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Review Article

Role of amino acid metabolism in tumor immune microenvironment of colorectal cancer

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Abstract: This review investigates the role of amino acid metabolism in the tumor microenvironment of colorectal cancer (CRC) and explores potential targeted therapeutic strategies. The paper synthesized current research on amino acid metabolism in the colorectal cancer tumor microenvironment, focusing on amino acids such as tryptophan, methionine, glutamine, and arginine. It examined their impact on tumor growth, immune evasion, and patient prognosis, as well as the metabolic reprogramming of tumor cells and complex tumor microenvironment interactions. Aberrant amino acid metabolism was a hallmark of colorectal cancer, influencing tumor proliferation, survival, and invasiveness. Key findings included: Tryptophan metabolism via the kynurenine and serotonin pathways significantly affected immune response and tumor progression in CRC. Methionine influenced T cell function and DNA methylation, playing a critical role in tumor development. Glutamine was extensively used by tumor cells for energy metabolism and supported immune cell function. Arginine metabolism impacted CD8+ T cell functionality and tumor growth. The review also discussed the dual roles of immune cells in the tumor microenvironment and the potential of targeting amino acid metabolic pathways for CRC treatment. In conclusion, amino acid metabolism significantly impacts the colorectal cancer tumor microenvironment and immunity. Understanding these metabolic pathways provides valuable insights into CRC pathogenesis and identifies potential therapeutic targets. Future research should focus on developing treatments that disrupt these metabolic processes to improve patient outcomes in CRC.

Keywords: Colorectal cancer, amino acid metabolism, tumor microenvironment, immune evasion, therapeutic targets

Introduction

Colorectal cancer (CRC) is marked by significant heterogeneity and invasiveness, with high incidence and mortality rates [1]. Early intervention is critical for improving clinical outcomes [2]. A comprehensive understanding of CRC's pathogenesis and cellular metabolic mechanisms is essential for identifying effective therapeutic targets and developing novel treatment strategies. Amino acids are crucial for cellular survival, serving as essential nutrients for all cell types, and their metabolism is reprogrammed in cancer cells [3]. The synthesis, breakdown, and transport of amino acids provide numerous potential drug targets. Investigating the mechanisms and characteristics of amino acid metabolism in CRC is therefore important for discovering new therapeutic targets [4]. The tumor microenvironment (TME) consists of the cellular environment surrounding tumor cells, including endothelial cells, immune cells, fibroblasts, mesenchymal stem cells (MSCs), and the extracellular matrix (ECM) [5]. A complex network of cytokines, chemokines, growth factors, and exosomes interact within the TME, enabling tumors to survive under increased stress. This network facilitates tumor metastasis, immune evasion, abnormal angiogenesis, and drug resistance.

Therefore, understanding the role of amino acid metabolism in the TME is crucial for unraveling

CRC development mechanisms and progression, as well as for developing targeted therapies. This review aims to summarize and analyze the impact of amino acid metabolic processes on the CRC tumor microenvironment and its progression, providing insights into the potential of targeting amino acid metabolism for CRC treatment.

Epidemiology of colorectal cancer

CRC is a common malignancy of the digestive system, with increasing incidence and mortality worldwide [6, 7]. CRC ranks among the top cancers in new cases for both men and women, and its global incidence continues to rise each year [8]. In China, CRC is the second most common cancer, following lung cancer, with an annual mortality rate of approximately 12 per 100,000. The affected population is also becoming younger [9]. CRC development results from the long-term interaction of multiple factors. According to the latest national cancer survey in China, CRC is among the leading malignant tumors, with overall incidence and mortality rates ranked third and fifth, respectively. The occurrence and progression of CRC are complex processes, involving multiple factors, stages, and links [10]. In this context, CRC cells and their surrounding environment form a unique TME. The interactions and co-evolution between CRC cells and various TME components drive tumor initiation and progression [11].

In recent years, CRC incidence in China has been rising, with the affected population becoming younger. It is also classified as an obesity-related cancer. Modern research indicates that adipose tissue is not just a calorie storage depot but also an active endocrine and metabolic organ [12]. As part of the TME, amino acid metabolism influences tumor tissues through inflammatory responses, hypoxic conditions, and the gut microbiota. Different amino acid components play distinct roles within the TME. Abnormal amino acid metabolism is considered a hallmark of malignancies like CRC, and certain metabolic pathways may become specific targets for CRC treatment [13]. The relationship between amino acid metabolism, CRC onset and progression, and its interaction with the TME is an area of active research [7]. Imaging technologies provide valuable tools for observing amino acid metabolism within the human body [14]. This article primarily summarizes amino acid metabolism in the CRC TME and introduces recent advances in amino acid metabolic imaging. In the CRC TME, amino acid metabolism and the inflammatory microenvironment are subjects of extensive study and recognition [15]. Therefore, this review focuses on the interplay among these factors in the development and progression of CRC.

Immune cells in tumor microenvironment

The TME is the milieu in which tumors originate and grow. It is a dynamic and complex system composed of four major components: non-tumor cells, the ECM, the vascular system, and soluble factors [16, 17]. The cellular components include immune cells, fibroblasts, endothelial cells, and neuronal cells. The ECM, a non-cellular component, forms a dynamic molecular network of various proteins that provides structural support and regulates cellular activity [18]. The vascular system is essential for supplying oxygen and nutrients to tumor cells, with a rich blood vessel network surrounding the tumor. Soluble factors in the TME, such as chemokines and regulatory proteins, influence the vital functions of the cellular components [19, 20].

Helper T cells

Interleukin-17 (IL-17), secreted by helper T cells 17, is a significant factor associated with inflammatory bowel disease (IBD), while IL-23, as an active regulator of Th17 cells, can influence IL-17 secretion [21]. Mouse experiments have found that blocking the IL-23 signaling pathway can induce apoptosis in Th17 cells, thereby attenuating colitis reactions [22]. This suggests that the inflammatory microenvironment plays a key role in CRC development, and immune suppression. When the intestine is stimulated by endogenous or exogenous factors, it activates inflammatory signaling pathways, producing inflammatory cytokines such as NF-κB, TNF-α, and IL-17, which promoteinflammation and even lead to carcinogenesis in intestinal cells [23].

Macrophages

Macrophages are essential innate immune cells that primarily function by phagocytosing

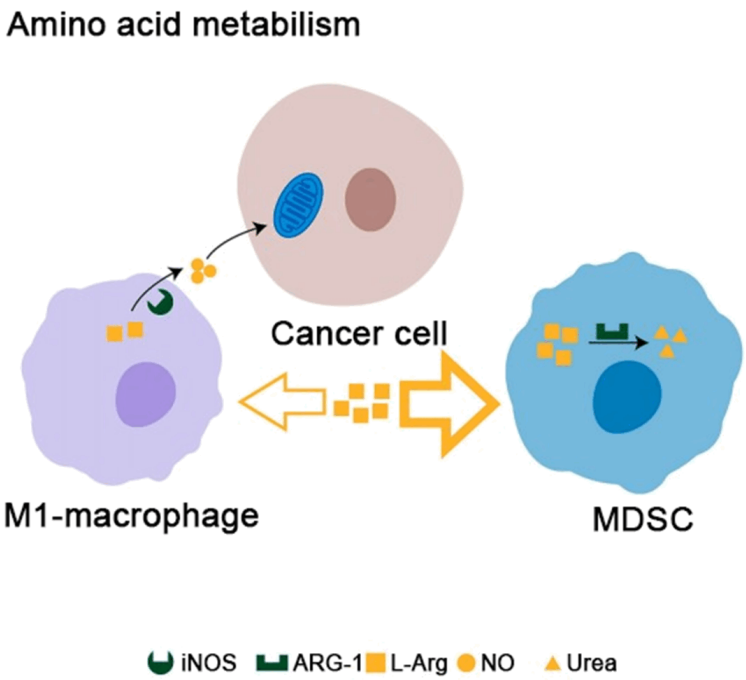

Figure 1. Amino acid metabolism myeloid-derived suppressor cells (MDSCs) with high expression of ARG1 compete with M1 type macrophages for the consumption of arginine, thereby reducing the release of nitric oxide (NO) by M1 type macrophages to block the mitochondrial respiration activity of colorectal cancer cells.

cellular debris and pathogens, as well as activating other immune cells to combat infections. As key components of the innate immune system, macrophages respond to pathogens by engulfing cell remnants and pathogens and triggering immune responses [24]. Tumor-associated macrophages (TAMs) within the TME exhibit significant plasticity and heterogeneity. Early in tumor development, pro-inflammatory factors, such as Toll-like receptor agonists, can drive TAMs toward an M1 phenotype. In this state, macrophages inhibit tumor growth and kill cancer cells through nitric oxide and reactive oxygen species (ROS) [25]. Understanding the complex interactions in the TME, including the role of arginine metabolism and macrophage function, is crucial for developing targeted therapies to improve outcomes for CRC and other malignancies. As tumors progress, factors such as interleukin-4 and colony-stimulating factor 1 guide TAMs toward an M2 phenotype [26].

Macrophages in the M1 and M2 states exhibit distinct metabolic profiles: M1 macrophages rely on glycolysis and the pentose phosphate pathway to generate pro-inflammatory cytokines and ROS [27, 28], while M2 macrophages, which are involved in tissue repair and fibrosis, secrete anti-inflammatory cytokines like TGF-β and IL-10 [29]. Among the M2 macrophages, a specialized subset known as TAMs has been identified in the TME (**Figure 1**). TAMs secrete immunosuppressive factors, including IL-10, TGF-β, and prostaglandin E2 (PGE2), which modulate the apoptosis of T lymphocytes and natural killer (NK) cells. These factors create an immune-tolerant environment that facilitates immune evasion, angiogenesis, and tumor progression [30]. Chronic inflammation, a precursor to CRC, is exacerbated by metabolic interactions among TAMs, tumor cells, and other TME components, accelerating tumor development and promoting CRC progression [31].

Lymphocytes

Historically, lymphocytes were viewed as immune cells infiltrating tumors to recognize and destroy cancer cells. However, recent studies have revealed their complex dual roles in cancer [32]. CD8+ cytotoxic T lymphocytes (CTLs) and NK cells actively perform their immune functions to inhibit tumor progression. In contrast, other subgroups, such as certain CD4+ T cells within the TME, including Th17 and regulatory T cells (Tregs), exhibit opposing roles. This paradoxical behavior of lymphocytes is linked to their intrinsic properties and the complex metabolic interactions with other TME components [33].

Neutrophils

Neutrophils are a critical component of the TME and play a pivotal role in the cancer immune response. Clinical studies have demonstrated that neutrophil-specific biomarkers

are highly predictive of the prognosis of various cancers, particularly CRC. Notably, an elevated neutrophil-lymphocyte ratio (NLR) is associated with poor clinical outcomes and is considered a reliable predictor of overall survival in CRC [34]. Neutrophils in the TME exhibit two opposing phenotypes: anti-tumoral and pro-tumoral, the latter known as tumor-associated neutrophils (TANs). The phenotypic shift of neutrophils is primarily regulated by signals such as INF-β, TGF-β, and PGE2. Blocking these pathways can activate TANs with anti-tumoral properties. Research indicates that TANs undergo metabolic reprogramming within the TME and engage in extensive metabolic interactions with CRC cells, playing a crucial role in the structural and functional remodeling of the TME [35].

Amino acid metabolism in the tumor immune microenvironment

Amino acids are essential substrates and products in various cellular processes. Key amino acids related to tumor metabolism and immunity include glutamate, arginine, and tryptophan [15, 36]. Dysregulated metabolism of glutamine, glycine, and tryptophan has been identified as a metabolic mechanism that supports cancer cell growth and serves unique roles as substrates for immune cells [37-39]. Tumor cells exhibit self-sufficiency in growth signals, resistance to cell death, and limitless proliferative potential, enabling rapid proliferation [40]. The cellular components within the TME compete for oxygen and nutrients, creating physicochemical conditions such as low pH and hypoxia [15, 41]. To meet their energy demands, tumor cells undergo metabolic reprogramming, adjusting energy supply pathways, such as utilizing amino acid metabolism to enter glycolytic and oxidative pathways. These metabolic alterations can influence immune cell function and impact the efficacy of immunotherapy [42, 43]. CRC cells, driven by rapid growth requirements, demand substantial energy and biosynthetic materials. Amino acids not only provide energy but also serve as building blocks for proteins, nucleic acids, and other biomolecules. For instance, glutamine is critical for tumor cells, supplying energy and contributing to the synthesis of nucleotides and non-essential amino acids [44]. The TME, including nutrient, oxygen, and growth factor availability, influences CRC development. Amino acid metabolism, particularly of arginine and tryptophan, impacts both tumor cells and immune cell function, contributing to tumor immune evasion [44]. In CRC, amino acid metabolic pathways such as glutamate metabolism, the methionine cycle, and tryptophan metabolism are often abnormally activated, closely associated with tumor proliferation, survival, and invasiveness [45, 46].

Tryptophan

Tryptophan, an essential amino acid, plays a critical role in cellular functions, with its concentration in the TME influencing T cell responsiveness and the efficacy of anti-tumor effects. Tumor cells express high levels of indoleamine 2,3-dioxygenase (IDO), which degrades tryptophan into kynurenine, leading to a tryptophan-depleted TME. The role of tryptophan and its metabolism in CRC is complex and multifaceted. Research shows that variations in tryptophan levels are closely associated with immune activation, quality of life deterioration, and disease progression in CRC patients. For example, studies have found that reduced serum tryptophan levels correlate with immune activation and impaired quality of life, suggesting that tryptophan metabolism impacts both overall health and disease trajectory [47].

Tryptophan metabolism through the kynurenine and serotonin pathways varies significantly between colon and rectal cancers, potentially affecting the TME and immune response. Increased activity of these metabolic pathways may lead to tryptophan depletion and the accumulation of immunosuppressive metabolites, thereby impairing immune cell function and facilitating tumor immune escape [48]. Metabolites such as kynurenine have been shown to regulate inflammatory bowel diseases and CRC by influencing immune system activity to either promote or inhibit tumor development. These metabolites may alter the TME by affecting T cell activity and other immune cells, thus influencing tumor growth and metastasis [49]. Furthermore, changes in fecal tryptophan metabolism, associated with alterations in the microbiota, may contribute to CRC pathogenesis, suggesting that the gut microbiome influences CRC development via its effect on tryptophan metabolism [50].

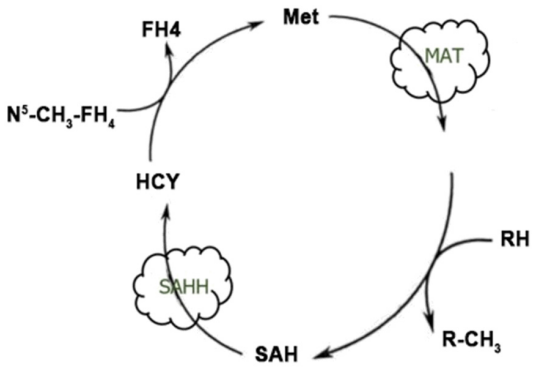

Figure 2. Methionine cycle.

Tryptophan metabolism is considered a potential therapeutic target for colon and gastrointestinal cancers, particularly for regulating inflammation and immune escape. Research is exploring how modulating tryptophan metabolic pathways can improve treatment outcomes and patient prognosis [51]. General control nonderepressible 2 (GCN2) kinase, a stress-response kinase, is activated by tryptophan depletion in CD8+ T cells, leading to downregulation of the CD3 chain, cell cycle arrest, and impaired cytotoxic function [52]. As an essential amino acid, tryptophan is integral to tumor development, immune escape, and patient prognosis in CRC. Increased metabolic activity through IDO and tryptophan dioxygenase (TDO) pathways leads to tryptophan depletion in the TME, generating immunosuppressive metabolites like kynurenine. These changes impair immune cell function, particularly T cells, promoting immune escape and favoring tumor growth and spread [53, 54].

IDO exists in two isoforms, IDO1 and IDO2, whose overexpression is closely linked to tumor progression. IDO1 accelerates tryptophan metabolism in the TME, recruiting and activating myeloid-derived suppressor cells (MDSCs). As tryptophan is depleted, T lymphocytes and NK cells undergo apoptosis due to energy deficiency, while free tRNAs, which transport tryptophan, directly activate regulatory T cells and inhibit the proliferation of effector T lymphocytes and the function of antigen-presenting cells through the stress kinase 2 pathway. Therefore, overexpression of IDO1 contributes to a highly immunosuppressive TME [55, 56]. Research has found that IDO2, with a much lower affinity for tryptophan than IDO1, is expressed in fewer than 1% of tumors. Its high expression may enhance Treg cell-mediated immune suppression, activate B lymphocytes, and produce autoantibodies, participating in tumor immune microenvironment formation [57]. Although the role of IDO2 in immune tolerance is not fully understood, its potential suppressive effect on the tumor immune microenvironment warrants further investigation [58]. Additionally, tryptophan and its metabolites directly influence tumor cell proliferation, survival, and death, affecting tumor cell metabolism through mechanisms such as mitochondrial regulation and oxidative stress induction.

Methionine

Methionine is a crucial amino acid in regulating T cell function. Tumor cells increase methionine uptake by upregulating the expression of methionine transport proteins, thereby depleting methionine levels in the TME and reducing methyl donors [59]. This affects the methylation status of lysine 79 on the histone H3 subunit (H3K79) in CD8+ T cells, impairing their anti-tumor functionality [60]. Current research indicates that the methionine cycle plays a significant role in tumor development and progression [61]. The methionine cycle is essential not only for cell growth and survival but also for DNA methylation and gene expression regulation, as shown in **Figure 2**. In CRC, aberrant activation or inhibition of this cycle can influence tumor cell proliferation, metabolic state, and response to therapy. Intermediate metabolites of the methionine cycle, such as S-adenosylmethionine (SAM) and S-adenosylhomocysteine (SAH), regulate DNA methylation and gene expression. These alterations can lead to the silencing of tumor suppressor genes or activation of oncogenes [62].

The importance of methionine in T cells is not determined by the difference between intracellular and extracellular methionine concentrations, but by the upregulation of the methionine transporter protein SLC7A5 in T cells following antigenic stimulation. Therefore, SLC7A5 is considered a rate-limiting factor for methylation during T cell activation [63].

Dietary intake of methionine has also been linked to CRC risk. Adequate methionine levels are essential for maintaining normal metabolism and cellular functions, while both excess

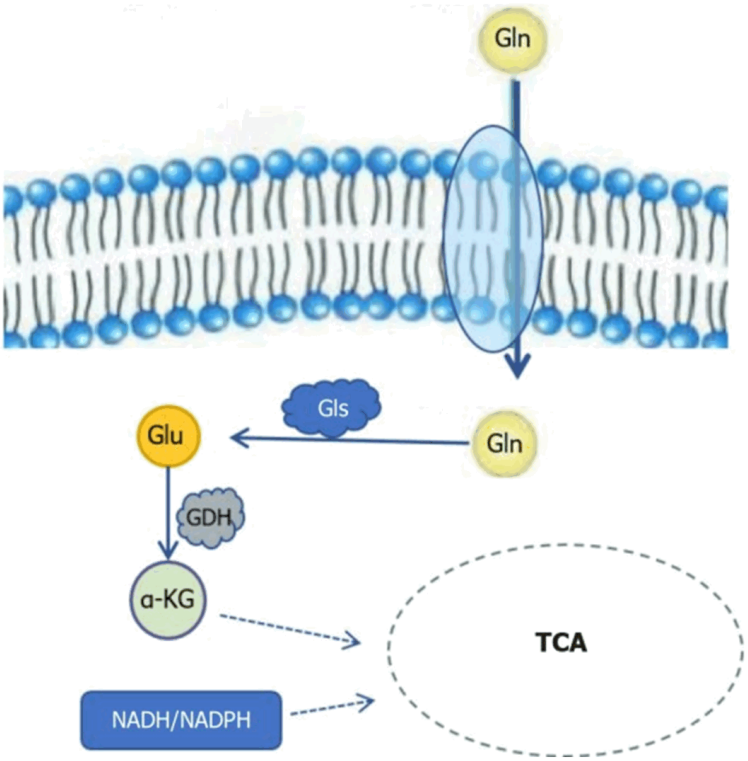

Figure 3. Metabolic pathways of glutamine.

and deficiency may increase disease risk. Understanding the balance of methionine metabolism and its impact on the TME and immune response is crucial for developing targeted therapies and dietary strategies in CRC management [64].

Glutamine

Glutamine plays a critical role in the energy metabolism of tumor cells, making it one of the most essential amino acids. Through its conversion to glutamate, glutaminase has become a key metabolic target in cancer therapy. In immune cells, alterations in glutamine metabolism are crucial for cell fate and profoundly impact the immune response [65]. The polarization shifts between functionally distinct M1 and M2 tumor-associated macrophages (TAMs) are central to the immune evasion mechanisms of tumors. Moreover, glutamine is decisive in TAM polarization and T cell differentiation, with its metabolic pathways significantly influencing the immune functions of TAMs and T cells.

Compared to normal cells, tumor cells exhibit distinct differences in amino acid metabolism, characterized by reduced amino acid catabolism and enhanced protein synthesis. Tumor cells experience an increased demand for glutamine, which becomes a critical metabolic pathway. Through metabolic processes, glutamine is converted into α-ketoglutarate, entering the tricarboxylic acid cycle, and contributes to the synthesis of amino acids, nucleotides, and fatty acids (**Figure 3**). Additionally, glutamine is converted into glutathione, maintaining intracellular redox balance, which is crucial for tumor cell survival and proliferation [65]. Glutamine deficiency has also been shown to promote epithelial-mesenchymal transition, enhancing the invasiveness and metastatic potential of tumors [66].

In terms of immune function, glutamine is vital for maintaining normal immune responses. A meta-analysis of CRC patients indicated that glutamine supplementation improved postoperative immune function and potentially reduced postoperative complications, suggesting that glutamine may influence the tumor microenvironment by regulating immune cell function [67]. On the molecular level, changes in glutamine metabolism, particularly the upregulation of glutaminase expression, are crucial in the development of CRC. Glutaminase, a key enzyme in glutamine metabolism, is overexpressed in CRC tissues and is associated with cancer progression and poor patient prognosis [68]. Additionally, laboratory studies indicate that glutamine regulates the phenotype of CRC cells and stimulates their proliferation, further emphasizing its significant role in tumor biology [69].

Overexpression of the glutamine transporter protein SLC38A1 significantly enhances mitochondrial function in CD4+ T cells exposed to ascites from ovarian cancer patients, a process linked to glucose metabolism [70]. Another glutamine transporter, SLC38A2, is essential for T cell production and memory, partly by regulating mTORC1 activity [71]. As a precursor for pro-

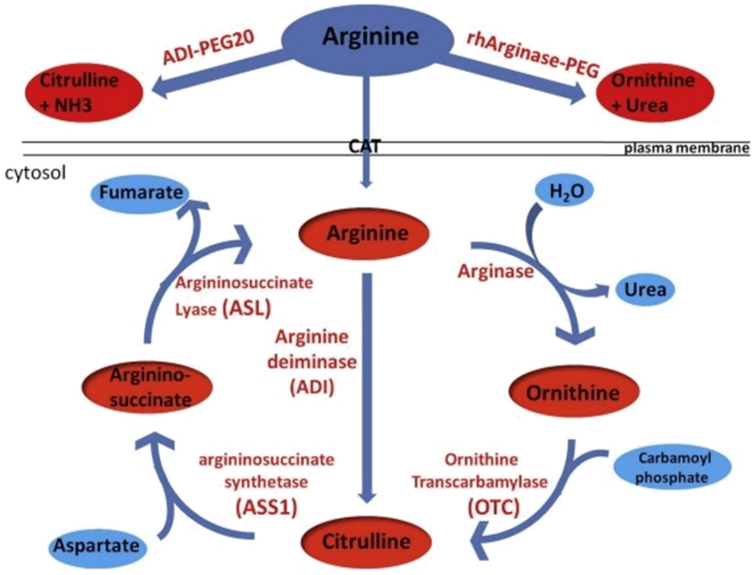

Figure 4. Introduction to the tumor microenvironment, its significant role in cancer progression, the impact of different amino acid metabolic processes on various immune cells (Macrophages, T Cells, Myeloid-Derived Suppressor Cells, etc.), and studies on the mechanism of action in colorectal cancer tumor immunity.

tein O-GlcNAc acylation, glutamine also regulates T cell self-renewal [72]. Additionally, glutamine maintains Teff cell ATP levels through glutamine-dependent mitochondrial metabolism [44]. Glutamine catabolism promotes the resynthesis of glutathione (GSH), which affects T cell differentiation, a process also influenced by mTOR activity [73, 74].

In summary, glutamine plays multiple roles in CRC development and prognosis, from affecting tumor cell metabolism and proliferation to regulating the immune microenvironment. These findings provide a deeper understanding of CRC biology and offer potential targets for future therapeutic strategies. As further research elucidates the role of glutamine in CRC, new approaches may emerge to improve treatment outcomes and the quality of life for patients.

Arginine

The arginine metabolic pathway significantly impacts the functionality of CD8+ T cells, particularly through the regulation of nitric oxide release via NOS metabolism. This not only affects the inflammatory response within the tumor microenvironment but also directly influences tumor cell growth and death [75, 76]. Arginine is a crucial amino acid for tumor cell metabolism and proliferation. It serves as both an intermediate in the urea cycle and a precursor for the synthesis of bioactive substances such as proteins, polyamines, creatine, and nitric oxide, as shown in **Figure 4** [77].

In both normal and cancerous cells, arginine synthesis pathways primarily include the ornithine cycle and uptake from the external environment via specific membrane transport proteins. Various enzymes, such as Arg-1, ADC, ADI, ASS1, and ASL, are involved in arginine metabolism, influencing its intracellular levels and distribution through different pathways [78, 79]. In the tumor microenvironment, an imbalance in arginine metabolism is closely linked to tumor development. For instance, the increased demand for arginine by tumor cells can suppress immune cell function, particularly T cells, by consuming large amounts of arginine [80]. This alters the metabolic state of immune cells, directly affecting their survival and functionality. Additionally, arginine metabolic products like polyamines and nitric oxide contribute to tumor cell proliferation, apoptosis, and interactions with immune cells [81].

Recent studies suggest that restricting arginine intake can reduce the incidence of CRC, highlighting the significance of arginine and its metabolism in tumor growth [82]. CRC cells are highly dependent on arginine, and its deficiency leads to inhibited growth, characterized by halted DNA replication and downregulated expression of cell cycle proteins. These effects can be reversed by supplementing exogenous arginine [83]. Furthermore, changes in arginine metabolic pathways, such as those involving eNOS and ODC in CRC, highlight their potential roles in regulating tumor growth, angiogenesis, and immune evasion. These findings not only reveal the complexity of arginine metabolism in tumor biology but also provide new possibilities for therapeutic strategies.

Memory T cell generation and persistence, but not effector T cells, can be reprogrammed by SLC7A1-transported arginine through a mechanism that partially depends on mTORC1 [71]. SLC38A9, a lysosomal transmembrane protein, regulates the interaction of intracellular arginine sensors with the lysosomal membrane-localized Rag GTPase. It acts as a scaffold, linking Rag GTPase with mTORC1 attached to the lysosome [84, 85].

Treatment of colorectal cancer based on amino acid metabolism

Amino acids are essential components of cellular metabolic processes, with glutamine emerging as a key target for modulating tumor progression and immune response [37]. In breast cancer models, the glutamine inhibitor JHU-083 has been shown to reduce CSF levels in the tumor microenvironment, decrease the recruitment of MDSCs, and promote MDSC polarization toward M1 macrophages, thereby slowing tumor growth and suppressing the expression of IDO in both tumors and MDSCs, which leads to a reduction in kynurenine levels [15]. In CRC mouse models, JHU-083 inhibits glutamine metabolism, enhances CD8+ T cell activity, and strengthens anti-tumor immune responses, leading to tumor regression and improved survival rates in mice [37]. Currently, targeting glutamine metabolism with DRP-104 in combination with atezolizumab (a programmed death receptor ligand 1 inhibitor) is undergoing clinical trials (NCT04471415) for the treatment of advanced non-small cell lung cancer and head and neck squamous cell carcinoma [86].

Tumor cells rely on de novo amino acid synthesis for energy, making fatty acid synthase (FASN) a promising therapeutic target. Restimulation-induced cell death (RICD) is an apoptotic pathway triggered in effector T cells after TCR reactivation [15]. When FASN is inhibited, T cells in the tumor microenvironment can avoid RICD induced by repeated TCR stimulation, enhancing their anti-tumor activity [46]. TVB-2640, the first FASN inhibitor to enter clinical trials, is currently being tested for various solid tumors, including CRC (NCT029800791, etc.) [43].

Arginine, a substrate for eNOS, plays a pivotal role in activating the tumor PI3K-Akt-eNOS (wild-type)-Ras pathway, which is associated with increased arginine metabolism in cancer cells [87]. Cells use a recycling mechanism involving intracellular argininosuccinate synthase (ASS) and argininosuccinate lyase (ASL) to generate citrulline for arginine synthesis. Many solid tumors, including hepatocellular carcinoma, malignant melanoma, malignant pleural mesothelioma, prostate cancer, and renal cancer, become arginine-auxotrophic due to the loss of ASS. However, some platinum-sensitive tumors, such as primary CRC, exhibit ASS overexpression, undermining the effectiveness of arginine deprivation strategies in CRC treatment [87].

The diagnosis and treatment of CRC based on amino acid metabolism is a complex, multidimensional research area, encompassing biomarker discovery and therapeutic strategy development [45]. Analyzing changes in the amino acid profile of CRC patient serum offers new avenues for early diagnosis and monitoring [88]. Understanding the relationship between amino acid metabolic genes and immune therapy responses, as well as CRC clinical prognosis, provides a new perspective for personalized medicine (**Table 1**) [88, 89].

Metabolomics plays a crucial role in discovering CRC-related biomarkers, highlighting its potential in disease management. “Metabolomics in diagnosis and biomarker discovery of colorectal cancer” discusses the application of metabolomics for CRC diagnosis and biomarker discovery, providing vital information for early detection and treatment [90]. Tissue metabolomics phenotyping for CRC diagnosis and prognosis prediction offers novel research perspectives and approaches [90]. This review reflects technological advancements in omics technologies for improving CRC diagnosis and treatment, showcasing future directions [91]. Non-invasive diagnostic methods based on the metabolic characteristics of urine from CRC patients are also being explored [92]. Investigating the link between serum amino acid metabolism and lymph node metastasis in CRC patients provides valuable insights into the metastatic mechanisms of the disease [93].

Studies have found that kynurenine (kyn) levels are elevated in colon cancer tissues compared to normal colon tissues and positively correlate with the overexpression of IDO1, TDO,

Table 1. Treatment of colorectal cancer based on amino acid metabolism

Target	Mechanism of Action	Effect
HIBCH	Valine metabolism	HIBCH as a critical enzyme of valine catabolism in CRC progression and resistance to anti-VEGF therapy [100]
Serum amino acid	Serum glycine and tyrosine	Multiple significant disease-associated alterations in the amino acid profile with promising diagnostic power [101]
Amino acid metabolism-related genes (AAMRGs)	Regulating serine and glycine metabolic pathways, affecting tumor cell one-carbon metabolism	Inhibiting cell proliferation, inducing apoptosis [102]
l-asparaginases	Altering glutamine metabolic pathways, increasing chemotherapy sensitivity	Improving chemotherapy response rate, improving survival rates [103]
Sulindac	Polyamine Metabolic Pathways	Reducing tumor cell energy production, inhibiting tumor growth [104]
NSAIDs	Polyamine Metabolic Pathways	Induce SAT1 expression in human cell and mouse models, which may be one of the reasons for the treatment effect of inflammatory colorectal cancer [105]

CRC: colorectal cancer; VEGF: vascular endothelial growth factor.

and AFMID [94]. However, research also indicates that 8-hydroxyquinoline acid, the terminal metabolite of the kynurenine pathway, can inhibit mitochondrial activity and DNA synthesis in colon cancer cells, thereby suppressing the proliferation and migration of HT-29 and LS-180 colon cancer cells [95]. Animal studies have confirmed that dual-targeting IDO1/TDO inhibitors, at higher doses (80 mg/kg), show stronger anti-tumor effects on CRC xenografts compared to using an IDO1 inhibitor alone. Additionally, TDO inhibitors combined with PD-1 inhibitors significantly inhibit the growth of CRC xenografts, outperforming monotherapy. Mice treated with a combination of PEG-KYNase and PD-1 inhibitors exhibit significantly smaller tumor volumes than those in the control and monotherapy groups, with PEG-KYNase enhancing the efficacy of PD-1 inhibitors more than IDO1 inhibitors [48]. Therefore, the combination of TDO inhibitors and PEG-KYNase with immune checkpoint inhibitors holds significant clinical potential [96]. Currently, the IDO1 inhibitor Epacadostat, in combination with pembrolizumab, is undergoing phase I/II clinical trials for highly microsatellite-unstable CRC [97].

Moreover, intracellular polyamine metabolism is tightly regulated. Disruption of this balance can lead to tumor formation, as observed in CRC. The catabolic metabolism of spermidine/spermine is regulated by key enzymes, including spermine oxidase (SMO), spermidine/spermine N1-acetyltransferase (SAT1 or SSAT), and N1-acetylpolyamine oxidase (APAO), all of which play significant roles in CRC treatment. Non-steroidal anti-inflammatory drugs (NSAIDs), such as sulindac, can induce SAT1 expression in both human cells and mouse models, potentially enhancing their therapeutic efficacy in inflammatory CRC [49]. Studies show that SAT1 overexpression reduces spermidine and spermine levels, impairing protein synthesis and cell growth, which suggests its potential utility in CRC therapy [98]. Therefore, enzymes such as SSAT, APAO, and SMO represent promising targets for CRC treatment strategies [99].

Summary and future perspectives

The body typically maintains internal homeostasis through three major metabolic pathways. These pathways, however, are reprogrammed during cancer development, influencing the TME and cellular immune efficacy. In CRC, alterations in amino acid, glucose, and lipid metabolism contribute to changes in CRC cell proliferation and growth through metabolic reprogramming and TME modifications. This paper reviews the impact of amino acid metabolism on the immune microenvironment in CRC patients. The intricate interaction between amino acid metabolism and the TME plays a pivotal role in CRC progression and treatment response.

This review emphasizes the significant roles of specific amino acids, such as tryptophan, methionine, glutamine, and arginine, in influencing tumor growth, immune response, and patient prognosis. Disruptions in these meta-

bolic pathways are not only hallmarks of CRC but also potential therapeutic targets. The dual nature of immune cells within the TME further complicates disease progression and response to treatment. By targeting these metabolic pathways, novel therapeutic strategies can be developed to inhibit tumor growth, overcome immune evasion, and improve patient outcomes.

Recent evaluations of targeting aberrant amino acid metabolism suggest its potential to enhance anticancer immunity. Combination therapies involving amino acid supplementation or inhibitors of metabolic enzymes may provide improved efficacy compared to monotherapies, such as anti-PD-1 or chemotherapy. Additionally, manipulation of amino acid metabolism could enhance the effectiveness of immunotherapies, including CAR-T cell therapy. However, it is crucial to recognize that amino acids are essential for many physiological processes, so caution must be exercised when targeting these pathways to avoid systemic cytotoxicity.

Future research should focus on elucidating the complex metabolic interactions within the TME, developing targeted therapies, and understanding the broader implications of amino acid metabolism in CRC pathogenesis and treatment. Given the structural complexity of the TME, the development of new cell culture systems, such as organoids, will provide a more physiological environment to simulate the TME in vitro. Incorporating immune cells into organoid cultures will offer a platform to quantitatively study the metabolic interactions between immune cells and tumor cells. Furthermore, the ability to replenish amino acids and metabolites in organoid cultures will provide valuable insights into their necessity and sufficiency for immunity against tumors.

However, potential regulatory mechanisms are still in the early stages of exploration. While broad molecular mechanisms are likely to exist, there may also be environmental factors that drive amino acid competition in different cancer types. Further mechanistic understanding of this metabolic rewiring will uncover new therapeutic targets to restore anti-tumor immunity in the TME and improve the efficacy of clinical immunotherapy. We hope this review provides a systematic overview of the field and highlights new research directions for studying the CRC immune microenvironment and related therapies.

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Disclosure of conflict of interest

None.

Abbreviations

CRC, Colorectal Cancer; TME, Tumor Microenvironment; MSCs, Mesenchymal Stem Cells; ECM, Extracellular Matrix; IDO, Indoleamine 2,3-Dioxygenase; TDO, Tryptophan Dioxygenase; GCN2, General Control Nonderepressible 2; SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine; TAMs, Tumor-Associated Macrophages; ASS1, Argininosuccinate Synthase 1; ASL, Argininosuccinate Lyase; Arg-1, Arginase-1; ADC, Arginine Decarboxylase; ADI, Arginine Deiminase; eNOS, Endothelial Nitric Oxide Synthase; ODC, Ornithine Decarboxylase; IL-17, Interleukin-17; IL-23, Interleukin-23; NF-κB, Nuclear Factor Kappa B; TNF-α, Tumor Necrosis Factor Alpha; TGF-β, Transforming Growth Factor Beta; PGE2, Prostaglandin E2; ROS, Reactive Oxygen Species; CTLs, Cytotoxic T Lymphocytes; NK, Natural Killer; NLR, Neutrophil-Lymphocyte Ratio; TANs, Tumor-Associated Neutrophils; INF-β, Interferon Beta; MDSCs, Myeloid-Derived Suppressor Cells; RICD, Re-stimulation-Induced Cell Death; TCR, T Cell Receptor; FASN, Fatty Acid Synthase; PI3K, Phosphoinositide 3-Kinase; Akt, Protein Kinase B; IBD, Inflammatory Bowel Disease; SMO, Spermine Oxidase; SAT1, Spermidine/Spermine N1-Acetyltransferase 1; APAO, N1-Acetylpolyamine Oxidase; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs.

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