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Review

The Kynurenine Pathway: A Primary Resistance Mechanism in Patients with Glioblastoma

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Abstract. *The failure of chemotherapy and radiation therapy to achieve long-term remission or cure in patients with glioblastoma (GBM) is, in a large part, due to the suppression of the immune system induced by the tumors themselves. These tumors adapt to treatment with chemotherapy or radiation therapy by stimulating secretion of molecules that cause tryptophan metabolism to be disrupted. Indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO) are produced, accelerating metabolism along the kynurenine pathway and resulting in excess levels of quinolinic acid, 3-hydroxyanthranilic acid and other neurotoxic molecules. IDO and TDO also act as checkpoint molecules that suppress T-cell function. GBM is particularly associated with severe immunosuppression, and this tumor type might be thought to be the ideal candidate for checkpoint inhibitor therapy. However, treatment with checkpoint inhibitors now in clinical use for peripheral solid tumors, such as those inhibiting cytotoxic T-lymphocyte-associated protein-4 (CTLA4) or programmed cell death-1 (PD1) receptors, results in further abnormalities of tryptophan metabolism. This implies that to obtain optimal results in the treatment of GBM, one may need to add an inhibitor of the kynurenine pathway to therapy with a CTLA4 or PD1 inhibitor, or use agents which can suppress multiple checkpoint molecules.*

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Glioblastoma multiforme (GBM) is a highly malignant primary brain tumor with a very poor prognosis. Median survival is 15 months. Two-year survival is less than 30% and only 5% of patients survive 5 years (1, 2). Genetic abnormalities, both inherited and acquired, are common, and there is a proven association of GBM with tuberous sclerosis, von Recklinghausen's disease, Lynch syndrome and Li-Fraumeni syndrome. Importantly, patients with asthma, eczema, hay fever and other allergies have as much as a 40% reduced risk of developing GBM, while patients with AIDS have an increased risk (2-4). It is well known that GBM is associated with systemic immunosuppression, and that much of this immunosuppression is caused by the GBM cells themselves (5-10). Current standard first-line treatment of GBM is surgery, if possible, followed by radiation therapy and the chemotherapy drug, temozolomide (11-13). Second-line treatment with nitrosoureas, avastin (bevacizumab), irinotecan, or combinations of some of these agents, has only minor activity, resulting in progression-free survival (PFS) of about 3-6 months and overall survival (OS) of 4-8 months (14-18). A number of new, promising treatment approaches are under investigation, but, unfortunately, none has yet proven to be an advance in GBM treatment (19-23). Additionally, the strategy of using chemotherapy in an attempt to cure GBM may be self-defeating, as chemotherapeutic agents may increase the immunosuppressive activity of GBM cells, causing recurrence (5, 24, 25).

Tryptophan Metabolites

Tryptophan is an essential amino acid and an important precursor of serotonin, melatonin and nicotinamide adenine dinucleotide (26, 27). Abnormal or unbalanced tryptophan metabolism plays a role in numerous diseases, including Alzheimer's disease (28), Parkinson's disease (29), Huntington's chorea (30), psychiatric disorders (31), as well as in cardiovascular disease (32) and diabetes (33). In the brain, for example, excess levels of the tryptophan

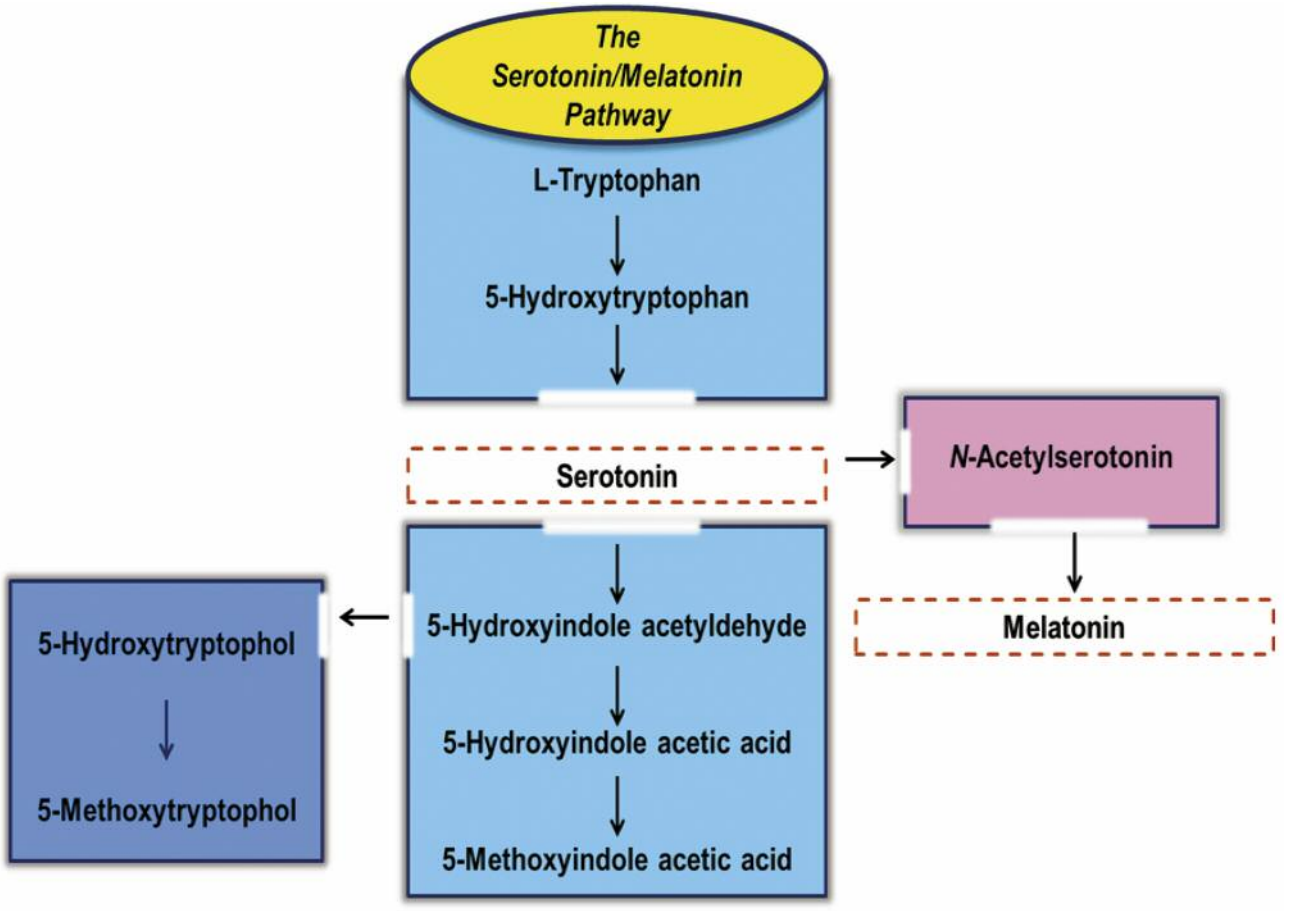

Figure 1. *Tryptophan metabolism through the serotonin/melatonin pathway.*

metabolite, quinolinic acid (see Figures 1 and 2), can cause neuronal death by, among other mechanisms, acting as an *N*-methyl-D-aspartate (NMDA) agonist and disrupting the glutamate-glutamine cycle (34-37). Abnormal glutamate metabolism results in direct toxicity to brain cells (38-40). Quinolinic acid potentiates lipid peroxidation (37), resulting in damage to cell membranes. This metabolite also stimulates nitric acid synthase production by neurons, thus increasing free radical production (35, 37). Numerous other mechanisms by which quinolinic acid causes neurotoxicity have been described (41). Quinolinic acid appears to be particularly toxic to the striatum, partially explaining the role of the kynurenine pathway in both Huntington's chorea and Parkinson's disease (36, 42-44). Other tryptophan metabolites, including 3-hydroxykynurenine and 3-hydroxyanthranilic acid, also have neurotoxic effects. Relative deficiencies of tryptophan, consistent with increased metabolism, are known to cause increased levels of ceramides and caspase-3 activation, resulting in cell apoptosis (45), and the kynurenine pathway is intimately involved in sphingolipid/ceramide metabolism (46).

Besides their neurotoxic effects, these tryptophan metabolites are known to cause cancer development and progression. Deranged tryptophan metabolism has been shown to be important in numerous types of cancer (47-52). Furthermore, the extent of the abnormality in tryptophan metabolism has been shown to correlate with the aggressiveness of the cancer (53-55). For example, Ino *et al.* showed that increased activity of the kynurenine pathway inversely correlated with both OS and PFS in patients with endometrial cancer (47). Heng *et al.* have shown that increased activity of the kynurenine pathway is associated with an unfavorable prognosis in patients with breast cancer (54). On the other hand, Sordillo *et al.* reported that increased tryptophan fluorescence with excitation wavelengths of 280 and 300 nm can distinguish cancer from adjoining normal tissue (56). Others have reported similar findings (57-59). We have also shown that increased tryptophan fluorescence

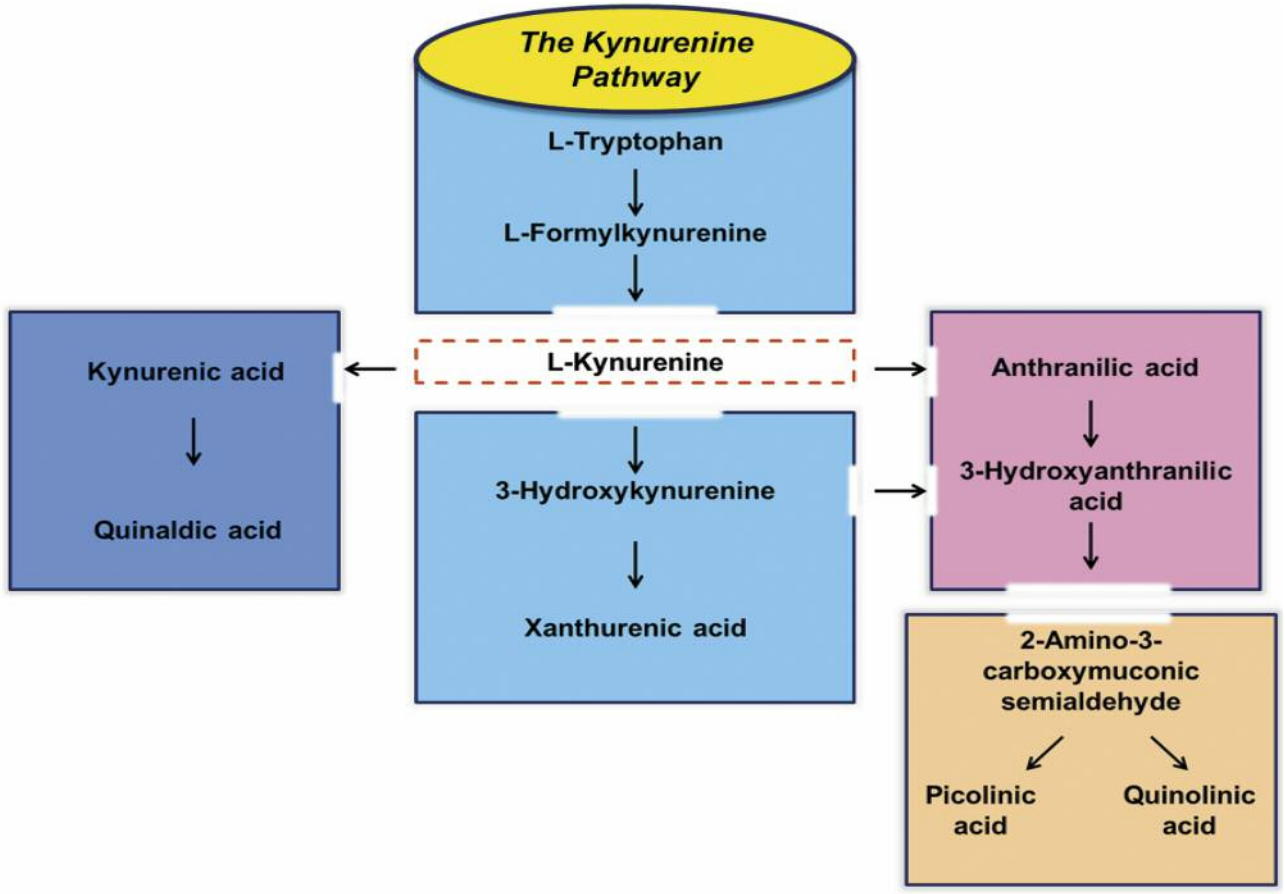

Figure 2. *Tryptophan metabolism through the kynurenine pathway.*

correlates strongly with increased breast cancer grade (60). Pu *et al*. reported increased tryptophan fluorescence from cell lines derived from highly aggressive prostate cancers compared to lines derived from less aggressive prostate cancers (61). Other techniques have given similar results. Zhou *et al*. used resonance Raman spectroscopy to show increasing tryptophan (1588 cm^{-1} mode, 532 nm excitation) in gliomas as the stage of these tumors increased from stage 1 to stage 4 (glioblastoma) (62). Yoracu *et al*. noted that it is the tryptophan buried within folded proteins, rather than exposed tryptophan, that accounts for tryptophan fluorescence (63). This may account for the consistent finding of increased tryptophan fluorescence in cancerous tissues in the face of accelerated tryptophan metabolism in patients with cancer.

Pro-inflammatory Cytokines and Indoleamine 2,3-Dioxygenase

The major cause of abnormal tryptophan metabolism in patients with GBM is an increased release of pro-inflammatory cytokines. It is well known that under stress conditions, major pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNFα), interleukin-1beta (IL1β), IL6 and interferon-γ (IFNγ) are released, both within the brain and in the periphery. Increases in these cytokines are known to be associated with many neurological conditions (64-67), as well as with many other diseases. Furthermore, high levels of these cytokines in the brain are associated with an increased severity of these diseases. For example, an elevated level of IL6 is correlated with increased mortality in patients with Parkinson's disease (65). In experimental models of Huntington's chorea, reducing levels of TNFα has therapeutic benefit (66). TNFα, IL1β, IL6, and other cytokines may be increased massively in the brain after traumatic brain injury, thousands of times more than corresponding levels in blood, and these increases are correlated with the severity of the traumatic brain injury (68). Yan *et al*. have shown that the degree of elevation of quinolinic acid also correlates with the degree of severity of brain injury (69). Likewise, although these pro-inflammatory

cytokines also have anticancer effects, they are involved intimately in cancer development, progression and metastasis (70-73). Bai *et al*. showed that TNFα, IL1β and IL6 promoted metastasis after surgery for primary hepatocellular carcinoma (70). Increased secretion of pro-inflammatory cytokines plays a particularly important role in GBM development and resistance to therapy (74-76). An important mechanism by which these cytokines cause and worsen these diseases is through of the kynurenine pathway (77-80). Campbell *et al*. showed that IFNγ activates the kynurenine pathway, and TNFα, IL1β and IL6 are synergistic with IFNγ in stimulating this pathway (77). Asp *et al*. emphasized the important role of IFNγ in stimulating this pathway in dermal fibroblasts (78). Zuo *et al*. showed that increases in inflammatory markers, and, in particular, increases in IFNγ-related inflammatory markers, correlated with increased levels of tryptophan metabolites, and also with increased mortality from neurodegenerative diseases and cancer (79). Chung and Gadupudi describe a number of ways these compounds have mutagenic properties, such as interaction with nitrites to form nitrosamine, or interaction with transition metals to form reactive oxygen species (50). Not only does abnormal glutamate metabolism caused by NDMA activity after increased production of these tryptophan metabolites result in neurotoxicity, glutamate can also act as a growth factor for cancer, which takes up this amino acid preferentially compared to normal cells (81-84).

Perhaps most importantly, metabolites of tryptophan such as quinolinic acid and 3-hydoxyanthranilic acid inhibit T-cell function, allowing tumor growth and metastasis (54, 85-89). Fallarino *et al*. showed that kynurenine metabolites, especially quinolinic acid and 3-hydroxyanthranilic acid, cause death of helper T1 (Th1) cells even at low doses, while sparing Th2 cells (85). Frumento *et al*. reported similar results and emphasized the important role of the enzyme indoleamine 2,3-dioxygenase (IDO) (87). As noted, this key enzyme is stimulated primarily by interferon-γ (90-94), and interferon-γ-induced activation of IDO appears to be the critical, necessary step in the initiation of kynurenine pathway induction of immunosuppression (90). IDO is ubiquitous in tissues, and after stimulation by interferon-γ, catalyzes the first step in this pathway, the conversion of tryptophan to N-formyl-L-kynurenine (86, 88, 90, 94). It is also widely expressed in human cancers, and its expression correlates with tumor progression and a shorter patient survival (95). As Prendergast has noted, cancers "eat" tryptophan in order to escape the immune system (53).

Indoleamine 2,3-Dioxygenase and Tryptophan 2,3-Dioxygenase

IDO is heme-containing enzyme which can degrade tryptophan by cleaving its aromatic indole ring (86). Two forms of this enzyme exist, IDO1 and IDO2. These enzymes are structurally similar, and the genes that encode them are situated next to each other on chromosome 8 (86, 96). IDO1 is expressed in a wide variety of tissues, including dendritic cells, endothelial cells, macrophages, fibroblasts and mesenchymal stromal cells, as well as in neurons and in cancer cells themselves. IDO2 is primarily expressed in the kidney, brain, colon, liver and reproductive tract (86, 95-98). IDO is critically important in inducing immune tolerance during pregnancy, and in protecting normal tissues against the immune system through its regulatory effects on T-cells (99-102). It has been shown to suppress T-lymphocyte-mediated graft rejection (95, 103). However, although this enzyme may play an important role in tumor apoptosis (93), IDO can also cause T-cell suppression after neoplastic transformation by acting as a checkpoint molecule, thus preventing the immune system from mounting an effective attack against the cancer (104-109). The local tryptophan deficiency induced by IDO stimulates the general control non-depressable-2 kinase pathway which alters protein translation and prevents T-lymphocyte activation (95). Moon *et al*. note that IDO inhibits activity of mechanistic target of rapamycin (mTOR), which leads to T-lymphocyte anergy (104). Other mechanisms by which IDO causes immunosuppression have been described (95, 99, 104).

A third, distinct enzyme, tryptophan 2,3-dioxygenase (TDO), has the same effect as IDO1 and IDO2 as the initial step in the kynurenine pathway, converting L-tryptophan into *N*-formyl-L-kynurenine. Like IDO, this enzyme is important in the maintenance of self-tolerance (110). TDO has been found to have a role in numerous neurological diseases, including Alzheimer's disease, Parkinson's disease and autism, and suppression of TDO appears to reduce neurodegeneration (111-114). Increased TDO activity is associated with cancer growth (115-117), as well as with increased tumor grade and decreased survival in triple-negative breast cancer cells (118).

Immune Checkpoint Inhibitors: Monotherapy

The failure of traditional approaches to have a significant impact on survival in patients with GBM suggests new strategies are necessary in the treatment of this cancer. One strategy which has had partial success against cancers other than GBM is to unleash the immune system by inhibition of immune checkpoint molecules. The most important checkpoint molecules are cytotoxic T-lymphocyte-associated protein 4 (CTLA4), programmed cell death-1 receptor (PD1) and IDO, and these checkpoint molecules are especially important in causing the profound immunosuppression associated with GBM (119-121). Grossauer *et al*. pointed out that all three of these checkpoint molecules are expressed at very high levels in GBM, that GBMs express much higher levels of these

checkpoint molecules than do low-grade gliomas, and that there is a close inverse correlation of these levels with survival. These checkpoint molecules are also crucial in protecting GBM stem cells (120). Other checkpoint molecules under investigation include T-cell immunoglobulin domain and mucin domain 3 (TIM3) (122), lymphocyte activation gene-3 (LAG3) (123), killer-cell immunoglobulin-like receptor (KIR) (124) and V-domain Ig suppressor of T-cell activation (VISTA) (125). Checkpoint inhibitors are now in widespread clinical use against a wide variety of cancer types. Ipilimumab (yervoy) is a standard treatment for patients with malignant melanoma (median OS=10.1 months even in heavily pre-treated patients, with some patients now having long-term survival), and is currently being investigated for the treatment of patients with non-small cell lung carcinoma (126, 127). The PD1 inhibitors, nivolumab (opdivo) and pembrolizumab (keytruda), and the programmed-death ligand-1 (PDL1) inhibitor atezolizumab (tecentrig), have major antitumor activity against multiple cancer types, including renal cell carcinoma, malignant melanoma, relapsed Hodgkin's disease, bladder cancer and non-small cell lung carcinoma (128-132). Nevertheless, a large majority of patients do not respond to these treatments and there can be considerable toxicity, including grade 3 and 4 pneumonitis, colitis and hepatitis in a significant number of patients.

Because of the profound immunosuppression caused by checkpoint molecules in GBM, checkpoint inhibitor therapy might be hypothesized to be the ideal type of therapy for this cancer. However, despite some promising pre-clinical results (5, 133, 134), early studies with PD1, PDL1 or CTLA4 inhibitors against GBM have, at least as monotherapy, not yet fulfilled this promise (120, 135-139). Grossauer *et al*. noted that neither CTLA4 inhibition nor PD1 inhibition increased efficacy against GBM when used as monotherapy (120). Schaff *et al*. reported only stable disease or progressive disease and no major or minor responses, a median PFS of only 2.8 months and an OS of 5.1 months in patients with recurrent GBM receiving ipilimumab (135). These results are consistent with experimental data. Zeng *et al*. studied mice implanted intracranially with GL 261 glioma cells. Mice treated with a PD1 inhibitor survived 27 days compared to controls who survived 25 days. Mice treated with a PD1 inhibitor plus radiation therapy survived 53 days (137). The less than expected activity of these inhibitors against GBM may be because, in this tumor in particular, the checkpoint inhibitor effects of these treatments are overcome by the immunosuppressive effects of other checkpoint molecules, the most important of which is IDO.

Inhibitors of the Kynurenine Pathway

Numerous IDO inhibitors are under investigation (140). Many medications and hundreds of natural products (141) also have anti-IDO activity (Tables I and II). A few studies of IDO inhibitors against GBM have been carried out and these agents do show some activity as single agents. Miyazaki *et al*. showed the IDO inhibitor 1-methyl L-tryptophan (1MT) prevented tryptophan consumption and suppressed the growth of LN 229 glioma cells (192). Hanihara *et al*. reported 1MT significantly suppressed tumor growth in a murine glioma model. 1MT also had synergistic effects with temozolomide (193). Li *et al*. showed that mice bearing intracranial GL 261 glioblastoma tumors that were treated with 1MT added to radiation therapy plus temozolomide and cytoxan, survived longer than mice treated with chemotherapy and radiation therapy alone (194). Interestingly, mice deficient in the complement component C3 did not experience increased survival after addition of 1MT (194). One agent, indoximod, the D-isomer of 1MT and a selective inhibitor of IDO2 (97, 195) is currently in clinical trials in combination with either temozolomide or bevacizumab for patients with GBM refractory to initial therapy, and a few objective responses have been seen (196, 197).

The importance of the kynurenine pathway as a mechanism of resistance to CTLA4 therapy has been shown in studies of other cancer types. Holmgaard *et al*. reported that Ido-knockout mice implanted with B16F10 melanoma cells had slower tumor growth and a markedly prolonged survival compared to wild-type mice. This effect was duplicated by the addition of an IDO inhibitor to CTLA4 inhibitor therapy (198). The increased antitumor effects correlated with increased T-effector to T-regulatory (Treg) ratios in the tumors. As noted, GBM tumors secrete high levels of IDO (119, 121). GBMs express significantly higher IDO levels than do low-grade gliomas, and IDO expression negatively correlates with survival (199, 200). Wainright *et al*. injected IDO-deficient and IDO-competent glioma cells into the cerebral hemispheres of mice, and demonstrated that the mice with IDO-deficient glioma cells survived far longer. The authors also showed that the addition of an IDO inhibitor to PD1 and CTLA4 inhibitors reversed the resistance to checkpoint inhibition, increasing T-cell activity, reducing the number of Treg cells and extending survival in mice with GBM. This effect was not seen in mice with intracranial melanoma, suggesting IDO inhibition would be more effective in a cancer dependent on stimulation of Treg cells, such as GBM (201).

As with CTLA4 inhibitors and PD1 inhibitors, the optimal use of IDO inhibitors may be in combination with other checkpoint inhibitors to give a more complete stimulation of the immune system. Additionally, the use of agents that can inhibit more than one checkpoint molecule should be investigated. It should be remembered that although these agents inhibit multiple checkpoint molecules, they may not be potent enough in the doses received to induce responses on their own, and thus also might be optimally used in combination with other agents.

Table I. *Common medications with indoleamine 2,3-dioxygenase (IDO)-inhibitory activity.*

Drug	Comment	Reference
Salicylates	Work by suppression of interferon gamma induction of IDO	142, 143, 144, 145
Indomethacin	Effect shown in human neural stem cells	143, 144
Other cyclo-oxygenase-2 (COX2) inhibitors	Anticancer effects of COX2 inhibitors correlate directly with inhibition of T-regulatory cells	146, 147, 148, 149, 150
Statins	May also increase IDO activity through increased interleukin-10 secretion	151, 152, 153
Anti-estrogens	Patients with aromatase-inhibitor resistant breast cancer who respond to fulvestrant have markedly decreased IDO activity. IDO activity correlates directly with number of metastases	154, 155, 156
Chloroquine	Also blocks PD1	157, 158, 159
Acyclovir	Also inhibits TDO	160, 161

COX2: Cyclo-oxygenase2; PD1: programmed cell death protein 1; TDO: tryptophan 2,3-dioxygenase.

Table II. *Important natural products with anti-indoleamine 2,3-dioxygenase (IDO) activity.*

Natural product	Comment	Reference
Curcumin	Also an inhibitor of PDL1, PDL2 and CTLA4. Synergistic with PD1 and CTLA4 inhibitors. Protects against quinolinic acid stimulation of NMDA receptors.	143, 162, 163, 164, 167, 168, 169, 170, 171, 172
Resveratrol	Also inhibits PD1, PDL1 and CTLA4.	172, 173, 174, 175, 176
Epigallocatechin-3-gallate	Major catechin in green tea. Activity comparable to 1-methyltryptophan in IDO suppression and in prevention of azoxymethane-induced colon carcinogenesis.	177, 178, 179, 180, 181, 182
Rosmarinic acid (rosemary extract)	Caffeic acid ester found in herbs such as basil, thyme and sage	183
Genistein	Isoflavone prominent in soy products. May have estrogenic effects	184, 185
Quercetin	Found in green tea, onions, red wine. Also in ginkgo biloba, St. John's wort	162, 185, 186
Brassinin	Phytoalexin, indole mimetic, found in cabbage, broccoli, cauliflower and other foods.	187, 188, 189, 190
Apigenin (4,5,7-trihydroxyflavone)	Found in celery, parsley, chamomile tea. Monoamine transporter activator. May stimulate neurogenesis. Also inhibits PDL1.	185, 191

PD1: Programmed cell death protein 1; PD2: programmed cell death protein 2; PDL1: programmed death-ligand 1; CTLA4: cytotoxic T-lymphocyte-associated protein-4.

Conflicts of Interest

Dr. Peter Sordillo is a member of the Scientific Advisory Board of SignPath Pharma, a developmental stage biotechnology company that is studying liposomal curcumin, liposomes and other agents. Dr. Helson is CEO of SignPath Pharma. Laura Sordillo reports no conflicts.

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