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REVIEW

# Exploring the Relationship Between Colitis-Associated Cancer and Lipid Metabolism Reprogramming from the Perspective of Inflammation-Cancer Transformation

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**Abstract:** Colitis-associated colorectal cancer (CAC) is the most severe complication of inflammatory bowel disease (IBD), characterized by multifocal lesions and poor prognosis. Aberrant lipid metabolism drives CAC progression by modulating the tumor microenvironment, activating oncogenic pathways, and facilitating immune escape. These metabolic alterations supply energy for tumor cells, disrupt the homeostasis of the tumor microenvironment, and contribute to gut microbiota dysbiosis, ultimately establishing a vicious cycle of "metabolism–inflammation–carcinogenesis." Although the role of lipid metabolism in sporadic colorectal cancer has been extensively studied, the specific metabolic rewiring that triggers the malignant switch during chronic colitis remains systematically unexplored. From the viewpoint of the dynamic transition toward malignancy, this review dissects the synergistic interactions between lipid metabolism and inflammatory signaling, immune microenvironment remodeling, and intestinal dysbiosis during this evolutionary process. It systematically summarizes key genes and potential therapeutic targets governing lipid metabolism in CAC and investigates the translational value of targeting lipid metabolic reprogramming for early intervention and combination therapies in CAC. By integrating current evidence, this article clarifies how lipid reprogramming orchestrates the inflammation-to-cancer shift, providing novel research insights and therapeutic strategies to improve clinical prognosis for CAC patients.

**Keywords:** colitis-associated cancer, lipid metabolism reprogramming, inflammation-cancer transformation

## Introduction

Colorectal cancer (CRC) is the third most common malignancy worldwide, and colitis-associated cancer (CAC) represents a type of CRC that transforms from inflammation to cancer.[1] CAC is caused by the occurrence of cancer in patients with inflammatory bowel disease (IBD). The pathogenesis of CAC is that the intestinal mucosa undergoes chronic inflammation or damage, gradually evolving into mild atypical hyperplasia, then developing into severe atypical hyperplasia, and finally progressing to cancerous tumors.[2] During the preceding stage of IBD, perturbations in lipid metabolism already demonstrate their importance.[3] As IBD progresses to CAC, alterations in lipid metabolism become increasingly pronounced.[4,5] Highly proliferative tumor cells exhibit an increased demand for lipids, such as phospholipids, cholesterol, and sphingolipids required for membrane synthesis, as well as triglycerides serving as energy sources or

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signaling molecules, resulting in aberrant accumulation of these lipids within the tumor milieu.[6] Disturbances in lipid metabolism potentially contribute to tumor cellular proliferation, migration, invasion, and inhibit apoptosis.[6–8] Moreover, it has also been found that 1,3-dipalmitoylglycerol (PSG) isolated from the ethanol solution extracted from fermented recombinant skim milk has the effect of reducing the viability of CRC cells.[9] In conclusion, lipid metabolism plays a crucial role in CAC. However, most existing reviews focus on the reprogramming of lipid metabolism in sporadic CRC, such as fatty acid synthase or cholesterol metabolic pathways,[10] there is a lack of systematic discussion regarding the regulatory mechanisms of lipid metabolism specific to the inflammation-associated phenotypic transition in CAC. Particularly, the cooperative roles of lipid metabolism with inflammatory signals (eg., NF-κB, STAT3), immune microenvironment, and dysbiosis of the gut microbiota during the IBD-to-CAC transition remain inadequately addressed. Therefore, this review analyzes the key genes and potential therapeutic targets regulating lipid metabolism in CAC from the perspective of inflammation-to-cancer progression, and explores the application value of targeting lipid metabolic reprogramming in CAC treatment, with the goal of providing new insights to improve the clinical prognosis of CAC patients.

## The Relationship Between Lipid Metabolic Reprogramming and CAC

Lipid metabolic reprogramming refers to the process by which tumor cells reshape metabolic pathways to meet the energetic and biosynthetic demands required for sustained growth and proliferation; this process profoundly influences therapeutic efficacy and prognosis in patients with cancer.[11] Lipid metabolism comprises both anabolic and catabolic processes, and an imbalance between them may result in pathological lipid accumulation. A high-fat diet (HFD) is associated with the development and/or exacerbation of multiple diseases, including colitis-associated cancer (CAC). However, the impact of HFD on CAC exhibits notable contradictions across different experimental models and dietary regimens. In the azoxymethane/dextran sulfate sodium (AOM/DSS) model, which primarily reflects inflammation-driven tumorigenesis, the effect of HFD is highly dependent on the timing and composition of the diet.[12] Studies have shown that early HFD intervention (eg., initiated at 4 weeks of age in male C57BL/6 mice) significantly increases tumor number and reduces tumor differentiation, while late-stage HFD intervention may have limited effects on tumor size or inflammation severity.[13] In contrast, the genetically susceptible ApcMin/+ model, which primarily reflects Wnt/β-catenin pathway-driven tumorigenesis, certain HFD regimens, particularly those enriched in specific fatty acids (eg., high in unsaturated fatty acids), has been shown to modulate fatty acid oxidation pathways and, under specific conditions, paradoxically reduce tumor burden.[14] Moreover, the strain-specific susceptibility (eg., Balb/c vs. C57BL/6) and dietary composition (proportion of saturated versus unsaturated fatty acids) collectively contribute to these divergent outcomes.[15] This review will systematically examine the relationship between lipid metabolic reprogramming and CAC, analyze the roles of key lipid metabolism–related genes in the inflammation-to-cancer transition, and discuss current therapeutic perspectives.

In CAC, lipid metabolic reprogramming may be linked to inflammatory signaling, tumorigenesis, and fatty acid, cholesterol, phospholipid, and sphingolipid metabolism. These aberrant metabolic programs provide tumor cells with ample energy, nutrients, and reducing equivalents to support malignant proliferation and metastasis. Meanwhile, such metabolic disturbances are accompanied by impaired metabolic flexibility within the tumor microenvironment and gut dysbiosis.[16]

### The Correlation Between Fatty Acid Metabolism and CAC

Fatty acid (FA) availability is derived primarily from exogenous fatty acids absorbed in the small intestine and endogenous hepatic production.[17] As a hallmark of cancer, cellular proliferation requires fatty acids for membrane biosynthesis, generation of signaling molecules, and energy storage.[18] Butyrate is a beneficial four-carbon short-chain fatty acid produced by the gut microbiota; it provides energy to intestinal epithelial cells and directly participates in fatty acid synthesis. Under CAC conditions, dysbiosis reduces the abundance or function of butyrate-producing bacteria, leading to insufficient butyrate production.[19] Reduced butyrate levels result in inadequate energy supply to intestinal epithelial cells, impair the intestinal barrier, and increase intestinal permeability, thereby facilitating the entry of harmful substances and triggering inflammatory responses.[20] Butyrate and Clostridium butyricum can inhibit the NF-κB/p65 and

NLRP3 inflammatory pathways, mitigate inflammation-mediated interference with fatty acid synthase, and directly or indirectly activate key regulators such as PPARγ and SREBP-1c. This, in turn, promotes a balance between acetyl-CoA carboxylase and fatty acid synthase, coordinating lipid synthesis with anti-inflammatory responses. This mechanism not only delays the inflammation-to-carcinoma transition but may also improve metabolic disorders such as obesity and fatty liver disease through metabolic reprogramming.[21,22]

Palmitic acid, also known as hexadecanoic acid, is a saturated fatty acid and the major end product of mammalian fatty acid synthase. Because fatty acid metabolic pathways are altered in patients with CAC, the activities of related metabolic enzymes (eg., acetyl-CoA carboxylase) become dysregulated, leading to increased palmitic acid synthesis or decreased degradation, consequently, elevated levels of palmitic acid have been observed in CAC.[23] Palmitic acid plays an important role in membrane structure and function. Elevated levels of palmitic acid have been associated with alterations in membrane fluidity and stability, potentially disrupting membrane-associated signaling pathways. This may lead to NF-xB activation and increased expression of proinflammatory cytokines such as IL-6 and TNF-a, which are associated with cellular proliferation and tumorigenesis.[24,25] Moreover, stearic acid (octadecanoic acid), which is generated from palmitic acid elongation and participates in the synthesis of complex lipids and desaturation reactions, is also highly expressed in the CAC context. Tumor cells reinforce the stearic acid synthetic pathway to support their rapid proliferation and membrane synthesis needs. They treated colorectal cancer cells (eg., DLD-1) with exogenous stearic acid at concentrations of 0, 50, 100, and 200 μM for 48 hours. High concentrations of stearic acid induced apoptosis, as evidenced by flow cytometry analysis using Annexin V-FITC/PI staining, which revealed a significant increase in both early and late apoptotic cell populations.[9,26,27]

## The Correlation Between Cholesterol Metabolism and CAC

Cholesterol is a major component of cellular membranes and a direct precursor of steroid hormones and bile acids. Most cholesterol is eliminated via conversion into bile acids. Studies have shown that expression of the low-density lipoprotein receptor gene is significantly upregulated in colon tumors and metastatic tissues.[28] LDLR primarily mediates the uptake of circulating low-density lipoproteins into cells, thereby maintaining intracellular cholesterol homeostasis. When systemic cholesterol levels rise, cells may further upregulate LDLR expression to acquire more cholesterol, potentially providing the lipid components required for tumor cell growth and proliferation.[29] Similar to the marked upregulation of FASN, a key enzyme in fatty acid metabolism, CPT1A—a key enzyme in fatty acid oxidation (FAO)—is also dysregulated in CAC, together constituting a network of metabolic imbalance.[30] Cholesterol has the potential to activate the NLRP3 inflammasome and promote the release of multiple proinflammatory cytokines, including IL1β and IL-18. These cytokines may contribute to remodeling the tumor microenvironment and potentially enhance tumor cell proliferation, survival, and metastatic capacity.[31] Moreover, inflammation induces tissue damage and oxidative stress, impairs normal cellular metabolism and function, and stimulates angiogenesis, thereby supplying nutrients and oxygen for tumor growth and dissemination.[32,33] A high-cholesterol diet has been associated with exacerbated inflammation and tumor burden in experimental models, suggesting a potential dietary factor that may be linked to CAC progression.[34] Integrated analyses combining metabolomics and single-cell RNA sequencing further indicate pronounced spatial heterogeneity of cholesterol metabolism within the CAC tumor microenvironment, for example, tumor epithelial cells and tumor-infiltrating immune cells exhibit markedly distinct expression profiles of genes involved in cholesterol uptake, synthesis, and efflux.[35] Single-cell RNA sequencing further reveals that this metabolic heterogeneity manifests functionally: tumor epithelial cells tend to rely on endogenous lipid synthesis to support proliferation, whereas infiltrating immune cells (eg., T cells) experience energy metabolic blockage in high DCA environments, suggesting that this metabolic mismatch may be an important mechanism of immune escape.[36,37] This heterogeneity profoundly affects local immune responses and the survival advantages of tumor cells. Therefore, cholesterol metabolism is closely associated with CAC, and inhibiting cholesterol biosynthesis can induce tumor cell apoptosis and suppress proliferation, suggesting that targeting cholesterol metabolism may represent an effective strategy for preventing CAC development. In addition, recent multi-omics studies have shown that mutations or epigenetic silencing of the bile acid receptor FXR (NR1H4) are frequently observed in tumor tissues from patients with CAC, directly leading to aberrant metabolism and signaling of secondary bile acids in tumor cells.[38,39] These gene-level alterations are strongly associated with metabolomics-detected elevations of

deoxycholic acid (DCA), confirming that the increase in this metabolite is not incidental but rather a consequence of tumor cell genomic reprogramming.

## Correlation Between Phosphatidic Acid Metabolism and CAC

Phosphatidic acid (PA) is an important intracellular lipid second messenger that interacts with multiple effector proteins and participates in signal transduction, cellular growth, and apoptosis.[40] Furthermore, LPIN1 modulates the inflammatory milieu by regulating the production of the cytokine IL-23. As a phosphatidic acid phosphatase, LPIN1 controls the intracellular levels of diacylglycerol (DAG), a critical second messenger for the activation of pro-inflammatory transcription factors such as NF-κB and AP-1. This regulation ensures the expression of IL-23, a cytokine essential for Th17 cell maintenance.[41] In CAC, inflammation may drive alterations in phosphatidic acid metabolism in intestinal cells, including abnormal phospholipid synthesis, degradation, and transport, as well as lipoprotein accumulation or monoacylglycerol lipase deficiency.[42–44] In addition to LPIN1, phospholipase D1 (PLD1) is another key enzyme in phospholipid metabolism, catalyzing the hydrolysis of phosphatidylcholine to generate PA. Studies indicate that PLD1 expression and activity are often upregulated in CAC, and the resulting PA can promote tumor cell proliferation, survival, and migration by activating signaling pathways such as mTORC1.[45] LPIN1 and PLD1 activities jointly regulate the dynamic balance of the PA/DAG metabolic pool; their dysregulation in CAC together constitutes a phospholipid signaling network that promotes tumor progression.[46]

## Regulation of Lipid Metabolism in CAC by Microbial Metabolites

The gut microbiota and its metabolites represent a key bridge linking diet, host metabolism, and CAC initiation and progression.[47] In addition to the short-chain fatty acid butyrate discussed above, other microbiota-derived metabolites also profoundly influence lipid metabolic reprogramming in CAC. On the one hand, primary bile acids can be converted by the microbiota into secondary bile acids, such as deoxycholic acid (DCA). DCA has been shown to influence lipid absorption, metabolism, and inflammatory responses in intestinal epithelial cells, potentially through activation of signaling pathways such as the farnesoid X receptor or G protein-coupled bile acid receptors. At high concentrations, DCA may contribute to DNA damage and exhibit tumor-promoting effects.[48,49] On the other hand, various lipid-related molecules generated by bacteria, including conjugated linoleic acid and bacterial lipopolysaccharide, can directly or indirectly modulate host fatty acid synthase activity, PPARγ signaling, and inflammatory pathways, thereby shaping metabolic microenvironments that favor or suppress tumor development. Dysregulation of these microbiota–host metabolic interactions is an important component of CAC metabolic reprogramming and a potential therapeutic target.[50]

## Correlation Between Sphingolipid Metabolism and CAC

Sphingolipids are amphipathic lipids characterized by a sphingosine backbone, with one end linked to a long-chain fatty acid and the other to a polar alcohol. They are essential for maintaining mucosal barrier integrity, regulating nutrient absorption, and functioning as signaling molecules that control epithelial regeneration and differentiation.[51] Sphingolipids such as sphingomyelin and sphingosine-1-phosphate are complex membrane lipids widely present in cellular membranes; they are downregulated in CAC and participate in regulating cellular signaling, differentiation, apoptosis, inflammation, and survival.[52] Studies have shown that oral administration of phytosphingosine (a plant-derived sphingolipid) in CAC model mice is associated with increased colonic sphingosine-1-phosphate lyase levels, reduced sphingosine-1-phosphate concentrations, and suppression of STAT3-dependent signaling, which may contribute to reduced tumorigenesis, highlighting the potential of SPL in preventing the inflammation-to-cancer transition in CAC.[53] Ceramide, as the core molecule of sphingolipid metabolism and a signal of nutrient excess, is downregulated in CAC.[54] Sphingolipid metabolism is tightly linked to CAC, and abnormalities in sphingolipid synthesis, degradation, or transport can influence intestinal epithelial cell proliferation, apoptosis, and signal transduction, thereby promoting or suppressing colorectal cancer development and progression.

# Key Genes/Enzymes/Proteins Regulating Lipid Metabolic Reprogramming in CAC

## Inflammation-Related Genes/Enzymes/Proteins

Dysregulation of lipid metabolism can influence the aggressiveness, invasiveness, and metastatic potential of colitis-associated colorectal cancer (CAC) by modulating multiple signaling pathways.[55] The SphK1/S1P/S1PR1 axis has been identified as a significant link between lipid signaling and the inflammatory milieu in CAC, suggesting a potential mechanistic association.[56–58] Upon binding to its receptors on macrophages, S1P has been observed to promote a pro-inflammatory Ml phenotype, which is associated with tumor-promoting inflammation.[59–61] Notably, this axis does not function in isolation. In dysplastic epithelial cells, elevated IL-6 and phosphorylated STAT3 (p-STAT3) are observed, forming a feedback loop where S1P can activate NF-κB, which in turn upregulates IL-6, further activating STAT3.[62–64] This SphK1-NF-κB-STAT3 axis operates alongside other metabolic regulators, such as FABP5, which is also a downstream target of STAT3, highlighting a cross-talk between sphingolipid signaling and fatty acid metabolism.[65–67]

In summary, upregulation of SphK1, increased production of S1P, and activation of S1PR1 receptors are particularly important during macrophage polarization, resulting in the release of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-12. These events perpetuate the activation of NF-κB and STAT3, thereby sustaining chronic inflammation and promoting CAC development.[68]

Sphingomyelin synthase 2 (SMS2), a key enzyme for sphingomyelin biosynthesis, regulates plasma membrane fluidity and microdomains[69] and is upregulated in various tumor cell types.[70,71] Studies have shown that SMS2 deficiency in knockout mice reduces DSS-induced inflammation, associated with downregulation of pro-inflammatory cytokines, chemokines, MAPK, and STAT3, as well as diminished leukocyte infiltration. In the AOM/DSS-induced CAC model, deletion of SMS2 significantly reduces colonic tumor incidence.[72] SMS2 knockout results in an accumulation of ceramide (Cer) and a decrease in sphingomyelin (SM) in colonic tissue. Ceramide has pro-apoptotic properties and may restrict tumor cell survival by activating PP2A phosphatase to inhibit the Akt/mTOR pathway.[73] Furthermore, SMS2 deficiency suppresses the Wnt/β-catenin pathway—a key oncogenic signal—and decreases the expression of COX-2 (a pro-inflammatory enzyme), thus impeding inflammation-to-carcinoma transition. Therefore, SMS2 likely contributes to suppression of DSS-induced colitis and CAC development by inhibiting inflammation mediated by colonic epithelial cells.

## Lipid Metabolism-Related Genes/Enzymes/Proteins

Lipid metabolic reprogramming is a hallmark of colitis colorectal cancer (CAC), characterized not only by aberrantly enhanced fatty acid synthesis but also by dysregulated fatty acid oxidation. Fatty acid synthase (FASN), a key enzyme catalyzing fatty acid biosynthesis, shows prominent upregulation in CAC and, together with other metabolic enzymes such as CPT1A, constitutes a metabolic reprogramming network. This abnormal activation leads to excessive intracellular lipid accumulation, thereby facilitating tumor progression.[74] In vitro, FASN knockdown inhibits the migration and invasion of SW480 and HT29 cells, potentially via reduced expression of Wnt pathway components including Wnt5a, Wnt5b, and Fzd2. Notably, FASN (responsible for synthesis) and carnitine palmitoyltransferase 1A (CPT1A, the rate-limiting enzyme for fatty acid β-oxidation) are concurrently dysregulated in CAC, disrupting the synthetic–catabolic dynamic equilibrium and forming a disturbed metabolic cycle.

Fatty acid-binding proteins (FABPs) are intracellular lipid chaperones that facilitate the transport of fatty acids and derivatives. Ten FABP-encoding genes (FABP1–9, FABP12) have been identified in the human genome,[75] with high expression in lipid-metabolically active tissues such as liver (FABP1), adipose (FABP4), and gastrointestinal tract (FABP5).[76] In colorectal cancer, several FABP isoforms are dysregulated. Upregulation typically promotes tumor cell proliferation and initiation.[77–80] FABP1, mainly expressed in small intestinal epithelium, is associated with colorectal tumorigenesis; its overexpression facilitates tumor formation,[77] while genetic deletion reduces both tumor number and size in mouse models, suggesting a role in enhancing exogenous fatty acid uptake and utilization to support proliferation.[78] FABP5, predominantly expressed in colonic epithelium, exerts a tumor-suppressive effect by promoting ubiquitination and proteasomal degradation of FABP1, thereby reducing intracellular lipid accumulation and tumor cell

proliferation.[55] FABP4, overexpressed in colorectal cancer, is mainly derived from adipocytes; it augments lipid transport, promotes lipid droplet formation, mitigates oxidative stress, and activates oncogenic pathways such as AKT and MAPK.[79] FABP7 is also expressed in colorectal cancer cells, with high levels correlating with increased proliferation.[80] FABP5 functionally complements FABP1 and FABP4 and is co-regulated by hypoxia-inducible factor 1α (HIF-1α) and NF-κB signaling.

Hypoxia-inducible factor 1α (HIF-1α) is a master transcriptional regulator of cellular adaptation to oxygen fluctuations, modulating metabolism-related genes to support cancer cell growth and survival.[81] In colorectal tumors, FABP5 mRNA is regulated and positively correlated with HIF-1α target gene enrichment. As a transporter of oleic acid (OA),[82] FABP5 mediates-induced activation of the FABP5/HIF-1α axis, thereby promoting lipid accumulation and tumor cell proliferation.[55] Under hypoxia, HIF-1α increases fatty acid uptake and storage while reducing β-oxidation and lipolysis, enhancing proliferative and migratory capacities of tumor cells.[83]

HAKAI, an E3 ubiquitin ligase, was the first post-translational modifier identified to regulate E-cadherin stability.[84] It plays a critical role in proliferation, epithelial–mesenchymal transition, and invasion by modulating the tumor suppressor E-cadherin.[85] In CAC mouse models, FASN and HAKAI display opposing expression patterns. HAKAI mediates FASN ubiquitination and lysosomal degradation, directly disrupting core lipid biosynthetic pathways. By targeting FASN degradation, HAKAI may indirectly decrease tumor cell membrane fluidity, impacting adhesion molecule function (eg., integrins) and suppressing invasive behavior.[86]

Carnitine palmitoyl transferases (CPTs) are rate-limiting enzymes in fatty acid β-oxidation. CPT1A is upregulated in CAC, promoting tumor cell proliferation and metastasis. Its expression is regulated by the Wnt/β-catenin pathway, which can also be activated by FASN metabolic products, forming a positive feedback loop that reinforces lipid metabolic reprogramming. CPT1A knockdown in vivo blocks the tumor-promoting effect of adipocytes and reduces xenograft and organoid formation, accompanied by decreased expression of cancer stem cell–related genes downstream of Wnt/β-catenin.[87]

Protein tyrosine phosphatases (PTPs) are critical contributors to tumorigenesis when aberrantly expressed. Protein tyrosine phosphatase receptor type O (PTPRO), a P family member, functions as a tumor suppressor in various cancers but is downregulated in CAC. Silencing PTPRO markedly promotes growth and metastasis colorectal tumor cells. Compared to wild-type mice, PTPRO knockout mice in the AOM/DSS model exhibit more aggressive tumor growth.[88] A summary of lipid metabolism–related genes, enzymes, and proteins in CAC is provided in Figure 1 and Table 1.

## Lipid Metabolism-Targeted Therapy in CAC

Lipid metabolic reprogramming is a key mechanism driving the inflammatory-to-carcinoma transition in colitis-associated colorectal cancer (CAC), forming a dynamic "metabolism-inflammation-carcinogenesis" vicious cycle by modulating the tumor microenvironment, activating oncogenic signaling pathways, and enabling immune surveillance evasion. Lipid metabolism-related molecules and pathways have thus been regarded as novel targets for anticancer therapy. Targeting key molecules involved in fatty acid, cholesterol, and sphingolipid metabolism not only inhibits inflammation-associated oncogenic initiation but also ameliorates the immunosuppressive microenvironment, offering new directions for both early intervention and combination therapy of CAC.

### Targeting Fatty Acid Metabolism

Certain fatty acid (FA) metabolic products are associated with CAC stage, grade, and prognosis.[55] The combined application of palmitic acid, stearic acid, and 1,3-dipalmitoylglycerol at specific ratios with 5-fluorouracil has been shown to enhance the inhibitory effects on cancer cells.[9,23] FA may promote tumor cell survival on one hand via Drp1 (dynamin-related protein 1)-dependent mitochondrial fission pathways, which involves Wnt signaling activation mediated by β-catenin acetylation; on the other hand, the Drp1 inhibitor Mdivi-1 can suppress oxidative metabolism in colon cancer cells, induce cell cycle arrest, and trigger apoptosis.[97–100] Therefore, targeting the FAO-Drp1 axis could present a novel therapeutic strategy for CAC.

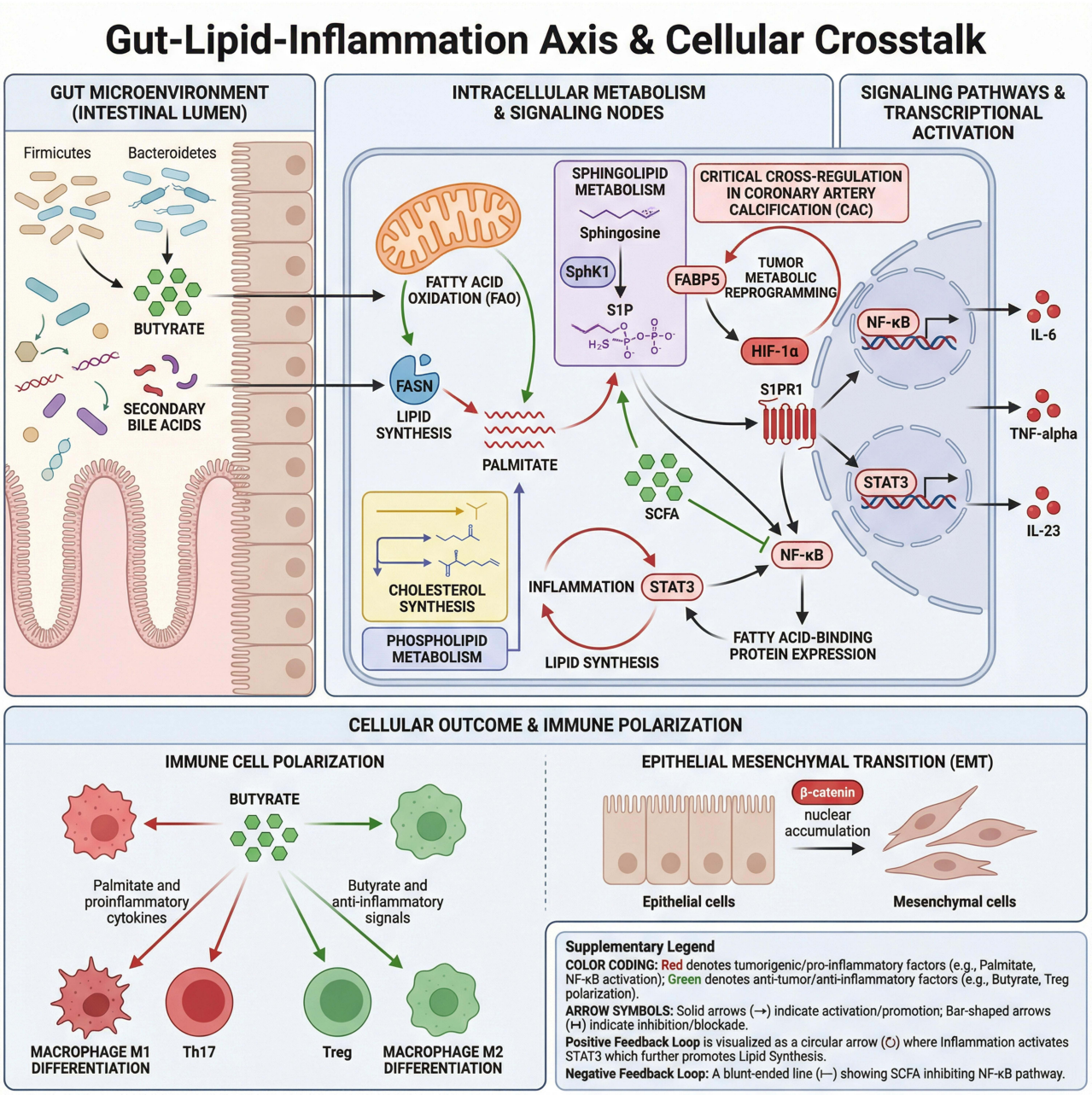


**Figure 1** The Gut-Lipid-Inflammation Axis: Comprehensive Mechanism Diagram.

## Targeting Cholesterol Metabolism

Statins, as inhibitors of cholesterol biosynthesis, have shown promise in preclinical models of CAC. However, their clinical translation remains limited. While observational studies suggest a reduced risk of CRC in statin users, randomized controlled trials (RCTs) have yielded mixed results, often due to dose-dependent myotoxicity and variable patient adherence. Moreover, in IBD patients, statins may exacerbate intestinal mucosal inflammation by altering bile acid composition, raising concerns about their long-term safety in this specific cohort.[101,102] Simvastatin has also been shown to induce tumor cell apoptosis, inhibit angiogenesis, and enhance LDL receptor expression, making it a potential chemopreventive and therapeutic agent for CAC.[103] Furthermore, targeting sterol O-acyltransferase 1 (SOAT1) can elevate cellular cholesterol levels and promote YAP expression; the SOAT1 inhibitor avasimibe reduces colorectal cancer cell viability,[103] providing new avenues for cholesterol metabolism-targeted therapy.


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**Table 1** Expression and Effects of Genes/Enzymes/Proteins Related to Lipid Metabolism in CAC

| Enzyme/Protein/Gene | Involved Lipid | Expression in CAC | Effects (Positive/Negative) |
|---|---|---|---|
| Sphingosine-1-phosphate (S1P)[59–61] | Sphingolipids | ↑ | S1P promotes CRC angiogenesis by activating S1PR1, suggesting that high S1P expression in CRC may facilitate tumor growth and spread. |
| Sphingomyelin synthase 2 (SMS2)[70,71,73] | Sphingolipids | ↑ | In CAC models induced by AOM/DSS, the absence of SMS2 significantly reduced the incidence of colon tumors. |
| Fatty acid synthase (FASN)[74,89] | Fatty acids | ↑ | Overexpression of FASN can promote CRC tumor growth, enhance invasion and metastasis, stimulate angiogenesis, and increase drug resistance. |
| Fatty acid-binding proteins (FABPs)[75,76,90] | Fatty acids | ↑ | Deletion of the FABP1 gene can inhibit the occurrence of colon tumors. |
| Hypoxia-inducible factor-1α (HIF-1α)[81,83] | Fatty acids | ↑ | High expression of HIF-1α mediates increased FA uptake and lipid storage, while downregulating fatty acid oxidation and lipolysis, enhancing CAC tumor cell proliferation and migration. |
| HAKAI[85,86] | Fatty acids | ↓ | HAKAI regulates FASN-mediated lipid accumulation by inducing the ubiquitination and degradation of FASN via the lysosome, with overexpression promoting CRC tumor growth, invasion, and metastasis. |
| Carnitine palmitoyl transferase (CPT)[91] | Fatty acid β-oxidation | ↑ | High expression in CAC promotes tumor cell proliferation and metastasis; knockdown of CPT1A blocks the tumor-promoting effects of adipocytes and suppresses xenograft tumor formation. |
| Protein tyrosine phosphatase receptor O (PTPRO)[88] | Fatty acids | ↓ | Silencing PTPRO significantly enhances cell growth and liver metastasis. PTPRO knockout mice developed more tumors and greater tumor burden compared to wild-type mice under azoxymethane and DSS treatment. |
| Acyl-CoA oxidase 1 (ACOX1)[92] | Fatty acids | ↓ | Depletion of ACOX1 promotes CRC cell proliferation in vitro and tumorigenesis in mouse models, while overexpression inhibits the growth of patient-derived xenografts. |
| Sterol regulatory element-binding proteins (SREBPs)[93] | Fatty acids/ Cholesterol | ↑ | SREBP1 expression is significantly higher in colorectal cancer tissues compared to non-cancerous tissues, particularly in aggressive tumor fronts. Overexpression of SREBP1 in CRC cell lines promotes angiogenesis, increases reactive oxygen species (ROS) levels, and enhances phosphorylation of NF-κB-p65 and MMP7 expression. |
| Squalene epoxidase (SQLE)[94] | Cholesterol | ↑ | Cells overexpressing SQLE or SQLE-transgenic mice show increased levels of HMGCR, FDFT1, and FDPS proteins, while knockdown of SQLE results in decreased protein levels of these genes in the cholesterol biosynthesis pathway, contributing to increased cell proliferation in CRC cells. |
| Sphingosine-1-phosphate lyase (SPL)[53] | Sphingolipids | ↓ | Upregulation of SPL may increase the degradation of S1P, reducing S1P levels and thereby decreasing growth-promoting and survival signals associated with S1P, potentially inhibiting tumor growth and progression. Conversely, the downregulation of SPL may have the opposite effect. |
| Monoacylglycerol lipase (MAGL)[95] | Phosphatidic acid | ↓ | MAGL, possibly through modulation of angiogenesis, plays a pivotal role in experimental colon carcinogenesis. The MAGL inhibitor URB602 reduced xenograft tumor volume. |
| Serine palmitoyl transferase (SPT)[96] | Sphingolipids | ↑ | Upregulation of SPT may lead to excessive production of sphingolipids, which could promote CRC cell proliferation and survival while potentially enhancing tumor cell invasion and metastasis. |

**Abbreviations**: AUC, area under the curve; AA, Arachidonic acid; Acyl-CoA, acyl coenzyme A; CAC, Colitis-associated cancer; CRC, Colorectal cancer; CPT, carnitine palmitoyl transferase; Drp1, dynamin-related protein 1; DAG, diacylglycerol; FAs, Fatty acids; FABPs, Fatty acid-binding proteins; FASN, Fatty acid synthase; HIF-1α, Hypoxia-inducible factor-1 alpha; HFD, high-fat diet; LS, least squares; IBD, inflammatory bowel disease; FTO, fat mass and obesity-associated protein; 5-FU, 5-fluorouracil; FAO, fatty acid β-oxidation; LDLR, low-density lipoprotein receptors; UC, ulcerative colitis; ROS, reactive oxygen species; PA, Phosphatidic acid; SPL, sphingosine-1-phosphate lyase; SphK1, sphingosine kinase 1; Sph, sphingosine; SMS2, Sphingomyelin synthase 2; PTPs, protein tyrosine phosphatases; NE, not estimable; PTPRO, O-type protein tyrosine phosphatase receptor; S1P, sphingosine-1-phosphate.

## Targeting Phosphatidic Acid Metabolism

Phosphatidic acid–producing enzymes, phospholipase D1/2 (PLD1/2), generate PA through the hydrolysis of phosphatidylcholine and have been shown to exert tumor-promoting effects in inflammatory mouse models. Pharmacological inhibition of PLD1 markedly reduces tumor burden in the AOM/DSS model, whereas PLD2 inhibitors effectively

alleviate DSS-induced colitis.[104,105] In contrast, phosphatidic acid phosphatase (LPIN1) converts PA to diacylglycerol (DAG). Studies have demonstrated that LPIN1-deficient mice are highly resistant to colitis and exhibit significant protection against CAC, largely attributable to altered expression of LPIN1-regulated proinflammatory cytokines (eg., IL-23).[106] Collectively, PLD1/2 inhibitors and strategies that modulate LPIN1 activity represent emerging therapeutic approaches to remodel the intestinal inflammatory microenvironment and suppress inflammation-driven tumor progression.

## Targeting Sphingolipid Metabolism

The S1P receptor modulator ozanimod has gained FDA approval for ulcerative colitis, marking a significant therapeutic breakthrough. Nevertheless, S1P signaling plays a pivotal role in immune surveillance. Long-term S1P inhibition can lead to cardiovascular side effects (eg., bradycardia, hypertension) and increased infection risk, which may counteract its anti-tumor benefits. Additionally, patient heterogeneity in S1P receptor expression necessitates biomarker-driven patient stratification to avoid adverse outcomes.[103,107] Animal studies have demonstrated that ONO-4641 and KRP-203 can alleviate inflammation in murine colitis models,[103] and several S1P receptor-targeted drugs are under development; in clinical research, FTY720 (fingolimod) has already been utilized to treat CAC.[108] Additionally, ginkgolide is a potent antagonist of the platelet-activating factor (PAF) receptor, capable of inhibiting platelet aggregation and thrombosis. Since PAF promotes tumor growth and angio-genesis, ginkgolide may suppress CAC progression.[108]

## Combination Therapy and Translational Prospects

The crosstalk among lipid metabolic pathways provides a rationale for combining lipid-targeted agents with traditional therapies. Researchers have isolated and characterized bioactive compounds from the ethanol extract of fermented recombinant skim milk with Lactobacillus paracasei subsp. NT4101 (NTU 101-FMEE), specifically a mixture of palmitic acid, stearic acid, and 1,3-dipalmitoylglycerol (PSG). It was found that PSG at a concentration of 125 μg/mL significantly reduced the viability of colorectal cancer (CRC) cells, without cytotoxic effects on healthy colon epithelial cells or macrophages. Moreover, the combination of 62.5 μg/mL PSG and 5-fluorouracil (5-FU) exerted a markedly greater inhibitory effect than 5-FU alone. Compared to controls, PSG upregulated the activity of apoptosis-associated proteins and downregulated the NF-κB signaling pathway.[9,23] Overall, PSG purified from NTU101-FMEE demonstrates the potential to enhance the efficacy and reduce the adverse effects of adjuvant chemotherapeutics, thus improving CAC outcomes.

Italian researchers have developed a novel doxorubicin liposome conjugated to a recombinant human apolipoprotein B100-derived LDLR-binding peptide. This LDL-masked doxorubicin ("apo-Lipodox") is efficiently internalized in HT29-dx cells via LDLR-mediated endocytosis, inducing cytotoxic effects and reversing drug resistance. Simvastatin upregulates LDLR levels and concurrently decreases P-glycoprotein activity, which increases liposome uptake and limits drug efflux, further enhancing therapeutic efficacy.[109] In summary, targeting lipid metabolism offers a multidimensional intervention strategy for CAC. Future studies should incorporate metabolomics and single-cell technologies to dissect tumor heterogeneity and optimize combination treatment regimens.

# Summary and Perspectives

In this review, we synthesized the current understanding of how lipid metabolic reprogramming contributes to the development and progression of colitis-associated colorectal cancer (CAC). A growing body of evidence suggests that dysregulated lipid metabolism is not merely a consequence of tumor growth but serves as a central driver of the inflammation-to-carcinoma transition. This review highlighted the critical roles of key lipid metabolic pathways—namely fatty acid metabolism, cholesterol homeostasis, and phosphatidic acid signaling—in modulating inflammatory responses and shaping the tumor microenvironment. Furthermore, we discussed how these metabolic alterations influence therapeutic efficacy, with emerging evidence supporting the potential of targeting enzymes such as FASN, PLD1/2, and LPIN1 for CAC treatment.

Nevertheless, the field is currently hampered by several significant knowledge gaps that limit the translation of these findings into clinical practice. First, contradictory results regarding the roles of specific lipid metabolites and enzymes in

CAC progression are common. These discrepancies may stem from differences in experimental models (eg., AOM/DSS versus Apc^Min^ models), the timing and composition of dietary interventions, and the complex interplay between host genetics and gut microbiota composition. Second, most studies have focused on individual lipid pathways in isolation, neglecting the potential synergistic or antagonistic interactions among multiple metabolic routes. For instance, the cross-talk between fatty acid oxidation and cholesterol synthesis, or the feedback mechanisms linking phosphatidic acid signaling to inflammatory cytokine production, remains poorly understood. Third, the translational pipeline from preclinical studies to human trials is underdeveloped. Many promising therapeutic agents (eg., PLD inhibitors, LPIN1 modulators) have demonstrated efficacy in mouse models but lack rigorous evaluation in clinical settings, and the long-term safety of interventions such as statins or S1P receptor modulators in the context of chronic inflammation remains uncertain.

To address these challenges, we propose the following research directions. Future studies should aim to delineate the precise mechanisms by which lipid metabolic reprogramming drives CAC, with a particular focus on the cross-talk between lipid metabolism and the gut microbiota. Integrating metabolomics, single-cell RNA sequencing, and microbiome analyses will be essential for uncovering the context-dependent effects of lipid metabolism on tumorigenesis. In addition, there is an urgent need to investigate combination therapeutic strategies that target multiple metabolic pathways simultaneously (eg., co-inhibition of FASN and PLD) or combine metabolic interventions with microbiota modulation (eg., butyrate supplementation) and immune checkpoint blockade. Clinical trials should prioritize rigorous design, including well-defined patient inclusion criteria, dose-response assessments, and long-term safety monitoring, to validate the efficacy of lipid metabolism-targeted therapies (such as statins, SOAT1 inhibitors, and S1P modulators) in CAC patients.

## Author Contributions

ZSS: writing—original draft preparation, methodology, formal analysis;
LKS: writing—original draft preparation, methodology, funding acquisition;
YDD: writing—original draft preparation, methodology, formal analysis;
LYY: writing—review and editing, project administration, formal analysis, funding acquisition;
ZL: methodology, resources, writing—review and editing, project administration;
WPH: software, resources, writing—review and editing;
LGN: writing—review and editing, formal analysis, supervision;
HY: writing—review and editing, formal analysis, supervision;
XHX: writing—review and editing, Conceptualization, formal analysis;
ZM: writing—review and editing, Conceptualization.

All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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