survival. The IDO expression in 343 glioma specimens and correlated to patient survival has been analyzed [134], this expression was associated with poor prognosis and was more frequently observed in high-grade glioma. Moreover, in an orthotopic GL261 cell tumor model was shown that IDO-competent brain tumors increased the recruitment of immunosuppressive Tregs, and decreased the frequency of CD8⁺ T cells compared with IDO-deficient brain tumors [134]. Another study, including 75 gliomas, showed higher expression of IDO in malignant gliomas compared with low-grade gliomas. Moreover, stronger IDO expression was associated with shortened survival time in GBM patients [135]. Additionally, it has been reported that glioma cells have increased mRNA

expression of IDO1 and IDO2 compared with human fetal astrocytes and human adult astrocytes cultures as well as decreased Kats mRNA expression, and these expression enhanced when cells were stimulated with IFN γ [75]; the same work also reported increased Kyn/Trp ratios and decreased Kyna/Kyn ratios in the plasma of glioblastoma patients compared with healthy people [75]. The levels of Trp and Kyn were evaluated in GBM patients before and after tumor resection. Interestingly, both Trp and Kyn significantly decreased after 48 h and 10 weeks after surgery. In addition, patients with a high-ratio Kyn/Trp had worse mean overall survival compared with patients with lower ratio [136].

The significantly increased expression of IDO in cancer cells and in the tumor microenvironment has arisen as a promising target for GBM treatment, based on the inhibition of IDO as a potential therapy for cancer patients. Among the first strategies, is the systemic administration of 1-methyl tryptophan (1-MT), a competitive inhibitor of the IDO, which delayed tumor development in a murine model of Lewis lung carcinoma [137]. Subsequently, it was described that the expression of IDO in immunogenic cells (P815B) avoided their rejection by preimmunized mice, an effect that was associated with the inhibition of specific T cell response [138]. This effect was partially reversed when preimmunized mice were administered with 1-MT [138]. Due to the results observed in animal models, 1-MT has been tested and approved on phase I clinical trials in patients with solid and solid metastatic neoplasms, lung, ovarian, Fallopian tube, and breast cancer showing disease stabilization in most cases [89, 139–141].

Concerning to GBM, at least three clinical trials involving IDO inhibitors are in recruiting status (Feb. 2017), but the use of 1-MT on *in vivo* GBM models has shown that when is used in combination with classical chemotherapeutic agents, such as temozolomide or cyclophosphamide, and additional radiotherapy, increases the overall survival as well as reduces the tumor volume [142, 143]. Additionally to this effect, inhibition of IDO has also shown increased complement component C3 deposition on the tumor region, which is necessary for tumor volume reduction [142], as well as increased CD4 $^{+}$ and CD8 $^{+}$ T cell population from animal spleens, treated with 1-MT [143], indicating that IDO inhibition rescues the host's immune activation.

Despite reports pointing that 1-MT has a greater affinity for IDO2 than for IDO [6, 7], it is of mention that the majority of reports about the targeting of the KP for cancer treatment are focused on IDO inhibition. But IDO is just one of the enzymes that fuel this catabolic route, so the better understanding of the roles of both IDO2 and TDO in cancer development and immunosuppression would result in better ways for combating cancer [144].

As mentioned above, in most cases, IDO expression as well as kynurenines production and immunosuppressive mechanisms are carried out by infiltrating tumor cells. For GBM, microglial cells are an important source of kynurenines so, the microglial depletion could be another important strategy for tumor mitigation. Studies focusing in microglial depletion through the use of CSF-1 receptor inhibitors have shown prolonged mice survival and enhanced antitumoral immune response when animals were treated in combination with DC vaccination [145, 146]. The effect of microglial elimination on IDO expression and on the levels of KP metabolites, still remains to be elucidated, but the immune response reported with the use of the CSF-1 receptor inhibitors settle down some clues about what could happen in the KP context.

Thus, the use of IDO inhibitors and microglial elimination in combination with classical chemotherapy and radiotherapy in GBM murine models, as well as the clinical trials that have tested 1-MT in different kinds of solid and metastatic tumors has shown promising results for targeting IDO and the KP against GBM.

2.4. Concluding remarks

GBM is an astrocyte-derived tumor, the most common of brain tumors, characterized by its high proliferation rates, genomic instability, and invasiveness, as well as to being a high immunosuppressive tumor. The nature of GBM results in a rapid expansion into the surrounding tissues, associated with poor prognosis and patient low survival despite classical treatment of these tumors, tumor extirpation, temozolomide therapy, and radiotherapy, which only prolongs median survival over 2 months.

In this chapter, we have discussed the importance of the tryptophan catabolism through the KP during GBM development. Activation of this catabolic route provides cancer cells a constant

Figure 3. Global scheme of the role of IDO expression and the kynurenine pathway on glioblastoma development. During glioblastoma formation, a population of tumor cells is recognized and eliminated by the host immune system (cytotoxic T lymphocytes, helper T lymphocytes, and natural killer cells). While eliminating the recognized tumor cells, cytotoxic T lymphocytes secrete IFN γ , TNF α , and other proinflammatory cytokines which strongly induce IDO expression and the kynurenine pathway activation in survivor glioblastoma cells and tumor infiltrating cells (dendritic cells and tumor-associated macrophages). Glioblastoma IDO expressing cells maintain a rich NAD⁺/NADH pool which provides redox balance, energy supply, and active DNA repairing mechanisms, facilitating genomic instability and tumor growth; also in glioblastoma cells, L-kyn also contributes to genomic instability by modulating DNA polymerase κ . In the tumor microenvironment, released L-kyn promotes Treg differentiation from naïve T cells. While 3-HAA, 3-HK, and Quin promote Treg recruitment and inhibit both cytotoxic and helper T lymphocytes activation and proliferation; and also promote T lymphocytes, natural killer cells, and nontumor cells apoptosis, promoting more invasiveness. Microenvironmental tryptophan depletion caused by high tryptophan uptake by IDO expressing cells enhances the kynurenines effect against T cell activation proliferation. Finally, the use of IDO inhibitor 1-methyl-tryptophan rises as a promising strategy for glioblastoma treatment.

supply of NAD⁺ and promotes the expression of damaged DNA repairing enzymes, which allow cancer cells to have an active metabolism, and to bypass redox stress and DNA damage pressure (**Figure 3**).

Furthermore, IDO expression and elevated Kyn/Trp ratios are related with poor prognosis and low survival of GBM patients. The expression of key enzymes of the KP is induced by stimulation of cytokines secreted during antitumoral immune responses, after this, tryptophan depletion and kynurenines production inhibit effector CD4⁺ and CD8⁺ T cell and NK cell proliferation, meanwhile promote Treg differentiation and MDSC infiltration into the tumor, attenuating antitumor responses. It is of note that IDO expression and immunosuppressive mechanisms are not carried out by cancer cells alone, but tumor infiltrating cells are also able to synthesize IDO and to promote an immunosuppressive environment (**Figure 3**).

The results of the use of IDO inhibitors, like 1-MT, in *in vivo* GBM models and in phase I and phase II clinical trials against lung, breast, and ovarian cancer, arise them as a promising strategy for combating GBM. However, detailed information about the role of key enzymes of the KP, KYNU, KAT, KMO, and QPRT, could provide more information for the development of more truthful treatments against GBM.

Conflict of interests

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the chapter.

Acknowledgements

This work was supported by CONACYT Grant 262010.

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References

- [1] Bender DA. Biochemistry of tryptophan in health and disease. *Molecular Aspects of Medicine*. 1982;**6**:101-197
- [2] Green AR, Aronson JK, Curzon G, Woods HF. Metabolism of an oral tryptophan load. I: Effects of dose and pretreatment with tryptophan. *British Journal of Clinical Pharmacology*. 1980;**10**(6):603-610
- [3] Heuther G, Hajak G, Reimer A, Poeggeler B, Blömer B, Rodenbeck A, Rütther E. The metabolic fate of infused l-tryptophan in men: Possible clinical implications of the accumulation of circulating tryptophan and tryptophan metabolites. *Psychopharmacology*. 1992;**109**(4):422-432
- [4] Chen Y, Guillemin GJ. Kynurenine pathway metabolites in humans: Disease and healthy states. *International Journal of Tryptophan Research*. 2009;**2**:1-19
- [5] Hayaishi O. Properties and function of indoleamine 2,3-dioxygenase. *Journal of Biochemistry*. 1976;**79**(4):13P-21P
- [6] Metz R, Duhadaway JB, Kamasani U, Laury-Kleintop L, Muller AJ, Prendergast GC. Novel tryptophan catabolic enzyme IDO2 is the preferred biochemical target of the antitumor indoleamine 2,3-dioxygenase inhibitory compound D-1-methyl-tryptophan. *Cancer Research*. 2007;**67**(15):7082-7087. DOI: 10.1158/0008-5472.CAN-07-
- [7] Ball HJ, Yuasa HJ, Austin CJ, Weiser S, Hunt NH. Indoleamine 2,3-dioxygenase-2; a new enzyme in the kynurenine pathway. *The International Journal of Biochemistry and Cell Biology*. 2009;**41**(3):467-471. DOI: 10.1016/j.biocel.2008.01.005
- [8] Phillips RS. Structure and mechanism of kynureninase. *Archives of Biochemistry and Biophysics*. 2014;**544**:69-74. DOI: 10.1016/j.abb.2013.10.020
- [9] Majewski M, Kozłowska A, Thoene M, Lepiarczyk E, Grzegorzewski WJ. Overview of the role of vitamins and minerals on the kynurenine pathway in health and disease. *Journal of Physiology and Pharmacology*. 2016;**67**(1):3-19
- [10] Nematollahi A, Sun G, Harrop SJ, Hanrahan JR, Church WB. Structure of the PLP-Form of the human kynurenine aminotransferase II in a novel spacegroup at 1.83 Å resolution. *International Journal of Molecular Sciences*. 2016;**17**(4):446. DOI: 10.3390/ijms17040446
- [11] Wang Q, Liu D, Song P, Zou MH. Deregulated tryptophan-kynurenine pathway is linked to inflammation, oxidative stress, and immune activation pathway in cardiovascular diseases. *Frontiers in Bioscience*. 2015;**20**:1116-1143
- [12] Han Q, Fang J, Li J. Kynurenine aminotransferase and glutamine transaminase K of *Escherichia coli*: Identity with aspartate aminotransferase. *The Biochemical Journal*. 2001;**360**(Pt 3):617-623. DOI: 10.1042/BSR20100117
- [13] Stavrum AK, Heiland I, Schuster S, Puntervoll P, Ziegler M. Model of tryptophan metabolism, readily scalable using tissue-specific gene expression data. *The Journal of Biological Chemistry*. 2013;**288**(48):34555-34566. DOI: 10.1074/jbc.M113.474908

- [14] Badawy AA. Tryptophan availability for kynurenine pathway metabolism across the life span: Control mechanisms and focus on aging, exercise, diet and nutritional supplements. *Neuropharmacology*. 2017;**112**(Pt B):248-263. DOI: 10.1016/j.neuropharm.2015.11.015
- [15] Kudo Y, Boyd CA. Human placental indoleamine 2,3-dioxygenase: Cellular localization and characterization of an enzyme preventing fetal rejection. *Biochimica et Biophysica Acta*. 2000;**1500**(1):119-124
- [16] Basran J, Rafice SA, Chauhan N, Efimov I, Cheesman MR, Ghamsari L, Raven EL. A kinetic, spectroscopic, and redox study of human tryptophan 2,3-dioxygenase. *Biochemistry*. 2008;**47**(16):4752-4760. DOI: 10.1021/bi702393b
- [17] Shinohara R, Ishiguro I. The purification and properties of formamidase from rat liver. *Biochimica et Biophysica Acta*. 1970;**198**(2):324-331
- [18] Krisch K, Arndt R, Junge W, Menge U, Michelssen K. Purification and some properties of formamidase from rat and pig liver. *Acta Vitaminologica et Enzymologica*. 1975;**29**(1-6):302-306
- [19] Han Q, Li J, Li J. pH dependence, substrate specificity and inhibition of human kynurenine aminotransferase I. *European Journal of Biochemistry*. 2004;**271**(23-24):4804-4814. DOI: 10.1186/1471-2091-11-19
- [20] Han Q, Cai T, Tagle DA, Robinson H, Li J. Substrate specificity and structure of human amino adipate aminotransferase/kynurenine aminotransferase II. *Bioscience Reports*. 2008;**28**(4):205-215. DOI: 10.1042/BSR20080085
- [21] Han Q, Robinson H, Cai T, Tagle DA, Li J. Biochemical and structural properties of mouse kynurenine aminotransferase III. *Molecular and Cellular Biology*. 2009;**29**(3):784-793. DOI: 10.1128/MCB.01272-08
- [22] Han Q, Calvo E, Marinotti O, Fang J, Rizzi M, James AA, Li J. Analysis of the wild-type and mutant genes encoding the enzyme kynurenine monooxygenase of the yellow fever mosquito, *Aedes aegypti*. *Insect Molecular Biology*. 2003;**12**(5):483-490
- [23] Lima S, Kristoforov R, Momany C, Phillips RS. Crystal structure of Homo sapiens kynureninase. *Biochemistry*. 2008;**46**(10):2735-2744. DOI: 10.1021/bi0616697
- [24] Malherbe P, Köhler C, Da Prada M, Lang G, Kiefer V, Schwarcz R, Lahm HW, Cesura AM. Molecular cloning and functional expression of human 3-hydroxyanthranilic-acid dioxygenase. *The Journal of Biological Chemistry*. 1994;**269**(19):13792-13797
- [25] Pucci L, Perozzi S, Cimadamore F, Orsomando G, Raffaelli N. Tissue expression and biochemical characterization of human 2-amino 3-carboxymuconate 6-semialdehyde decarboxylase, a key enzyme in tryptophan catabolism. *The FEBS Journal*. 2007;**274**(3):827-840. DOI: 10.1111/j.1742-4658.2007.05635.x
- [26] Liu H, Woznica K, Catton G, Crawford A, Botting N, Naismith JH. Structural and kinetic characterization of quinolinate phosphoribosyltransferase (hQPRase) from Homo sapiens. *Journal of Molecular Biology*. 2007;**373**(3):755-763. DOI: 10.1016/j.jmb.2007.08.043

- [27] Boado RJ, Li JY, Nagaya M, Zhang C, Pardridge WM. Selective expression of the large neutral amino acid transporter at the blood-brain barrier. *Proceedings of the National Academy of Sciences of the United States of America*. 1999;**96**(21):12079-12084
- [28] Schwarcz R, Stone TW. The kynurenine pathway and the brain: Challenges, controversies and promises. *Neuropharmacology*. 2017;**112**(Pt B):237-247. DOI: 10.1016/j.neuropharm.2016.08.003
- [29] Okuda S, Nishiyama S, Saito H, Katsuki H. 3-Hydroxykynurenine, an endogenous oxidative stress generator, causes neuronal cell death with apoptotic features and region selectivity. *Journal of Neurochemistry*. 1998;**70**(1):299-307
- [30] Nakagami Y, Saito H, Katsuki H. 3-Hydroxykynurenine toxicity on the rat striatum *in vivo*. *Japanese Journal of Pharmacology*. 1996;**71**(2):183-186
- [31] Goldstein LE, Leopold MC, Huang X, Atwood CS, Saunders AJ, Hartshorn M, Lim JT, Faget KY, Muffat JA, Scarpa RC, Chylack Jr LT, Bowden EF, Tanzi RE, Bush AI. 3-Hydroxykynurenine and 3-hydroxyanthranilic acid generate hydrogen peroxide and promote alpha-crystallin cross-linking by metal ion reduction. *Biochemistry*. 2000;**39**(24):7266-7275
- [32] Vazquez S, Aquilina JA, Jamie JF, Sheil MM, Truscott RJ. Novel protein modification by kynurenine in human lenses. *The Journal of Biological Chemistry*. 2002;**277**(7):4867-4873. DOI: 10.1074/jbc.M107529200
- [33] Quagliariello E, Papa S, Saccone C, Alifano A. Effect of 3-hydroxyanthranilic acid on the mitochondrial respiratory system. *The Biochemical Journal*. 1964;**91**(1):137-146
- [34] Goshima N, Wadano A, Miura K. 3-Hydroxykynurenine as O₂- scavenger in the blow-fly, *Aldrichina grahami*. *Biochemical and Biophysical Research Communications*. 1986;**139**(2):666-672. DOI: 10.1016/S0006-291X(86)80042-0
- [35] Wadano A, Takenaka Y, Matumoto M. 3-Hydroxykynurenine as a radical scavenger in the blowfly, *Aldrichina grahami*. *Insect Biochemistry and Molecular Biology*. 1993;**23**(8):919-925. DOI: 10.1016/0965-1748(93)90109-6
- [36] Leipnitz G, Schumacher C, Dalcin KB, Scussiato K, Solano A, Funchal C, Dutra-Filho CS, Wyse AT, Wannmacher CM, Latini A, Wajner M. *In vitro* evidence for an antioxidant role of 3-hydroxykynurenine and 3-hydroxyanthranilic acid in the brain. *Neurochemistry International*. 2007;**50**(1):83-94. DOI: 10.1016/j.neuint.2006.04.017
- [37] Quagliariello E, Palmieri F, Alifano A, Papa S. 3-hydroxyanthranilic acid-mediated respiration in the inhibited respiratory chain. *Biochimica et Biophysica Acta*. 1966;**113**(3):482-489
- [38] Foster AC, Vezzani A, French ED, Schwarcz R. Kynurenic acid blocks neurotoxicity and seizures induced in rats by the related brain metabolite quinolinic acid. *Neuroscience Letters*. 1984;**48**(3):273-278
- [39] Lugo-Huitrón R, Blanco-Ayala T, Ugalde-Muñiz P, Carrillo-Mora P, Pedraza-Chaverri J, Silva-Adaya D, Maldonado PD, Torres I, Pinzón E, Ortiz-Islas E, López T, García E,

- Pineda B, Torres-Ramos M, Santamaría A, La Cruz VP. On the antioxidant properties of kynurenic acid: Free radical scavenging activity and inhibition of oxidative stress. *Neurotoxicology and Teratology*. 2011;**33**(5):538-347. DOI: 10.1016/j.ntt.2011.07.002
- [40] Wang J, Simonavicius N, Wu X, Swaminath G, Reagan J, Tian H, Ling L. Kynurenic acid as a ligand for orphan G protein-coupled receptor GPR35. *The Journal of Biological Chemistry*. 2006;**281**(31):22021-22028. DOI: 10.1074/jbc.M603503200
- [41] Cosi C, Mannaioni G, Cozzi A, Carlà V, Sili M, Cavone L, Maratea D, Moroni F. G-protein coupled receptor 35 (GPR35) activation and inflammatory pain: Studies on the antinociceptive effects of kynurenic acid and zaprinast. *Neuropharmacology*. 2011;**60**(7-8):1227-1231. DOI: 10.1016/j.neuropharm.2010.11.014
- [42] Berlinguer-Palmini R, Masi A, Narducci R, Cavone L, Maratea D, Cozzi A, Sili M, Moroni F, Mannaioni G. GPR35 activation reduces Ca²⁺ transients and contributes to the kynurenic acid-dependent reduction of synaptic activity at CA3-CA1 synapses. *PloS One*. 2013;**8**(11):e82180. DOI: 10.1371/journal.pone.0082180
- [43] Moroni F1, Cozzi A, Sili M, Mannaioni G. Kynurenic acid: a metabolite with multiple actions and multiple targets in brain and periphery. *Journal of Neural Transmission*. 2012;**119**(2):133-139. DOI: 10.1007/s00702-011-0763-x
- [44] Kumar A, Babu GN. *In vivo* neuroprotective effects of peripheral kynurenine on acute neurotoxicity induced by glutamate in rat cerebral cortex. *Neurochemical Research*. 2010;**35**(4):636-644. DOI: 10.1007/s11064-009-0114-6
- [45] Carrillo-Mora P, Méndez-Cuesta LA, Pérez-De La Cruz V, Fortoul-van Der Goes TI, Santamaría A. Protective effect of systemic L-kynurenine and probenecid administration on behavioural and morphological alterations induced by toxic soluble amyloid beta (25-35) in rat hippocampus. *Behavioural Brain Research*. 2010;**210**(2):240-250. DOI: 10.1016/j.bbr.2010.02.041
- [46] Silva-Adaya D, Pérez-De La Cruz V, Villeda-Hernández J, Carrillo-Mora P, González-Herrera IG, García E, Colín-Barenque L, Pedraza-Chaverri J, Santamaría A. Protective effect of L-kynurenine and probenecid on 6-hydroxydopamine-induced striatal toxicity in rats: Implications of modulating kynurenate as a protective strategy. *Neurotoxicology and Teratology*. 2011;**33**(2):303-312. DOI: 10.1016/j.ntt.2010.10.002
- [47] Ribeiro CA, Grando V, Dutra Filho CS, Wannmacher CM, Wajner M. Evidence that quinolinic acid severely impairs energy metabolism through activation of NMDA receptors in striatum from developing rats. *Journal of Neurochemistry*. 2006;**99**(6):1531-1542
- [48] Goda K, Kishimoto R, Shimizu S, Hamane Y, Ueda M. Quinolinic acid and active oxygens. Possible contribution of active Oxygens during cell death in the brain. *Advances in Experimental Medicine and Biology*. 1996;**398**:247-254
- [49] Moroni F, Lombardi G, Moneti G, Aldinio C. The excitotoxin quinolinic acid is present in the brain of several mammals and its cortical content increases during the aging process. *Neuroscience Letters*. 1984;**47**(1):51-55

- [50] Bordelon YM, Chesselet MF, Nelson D, Welsh F, Erecińska M. Energetic dysfunction in quinolinic acid-lesioned rat striatum. *Journal of Neurochemistry*. 1997;**69**(4):1629-1639
- [51] Tavares RG, Tasca CI, Santos CE, Alves LB, Porciúncula LO, Emanuelli T, Souza DO. Quinolinic acid stimulates synaptosomal glutamate release and inhibits glutamate uptake into astrocytes. *Neurochemistry International*. 2002;**40**(7):621-627
- [52] Braidy N, Brew BJ, Inestrosa NC, Chung R, Sachdev P, Guillemin GJ. Changes in Cathepsin D and Beclin-1 mRNA and protein expression by the excitotoxin quinolinic acid in human astrocytes and neurons. *Metabolic Brain Disease*. 2014;**29**(3):873-883. DOI: 10.1007/s11011-014-9557-9
- [53] Beal MF, Kowall NW, Ellison DW, Mazurek MF, Swartz KJ, Martin JB. Replication of the neurochemical characteristics of Huntington's disease by quinolinic acid. *Nature*. 1986;**321**(6066):168-171. DOI: 10.1038/321168a0
- [54] Stone TW. Neuropharmacology of quinolinic and kynurenic acids. *Pharmacological Reviews*. 1993;**45**(3):309-379
- [55] Lugo-Huitrón R, Ugalde Muñoz P, Pineda B, Pedraza-Chaverrí J, Ríos C, Pérez-de la Cruz V. Quinolinic acid: an endogenous neurotoxin with multiple targets. *Oxidative Medicine and Cellular Longevity*. 2013;**2013**:104024. DOI: 10.1155/2013/104024
- [56] Heyes MP, Saito K, Jacobowitz D, Markey SP, Takikawa O, Vickers JH. Poliovirus induces indoleamine-2,3-dioxygenase and quinolinic acid synthesis in macaque brain. *FASEB Journal*. 1992;**6**(11):2977-2989
- [57] Yan EB, Frugier T, Lim CK, Heng B, Sundaram G, Tan M, Rosenfeld JV, Walker DW, Guillemin GJ, Morganti-Kossmann MC. Activation of the kynurenine pathway and increased production of the excitotoxin quinolinic acid following traumatic brain injury in humans. *Journal of Neuroinflammation*. 2015;**12**:110. DOI: 10.1186/s12974-015-0328-2
- [58] Brooks AK, Lawson MA, Smith RA, Janda TM, Kelley KW, McCusker RH. Interactions between inflammatory mediators and corticosteroids regulate transcription of genes within the Kynurenine Pathway in the mouse hippocampus. *Journal of Neuroinflammation*. 2016;**13**(1):98. DOI: 10.1186/s12974-016-0563-1
- [59] Ueland PM, McCann A, Midttun Ø, Ulvik A. Inflammation, vitamin B6 and related pathways. *Molecular Aspects of Medicine*. 2017;**53**:10-17. DOI: 10.1016/j.mam.2016.08.001
- [60] Müller A, Heseler K, Schmidt SK, Spekter K, Mackenzie CR, Däubener W. The missing link between indoleamine 2,3-dioxygenase mediated antibacterial and immunoregulatory effects. *Journal of Cellular and Molecular Medicine*. 2009;**13**(6):1125-1135. DOI: 10.1111/j.1582-4934.2008.00542.x
- [61] Wang Q, Liu D, Song P, Zou MH. Tryptophan-kynurenine pathway is dysregulated in inflammation, and immune activation. *Frontiers in Bioscience*. 2015b;**20**:1116-1143

- [62] Routy JP, Routy B, Graziani GM, Mehraj V. The kynurenine pathway is a Double-Edged sword in Immune-Privileged sites and in cancer: Implications for immunotherapy. *International Journal of Tryptophan Research*. 2016;**9**:67-77. DOI: 10.4137/IJTR.S38355
- [63] Moretti S, Menicali E, Voce P, Morelli S, Cantarelli S, Sponziello M, Colella R, Fallarino F, Orabona C, Alunno A, de Biase D, Bini V, Mameli MG, Filetti S, Gerli R, Macchiarulo A, Melillo RM, Tallini G, Santoro M, Puccetti P, Avenia N, Puxeddu E. Indoleamine 2,3-dioxygenase 1 (IDO1) is up-regulated in thyroid carcinoma and drives the development of an immunosuppressant tumor microenvironment. *The Journal of Clinical Endocrinology and Metabolism*. 2014;**99**(5):E832-E840. DOI: 10.1210/jc.2013-3351
- [64] Thaker AI, Rao MS, Bishnupuri KS, Kerr TA, Foster L, Marinshaw JM, Newberry RD, Stenson WF, Ciorba MA. IDO1 metabolites activate β -catenin signaling to promote cancer cell proliferation and colon tumorigenesis in mice. *Gastroenterology*. 2013;**145**(2):416-425. DOI: 10.1053/j.gastro.2013.05.002
- [65] Bostian AC, Eoff RL. Aberrant kynurenine signaling modulates DNA replication stress factors and promotes genomic instability in gliomas. *Chemical Research in Toxicology*. 2016;**29**(9):1369-1380. DOI: 10.1021/acs.chemrestox.6b00255
- [66] Heyes MP, Saito K, Milstien S, Schiff SJ. Quinolinic acid in tumors, hemorrhage and bacterial infections of the central nervous system in children. *Journal of the Neurological Sciences*. 1995;**133**(1-2):112-118
- [67] Di Serio C, Cozzi A, Angeli I, Doria L, Micucci I, Pellerito S, Mirone P, Masotti G, Moroni F, Tarantini F. Kynurenic acid inhibits the release of the neurotrophic fibroblast growth factor (FGF)-1 and enhances proliferation of glia cells, *in vitro*. *Cellular and Molecular Neurobiology*. 2005;**25**(6): 981-993. DOI: 10.1007/s10571-005-8469-y
- [68] Sahm F, Oezen I, Opitz CA, Radlwimmer B, von Deimling A, Ahrendt T, Adams S, Bode HB, Guillemin GJ, Wick W, Platten M. The endogenous tryptophan metabolite and NAD⁺ precursor quinolinic acid confers resistance of gliomas to oxidative stress. *Cancer Research*. 2013;**73**(11):3225-3234. DOI: 10.1158/0008-5472.CAN-12-3831
- [69] Pecorino L. 2012. *Molecular Biology of Cancer. Mechanisms, Targets and Therapeutics*. 3rd ed. Italy: Oxford University Press
- [70] Rabinovich GA, Gabrilovich D, Sotomayor EM. Immunosuppressive strategies that are mediated by tumor cells. *Annual Review of Immunology*. 2007;**25**:267-296. DOI: 10.1146/annurev.immunol.25.022106.141609
- [71] Dunn GP, Bruce AT, Ikeda H, Old LJ, Schreiber RD. Cancer immunoediting: From immunosurveillance to tumor escape. *Nature Immunology*. 2002;**3**(11):991-998. DOI: 10.1038/ni1102-991
- [72] Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting. *Annual Review of Immunology*. 2004;**22**:329-360. DOI: 10.1146/annurev.immunol.22.012703.104803
- [73] Yaguchi T, Kawakami Y. Cancer-induced heterogeneous immunosuppressive tumor microenvironments and their personalized modulation. *International Immunology*. 2016;**28**(8):393-399. DOI: 10.1093/intimm/dxw030

- [74] van Baren N, Van den Eynde BJ. Tumoral immune resistance mediated by enzymes that degrade tryptophan. *Cancer Immunology Research*. 2015;**3**(9):978-985. DOI: 10.1158/2326-6066.CIR-15-0095
- [75] Adams S, Teo C, McDonald KL, Zinger A, Bustamante S, Lim CK, Sundaram G, Braidy N, Brew BJ, Guillemin GJ. Involvement of the kynurenine pathway in human glioma pathophysiology. *PloS One*. 2014;**9**(11):e112945. DOI: 10.1371/journal.pone.0112945
- [76] Munn DH, Mellor AL. IDO in the tumor microenvironment: Inflammation, Counter-Regulation, and tolerance. *Trends in Immunology*. 2016;**37**(3):193-207. DOI: 10.1016/j.it.2016.01.002
- [77] Mellor AL, Munn DH. Tryptophan catabolism and T-cell tolerance: Immunosuppression by starvation? *Immunology Today*. 1999;**20**(10):469-473
- [78] Munn DH, Shafizadeh E, Attwood JT, Bondarev I, Pashine A, Mellor AL. Inhibition of T cell proliferation by macrophage tryptophan catabolism. *The Journal of Experimental Medicine*. 1999;**189**(9):1363-1372
- [79] Poormasjedi-Meibod MS, Jalili RB, Hosseini-Tabatabaei A, Hartwell R, Ghahary A. Immuno-regulatory function of indoleamine 2,3 dioxygenase through modulation of innate immune responses. *PloS One*. 2013;**8**(8):e71044. DOI: 10.1371/journal.pone.0071044
- [80] Jochems C, Fantini M, Fernando RI, Kwilas AR, Donahue RN, Lepone LM, Grenga I, Kim YS, Brechbiel MW, Gulley JL, Madan RA, Heery CR, Hodge JW, Newton R, Schlom J, Tsang KY. The IDO1 selective inhibitor epacadostat enhances dendritic cell immunogenicity and lytic ability of tumor antigen-specific T cells. *Oncotarget*. 2016;**7**(25):37762-37772. DOI: 10.18632/oncotarget.9326
- [81] Mezrich JD, Fechner JH, Zhang X, Johnson BP, Burlingham WJ, Bradfield CA. An interaction between kynurenine and the aryl hydrocarbon receptor can generate regulatory T cells. *Journal of Immunology*. 2010;**185**(6):3190-3198. DOI: 10.4049/jimmunol.0903670
- [82] Frumento G, Rotondo R, Tonetti M, Damonte G, Benatti U, Ferrara GB. Tryptophan-derived catabolites are responsible for inhibition of T and natural killer cell proliferation induced by indoleamine 2,3-dioxygenase. *The Journal of Experimental Medicine*. 2002;**196**(4):459-468
- [83] Terness P, Bauer TM, Röse L, Dufter C, Watzlik A, Simon H, Opelz G. Inhibition of allogeneic T cell proliferation by indoleamine 2,3-dioxygenase-expressing dendritic cells: Mediation of suppression by tryptophan metabolites. *The Journal of Experimental Medicine*. 2002;**196**(4):447-457
- [84] Belladonna ML, Puccetti P, Orabona C, Fallarino F, Vacca C, Volpi C, Gizzi S, Pallotta MT, Fioretti MC, Grohmann U. Immunosuppression via tryptophan catabolism: The role of kynurenine pathway enzymes. *Transplantation*. 2007;**84**(1 Suppl):S17-S20. DOI: 10.1097/01.tp.0000269199.16209.22
- [85] Zaher SS, Germain C, Fu H, Larkin DF, George AJ. 3-hydroxykynurenine suppresses CD4⁺ T-cell proliferation, induces T-regulatory-cell development, and prolongs corneal

- allograft survival. *Investigative Ophthalmology and Visual Science*. 2011;**52**(5):2640-2648. DOI: 10.1167/iovs.10-5793
- [86] Ninomiya S, Narala N, Huye L, Yagyu S, Savoldo B, Dotti G, Heslop HE, Brenner MK, Rooney CM, Ramos CA. Tumor indoleamine 2,3-dioxygenase (IDO) inhibits CD19-CAR T cells and is downregulated by lymphodepleting drugs. *Blood*. 2015;**125**(25):3905-3916. DOI: 10.1182/blood-2015-01-621474
- [87] Ochs K, Sahm F, Opitz CA, Lanz TV, Oezen I, Couraud PO, von Deimling A, Wick W, Platten M. Immature mesenchymal stem cell-like pericytes as mediators of immunosuppression in human malignant glioma. *Journal of Neuroimmunology*. 2013;**265**(1-2):106-116. DOI: 10.1016/j.jneuroim.2013.09.011
- [88] Ling W, Zhang J, Yuan Z, Ren G, Zhang L, Chen X, Rabson AB, Roberts AI, Wang Y, Shi Y. Mesenchymal stem cells use IDO to regulate immunity in tumor microenvironment. *Cancer Research*. 2014;**74**(5):1576-1587. DOI: 10.1158/0008-5472.CAN-13-1656
- [89] Vacchelli E, Aranda F, Eggermont A, Sautès-Fridman C, Tartour E, Kennedy EP, Platten M, Zitvogel L, Kroemer G, Galluzzi L. Trial watch: IDO inhibitors in cancer therapy. *Oncoimmunology*. 2014;**3**(10):e957994. DOI: 10.4161/21624011.2014.957994
- [90] Kimelberg HK. The problem of astrocyte identity. *Neurochemistry International*. 2004;**45**(2-3):191-202. DOI: 10.1016/j.neuint.2003.08.015
- [91] Matyash V, Kettenmann H. Heterogeneity in astrocyte morphology and physiology. *Brain Research Reviews*. 2010;**63**(1-2):2-10. DOI: 10.1016/j.brainresrev.2009.12.001
- [92] American Brain Tumor Association. Astrocytoma [Internet]. 2017. Available from: <http://www.abta.org/brain-tumor-information/types-of-tumors/astrocytoma.html> [Accessed: 16-February-2017]
- [93] American Brain Tumor Association. Glioblastoma [Internet]. 2017. Available from: <http://www.abta.org/brain-tumor-information/types-of-tumors/glioblastoma.html> [Accessed: 16-February-2017]
- [94] Ostrom QT, Gittleman H, Farah P, Ondracek A, Chen Y, Wolinsky Y, Stroup NE, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: Primary brain and central nervous system tumors diagnosed in the United States in 2006-2010. *Neuro-oncology*. 2013;**15**(Suppl 2):ii1-ii56. DOI: 10.1093/neuonc/not151
- [95] Thakkar JP, Dolecek TA, Horbinski C, Ostrom QT, Lightner DD, Barnholtz-Sloan JS, Villano JL. Epidemiologic and molecular prognostic review of glioblastoma. *Cancer Epidemiology, Biomarkers & Prevention: A publication of the American Association of Cancer Research, cosponsored by the American Society of Preventive Oncology*. 2014;**23**(10):1985-1996. DOI: 10.1158/1055-9965.EPI-14-0275
- [96] MacDonald TJ, Aguilera D, Kramm CM. Treatment of high-grade glioma in children and adolescents. *Neuro-oncology*. 2011;**13**(10):1049-1058. DOI: 10.1093/neuonc/nor092

- [97] Fangusaro J. Pediatric high grade glioma: A review and update on tumor clinical characteristics and biology. *Frontiers in Oncology*. 2012;**2**:105. DOI: 10.3389/fonc.2012.00105
- [98] Song KS, Phi JH, Cho BK, Wang KC, Lee JY, Kim DG, Kim IH, Ahn HS, Park SH, Kim SK. Long-term outcomes in children with glioblastoma. *Journal of Neurosurgery. Pediatrics*. 2010;**6**(2):145-149. DOI: 10.3171/2010.5.PEDS09558
- [99] Dana Farber Cancer Institute [Internet]. 2017. Available from: <http://www.dana-farber.org/Adult-Care/Treatment-and-Support/Glioblastoma.aspx> [Accessed: February 20, 2017]
- [100] Simpson JR, Horton J, Scott C, Curran WJ, Rubin P, Fischbach J, Isaacson S, Rotman M, Asbell SO, Nelson JS, Weinstein AS, Nelson DF. Influence of location and extent of surgical resection on survival of patients with glioblastoma multiforme: Results of three consecutive Radiation Therapy Oncology Group (RTOG) clinical trials. *International Journal of Radiation Oncology, Biology, Physics*. 1993;**26**(2):239-244
- [101] Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E, Mirimanoff RO. European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups; National Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *The New England Journal of Medicine*. 2005;**352**(10):987-996. DOI: 10.1056/NEJMoa043330
- [102] Mahvash M, Hugo HH, Maslehaty H, Mehdorn HM, Stark AM. Glioblastoma multiforme in children: Report of 13 cases and review of the literature. *Pediatric Neurology*. 2011;**45**(3):178-180. DOI: 10.1016/j.pediatrneurol.2011.05.004
- [103] Verhaak RG, Hoadley KA, Purdom E, Wang V, Qi Y, Wilkerson MD, Miller CR, Ding L, Golub T, Mesirov JP, Alexe G, Lawrence M, O'Kelly M, Tamayo P, Weir BA, Gabriel S, Winckler W, Gupta S, Jakkula L, Feiler HS, Hodgson JG, James CD, Sarkaria JN, Brennan C, Kahn A, Spellman PT, Wilson RK, Speed TP, Gray JW, Meyerson M, Getz G, Perou CM, Hayes DN. Cancer Genome Atlas Research Network. Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. *Cancer Cell*. 2010;**17**(1):98-110. DOI: 10.1016/j.ccr.2009.12.020
- [104] Herwig S, Strauss M. The retinoblastoma protein: A master regulator of cell cycle, differentiation and apoptosis. *European Journal of Biochemistry*. 1997;**246**(3):581-601
- [105] Urbańska K, Sokołowska J, Szmidt M, Sysa P. Glioblastoma multiforme — An overview. *Contemporary Oncology*. 2014;**18**(5):307-312. DOI: 10.5114/wo.2014.40559
- [106] Linkous AG, Yazlovitskaya EM. Angiogenesis in glioblastoma multiforme: Navigating the maze. *Anti-cancer Agents in Medicinal Chemistry*. 2011;**11**(8):712-718

- [107] Forrester JV, Xu H, Lambe T, Cornall R. Immune privilege or privileged immunity? *Mucosal Immunology*. 2008;**1**(5):372-381. DOI: 10.1038/mi.2008.27
- [108] Loveau A, Harris TH, Kipnis J. Revisiting the concept of CNS immune privilege. *Trends in Immunology*. 2015;**36**(10):569-577. DOI: 10.1016/j.it.2015.08.006
- [109] Razavi SM, Lee KE, Jin BE, Aujla PS, Gholamin S, Li G. Immune evasion strategies of glioblastoma. *Frontiers in Surgery*. 2016;**3**:11. DOI: 10.3389/fsurg.2016.00011
- [110] Galea I, Bernardes-Silva M, Forse PA, van Rooijen N, Liblau RS, Perry VH. An antigen-specific pathway for CD8 T cells across the blood-brain barrier. *The Journal of Experimental Medicine*. 2007;**204**(9):2023-2030. DOI: 10.1084/jem.20070064
- [111] Woodworth GF, Dunn GP, Nance EA, Hanes J, Brem H. Emerging insights into barriers to effective brain tumor therapeutics. *Frontiers in Oncology*. 2014;**4**:126. DOI: 10.3389/fonc.2014.00126
- [112] Gorbachev, AV, Kobayashi H, Kudo D, Tannenbaum CS, Finke JH, Shu S, Farber JM, Fairchild RL. CXCL chemokine ligand 9/monokine induced by IFN- γ production by tumor cells is critical for T cell-mediated suppression of cutaneous tumors. *Journal of Immunology*. 2007;**178**(4):2278-2286
- [113] Sakai K, Shimodaira S, Maejima S, Udagawa N, Sano K, Higuchi Y, Koya T, Ochiai T, Koide M, Uehara S, Nakamura M, Sugiyama H, Yonemitsu Y, Okamoto M, Hongo K. Dendritic cell-based immunotherapy targeting Wilms' tumor 1 in patients with recurrent malignant glioma. *Journal of Neurosurgery*. 2015;**123**(4):989-997. DOI: 10.3171/2015.1.JNS141554
- [114] Yang I, Han SJ, Sughrue ME, Tihan T, Parsa AT. Immune cell infiltrate differences in pilocytic astrocytoma and glioblastoma: Evidence of distinct immunological microenvironments that reflect tumor biology. *Journal of Neurosurgery*. 2011;**115**(3):505-511. DOI: 10.3171/2011.4.JNS101172
- [115] Prins RM, Soto H, Konkankit V, Odesa SK, Eskin A, Yong WH, Nelson SF, Liao LM. Gene expression profile correlates with T-cell infiltration and relative survival in glioblastoma patients vaccinated with dendritic cell immunotherapy. *Clinical Cancer Research*. 2011;**17**(6):1603-1615. DOI: 10.1158/1078-0432.CCR-10-2563
- [116] Prins RM, Wang X, Soto H, Young E, Lisiero DN, Fong B, Everson R, Yong WH, Lai A, Li G, Cloughesy TF, Liao LM. Comparison of glioma-associated antigen peptide-loaded versus autologous tumor lysate-loaded dendritic cell vaccination in malignant glioma patients. *Journal of Immunotherapy*. 2013;**36**(2):152-157. DOI: 10.1097/CJI.0b013e3182811ae4
- [117] Schmittling RJ, Archer GE, Mitchell DA, Heimberger A, Pegram C, Herndon JE 2nd, Friedman HS, Bigner DD, Sampson JH. Detection of humoral response in patients with glioblastoma receiving EGFRvIII-KLH vaccines. *Journal of Immunological Methods*. 2008;**339**(1):74-81. DOI: 10.1016/j.jim.2008.08.004

- [118] Fadul CE, Fisher JL, Hampton TH, Lallana EC, Li Z, Gui J, Szczepiorkowski ZM, Tosteson TD, Rhodes CH, Wishart HA, Lewis LD, Ernstoff MS. Immune response in patients with newly diagnosed glioblastoma multiforme treated with intranodal autologous tumor lysate-dendritic cell vaccination after radiation chemotherapy. *Journal of Immunotherapy*. 2011;**34**(4):382-389. DOI: 10.1097/CJI.0b013e318215e300. DOI: 10.1097/CJI.0b013e318215e300
- [119] Sampson JH, Heimberger AB, Archer GE, Aldape KD, Friedman AH, Friedman HS, Gilbert MR, Herndon 2nd JE, McLendon RE, Mitchell DA, Reardon DA, Sawaya R, Schmittling RJ, Shi W, Vredenburgh JJ, Bigner DD. Immunologic escape after prolonged progression-free survival with epidermal growth factor receptor variant III peptide vaccination in patients with newly diagnosed glioblastoma. *Journal of Clinical Oncology*. 2010;**28**(31):4722-2729. DOI: 10.1200/JCO.2010.28.6963. DOI: 10.1200/JCO.2010.28.6963
- [120] Sampson JH, Aldape KD, Archer GE, Coan A, Desjardins A, Friedman AH, Friedman HS, Gilbert MR, Herndon JE, McLendon RE, Mitchell DA, Reardon DA, Sawaya R, Schmittling R, Shi W, Vredenburgh JJ, Bigner DD, Heimberger AB. Greater chemotherapy-induced lymphopenia enhances tumor-specific immune responses that eliminate EGFRvIII-expressing tumor cells in patients with glioblastoma. *Neuro-oncology*. 2011;**13**(3):324-333. DOI: 10.1093/neuonc/noq157
- [121] Huettner C, Palaus W, Roggendorf W. Messenger RNA expression of the immunosuppressive cytokine IL-10 in human gliomas. *American Journal of Pathology*. 1995;**146**(2):317-322
- [122] Yang I, Han SJ, Kaur G, Crane C, Parsa AT. The role of microglia in central nervous system immunity and glioma immunology. *Journal of Clinical Neuroscience*. 2010;**17**(1):6-10. DOI: 10.1016/j.jocn.2009.05.006
- [123] Badie B, Schartner J, Prabakaran S, Paul J, Vorpahl J. Expression of Fas ligand by microglia: Possible role in glioma immune evasion. *Journal of Neuroimmunology*. 2001;**120**(1-2):19-24
- [124] Hao C, Parney IF, Roa WH, Turner J, Petruk KC, Ramsay DA. Cytokine and cytokine receptor mRNA expression in human glioblastomas: Evidence of Th1, Th2 and Th3 cytokine dysregulation. *Acta Neuropathologica*. 2002;**103**(2):171-178. DOI: 10.1007/s004010100448
- [125] Jackson C, Ruzevick J, Phallen J, Belcaid Z, Lim M. Challenges in immunotherapy presented by the glioblastoma multiforme microenvironment. *Clinical and Developmental Immunology*. 2011;**2011**:732413. DOI: 10.1155/2011/732413
- [126] Parney IF, Farr-Jones MA, Chang LJ, Petruk KC. Human glioma immunobiology *in vitro*: Implications for Immunogene Therapy. *Neurosurgery*. 2000;**46**(5):1169-1177
- [127] Fontana A, Kristensen F, Dubs R, Gemsa D, Weber E. Production of prostaglandin E and an interleukin-1 like factor by cultured astrocytes and C6 glioma cells. *Journal of Immunology*. 1982;**129**(6):2413-2419

- [128] Siepl C, Bodmer S, Frei K, MacDonald HR, De Martin R, Hofer E, Fontana A. The glioblastoma-derived T cell suppressor factor/transforming growth factor-beta 2 inhibits T cell growth without affecting the interaction of interleukin 2 with its receptor. *European Journal of Immunology*. 1988;**18**(4):593-600. DOI: 10.1002/eji.1830180416
- [129] Kuppner MC, Hamou MF, Sawamura Y, Bodmer S, de Tribolet N. Inhibition of lymphocyte function by glioblastoma-derived transforming growth factor beta 2. *Journal of Neurosurgery*. 1989;**71**(2):211-217. DOI: 10.3171/jns.1989.71.2.0211
- [130] Wischhusen J, Jung G, Radovanovic I, Beier C, Steinbach JP, Rimner A, Huang H, Schulz JB, Ohgaki H, Aguzzi A, Rammensee HA, Weller M. Identification of CD70-mediated apoptosis of immune effector cells as a novel immune escape pathway of human glioblastoma. *Cancer Research*. 2002;**62**(9):2592-2599
- [131] Chahlavi A, Rayman P, Richmond AL, Biswas K, Zhang R, Vogelbaum M, Tannenbaum C, Barnett G, Finke JH. Glioblastomas induce T-lymphocyte death by two distinct pathways involving gangliosides and CD70. *Cancer Research*. 2005;**65**(12):5428-5438. DOI: 10.1158/0008-5472.CAN-04-4395
- [132] Weathers SP, de Groot J. VEGF manipulation in glioblastoma. *Oncology (Williston Park)*. 2015;**29**(10):720-727
- [133] Lin EY, Li JF, Gnatovskiy L, Deng Y, Zhu L, Grzesik DA, Qian H, Xue XN, Pollard JW. Macrophages regulate the angiogenic switch in a mouse model of breast cancer. *Cancer Research*. 2006;**66**(23):11238-11246. DOI: 10.1158/0008-5472.CAN-06-1278
- [134] Wainwright DA, Balyasnikova IV, Chang AL, Ahmed AU, Moon KS, Auffinger B, Tobias AL, Han Y, Lesniak MS. IDO expression in brain tumors increases the recruitment of regulatory T cells and negatively impacts survival. *Clinical Cancer Research*. 2012;**18**(22):6110-6121. DOI: 10.1158/1078-0432.CCR-12-2130
- [135] Mitsuka K, Kawataki T, Satoh E, Asahara T, Horikoshi T, Kinouchi H. Expression of indoleamine 2,3-dioxygenase and correlation with pathological malignancy in gliomas. *Neurosurgery*. 2013;**72**(6):1031-1038. DOI: 10.1227/NEU.0b013e31828cf945
- [136] Zhai L, Dey M, Lauing KL, Gritsina G, Kaur R, Lukas RV, Nicholas MK, Rademaker AW, Dostal CR, McCusker RH, Raizer JJ, Parsa AT, Bloch O, Wainwright DA. The kynurenine to tryptophan ratio as a prognostic tool for glioblastoma patients enrolling in immunotherapy. *Journal of Clinical Neuroscience*. 2015a;**22**(12):1964-1968. DOI: 10.1227/NEU.0b013e31828cf945
- [137] Friberg M, Jennings R, Alsarraj M, Dessureault S, Cantor A, Extermann M, Mellor AL, Munn DH, Antonia SJ. Indoleamine 2,3-dioxygenase contributes to tumor cell evasion of T cell-mediated rejection. *International Journal of Cancer*. 2002;**101**(2):151-155. DOI: 10.1002/ijc.10645
- [138] Uyttenhove C, Pilotte L, Théate I, Stroobant V, Colau D, Parmentier N, Boon T, Van den Eynde BJ. Evidence for a tumoral immune resistance mechanism based on tryptophan

- degradation by indoleamine 2,3-dioxygenase. *Nature Medicine*. 2003;**9**(10):1269-1274. DOI: 10.1038/nm934
- [139] Iversen TZ, Engell-Noerregaard L, Ellebaek E, Andersen R, Larsen SK, Bjoern J, Zeyher C, Gouttefangeas C, Thomsen BM, Holm B, Thor Straten P, Mellemgaard A, Andersen MH, Svane IM. Long-lasting disease stabilization in the absence of toxicity in meta-static lung cancer patients vaccinated with an epitope derived from indoleamine 2,3 dioxygenase. *Clinical Cancer Research*. 2014;**20**(1):221-232. DOI: 10.1158/1078-0432.CCR-13-1560
- [140] A Phase 2 Study of the IDO Inhibitor INCB024360 Versus Tamoxifen for Subjects With Biochemical-recurrent-only EOC, PPC or FTC Following Complete Remission With First-line Chemotherapy [Internet]. 2017. Available from: <https://clinicaltrials.gov/ct2/show/NCT01685255?term=NCT01685255&rank=1> [Accessed: February 25, 2017]
- [141] Vaccination with Peptides in Combination with Either Ipilimumab or Vemurafenib for the Treatment of Unresectable Stage III or IV Malignant Melanoma [Internet]. 2017. Available from: <https://clinicaltrials.gov/ct2/show/NCT02077114?term=NCT02077114&rank=1> [Accessed: February 25, 2017]
- [142] Li M, Bolduc AR, Hoda MN, Gamble DN, Dolisca SB, Bolduc AK, Hoang K, Ashley C, McCall D, Rojiani AM, Maria BL, Rixe O, MacDonald TJ, Heeger PS, Mellor AL, Munn DH, Johnson TS. The indoleamine 2,3-dioxygenase pathway controls complement-dependent enhancement of chemo-radiation therapy against murine glioblastoma. *Journal of Immunotherapy for Cancer*. 2014;**2**:21. DOI: 10.1186/2051-1426-2-21
- [143] Hanihara M, Kawataki T, Oh-Oka K, Mitsuka K, Nakao A, Kinouchi H. Synergistic antitumor effect with indoleamine 2,3-dioxygenase inhibition and temozolomide in a murine glioma model. *Journal of Neurosurgery*. 2016;**124**(6):1594-1601. DOI: 10.3171/2015.5.JNS141901
- [144] Zhai L, Spranger S, Binder DC, Gritsina G, Lauing KL, Giles FJ, Wainwright DA. Molecular pathways: Targeting IDO1 and other tryptophan dioxygenases for cancer immunotherapy. *Clinical Cancer Research*. 2015b;**21**(24):5427-5433. DOI: 10.1158/1078-0432.CCR-15-0420
- [145] Antonios JP, Soto H, Everson RG, Moughon D, Orpilla JR, Shin NP, Sedighim S, Treger J, Odesa S, Tucker A, Yong WH, Li G, Cloughesy TF, Liao LM, Prins RM. Immunosuppressive tumor-infiltrating myeloid cells mediate adaptive immune resistance via a PD-1/PD-L1 mechanism in glioblastoma. *Neuro-oncology*. 2017;**19**(6): 796-807.
- [146] Zhai L, Ladomersky E, Dostal CR, Lauing KL, Swoap K, Billingham LK, Gritsina G, Wu M, McCusker RH, Binder DC, Wainwright DA. Non-tumor cell IDO1 predominantly contributes to enzyme activity and response to CTLA-4/PD-L1 inhibition in mouse glioblastoma. *Brain, Behavior, and Immunity*. 2017. **62**:S0889-1591(17)30020-X. DOI: 10.1016/j.bbi.2017.01.022