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Research Advances in Lipid Metabolic Reprogramming Mechanisms of Colorectal Cancer Cells

Jin Meng [1], Yufeng Li [2], Jingwu Li [3,*]

[1] Graduate School of North China University of Science and Technology, Tangshan 063000, China

[2] Hebei Key Laboratory of Molecular Oncology, Tangshan 063000, China

[3] Central Laboratory, Tangshan People's Hospital, Tangshan 063000, China

*** Correspondence**:

Jingwu Li

tslijingwu@163.com

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Abstract

Colorectal cancer (CRC) is a highly aggressive form of cancer that poses a significant threat to public health worldwide. The progression of this disease is primarily driven by metabolic changes, especially the disruption of lipid metabolism. Cancerous CRC cells proliferate uncontrollably and invade surrounding tissues due to abnormal modifications in fatty acid synthesis, lipid uptake, storage, and β-oxidation. These metabolic shifts are influenced by key oncogenic signaling pathways, such as the PI3K/AKT/mTOR pathway and the MYC transcriptional network, which also enhance interactions with the tumor microenvironment's stromal elements. Recent research suggests that targeting lipid metabolism through pharmacological means could offer substantial clinical benefits. This article provides a comprehensive analysis of the molecular mechanisms involved in the reprogramming of lipid metabolism in CRC development and assesses its potential for innovative therapeutic approaches.

Keywords: Colorectal Cancer; Lipid Metabolism; Metabolic Reprogramming

1. Introduction

Colorectal carcinoma (CRC) represents a major global health burden, ranking as the third most frequently diagnosed malignancy and the second leading contributor to cancer-related mortality (Cao et al., 2024). The pathogenesis of CRC involves complex interactions between genetic alterations, epigenetic modifications, and metabolic dysregulation. A hallmark feature of this malignancy is the metabolic reprogramming phenomenon, with particular emphasis on the dysregulation of lipid metabolic pathways that significantly influence tumor biology (Hanahan & Weinberg, 2011).

Emerging evidence indicates that CRC cells adapt their lipid metabolism to survive under the challenging conditions of the tumor microenvironment (TME), including hypoxia and nutrient deprivation. These metabolic adaptations support tumor progression by providing essential energy substrates, maintaining cellular membrane integrity, and regulating critical signaling cascades (Capece et al., 2021). Notably, the NF-κB signaling pathway has been implicated in mediating lipid metabolic reprogramming in aggressive CRC subtypes through upregulation of triglyceride lipase CES1 expression, thereby establishing a molecular link between obesity-associated inflammation and tumor cell metabolic plasticity (Capece et al., 2021; Dobre et al., 2022).

The dysregulation of lipid metabolism during CRC development follows a dynamic temporal pattern. Transcriptomic profiling across disease stages from adenoma to carcinoma identified 149 lipid metabolism-associated genes that segregate into three progressively evolving molecular clusters (Chen et al., 2023). Early adenoma stages demonstrate progressive depletion of immune cell infiltration, fostering an immunosuppressive milieu. In contrast, carcinoma stages exhibit immune reactivation and the development of pro-inflammatory microenvironments. This temporal correlation suggests coordinated regulation between lipid metabolic remodeling and immune landscape transformation during CRC progression.

Comprehensive lipidomic analyses have revealed significant differences in fatty acid composition between tumor tissues and adjacent normal tissues. CRC specimens displayed increased levels of saturated and polyunsaturated fatty acids, while surrounding normal tissues were predominantly enriched in monounsaturated fatty acids (Mika et al., 2020; Yang et al., 2015). These metabolic signatures hold substantial clinical relevance, as they correlate with immune escape mechanisms and may serve as prognostic indicators.

This review provides a systematic evaluation of lipid metabolic alterations during CRC development, focusing on the dysregulated control mechanisms and molecular pathways governing fatty acid synthesis and breakdown. Furthermore, the study explores the complex interplay between these metabolic changes and tumor immunosuppression, providing valuable conceptual frameworks for developing novel combination therapies targeting metabolic vulnerabilities.

2. Metabolic Changes in Lipid Pathway of Colorectal Cancer Cells

2.1. Molecular Mechanisms of Lipid Metabolism Reprogramming in CRC

2.1.1. Dysregulation of Fatty Acid Biosynthesis Pathway

In CRC, malignant cells exhibit profound dysregulation of lipid homeostasis, characterized by aberrant activation of adipogenesis. The dyshomeostasis of fatty acid biosynthesis in CRC is predominantly manifested through upregulated expression of acetyl-CoA carboxylase (ACC) and fatty acid synthase (FASN). ACC functions as the rate-limiting enzyme in fatty acid synthesis, catalyzing the conversion of acetyl-CoA to malonyl-CoA, while FASN mediates the elongation of malonyl-CoA and acetyl-CoA into saturated long-chain fatty acids (Terado et al., 2022). Substantial evidence demonstrates that ACC and FASN are markedly overexpressed in CRC cells,

driving excessive fatty acid biosynthesis that provides essential lipid components for tumor cell proliferation and membrane remodeling (Terado et al., 2022). Notably, FASN overexpression correlates significantly with chemoresistance in malignant cells, highlighting its therapeutic potential in CRC management (Terado et al., 2022).

Transcriptomic profiling utilizing GEO datasets demonstrated a robust correlation between FASN expression and oxaliplatin resistance. Subsequent pharmacologic studies revealed that FASN inhibition could overcome chemoresistance through modulation of both MAPK/ERK and PI3K/AKT signaling cascades (Han et al., 2023; Lu et al., 2019).

Furthermore, perturbations in fatty acid biosynthetic pathways are associated with constitutive activation of multiple oncogenic signaling networks. The Wnt/β-catenin pathway, frequently hyperactivated in CRC, enhances fatty acid production via transcriptional upregulation of ACC and FASN (Dai et al., 2023). Additionally, prevalent KRAS mutations in CRC activate downstream MAPK effectors that reprogram lipid metabolism, including stimulation of de novo lipogenesis (Terado et al., 2022). These signaling aberrations not only disrupt fatty acid homeostasis but also profoundly influence tumor cell behavior by modifying lipid metabolism-related gene expression profiles (Terado et al., 2022).

Of particular interest, elevated fatty acid desaturation has been observed in obesity-associated CRC subtypes, where dysregulated arachidonic acid metabolism and PPAR signaling contribute to tumor progression (Ikeda et al., 2024; Kibriya et al., 2023). Experimental data show that linoleic acid supplementation markedly attenuates both migratory capacity and proliferative potential in HT-29 cells. The therapeutic targeting of lipid metabolic pathways warrants further exploration as a promising strategy for CRC intervention (Gonzalez-Fernandez et al., 2020).

2.1.2. Dysregulation of Cholesterol Homeostasis

Disturbances in cholesterol homeostasis represent a critical pathological feature of hepatic metastasis in colorectal carcinoma, predominantly mediated by the preferential activation of sterol biosynthesis pathways regulated by sterol regulatory element-binding proteins-2 (SREBP-2). Emerging preclinical evidence demonstrates that pharmacological suppression of cholesterol biosynthesis using agents like bivalirudin or simvastatin can markedly inhibit the establishment of metastatic foci in hepatic parenchyma (Du et al., 2023; Zheng et al., 2023). Furthermore, cholesterol-derived bioactive molecules promote Th17 cell polarization through RORγt-dependent mechanisms, fostering an immunosuppressive milieu in colorectal malignancies (Perucha et al., 2019; Sun et al., 2021). Notably, recent investigations reveal that polyamine metabolism inhibitors can mitigate cholesterol-mediated apoptosis by maintaining SREBP-2 stability, underscoring key metabolic networks that govern colorectal cancer aggressiveness (Kakimoto et al., 2020).

The immunomodulatory protein B7H3 exerts regulatory control over SREBP-2 activity by downregulating its expression via AKT pathway stimulation, thereby enhancing ferroptosis resistance (a form of cell death resistance characterized by impaired, iron-dependent lipid peroxidation) in CRC cells. This observation elucidates a sophisticated interplay between sterol

metabolism and ferroptotic cell death, potentially informing innovative therapeutic approaches for CRC management (Jin et al., 2023). Moreover, cholesterol metabolic processes exhibit complex associations with lipid peroxidation dynamics and mitochondrial function, collectively influencing neoplastic cell fate decisions (Shen et al., 2024).

Within the broader context of lipid metabolic reprogramming, cholesterol homeostasis perturbations significantly impact both intrinsic tumor cell properties and extrinsic tumor microenvironment modulation. Specifically, CRC cells can evade immune surveillance by altering cholesterol biosynthesis and uptake pathways, consequently impairing immune effector functions within the tumor niche. Mechanistic studies indicate that ZDHHC6, a palmitoyl acyltransferase, stabilizes peroxisome proliferator-activated receptor γ (PPARγ) and facilitates its nuclear translocation through palmitoylation modification. This post-translational regulation upregulates ATP citrate lyase (ACLY) expression, thereby stimulating lipogenesis and driving CRC pathogenesis. Elevated ZDHHC6 expression correlates significantly with advanced disease stage and poor prognosis in CRC patients, highlighting its therapeutic relevance (Shan et al., 2024).

2.1.3. Lipid Droplet Accumulation and Tumor Cell Survival

In CRC, excessive lipid droplet deposition serves as a crucial reservoir of neutral lipids, providing malignant cells with essential metabolic precursors for both bioenergetic demands and phospholipid bilayer assembly. The recently identified SARIFA biomarker, defined by distinct histopathological features of tumor-infiltrating adipocytes without accompanying stromal reaction, elucidates the pathogenic process whereby CRC cells internalize exogenous lipids to support their proliferation (Reitsam, Grosser, et al., 2024; Reitsam et al., 2023). SARIFA-positive CRC cells meet their rapid proliferation demands by directly contacting adipocytes and taking up exogenous lipids (Markl et al., 2024; Reitsam, Grozdanov, et al., 2024). This metabolic reprogramming not only enhances the survival ability of CRC cells but also promotes their invasiveness and metastatic potential. For instance, transcriptome analysis shows that genes related to lipid metabolism (such as FABP2, FABP4, and COL15A1) are significantly upregulated in SARIFA-positive tumors, further confirming the importance of lipid metabolism in SARIFA-related tumor biology (Reitsam, Grozdanov, et al., 2024). Additionally, SARIFA-positive tumors exhibit higher cholesterol biosynthesis activity, which is closely related to their invasiveness and resistance to conventional treatments (Reitsam, Grozdanov, et al., 2024).

This lipid droplet enrichment correlates with enhanced oxidative stress tolerance, mediated through NF-κB-dependent upregulation of CES1-mediated triglyceride hydrolysis, thereby alleviating lipotoxicity. Pharmacological intervention targeting lipid droplet biogenesis represents a viable treatment strategy that may impair neoplastic cell viability by concurrently modulating both bioenergetic pathways and membrane homeostasis (Ackerman et al., 2018; Cotte et al., 2018; Peng et al., 2022; Wang et al., 2024).

In addition, lipid metabolic reprogramming also affects the fate of tumor cells by regulating processes such as Ferroptosis and autophagy-dependent cell death. Specifically, Timosaponin AIII (TA-III) can induce Ferroptosis in CRC cells by activating Rab7-mediated lipophagy and

then promoting lipid droplet degradation and free fatty acid release (Zheng et al., 2022).

2.1.4. Stage-Specific Lipidomic Remodeling in CRC Progression

In the development and progression of CRC, alterations in lipid metabolism play a pivotal role (Chen et al., 2023; Chen et al., 2024; Pakiet et al., 2019). During the transition from colorectal adenoma to carcinoma, the remodeling of the lipidome exhibits stage-specific characteristics. These changes not only influence the biological behavior of tumor cells but also regulate the immune status of the tumor microenvironment (Chen et al., 2023; Wang et al., 2020; Yang et al., 2021).

In the stage of colorectal adenoma, changes in the expression of lipid metabolism-related genes have already begun to occur (Chen et al., 2023). Research indicates that some enzymes related to fatty acid synthesis, such as FASN and ACC, may be upregulated, promoting the synthesis of fatty acids to provide energy for cell proliferation and the construction of cell membranes (Chen et al., 2023; Liu et al., 2022). Additionally, the expression of the low-density lipoprotein receptor (LDLR) may also increase to facilitate cellular uptake of cholesterol (Pakiet et al., 2019). These changes may lay the foundation for the growth of adenomas and their further malignant transformation. indicates that lipid metabolism reprogramming is a hallmark of many malignancies, including colorectal cancer (Chen et al., 2023).

As colorectal adenomas progress to carcinoma, alterations in lipid metabolism become more pronounced (Wang et al., 2020). Genome-wide association studies have shown that the expression of lipid metabolism-related genes is closely associated with immune infiltration in colorectal cancer (Chen et al., 2023). In cancerous tissues, the de novo fatty acid synthesis pathway is further activated, supplying tumor cells with a substantial amount of lipids (Chen et al., 2023; Liu et al., 2022). Wang et al. characterized the lipid metabolism landscape of CRC through shotgun lipidomics, revealing significant alterations in both the types and quantities of lipids present in tumor tissues (Wang et al., 2020). Moreover, the expression of certain enzymes related to lipid degradation, such as carnitine palmitoyltransferase 1 (CPT-1), may be downregulated. This downregulation reduces the oxidative breakdown of fatty acids, allowing more fatty acids to be utilized for the growth and metastasis of tumor cells (Chen et al., 2024; Yang et al., 2021).

2.2. Interactions Between Lipid Metabolic Reprogramming and TME

2.2.1. Effects of Cancer Cell-Associated Fibroblasts (CAFs) on Lipid Metabolism

As crucial constituents of the tumor stroma, CAFs play a pivotal role in modulating lipid homeostasis through the secretion of diverse signaling factors and metabolic byproducts. Contemporary investigations have demonstrated that CAFs provide essential lipid substrates, including fatty acids and sterols, to adjacent malignant cells through paracrine mechanisms, thereby supporting their anabolic and bioenergetic demands (Yin et al., 2024). A central mediator in this metabolic crosstalk is FABP4, a lipid chaperone abundantly expressed by CAFs that facilitates efficient fatty acid shuttling to neoplastic cells, consequently augmenting their lipid uptake capacity (Liu et al., 2016). Furthermore, dysregulated lipid metabolism in CAFs enhances the biosynthesis of tumor-promoting signaling molecules, which may potentiate the metastatic potential of neighboring cancer cells. Notably, CAFs also contribute to immune evasion by

secreting polyunsaturated fatty acids that create an immunotolerant niche conducive to tumor progression (Gong et al., 2020).

Through mechanisms involving redox imbalance and metabolic remodeling, CAFs profoundly alter the metabolic landscape of malignant cells. Emerging evidence suggests that CAF-colorectal cancer cell interactions can induce profound metabolic adaptations in tumor cells, triggering aberrant activation of both lipogenic and lipolytic pathways (Wang et al., 2024). Specifically, CAF-derived lactate and reactive oxygen species activate the NF-κB and hypoxia-inducible factor-1α (HIF-1α) cascades in tumor cells, upregulating key lipogenic enzymes and resulting in intracellular lipid accumulation (Liu et al., 2023; Wang et al., 2024).

The functional heterogeneity of CAFs populations significantly impacts lipid metabolic regulation. Distinct CAF subpopulations, particularly myCAF, iCAF, and apCAF variants, exhibit specialized metabolic signatures and functional attributes (Chen et al., 2024; Neil et al., 2024). MyCAFs, for instance, promote tumor cell lipogenesis through exosomal transfer of long non-coding RNAs such as PWAR6, thereby enhancing stemness and invasive properties (Deng et al., 2023). Conversely, iCAFs modulate tumor lipid metabolism via secretion of pro-inflammatory cytokines (e.g., IL-1β, TGF-β) that facilitate immune escape and therapeutic resistance (Deng et al., 2023; Koncina et al., 2023). This CAFs subtype-specific metabolic specialization presents novel therapeutic opportunities, where selective targeting of subtype-specific metabolic pathways or intercellular communication mechanisms may offer innovative strategies to impede tumor progression and dissemination (Chen et al., 2024; Yan et al., 2023).

2.2.2. Interaction Between Immune Cells and Lipid Homeostasis

The tumor microenvironment exhibits complex crosstalk between immune components, particularly macrophages and T lymphocytes, and the lipid metabolic networks of malignant cells. Emerging evidence indicates that colorectal carcinoma cells enhance lipogenesis and lipid storage through upregulation of key metabolic regulators including FASN and SREBP family members, thereby promoting tumor proliferation and metastatic potential (Yao et al., 2023). Tumor-derived lipid mediators such as PGE2 and lysophosphatidic acid initiate immunosuppressive signaling through TGF-β and IL-10 pathways. These mechanisms impair cytotoxic T cell and NK cell activity while expanding regulatory T cells (Tregs) populations and polarizing TAMs, collectively reinforcing immune escape mechanisms within the TME (Sampaio-Ribeiro et al., 2023).

Immune cell lipid metabolic reprogramming represents a critical determinant of functional polarization and antitumor capacity in the TME. Tumor-infiltrating lymphocytes often exhibit dysregulated lipid metabolism that contributes to functional exhaustion and apoptosis (Valente et al., 2023). Studies demonstrate that cholesterol accumulation and oxidized LDL in CRC microenvironments activate LXR and PPARγ pathways, suppressing T cell proliferation and effector functions while promoting Treg expansion (Gomes et al., 2023). Additionally, TAMs preferentially utilize fatty acid oxidation as their primary energy source in the TME, driving M2 polarization and subsequent secretion of immunosuppressive cytokines including IL-10 and TGF-β, which collectively attenuate antitumor immunity (Lin et al., 2023).

Lipid metabolic rewiring significantly influences tumor progression by mediating intercellular

communication within the TME. Bioactive lipids like sphingosine-1-phosphate (S1P) promote tumor dissemination and metastatic niche formation via S1PR-mediated signaling cascades that stimulate angiogenesis and lymphangiogenesis (Wu et al., 2023).

2.3. Key Signaling Pathways Regulating Lipid Metabolism Reprogramming

2.3.1. PI3K/AKT/mTOR Signaling Axis

The PI3K/AKT/mTOR cascade represents a pivotal regulatory axis that orchestrates lipid metabolic reprogramming, playing an indispensable role in oncogenesis, particularly in colorectal carcinoma pathogenesis. mTORC1 activation induces substantial upregulation of key lipogenic enzymes including fatty acid synthases and ATP citrate lyase, thereby augmenting the metabolic plasticity of neoplastic cells (Jones et al., 2019; Ricoult et al., 2015). Aberrant activation of this signaling network not only promotes intracellular lipid accumulation but also mediates metabolic rewiring via downstream mediators such as SREBP-1 and FASN (Cheng et al., 2023; Zheng et al., 2024). Notably, SREBP-1, a master transcriptional regulator of lipogenesis, demonstrates significant overexpression under PI3K/AKT/mTOR pathway stimulation in colorectal malignancies, driving fatty acid and cholesterol biosynthesis to fulfill both energetic demands and membrane biogenesis requirement (Guo et al., 2023; Zheng et al., 2024). Additionally, this signaling axis exerts regulatory control over lipid homeostasis by influencing autophagic flux and oxidative stress responses (Shi et al., 2025). Of particular interest, elevated acyl-CoA oxidase 1 expression increases reactive oxygen species generation during fatty acid β-oxidation, which subsequently suppresses mTOR phosphorylation, enhances autophagy, and attenuates colorectal cancer cell proliferation and metastatic potential (Shi et al., 2025). These observations underscore the complex interplay between PI3K/AKT/mTOR signaling and autophagic processes in lipid metabolic regulation.

Furthermore, immune cell populations within the tumor niche, particularly macrophages and T lymphocytes, establish complex metabolic dialogues with malignant cells through lipid metabolic reprogramming (Liu et al., 2023). A compelling example involves CYP19A1, which upregulates PD-L1 expression via GPR30-AKT signaling, consequently impairing CD8+ T cell-mediated antitumor immunity. Conversely, pharmacological inhibition of CYP19A1 significantly potentiates the therapeutic efficacy of PD-1 blockade strategies (Liu et al., 2023).

2.3.2. Regulation of Lipid Metabolism by Hypoxia Mediated by HIF-1α

The HIF-1α plays a pivotal role in mediating the metabolic reprogramming triggered by oxygen deprivation during colorectal cancer progression, enabling tumor survival through transcriptional regulation of hypoxia-responsive genes. Notably, HIF-1α upregulates vascular endothelial growth factor (VEGF) production, thereby establishing a pro-angiogenic microenvironment that sustains tumor vascularization and malignant growth (Qiu et al., 2015). Clinical investigations have revealed a significant association between increased HIF-1α/VEGF expression and advanced disease stages, highlighting their potential as valuable biomarkers for disease prognosis in colorectal cancer patients (Qiu et al., 2015).

In addition to its angiogenic functions, HIF-1α activation promotes critical oncogenic processes including epithelial-mesenchymal transition and the development of vasculogenic mimicry, where

highly invasive tumor cells autonomously form primitive vascular networks independent of endothelial cell participation (Li et al., 2016). These HIF-1α-mediated adaptive mechanisms not only enhance metastatic dissemination but also contribute to therapeutic resistance. Given these multifaceted roles, HIF-1α has emerged as both a reliable prognostic marker and an attractive molecular target for therapeutic intervention in colorectal cancer management (Li et al., 2016; Qiu et al., 2015).

2.3.3. SREBPs Transcription Factor is Involved in lipid Generation Pathway

Sterol regulatory element-binding proteins (SREBPs), particularly the SREBP-1 and SREBP-2 isoforms, play a pivotal role in tumorigenesis by modulating lipid biosynthesis pathways. It has been stated previously that the PI3K/AKT/mTOR axis transcriptionally activates SREBP, which in turn upregulates key lipogenic enzymes such as FASN and ACC, thereby synergistically driving lipid anabolism in CRC cells. In addition, there is experimental evidence demonstrates that SREBP-mediated adipogenic activation substantially enhances the proliferative capacity and viability of neoplastic cells. In colorectal carcinoma models, genetic knockdown of both SREBP-1 and SREBP-2 has been shown to effectively suppress adipocyte differentiation, resulting in pronounced inhibition of cellular proliferation and attenuated tumorigenic potential across both cellular and animal model systems (Wen et al., 2018). These findings establish a mechanistic link between adipogenic regulation and the survival mechanisms of malignant cells.

Clinical investigations have revealed significantly elevated SREBP-1 expression levels in colorectal adenocarcinoma specimens compared to adjacent normal tissues, with this molecular signature demonstrating strong correlation with poor prognostic indicators. These observations not only position SREBP-1 as a central regulator of cancer metabolism but also suggest its potential utility as a biomarker for disease progression (Fowler et al., 2023; Gao, Nan, et al., 2019). Furthermore, SREBP-1 has been implicated in promoting colorectal cancer metastasis through the transcriptional activation of epithelial-mesenchymal transition markers, highlighting its critical involvement in tumor invasiveness. At the molecular level, SREBP-1/2 appears to drive lipid deposition via oncogenic signaling cascades, particularly through the mTORC1 pathway, thereby supporting tumor expansion. Collectively, these data indicate that SREBPs contribute substantially to malignant progression by satisfying the heightened metabolic demands of transformed cells, presenting them as attractive candidates for metabolic intervention strategies in oncology (Gao, Zhao, et al., 2019).

2.4. Functional Significance of Lipid Metabolism Remodeling

2.4.1. Metabolic Energy Adaptation

The pathogenesis of colorectal carcinoma is marked by profound metabolic alterations, with dysregulated lipid metabolism emerging as a pivotal driver of neoplastic proliferation and bioenergetic homeostasis. Malignant cells employ this metabolic reprogramming to meet their amplified energetic demands during uncontrolled proliferation, particularly under glucose-deprived conditions. Central to this adaptive mechanism is the activation of fatty acid β-oxidation pathways, wherein lipid derivatives are catabolized into acetyl-CoA moieties. These metabolic intermediates subsequently fuel the tricarboxylic acid cycle, culminating in robust ATP

generation (Rashid et al., 2020; Wang et al., 2023). Such metabolic plasticity proves particularly critical in colorectal malignancies, given the characteristic nutrient-deficient tumor microenvironment where glucose availability is frequently limited. Through lipid metabolic rewiring, neoplastic cells acquire enhanced metabolic versatility, permitting sustained proliferation and disease progression despite these hostile conditions (Diao & Lin, 2019; Song et al., 2020).

Contemporary investigations have elucidated a robust association between elevated fatty acid β-oxidation in colorectal malignancies and aberrant expression patterns of key metabolic regulators. Notably, enzymatic mediators FASN and ACC demonstrate marked overexpression in neoplastic tissues, concurrently promoting de novo lipogenesis while providing essential substrates for β-oxidation pathways (Diao & Lin, 2019; Wang et al., 2023). Additionally, the upregulation of lipid transporter CD36 in malignant cells augments their capacity for extracellular lipid uptake, thereby sustaining their bioenergetic requirements (Diao & Lin, 2019; Song et al., 2020). These findings not only underscore the fundamental involvement of lipid metabolic pathways in colorectal carcinogenesis but also reveal promising molecular targets for metabolic intervention strategies (Diao & Lin, 2019; Song et al., 2020).

Under conditions of glucose deprivation, colorectal carcinoma cells maintain energetic equilibrium through upregulated fatty acid β-oxidation, which concomitantly mitigates oxidative damage. Experimental evidence demonstrates that enhanced mitochondrial oxidative phosphorylation directly correlates with intensified lipid catabolic activity. This coordinated metabolic adaptation not only provides substantial energetic support for rapidly proliferating tumor populations but also reinforces their resistance to programmed cell death mechanisms (Li et al., 2019; Rashid et al., 2020).

2.4.2. Biofilm Synthesis

The pathogenesis and progression of CRC are fundamentally associated with dysregulation of lipid metabolic pathways, particularly their pivotal role in cellular membrane formation. This metabolic reprogramming provides essential structural components for the plasma membranes of rapidly dividing neoplastic cells. Malignant cells significantly upregulate fatty acid and phospholipid biosynthesis through activation of key lipogenic enzymes, including FASN and ACC, which collectively contribute to the generation of membrane bilayers required for tumor proliferation (Diao & Lin, 2019; Liu et al., 2020).

Additionally, this metabolic adaptation promotes cholesterol biosynthesis via modulation of the mevalonate pathway, frequently characterized by elevated expression of squalene monooxygenase (Li et al., 2022). These biochemical alterations not only reinforce membrane integrity but also potentiate critical signal transduction mechanisms in transformed cells. At the molecular level, lipid metabolic remodeling activates protumorigenic signaling cascades such as Wnt/β-catenin and mTOR pathways, thereby augmenting membrane biogenesis capacity through regulation of key lipogenic enzymes (Liu et al., 2020; Ye et al., 2023). Notably, fatty acid-binding protein 5 (FABP5) cooperates with FASN to facilitate lipid anabolism and storage, ultimately driving oncogenic growth and metastatic dissemination (Ye et al., 2023). The metabolic shift

further enhances extracellular lipid uptake via transcriptional control of membrane transporters and lipolytic enzymes including CD36 and lipoprotein lipase (LPL), thus satisfying the biosynthetic demands of malignant cells (Diao & Lin, 2019; Montero-Calle et al., 2022).

2.4.3. Antioxidant Defense Mechanism

In CRC, dysregulated lipid metabolism serves dual physiological roles by providing both energetic substrates for cellular proliferation and structural components for membrane biogenesis, while simultaneously contributing to oncogenic transformation, tumor progression, and metastatic dissemination through enhanced antioxidant capacity. The tripeptide glutathione (GSH), a principal intracellular antioxidant, is biosynthesized from lipid-derived precursors including glutamate, cysteine, and glycine. Malignant cells in CRC maintain elevated GSH concentrations through upregulation of lipid metabolic pathways, thereby conferring protection against oxidative injury and promoting neoplastic survival (Čipak Gašparović et al., 2021). Oxidative stress, recognized as a pivotal driver of colorectal carcinogenesis, induces DNA damage and disrupts cellular homeostasis, collectively facilitating the malignant conversion of normal colonic epithelium and disease advancement.

Extensive research has elucidated the intricate interplay between oxidative stress regulation and lipid metabolic reprogramming in CRC. The redox-sensitive transcription factor Nuclear factor erythroid 2-related factor 2 serves as a master regulator by inducing the expression of cytoprotective enzymes including glutathione synthetase and catalase. Additionally,PPARγ significantly influences oxidative stress responses in CRC through metabolic gene network remodeling, which subsequently affects GSH biosynthesis and cellular redox status (Čipak Gašparović et al., 2021).

Emerging evidence has revealed that lipid metabolic alterations promote colorectal carcinogenesis via modulation of hydrogen peroxide (H_2O_2) signaling pathways. This reactive oxygen species, serving as a key redox signaling molecule, is tightly regulated by both lipid metabolic processes and antioxidant defense systems. Comparative studies have demonstrated significant upregulation of specific peroxisomal aquaporin isoforms (including AQP1, AQP3, and AQP5) in CRC models. These transmembrane channel proteins mediate H_2O_2 transport across biological membranes, thereby participating in redox homeostasis maintenance and malignant progression (Čipak Gašparović et al., 2021). Notably, experimental investigations utilizing HT-29 and Caco-2 colorectal adenocarcinoma cell lines have established that AQP3 overexpression correlates with enhanced oxidative stress resistance, highlighting the critical role of lipid metabolic rewiring in antioxidant defense mechanism adaptation during colorectal tumorigenesis (Čipak Gašparović et al., 2021).

Collectively, lipid metabolic reprogramming in CRC provides crucial antioxidant defense, primarily through enhancing GSH synthesis and modulating lipid species (e.g., via lipid droplet accumulation). However, this metabolic rewiring represents a double-edged sword. By altering the composition and abundance of specific lipids, particularly PUFAs within cellular membranes, CRC cells simultaneously modulate their susceptibility to ferroptosis, an iron-dependent form of cell death driven by lipid peroxidation. Thus, the reprogrammed lipid metabolism delicately

balances antioxidant protection against oxidative stress with the regulation of ferroptosis sensitivity, a critical adaptation for CRC cell survival.

2.5. Reprogramming of Lipid Metabolic Pathway and Treatment Resistance in Colorectal Cancer

2.5.1. Drug Resistance Mechanisms Related to Lipid Metabolism Changes

Emerging evidence highlights a strong association between dysregulated lipid metabolism and the development of chemoresistance in CRC. The administration of chemotherapeutic agents such as Irinotecan and 5-fluorouracil (5-FU) during CRC treatment often induces hepatic lipid metabolic disturbances, precipitating pathological conditions including hepatic steatosis and steatohepatitis. These metabolic perturbations not only impair hepatic function but also compromise therapeutic efficacy, thereby exacerbating treatment resistance (Chen et al., 2023; Zhao et al., 2024).

Clinical investigations have demonstrated a substantial elevation in hepatic triglyceride concentrations following chemotherapy, concomitant with a pronounced reduction in long-chain polyunsaturated fatty acids (PUFAs), particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). This exacerbates the dysregulation of lipid homeostasis (Monirujjaman et al., 2022). Additionally, chemotherapy modulates the transcriptional profile of hepatic lipid metabolic genes, characterized by upregulated FASN expression and suppressed mitochondrial β-oxidation activity. These molecular alterations collectively promote hepatic lipid accumulation, ultimately diminishing chemotherapeutic responsiveness (Ming-Bin et al., 2023; Yan et al., 2023).

Beyond direct metabolic effects, lipid imbalance contributes to chemoresistance by modulating immune regulation and inflammatory signaling within the tumor microenvironment. Post-chemotherapy, hepatic levels of pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), are significantly elevated. These mediators not only intensify peritumoral inflammation but also promote tumor cell survival and proliferation through activation of pathways such as NF-κB (Liu, Xiao, et al., 2023; Monirujjaman et al., 2023).

At the molecular level, resistance mechanisms involve profound perturbations in sphingolipid metabolism. 5-FU-resistant cell lines exhibit elevated sphingolipid content alongside impaired ceramide biosynthesis, attributable to reduced acid sphingomyelinase (ASMase) expression (Criscuolo et al., 2020; Mehdizadeh et al., 2017). This reduction in ceramide levels has direct consequences for cellular membrane properties. Ceramide is a key structural lipid that promotes the formation of ordered membrane microdomains (lipid rafts) and influences membrane fluidity. Consequently, diminished ceramide biosynthesis alters the membrane lipid composition, leading to decreased membrane fluidity and permeability (Ogretmen, 2018). These metabolic adaptations alter membrane biophysical properties, facilitating chemoresistance. Furthermore, CRC cells demonstrate metabolic plasticity via the coordinated induction of fatty acid β-oxidation and de novo lipogenesis, mediated by upregulated FASN and ACC. This metabolic reprogramming not only sustains energy homeostasis but also correlates with enhanced tumor aggressiveness and therapeutic resistance (Notarnicola et al., 2018).

Aberrant cholesterol metabolism represents another critical determinant of treatment resistance. Chemoresistant cell populations exhibit dysregulated cholesterol biosynthesis, leading to intracellular cholesterol accumulation. This not only impedes drug efficacy but also enhances cellular survival mechanisms, further reinforcing chemoresistance (Tam et al., 2023). Sphingosine epoxide synthetase, a crucial enzyme in the cholesterol production pathway, modulates the NF-κB signaling pathway, which in turn fortifies the resistance of colorectal cancer cells to 5-FU (Dai et al., 2023).

2.5.2. Therapies for CRC Rreatment that Regulate Lipid Metabolism

Emerging research has increasingly highlighted the significance of lipid metabolic dysregulation in CRC pathogenesis and treatment. The therapeutic potential of targeting lipid metabolism stems from its dual capacity to suppress malignant proliferation while potentiating conventional therapies through microenvironmental modulation (Cheng et al., 2023; Wang et al., 2023; Zheng et al., 2023). Substantial evidence indicates that perturbations in fatty acid, cholesterol, and glycerophospholipid metabolism correlate strongly with tumor progression and clinical prognosis, establishing these pathways as promising intervention targets.

The oncogenic dependence of CRC cells on lipid metabolic pathways underscores their therapeutic vulnerability. Tumor cells exhibit heightened requirements for fatty acid β-oxidation and cholesterol biosynthesis to sustain their proliferative demands (Zheng et al., 2023). Notably, accumulating data implicate cholesterol metabolites, particularly secondary bile acids, as critical mediators of CRC progression. Pharmacological inhibition of cholesterol synthesis or intestinal absorption, exemplified by Ezetimibe administration, demonstrates potent antitumor effects through multiple mechanisms: induction of apoptotic pathways, disruption of mitochondrial integrity, and modulation of mTOR signaling cascades (Zheng et al., 2023). These findings validate lipid metabolic intervention as a viable therapeutic paradigm in CRC management.

Fatty acid metabolic reprogramming represents another promising therapeutic avenue in CRC. The oncogenic reliance on fatty acid oxidation (FAO) manifests through dysregulated expression of rate-limiting enzymes including FASN and CPT1 (Cheng et al., 2023; Kopetz et al., 2024; Wang et al., 2023). Preclinical investigations demonstrate that pharmacological inhibition of these enzymatic activities, particularly in the context of high-fat dietary conditions, effectively suppresses tumorigenic progression. The therapeutic compound ECD exemplifies this approach by simultaneously modulating fatty acid synthesis and catabolism (Liao et al., 2023). Additionally, dietary supplementation with n-3 polyunsaturated fatty acids exhibits antitumor efficacy through both direct growth inhibition and anti-inflammatory microenvironmental remodeling (Liao et al., 2023). These collective observations substantiate fatty acid metabolism as a therapeutically targetable vulnerability in CRC.

Within clinical oncology, modulation of lipid homeostasis has emerged as a critical adjunct to conventional therapeutic interventions. HMG-CoA reductase inhibitors (statins), for instance, demonstrate dual efficacy by both lowering serum cholesterol concentrations and potentiating chemosensitivity in CRC cells (Elez et al., 2025; Zheng et al., 2023). Although there are no large-scale randomized controlled trials (RCTs) specifically evaluating the efficacy of statins in CRC at

present, a retrospective study found that statins significantly reduced the recurrence rate and mortality of tumors in patients with breast cancer, endometrial cancer and ovarian cancer (Markowska et al., 2020). Contemporary molecular stratification systems incorporating lipid metabolic signatures, particularly the consensus molecular subtype (CMS) classification, provide a framework for precision medicine in CRC management (Cheng et al., 2023). Distinct metabolic vulnerabilities have been identified across subtypes - CMS1 tumors exhibit pronounced fatty acid β-oxidation activity, while CMS4 malignancies demonstrate marked dependence on de novo cholesterol biosynthesis (Cheng et al., 2023). These metabolic distinctions enable identification of subtype-specific therapeutic targets.

Recent investigations into lipid metabolic reprogramming-associated chemoresistance in CRC have yielded several mechanistically distinct therapeutic strategies. Microenvironment-focused approaches involve metabolic modulation to reinstate immune surveillance, with prostaglandin E2 (PGE2) synthesis blockade demonstrating particular promise in augmenting T-cell effector functions and potentiating immune checkpoint blockade (Barnell et al., 2023). Furthermore, targeting metabolic adaptations in cancer stem cell populations has led to development of small-molecule inhibitors (e.g., fatty acid oxidation blockers) that disrupt energy homeostasis in treatment-resistant cellular subpopulations (Andre et al., 2024).

In summary, pharmacological manipulation of lipid metabolic pathways represents a promising therapeutic paradigm in CRC. This approach targets three principal metabolic axes (cholesterol homeostasis, fatty acid metabolism, and bile acid signaling) that collectively influence both intrinsic tumor cell proliferation and extrinsic microenvironmental modulation, thereby synergizing with standard treatments.

3. Conclusions and Future Perspectives

CRC exhibits profound alterations in lipid metabolism that facilitate tumorigenesis by modulating fatty acid biosynthesis, uptake, storage, and oxidation. These metabolic adaptations serve as fundamental mechanisms for sustaining energy production, remodeling cellular membranes, and activating oncogenic signaling cascades under microenvironmental stress conditions. The PI3K/AKT/mTOR axis, HIF-1α signaling, and SREBP-mediated pathways constitute central regulatory networks that coordinate this metabolic reprogramming while establishing crosstalk with tumor-associated immune cells (CAFs, TAMs, and T lymphocytes) to foster an immunosuppressive and therapy-resistant tumor niche.

Pharmacological targeting of critical lipid metabolic enzymes, including FASN or modulation of cholesterol transport mechanisms has shown promise in restoring chemosensitivity and improving immune recognition. Nevertheless, the clinical implementation of such strategies faces substantial obstacles due to metabolic plasticity, spatial heterogeneity, and compensatory pathway activation in CRC.

Future investigations should leverage advanced technologies such as single-cell transcriptomics, single-cell/spatial lipidomics, spatial metabolic profiling, and patient-derived organoid (PDO) systems to identify subtype-specific metabolic vulnerabilities, particularly those within the

reprogrammed lipid metabolism landscape of CRC. For example:

Single-cell lipidomics can be employed to comprehensively map intratumoral heterogeneity in lipid species abundance and metabolic pathway activity across distinct cellular compartments within the CRC TME, including cancer cells, CAFs, TAMs, and T lymphocytes. This will reveal how lipid metabolic rewiring is coordinated and exploited by different cell types to support tumor progression and immune evasion (Kopetz et al., 2024; Lu et al., 2023).

PDOs provide a powerful platform to model patient-specific lipid metabolic dependencies and perform high-throughput screening of combinatorial therapies targeting lipid metabolism, such as previous studies have used CRC patient-derived organoid systems to successfully screen compounds sensitive to specific metabolic pathways, such as the Warburg effect, and verified their anti-tumor effects in vivo (Babaei-Jadidi et al., 2022). In addition, PDOs can also be used to study the interaction between tumor metabolism and immune microenvironment, and provide experimental basis for the development of strategies for combined metabolic regulation and immunotherapy (Courneya et al., 2025; Zaramella et al., 2023).

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