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## Review Article

# Immunosuppression in the Tumor Microenvironment Mediated by Metabolites Derived from the Gut Microbiota

Anastasia A. Zabolotneva[1,2*], Olga P. Shatova[1,3], Peter V. Shegai[4] and Aleksandr V. Shestopalov[2,5]

*[1]Department of Biochemistry and Molecular Biology, Pirogov Russian National Research Medical University, Moscow, Russia; [2]Department of Biochemistry of Signaling Pathways, Russian National Medical Research Center for Endocrinology, Moscow, Russia; [3]Department of Biochemistry, Peoples' Friendship University of Russia, Moscow, Russia; [4]Department of Oncourology, National Medical Research Radiological Center of the Ministry of Health of the Russian Federation, Moscow, Russia; [5]Department of Pediatric Oncology, Dmitry Rogachev National Medical Research Center Of Pediatric Hematology, Oncology, and Immunology, Moscow, Russia*

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## Abstract

Tumors interact with various populations of nonmalignant cells, such as endothelial, stromal, and immune cells, to create a favorable tumor microenvironment (TME) for invasion and metastasis of cancer cells. A key mechanism for maintaining the pro-oncogenic properties of the TME is the formation of an immunosuppressive environment that allows the tumor to avoid an immune response. A strictly immunosuppressive environment is supported mainly by the activity of engaged immune cells that secrete inflammatory cytokines and factors that inhibit the function of cytotoxic T lymphocytes. On the other hand, the activity of tumor-associated immune cells depends not only on cancer-cell signals but also on microbial metabolites derived from the gut microbiota. The gut microbiota consists of bacteria, viruses, protozoans, archaea, and fungi that influence the host immune response, DNA damage, and chronic inflammation in gastrointestinal and other cancers, such as breast cancer. In particular, intestinal dysbiosis can lead to restructuring of the TME and the promotion of tumor growth. Recently, a wide spectrum of bacterial metabolites, such as short-chain fatty acids, tryptophan catabolites, secondary bile acids, etc., have been shown to have a signaling function that affects not only the formation of the TME but also the response of cancer cells to therapeutic agents, including immunotherapy. Therefore, studying the effects of microbiota metabolites in relation to cancer development and cancer therapy effectiveness is strictly necessary. In this review, we briefly describe key microbiota factors that influence the formation of immunosuppressive TMEs.

## Introduction

The molecular mechanisms of carcinogenesis are complex and, at the same time, possess individual characteristics. Many factors, including genetic and epigenetic characteristics, age, lifestyle, diet habits, smoking, exposure to ultraviolet or ionizing radiation, chemical substances, etc., determine the initiation of malignant cell transformation and contribute to progressive tumor growth.[1] In recent years more attention has been paid to research on the influence of the symbiotic microbiota on host health.[2] Evolving along with the host organism, the microbiota largely formed the phenotypes of our ancestors.[3–5] The conjugation of the metabolism of the host and the microbiota, as well as the unification of signaling molecules used for their communication, led to a significant involvement of microorganisms, or rather, their metabolites, in the pathogenesis of many human diseases.[6] Mostly, these diseases include metabolic disorders, obesity, nonalcoholic fatty liver, dyslipidemia, insulin resistance, and type 2 diabetes mellitus.[7,8] However, the development of several cancers is also associated with the impact of microorganisms.[9] The intestinal microbiota can influence the process of malignant transformation of cells, either increasing or decreasing the risk of developing host disease, in three ways: (1) by changing the balance between proliferation and

**Keywords:** Tumor microenvironment; Gut microbiota; Short-chain fatty acids; Secondary bile acids; Lipopolysaccharide; Tryptophan metabolites.

**Abbreviations:** CSC, cancer stem-like cell; DCA, deoxycholic acid; DCs, dendritic cells; FXR, farnesoid X receptor; HDAC, histone deacetylase; IDO1, indolamine 2,3-dioxygenase 1; IL, interleukin; INF-γ, interferon γ; IgE/G, immunoglobulin E/G; LCA, lithocholic acid; LPS, lipopolysaccharide; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NK cells, natural killer cells; Nlrp1, NLR family pyrin domain containing 1.; PD-1, programmed cell death protein 1; PD-L1, a ligand for the PD-1 receptor; SBA, secondary bile acids; SCFAs, short-chain fatty acids; TME, tumour microenvironment; TNF-α, tumour necrosis factor α; Th1/17, T helper cells 1/17; Tregs, regulatory T cells; UDCA, ursodeoxycholic acid; VEGF, vascular endothelial growth factor; iNOS, inducible NO-synthase.

[*]**Correspondence to:** Anastasia A. Zabolotneva, Pirogov Russian National Research Medical University, 1 Ostrovitianov Str., Moscow 117997, Russia. ORCID: https://orcid.org/0000-0002-7633-9460. Tel: +7-906-703-9402, Fax: +7-495-434-61-29, E-mail: a.zabolotneva@gmail.com

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**Table 1. Metabolites derived from gut microbiota that influence the efficiency of immunotherapy**

| Metabolite | Mechanism of action | Reference |
|---|---|---|
| Peptidoglycan derivatives (muramyl dipeptide and N-acetylglucosamine muramyl dipeptide) | Nucleotide binding oligomerization domain containing 2 binds to peptidoglycan receptors to activate the NF-κB signaling pathway in a variety of immune cells; this further stimulates the activation of the immune system by promoting the expression of IL1b and Nlrp3 | 19,20 |
| Inosine | Directly suppresses the ubiquitin-like modifier activating enzyme 6 in tumor cells, making tumor cells more immunogenic and enhancing T cells' capacity to eradicate tumors | 21 |
| Indole-3-carboxaldehyde | Optimizes immunotherapy by preventing intestinal damage | 22 |
| Trimethylamine N-oxide | Drives activation of the immune system, increasing the efficacy of immunotherapy for pancreatic cancer | 23 |
| Short-chain fatty acids | Restrict the efficiency of metastatic melanoma treatment due to their ability to increase the proportion of Tregs while decreasing the accumulation of tumor-specific and memory T cells | 24 |

IL, interleukin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; Nlrp1, NLR family pyrin domain containing 1.

death of host cells, (2) by modulation of the functions of the immune system, and (3) by influencing the formation of metabolites synthesized by the host organism, supplied with food, and formed by the microbiota itself.[10]

Tumor growth is accompanied by the formation of a specific tumor microenvironment (TME) that facilitates tumor progression and invasion.[11] The peritumoral environment consists not only of tumor cells but also of immune, stromal, and other cells, as well as intercellular substances, microvessels, and metabolites transferred from the circulation.[12] The formation of an immunosuppressive environment that allows the tumor to avoid an immune response contributes to the pro-oncogenic properties of the TME.[13] A strictly immunosuppressive environment is supported mainly by the activity of attracted immune cells that secrete inflammatory cytokines and factors that inhibit the functions of cytotoxic T lymphocytes.[11] In addition, the activity of tumor-associated immune cells depends not only on cancer-cell signals but also on microbial metabolites derived mainly from the gut microbiota.[14] As demonstrated in various studies, the gut microbiota supports malignant transformation and the spread of tumor cells. It also contributes to a microenvironment that is favorable for tumor growth. The development of both gastrointestinal and tumors of other origins has been shown to be associated with the metabolic activity of the gut microbiota. For example, most of the available data show a link between bacterial dysbiosis and breast cancer.[15] In particular, bacterial beta-glucuronidase appears to modulate estrogen resorption and enterohepatic circulation, which increases the risk of hormone-dependent breast cancer. Additionally, as bacterial metabolites influence the risk and prognosis of breast cancer, active phytoestrogens, short-chain fatty acids (SCFAs), lithocholic acid (LCA), and cadaverine have been identified as bacterial metabolites that influence the risk and prognosis of such.[16] When entering the host circulation, these metabolites participate in the formation of a unique TME. Both microorganisms and the TME participate in inflammatory processes that can cause the onset and progression of colorectal cancer (CRC). In the past 10 years, significant progress has been made in understanding the synergistic interaction between the TME and intestinal microorganisms that determine the identity of CRC.[17] Furthermore, as established in preclinical models and cancer patients, the composition of the gut microbiota correlates with the effectiveness of anti-programmed cell death protein 1 (PD-1) immunotherapy (Table 1).[18–24] Therefore, cancer immunotherapy greatly benefits from a thorough understanding of the mechanisms by which the gut microbiota and its metabolites interact with the host immune system to reshape and regulate the TME.

The enormous heterogeneity in the composition of the gut microbiota between individuals can be resolved by determining each person's unique composition. During the development and treatment of cancer, the composition of the gut microbiota changes, and the change presents difficulties.[14] Therefore, study of the metabolic activity of the gut microbiota is extremely important in the context of cancer research and cancer treatment. In this review, we set out to briefly consider the role of the commensal microbiota and its metabolites in the functioning of the tumor-associated immune cells that form the immunosuppressive TME.

## Regulatory and metabolic deviations of immune cells in the TME

Activated cancer-associated fibroblasts are known to produce various cytokines such as tumor growth factor beta 1, hepatocyte growth factor, epidermal growth factor, VEGF (vascular endothelial growth factor), stromal factor-1, fibroblast growth factor, chemokine CXCL14, interleukin (IL)-1, IL6, IL8, and matrix metalloproteinase (MMP)-1, MMP2, MMP3, MMP9, MMP13, and MMP1.[25] Furthermore, tumor-associated myofibroblasts are the main producers of the extracellular matrix surrounding the tumor, as they secrete the extracellular matrix protein CCN2, collagens, tenascin C, fibronectin, and elastins.[26] The transformed cellular microenvironment, altered extracellular matrix, presence of a wide range of cytokines and chemokines, local anoxia, inflammation, and high lactate levels all contribute to the attraction of monocytes to the microenvironment and also to their transformation into tumor-associated macrophages or M2-type macrophages.[27] Tumor-associated macrophages are also capable of synthesizing and secreting procarcinogenic signaling molecules. Defense cells (e.g., macrophages and T effector cells) capable of attacking tumor cells carry PD-1, and antigen-presenting cells (e.g., cancer cells) express a ligand for the PD-1 receptor (PD-L1) that appears in response to the stimulation of interferon-gamma (IFN-γ).[28] After the interaction of PD-1 and PD-L1, T lymphocyte activation is suppressed (their autoimmunity decreases and their autotolerance increases). This event causes effector T cells to decide that tumor cells are a normal part of the body, and thus T cells cannot destroy

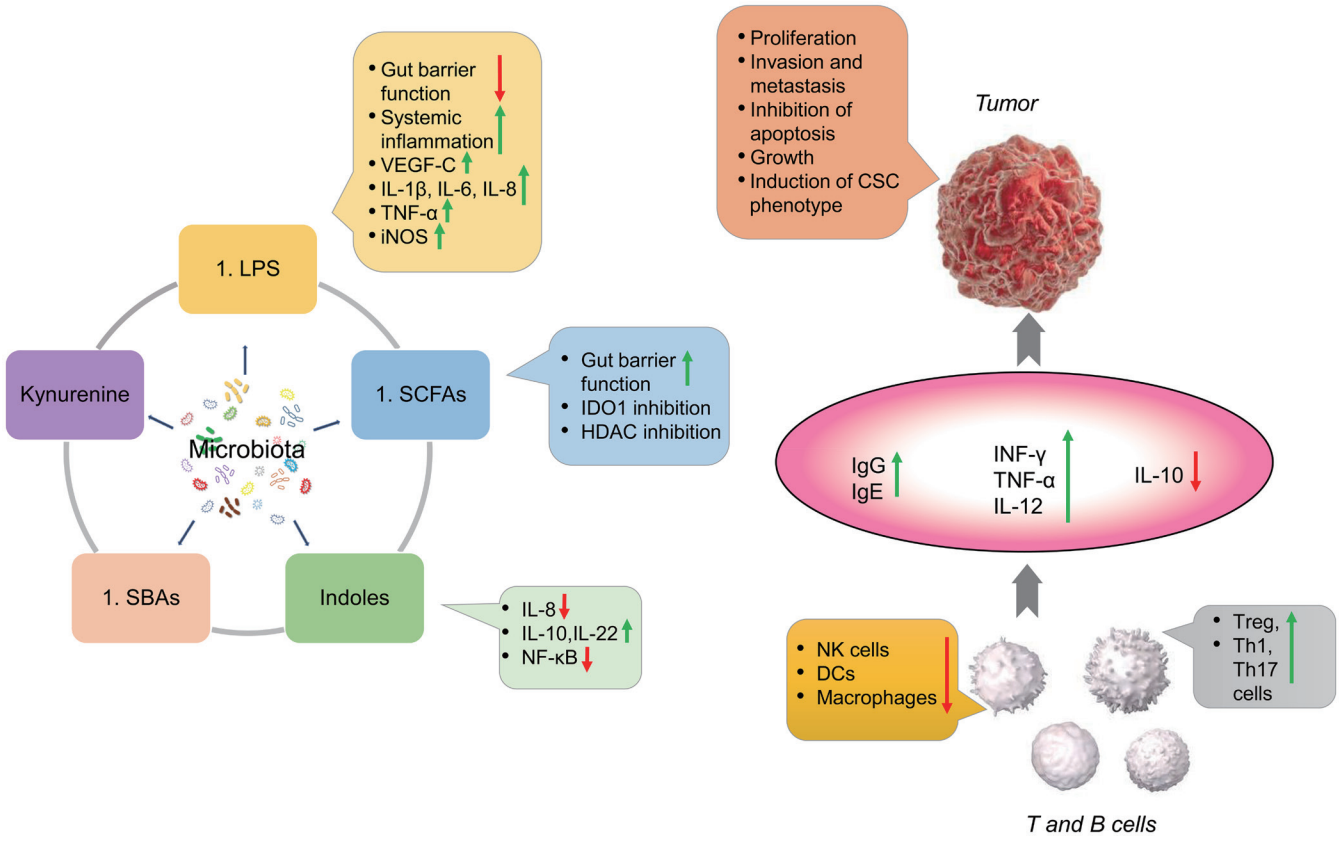


**Fig. 1. Relationships of various metabolites of the gut microbiota with tumor development.** CSC, cancer stem-like cell; DC, dendritic cell; HDAC, histone deacetylase; IDO1, indolamine 2,3-dioxygenase 1; IFN-γ, interferon-gamma; IgE/G, immunoglobulin E/G; IL, interleukin; iNOS, inducible nitric acid synthase; LPS, lipopolysaccharide; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NK, natural killer; SBA, secondary bile acid; SCFA, short-chain fatty acid; Th1, T helper cell 1; TNF-α, tumor necrosis factor-alpha; Treg, regulatory T cell; VEGF, vascular endothelial growth factor.

astute invaders.[29]

The PD-1/L1 signaling pathway facilitates the evasion of immune surveillance by tumors, as it limits the functions of T effector cells, natural killer (NK) cells, dendritic cells (DCs), and tumor-associated macrophages, suppressing their activation, proliferation, and cytokine activity.[30] Intratumoral neoangiogenesis is accelerated, leading to the formation of immature vessels with poorly connected endothelial cells, leaky membranes, and loosely attached pericytes. Ultimately, this leads to impaired transport of immune cells from microvessels through the interstitial space to tumor cells.[31] Anatomical and rheological abnormalities in tumor vessels disrupt the delivery of immunocompetent cells to the peritumoral area, which disrupts the immune surveillance by transformed cells. In addition, T cells require an increased intake of nutrients to elicit a proper immune response. The failure to obtain sufficient components or engage the appropriate metabolic pathways can alter or prevent effector T cell differentiation and function. By limiting the supply of nutrients, a metabolically hostile TME affects T cell differentiation and function.[31]

In particular, T cells switch on different metabolic programs at different stages of development. After exiting the thymus, T cells depend on aerobic glucose oxidation. Stimulated T cells rely on glycolysis to acquire effector function. Glycolysis allows them to emerge from a dormant state and ensures their evolution, providing the substrates necessary for growth and differentiation.[32] In effector T cells of the TME, metabolic reprogramming of energy metabolism for glycolytic oxidation occurs. This event is associated with activation of the PI3K/AKT/mTORC1 signaling pathway. Furthermore, inhibition of glycolysis has been shown to affect T cell proliferation and cytokine production.[33] It is known that during malignant growth or chronic infection, effector T cells cannot effectively remove antigens, and as a result, they are depleted. Such cells are called Schrödinger cells.[34] T cell depletion refers to the progressive loss of effector functions caused by chronic exposure to antigens, which certainly characterizes tumor growth. Some T cell subsets have properties similar to stem cells.[34] Exhausted T cells begin to express high levels of inhibitory receptors, and cytokine secretion [for example, IFN-γ and tumor necrosis factor-alpha (TNF-α)] and proliferation are decreased.[35]

Although the functions of tumor-associated immune cells depend on cancer-cell signals and TME components, these are not the only factors that comprise the immunosuppressive environment. Microbial metabolites that enter the blood from the gut are also involved in both tumor progression and cancer prevention (Fig. 1).[14]

## Influence of gut-derived microbial metabolites on immune cell function in the TME

### *Bile acids*

Secondary bile acids (SBAs) are important metabolites produced by microbial fermentation of primary bile acids in the intestinal

tract. The main SBAs are deoxycholic acid (DCA), LCA, and ursodeoxycholic acid (UDCA). Some studies have shown that SBAs are important regulatory molecules and activate many signaling pathways.[36,37] SBAs influence the induction and inhibition of tumor cell proliferation, stimulation of tumor-cell invasion and metastasis, and induction of the transformation of malignant cells into cancer stem-like cells.[36] Furthermore, SBAs promote carcinogenesis by regulating the function of immune cells.[37]

SBAs mediate their effects via the nuclear farnesoid X receptor (FXR), G protein-coupled bile acid receptor 1 (TGR5), vitamin D receptor, pregnane X receptor, and the constitutive androstane receptor.[38,39] Although primary bile acids mainly activate FXR, SBAs activate TGR5.[40] Activation of TGR5 inhibits the functions of NK cells, B cells, DCs, and macrophages. DCA and LCA can thus inhibit the activation of the spleen and intestinal macrophages, which are induced by Toll-like receptor-4 (TLR-4).[41] They can also inhibit the secretion of IL6, IFN-γ, and TNF-α, which induces the polarization of antitumor M1 macrophages to procancerogenic M2 macrophages.[42] DCA and LCA suppress the secretion of TNF-α and IL12, thus inhibiting DC function.[38] SBAs can inhibit antitumor functions of B cells, including their secretion of antibodies, phagocytosis, and activation of the complement system.[43] DCA and LCA inhibit the secretion of IL6 and suppress B cell maturation, thus reducing the levels of IgE and IgG immunoglobulins.[41] It is known that NK cells secrete IFN-γ and TNF-α to stimulate tumor cell apoptosis.[44] However, DCA and LCA inhibit the secretion of IFN-γ and TNF-α, thereby suppressing the function of NK cells.[42] Furthermore, DCA and LCA stimulate IL10 secretion by NK T cells, leading to suppression of TNF-α secretion and T lymphocyte activity.[45]

A number of studies have reported that DCA and UDCA had opposite effects on cells and activated different oncogenic signaling pathways,[46] which might explain the different effects of the two molecules on colon cancer progression. Protooncogenes (such as AP-1) and inflammation markers are activated when DCA activates MAPK signaling, and tumor suppressor genes (e.g., p53) are suppressed. On the other hand, UDCA has a tendency to reduce MAPK signaling and has negative global regulatory effects on the epidermal growth factor receptor-MAPK pathway.[47] Furthermore, UDCA induces ubiquitination of tumor growth factor-beta through the action of carboxyl terminus of Hsc70-interacting protein (CHIP), which promotes autophagic sorting and the subsequent degradation of tumor growth factor-beta . In this way, UDCA severely restricts regulatory T cell (Treg) differentiation and activation, which lessens the immunosuppressive activity of Treg cells. Thus, the combination of UDCA treatment and anti-PD-1 therapy is proposed to improve the effectiveness of antitumor therapy.[48]

SBAs can enhance the function of Tregs, which are known to promote the formation of an immunosuppressive microenvironment and tumor progression. Foxp3 is one of the key transcription factors of the FOX family of proteins that control the development and function of Tregs.[49] A derivative of LCA, isoalloLCA, can increase Foxp3 expression in naive CD4+ T cells by increasing reactive oxygen species production in mitochondria.[50] SBAs have been found to bind not only to TGR5 but also to FXR, which are both nuclear receptors expressed mainly in the intestine, liver, and immune cells.[41] Macrophages and DCs express both TGR5 and FXR, but NK T cells only express FXR. Activation of these receptors by bile acids causes macrophages to produce more IL10 and less IL6 and IFN-γ, DCs to produce less TNF-α and IL12, and NK cells to produce less osteopontin.[41] Therefore, SBA signaling activity is associated with an increased risk of developing CRC, as well as some extraintestinal tumors, and cancers of the liver, pancreas, esophagus, lung, and stomach.[51,52]

### *Lipopolysaccharide (LPS)*

LPS with its internal component, lipid A, is the most effective protective toxin of the cell wall of Gram-negative bacteria that causes a pro-inflammatory effect on the host organism.[53] The intestinal lumen, a habitat for many trillions of commensal bacteria, is the main reservoir of LPS in the human body.[54] When transported to the blood, LPS binds to LPS-binding protein or plasma lipoproteins and causes systemic inflammation.[55] LPS is involved in the oncogenic process through a variety of mechanisms. LPS induces M1 macrophages, which produce and secrete higher levels of pro-inflammatory cytokines such as TNF-α, IL1α, IL1β, IL6, IL12, IL23, and cyclooxygenase-2, and low levels of IL10.[56] By activating protein kinases and transcription factors like nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and p38 kinase, as well as the cell-surface TLR-4, LPS has been shown to stimulate immune system cells. As a result, it has been demonstrated that pro-inflammatory cytokines are produced at higher levels, and matrix-degrading enzymes and cell adhesion molecules are overexpressed.[57]

Therefore, LPS can stimulate TNF-α, which subsequently leads to the recruitment of intracellular NF-κB followed by the release of chemokines and inflammatory cytokines, including IL1β, IL6, IL8, and TNF-α.[58] Acting as a trigger for inflammatory reactions, LPS has been associated with the pathogenesis of cancer, including the development of mast cell tumors of the gastrointestinal tract.[59,60] Several studies have shown that various microbial metabolites acting as inductors of signaling pathways associated with TLR-4 play a key role in regulating the survival and progression of tumor cell growth in the colon and pancreas, liver, and mammary gland.[61,62] For example, overexpression was found in CRC. It contributed to increased cell proliferation, protection of malignant cells from apoptosis, increased invasion and metastasis, and the creation of a favorable cellular microenvironment for the tumor.

### *Tryptophan metabolites*

Tryptophan metabolism through the kynurenine pathway and microbial conversion of tryptophan to indole compounds are crucial to host health and are particularly critical in colon cancerogenesis.[63] The microbial community is a key part of the TME and influences the initiation of malignant transformation, the progression of tumor growth, and the response to treatment. Changes in tryptophan metabolism begin at an early stage of tumor growth as an adaptive mechanism that allows malignant cells to avoid immune surveillance and metastasis.[64] One of the key enzymes that limit the rate of tryptophan catabolism is indolamine 2,3-dioxygenase 1 (IDO1), which is present in *Firmicutes*.[65] IDO1 is expressed most actively in the genera *Clostridium*, *Lachnoclostridium*, *Ruminoclostridium,* and *Roseburia*.[65] Pro-inflammatory cytokines, IFN-γ, TNF-α, prostaglandins, and LPSs, have an activating effect on IDO1 expression.[66] IDO1 converts tryptophan to N-formylkynurenine with its subsequent rapid transformation to kynurenine, the first stable catabolite in this pathway. Then, various metabolites are formed from kynurenine, which regulate the activity of immune cells.[66]

Kynurenine regulates immune homeostasis in the host organism. These effects are achieved by reducing the number of activated T cells, DCs, and NK T cells, as well as inducing T helper 1 (Th1) cell apoptosis of Th1 cells to control the excessive inflammatory response.[64] Each downstream metabolite of kynurenine

performs specific functions. Kynurenic acid induces an anti-inflammatory response due to its antioxidant properties, while picolinic acid exhibits antitumor activity by inhibiting the activation of T cells and c-Myc, the Myc proto-oncogenic transcription factor. At the same time, c-Myc itself accelerates tryptophan uptake in colon cancer cells by enhancing the expression of tryptophan transporters (SLC7A5 and SLC1A5).[67]

An increase in IDO1, arylformamidase activity, and kynurenine have been established during tumor growth.[68] It is important to note that serum kynurenine concentrations in cancer patients are higher than in healthy people. At the same time, the expression and activity of enzymes for the further conversion of kynurenine do not change during tumor growth, suggesting that kynurenine is the dominant metabolite of tryptophan metabolism, elevated in CRC.[68] Elevated levels of kynurenine promote oncogenesis predominantly in two ways. (1) Some of the kynurenine produced can directly induce T cell inactivation and apoptosis, leading to evasion of immune surveillance. (2) The remaining kynurenine can constitutively activate arylhydrocarboxylic receptors, which in turn activate the transcription of genes responsible for the escape of the tumor from immune surveillance, as well as proliferation and metastasis of malignantly transformed cells. Therefore, the kynurenine/arylhydrocarboxylic receptor signaling pathway is one of the main factors contributing to the development of colon cancer.[64,68]

At the same time, it should be noted that an increase in the systemic level of kynurenine is characteristic of patients with tumors of various localizations. Many researchers attribute this fact to stimulation of IDO1 expression by pro-inflammatory cytokines, the level of which increases in the body during the growth of malignant tumors. Of the indole derivatives of tryptophan metabolism, the most represented in the intestine are indole-3-acetamide, indole-3-acetaldehyde, indole-3-pyruvate, indole-3-aldehyde, indole-3-acetate, tryptamine, indole-3-propionic acid, and indole-3-acrylic acid. In the host organism, indoles activate signaling pathways that lead to changes in intestinal epithelium barrier function, reduce permeability, promote immune tolerance, eradicate pathogens, reduce inflammation, and control mucin production.[69] Indole compounds can also act through arylhydrocarboxylic receptors, having pro- and anti-inflammatory effects.[70] Indoles can reduce the expression of pro-inflammatory factors IL8 and NF-κB and promote the expression of anti-inflammatory cytokines, including IL10. Furthermore, indole compounds regulate intestinal homeostasis by inducing IL22 secretion, which improves barrier function; however, in the context of tumor growth (late stages of the disease), IL22 production can contribute to the progressive development of neoplasm.[71]

### *SCFAs*

SCFAs are important mediators of the metabolic interface between the intestinal microbiota and the host organism. SCFAs can affect not only the large intestine but also various organs and systems through the systemic circulation. In recent epidemiological studies, the development of stomach and breast cancer was found to be correlated with a low SCFA content in feces.[72] Furthermore, recent clinical studies have shown that the concentration of SCFA in the stool of patients with CRC is lower compared to healthy people. Researchers explain this observation by a decrease in the content of bacteria that synthesize SCFA, such as *Lachnospiraceae*, *Roseburia spp*., *Bifidobacterium spp*., in patients with these types of cancers.[73] SCFAs are capable of mediating immunoregulation through Tregs and therefore exhibit anti-inflammatory and anticarcinogenic effects.[40]

Acetate and propionate can bind to the G-protein-associated receptors GPR41 and GPR43. As in the case of butyrate, cells stimulated via GPR41/43 with acetate and propionate can trigger a signaling pathway that prevents inflammation and reduces the risk of malignant transformation. The anti-inflammatory effects of SCFAs mediated by GPR41/43 activation have been shown in human renal epithelial cells. Therefore, according to the study results, SCFA was able to reduce the TNF-α stimulatory production of monocyte chemoattractant protein-1 by inhibiting phosphorylation of p38 and JNK.

Regulation of inflammation in human cell lines (HeLa, HEK293) was also shown to be carried out due to desensitization of GPR41/43 under the influence of β-arrestins. In the case of GPR43, β-arrestin blocked the degradation of the NF-κB complex with the inhibitor protein IκB and nuclear translocation of NF-κB, which led to a decrease in the expression of pro-inflammatory cytokines IL6 and IL1β.[74]

In summary, SCFA can be observed to activate various cellular mechanisms associated with the prevention of carcinogenesis. This influence of SCFAs is associated with the regulation of signaling pathways, transcription factors, and epigenome status. SCFAs can act not only as ligands for transmembrane receptors but also penetrate the cell and interact directly with intracellular targets. However, it should be considered that the effects of SCFAs can change to the opposite (procancerogenic) in the presence of certain genetic characteristics of tumor cells and also depending on the concentration of SCFAs in the TME.

## Conclusions

There is no doubt that the TME plays a key role in tumor formation, progression, and metastasis. A century ago, Stephen Paget discovered that breast cancer metastases show a preference for an organ or tissue that is naturally associated with the cellular environment. Paget boldly suggested that tumor progression was controlled by the interaction of tumor cells and the environment and pioneered the concept of the TME.[75] Thus, the theory of the TME has replaced the theory that the fate of tumor cells is determined only by their genetic material and has opened up a new perspective for a comprehensive understanding of the mechanisms of invasion, tumor metastasis, and the development of resistance to therapy.[76]

At the same time, it has become clear that immunosuppressive TMEs are formed not only because of cancer cell signals but also by the influence of gut-derived microbiota signals. SBAs, tryptophan metabolites, SCFAs, and LPSs are major microbial compounds that enter the host circulation and interact specifically with host cell receptors, thus affecting the immune response and modulating the structure of the TME. Furthermore, the effectiveness of anticancer immunotherapies based on targeting the CTLA-4 or PD-1, PD-L1 axis, is significantly influenced by the composition of the intestinal microbiota, according to studies conducted over the past 5 years.[14] Therefore, in the perspectives we consider the development of more precise cancer therapies based on the interrelationship of gut microbiota metabolic activity and TME. Additionally, it is recommended that future research concentrate on the precise targets and mechanisms of action in this area.

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## Conflict of interest

The authors have no conflicts of interest related to this publication.

## Author contributions

Manuscript writing (AAZ, OPS) and manuscript editing and final proofing (PVS, AVS).

## References

[1] Maomao C, He L, Dianqin S, Siyi H, Xinxin Y, Fan Y, *et al*. Current cancer burden in China: epidemiology, etiology, and prevention. Cancer Biol Med 2022;19(8):1121–1138. doi:10.20892/j.issn.2095-3941.2022.0231, PMID:36069534.

[2] Gomaa EZ. Human gut microbiota/microbiome in health and diseases: a review. Antonie Van Leeuwenhoek 2020;113(12):2019–2040. doi:10.1007/s10482-020-01474-7, PMID:33136284.

[3] Vandenplas Y, Carnielli VP, Ksiazyk J, Luna MS, Migacheva N, Mosselmans JM, *et al*. Factors affecting early-life intestinal microbiota development. Nutrition 2020;78:110812. doi:10.1016/j.nut.2020.110812, PMID:32464473.

[4] Adak A, Khan MR. An insight into gut microbiota and its functionalities. Cell Mol Life Sci 2019;76(3):473–493. doi:10.1007/s00018-018-2943-4, PMID:30317530.

[5] Moeller AH, Sanders JG. Roles of the gut microbiota in the adaptive evolution of mammalian species. Philos Trans R Soc Lond B Biol Sci 2020;375(1808):20190597. doi:10.1098/rstb.2019.0597, PMID:32772670.

[6] Chen Y, Zhou J, Wang L. Role and Mechanism of Gut Microbiota in Human Disease. Front Cell Infect Microbiol 2021;11:625913. doi:10.3389/fcimb.2021.625913, PMID:33816335.

[7] Afzaal M, Saeed F, Shah YA, Hussain M, Rabail R, Socol CT, *et al*. Human gut microbiota in health and disease: Unveiling the relationship. Front Microbiol 2022;13:999001. doi:10.3389/fmicb.2022.999001, PMID:36225386.

[8] Vandana UK, Barlaskar NH, Gulzar ABM, Laskar IH, Kumar D, Paul P, *et al*. Linking gut microbiota with the human diseases. Bioinformation 2020;16(2):196–208. doi:10.6026/97320630016196, PMID:32405173.

[9] Tsvetikova SA, Koshel EI. Microbiota and cancer: host cellular mechanisms activated by gut microbial metabolites. Int J Med Microbiol 2020;310(4):151425. doi:10.1016/j.ijmm.2020.151425, PMID:32423739.

[10] Oh JK, Weiderpass E. Infection and cancer: global distribution and burden of diseases. Ann Glob Health 2014;80(5):384–392. doi:10.1016/j.aogh.2014.09.013, PMID:25512154.

[11] Li L, Yu R, Cai T, Chen Z, Lan M, Zou T, *et al*. Effects of immune cells and cytokines on inflammation and immunosuppression in the tumor microenvironment. Int Immunopharmacol 2020;88:106939. doi:10.1016/j.intimp.2020.106939, PMID:33182039.

[12] Xiao Y, Yu D. Tumor microenvironment as a therapeutic target in cancer. Pharmacol Ther 2021;221:107753. doi:10.1016/j.pharmthera.2020.107753, PMID:33259885.

[13] Yang L, Li A, Lei Q, Zhang Y. Tumor-intrinsic signaling pathways: key roles in the regulation of the immunosuppressive tumor microenvironment. J Hematol Oncol 2019;12(1):125. doi:10.1186/s13045-019-0804-8, PMID:31775797.

[14] Qiu Q, Lin Y, Ma Y, Li X, Liang J, Chen Z, *et al*. Exploring the Emerging Role of the Gut Microbiota and Tumor Microenvironment in Cancer Immunotherapy. Front Immunol 2020;11:612202. doi:10.3389/fimmu.2020.612202, PMID:33488618.

[15] Laborda-Illanes A, Sanchez-Alcoholado L, Dominguez-Recio ME, Jimenez-Rodriguez B, Lavado R, Comino-Méndez I, *et al*. Breast and Gut Microbiota Action Mechanisms in Breast Cancer Pathogenesis and Treatment. Cancers (Basel) 2020;12(9):2465. doi:10.3390/cancers12092465, PMID:32878124.

[16] Alpuim Costa D, Nobre JG, Batista MV, Ribeiro C, Calle C, Cortes A, *et al*. Human Microbiota and Breast Cancer-Is There Any Relevant Link?-A Literature Review and New Horizons Toward Personalised Medicine. Front Microbiol 2021;12:584332. doi:10.3389/fmicb.2021.584332, PMID:33716996.

[17] Zheng Z, Hou X, Bian Z, Jia W, Zhao L. Gut microbiota and colorectal cancer metastasis. Cancer Lett 2023;555:216039. doi:10.1016/j.canlet.2022.216039, PMID:36528182.

[18] Xu MQ, Cao HL, Wang WQ, Wang S, Cao XC, Yan F, *et al*. Fecal microbiota transplantation broadening its application beyond intestinal disorders. World J Gastroenterol 2015;21(1):102–111. doi:10.3748/wjg.v21.i1.102, PMID:25574083.

[19] Yang Q, Wang B, Zheng Q, Li H, Meng X, Zhou F, *et al*. A Review of Gut Microbiota-Derived Metabolites in Tumor Progression and Cancer Therapy. Adv Sci (Weinh) 2023;10(15):e2207366. doi:10.1002/advs.202207366, PMID:36951547.

[20] Griffin ME, Espinosa J, Becker JL, Luo JD, Carroll TS, Jha JK, *et al*. Enterococcus peptidoglycan remodeling promotes checkpoint inhibitor cancer immunotherapy. Science 2021;373(6558):1040–1046. doi:10.1126/science.abc9113, PMID:34446607.

[21] Zhang L, Jiang L, Yu L, Li Q, Tian X, He J, *et al*. Inhibition of UBA6 by inosine augments tumour immunogenicity and responses. Nat Commun 2022;13(1):5413. doi:10.1038/s41467-022-33116-z, PMID:36109526.

[22] Renga G, Nunzi E, Pariano M, Puccetti M, Bellet MM, Pieraccini G, *et al*. Optimizing therapeutic outcomes of immune checkpoint blockade by a microbial tryptophan metabolite. J Immunother Cancer 2022;10(3):e003725. doi:10.1136/jitc-2021-003725, PMID:35236743.

[23] Mirji G, Worth A, Bhat SA, El Sayed M, Kannan T, Goldman AR, *et al*. The microbiome-derived metabolite TMAO drives immune activation and boosts responses to immune checkpoint blockade in pancreatic cancer. Sci Immunol 2022;7(75):eabn0704. doi:10.1126/sciimmunol.abn0704, PMID:36083892.

[24] Coutzac C, Jouniaux JM, Paci A, Schmidt J, Mallardo D, Seck A, *et al*. Systemic short chain fatty acids limit antitumor effect of CTLA-4 blockade in hosts with cancer. Nat Commun 2020;11(1):2168. doi:10.1038/s41467-020-16079-x, PMID:32358520.

[25] Nurmik M, Ullmann P, Rodriguez F, Haan S, Letellier E. In search of definitions: Cancer-associated fibroblasts and their markers. Int J Cancer 2020;146(4):895–905. doi:10.1002/ijc.32193, PMID:30734283.

[26] Otranto M, Sarrazy V, Bonté F, Hinz B, Gabbiani G, Desmoulière A. The role of the myofibroblast in tumor stroma remodeling. Cell Adh Migr 2012;6(3):203–219. doi:10.4161/cam.20377, PMID:22568985.

[27] Zhou J, Tang Z, Gao S, Li C, Feng Y, Zhou X. Tumor-Associated Macrophages: Recent Insights and Therapies. Front Oncol 2020;10:188. doi:10.3389/fonc.2020.00188, PMID:32161718.

[28] Thiem A, Hesbacher S, Kneitz H, di Primio T, Heppt MV, Hermanns HM, *et al*. IFN-gamma-induced PD-L1 expression in melanoma depends on p53 expression. J Exp Clin Cancer Res 2019;38(1):397. doi:10.1186/s13046-019-1403-9, PMID:31506076.

[29] Han Y, Liu D, Li L. PD-1/PD-L1 pathway: current researches in cancer. Am J Cancer Res 2020;10(3):727–742. PMID:32266087.

[30] Gordon SR, Maute RL, Dulken BW, Hutter G, George BM, McCracken MN, *et al*. PD-1 expression by tumour-associated macrophages inhibits phagocytosis and tumour immunity. Nature 2017;545(7655):495–499. doi:10.1038/nature22396, PMID:28514441.

[31] Lim AR, Rathmell WK, Rathmell JC. The tumor microenvironment as a metabolic barrier to effector T cells and immunotherapy. Elife 2020;9:e55185. doi:10.7554/eLife.55185, PMID:32367803.

[32] Chapman NM, Boothby MR, Chi H. Metabolic coordination of T cell quiescence and activation. Nat Rev Immunol 2020;20(1):55–70. doi:10.1038/s41577-019-0203-y, PMID:31406325.

[33] Kono M, Maeda K, Stocton-Gavanescu I, Pan W, Umeda M, Katsuyama E, *et al*. Pyruvate kinase M2 is requisite for Th1 and Th17 differentiation. JCI Insight 2019;4(12):127395. doi:10.1172/jci.insight.127395, PMID:31217348.

[34] Gonzalez NM, Zou D, Gu A, Chen W. Schrödinger's T Cells: Molecular Insights Into Stemness and Exhaustion. Front Immunol 2021;12:725618. doi:10.3389/fimmu.2021.725618, PMID:34512656.

[35] Kallies A, Zehn D, Utzschneider DT. Precursor exhausted T cells: key to successful immunotherapy? Nat Rev Immunol 2020;20(2):128–136. doi:10.1038/s41577-019-0223-7, PMID:31591533.
[36] Mikó E, Kovács T, Sebő É, Tóth J, Csonka T, Ujlaki G, *et al*. Microbiome-Microbial Metabolome-Cancer Cell Interactions in Breast Cancer-Familiar, but Unexplored. Cells 2019;8(4):293. doi:10.3390/cells8040293, PMID:30934972.
[37] Cai J, Sun L, Gonzalez FJ. Gut microbiota-derived bile acids in intestinal immunity, inflammation, and tumorigenesis. Cell Host Microbe 2022;30(3):289–300. doi:10.1016/j.chom.2022.02.004, PMID:35271802.
[38] Biagioli M, Marchianò S, Carino A, Di Giorgio C, Santucci L, Distrutti E, *et al*. Bile Acids Activated Receptors in Inflammatory Bowel Disease. Cells 2021;10(6):1281. doi:10.3390/cells10061281, PMID:34064187.
[39] Cai X, Young GM, Xie W. The xenobiotic receptors PXR and CAR in liver physiology, an update. Biochim Biophys Acta Mol Basis Dis 2021;1867(6):166101. doi:10.1016/j.bbadis.2021.166101, PMID:33600998.
[40] Meng C, Bai C, Brown TD, Hood LE, Tian Q. Human Gut Microbiota and Gastrointestinal Cancer. Genomics Proteomics Bioinformatics 2018;16(1):33–49. doi:10.1016/j.gpb.2017.06.002, PMID:29474889.
[41] Fiorucci S, Biagioli M, Zampella A, Distrutti E. Bile Acids Activated Receptors Regulate Innate Immunity. Front Immunol 2018;9:1853. doi:10.3389/fimmu.2018.01853, PMID:30150987.
[42] Fiorucci S, Carino A, Baldoni M, Santucci L, Costanzi E, Graziosi L, *et al*. Bile Acid Signaling in Inflammatory Bowel Diseases. Dig Dis Sci 2021;66(3):674–693. doi:10.1007/s10620-020-06715-3, PMID:33289902.
[43] Davis SK, Selva KJ, Kent SJ, Chung AW. Serum IgA Fc effector functions in infectious disease and cancer. Immunol Cell Biol 2020;98(4):276–286. doi:10.1111/imcb.12306, PMID:31785006.
[44] Yang P, Peng Y, Feng Y, Xu Z, Feng P, Cao J, *et al*. Immune Cell-Derived Extracellular Vesicles - New Strategies in Cancer Immunotherapy. Front Immunol 2021;12:771551. doi:10.3389/fimmu.2021.771551, PMID:34956197.
[45] Mirlekar B. Tumor promoting roles of IL-10, TGF-β, IL-4, and IL-35: Its implications in cancer immunotherapy. SAGE Open Med 2022;10:20503121211069012. doi:10.1177/20503121211069012, PMID:35096390.
[46] Goossens JF, Bailly C. Ursodeoxycholic acid and cancer: From chemoprevention to chemotherapy. Pharmacol Ther 2019;203:107396. doi:10.1016/j.pharmthera.2019.107396, PMID:31356908.
[47] Centuori SM, Martinez JD. Differential regulation of EGFR-MAPK signaling by deoxycholic acid (DCA) and ursodeoxycholic acid (UDCA) in colon cancer. Dig Dis Sci 2014;59(10):2367–2380. doi:10.1007/s10620-014-3190-7, PMID:25027205.
[48] Shen Y, Lu C, Song Z, Qiao C, Wang J, Chen J, *et al*. Ursodeoxycholic acid reduces antitumor immunosuppression by inducing CHIP-mediated TGF-β degradation. Nat Commun 2022;13(1):3419. doi:10.1038/s41467-022-31141-6, PMID:35701426.
[49] He B, Liu Y, Hoang TK, Tian X, Taylor CM, Luo M, *et al*. Antibiotic-modulated microbiome suppresses lethal inflammation and prolongs lifespan in Treg-deficient mice. Microbiome 2019;7(1):145. doi:10.1186/s40168-019-0751-1, PMID:31699146.
[50] Hang S, Paik D, Yao L, Kim E, Trinath J, Lu J, *et al*. Bile acid metabolites control T(H)17 and T(reg) cell differentiation. Nature 2019;576(7785):143–148. doi:10.1038/s41586-019-1785-z, PMID:31776512.
[51] Yang R, Qian L. Research on Gut Microbiota-Derived Secondary Bile Acids in Cancer Progression. Integr Cancer Ther 2022;21:15347354221114100. doi:10.1177/15347354221114100, PMID:35880833.
[52] Caliceti C, Punzo A, Silla A, Simoni P, Roda G, Hrelia S. New Insights into Bile Acids Related Signaling Pathways in the Onset of Colorectal Cancer. Nutrients 2022;14(14):2964. doi:10.3390/nu14142964, PMID:35889921.
[53] Heinbockel L, Weindl G, Martinez-de-Tejada G, Correa W, Sanchez-Gomez S, Bárcena-Varela S, *et al*. Inhibition of Lipopolysaccharide- and Lipoprotein-Induced Inflammation by Antitoxin Peptide Pep19-2.5. Front Immunol 2018;9:1704. doi:10.3389/fimmu.2018.01704, PMID:30093904.
[54] Sahoo DK, Borcherding DC, Chandra L, Jergens AE, Atherly T, Bourgois-Mochel A, *et al*. Differential Transcriptomic Profiles Following Stimulation with Lipopolysaccharide in Intestinal Organoids from Dogs with Inflammatory Bowel Disease and Intestinal Mast Cell Tumor. Cancers (Basel) 2022;14(14):3525. doi:10.3390/cancers14143525, PMID:35884586.
[55] Ghosh SS, Wang J, Yannie PJ, Ghosh S. Intestinal Barrier Dysfunction, LPS Translocation, and Disease Development. J Endocr Soc 2020;4(2):bvz039. doi:10.1210/jendso/bvz039, PMID:32099951.
[56] Shapouri-Moghaddam A, Mohammadian S, Vazini H, Taghadosi M, Esmaeili SA, Mardani F, *et al*. Macrophage plasticity, polarization, and function in health and disease. J Cell Physiol 2018;233(9):6425–6440. doi:10.1002/jcp.26429, PMID:29319160.
[57] Balasubramanyam M. LPS-Is It a Major Liability Factor for Cancer Risk and Severity? Explor Res Hypothesis Med 2020;5(2):39–40. doi:10.14218/ERHM.2020.00037.
[58] Zhang Y, Zhu X, Yu X, Novák P, Gui Q, Yin K. Enhancing intestinal barrier efficiency: A novel metabolic diseases therapy. Front Nutr 2023;10:1120168. doi:10.3389/fnut.2023.1120168, PMID:36937361.
[59] Donald K, Finlay BB. Early-life interactions between the microbiota and immune system: impact on immune system development and atopic disease. Nat Rev Immunol 2023;23(11):735–748. doi:10.1038/s41577-023-00874-w, PMID:37138015.
[60] Manilla V, Di Tommaso N, Santopaolo F, Gasbarrini A, Ponziani FR. Endotoxemia and Gastrointestinal Cancers: Insight into the Mechanisms Underlying a Dangerous Relationship. Microorganisms 2023;11(2):267. doi:10.3390/microorganisms11020267, PMID:36838231.
[61] Zhao H, Wu L, Yan G, Chen Y, Zhou M, Wu Y, *et al*. Inflammation and tumor progression: signaling pathways and targeted intervention. Signal Transduct Target Ther 2021;6(1):263. doi:10.1038/s41392-021-00658-5, PMID:34248142.
[62] Guo J, Liao M, Wang J. TLR4 signaling in the development of colitis-associated cancer and its possible interplay with microRNA-155. Cell Commun Signal 2021;19(1):90. doi:10.1186/s12964-021-00771-6, PMID:34479599.
[63] Venkateswaran N, Conacci-Sorrell M. Kynurenine: an oncometabolite in colon cancer. Cell Stress 2020;4(1):24–26. doi:10.15698/cst2020.01.210, PMID:31922097.
[64] Wyatt M, Greathouse KL. Targeting Dietary and Microbial Tryptophan-Indole Metabolism as Therapeutic Approaches to Colon Cancer. Nutrients 2021;13(4):1189. doi:10.3390/nu13041189, PMID:33916690.
[65] Martin-Gallausiaux C, Larraufie P, Jarry A, Béguet-Crespel F, Marinelli L, Ledue F, *et al*. Butyrate Produced by Commensal Bacteria Down-Regulates Indolamine 2,3-Dioxygenase 1 (IDO-1) Expression via a Dual Mechanism in Human Intestinal Epithelial Cells. Front Immunol 2018;9:2838. doi:10.3389/fimmu.2018.02838, PMID:30619249.
[66] Savitz J. The kynurenine pathway: a finger in every pie. Mol Psychiatry 2020;25(1):131–147. doi:10.1038/s41380-019-0414-4, PMID:30980044.
[67] Venkateswaran N, Lafita-Navarro MC, Hao YH, Kilgore JA, Perez-Castro L, Braverman J, *et al*. MYC promotes tryptophan uptake and metabolism by the kynurenine pathway in colon cancer. Genes Dev 2019;33(17-18):1236–1251. doi:10.1101/gad.327056.119, PMID:31416966.
[68] Venkateswaran N, Lafita-Navarro MC, Hao YH, Kilgore JA, Perez-Castro L, Braverman J, *et al*. MYC promotes tryptophan uptake and metabolism by the kynurenine pathway in colon cancer. Genes Dev 2019;33(17-18):1236–1251. doi:10.1101/gad.327056.119, PMID:31416966.
[69] Chew SS, Tan LT, Law JW, Pusparajah P, Goh BH, Ab Mutalib NS, *et al*. Targeting Gut Microbial Biofilms-A Key to Hinder Colon Carcinogenesis? Cancers (Basel) 2020;12(8):2272. doi:10.3390/cancers12082272, PMID:32823729.
[70] Alexeev EE, Lanis JM, Kao DJ, Campbell EL, Kelly CJ, Battista KD, *et al*. Microbiota-Derived Indole Metabolites Promote Human and Murine Intestinal Homeostasis through Regulation of Interleukin-10 Receptor. Am J Pathol 2018;188(5):1183–1194. doi:10.1016/j.ajpath.2018.01.011, PMID:29454749.
[71] Busbee PB, Menzel L, Alrafas HR, Dopkins N, Becker W, Miranda K, *et al*. Indole-3-carbinol prevents colitis and associated microbial dysbiosis in an IL-22-dependent manner. JCI Insight 2020;5(1):127551. doi:10.1172/jci.insight.127551, PMID:31941837.

[72] Mirzaei R, Afaghi A, Babakhani S, Sohrabi MR, Hosseini-Fard SR, Babolhavaeji K, *et al*. Role of microbiota-derived short-chain fatty acids in cancer development and prevention. Biomed Pharmacother 2021;139:111619. doi:10.1016/j.biopha.2021.111619, PMID:33906079.
[73] Yusuf F, Adewiah S, Syam AF, Fatchiyah F. Altered profile of gut microbiota and the level short chain fatty acids in colorectal cancer patients. J Phys Conf Ser 2019;1146:012037. doi:10.1088/1742-6596/1146/1/012037.
[74] Tian Y, Xu Q, Sun L, Ye Y, Ji G. Short-chain fatty acids administration is protective in colitis-associated colorectal cancer development. J Nutr Biochem 2018;57:103–109. doi:10.1016/j.jnutbio.2018.03.007, PMID:29694938.
[75] Paget S. The distribution of secondary growths in cancer of the breast. 1889. Cancer Metastasis Rev 1989;8(2):98–101. PMID:2673568.
[76] Cheng YQ, Wang SB, Liu JH, Jin L, Liu Y, Li CY, *et al*. Modifying the tumour microenvironment and reverting tumour cells: New strategies for treating malignant tumours. Cell Prolif 2020;53(8):e12865. doi:10.1111/cpr.12865, PMID:32588948.