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Targeting regulation of tryptophan metabolism for colorectal cancer therapy: a systematic review

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Colorectal cancer (CRC) is one of the most malignant cancers resulting from abnormal metabolism alterations. As one of the essential amino acids, tryptophan has a variety of physiological functions, closely related to regulation of immune system, central nervous system, gastrointestinal nervous system and intestinal microflora. Colorectal cancer, a type of high-grade malignancy disease, stems from a variety of factors and often accompanies inflammatory reactions, dysbacteriosis, and metabolic disorders. Colorectal cancer accompanies inflammation and imbalance of intestinal microbiota and affects tryptophan metabolism. It is known that metabolites, rate-limiting enzymes, and ARH in tryptophan metabolism are associated with the development of CRC. Specifically, IDO1 may be a potential therapeutic target in colorectal cancer treatment. Furthermore, the reduction of tryptophan amount is proportional to the poor quality of life for colorectal cancer patients. This paper aims to discuss the role of tryptophan metabolism in a normal organism and investigate the relationship between this amino acid and colorectal cancer. This study is expected to provide theoretical support for research related to targeted therapy for colorectal cancer. Furthermore, strategies that modify tryptophan metabolism, effectively inhibiting tumor progression, may be more effective for CRC treatment.

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1 Introduction

Tryptophan (TRP) is one of the essential amino acids for humans. It is an important functional amino acid with a variety of nutritional and physiological functions.¹ It is indicated that many diseases are associated with TRP metabolism disorders, such Huntington's disease,³ and gastrointestinal diseases⁴ to name a few, also, miscarriage.² In recent years, a large number of studies have shown that tumor growth is closely related to TRP metabolism.⁵ TRP is mainly a part of two metabolic pathways *in vivo*: serotonin metabolism and kynurenine metabolism (Fig. 1). Kynurenine metabolism is the main metabolic pathway of TRP. Under normal circumstances, serotonin metabolism is closely related to the nervous system and provides an important neurotransmitter 5-HT. Relatively speaking, the kynurenine pathway also plays an important role which is associated with the function of the immune system.⁶ Generally, TRP is an important regulator of mucosal homeostasis. The endogenous

TRP metabolites play an important role in intestinal immune homeostasis in mammals.^{7,8}

Colorectal cancer (CRC), one of the most common worldwide malignancies, always starts with an inner tumor or tissue in the rectum or colon, grows abnormally after becoming a polyp, and

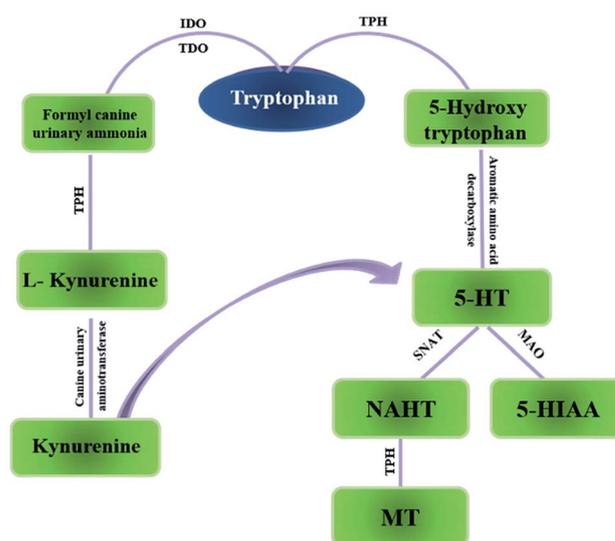


Fig. 1 The two main pathways of tryptophan metabolism *in vivo*. IDO: indoleamine-2,3-dioxygenase; TDO: toluene dioxygenase; TPH: tryptophan hydroxylase MAO: monoamine oxidase; SNAT: N-acetyltransferase.

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eventually transform into cancer. The incidence of CRC is always occult, and many advanced-stage cancer patients, so the mortality rate is high. In 2016, CRC became the third most deadly cancer in the United States⁹ and the number of patients is on the rise. Gene mutations, inflammatory stimuli, and immune disorders can lead to precancerous lesions. In addition, many studies have confirmed that improper diet and unhealthy lifestyle play a role in the development of CRC.¹⁰ In addition, various metabolic abnormalities affect the development of the disease.¹¹ Among them, TRP metabolic disorder is one of the metabolic pathways closely associated with CRC. The article summarizes the role of TRP metabolism in the development of CRC and aims to guide related scientific research.

2 The status of CRC related studies

CRC is divided into several fields by Traditional Chinese Medicine (TCM) as follows: “intestinal accumulation”, “accumulation”, “diagnosis”, “intestinal fistula”, “intestinal wind”, “dirty poison” and “snoring” as well as “anal fistula”. The hypostatic cause of malignancy is caused by healthy energy deficiency and evil excess, dyspeptic convulsion with internal injury and self-mood disorders. The viscera deficiency with deficiency of Qi and blood is the core reason for CRC.¹² Modern studies have shown that the occurrence of CRC is related to various factors, such as inflammation and gene mutations. It was reported earlier that the inflammatory cytokine interleukin-6 (IL-6), isolated from mesenchymal stem cells, promotes the progression of colorectal cancer cells *via* IL-6/JAK2/STAT3 signaling.¹³ The classical “adenomas-carcinoma” doctrine describes CRC as a multi-gene and multi-step complex process. Cancer progresses slowly from normal epithelium to dysplasia, adenoma, carcinogenesis, and cancer metastasis in turn. Some of the mutated genes associated with CRC lesions include *APC*,¹⁴ *TP53*,^{15,16} *KRAS*,¹⁷ which are mainly involved Wnt, TGF- β , and p53 pathways. Mutations in the gene *APC* initiate CRC tumor progression, resulting in 50% of all CRC cases.^{18,19} At the same time, at the genomic level, the study of the gene mutation collaboration effect on CRC development has also received attention.²⁰ A series of gene mutations, mismatches, activation of oncogenes, and inactivation of tumor suppressor genes have constituted a process of malignant disease. In addition, diet, lifestyle and other factors affect the development and prognosis of CRC.²¹ For example, obesity can accelerate the progression of CRC.²² The negative habits need to ameliorate in time, such as high-fat diet, smoking, and drinking.^{23–27} In other words, the occurrence of CRC is mainly caused by the combination of genetic and environmental factors. According to epidemiological statistics data, there are more than 1 million new cases of enlarged bowel cancer each year.²⁸ Therefore, healthy lifestyle, active prevention, and accurate diagnosis and treatment programs are effective measures to curb CRC.

At present, fecal occult blood tests²⁹ and colonoscopy³⁰ are the main screening technologies for CRC. However, fecal occult blood tests are not always accurate and colonoscopy is an invasive procedure. Therefore, a non-invasive fecal exfoliated cell technology and serum markers such as CEA, CEA199, CEA242, CA742, and CA125 are often used in clinical

practice.^{31,32} Drugs, nutritional supplements, diet, and exercise can effectively prevent the occurrence of CRC. In addition to medication, clinicians often use colonoscopy and other methods to treat CRC. However, the results are not satisfactory, owing to the hidden incidence of CRC. In addition, surgery removes only the local lesions and cannot intrinsically treat the disease. It is noteworthy that immunotherapy has brought new hopes for malignant disease.^{33–35} The common immunosuppressive sites are programmed death 1(PD-1),³⁶ cytotoxic T-lymphocyte-associated antigen (CTLA-4),^{37,38} *etc.* However, most of the current immunotherapy is to achieve immune activators, such as T cell activation,³⁹ and the realization of therapy depends on microbiota in a certain extent. In summary, the urgent need for diagnosis and treatment of CRC requires more sensitive screening and effective therapy.

Intestinal microorganisms are one of the important micro-environmental factors associated with occurrence of intestinal tumors. At present, various studies have confirmed the role of intestinal microbiota in carcinomatosis, especially in colorectal cancer. Intestinal microbiota affects inflammatory response, chemotherapy resistance, and prognosis, as well as therapeutic target research.^{40–43} For example, *Ackermania* can induce remodeling of intestinal flora⁴⁴ and *Bifidobacteria* and *Lactobacillus* are associated with immune response. In addition, intestinal microbes impact the treatment of cancer tumor suppressors.⁴⁵ Notably, the role of metabolites of the gut microflora on host diseases cannot be ignored, such as indoles, short-chain fatty acids (SCFAs) and fatty acids *etc.*,^{46,47} which are closely related to host immunity, cancer progression, and participate in immune regulation and metabolism.⁴⁸ Metabolomics is an effective way to study small molecule metabolites,^{49–68} and it has shown that CRC precancerous lesions are highly correlated with TRP metabolism, energy metabolism, polyamine metabolism, and composition of the intestinal flora. Abnormal metabolism in the pathogenesis of CRC is very important for clinical diagnosis, treatment, and prognosis evaluation, especially for screening of early adenomas.⁶⁹ It is worth noting that TRP metabolism affects multiple systems, such as central nervous system, gastrointestinal tract, and immunity, which is closely related to intestinal flora. These factors are closely related to the occurrence, development, and prognosis of CRC. For example, indoles is an important class of bacterial-host co-metabolites, which is the metabolite in the TRP metabolism pathway.⁷⁰ Therefore, TRP metabolism and CRC are inextricably linked.

3 The physiological function of TRP metabolism

TRP is mainly obtained from food and has a variety of physiological functions. *In vivo*, TRP metabolism mainly occurs in the small intestine and central nervous system. The main metabolic pathways and metabolites of TRP are shown in Fig. 2.

3.1 TRP metabolism on the nervous system

TRP metabolic pathways are associated with sleep and wakefulness, mental and emotional activity, and endocrine



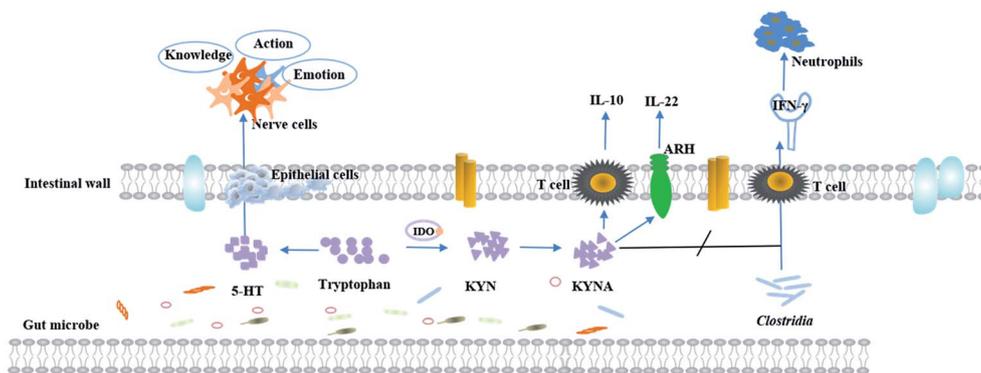


Fig. 2 A schematic diagram of the physiological function of tryptophan metabolism.

regulation. The lacking TRP in diet can cause inflammation of the central nervous system in mice.^{70,71} TRP is an important precursor of the neurotransmitter serotonin. In the central nervous system, 5-HT is an important neurotransmitter.⁷² 95% of 5-HT production occurs in the gastrointestinal tract, and 90% of 5-HT is stored in the intestinal chromaffin cell, and serotonin can use intestinal chromaffin cells as chemoreceptors to transmit perceived chemical information to the nervous system.⁷³ Recently, serotonin is considered as a type of neurotransmitter that transmits intestinal signals to the brain quickly.⁷⁴ Therefore, local changes in the gastrointestinal tract are affected by the concentration of serotonin, signals are transmitted along the stent along the intestine axis to affect central neurotransmission.^{72,75} During the process, the symbiotic bacteria are involved in the biosynthesis of 5-HT.⁷⁶ In the central nervous system, 5-HT participates in a series of emotional, behavioral and cognitive functions and is the target of many psychotic drugs. TRP is converted to 5-hydroxy tryptophan by the action of enzymes, further decarboxylation to 5-HT, and finally metabolized to 5-hydroxy indole acetic acid (5-HIAA) *in vivo*. Reduced levels of TRP can decrease the production of 5-HT, which causes the emotional disturbances, depression, and cognitive impairment. 90% of TRP is metabolized into the kynurenine (KYN) metabolic pathway, which is one of the activation pathways of the intestinal brain axis. The imbalance of metabolites is associated with multiple neurodegenerative and psychiatric diseases, such as the Alzheimer's syndrome, depression, *etc.*⁷⁷

3.2 Immunoregulatory effects of TRP metabolites

TRP is a key regulator of inflammation and immunity. Its metabolites are thought to be endogenous ligands of the aryl hydrocarbon receptor (AHR),^{78,79} which regulates intestinal immune function^{80,81} and plays an important role in mammalian intestinal immune homeostasis. Animal experiments have indicated that the lack of TRP affects the intestinal immunity in mice. For example, CD4⁺CD8 $\alpha\alpha$ ⁺ double positive intraepithelial T cells (DP IELs) in the small intestine have immunoregulatory functions and are derived from CD4⁺ T cells. Activation of DP IELs depends on *Lactobacillus reuteri* metabolizing the product of TRP indole-3-lactic acid. Experimental results suggest that high TRP intake from the diet and *Lactobacillus reuteri* can

increase the number of immune T cells.⁸² Predictive experiments of host–microbe interactions have shown that TNF- α and IFN- γ are associated with specific microbial metabolic pathways and palmitic acid and TRP degrade alcohols.⁸³ Intestinal diseases are usually accompanied by inflammatory reactions.⁸⁴ The indole acrylic acid, a metabolite of TRP, improves the intestinal epithelial barrier function, reduces the inflammatory response, and has a therapeutic effect.⁶⁹ Furthermore, experiments have shown that TRP and its metabolites (such as kynurenine) have inhibitory effects on inflammation. A certain concentration of TRP can significantly inhibit gene expression of inflammatory factors, thereby, curbing the disease progression and playing an active role in human health. Metabolites 3-hydroxy ethyl amino benzoic acid (3-HAA) and quinolinic acid, produced by the TRP-kynurenine pathway, can induce apoptosis of murine lymphocytes (mainly Th1 cells) *in vitro*.⁸⁵ Studies have shown that swollen cells can consume a large amount of TRP to produce a tumor microenvironment with immunosuppressive effects, which facilitates their own proliferation.

4 The relationship between TRP metabolism and CRC

4.1 The function of callback immune system

Under normal conditions, the immune system is its own line of defense against disease, which can effectively regulate the balance between the organism and the disease. However, while the tumor occurs *in vivo*, its microenvironment can produce immune tolerance against tumor antigens. Studies have shown that tumor cells can consume a large amount of TRP to produce a tumor microenvironment with immunosuppressive effects that facilitate their proliferation. Microorganisms can regulate the metabolism of tryptophan and, thus, regulate intestinal immunity.⁸¹ In addition, the development of CRC is accompanied by various inflammatory processes, and inflammation has been one of the hallmarks of cancer.⁸⁶ It means that anti-inflammatory agents should be effective in preventing and treating CRC.

CRC is the fourth most fatal malignancy after lung cancer, liver cancer, and gastric cancer.⁸⁷ The survival rates of CRC are related to the extent of the spread of cancer cells from primary



tumors to regional lymph nodes.^{88,89} Surveys have revealed that the quality of life of CRC patients is positively correlated with the serum TRP levels. Studies have shown that KYNA reduces PI3K/Akt and p38, ERK1/2 cellular kinases in the HT-29 cell line, and inhibits the Wnt pathway.⁹⁰ Tryptophan is mainly degraded by IDO (indoleamine 2,3-dioxygenase (IDO1)) in tumor cells.^{91,92} The KYNA pathway is closely related to the tumor immune escape mechanisms⁹³ within gastrointestinal anti-inflammatory properties⁹⁴ and inhibit the proliferation of colon cancer cells, which would be the way to immunotherapy for CRC.⁹⁵ It is known that the risk of developing CRC is associated with *Clostridia* which is an intrinsic inflammatory bacterium.⁹⁶ KYNA inhibits *Clostridium*-mediated IFN- γ -induced neutrophils and, thereby, counteracts the infection.⁹⁷ The prerequisite for this process is that KYNA is synthesized by IDO1. Inhibitors of the TRP metabolic enzyme IDO1 may accelerate the infection by *Clostridium*.⁹⁸ There have been reports of an increased expression of IDO1 in many types of cancer⁹⁹ and processes related to tumor immune tolerance, which has implications for targeted immunotherapy.¹⁰⁰ For example, experiments confirmed that *Salmonella* can achieve anti-tumor effects by inhibiting IDO1 expression and eliciting T cell immune responses *in vitro*.⁹² It means that IDO1 plays a role in regulating immunity in the TRP metabolism, and blocking or eliminating IDO1 causes a significant increase in inflammation.^{101,102} IDO can cause anti-regulation to inhibit T cell activity, which leads to inhibition of the immune system's response to tumors and promotes tumor progression. Therefore, IDO is an important point of immunosuppression in CRC immunotherapy.¹⁰³ Tryptophan receptor ARH, mentioned above, is associated with maintaining mucosal homeostasis.¹⁰⁴ It has been reported that ARH has a dual role in the regulation of tumors. While ARH is activated, it will have an effect on tumor progression. ARH has been used as an anti-tumor target for anti-tumor therapy.¹⁰⁵ Based on the data mentioned above, the KYNA-IDO1-ARH pathway becomes a new therapeutic target for CRC. The immunomodulation process of TRP metabolism in the process of CRC development is presented in Fig. 3.

4.2 Repair of the intestinal barrier structure

Normally, intestinal epithelial cells are barriers which can block the external environment and the internal environment.¹⁰⁶ Dysfunction of the intestinal barrier may lead to increased intestinal permeability and bacterial translocation of the intestinal mucosa, which promote local and whole immune activation. TRP metabolites have an inhibitory effect on activated T cells and mediate immune tolerance and response. Compared with the healthy group, if inflammatory factors are detected in the normal mucosa of patients with colonic adenomas, the synthesis of 5-HT in the intestine increases at the same time. Beside mediating anti-inflammatory factors and fighting inflammation associated with cancer, TRP can increase the length of the intestinal wall and glandular villous, and crypt depth. It means that TRP can repair the intestinal wall and delay the progression of cancer.¹⁰⁷ In the disease state, it is necessary to ingest more TRP to provide raw materials for TRP

metabolism to meet the need of the body for TRP, and it may also help to elevate the patient's mood.

4.3 Interaction between TRP metabolism and intestinal microecology

TRP is a complex amino acid, which is a biosynthetic precursor to a great many complex microbial natural products.¹⁰⁸ Intestinal ecosystem is the largest micro-ecological system in the human body which plays an important role in shaping host immune and metabolic activities.¹⁰⁹ As a part of the intestinal microflora metabolism, TRP produces indole-3-acetic acid, indophenol-3-sulfate, indole-3-propionic acid, indole-3-acetaldehyde and other derivatives.⁸⁰ Under the action of *Lactobacillus*, activation of ARH receptors mediates transcription of IL-22,¹¹⁰ protecting the mucosa from inflammation.¹¹¹ The intestinal flora regulates kynurenine metabolism *via* numerous mechanisms, which affect the nervous system and gastrointestinal function.¹¹² For example, both spore producing bacteria (SP) and short-chain fatty acids (SCFA) affect the synthesis of 5-HT. Specifically, SP promotes the expression of IDO1 to increase 5-HT production.⁹⁷ Meanwhile, it was reported that the tryptophan metabolites, produced by the colonic bacteria, will have some adverse effects.¹¹³ Under normal physiological conditions, though the intestinal structure of adults varies, the type and the total amount of bacterial flora are basically unchanged, mainly containing *Bacteroidetes*, *Firmicutes*, *actinomyces*, and *Verrucomicrobia*.¹¹² With the presence of the digestive tract tumor, the intestinal wall barrier is damaged and the intestinal wall is prone to congestion and edema, which induces a change in colonization environment of the gut microbiota. Meanwhile, inflammation can induce the synthesis of genotoxic gut microbiota and abnormal composition of the intestinal flora, which promotes tumorigenesis.¹¹⁴ Dysregulated intestinal microflora can affect the TRP metabolism, disturb the intestinal immune balance, and worsen the disease.

TRP, an important precursor of neurotransmitter and metabolic regulator, plays an important role in the regulation of nutrient metabolism. Compared with mice in the control group, the villus height and villus height/crypt depth are increased in the TRP supplemented group, which suggests that TRP uptake positively affects the intestinal structure.⁴ In addition, the intake of TRP has an impact on bacterial diversity. For example, healthy pig larvae with *Escherichia coli* F4 susceptibility need to consume more TRP to increase intestinal flora diversity.¹¹⁵ TRP protects against CD4 T cell-mediated death of *Mycobacteria* in an emergency state.¹¹⁶ More and more experiments have confirmed the role of intestinal flora and TRP metabolites in the central nervous system health, and the relationship between the metabolites of the two pathways of 5-HT and KYNA mentioned above and neurological diseases. In conclusion, dietary intake of TRP exerts a physiological effect on metabolism of the intestinal microflora and affects the intestinal microecology.¹¹⁷ The process is in a dynamic equilibrium state. Once this relationship is broken, it will tremendous influence an organism.



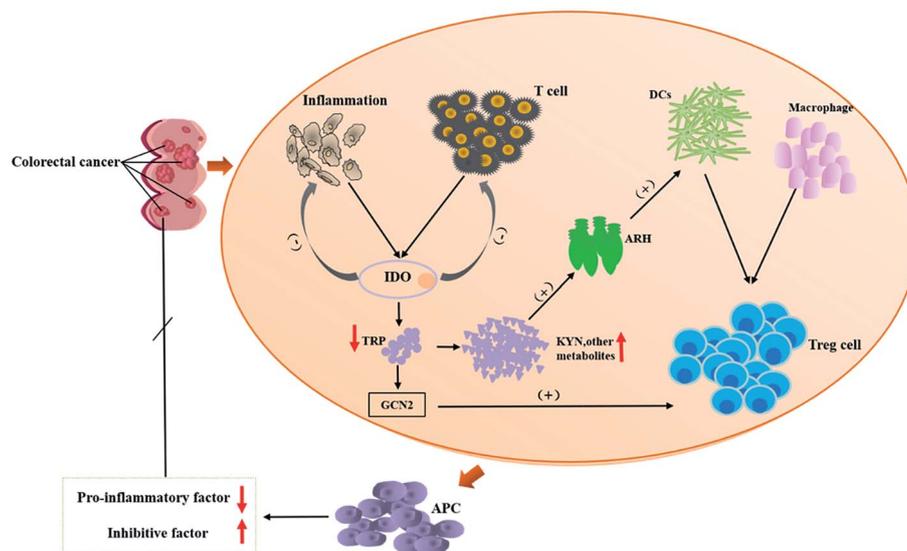


Fig. 3 Schematic representation of tryptophan metabolism in the process of CRC development. TRP: tryptophan; DC: dendritic cells; IDO: indoleamine-2,3-dioxygenase, IDO mainly is IDO1 in this paper; ARH: aromatic hydrocarbon receptor; GCN2: stress response kinase GCN2; APC: antigen-presenting cell.

4.4 The role of prevention

Because of the inhibition of TRP in potential carcinogenic diseases of colorectal cancer, it is usually used for the prevention of CRC. Tryptophan immunomodulators play a key role in the intestinal barrier maintenance and the integrity of its functions. In addition, CRC patients have reduced levels of TRP that impair quality of life.¹¹⁸ Therefore, nutritional supplements, such as probiotics, regulate tryptophan metabolism and can also be used for prevention of CRC.¹¹⁹ It has been reported that indoleamine 2,3-dioxygenase (IDO) activity is the first line of defense against invading cells. In the first stage of infection, IDO-mediated TRP consumption is mainly antimicrobial. At a further stage, it is an inhibitor of cell growth.¹²⁰

5 Conclusions

TRP is an essential amino acid in animals. It not only participates in regulation of physiological processes, such as pain and sleep, but also takes part in relieving stress. Tryptophan is a precursor of biologically active substances 5-HT and KYNA and plays an important role in regulating immune function. During the development of CRC, an organism produces substances that cause inflammatory reactions, and the intestinal microenvironment simultaneously changes. The intestinal barrier is damaged and its permeability increases, leading to an outflow of endotoxin-like toxic substances which affect other sites. Composition of the intestinal microflora changes and the proportion of harmful bacteria, such as *Enterococci* and *Clostridium*, is increased to postpone the development of CRC. Metabolites of TRP *in vivo* not only inhibit inflammation, but also repair the intestinal wall structure and interact with beneficial bacteria in the intestinal tract, which can delay the progression of CRC. TRP metabolism plays an active role in

inhibiting the development of CRC, and clarifying the relationship between the TRP metabolism and CRC is beneficial to subsequent studies.

Conflicts of interest

There are no conflicts to declare.

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