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Microbial metabolic profiling reshapes NF-κB-mediated immune metabolic network: a new mechanism for CRC development

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Abstract

Background The progression of colorectal cancer (CRC) is driven by multiple factors, including genetic mutations, metabolic reprogramming, immune escape, and dysbiosis of the intestinal microbiota. NF-κB acts as a central signaling hub within the tumor microenvironment that integrates inflammatory, metabolic, and immune cues to promote CRC progression.

Methods This review systematically summarizes the roles of key immune pathways and metabolic reprogramming in CRC pathogenesis and outlines CRC-associated alterations in gut microbial profiles. The synthesis of functional microbial metabolites, including short-chain fatty acids (SCFAs), secondary bile acids, and hydrogen sulfide (H_2S), modulates NF-κB activity through receptor-mediated signaling, regulation of signal transduction complexes, and epigenetic mechanisms, thereby reshaping tumor metabolism and immune responses. Notably, several metabolites demonstrate concentration-dependent biphasic effects on NF-κB signaling, highlighting the dynamic and context-dependent nature of microbial–host interactions during tumor progression.

Conclusions Targeting the metabolic activities of gut microbiota to regulate NF-κB signaling represents a promising multi-target strategy for CRC prevention and therapy. Future research should prioritize the construction of integrated "microbiota–metabolite–target" regulatory networks and the development of individualized microecological intervention strategies.

Highlights

- Gut microbial metabolites (GMMs) reshape NF-κB-mediated metabolic-immune networks in CRC.
- NF-κB is the regulatory hub of CRC, integrating inflammatory signals, metabolic reprogramming, and immune evasion mechanisms.

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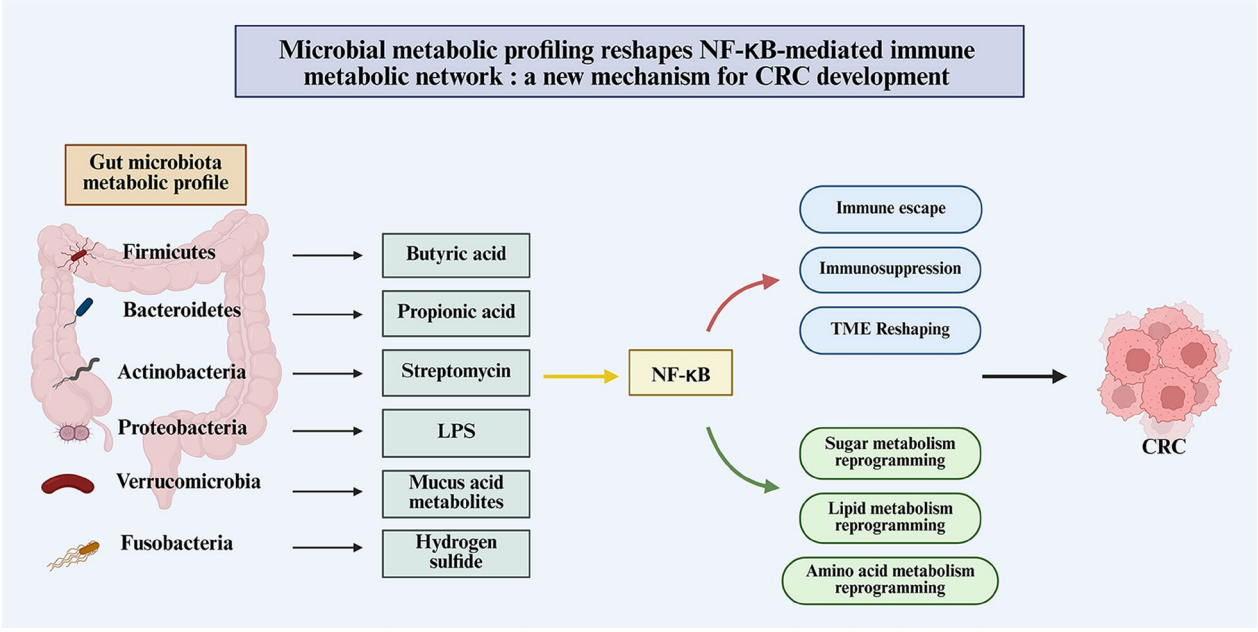
- Phylum-specific microbial metabolic profiles offer multi-target strategies for precision microbiota-based CRC therapy.

Keywords Gut microbiome, Gut microbiome metabolites, Colorectal cancer, Metabolic pathway, Immunoregulation, Tumor microenvironment, NF-κB

Graphical Abstract



Introduction

Colorectal cancer (CRC) ranks third in incidence and second in mortality among all cancers, posing a serious threat to global health. Currently, surgery is the preferred clinical treatment strategy for early colorectal cancer. For advanced colorectal cancer, the preferred approach involves surgery combined with adjuvant therapy, or surgery following neoadjuvant therapy [1, 2]. Metastatic colorectal cancer is managed primarily through chemotherapy, targeted therapy and immunotherapy. Studies have shown that the incidence of CRC is associated with factors such as lack of physical exercise, smoking history, Western-style diet, low fiber/high alcohol intake, and obesity, all of which can induce changes in the gut microbiota. Therefore, the environmental and ecological imbalance of gut microbiota, along with changes in metabolic pathways and immune pathways, as well as microbiota-host interactions are closely linked to the pathogenesis, progression, and clinical management of CRC [3]. In addition, gut microbiome (GM) -related metabolism and immune crosstalk play a critical role in regulating the development and progression of CRC.

The pathogenesis of CRC

The pathogenesis of CRC involves genetic mutations, epigenetic disorders, tumor microenvironment remodeling, immune system disorders, metabolic dysfunction and changes in intestinal microbial abundance, which collectively drive the malignant transformation of normal colorectal epithelial cells. Genetic mutations, such as KRAS activation, TP53 inactivation, and epigenetic disorders, including m6A methylation, non-coding RNA abnormalities, directly promote malignant transformation of cells [4]. Simultaneously, immune system disorders such as immune surveillance failure due to innate immune dysfunction, aberrant immune pathways forming an immune suppression network, abnormal immune checkpoints, and TME remodeling facilitate immune escape and promote CRC progression [5]. In addition, excessive activation of the Wnt signaling pathway, along with abnormal activation of PI3K/AKT/mTOR and MAPK pathways, drives tumor proliferation and malignant transformation. Metabolic dysfunctions, such as glycolysis (the Warburg effect), elevated lipid synthesis (FASN overexpression), and amino acid metabolic reprogramming further exacerbate CRC progression [6].

Immune-related mechanisms

The progression of CRC is closely associated with dysregulation of intestinal immune microenvironment, which is mainly manifested through: the dysfunction of type I/III interferon leading to the failure of immune surveillance, persistent activation of the CD39/CD73/adenosine pathway, abnormalities in the NF-κB-JNK axis resulting in anti-tumor immunosuppression, abnormal activation of PD-1/PD-L1 signaling pathway and recruitment of immunosuppressive cells promoting immune escape, the dysregulation of the Wnt/MAPK/PI3K-Akt pathway mediates tumor microenvironment remodeling. Under the coordinated influence of these signaling networks, an immunosuppressive microenvironment is established, driving therapeutic resistance and malignant progression of CRC.

Functional defects of type I/III interferons lead to immune surveillance failure

The functional defects of the type I/III interferon system promote the progression of CRC through a multifaceted mechanism. In the early stage, impaired expression of type III interferon (IL-28 A) compromises the integrity of the intestinal epithelial barrier, diminishes mucosal defense function, and increases the risk of carcinogenesis. The functional defect of type I interferon (IFN-I) inhibits the cGAS-STING signaling pathway, which impairs T cell activation and dendritic cell maturation, and enables tumor cells to evade immune clearance [7]. In the tumor microenvironment (TME), reduced expression of type I interferon (IFN-α13 and IFN-β), combined with the gene mutation of the IFN signaling pathway contributes to tumor immunotherapy resistance and weakens the innate immune surveillance function [8]. The dysfunction of interferon system leads to the imbalance of cGAS-STING-IFN-I axis, facilitating tumor cells evade immune surveillance and promoting treatment resistance and invasion and metastasis (Fig. 1A).

CD73/CD39/adenosine pathway mediates CRC immunosuppression

In the TME, the CD39-CD73-adenosine pathway converts pro-inflammatory ATP into immunosuppressive adenosine (ADO) through a cascade enzymatic reaction, CD39 (ENTPD1) catalyzes the hydrolysis of ATP/ADP to AMP as a rate-limiting enzyme, while CD73 (NT5E) converts AMP to adenosine [9]. Sustained activation of this pathway, driven by high expression of tumor cells, exosomes, stromal cells and immune cells (Tregs and macrophages), leads to substantial accumulation of adenosine. Adenosine inhibits the activation and cytotoxic function of $CD8^+$T cells and NK cells through A2A/A2B receptors (ARs). It also promotes the activation of regulatory T cells (Treg) and myeloid-derived suppressor cells (MDSC), inhibits the maturation of dendritic cells, enhances Th17 response, builds an immunosuppressive microenvironment [10]. Simultaneously, in effector T cells, A2A receptors inhibit IKK activity through cAMP-PKA, thereby suppressing NF-κB pro-inflammatory transcription and reducing glycolytic activity. A2B receptor synergistically activates NF-κB via the PI3K/AKT-MAPK axis, inducing immunosuppressive cytokines, and promoting the transformation of M1 macrophages into M2 phenotype characterized by fatty acid oxidation [11, 12]. In addition, NF-κB and hypoxia signaling can reciprocally up-regulate the expression of CD39/CD73, forming a positive feedback loop that amplifies adenosine accumulation and immune-metabolic inhibition, thereby reinforcing the immune escape ability in CRC (Fig. 1A).

NF-κB-JNK axis drives immunosuppressive microenvironment

NF-κB and JNK signaling pathways act in concert to drive CRC progression and immune escape. Abnormal activation of the NF-κB pathway fosters a chronic inflammatory environment by sustained secretion of pro-inflammatory factors like IL-6 and TNF-α, leading to ROS accumulation and defective DNA repair. Furthermore, NF-κB enhances tumor cell survival through STAT3/NF-κB positive feedback loop and enhances VEGF expression to promote tumor angiogenesis [13]. Concurrently, abnormal JNK pathway up-regulates PD-L1 expression, and induces T cell dysfunction. Through the ROS/ASK1/JNK axis, it also activates c-Jun/MMP-1 signaling to enhance tumor metastasis [14]. Critically, these pathways engage in a cross-regulation between NF-κB and JNK pathway: JNK positively regulates NF-κB activity through p65 phosphorylation, while NF-κB regulates PD-L1 expression and M2 macrophage polarization. Together, they shape an TME, characterized by enrichment of immunosuppressive cells (M2-TAMs, Tregs), effector T cell failure [15], ultimately driving CRC immune escape, treatment resistance and distant metastasis (Fig. 1B).

PD-1/PD-L1 mediates CRC immune escape

In CRC progression, high expression of PD-L1 is significantly associated with poor prognosis. At the molecular regulatory level, histone demethylase (JMJD2D) up-regulates PD-L1 through epigenetic modification, while nuclear coactivator (SRC-1) and transcription factor (ZEB1) positively regulate its expression, conversely, the loss of PPARα promotes PD-L1 transcription [16, 17]. Furthermore, miRNA network involving miR-497 inhibition and miR-548b-5p/c-5p overexpression, m6A RNA modification mediated by HNRNPC, and the ubiquitination/deubiquitination process collectively regulate PD-L1 stability. Integrin αvβ6 activates ERK/MAPK pathway and IFNγ signaling in the TME. IL-17 directly up-regulates PD-L1 expression, and IL-33 synergistically

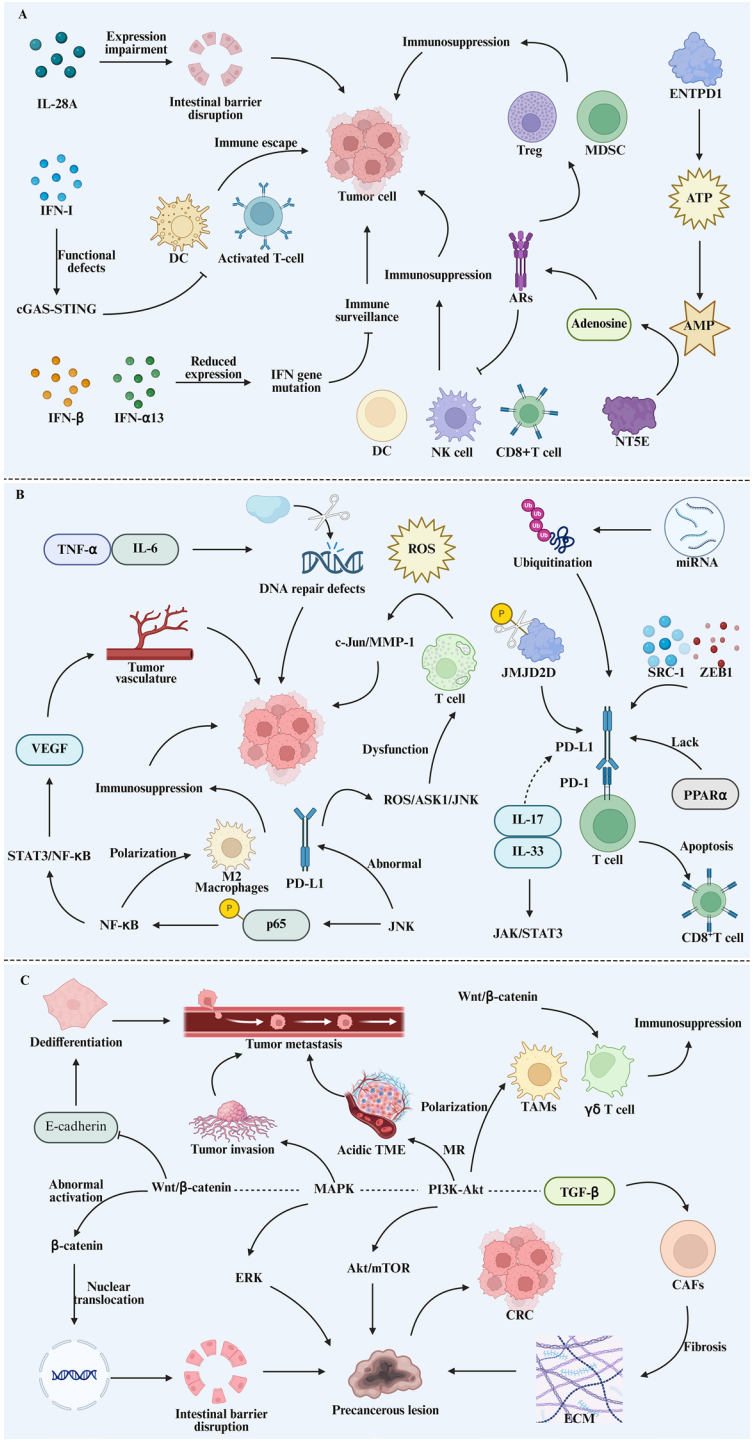


Fig. 1 The immune mechanism of CRC. **A**: Dysregulation of interferon system and adenosine-mediated immunosuppression promote CRC progression. **B**: The NF-κB-JNK signaling axis and PD-L1 regulatory network collectively drive CRC immune escape. **C**: The interaction of Wnt-MAPK-PI3 K pathway and tumor microenvironment fibrosis collectively promote CRC progression

activates the JAK/STAT3 pathway to enhance the sensitivity of tumor cells to IFN-γ [18]. In the TME, changes in acidity and stromal cell interactions (CAFs) reinforce the immunosuppressive network; meanwhile, M2 macrophage polarization and Treg cell activation promote PD-L1 expression through the JAK/STAT3 axis, and collectively constructing an immunosuppressive microenvironment. In CRC, PD-L1 and NF-κB synergistically activate the PI3K/Akt/mTOR pathway, enhance the expression of glycolytic enzymes (GLUT1, HK2, PDK1)

and lipid synthesis genes, promote lactic acid accumulation, and aggravate local acidic TME. Lactic acid, hypoxia and inflammatory factors then reciprocally activate NF-κB and stabilize PD-L1, forming a positive feedback loop of inflammation-metabolism-immunosuppression [19, 20]. Simultaneously, on immune cells, PD-1 engagement by PD-L1 inhibits Akt/mTOR signaling, reduces the glycolytic capacity of T cells, induces $CD8^+$ T toward inefficient fatty acid oxidative metabolism, forcing them into an exhausted state, promoting CRC immune escape (Fig. 1B).

Synergistic immunosuppressive cell network in CRC immune escape

M2 tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) constitute a powerful immunosuppressive network that drive CRC progression through multi-level synergy [21]. Driven by the IL-4/IL-13-IL-4Rα axis and intestinal flora (Porphyromonas gingivalis), M2-type TAMs promote tumor angiogenesis through VEGF, and cooperate with CAFs to enhance tumor metastasis. MDSCs maintain their immunosuppressive phenotype through excessive activation of the STAT3 signaling pathway [22]. The PMN-MDSCs and M-MDSCs subsets exert heterogeneous inhibitory effects through $CCR2^+$ accumulation and $CD15^+$ expression, respectively, and induce EMT through the IL-23/Stat3 axis leading to chemoresistance. Tregs inhibit $CD8^+$ T cell function through secreting TGF-β and IL-10 to form a synergistic network with TAMs. Furthermore, Tregs lead to immune system inhibition by high expression of immune checkpoint molecules (PD-1 and CTLA-4), collectively promoting CRC immune escape and TME heterogeneity [23].

TME remodeling mediated by dysregulation of the Wnt/MAPK/PI3K-Akt pathway

Synergistic dysregulation of Wnt/β-catenin, MAPK and PI3K-Akt signaling pathways promotes CRC progression by driving cell mutation and remodeling TME. In the early stage of CRC, abnormal activation of Wnt/β-catenin pathway promotes β-catenin nuclear translocation and disrupts intestinal stem cell homeostasis [24]. Concurrently, abnormal MAPK and PI3K-Akt pathways lead to sustained ERK activation and amplified Akt/mTOR proliferation signals, which synergistically induce precancerous lesions. During the progression of CRC, the Wnt pathway down-regulates E-cadherin expression, leading to cell dedifferentiation, while abnormal MAPK pathway enhances tumor invasiveness. The PI3K-Akt pathway creates acidic TME through metabolic reprogramming that promotes CRC metastasis [25]. In terms of TME remodeling, Wnt/β-catenin inhibits γδT cell infiltration, and PI3K-Akt induces TAMs polarization, collectively fostering immunosuppressive microenvironment. Furthermore the activation of CAFs by the PI3K/Akt/mTOR and the TGF-β signaling leads to ECM fibrosis [26, 27]. The comprehensive TME remodeling protects CRC from immune clearance through physical barriers (fibrosis) and biochemical barriers (immunosuppression). It also maintains cancer stem cell characteristics (led by Wnt) and apoptosis resistance (mediated by PI3K-Akt/MAPK), ultimately leading to a high heterogeneity and metastatic potential of CRC (Fig. 1C).

Metabolic-related mechanisms

In addition to the immune microenvironment, CRC progression is also closely related to the intestinal metabolic microenvironment, the main manifestation include: glucose metabolism reprogramming where enhanced Warburg effect and inhibited mitochondrial oxidative phosphorylation lead to abnormal energy supply; lipid metabolism disorders (enhanced fatty acid synthesis and β-oxidation) promote membrane structure formation and the accumulation of inflammatory mediators, dysregulation of amino acid metabolism (glutamine-dependent enhancement and tryptophan-kynurenine axis activation) supports tumor proliferation and induces immunosuppression. These metabolic reprogrammings drive CRC malignant proliferation and metastasis through core mechanisms such as sustained activation of the mTOR-HIF-1α axis, abnormal PPAR-γ signaling pathway, and IDO1-mediated immune escape. Together these mechanisms promote acidification of the metabolic microenvironment, increased nutritional competition, and abnormal epigenetic modifications.

Warburg effect and OXPHOS Inhibition synergistically drive CRC immune escape

Abnormal energy metabolism is characterized by enhanced Warburg effect and inhibited mitochondrial oxidative phosphorylation (OXPHOS), which together form core cancer-promoting metabolic reprogramming. Numerous in vitro and clinical studies have shown that by up-regulating GLUT transporters and key enzymes of glycolysis (PKM2, PDK1), CRC cells still preferentially undergo glycolysis under sufficient oxygen conditions [28]. By rapidly generating ATP, it provides precursors for nucleotide and lipid synthesis and supports tumor cell proliferation. The Warburg effect is accompanied by massive accumulation of lactic acid which remodels the TME. In vitro and animal studies confirm that lactic acid induces M2 macrophage polarization and inhibits T cell function to form an immunosuppressive TME [29]. Concurrently, VEGF upregulation promotes tumor angiogenesis and induces EMT, leading to CRC metastasis. Non-coding RNA (lncRNA RUNDC3A-AS1) and transcription factor (ONECUT3) have been reported to

enhance the Warburg effect by up-regulating the expression of glycolytic enzymes, thereby promoting tumor survival and proliferation.

In parallel, the inhibition of OXPHOS function aggravates energy metabolism disorders. Mitochondrial dysfunction leads to insufficient ATP production, resulting in CRC relying on the AKT/mTOR pathway to maintain energy supply and triggering metabolic-related genomic instability. Abnormalities in the electron transport chain can increase intracellular ROS levels, low-dose ROS activates the MAPK/ERK signaling to promote proliferation in cells and animal models, while sustained or high-level ROS increases genomic instability (KRAS, TP53) through oxidative damage and triggers NF-κB-mediated inflammatory responses [30]. Furthermore OXPHOS deficiency disrupts histone deacetylation and silences tumor suppressor gene expression by altering NAD^+/NADH ratio and acetyl-CoA level. Critically, OXPHOS inhibition and Warburg enhancement interact reciprocally. The HIF-1α pathway is activated by ROS to enhance glycolysis [31], while the accumulation of glycolysis metabolites like lactic acid inhibits mitochondrial function. These processes jointly promote CRC immune escape, metastasis and treatment resistance (Fig. 2A).

Enhanced fatty acid synthesis and β-oxidation disorder synergistically drive the remodeling of the CRC metabolic inflammatory microenvironment

In CRC, fatty acid synthesis is enhanced while β-oxidation is blocked to build a cancer-promoting metabolic microenvironment. The expression of FASN, a key enzyme in fatty acid synthesis, is up-regulated in cells and animal models, activating the FakAB kinase system, promoting acyl-ACP conversion and accelerating membrane phospholipid synthesis to provide a membrane structure basis for tumor cell proliferation [32]. The increased proportion of saturated fatty acids like palmitic acid has a clear clinical correlation, and in vitro evidence shows that enhanced membrane rigidity affects signal transduction and induces IL-6 secretion through the NF-κB pathway [33]. Furthermore, ω-6 polyunsaturated fatty acids are catalyzed by the FADS enzyme to generate arachidonic acid, which is subsequently converted into a pro-inflammatory mediator like prostaglandin to form a sustained inflammatory cascade. Clinical stduies indicate that these lipid mediators inhibit NK cell function and help shape an immunosuppressive microenvironment [34]. CAFs activation and ECM remodeling promote tumor invasion and metastasis.

Concurrently, β-oxidation dysfunction leads to the abnormal accumulation of fatty acids and triggers a chain reaction of lipid peroxidation. Damage to the carnitine transport system and down-regulation of CPT1A expression prevent long-chain fatty acids from entering mitochondria for oxidation, resulting in their abnormal insertion into membrane phospholipid structures [35]. These accumulated long-chain fatty acids are converted by ROS into active lipid mediators such as 4-hydroxynonenal, which induce DNA damage, drive gene mutation, and activate NLRP3 inflammasome. This promotes the release of IL-1β and TNF-α, induces chronic inflammation, and inhibits the expression of β-oxidase [36]. This process aggravates the accumulation of fatty acids, forming a vicious cycle of lipid metabolism disorder and inflammatory microenvironment that ultimately drives CRC progression (Fig. 2B).

Glutamine and Tryptophan metabolic reprogramming synergistically regulate CRC epigenetics

In CRC, glutamine is largely taken up by tumor cells through the SLC1A5/GLS axis and is catalyzed by glutamine enzyme to produce glutamic acid, which is then converted into α-ketoglutarate and returned to the TCA cycle. This process provides key intermediates (pyruvate, oxaloacetate) for glucose metabolism reprogramming. Glutamine also supports nucleotide and fatty acid synthesis through transamination. Glutamine metabolism is precisely regulated by transcription factors such as c-MYC. By inhibiting TET enzyme activity, c-MYC leads to hypermethylation of tumor suppressor genes and recruits histone acetyltransferase to activate oncogene expression, forming a vicious cycle at the epigenetic level.

Concurrently, tryptophan promotes EMT process and immune escape through IDO1/TDO-mediated kynurenine metabolism and activation of AhR signaling pathway [37]. In in vitro immune cell culture and mouse tumor models, glutamine dysfunction abnormally inhibits the function of T cells and dendritic cells, and tryptophan depletion inhibits $CD8^+$T cell activity through the GCN2-mTOR axis [38]. In the tissue and plasma studies of CRC patients, metabolic derivatives like α-ketoglutarate and kynurenine are associated with immune escape characteristics, while kynurenine-AhR signaling promotes EMT and PD-L1 expression. Causal evidence for these mechanisms has been provided by numerous cell and animal experiments. The proliferation and activation of immunosuppressive cells such as Treg, MDSCs and TAMs, induced by epigenetic modification and AhR-PD-L1 axis, are mainly observed as correlative co-occurrences in clinical practice [39]. This multi-level metabolic network accelerates cell cycle progression by activating cyclin D/E, forming a persistent cancer-promoting vicious cycle that drives CRC proliferation, metastasis and therapeutic resistance (Fig. 2C).

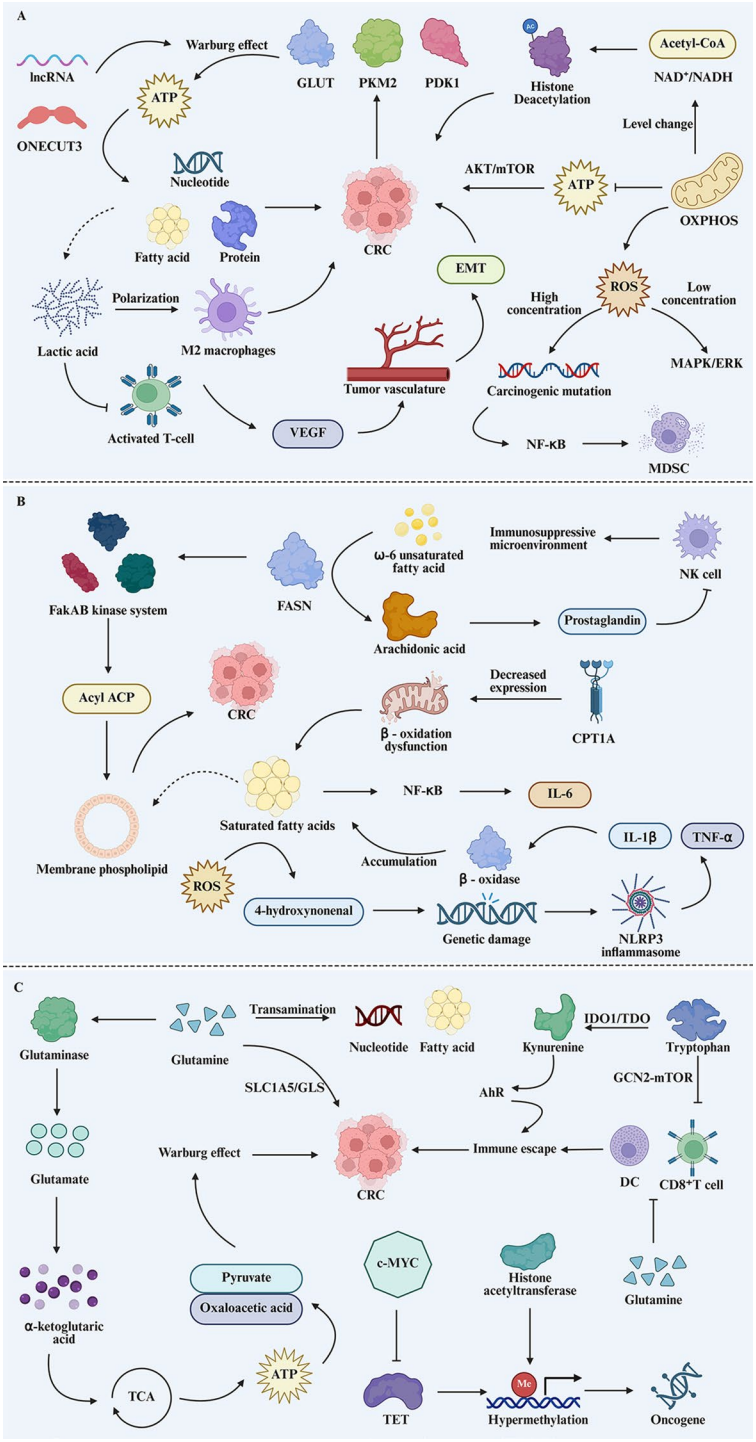


Fig. 2 The metabolic mechanism of CRC. **A**: Warburg effect and OXPHOS deficiency promote the progression of colorectal cancer. **B**: Fatty acid synthesis and β-oxidation imbalance synergistically enhance the invasion and metastasis of colorectal cancer. **C**: Glutamine metabolic reprogramming and tryptophan depletion synergistically mediate immunosuppression to promote CRC progression

Metabolic-immune crosstalk at NF-κB signaling drives CRC progression

In CRC progression, the NF-κB signaling pathway serves as a core hub for metabolic-immune regulation, integrating inflammatory response, metabolic reprogramming and immune escape mechanisms to form a persistent cancer-promoting vicious cycle. Clinical and multi-omics studies suggest that NF-κB is in a state of sustained activation in CRC tissues and is significantly correlated with inflammatory factors, metabolic reprogramming

characteristics and immunosuppressive phenotypes, with causality established through cells and animal models [40]. Excessive ROS from glucose metabolism reprogramming, lipid peroxidation product 4-hydroxynonenal (4-HNE) and inflammatory factors (TNF-α and IL-1β) collectively activate the IKK complex, leading to the phosphorylation and degradation of IκBα and the release of NF-κB dimer into the nucleus [41].

Activated NF-κB acts as a driver of CRC metabolic reprogramming by transcriptionally up-regulating genes such as GLUT1, PKM2, LDHA, FASN, SCD1 and glutamine metabolism-related genes (SLC1A5, GLS), a finding confirmed by transcriptome analysis and functional experiments. Tumor metabolic pathway also provides negative feedback that influences NF-κB activity. For instance, lactic acid enhances NF-κB activity through GPR81, PGE2 promotes its transcription through EP4, and α-KG inhibits TET to maintain pro-inflammatory gene hypomethylation [42], these mechanisms primarily elucidated from cell models and animal studies. In addition to metabolic regulation, NF-κB shapes immunosuppressive microenvironment through multiple mechanisms: it directly up-regulates the expression of PD-L1 and CD274, promotes IDO1-mediated tryptophan metabolism, enhances the transcription of CD39/CD73, leads to adenosine accumulation, drives the secretion of IL-6 and IL-10, induces M2 macrophage polarization and Treg expansion, and inhibits the activation and cytotoxicity of $CD8^+$ T cells, as confirmed in a variety of tumor models [43]. Furthermore, NF-κB cooperates with Wnt/β-catenin to maintain the characteristics of tumor stem cells, enhances survival signals through STAT3 positive feedback loop, and cooperates with HIF-1α to adapt to hypoxic environment [44]. This metabolic-immune crosstalk regulatory network, supported largely by in vitro mechanic studies and animal models, establishes the NF-κB pathway as a key driver of CRC malignant progression (Fig. 3).

It is worth noting that metabolites-mediated regulation of NF-κB exhibits a typical concentration-dependent bidirectional effect. Low to moderate levels of metabolites (e.g. lactic acid, moderate ROS, short-chain fatty acids) promote IKK activation and enhance NF-κB activity through receptor (GPR81), upstream kinase (TAK1/MAPK) or signal complex assembly [45]. In contrast, high level of metabolite accumulation in the tumor microenvironment can induce negative feedback through mechanisms such as receptor desensitization, kinase damage, redox imbalance, HDAC inhibition or stress response (AMPK/UPR), which subsequently suppress

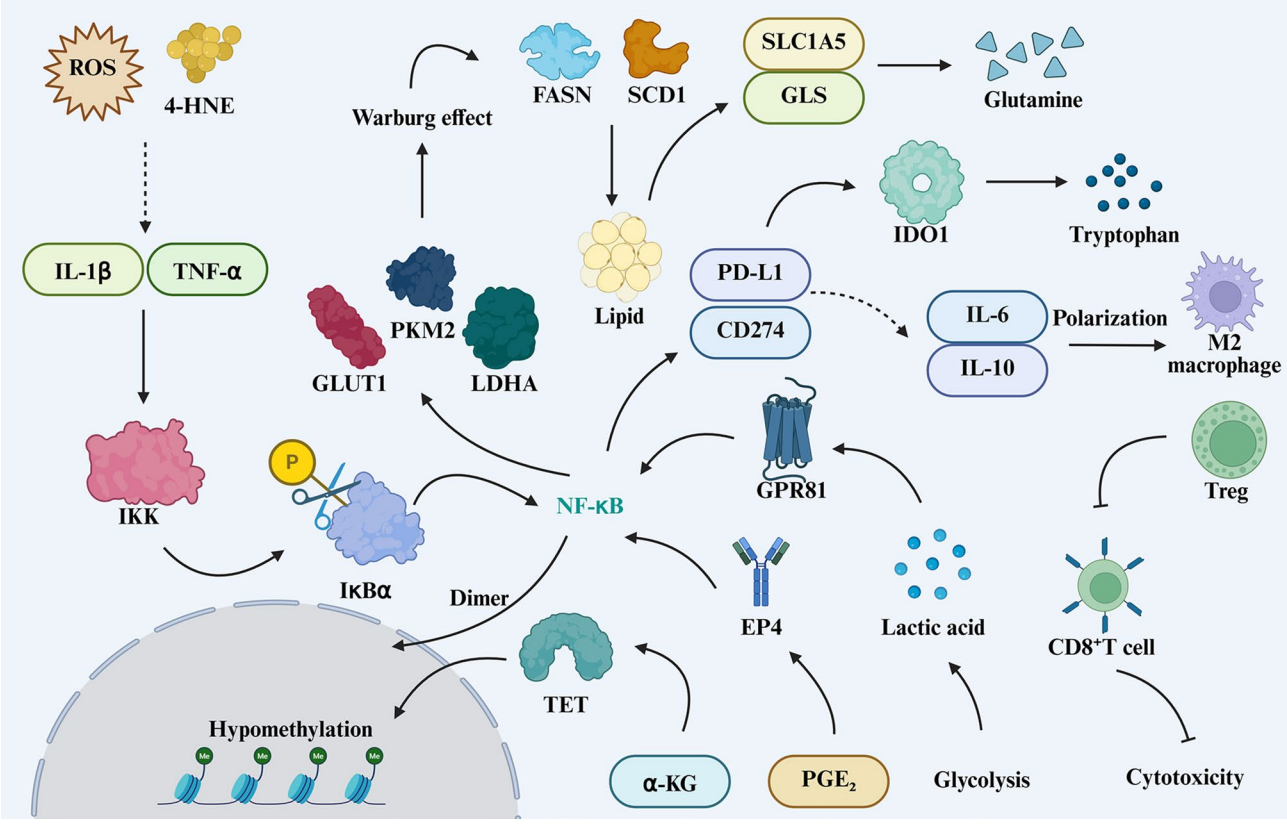


Fig. 3 Metabolic-immune synergistic regulation of NF-κB pathway promotes CRC. ROS and inflammatory factors activate NF-κB, up-regulates glycolysis, lipid synthesis and Gln metabolism, promotes PD-L1/IDO1 expression and immunosuppressive cell expansion, thereby promoting CRC progression

NF-κB signaling. The regulatory impact of metabolites on NF-κB signaling does not have a fixed threshold, but depends on relative concentration, exposure time, cell type, redox buffering capacity, and the presence of co-stimulatory signals such as TNF-α, IL-1β [46]. For example, lactic acid promotes NF-κB at a lower level, but can inhibit it under severe acidification and oxidative stress environments. Similarly, butyric acid maintains immune homeostasis at low concentrations, and blocks NF-κB target gene expression by HDAC inhibition at high concentrations. Therefore, understanding the bidirectional regulation of metabolites requires a multidimensional framework that integrates concentration, time, and cellular context to accurately correspond to the actual biological effects within the CRC microenvironment [47].

A microbial metabolite-based strategy to modulate NF-κB and improve CRC

Construction of gut Microbiome metabolic profile

Gut microbiome is one of the most complex symbiotic ecosystems in the human body, with a close interaction between community structure and host health. The six main phylums of human gut microbiota, including Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Verrucomicrobia and Fusobacteria, produce differential metabolites by fermenting complex carbohydrates such as dietary fiber, thereby influencing gut homeostasis.

Metabolic spectrum of firmicutes

The metabolic profile of Firmicutes plays a key role in the synthesis of bioactive substances, environmental adaptation and host microecological regulation. Several classes of bacteria have shown significant functional differences in their potential for CRC treatment. *Bacillus* species mainly produce antimicrobial peptides and probiotic metabolites (e.g. Reuterin, Plantaricin A, lactic acid), and synthesizes osmotic protective agents and heat-stable enzymes, which help maintain intestinal barrier and inhibit pathogenic bacteria to assist in reconstructing intestinal homeostasis [48]. *Clostridia* are characterized by SCFAs metabolism. Butyrate bacteria, such as *Faecalibacterium*, *Roseburia*, Anaerostipes, play a significant role in epithelial homeostasis and anti-inflammation. The genera involved in acetic acid, hydrogen or sulfur metabolism can regulate energy supply and redox balance, thereby maintaining the intestinal mucosa and inhibiting inflammation [49]. They are involved in energy metabolism and epithelial nutrition supply. *Negative Clostridia* and *non-Bacillus* (e.g. V*eillonella*, *Phascolarctobacterium*, *Selenomonas*, *Turicibacter*) regulate immune response and metabolic homeostasis by producing propionic acid, succinic acid or selenides and gut-brain axis signals.

Current studies have shown that such changes in microbial spectrum can be a cause of CRC [50]. Decreased butyric acid production, increased secondary bile acids, and abnormal proliferation of molds (e.g. *Aspergillus*, *Candida*) activate the Dectin-1/CARD9-mediated NF-κB and Th17 pathways through β-glucan, triggering chronic mucosal inflammation, ROS accumulation and metabolic disorders that promote epithelial damage and carcinogenesis [51]. Conversely, microbial spectrum changes can also be a consequence of disease development. Local hypoxia, an impaired mucus barrier and immunosuppression in tumors lead to enrichment or depletion of specific flora. These changes regulate epithelial energy metabolism, redox status and SCFAs/bile acid signals through metabolites, and impact inflammation and anti-tumor immunity through immune pathways (e.g. NF-κB, STAT3, IL-17, Th17 response), forming a positive or negative feedback loop [52]. For instance, significant reductions in *Faecalibacterium prausnitzii*, *Roseburia*, *Anaerostipes*, and *Eubacterium* result in insufficient epithelial energy supply, impaired barrier repair, and chronic inflammation [53]. The selective enrichment of *Clostridium XIVa* and *Peptostreptococcus stomatis* in hypoxic and mucus barrier-damaged environments exacerbates immunosuppression and metabolic abnormalities and promotes CRC progression (Table 1A).

Bacteroidetes metabolic spectrum

The metabolic profile of Bacteroidetes involves SCFAs production, bile acid conversion, the degradation of complex organic matter and participates in the nitrogen-sulfur cycle, and has potential intervention value in CRC treatment through specific secondary metabolite synthesis. Certain characteristic flora (*Bacteroides*, *Alistipes*) proliferates in advance due to diet, inflammation and mucus barrier damage in the adenoma stage, triggers SCFAs imbalance, elevates secondary bile acids and abnormal indole metabolism, with a clear precursor tumorigenic effect. After tumor formation, hypoxia, inflammation and immune stress reciprocally increase the abundance of bacteria and sustaining a tumor-promoting state [54].

Bacteroidia (e.g. *Bacteroides*, *Parabacteroides*, *Prevotella*, *Alistipes*) efficiently produce acetic acid, propionic acid, butyric acid and secondary bile acids, thereby regulating host immunity and intestinal microenvironment homeostasis. Notably secondary bile acids (DCA) can persistently activate NF-κB and induce DNA damage [55]. *Alistipes* and *Prevotella* are also involved in tryptophan metabolism, synthesis of indoles and neuroactive metabolites that play an important role in the regulation of intestinal-brain axis and immune escape [56]. *Cytophagia* (e.g. *Cytophaga and Microscilla*) specializes in the degradation of complex organic matter (cellulose,

Table 1A The main products of the metabolic spectrum of firmicutes

Class	Genus	Metabolite
Bacillus	*Bacillus\Brevibacillus\Carnobacterium\ GracilibacillusPaenibacillus\ Pediococcus\Sporosarcina\Weissella*	Bacteriocin, Surfactin, Cyclic lipopeptide
	Lactobacillus\Lactococcus\Leuconostoc Streptococcus\Tetragenococcus\ Vagococcus	Lactic acid
	Geobacillus\Marinococcus\Virgibacillus	Ectoine, heat-stable enzyme
	Staphylococcus\Macrococcus	Flavor lipids
	Exiguobacterium	Heavy metal conversion
	Halobacillus\Jeotgalibacillus	Flavor compounds
Fusobacterium	*Acetobacterium\Caloramator\Dorea\ Eubacterium\Terrisporobacter*	Acetic acid
	Anaerostipes\Anaerotruncus\ Butyrivibrio\ Faecalibacterium\Roseburia	Butyric acid
	Ruminococcus	Propionic acid, Butyric acid
	Carboxydothermus\Paraclostridium	H_2
	Desulfotomaculum	H_2S
	Thermoanaerobacter\ Thermoanaerobacterium	Ethyl alcohol
	Clostridioides	Characteristic toxins
	Oscillibacter	Cholesterol
	Hungatella	Bile acid
	Peptoclostridium	Indole lactic acid
Negativicutes	*Acidaminococcus\Anaeroglobus\ Dialister*	Butyric acid
	Veillonella	Propionic acid
	Pectinatus\Sporomusa	Acetic acid
	Megasphaera	Mid-chain fatty acid
	Mitsuokella	Phytate degradation
	Negativicoccus	Alkylpyranone
	Phascolarctobacterium	Succinic acid
	Selenomonas	Selenium
Tissierellia	*Gallicola\Parvimonas*	Acetic acid, propionic acid, butyric acid
Limnochordia	*Limnochorda*	Formate

protein), and produces butyric acid and lactic acid, which promotes nutrient release and local pH regulation. *Ohtaekwangia* is also involved in the nitrogen and sulfur cycle, influencing the redox state of the TME. *Flavobacteriia* (e.g. *Flavobacterium*, *Chryseobacterium*) synthesizes

Table 1B The main products of bacteroidetes metabolic spectrum

Class	Genus	Metabolite
Bacteroidia	*Alistipes\Bacteroides\Coprobacter\ Dysgonomonas\Parabacteroides\ Paraprevotella\Prevotella\ Proteiniphilum*	Acetic acid, propionic acid, butyric acid, valeric acid, bile acid Tryptophan
Cytophagia	*Cytophaga\Flexibacter\ Reichenbachiella\Microscilla*	Organic degradation
Flavobacteriia	*Flavobacterium\Chryseobacterium\ Tenacibaculum\Zobellia\Formosa*	Alkaloids
Sphingobacteriia	*Sphingobacterium\Flavisolibacter\ Pedobacter\Mucilaginibacter*	Sphingolipids, quinones
	Parapedobacter\Sphingobium	Humic acid

pigments, alkaloids and lipid compounds with antibacterial, anti-inflammatory or antioxidant activities on the basis of polysaccharide degradation, thereby modulating local inflammation and intestinal barrier function [57].

Sphingobacteriia is characterized by the metabolism of sphingolipids, quinones and extracellular polysaccharides. Some bacteria (e.g. *Pedobacter*, *Sphingobium*) accumulate PHA or synthesize humic acid, which is involved in barrier protection and metabolic regulation [58]. CRC microecological imbalance is often accompanied by significant mold proliferation. Mold metabolites (e.g. alcohols, organic acids, ergosterol derivatives) can change the local redox state and pH, drive bile acid imbalance and indole pathway disorder, and form a positive feedback cancer-promoting loop of microorganism-immunity-metabolism [59]. Collectively, the metabolic profile of Bacteroidetes reveals a significant potential for multi-target and cross-level regulation of CRC progression (Table 1B).

Actinobacteria metabolic spectrum

The actinobacteria metabolic profile demonstrates important physiological functions in antibiotic synthesis, organic acid fermentation, lignocellulose degradation and steroid transformation, showing potential intervention value in CRC treatment through various secondary metabolites. *Streptomyces* and *Micromonospora* in *Streptomycetia* are classic strains producing antibiotics and anti-tumor active substances. They synthesize a wide of compounds, including streptomycin, tetracycline, gentamicin and anti-tumor enediynes, and secrete a variety of hydrolases which have a synergistic effect on the degradation of carcinogens in the TME [60].

Nocardia and *Pseudonocardia* in *the class Nocardiaceae* are good at synthesizing non-ribosomal peptides and immunoregulatory metabolites, and exhibiting anti-inflammatory and tumor suppression potential [61].

Corynebacterium and *Mycobacterium* in the class *Corynebacteriia* synthesize characteristic lipids (mycolic acid) and a variety of immune regulatory molecules, demonstrating functional potential in regulating intestinal mucosal barrier and metabolic homeostasis. *Bifidobacterium*, *Propionibacterium*, *Cutibacterium* of *Bifidobacterium* and *Propionibacterium* can produce acetic acid, propionic acid and vitamin B12, which is helpful for intestinal flora balance and anti-inflammatory regulation [62]. *Micrococcus*, *Kocuria and Staphylococcus* in *Micrococcales* are characterized by the synthesis of carotenoids, antimicrobial peptides and surfactants, conferring antioxidant and immune enhancement effects. *Planococcus* produces phenolic pigments like astaxanthin, which possesses anti-inflammatory and anti-cancer potential [63]. Furthermore, *Rhodococcus*, *Gordonia* and *Arthrobacter* have the ability to degrade pollutants and participate in the remodeling of CRC metabolic microenvironment through regulating intestinal environment and oxidative stress (Table 2A).

Proteobacteria metabolic spectrum

The proteobacteria metabolic spectrum is involved in nitrogen fixation, hydrocarbon degradation, sulfur/iron redox and single carbon metabolism, contributing to the maintenance of intestinal microenvironment homeostasis. In *Alphaproteobacteria*, *Rhizobium* is involved in the regulation of host immunity and epithelial homeostasis by producing IAA, EPS and ammonia nitrogen fixation products. *Sphingomonadaceae* degrades aromatic carcinogens and synthesizes antioxidant pigments (carotenoids). *Methylotrophs* interfere with the intestinal metabolic environment through methanol/formic acid metabolism and the synthesis of secondary product (vitamin B12, PHA) [64].

In *Betaproteobacteria*, *Burkholderiales* and *Nitrobacteria* participate in antibacterial defense and nutritional balance, regulating the sulfur cycle within intestinal microecology through the synthesis of antibiotics, siderophore synthesis and nitrogen oxidation [65]. In *Gammaproteobacteria*, *Enterobacteriaceae* can secrete siderophores and 2,3-butanediol to enhance cancer-promoting signals. *Pseudomonas* synthesizes phenazine antibiotics which possess antibacterial and ROS regulatory functions. *Vibrio* and *Methylococcaceae* participate in carbon source recycling and epithelial barrier regulation through extracellular enzymes and methane metabolism [66]. In *Deltaproteobacteria*, *Sulphatebacteria* and *Sulfur-reducing* bacteria affect the redox balance of the TME through sulfur cycle products (H_2S). *Myxobacteria* synthesize polyketides as anti-tumor substances, while succinic acid produced by *Terrabacter* participates in energy metabolism and cell proliferation regulation. *Epsilonproteobacteria*, including *Campylobacteria and Helicobacter*, affect epithelial cell metabolism and immune response through carbohydrates and lactate-derived metabolites. *Sulfurspiral* is involved in the regulation of sulfur/nitrogen cycle [67].

Metabolites and toxic molecules, such as LPS, phenazines, 2,3-butanediol, indole/sulfides, bacterial products, produced by the genus like *Enterobacteriaceae*, *Pseudomonas*, *Vibrio*, and *Burkholderiales* can up-regulate TLR/NF-κB, NLRP3 inflammasome and IL-6/STAT3 pathways in epithelial cells, their metabolites cause pro-inflammatory immune infiltration, destroy mucosal barrier, directly or indirectly induce DNA damage and oxidative stress, collectively promoting epithelial cell proliferation and pro-cancer metabolic reprogramming [68, 69]. In contrast, *Sphingomonadaceae* can maintain epithelial homeostasis by generating immunomodulatory molecules, inhibiting HDAC, promoting Treg and antagonizing oxidative stress, thereby exerting a tumor suppressor effect (Table 2B).

Table 2A The main products of actinobacteria metabolic spectrum

Class	Genus	Metabolite
Streptomycetia	*Streptomyces*	Streptomycin, Tetracycline, Antibiotics, Gentamicin
	Micromonospora	
Nocardiaceae	*Nocardia\Pseudonocardia*	Non-ribosomal peptide
Corynebacteriia	*Corynebacterium\Brevibacterium*	Mycolic acid
	Mycobacterium	
Bifidobacteriia	*Bifidobacterium*	Acetic acid
Propionibacteriia	*Propionibacterium\Cutibacterium*	Propionic acid, vitamin B12
Micrococcales	*Micrococcus\Kocuria*	Carotenoid pigment, antibiotics, biosurfactants
	Staphylococcus	Antimicrobial peptides
	Planococcus	Astaxanthin, industrial protease

Metabolic spectrum of verrucomicrobia

The metabolic profile of Verrucomicrobia plays an important role in SCFAs (acetic acid, propionic acid) synthesis, polyhydroxyalkanoate (PHA/PHB) accumulation, complex polysaccharide and plastic degradation, and nitrogen oxide conversion. *Verrucomicrobiae*, such as *Prosthecobacter*, *Puniceicoccus*, *Cerasicoccus* can synthesize acetic acid/propionic acid and produce antioxidant metabolites like carotenoids and terpenoids [70, 71]. *Haloferula* secretes special glycosidases to participate in carbon source degradation, while *Luteolibacter* produces terpenoids with immunomodulatory potential

Table 2B The main products of Proteobacteria metabolic spectrum

Class	Genus	Metabolite
Alphaproteobacteria	*Rhizobium*	IAA, EPS, NH_3
	Sphingomonadaceae	Carotenoid
	Methylotroph	Methanol, Formic acid, Vitamin B12
	Rhodospirillum\Rhodobacter Rhodopseudomonas	Coenzyme Q, H_2
Betaproteobacteria	*Burkholderiales*	Antibiotics, Siderophores
	Nitrobacteria	Nitrite
	Thiobacillus\Sulfuritalea	Sulfate, iron oxide
Gammaproteobacteria	*Enterobacteriaceae*	Iron carrier, Tunning
	Pseudomonad	Phenazine derivatives
	Vibrio	Chitinase
	Methylococcaceae	Organic acid
Deltaproteobacteria	*Sulphatebacteria*	H_2S
	Myxobacteria	Polyketides
	Terrabacter	Succinic acid
Epsilonproteobacteria	*Campylobacteria*	Saccharometabolism
	Sulfurspiral	H_2S, NH_3
	Helicobacter	Lactic acid derivative

[72]. In *Opitutae*, *Opitutus* is involved in immune regulation through the synthesis of ammonia and vitamin derivatives, and exhibits heavy metal chelating function. In *Lentisphaeria*, *Victivall* participate in pectin/cellulose degradation. *Candidatus Cloacimonas* can degrade plastics and synthesize propionic acid and signal molecules (3,4-DHPPA), indicating potential for regulating host metabolism and microbial interaction [73].

Spartobacteria (*Chthoniobacter*) participates in the regulation of amino acid metabolism and affects the homeostasis of host nitrogen metabolism. *Kiritimatiellae*, including *Kiritimatiella*, *Candidatus Venterella* primarily synthesize lipid and polyketide secondary metabolites, with the potential roles in regulating intestinal epithelium and immune response [74]. *Methylacidiphilae* like *Methylacidiphilum* synthesizes PHB, acetyl-CoA and NRPS/PKS products by methane oxidation, and participates in nitrogen oxide reduction and TME metabolism. *Verrucomicrobia* including *Methylacidiphilum*, *Kiritimatiella*, *Candidatus*, *Venterella*, reshapes energy metabolism and the TME through secondary metabolites such as PHA/PHB, NRPS/PKS. With the increased fungal abundance, the Dectin-1/CARD9-Th17 axis amplifies chronic inflammation and barrier damage, and synergistically promoting carcinogenesis [75, 76]. The metabolic profile of Verrucomicrobia has potential value for CRC intervention and metabolic reprogramming, improvement of intestinal environment, and regulation of redox and immune status (Table 3A).

Table 3A The main products of the metabolic spectrum of verrucomicrobia

Class	Genus	Metabolite
Verrucomicrobiae	*Prosthecobacter\Alteroc occus*	Propionic acid, Cetic acid
	Puniceicoccus*Cerasic occus*	Propionic acid, Acetic acid, Carotenoids, Terpenoids
	Haloferula	β-N-acetylhexosaminidase, β-lactone enzymes
	Luteolibacter	Antibacterial terpenoids
Opitutae	*Opitutus*	Vitamin derivatives
Lentisphaeria	*Victivallis*	Pectin, Cellulose
	Candidatus Cloacimonas	Propionic acid,
Spartobacteria	*Chthoniobacter*	Amino acid
Kiritimatiellae	*Kiritimatiella\ Candidatus Venterella*	Propionic acid, Polyketides, Terpenoids
Methylacidiphilae	*Methylacidiphilum*	PHB, Acetyl coenzyme A

Fusobacteria metabolic spectrum

The metabolic profile of *Fusobacteria* is centered on the synthesis of propionic acid, acetic acid, butyric acid, H_2S and sulfur-containing metabolites. It functions in protein degradation, carcinogenic metabolite production and host interaction. *Fusobacteria* directly affects the host epithelium and immune homeostasis through metabolites, leading to intestinal barrier damage and inflammatory microenvironment changes, driving CRC progression [77, 78]. Within *Fusobacteriia*, *Fusobacterium* and *Streptobacillus* exhibit carcinogenic potential by the synthesis of H_2S and 2-hydroxyglutaric acid through the cysteine metabolic pathway. *Propionigenium* and *Cetobacterium* produce propionic acid as major metabolites. *Additionally*, *Cetobacterium* synthesizes vitamin B12 to regulate the immune and metabolic status of the host [79]. *Ilyobacter* and *Mucispirillum* are involved in PHB degradation and ketone body (acetoacetic acid, β-hydroxybutyric acid) production, affecting TME energy metabolism [80].

Fusobacteriia is involved in organic acid metabolism, bile acid regulation, indole/ornithine synthesis, and carbohydrate utilization, which helps to form an inflammatory microenvironment and regulate the redox state of the host. In terms of secondary metabolism, *Psychrilyobacter* shows the ability to synthesize glycoside and macrolide antibacterial substances, exhibiting both niche competition and antibacterial functions [81]. The

metabolic profile of Fusobacteria directly enhances the cancer-promoting signal through the production of H_2S and other carcinogens, and regulates host immunity and energy metabolism through vitamin B12, bile acid and secondary metabolism. This positions *Fusobacteria* as a key mediator for CRC metabolism-immune interaction [82, 83]. Increased abundance and functional changes of *Fusobacteriota* accelerate the CRC process, reflecting the microbial adaptation in response to TME remodeling (Table 3B).

Table 3B The main products of fusobacteria metabolic spectrum

Class	Genus	Metabolite
Fusobacteriia	*Fusobacterium\Streptobacillus*	Propionic acid, Acetic acid, H_2S,
	Propionigenium	Propionic acid
	Cetobacterium	Propionic acid, Vitamin B12
	Ilyobacter	PHB
	Mucispirillum	Acetic acid, β-hydroxybutyric acid
	Sebaldella	Bile acid
	Psychrilyobacter	Indole, Ornithine, Glycosides,

Gut Microbiome metabolic profile improves CRC by regulating NF-κB pathway

Through action at multiple molecular levels, the intestinal microbial metabolic spectrum shapes the activation state of NF-κB. Key effector molecules are SCFAs, secondary bile acids and H_2S, which are produced by the representative flora of Firmicutes, Bacteroidetes and Fusobacteria, respectively. Fine regulation of NF-κB is achieved by receptor binding, signal complex regulation and epigenetic effects [84]. SCFAs (e.g. butyric acid and propionic acid) produced by *Firmicutes* and *Bacteroidetes* directly bind to GPR41/43/109A, up-regulate IκBα and limit IKK activity. Butyric acid inhibits the upstream pro-inflammatory signal by reducing the formation threshold of TLR-MyD88 complex, enhances histone acetylation by HDAC inhibitor, maintains p65 in an inhibitory acetylation state, and blocks NF-κB nuclear translocation [85, 86]. The effect of butyric acid is the most significant in colonic epithelial cells and Treg, showing a marked concentration dependence.

The secondary bile acids (DCA, LCA) produced by *Oscillibacter*, *Hungatella* and *Bacteroides* inhibit IKKβ under the regulation of FXR/TGR5 receptor, thereby maintaining NF-κB in inactivated state. However, in a low dose or oxidative stress-enhanced environment, DCA can reversely activate NF-κB through mild membrane damage and ROS accumulation, forming a typical biphasic response that depends on local receptor expression profile and cell type [87].

Fusobacterium-derived H_2S enhances IKKβ and p65 activity by phosphorothioate modification and induces mitochondrial stress, ROS and mtDNA release. H_2S further amplify the NF-κB signal through the NLRP3-IKK axis. TLR-mediated pro-inflammatory amplification is more likely to occur under the condition of barrier damage, an effect particularly significant in intestinal epithelial cells and highly dependent on environment and dose [88, 89]. In summary, SCFAs tended to down-regulate NF-κB in a dual mechanism of receptor signaling and epigenetic inhibition. Secondary bile acids regulated by FXR/TGR5, exhibit a concentration-dependent and environment-sensitive biphasic effect. In contrast, H2S consistently enhances NF-κB activity through thio-modification and mitochondrial damage [90]. These three key metabolites together constitute a phylum-specific NF-κB regulatory network within the inflammatory microenvironment of CRC.

Discussion and outlook

By systematically reviewing the related metabolic and immune signaling pathways in the progression of CRC, the pivotal role of NF-κB signaling in the metabolic-immune network has been identified, suggesting it potential as an important target for CRC microecological intervention [91, 92]. During CRC development, the gut microecology first undergoes structural disturbance. The imbalance of microbiota composition leads to reduced mucosal barrier integrity and the migration of certain conditional pathogenic bacteria such as *Fusobacterium*, *Proteobacteria* to tumor-associated mucosal regions. The resulting shift in metabolic spectrum are characterized by decreased SCFAs and the accumulation of secondary bile acids and H_2S. These changes alter the local immune homeostasis and drives early activation of NF-κB signaling to form a pro-inflammatory microenvironment [93, 94].

Subsequently, immune signals, includingPD-1/PD-L1, CD73-adenosine, interferon axis and metabolic reprogramming, such as Warburg effect, fatty acid synthesis and amino acid metabolism, cross-amplify with NF-κB that forms a sustained inflammation-metabolic coupling network and promote tumorigenesis and progression. At the level of functional differences in phylum, the metabolites of *Firmicutes* and *Bacteroidetes* mainly regulate NF-κB and its downstream inflammatory axis through SCFAs, secondary bile acids and indole derivatives. Certain secondary metabolites from *Actinobacteria* have the potential to directly inhibit NF-κB activity [95]. *Proteobacteria* and *Fusobacteria* exhibit a dual (promoting or suppressing) regulatory role in the process of tumor formation and progression, providing a multi-layer mechanism basis for the staged regulation of NF-κB [96].

Furthermore, several key metabolites including deoxycholic acid, hydrogen sulfide, 4-hydroxynonenal demonstrate a concentration-dependent or context-dependent dual effects. This highlights a close relationship between the dynamic GM metabolic profile and fluctuating metabolic concentrations [97].

The research on the intervention of intestinal microecology for CRC should focus on the ternary network of key bacteria, metabolites and host targets. Numerous of clinical and animal studies have shown that microbial regulation exhibits good safety and feasibility, especially targeted modulation based on specific phylum metabolic profiles, which can effectively alleviate inflammation and reshape metabolic homeostasis [98].

With advances in dynamic metabolite detection and spatial quantitative imaging technology, probiotics, metabiotic and synthetic microbial strategies can achieve precise intervention in microbial metabolic pathways. Interventions at key nodes of CRC, such as adenoma formation, chronic mucosal inflammation, or microbial imbalance, can yield significant anti-tumor effects, suggesting that the sensitivity of microecological regulation is determined by the stage of disease progression [99]. Furthermore, individual differences in microbiome structure, diet, genetic background and environmental exposure profoundly influence metabolite abundance, immune signal thresholds and NF-κB reactivity, thus shaping the variations in the efficacy of personalized microecological intervention [100]. This review, through in-depth investigation of intestinal microecosystem's regulatory potential in metabolic-immune interference, provides novel insights and innovative solutions for the clinical treatment of CRC.

Abbreviations

CRC	Colorectal Cancer
GM	Gut Microbiome
GMM	Gut Microbiome metabolites
SCFAs	Short-chain fatty acid
TNF-α	Tumor necrosis factor-α
IL-6	Interleukin – 6
ROS	Active oxygen
CTL	Cytotoxic T cell
TME	Tumor microenvironment
FASN	Fatty acid synthetase
PKA	Protein kinase A; H_2S, Hydrogen sulfide
DC	Dendritic cell
TAMs	Tumor associated macrophage

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Data availability
Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Declarations

Ethics approval and consent to participate
Not applicable. This manuscript is a narrative review and did not involve any original studies involving human participants or animals.

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