Review

The Kynurenine Pathway in Brain Tumor Pathogenesis

Seray Adams3,5, Nady Braidy1,2, Alban Bessesde1, Bruce J. Brew4,5, Ross Grant1,7, Charlie Teo6, and Gilles J. Guillemin1,5,7

Abstract

Brain tumors are among the most common and most chemoresistant tumors. Despite treatment with aggressive treatment strategies, the prognosis for patients harboring malignant gliomas remains dismal. The kynurenine pathway (KP) is the principal route of l-tryptophan catabolism leading to the formation of the essential pyridine nucleotide, nicotinamide adenine dinucleotide (NAD+), and important neuroactive metabolites, including the neurotoxin, quinolinic acid (QUIN), the neuroprotective agent, picolinic acid (PIC), the T↓3/↑7creg balance modulator, 3-hydroxanthranilic acid (3-HAA), and the immunosuppressive agent, L-Kynurenine (KYN). This review provides a new perspective on KP dysregulation in defeating antitumor immune responses, specifically bringing light to the lower segment of the KP, particularly QUIN-induced neurotoxicity and downregulation of the enzyme α-amino-β-carboxymuconate-ε-semialdehyde decarboxylase (ACMSD) as a potential mechanism of tumor progression. Given its immunosuppressive effects, 3-HAA produced from the KP may also play a role in suppressing antitumor immunity in human tumors. The enzyme indoleamine 2, 3-dioxygenase (IDO-1) initiates and regulates the first step of the KP in most cells. Mounting evidence directly implicates that the induction and overexpression of IDO-1 in various tumors is a crucial mechanism facilitating tumor immune evasion and persistence. Tryptophan 2, 3-dioxygenase (TDO-2), which initiates the same first step of the KP as IDO-1, has likewise recently been shown to be a mechanism of tumoral immune resistance. Further, it was also recently shown that TDO-2-dependent production of KYN by brain tumors might be a novel mechanism for suppressing antitumor immunity and supporting tumor growth through the activation of the Aryl hydrocarbon receptor (AhR). This newly identified TDO-2-KYN-AhR signaling pathway opens up exciting future research opportunities and may represent a novel therapeutic target in cancer therapy. Our discussion points to a number of KP components, namely TDO-2, IDO-1, and ACMSD, as important therapeutic targets for the treatment of brain cancer. Targeting the KP in brain tumors may represent a viable strategy likely to prevent QUIN-induced neurotoxicity and KYN and 3-HAA-mediated immune suppression. Cancer Res; 72(22); 5649-57. ©2012 AACR.

Introduction

Primary brain tumors are the most common form of solid malignancy among children (1), and the second leading cause of cancer death in males under 29 years of age and females under 20 years of age (2). As such, they are among the leading causes of cancer-related morbidity and mortality during childhood. Glioblastoma multiforme (GBM) is, by far, the most prevalent and most malignant type of primary brain tumor in adults (3). It is an aggressive tumor that progresses rapidly; the median survival of patients with GBM is approximately 14.6 months (4). Despite technological advancements on all fronts of neurological practice, the prognosis for patients with malignant gliomas remains dismal (5). The poor prognosis for patients with malignant gliomas and the lack of effective therapies highlight the importance of developing novel pharmacologic therapies with greater clinical efficacy than those that are currently available. During tumor development, malignant cells evolve to a state in which they have the capacity for immune escape (6). Ultimately, mechanisms of immune escape enable the evasion and/or suppression of the immune response that tumor antigens elicit, which is central to tumor survival, growth, local invasion, and metastasis (6, 7). Establishing the importance of immune escape to malignant progression has been a relatively recent development. Although several contributing mechanisms have been identified, one that has received a considerable amount of attention during the past decade is tryptophan catabolism via the kynurenine pathway (KP; ref. 8).

This review will focus on the contribution KP dysregulation has to cancer progression through the action of preventing effective antitumor immune responses, particularly in the context of brain tumors. This review will also highlight the immunomodulatory function of IDO-1 and TDO-2 in primary
glioblastomas. Elucidating these particular mechanisms used by high-grade brain tumors is an important direction of future research, which may highlight novel therapeutic targets that exploit the dysregulated state of KP metabolism.

The Kynurenine Pathway

Tryptophan is an essential amino acid. Its catabolism is accurately controlled by a number of metabolic pathways. Within the CNS, the KP is responsible for 95% of daily L-tryptophan turnover (9). As the major route of L-tryptophan catabolism, KP metabolism leads to the production of the essential pyridine nucleotide NAD⁺, and a number of neuroactive metabolites, including kynurenine (KYN), kynurenic acid (KYNA), the neurotoxic free-radical generator 3-hydroxykynurenine (3-HK), anthranilic acid, 3-HAA, picolinic acid (PIC), and the excitatory N-methyl-D-aspartate (NMDA) receptor agonist and neurotoxin, QUIN (Fig. 1; ref. 10).

The branch point in KP metabolism between complete tryptophan catabolism and NAD⁺ biosynthesis takes place at the intermediate 2-aminocarboxymuconate semialdehyde (ACMS; Fig. 1; ref. 11). ACMSD is the rate-limiting enzyme for PIC production (11). Nonenzymatic rearrangement of ACMS occurs when ACMSD is saturated with substrate allowing the production of QUIN. Under normal physiologic conditions, these 2 pathways control equal flux (12). ACMSD is therefore a key enzyme directing KP metabolism towards PIC production and is expressed at a ratio of 1:300:30:1 in human kidney, liver, and brain, respectively (13).

In mammals, 3 different haem-enzymes catalyze the first, rate-limiting step in the catabolism of tryptophan via the KP to produce N-formylkynurenine (NFK); tryptophan 2,3-dioxygenase (TDO-2), indoleamine 2,3-dioxygenase (IDO-1), and the recently discovered IDO-related enzyme, IDO-2 (or INDOL1; ref. 14; Fig. 1). The enzyme formylkynurenine formamidase (FKF) rapidly converts NFK to KYN (15). The release of the proinflammatory cytokine, IFN-γ, represents the most potent inducer of IDO-1, switching on gene expression and activity (16). Structurally similar to IDO-1, IDO-2 is encoded by a gene downstream of the IDO-1 gene (14). TDO-2, which is primarily expressed within the liver (17–19), but also expressed in a variety of other tissues including the brain (18, 20–23), catalyzes the majority of dietary tryptophan for the maintenance of basal serum levels (24) and is induced by the availability of dietary tryptophan as well as tyrosine, histidine, glucocorticoids, and kynurenine (25, 26).

Involvement of the KP in neurotoxicity

In addition to its participation in tryptophan and NAD⁺ homeostasis, the KP generates a number of biologically active intermediate metabolites (27). Of these neuroactive KP metabolites, QUIN is likely to represent the most important in terms of bioactivity. QUIN has been implicated in the pathogenesis of a number of neurodegenerative and neuroinflammatory disorders, including the HIV-associated dementia (HAD), Alzheimer disease, Huntington disease, amyotrophic lateral sclerosis, and multiple sclerosis. QUIN has been shown to induce neuronal death in indirect intracerebral administration and in neuronal cell cultures. Similarly, chronic exposure to submicromolar concentrations of QUIN on neurons produces an adverse effect. QUIN is also known to promote oligodendrocyte and astrocytic apoptosis at pathophysiologic concentrations (reviewed in ref. 28).

The mechanisms of QUIN-induced neuronal toxicity are multifactorial. These have been well reviewed elsewhere (reviewed in ref. 28). Briefly, one mechanism for QUIN-induced toxicity in human neurons is related to NMDA receptor overactivation with subsequent excessive free-radical-mediated damage, namely mitochondrial dysfunction, DNA damage, PARP activation, and subsequent NAD⁺ depletion. NMDA receptor activation, followed by excess free-radical production, is also a primary mechanism for QUIN-associated toxicity in human astrocytes, which is a relatively recent finding. The production of reactive oxygen species (ROS) has also been shown to mediate lipid peroxidation. QUIN can also inhibit glutamate uptake into the synaptic vesicle, which leads to excessive microenvironment glutamate concentrations and neurotoxicity (reviewed in ref. 28).

In contrast to the neurotoxic activity of QUIN, KYNA, and PIC exhibit neuroprotective effects. As an endogenous neuroprotectant, KYNA at low concentrations acts as an antagonist to QUIN by blocking NMDA receptor function through its action on the glycine modulatory site of the NMDA receptor (29). At higher concentrations, it acts at the glutamate site of the NMDA receptor (29). PIC also contributes to brain homeostasis by similarly blocking the neurotoxic effects of QUIN (30). However, it has been suggested that the constitutive synthesis of PIC is overwhelmed by de novo QUIN production during neuroinflammation (31). Neurotoxicity would then negate these neuroprotective effects. The exact mechanism by which neuroprotection occurs is unclear, as PIC does not seem to interfere with the glutamate/NMDA binding site on the NMDA receptor (32). Thus, a highly regulated balance in the production of QUIN, PIC, and KYNA is required for normal neuronal function.

IDO-1–Mediated Immune–Immune Evasion

An increasing body of experimental data in the last decade supports a major role of IDO-1 induction and overexpression in the facilitation of immune–immune evasion. IDO-1 expression has been proposed to create an immunosuppressive microenvironment through the action of 2 mechanisms, tryptophan depletion and by accumulating tryptophan toxic metabolites. These mechanisms have been well reviewed elsewhere (33–35). It seems probable that the tryptophan depletion, and tryptophan-derived apoptotic and immunosuppressive metabolites pathways may not be mutually exclusive, and function synergistically, each possibly differentiated for specific T-cell subtypes and all concurring to produce an overall immune-suppressive effect (36).

Briefly, IDO-1-mediated depletion of tryptophan from the tissue microenvironment or culture medium has been shown to suppress T-cell proliferation (37–39). With regard to the immunosuppressive effects of specific metabolites, KYN, PIC (40), 3-HK, and 3-HAA (41) in micromolar concentrations were found to inhibit T-cell proliferation in vitro. Furthermore, it was shown that 3-HAA and QUIN induced selective apoptosis of murine thymocytes and of antigen-specific CD4⁺ T-helper 1
(TH1) cells both in vitro and in vivo (41). Another notable effect 3-HAA has on T cells is its ability to cause a reduction in CD4\(^{+}\) TH17 cells and a reciprocal increase in the fraction of Tregs (42). The loss of TH17/Treg balance was suggested to be mediated directly by 3-HAA from IDO-1 induction by myeloid antigen-presenting dendritic cells (DC; ref. 42). Furthermore, an intriguing developmental link also exists between IDO-1 expression and Treg differentiation. In vitro studies have indicated that IDO-1 expression by DCs can also promote the differentiation of new Tregs from naive CD4\(^{+}\) T cells (43). In addition, Tregs can trigger high levels of functional IDO-1 expression in mouse DCs in vitro. If these observations are shown in vivo, however, then IDO-1, 3-HAA, and Tregs would be revealed as a closely coupled positive-feedback system. 3-HAA production may likely play a significant role in suppressing effective antiimmune immunity in human tumors. Furthermore, Tregs are emerging as a key component of acquired tolerance to tumors (44). Increased Treg activity facilitates immune growth (45), whereas depletion of Tregs allows effective antitumor immune responses to occur (reviewed in ref. 46). Thus, the inhibitory potential of tumor-infiltrating Tregs has been discussed as a very effective pathway of tumor-driven immune evasion (47).

IDO-1 expression has been observed in a variety of cancer cell types with or without IFN-\(\gamma\) stimulation (8). IDO-1 overexpression has been shown to be a powerful predictor of poor clinical prognosis in patients with various cancers (48). In a series of experiments, Uyttenhove and colleagues (8) provided

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**Figure 1.** Schematic diagram of tryptophan catabolism along the KP.

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strong evidence for the immunosuppressive role of IDO-1 in tumor cells. The majority of preimmunized mice injected with IDO-1–expressing P815B cells (mastocytoma cell line) developed progressive tumors and died. In contrast, most preimmunized mice injected with P815B cells not expressing IDO-1 completely rejected the tumor challenge. These results suggest that IDO-1 expression plays a pivotal role in the inhibition of tumor-specific immunity (8).

IDO-1 induction in the hosts antigen-presenting cells (APC), namely the IDO-1–expressing DCs, has been proposed as another mechanism for inducing tumor-immune tolerance, through suppressing, or energizing reactive T cells responding to tumor antigens (48). Extensive literature confirms this hypothesis (reviewed in ref. 49).

**IDO-1/IDO-2–Mediated Tumor-Immune Evasion—Relevance to Brain Tumor Persistence**

Despite the previously described observations, several questions regarding the mechanism of IDO-1–mediated tumor evasion remain unanswered. First, are the previously discussed observations limited to systemic tumors and brain tumor cell lines, that is, is IDO-1 overexpression characteristic of primary glioblastoma or other brain tumors for that matter and would this reflect clinical prognosis? Second, can IDO-1 expression in brain tumors suppress antitumor immunity in the brain? Answers to these questions are crucial to understanding brain tumor-immune evasion, whereby IDO-1 may provide a powerful driver of malignant progression. The application of the "IDO-1–dependent tumor-immune escape" hypothesis (50) to the study of human brain tumors, particularly malignant glioma, thus warrants further investigation.

In the following section, we present a hypothetical model where IDO-1 expression in brain tumors is postulated as a possible immune escape mechanism. To conceptualize this model, we review normal antitumor immune responses in the brain and discuss whether the IDO-1–driven tolerance mechanisms seen in systemic tumors could potentially have a role in defeating antitumor immunity in brain tumors.

**Initiation of antitumor immune responses: key mechanisms and those applicable to the brain**

It is now well accepted that the CNS is an "immunologically specialized" site that is unable to initiate immune responses efficiently, rather than a site that is completely devoid of effector immune responses altogether (51). At later stages of tumor growth, when massive tissue damage with destruction of the blood–brain barrier and antigen drainage to the periphery occurs, brain tumors become accessible to the peripheral immune system (52). In this case, albeit to varying degrees, immune cell infiltrates can regularly be found within malignant gliomas (52) and other CNS malignancies (53). Perrin and colleagues (54) have also provided evidence for immune responses to CNS malignancies, showing the presence of significant T-cell clonal expansion in the tumor bed of a large series of astrocytomas. These T-cell clones were almost exclusively confined to the CD8⁺ subset (54). However, the findings of this study raise the question as to the exact function and specificity of the infiltrating CD8⁺ T cells. Are these inflammatory cells recruited to the tumor site, but not specific for any locally expressed antigen? CNS antigens have been detected in the cervical nymphp node (55). However, it is unclear whether these antigens passively drain into the lymph nodes or whether perivascular macrophages or DC populations within CNS sites capture and actively transport the antigen to the cervical lymph node (55). In the absence of a definition of the specificity and function of brain tumor–infiltrating T cells, the significance of these findings remains unclear. Indeed, over the past 3 decades, many defects have been reported in the functional status of T cells in patients with brain tumor, concerning circulating T cells as well as those infiltrating the tumor (56). Particularly, in patients with astrocytoma, low numbers of circulating T cells and impaired T-cell cytotoxicity is found (reviewed in ref. 56).

Constitutive IDO-1 expression has been shown in 9 of 10 human glioblastoma biopsies (8) and in brain tumor cell lines (50). It is also known that IDO-1 activity in human glial and malignant glioma cell lines is increased by IFN-γ (50). Thus, expression of IDO-1 in brain tumor cells is likely to be triggered when IFN-γ is produced from activated T cells and/or microglia and neurons. Furthermore, gliomas and glioneuronal tumors have an elevated tryptophan uptake and catabolism in vivo (57). Miyazaki and colleagues showed that in several cultured human malignant glioma cell lines, exposure to IFN-γ significantly decreased the levels of l-tryptophan in the culture medium concomitant with greatly increased IDO-1 expression. They also showed that the IDO-1 inhibitor 1-methyl-tryptophan (1-MT) effectively prevented l-tryptophan depletion (50).

Another mechanism for facilitating tumor-immune escape has recently emerged and involves the generation of KYN by TDO-2 activation (58). Opitz and colleagues showed that TDO-2 is frequently activated and constitutively expressed in gliomas and also identified KYN, which is constitutively generated by human tumor cells via TDO-2 and not IDO-1 and IDO-2, as an endogenous ligand for the human aryl hydrocarbon receptor (AhR; ref. 58). TDO-2–derived KYN was shown to suppress antitumor immune responses and promote tumor-cell survival and motility through the AhR in an autocrine manner. These results suggest that the TDO-2-KYN-AhR signaling pathway might dynamically modulate inflammation and immunity (59). These findings have profound implications for cancer and immune biology as they are the first to implicate TDO-2 in cancer biology. The TDO-2-KYN-AhR signaling pathway may represent a novel therapeutic target in cancer therapy.

A recent study further provides strong evidence for the immunosuppressive role of TDO-2 in tumors (60). It was shown that TDO-2 is elevated in human hepatocellular carcinomas and detected sporadically in other cancers and that in a preclinical model, TDO-2 expression prevented rejection of tumor grafts by preimmunized mice (60). Systemic administration of the TDO-2 inhibitor, LM10, restored the ability of mice to reject TDO-2–expressing tumors. These studies suggest that blocking both TDO-2 and IDO-1 to improve the efficacy of cancer immunotherapy would be complementary and might represent a safe and efficient approach for cancer therapy acting by promoting tumoral immune rejection (60).
However, whether the potential overactivation of the KP in human brain tumors will play a role in mediating brain tumor immune evasion via IDO-1/TDO-2–mediated modulation of antitumor immunity, remains an important question, but one that cannot be answered without more knowledge of the function and specificity of these infiltrating T cells. In particular, whether these cells recruited to the tumor site are specific for any tumor-expressed antigen. However, given the evidence, its potential for inhibiting tumor-specific immunity and driving malignant progression can be envisaged.

ACMSD Dysregulation in Tumor Cells: A Speculative Role for Brain Tumor Neurotoxicity and Pathogenesis

Although mounting evidence exists for IDO-1–mediated tumor-immune escape as a fundamental hallmark of tumor progression (61), and the emerging evidence indicating TDO-2–driven tumor immunosuppression, the involvement of the downstream machinery of the KP in tumor progression has been virtually unexplored. For the remainder of this review, we provide a new prospective on KP-mediated tumor progression, examining the involvement of the lower segment of the KP, particularly QUIN-induced neurotoxicity as a potential mechanism for tumor progression.

As an endogenous metabolite of L-tryptophan, PIC has been shown to possess neuroprotective and a number of antiproliferative effects within the CNS (62). In vitro studies have shown that PIC and IFN-γ synergistically enhance macrophage effector functions through inducing the transcriptional activation of the inducible isoform of the nitric oxide synthase (iNOS) gene in a macrophage cell line thus stimulating production of nitric oxide (NO₂; ref. 63). This is of particular significance as a number of studies have shown an involvement of...
NO\textsuperscript{−2} in the generation of potential tumorcidal activity by murine macrophages (63). Furthermore, a number of studies have shown the ability of PIC to inhibit cell proliferation of transformed cells \textit{in vitro} (64) and \textit{in vivo} (65). Consistent with the above findings, one \textit{in vivo} study using mice inoculated with MBL-2 lymphoma cells showed that intravenous injections of PIC in combination with activated macrophages augmented the cytotoxic and tumoricidal activities of macrophages, resulting in a significantly increased lifespan and reduced tumor growth compared with the control group (66). These effects are arguably due to macrophage activation mechanisms through IFN-γ-mediated mechanisms as suggested previously (66).

The activity of ACMSD determines whether the metabolites in the KP are converted to QUIN for NAD\textsuperscript{+} biosynthesis or to PIC (67). A number of studies have shown a link between the regulation of NAD\textsuperscript{+} synthesis and ACMSD activity in the brain. Ikeda and colleagues (68) first presented evidence of this relationship showing that the activity of ACMSD is inversely proportional to the amount of NAD\textsuperscript{+} synthesized from tryptophan. Furthermore, \textit{in vivo} studies have observed that rats fed a diet containing an ACMSD inhibitor, produced markedly elevated urinary QUIN levels and QUIN catabolites (68). ACMSD therefore appears to be an important regulator of \textit{de novo} NAD\textsuperscript{+} synthesis.

Cells possess a limited pool of NAD\textsuperscript{+}, yet this molecule exists as an important contributor to energy (ATP) production and is an exclusive substrate for the DNA repair-associated enzyme PARP (69). PARP activation from free-radical–induced DNA damage leads to regulation of numerous processes, including DNA repair, recovery of normal cellular function, genomic stability, replication, and cell division (69, 70). However, PARP hyperactivation by DNA strand breaks induced by ROS as can occur during inflammation, greatly results in depletion of intracellular NAD\textsuperscript{+} and ATP stores culminating in cell death due to reduced energy metabolism (71). Thus, continuous biosynthesis of NAD\textsuperscript{+} is vital to the maintenance and ongoing cell division of all cells (70).

The induction of IDO-1 and subsequent \textit{de novo} NAD\textsuperscript{+} synthesis has been shown to contribute to the maintenance of intracellular NAD\textsuperscript{+} levels and cell viability during conditions of increased PARP activation following oxidative DNA damage (72). Most cancer cells show a high rate of NAD\textsuperscript{+} turnover due to continuous and elevated PARP activation from DNA damage and genomic instability (73), and have significantly higher energy consumption compared with nontransformed cells (74).

Interestingly, we have previously shown that ACMSD expression is absent and IDO-1 is overexpressed in the neuroblastoma cell line compared to human neurons, which express ACMSD (32). We also showed that QUIN was catabolized and PIC was produced in human neurons, whereas the neuroblastoma cell line showed a preference towards QUIN production and PIC consumption (32). This differential activation of the KP is of significance, as it may suggest a preferential skewing towards the neurotoxic branch of the KP and away from neuroprotection in the tumor cell. This imbalance in KP metabolism may potentially represent a mechanism conferring tumor survival advantages. Because ACMSD is an important regulator of NAD\textsuperscript{+} synthesis, ACMSD expression absence may preferentially direct tryptophan metabolism towards QUIN production and subsequently increased intracellular NAD\textsuperscript{+} concentrations at the expense of the neuroprotective and potentially antitumoral PIC. This may also contribute to the neurotoxicity associated with tumorigenesis, as a result of increased production of the neurotoxin, QUIN, and providing a more efficient supply of NAD\textsuperscript{+} substrate for PARP. Induction of IDO-1 and subsequent \textit{de novo} NAD\textsuperscript{+} synthesis in brain tumors may be a mechanism that provides an important survival strategy for these tumor cells. Increased NAD\textsuperscript{+} levels will provide an improved supply of substrate to PARP (75), assisting in tumor cell DNA replication and repair and promote the maintenance of high metabolic activity, ultimately promoting tumor cell viability and proliferation (Fig. 2). This variation in kynurenine pathway activation in neuroblastoma cells may provide a key to understanding tumor persistence and associated neurotoxicity; a weakening in neuroprotection may exacerbate the adverse effects of neurotoxicity (76).

The study conducted by Guillemin and colleagues (32) remains the only study to date comprehensively characterizing the KP in tumor cells and exploring the importance of the imbalance between QUIN and PIC production for tumor persistence. Indeed, whether a similar trend is also observed in brain tumor cell lines and primary brain tumors requires further investigation. Furthermore, given its antiproliferative effect on tumor cells, the switch to PIC consumption in neuroblastoma cells may also suggest a mechanism for promoting tumor persistence through reducing PIC induced antitumor activities. However, the lack of literature on the direct antitumoral activity of PIC precludes the drawing of a firm conclusion regarding the significance of reduced PIC production as a mechanism for reducing PIC induced antitumor activities.

If these observations are shown to have wider brain tumor applicability, that is, if increased QUIN production is characteristic of primary brain tumors and not just cell lines, then it is tempting to speculate that increased QUIN production may contribute to the neurotoxicity associated with brain tumors, a speculation that is comparable with the findings of Ye and Sontheimer (77), which have found that the release of glutamate by glioma cells is directly relative to tumor growth and that glioma cells release sufficient amounts of glutamate to induce widespread toxicity in cultured neurons. The results of this study suggested that growing gliomas may actively kill surrounding neuronal cells through the release of glutamate (77). Similarly, QUIN may etch a neurotoxic pathway of destruction through surrounding neuronal and glial cells, which may promote tumor growth. Interestingly, CSF QUIN levels were moderately elevated in patients with CNS tumors (78). Necrosis is a hallmark feature of glioblastoma (79) and has been shown to occur through a number of mechanisms (reviewed in ref. 80). One mechanism of necrosis in glioma has been suggested to involve the accumulation of the neurotransmitter, glutamate, in the extracellular space in the brain (81). This is particularly relevant to our discussion, as QUIN, like glutamate, acts on the NMDA receptor leading to neuronal...
and astrocytic toxicity. We propose that glioma QUIN release may also cause necrosis of the surrounding neurons and astrocytes, which may explain the particularly invasive and destructive nature of gliomas. Whether these observations are reflected in primary glioblastoma or other primary brain tumors remains to be elucidated.

Conclusions

We herein have reviewed evidence implicating a novel mechanism, in which the cooperation of ACMSD downregulation, IDO-1 overexpression, and TDO-2 expression, together contribute to tumor cell persistence and pathogenesis through directing KP metabolism towards the neurotoxic metabolite, QUIN, and limiting neuroprotection. The 3-HAA-Treg immunosuppressive pathway may be a significant mediator of suppressing antitumor immunity in human tumors. Targeting this pathway may provide a novel therapeutic strategy for the treatment of cancer. Furthermore, the emerging evidence implicating TDO-2-dependent production of KYN by brain tumors in mediating antitumor immunity through activation of the AhR opens up exciting new future research opportunities. The newly identified immunosuppressive role of TDO-2 in tumors suggests that targeting both IDO-1 and TDO-2 may provide improved efficacy of cancer immunotherapy (60).

The immunomodulatory function of IDO-1 in brain tumors remains to be fully elucidated and warrants further investigation. Further research is required to determine whether IDO-land TDO-2 expression is a common feature in glioblastoma and other brain tumors and whether potential overexpression of IDO-1 can induce the suppression of T cells infiltrating the tumor. However, in the absence of a definition of the specificity and function of infiltrating T cells, the significance of potential findings will remain unclear. Furthermore, elucidating the above proposed mechanisms used by tumor cells is an important direction of future research and will provide the foundation for the identification of novel therapeutic strategies that exploit the dysregulated state of the KP metabolism we have reviewed here. Future therapeutic approaches aimed at modulating the endogenous concentrations of KP metabolites (e.g., KYN, 3-HAA QUIN, and PIC) by manipulating specific KP enzymes might provide an additional novel therapeutic modality and ultimately broaden the combinatorial attack on cancers, where altered KP metabolism provides crucial support. Perhaps, the involvement of the downstream machinery of the KP in tumor progression will gain momentum in tumor research.

In preclinical studies, the IDO inhibitor, 1-MT, compromises tumor-mediated immunosuppression resulting in the regression of systemic tumors. These results have subsequently led to the entering of 1-MT in phase II clinical trials in early 2010, for patients with advanced malignancies (http://www.clinicaltrial.gov). Certainly, 1-MT offers one innovative strategy for the therapeutic correction of immune escape. However, its application in brain tumors may not represent a practical therapeutic modality, as it does not seem to penetrate the BBB. Future approaches aimed at inhibiting IDO-1 will need to consider this hindrance. The eventual success of treatment for brain tumors will be dependent not only on an in-depth understanding of the immunology behind the brain and brain tumors, but also the implementation of therapies that show and address multiple layers of challenges in glioma (82).

Disclosure of Potential Conflicts of Interest

R. Grant is employed (other than primary affiliation, e.g., consulting) as a CEO in Australasian Research Institute. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions

Conception and design: S. Adams, N. Braidy, B.J. Brew, G.J. Guillemin

Development of methodology: S. Adams, B.J. Brew

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): B.J. Brew, C. Teo

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S. Adams, B.J. Brew

Writing, review, and/or revision of the manuscript: S. Adams, N. Braidy, A. Bessede, B.J. Brew, R. Grant, C. Teo, G.J. Guillemin

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): R. Grant, G.J. Guillemin

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References


Correction: The Kynurenine Pathway in Brain Tumor Pathogenesis

In this article (Cancer Res 2012;72:5649–5657), which appeared in the November 15, 2012 issue of Cancer Research (1), the last name of one of the contributing authors, Alban Bessede, was misspelled. The correct author listing is given below. The authors regret this error.

Seray Adams, Nady Braidy, Alban Bessede, Bruce J. Brew, Ross Grant, Charlie Teo, and Gilles J. Guillemin

Reference


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