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Metabolic control of tumor progression and anti-tumor immunity

Lei Huang and **Andrew L. Mellor**[1]
Cancer immunology, Inflammation and Tolerance Program, Cancer Center, Georgia Regents University, Augusta GA 30912

Abstract

Purpose of review—Loss of cell growth control does not explain why tumors form as the immune system recognizes many malignant cells and keeps them in check. The local inflammatory microenvironment is a pivotal factor in tumor formation as tumor associated inflammation actively suppresses anti-tumor immunity. The purpose of this review is to evaluate emerging evidence that amino acid catabolism is a key feature of tumor-associated inflammation that supports tumor progression and immune resistance to therapy.

Recent findings—Enhanced amino acid catabolism in inflammatory tumor microenvironments correlates with carcinogen resistance and immune regulation mediated by tumor-associated immune cells that protect tumors from natural and vaccine-induced immunity. Interfering with metabolic pathways exploited by tumors is a promising anti-tumor strategy, especially when combined with other therapies. Moreover, molecular sensors that evolved to detect pathogens may enhance evasion of immune surveillance to permit tumor progression.

Summary—Innate immune sensing that induces amino acid catabolism in tumor microenvironments may be pivotal in initiating and sustaining local inflammation that promotes immune resistance and attenuates anti-tumor immunity. Targeting molecular sensors that mediate these metabolic changes may be an effective strategy to enhance anti-tumor immunity that prevents tumor progression, as well as improving the efficacy of cancer therapy.

Keywords

Amino acid catabolism; tumor tolerance; anti-tumor immunity; interferons; innate immune sensors

Introduction

Malignant cells with defective growth control create tumors but the immune system impedes tumor formation by eliminating many malignant cells (Fig. 1). Some malignant cells progress to form tumors by evading immune checkpoints to establish local microenvironments that protect malignant cells from immune-mediated destruction (1). Pre-established immune privilege explains tumor resistance to vaccines, which elicit weak clinical responses even if robust immune responses manifest. Tumor cells may suppress

[1]Corresponding author: Andrew L. Mellor, Cancer immunology, Inflammation and Tolerance Program, Cancer Center, Georgia Regents University, 1120 15th St., Augusta GA 30912; Tel;: 706 721 8735; Fax: 706 721 8732; amellor@gru.edu.

anti-tumor immunity themselves but tumor-associated inflammation, which extends to draining lymph nodes, is a critical factor regulating anti-tumor immunity.

The focus of this review is the emerging paradigm that increased amino acid catabolism is a frequent and important feature of inflammation that promotes tumor progression and inhibits anti-tumor immunity (Fig. 2). Recent reviews describe immune regulatory pathways involving dendritic cells (DCs), macrophages (MΦs), myeloid-derived suppressor cells (MDSCs), Natural Killer (NK), mast cells, and Foxp3-lineage regulatory CD4 T cells (Tregs) in chronic inflammatory syndromes (Table 1), including roles in tumor progression and immunotherapy (2–6). Biologic significance is still emerging but increased amino acid catabolism is commonly associated with inflammation that regulates rather than stimulates - immunity.

Inflammation can stimulate or regulate immunity

The paradigm that inflammation *stimulates* immunity is a fundamental tenet of immunology but inflammation may also drive immune *regulation*. Thus interferons (IFNs) are known as ‘pro-inflammatory’ cytokines but they also induce immune regulation; moreover which functional response to IFNs is dominant is not always obvious (7). Local inflammation incited by malignancies that transition into tumors regulates tumor-specific immunity; hence, a therapeutic goal is to convert immune regulatory inflammation into stimulatory inflammation (Fig. 2).

Increased amino acid catabolism inhibits immunity in many chronic inflammatory syndromes (7–9). Immune tolerance to transplanted skin in mice correlated with enhanced amino acid catabolism in graft-associated DCs (10), and mast cells expressing tryptophan hydroxylase-1 (TPH-1) promoted tumor relapse after therapy and allograft tolerance (3). Genetically enhanced Trp catabolism mediated by indoleamine 2,3 dioxygenase (IDO) also suppressed rat lung allograft rejection (11, 12). Microbial infections often induce IDO (via IFNs), which may impede host immunity to promote pathogen persistence, a situation analogous to tumor persistence (8). Likewise, tumor tolerance is often linked to increased amino acid catabolism, though other regulatory pathways (Table 1) may be active simultaneously (13, 14). Thus tumors exploit natural immune regulatory pathways that evolved to protect healthy tissues from hyper-immunity. The paradigm that tumors are analogous to aseptic wounds that do not heal is useful since dying cells release cell contents such as DNA that are potentially immunostimulatory but natural regulation may reinforce ‘self’ tolerance under aseptic conditions.

Amino acid catabolism and tumor development

Genetic predisposition, carcinogens, radiation (UVB, ionizing) or oncogenic viruses synergize to generate malignant dividing cells (Fig. 1). Malignant cells depend on access to essential nutrients such as iron, and iron chelation impedes tumor growth (15). Correlations between tumor growth and increased local amino acid catabolism (i.e. elevated nutrient consumption) are not consistent with this paradigm. It is important to emphasize that amino acid catabolism triggers profound changes in immune cell functions via amino acid sensors and catabolite receptors, and it may not be necessary to actually ‘starve’ cells for immune

regulatory effects to manifest. Merely reducing the pool of available amino acids may suffice to induce regulatory responses; if so, inhibiting amino acid catabolism may offer therapeutic opportunities. Trp catabolism is the most studied aspect of amino acid catabolism in tumor microenvironments and the recent literature reflects this bias, which was initiated by the finding that IDO activity protected fetal tissues from maternal immunity during pregnancy in mice (16, 17). However this discovery was perhaps anticipated by reports over 40 years ago describing increased Trp catabolism in breast and cervical cancer patients (18, 19).

Increased IDO activity often manifests in inflammatory lesions induced by tumor promoters such as oncogenic human papilloma (HPV) and murine leukemia virus (MuLV), phorbol myristate acetate (PMA or TPA) and UVB radiation (20–24), suggesting that Trp catabolism may suppress immune surveillance mechanisms. Indeed, IDO1-deficient (IDO1-KO) mice were more resistant to papilloma formation in the DMBA/TPA model of inflammation-driven carcinogenesis (24). IDO1-KO mice also exhibited more resistance to lung and breast tumors (25), and IDO1 loss correlated with reduced neo-vascularization, metastasis and functional maturation of myeloid derived suppressor cells (MDSCs) in the lung tumor model, suggesting that IDO facilitates these tumor supportive functions. However, it is unclear how developing tumors induce IDO. An emerging possibility is that dying tumor cells may trigger local IFN type I (IFNαβ) production via DNA sensors such as Toll-Like receptor-9 (TLR9) or the Stimulator of Interferon Genes (STING) adaptor, which then induces IDO (26, 27), though excessive STING activation also promotes autoimmunity (28, 29). Trp catabolites may also promote tumorigenesis as Trp catabolites activated β-catenin signaling to promote colon tumorigenesis via a T cell independent pathway in mice (30). Targeting amino acid catabolism may help prevent malignancies developing into tumors, though increased risk of autoimmunity is a potential undesirable consequence of such interventions.

Amino acid catabolism in tumor microenvironments

Elevated Trp and arginine (Arg) catabolism have been linked to regulation of anti-tumor immunity. Two different enzymes with oxygen binding iron-tetrapyrrole co-factors - IDO and tryptophan 2,3 dioxygenase (TDO) - catalyze oxidative Trp catabolism to generate kynurenine, and TPH-1 converts Trp into serotonin. IDO transcription is induced by IFNαβ and IFNγ in a range of cell types, including selected immune cells but measuring IDO enzyme activity is important as post-translational modifications may be required for IDO activity. Mice and humans possess two linked genes encoding IDO enzymes (IDO1, IDO2). IDO1 mediates regulatory responses to many inflammatory stimuli, including tumor growth (8). A role for IDO2 has not been defined, though recent studies on IDO2-deficient mice showed that IDO2 and IDO1 control cytokine expression differently and IDO2 did not phenocopy IDO1 in promoting inflammatory skin cancer (G. Prendergast, personal communication). IDO expression occurs in some cancer cells, stromal cells and certain immune cells such as some DCs and MΦs in tumor lesions and tumor-draining lymph nodes (TDLNs) in mice and cancer patients. Recent reports continue this trend with studies describing elevated IDO expression in endometrial carcinomas, brain (glioma), chronic lymphocytic leukemias, non-small cell lung cancers and laryngeal squamous cell carcinomas

(31–36). These studies support the paradigm that IDO regulates anti-tumor immunity and is a potential prognostic marker for cancer, reinforcing the rationale for using IDO inhibitors to improve cancer therapy (37). Phase II oncology trials using IDO inhibitors are ongoing and it remains to be seen if this novel approach is effective in the clinic, though IDO was identified recently as a immune resistance factor following immunotherapy to block regulatory pathways involving CTLA4, PD-1/L and glucocorticoid-induced TNF receptor-related (GITR protein signaling (38).

Unlike IDO, TDO is expressed primarily in liver and is induced in the central nervous system (CNS) in response to stress-induced glucocorticoids. In liver, TDO regulates serum Trp levels by catabolizing Trp from dietary intake, and TDO expression in liver may account for the observed resistance of liver allografts to rejection (39). However, some tumor cells express TDO and potential roles for TDO in tumors were reviewed recently revealing striking parallels with the effects of IDO (40, 41). Thus, TDO transduced tumor cells were resistant to anti-tumor immunity and TDO-specific inhibitors restored the ability of mice to reject TDO-expressing tumors (42). Thus, tumors may evade innate immune tumor surveillance and regulate tumor-specific adaptive immunity by inducing IDO or TDO.

A critical role for TPH-1 in regulating anti-tumor immunity emerged from studies with TPH-1 deficient mice, which were more resistant to bladder carcinoma cell growth than TPH-1-suffiicent mice (3). Immune resistance was not serotonin dependent, implicating Trp depletion due to TPH-1 enzyme activity in mast cells in metabolic control of anti-tumor immunity. TPH-1 activity was also shown to be important in regulating skin allograft rejection and suppressing experimental autoimmune encephalitis (EAE). Thus, TPH-1 mediates immune regulation in several inflammatory settings of clinical significance.

Arg is catabolized by two iso-enzymes arginase (ARG) I and II. ARG-I is often co-expressed with nitric oxide synthase (NOS), which competes for Arg as a substrate. Retinoic acid induced ARG-I expression in DCs that promoted Treg differentiation (43), though MDSCs were reported to inhibit Treg differentiation (44). Several studies suggest that elevated Arg consumption regulates anti-tumor immunity. Increased ARG-I expression was detected in MDSCs from cancer patients with squamous cell carcinoma (45) and ARG-II expression was elevated in cancer-associated fibroblasts and correlated with worse outcomes in pancreatic cancer (46). MDSCs facilitate tumor immune resistance, though these enigmatic cells may use multiple immune regulatory mechanisms, including Trp (47) and Arg catabolism (48). Moreover MDSCs developed from fibrocyte precursors in some cancer patients and glutamine (Gln) catabolism promoted MDSC maturation (49, 50).

Mechanisms of immune regulation driven by amino acid metabolism

How does increased amino acid catabolism inhibit tumorigenesis and therapy? Though not fully resolved, studies in mice with chronic inflammatory syndromes such as tumors have provided some key insights. Amino acid catabolism depletes local pools and generates new catabolites, and amino acid sensors and catabolite receptors sense these changes in immune cells (Fig. 3).

Amino acid levels are sensed via the mammalian target of rapamycin (mTOR) and general control non-repressed-2 (GCN2). mTOR is a pivotal checkpoint governing cell cycle entry. Tumor cells may mutate this pathway to facilitate tumor growth and mTOR inhibitors such as everolimus may be effective therapies to control some cancers (51, 52). Amino acid depletion also restrains anti-tumor immunity since mTOR signals promote T cell responses. Hence local amino acid depletion and treatment with mTOR inhibitors may inhibit anti-tumor immunity despite the potential to inhibit tumor growth. Trp depletion via IDO to prevent mTOR activation and promote tumor autophagy has been reported (53), but effects on T cell mediated anti-tumor immunity were not evaluated.

GCN2 is a ribosome-associated kinase that senses binding of uncharged tRNAs. Activated GCN2 kinase incites the integrated stress response to shut down cellular protein synthesis and induce autophagy. GCN2 activation in T cells cultured with IDO-expressing DCs from TDLNs blocked T cell responses to antigens presented by DCs (54). GCN2 was also required for TDLN DCs to induce Tregs to acquire regulatory phenotypes via IDO (55). Thus GCN2 suppresses immunity and promotes immune regulation, though GCN2 activation in tumor cells may block proliferation and induce autophagy. Recent studies attest to the diverse effects of GCN2-mediated cell stress responses on tumor growth and anti-tumor immunity. Thus GCN2 promoted tumor angiogenesis (56), inhibited the anti-tumor effects of IFNαβ (57), modified mitochondrial functions in colon cancer cells (58), and supported tumor cell proliferation during restricted access to serine (59). GCN2 may also impact cancer therapy since GCN2 induced asparagine synthetase activity (a therapy resistance factor) in pediatric acute lymphoblastic leukemia (ALL) patients and GCN2 attenuated the efficacy of glucose competitors as anti-tumor drugs (60, 61), though GCN2 also promoted the anti-leukemic effects of pegylated ARG-I in ALL (62). Some anti-tumor reagents mimic the effects of amino acid depletion by inhibiting tRNA charging enzymes to activate GCN2. Thus the antibiotic borrelidin, which inhibits human threonine tRNA synthetase, induced apoptosis of ALL cells and GCN2 activation was elevated (63). Similarly, the anti-protozoal compound halofuginone, which inhibits prolyl-tRNA synthetase, may also inhibit cancers (64). However like mTOR, potential diametric effects on tumor cell growth and survival versus immune cell activation and differentiation need to be evaluated carefully as halofuginone inhibits effector TH17 T cell responses in autoimmune syndromes (65).

Trp catabolites also mediate potent effects on tumor and immune cells (Fig. 3). Kynurenine (Kyn), a Trp catabolite made by cells expressing IDO or TDO, is a natural ligand for the aryl hydrocarbon receptor (AhR), an orphan receptor expressed by many cells (66). Chemical toxins, known as dioxins, are artificial AhR ligands that have been studied extensively by toxicologists but relatively little is known about natural AhR ligands such as Kyn. Studies in mice have identified requirements for AhR signaling in T cells, Tregs and DCs to regulate immunity (7, 9). These findings provide a rationale for mechanistic links between IDO and TDO activity and regulation of anti-tumor immunity, justifying the use of AhR antagonists as potential therapies to block suppression of anti-tumor immunity. AhR signaling also enhanced NK cell anti-tumor activity in mice (67), indicating that AhR signaling can enhance or inhibit immunity, contingent on the physiologic setting (68). It is unclear how modulation of AhR signals will impact outcomes in cancer as AhR signals may mediate

direct effects on tumor, stromal or immune cells to impede or promote tumor progression, survival, angiogenesis and anti-tumor immunity. Hence, the effects of ligands that modulate AhR signaling (in either direction) in settings of tumor growth and treatment requires more rigorous evaluation in physiologic settings of tumor growth to discern the impact of such interventions. For example, reports that Trp catabolites made by cells expressing IDO and TDO confer resistance to gliomas should be weighed against the known neurotoxic effects of some Trp catabolites (69, 70).

In summary, the downstream consequences of increased amino acid catabolism in tumor microenvironments are profound but complex, diametric and poorly defined. More studies to evaluate the role of specific pathways in physiologic settings of tumor development and therapy will be necessary to further elucidate specific contributions to tumor growth, survival and anti-tumor immunity.

Concluding remarks

Immune tolerance created by tumors is a major barrier to effective chemotherapy, radiotherapy and immunotherapy, and subsequent tumor relapse is associated with renewal of local tolerance. Increased amino acid catabolism may occur from the earliest stages of tumorigenesis due to inflammation associated with the formation malignant lesions that protects malignant cells from immune surveillance. Oncogenic viral infections, chemicals and radiation that promote carcinogenesis also stimulate increased amino acid catabolism that contributes to the local inflammatory responses to these insults and promotes resistance to natural and therapy-induced anti-tumor immunity.

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Key Points

1. Amino acid catabolism regulates immunity in settings of chronic inflammation, including cancer
2. Amino acid catabolism is enhanced prior to clinical presentation and may facilitate tumor progression
3. Amino acid depletion and production of catabolites both regulate immunity
4. Interventions targeting amino acid catabolism may be effective adjunct cancer therapies
5. Altered amino acid metabolism may yield useful prognostic markers as well as therapeutic targets.

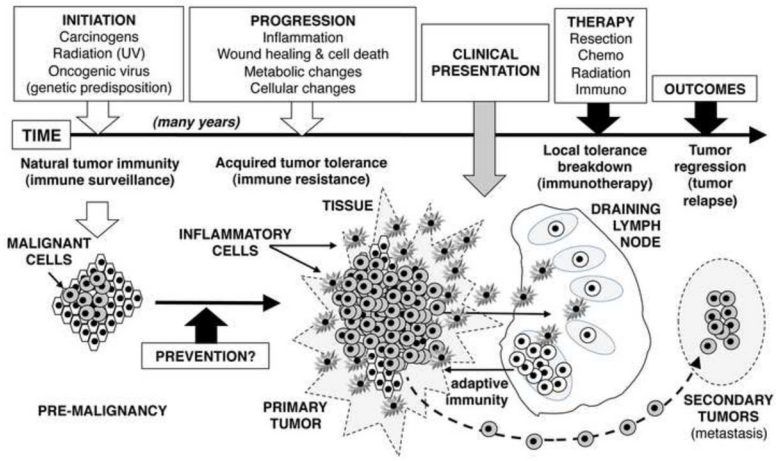

Figure 1. Stages in tumor formation and therapy

Once initiated, malignant lesions promote local inflammation that inhibits immune surveillance to facilitate tumor progression. Eventually, local lymph node involvement suppresses anti-tumor immunity. Tumor tolerance established prior to clinical presentation is a barrier to successful therapy and creates niches for metastasis and relapse.

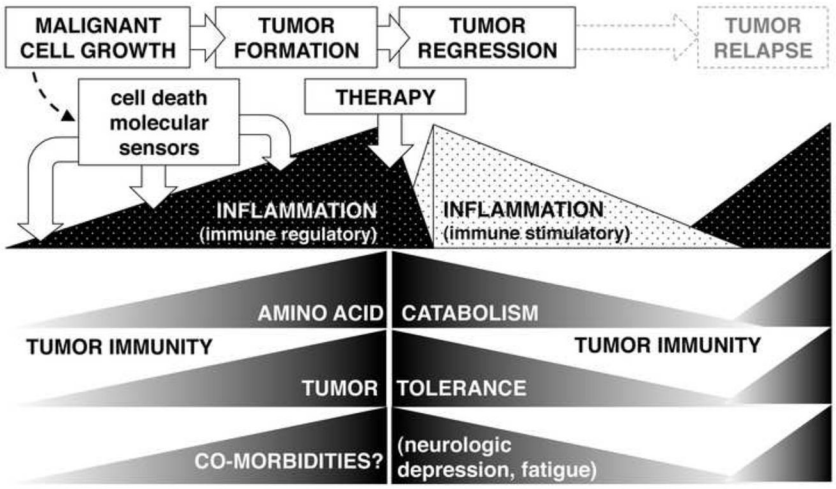

Figure 2. Amino acid catabolism during tumor progression, regression and relapse

Amino acid catabolism increases during tumor formation, and correlates with increased local inflammation and cancer-associated morbidities. Therapeutic interventions modify local inflammation to break tumor tolerance and reduce amino acid catabolism and co-morbidities, while relapse correlates with the return of processes linked to cancer.

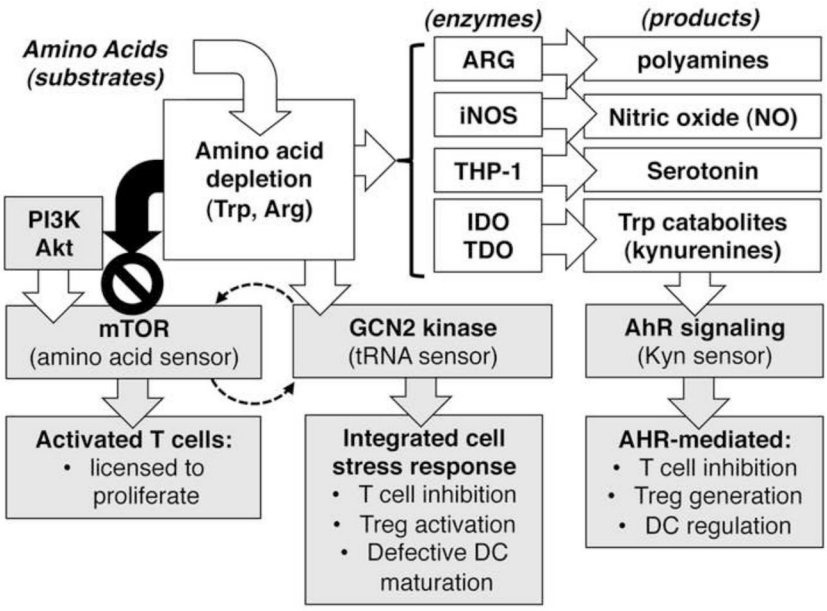

Figure 3. Downstream effects of amino acid catabolism on tumor and immune cells

Amino acid depletion and catabolite production have profound downstream effects on tumor and immune cells by triggering pathways that impact cell growth, proliferation, survival and cellular stress responses. Trp catabolites activate the AhR pathway but metabolites produced by other enzymes depicted may mediate critical effects via other pathways

Table 1

Immune regulatory pathways linked to tumor tolerance

Pathway	Description
cell types:	
MDSCs	tumor infiltrating & circulating monocytic regulatory cells
DCs	specialized subsets suppress effector T cells & activate Tregs
MΦs	Specialized subsets are tumor infiltrating regulatory cells
Tregs	potent regulatory CD4 T cells (auto/tumor antigen-specific)
NK cells	non-antigen specific regulatory lymphocytes
Mast cells	innate immune cells active in wound healing, host defense & allergy
molecules:	
CTLA4	induces T cell anergy & induces IDO in DCs (blocked by Ipilimumab)
PD-1(PD-L)	inhibitory co-stimulator pathway in T cells & Tregs
GITR	mediates immune regulation to steroids
TGFβ, IL-10	regulatory cytokines
metabolic pathways:	
IFNs (I, II)	immune activating cytokines that can stimulate or suppress immunity
IDO1 (IDO2?)	catabolizes Trp to suppress effector T cells & activate Tregs
TDO	as for IDO
TPH-1	consumes Trp to promote tolerance
ARG (I, II)	catabolizes Arg to suppress effector T cells and induce Tregs
mTOR	senses amino acid availability (nutrient check point control)
GCN2 kinase	amino acid depletion sensor (via tRNA); induces cell stress responses
AhR	senses Kyn (and other Trp catabolites) to regulate immunity