

Macrophage Metabolic Reprogramming in Inflammatory Bowel Diseases: From Pathogenesis to Therapy

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Abstract: Inflammatory bowel disease (IBD), encompassing two subtypes, ulcerative colitis, and Crohn's disease, is a chronic, non-specific gastrointestinal disorder with a complex etiology stemming from various factors. The incidence of IBD has been steadily rising in the past few years, causing great physical and mental strain on patients. Traditional IBD therapeutic drugs include anti-inflammatory drugs, immunosuppressants, and biologics; however, they may have serious adverse effects. This has fueled active clinical research exploring new targets for IBD treatment, focusing on the unique metabolic pathways and functions of macrophages. Macrophage immune metabolism plays a crucial role in IBD; however, the mechanism is unclear. This review discussed the role and potential mechanisms of macrophage metabolic reprogramming in IBD and the link between macrophages and ferroptosis. While these findings from preclinical models suggest novel therapeutic avenues for IBD, such as targeting macrophage metabolic reprogramming and hypothetical approaches like ferroptosis modulation, their clinical applicability remains speculative; rigorous disease-specific validation is imperative.

Keywords: macrophage, metabolic reprogramming, inflammatory bowel diseases, pathogenesis, therapy

Introduction

Inflammatory bowel disease (IBD) is a chronic, non-specific gastrointestinal disorder encompassing two subtypes: Crohn's disease (CD) and ulcerative colitis (UC). CD is characterized by transmural, progressive, and destructive chronic inflammation that can attack any segment of the gastrointestinal tract,¹ while UC typically presents with superficial mucosal inflammation originating in the rectum and extends proximally.² The rising prevalence of IBD in recent years poses a considerable burden on the quality of life and socioeconomic status of affected individuals.³ Although the exact etiology of IBD remains elusive, its pathogenesis involves genetic susceptibility, environmental influences, internal immunity, and the microbiota.⁴ Current IBD management relies on immunosuppressants, biologics, and small-molecule inhibitors. While these therapies can induce remission, significant limitations persist—including non-response in 30–40% of patients, risk of serious infections, and loss of efficacy over time.⁵ Under dual biologic therapy (DBT), for instance, the clinical response rate in refractory Crohn's disease (CD) patients is only 50%, highlighting the therapeutic challenges in this patient population. This underscores an urgent need for novel therapeutic strategies targeting alternative pathways.⁶

Macrophages are immune cells derived from bone marrow progenitors and are present in various tissues.^{7,8} Macrophages and dendritic cells, collectively referred to as antigen-presenting cells (APCs), play a crucial role in maintaining homeostasis within the intestinal lamina propria.⁹ These cells are essential for immune surveillance, tolerance induction, and the regulation

of inflammatory responses, ensuring the balance between immune activation and suppression in the gut environment. Macrophages undergo polarization into distinct functional phenotypes (M1/M2) from a resting state (M0) in response to various cytokines, growth factors, or other microenvironmental stimuli, a dynamic and reversible process.¹⁰ The intestine is enriched with macrophages of different phenotypes and functions, which synergistically maintain a healthy intestinal flora and tolerance to dietary antigens.^{8,11,12} One of the critical drivers of macrophage polarization is metabolic reprogramming in a variety of inflammatory diseases, including IBD.^{13,14} Macrophages undergo adaptive modifications in their metabolic pathways (such as glycolysis, oxidative phosphorylation, and fatty acid oxidation) during differentiation and activation to satisfy functional requirements under diverse physiological or pathological conditions, a process termed metabolic reprogramming.¹⁵ This process is termed metabolic reprogramming. Studies have shown that key metabolic regulators such as PPAR- γ and HIF can induce the polarization direction of macrophages to repair the intestinal mucosal barrier.¹⁶ Moreover, the metabolic process of macrophages also influences the polarization direction through transcriptional and post-transcriptional events. For example, N6-methyladenosine (m6A) modification has been proposed as a potential regulatory mechanism during macrophage metabolic reprogramming, though its role in IBD remains hypothetical and requires validation.¹⁷ However, critical knowledge gaps persist, such as regulatory nodes controlling metabolic switching (eg, the ROS-hexokinase/pyruvate kinase M2 isoform axis); microbiota-metabolite-epigenetic crosstalk; metabolic heterogeneity driving functional macrophage subsets. Unraveling these mechanisms is vital for developing precise metabolic interventions in inflammatory bowel disease (IBD). While recent reviews have comprehensively covered macrophage metabolism in IBD,^{16,18} they lack in-depth analysis of ferroptosis as a pathogenic hub and nanoparticle-based therapeutic targeting. This review uniquely integrates macrophage metabolic reprogramming with ferroptosis-driven immunopathology and critically evaluates emerging nanotherapies, bridging mechanistic insights to clinical translation gaps.

Ferroptosis is a distinct form of regulated cell death, distinguished by disturbed iron metabolism, lipid peroxidation, and glutathione (GSH) depletion.¹⁹ Ferroptosis is emerging as a key pathogenic driver in IBD macrophages. Unlike other death pathways, ferroptosis directly links iron dysregulation, oxidative stress, and chronic inflammation, amplifying tissue damage and fibrosis. Its unique mechanism and therapeutic tractability justify focused discussion in this review. An intrinsic link exists between ferroptosis and macrophage polarization, suggesting that ferroptosis can regulate macrophage polarization status. Therefore, elucidating this complex relationship between ferroptosis and macrophages will lay the groundwork for innovative targeted therapies. While preclinical data suggest a mechanistic link, ferroptosis-targeted therapies in IBD remain speculative and warrant rigorous disease-specific investigation. This article reviews and discusses the role and possible mechanisms of macrophage metabolic reprogramming in IBD and the connection between macrophages and ferroptosis. Moreover, the findings from this study may lead to the development of targeted therapies for IBD using macrophage metabolic reprogramming.

Discussion

IBD and Macrophage

IBD

IBD comprises a group of chronic inflammatory conditions affecting the gastrointestinal tract. Recent studies show that the development of IBD is intricately linked to the interaction of genetic factors, the gut microbiota, and the host immune system. Regarding genetic factors, genome-wide association studies have identified several genomic regions associated with the risk of IBD. Notably, the *nucleotide-binding oligomerization domain-containing 2 (NOD2)*, *autophagy-related 16-like 1 gene (ATG16L1)*, *transforming growth factor β 1 (TGF- β 1)*, *interleukin 23 receptor (IL23R)* and *toll-like receptor 4 (TLR4)* are crucial in the progression of IBD fibrosis.^{20–24} Additionally, 28 genes shared between CD and UC have been identified.²⁵ The immune system regulates the interaction between the host and the gut microbiota. Macrophages help to maintain intestinal homeostasis, and different subtypes are recruited to relevant sites of inflammation at different stages of disease.²⁶ CD14⁺ macrophages, a subset of intestinal macrophages, are increased in Crohn's disease (CD) patients. These cells exacerbate inflammation by initiating Th17/Th1 responses through the excessive secretion of IL-23 and TNF- α .²⁷ Th17 cells play a critical role in the pathogenesis of inflammatory bowel disease (IBD), with an increased proportion observed in the blood of IBD patients.²⁸ Th17 cells secrete IL-17 and IL-21, and excessive levels of these cytokines can disrupt the intestinal epithelial barrier.²⁹ Reportedly, patients with IBD exhibit reduced

bacterial diversity and abundance in their gut microbiota,³⁰ particularly obligate anaerobes from the Bacteroidetes and Firmicutes phyla.^{31,32} Certain bacterial groups, such as *Fusobacterium nucleatum* and *Escherichia coli*, significantly influence the development and progression of colorectal cancer.^{33,34}

Macrophage

Macrophages derived from blood monocytes exhibit remarkable plasticity, with phagocytosis and pathogen clearance as their primary function.³⁵ However, recent studies using transgenic mouse models and cell tracking techniques revealed myb-independent hematopoiesis in early embryonic and adult stages.

These studies suggest that some tissue-resident macrophages originate from progenitor cells in the the yolk sac or fetal liver rather than from circulating blood monocytes.³⁶ They include Kupffer cells in the liver, Langerhans cells in the epidermis, and microglia in the central nervous system. These macrophages are integral to various tissues, performing a range of supportive functions in the intestine, such as regulating immune responses, maintaining mucosal barrier integrity, regulating smooth muscle contraction, and protecting vascular function.^{37,38} Intestinal macrophages have a high phagocytic capacity and are responsible for preserving the integrity of the intestinal mucosal barrier by removing apoptotic and senescent epithelial cells. They promote epithelial integrity by secreting tissue-remodeling metalloproteinases and stimulatory factors that promote epithelial stem cell renewal, such as prostaglandin E2, hepatocyte growth factor, and Wnt ligands.³⁸ The regulation of gastrointestinal motility is controlled by interactions between muscular layer macrophages and intestinal neurons. Studies have found that macrophages secrete bone morphogenetic protein 2, while enteric neurons release cytokine CSF1, together regulating intestinal activity and influencing gastrointestinal motility.³⁹

Macrophages are traditionally classified into M1 and M2 based on the stimuli obtained in vitro. Lipopolysaccharide (LPS) stimulates the polarization of macrophages toward the M1 phenotype, while interleukin-4 (IL-4) induces polarization toward the M2 phenotype.⁴⁰ Classically activated M1 macrophages exhibit pro-inflammatory properties and secrete various pro-inflammatory cytokines, including IL-6, TNF- α , IL-1, and IL-12. In contrast, alternatively activated M2 macrophages possess anti-inflammatory and pro-tumorigenic functions.^{41–43} Classically activated M1 macrophages have pro-inflammatory effects, whereas alternatively activated M2 macrophages have anti-inflammatory effects.^{41–43} M2 macrophages can be further classified into four subtypes: M2a, M2b, M2c, and M2d.⁴⁴ The biomarkers of M1 and M2 macrophages also differ significantly. M1 macrophages are characterized by the expression of CD80, CD86, CD64, and CD32, while M2 macrophages predominantly express CD163 and CD206.^{45,46}

Metabolic Reprogramming of Macrophages

Recent research on cellular metabolism underscores the critical of metabolic reprogramming in macrophage activation. Macrophage function is influenced by various metabolic pathways, including glycolysis, the tricarboxylic acid cycle (TCA), the pentose phosphate pathway (PPP), and lipid, amino acid, and macrophage micronutrient metabolism. They coordinate immune responses based on altered nutrient metabolism and polarize into M1 or M2 types, each with different metabolic and energy requirements. Therefore, we will discuss how disruptions in intracellular nutrient metabolism affect macrophage polarization and function in IBD.

Glucose Metabolism

Hypoxia is a key pathogenic mechanism of inflammatory tissues. In chronic inflammatory patho-immune environments, hypoxia and inflammation are often interdependent. Growing evidence suggests a link between IBD and mucosal hypoxia.⁴⁷ Under hypoxic conditions, degradation of *hypoxia-inducible factor 1 α* (*HIF-1 α*) is inhibited,⁴⁸ and expression of key glycolytic proteins is increased, causing macrophage metabolism to shift from oxidative phosphorylation (OXPHOS) to glycolysis.¹⁸ This metabolic reprogramming is a characteristic feature of M1 macrophages. Increased glycolysis enables rapid adaptation to the hypoxic tissue microenvironment to meet energy demands.⁴⁹ During IBD, *PKM2*, a key glycolysis enzyme, translocates to the nucleus as a dimer, binds to *HIF-1 α* , and stimulates aerobic glycolysis.⁵⁰ Shikonin alleviates colitis in mice by inhibiting *PKM2* dimerization and tetramerization in macrophages, hindering aerobic glycolytic reprogramming.⁵¹

HIF-1 α is a pivotal regulator of inflammatory cell metabolism. It plays a crucial role in the response to hypoxia and promotes the expression of inflammatory genes.⁴⁸ Specific deletion of *HIF-1 α* in bone marrow cells ameliorates acute colitis.⁵² By integrating metabolomics and transcriptomic data, Jha et al revealed that pro-inflammatory M1 macrophages exhibit disrupted TCA carbon flux at two breakpoints, causing citrate and succinate accumulation.^{53–55} Succinate inhibits *HIF-1 α* degradation, enhances HIF-1 stability, and induces IL-1 α production via HIF-1 β .⁵⁶ Activated macrophages release succinate into the extracellular environment, increasing SUCNR1 expression and promoting IL-1 β production, creating a positive feedback loop, and increasing SUCNR1 levels.¹⁴ SUCNR1 expression is elevated in the intestinal tissues of patients with CD, and its activation can trigger and progress inflammatory responses and fibrosis.⁵⁷ Inhibition of citrate efflux leads to histone deacetylation, inactivating *HIF-1 α* target genes, which causes metabolic inhibition of aerobic glycolysis and inflammatory responses.⁵⁸

While inflammatory hypoxia typically promotes *HIF-1 α* -driven glycolysis and M1 polarization, recent studies reveal context-dependent duality in its function. In colitis, *HIF-1 α* activation via roxadustat (ROX) or HIF-overexpressing MSC-derived extracellular vesicles (EVs) promotes M2 polarization and mucosal healing.^{59,60} This apparent paradox may stem from two key factors. Firstly, *HIF-1 α* initially exacerbates inflammatory responses in the early stages of disease (eg, via succinate/IL-1 β), which subsequently facilitates tissue repair by inducing anti-inflammatory mediators such as IL-10. Secondly, microenvironmental signals, including pro-inflammatory priming factors like TNF- α , synergize with *HIF-1 α* to optimize the cargo of extracellular vesicles (EVs), thereby promoting M2 reprogramming (Figure 1).

Lipid Metabolism

Studies indicate that lipid metabolism is critical for regulating immune cells, influencing inflammation and host defense. The peroxisome proliferator-activated receptor (PPAR) family includes ligand-activated transcription factors, with PPAR- γ mainly active in adipose tissue and macrophages.^{61,62} PPAR- γ serves as a pivotal immunometabolic regulator

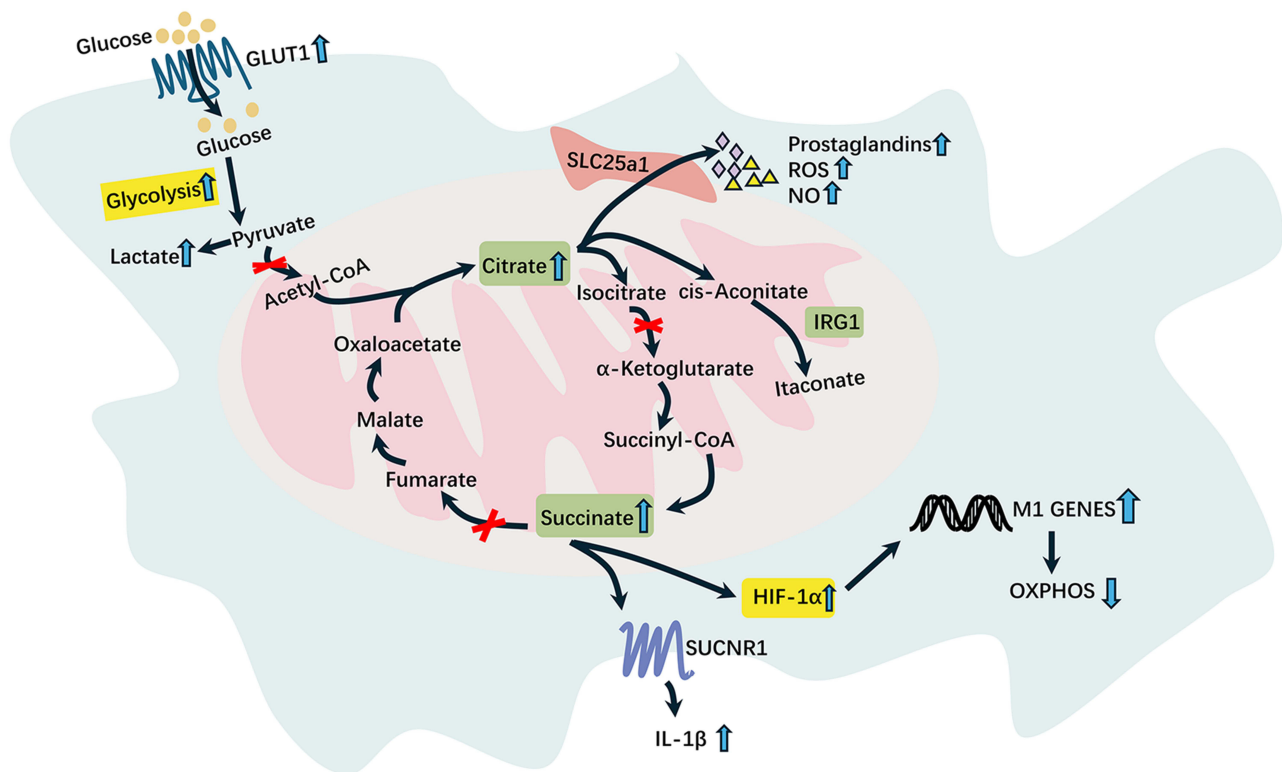


Figure 1 Macrophage glucose metabolism in IBD. During inflammatory bowel disease (IBD), macrophages shift from oxidative phosphorylation to glycolytic metabolism. In the mitochondria, the tricarboxylic acid cycle presents two break points, resulting in the accumulation of citrate and succinate. Citrate can be transported to the cytoplasm via the SLC25a1 transporter on the mitochondrial membrane to produce reactive oxygen species (ROS), nitric oxide, and Prostaglandins. Succinate activates *HIF-1 α* . Succinate can bind to SUCNR1 on the cell membrane and increase IL-1 β .

in the pathogenesis of IBD, yet the dichotomy of its functions and therapeutic translation remains contentious. Canonical perspectives posit that PPAR- γ activation exerts potent anti-inflammatory effects by suppressing NF- κ B signaling and production of pro-inflammatory cytokines (eg, TNF- α , IL-6, IL-1 β).⁶³ PPAR- γ drives macrophage polarization toward an anti-inflammatory M2 phenotype, enhancing efferocytic clearance, promoting IL-10 secretion, and facilitating tissue repair through metabolic reprogramming toward fatty acid oxidation.⁶⁴ In macrophages, PPAR- γ can inhibit pro-inflammatory molecule expression and regulate macrophage migration.⁶⁵ Studies have reported that the differentiation of M2a macrophages is dependent on the ligand-activated transcription factor PPAR γ .⁶⁶ PPAR- γ activation promotes macrophage polarization toward M2 phenotype by increasing STAT6 phosphorylation.⁶⁷ Animal studies demonstrate that in dextran sulfate sodium (DSS)-induced colitis, PPAR- γ gene-deficient mice exhibit exacerbated colonic injury compared to wild-type controls.⁶⁸ PPAR- γ agonists have been shown to alleviate colonic inflammation induced by DSS.⁶⁹ Macrophage-specific PPAR- γ knockout reduces the number of regulatory T (Treg) cells, increasing the susceptibility of mice to IBD and exacerbating disease severity.⁷⁰ However, significant paradoxical aspects exist in its biological functions. On one hand, mice with intestinal epithelium-specific PPAR- γ deletion exhibit markedly increased tumor incidence in carcinogenesis models, supporting its tumor-suppressive role.⁷¹ On the other hand, early studies suggest that PPAR- γ activation may potentially promote colorectal tumorigenesis, sparking controversy regarding its function in IBD-associated colorectal cancer.⁷² Clinical evidence demonstrates that the expression level of PPAR- γ in the rectal tissue is significantly reduced in patients with active UC, whereas it is increased in patients with UC in remission.⁷³ Downregulation of PPAR- γ is observed in both active and inactive stages of ulcerative colitis (UC) and Crohn's disease (CD), suggesting it may represent a chronic pathological feature of inflammatory bowel disease (IBD) rather than being solely associated with inflammatory activity.⁷⁴ Mechanistically, PPAR γ enhances glucose uptake by upregulating *Glucose transporter type 1 (GLUT1)* expression, thereby providing substrates for lipid synthesis and playing a pivotal role in regulating glucose and lipid metabolism. PPAR- γ also suppresses the expression of *HIF-1 α* —a key regulator of glycolysis—while promoting arginase-1 expression.⁷⁵ Arginase depletes its substrate arginine, consequently reducing nitric oxide (NO) production. This NO reduction mitigates oxidative stress and inflammatory responses, thereby facilitating the transition of macrophages from a pro-inflammatory M1 phenotype to an anti-inflammatory M2 state.⁶⁸ Furthermore, PPAR- γ promotes the expression of mitochondrial fatty acid transport proteins. The carnitine palmitoyltransferase (CPT) system comprises two isozymes—CPT1 and CPT2—which collectively constitute the carnitine shuttle and function synergistically in FAO. CPT1 transports activated fatty acids into mitochondria, whereas CPT2 regenerates oxidizable fatty acyl-CoA within the mitochondrial matrix. PPAR- γ agonists (eg, troglitazone) significantly upregulate mRNA levels of carnitine palmitoyltransferase I (CPT-1).⁷⁶ Nomura et al observed high expression of M2 macrophage markers, production of anti-inflammatory factors, and impaired FAO in a mouse model with macrophage-specific CPT2 deficiency.⁷⁷ In human and murine macrophages, the inflammatory factors IFN- γ and TNF α reduced PPAR- γ expression and activity, affecting lipid metabolic homeostasis and altering metabolism and inflammatory disease progression.⁷⁸ Research has shown that arachidonic acid inhibits the polarization of M2 macrophages. However, its metabolite, prostaglandin E2 (PGE2), promotes M2 polarization and enhances OXPHOS by inhibiting PPAR- γ .⁷⁹ A study found that PPAR- γ expression in both inflamed and non-inflamed regions of UC was lower than that in the control group and CD group.⁸⁰ This reduction may be attributed to impaired *TLR4* and PPAR- γ signaling. In *TLR4*-SNP mice treated with DSS, the capacity for PPAR γ activation and M2a macrophage marker expression was found to be impaired.⁸¹ During IBD, inflammatory factors such as IFN- γ and TNF α down-regulate PPAR- γ expression, resulting in reduced FAO, impaired polarization, and increased FAS in M2 macrophages.

While PPAR- γ primarily governs FAO, macrophage lipogenesis is coordinately regulated by sterol regulatory element binding proteins (SREBPs), which control de novo fatty acid synthesis.⁸² Sterol regulatory element-binding proteins (SREBPs), master transcriptional regulators of cellular fat metabolism, promote lipid accumulation. This dual regulatory axis—PPAR- γ -driven FAO and SREBP-mediated synthesis—collectively shapes lipid metabolism during macrophage polarization. SREBP-1a is responsible for regulating two key enzymes involved in lipid synthesis: acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS). In M1 macrophages, the activation of SREBP-1a leads to enhanced fatty acid and cholesterol synthesis, thereby supporting the energy demands associated with inflammation and immune responses. Srebp1-a, which is abundantly expressed in macrophages, plays a positive regulatory role in the inflammatory response.

Reportedly, lipopolysaccharide (LPS) induction in macrophages upregulates Srebp1-a expression. Bone marrow-derived macrophages lacking SREBP-1a exhibit reduced lipogenesis and phagocytosis.⁸³ Additionally, mice lacking SREBP-1a show defects in innate immune responses.⁸⁴ The activation of SREBP1 is closely associated with the activation of M2 macrophages. IL-4 stimulation leads to the activation of SREBP1, resulting in increased fatty acid synthesis.⁸⁵ In patients with ulcerative colitis (UC), SREBP2 is significantly elevated, and SREBP2 can promote intestinal mucosal healing by regulating cholesterol synthesis⁸⁶ (Figure 2).

Amino Acid Metabolism

Amino acids are pivotal regulators of various metabolic processes, especially in immune and inflammatory responses. The relationship between specific amino acids and IBD has recently garnered significant attention. Glutamine levels are significantly reduced in the serum of patients with IBD and DSS-induced colitis mice. Additionally, the absence of ATF4 reduces intestinal glutamine uptake.^{87–89} Some researchers proposed that glutamine is a significant factor in activating HIF-1 signaling and mTOR1C in LPS-induced M1 macrophages.^{56,90,91} Conversely, some studies indicated that glutamine metabolism favors M2 polarization. As a key regulator of macrophage phenotype, glutamine metabolism responds to different environmental stimuli.⁹² For instance, glutamine promotes macrophage M2 polarization by inhibiting SIRT5-mediated pyruvate dehydrogenase (PDH) desuccinylation.⁹³ On the other hand, succinate, produced through glutamine-dependent anaerobic glycolysis or the γ -aminobutyric acid pathway, promotes M1-type macrophage polarization.⁹⁴ Ala-Gln inhibits Th17 cell production, reduces inflammation, and decreases chemokine concentrations in intestinal tissues, thereby attenuating DSS-induced colitis-induced weight loss and colonic edema.⁹⁵ A high α -KG/succinate ratio stimulates M2 macrophage activation whereas a low ratio favors M1 macrophage activation.⁹⁶ This ratio regulates M1 polarization through PHD-dependent IKKb proline hydroxylation.⁹⁷ SENP1-SIRT3 signaling deacetylates glutamate dehydrogenase 1, which promotes the hydrolysis of glutamine to α -KG, leading to macrophage M2 polarization.⁹⁸

Arginine (Arg) is widely utilized in metabolism and supplemented in various disease states.⁹⁹ In macrophages, Arg serves as a precursor of two crucial metabolic pathways. In M1 macrophage, it is converted to nitric oxide (NO) and citrulline by inducible NO synthase (iNOS).¹⁰⁰ Endogenous NO restricts aconitase 2 and PDH, resulting in M1 macrophage entry into glycolysis.¹⁰¹ In M2 macrophages, Arg is converted to ornithine and urea by arginase-1 (Arg-1).¹⁰² A clinical study confirmed

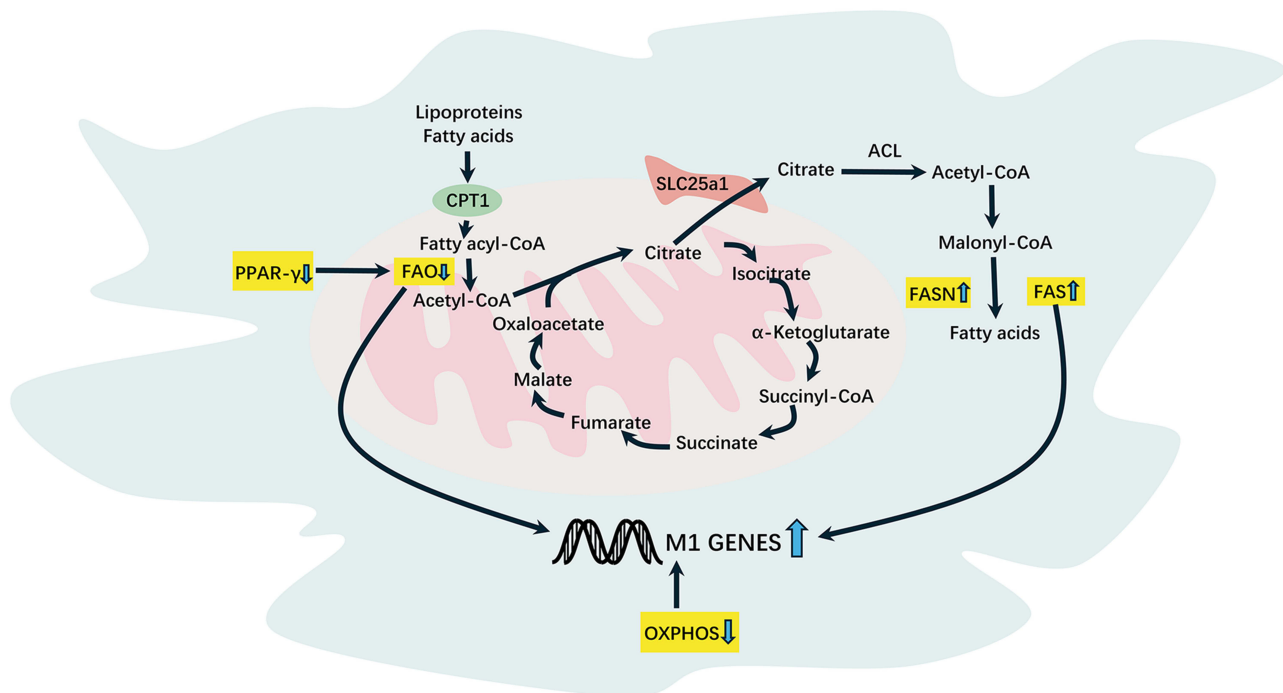


Figure 2 Macrophage lipid metabolism in IBD. Downregulation of PPAR- γ expression leads to reduced fatty acid oxidation during IBD. Citrate can be transported to the cytoplasm via the SLC25a1 transporter on the mitochondrial membrane to generate Fatty acids in response to FASN, resulting in increased fatty acid synthase.

that L-Arg levels positively correlate with the severity of UC, with elevated levels observed in patients with severe colitis.¹⁰³ Reportedly, patients with UC had reduced cellular uptake, increased NOS2 consumption, and decreased ARG1 expression, leading to decreased L-arginine in the tissues.¹⁰⁴ Additionally, L-arginine supplementation attenuated the damage and inflammatory response in DSS-induced colitis.¹⁰⁵ The active transport of L-arginine is mediated by a family of cationic amino acid transporter proteins, including SLC7A1 and SLC7A2.¹⁰⁶ Deletion of SLC7A2 increased inflammatory factors in the colonic tissues and exacerbated colonic tumor development.¹⁰⁷

Tryptophan (Trp) plays a role in various pathophysiological processes, mainly through metabolites that affect inflammatory responses, oxidative stress, immune responses, and intestinal homeostasis.¹⁰⁸ M1 macrophages use Trp as a precursor for the synthesis of NO via the nitrate pathway.

The NO produced has antimicrobial defense and contributes to microbial killing in inflammatory sites. Emerging evidence links Trp metabolism disorders to IBD development. During IBD, macrophages typically exhibit increased Trp uptake to satisfy their needs in immunomodulation and antimicrobial activity. Patients with IBDs have reduced serum Trp levels and increased indoleamine 2,3-dioxygenase 1 (IDO1) expression in the colon.^{109,110} *Ido1^{-/-}* mice suffered from more severe colitis induced by 2,4,6-trinitrobenzene sulfonic acid (TNBS).¹¹¹ However, recent studies have shown no significant differences in KYN/TRP levels between patients with UC and CD.¹¹² L-tryptophan significantly regulates serotonin levels in the colon and alleviates inflammatory responses in a DSS-induced colitis mouse model.¹¹³ New research suggests that supplementing with xanthurenic acid (XANA) and kynurenic acid (KYNA) can alleviate symptoms of colitis.¹¹⁴

α -aminobutyric acid (AABA) inhibits M1 macrophage polarization and function, reducing the severity of colitis by promoting OXPHOS metabolism as well as glutamine and Arg while inhibiting glycolysis.¹¹⁵ Glycine metabolism inhibits M1 macrophage polarization. Tsune et al found that glycine attenuates TNBS and DSS-induced colitis.^{116,117} Hydroxyproline significantly attenuated symptoms and inflammatory responses in DSS-induced colitis mice, reducing inflammatory cytokines levels and inhibiting activation of NF- κ B and STAT3 signaling pathways.¹¹⁸ Plasma levels of D-alanine (D-Ala) were low in DSS-induced colitis mice, UC mouse models, and mice with active intestinal inflammation.¹¹⁹ D-Ala inhibits the differentiation of M1 macrophages into M2.¹¹⁹

Characteristics of amino acid metabolism in macrophages are presented in Table 1.

Macrophage Micronutrient Metabolism

Patients with IBD frequently experience malnutrition during active and remission phases, characterized by micronutrient deficiencies such as B12, folate, iron, and vitamin D, essential for various physiological processes.¹²⁰ Selenium is a trace element that plays a critical role in the antioxidant defense system of cells in the form of selenoproteins. Reduced selenoprotein P (SEPP1) function significantly increased M2 macrophages. In a DSS-induced colitis model, SEPP1 deficiency exacerbates severe inflammation and intestinal damage.¹²¹ SELENOW is a small selenoprotein that affects glucose and Arg metabolism in macrophages during inflammation. Its absence during inflammation affects macrophage metabolism.¹²² Macrophage selenoprotein expression is closely related to 15-hydroxyprostaglandin dehydrogenase (15-PGDH). Selenoproteins in macrophages alleviate colitis in mice by inhibiting pro-inflammatory mediators.¹²³ These findings suggest that selenium and its related

Table 1 Amino Acid Metabolism and Macrophage Polarization

Amino Acid	Signaling Pathway(s) and/or Processes	Macrophage Polarization
Glutamine	HIF-1 ⁵⁶	Favors M1 polarization
	mTOR1c ⁹¹	Favors M1 polarization
	SIRT5 ⁹⁴	Favors M2 polarization
Arginine	iNOS ¹⁰⁰	Favors M1 polarization
	ARG1 ¹⁰²	Favors M2 polarization
Tryptophan	IDO1 ^{109,110}	Favors M2 polarization
α -aminobutyric acid	OXPHOS ¹¹⁵	Favors M2 polarization
D-Alanine	Unknown ¹¹⁹	Inhibit M1 polarization

proteins are crucial in modulating the immune system and inflammatory response, particularly in colitis models exhibiting significant protective effects.

Vitamin A is a lipid-soluble vitamin essential for preserving intestinal homeostasis, influencing immune function, and supporting epithelial barrier function. Its deficiency impairs macrophage function and increases susceptibility to induced colitis pathology. Vitamin A supplementation protects by reducing inflammation and apoptosis through the inhibition of NLRP3 inflammasome and caspase-1 activity.^{124,125} Conversely, vitamin D is an immunomodulator. The active form 1,25(OH)₂D has immunosuppressive effects on various immune cells.¹²⁶ Deficient levels of vitamin D heighten the risk of developing IBD, and supplementation significantly improves the prognosis of IBD in humans.¹²⁷ Wang et al found that 1,25-dihydroxyvitamin D directly inhibits M1 polarization.¹²⁸

Niacin, a vitamin B complex, ameliorates UC by activating the D-prostanoid receptor 1. This activation reduces the infiltration of inflammation-associated cells and increases the number of anti-inflammatory cells.¹²⁹ Despite vitamins's role in regulating macrophage immunity, evidence of the effects of vitamins on macrophage immune metabolism in IBD remains limited. A deeper understanding of these modulators of immunometabolism is required to develop new therapeutic strategies to modulate macrophage function and prevent IBD.

Roles of micronutrients on macrophages are presented in Table 2.

Macrophages and Ferroptosis

Iron Metabolism and Macrophage Polarization

Iron deficiency anemia is prevalent systemic complication of IBD.^{130,131} Iron is crucial for various physiological processes, encompassing cell proliferation, metabolism, and energy production. Its regulation is closely linked to macrophage polarization. Studies have shown that excess iron ions direct macrophages toward inflammation-activated polarization, increasing the expression of M1 markers such as IL-1 β , TNF- α , and iNOS.^{132–134} M1 macrophages exhibited significantly higher ferritin H levels and lower transferrin receptor 1 than M2 macrophages.¹³⁵ Iron overload increases reactive oxygen species (ROS) and hepcidin levels, promoting M1 macrophage polarization by inducing p53 acetylation and 4E-BP1 phosphorylation.^{133,136} During iron overload in macrophages, elevated hepcidin expression enhances STAT3 phosphorylation while inhibiting STAT6 expression, further driving M1 macrophage polarization.^{137–139} In M1 and colonic macrophages from mice with UC, a positive correlation was observed between Fe²⁺ accumulation and the production of inflammatory factors.¹⁴⁰ Handa et al revealed that dietary iron overload triggered M1 activation in hepatic macrophages of mice, resulting in significant up-regulation of inflammation-related genes, and significant downregulation of M2 pathway-related genes.¹³⁴ Treatment of IBD-associated anemia often involves oral or parenteral iron supplementation. Although oral iron may improve iron deficiency anemia, it may trigger oxidative stress, causing bowel inflammation and mucosal injury.^{141,142} Dietary iron has been shown to increase colonic iron levels and lipid peroxidation, promoting colitis development. This was achieved by activating the IL-6/IL-11-STAT3 signaling pathway, further promoting colitis and tumor progression.¹⁴¹ Future studies may delve into the mechanisms regulating iron metabolism in macrophages to identify new therapeutic targets to prevent excess iron-induced inflammation. Additionally, efforts should focus on finding safer and more effective iron supplementation strategies to reduce oral iron-induced oxidative stress and intestinal damage.

Table 2 Role of Micronutrients on Macrophages

Micronutrient	Cellular Target(s)	Effect on Macrophages
SEPP1 SELENOW	Alter the tumor microenvironment Reduced expression of arginase-I	Increased M2-polarized macrophages ¹²¹ Augmented mitochondrial respiration Lacked the characteristic increase in glycolysis Decrease glycolytic respiration ¹²²
Vitamin A	Increase IL-1 and IL-12 Increase LC3B-II expression	Impaired phagocytic capacity ¹²⁴
1,25-Dihydroxyvitamin D	Suppress miR125b	Increased M2-polarized macrophages ¹²⁸
Niacin	Activate prostaglandin D2-mediated D prostanoid receptor I	Suppress pro-inflammatory gene expression of macrophages ¹²⁹

The Role of Macrophages in Ferroptosis

Ferroptosis is an iron-dependent, non-apoptotic cell death characterized by iron accumulation, excessive reactive oxygen species (ROS) production, and high lipid peroxidation levels. Impaired iron metabolism underlies ferroptosis and influences the development and progression of various diseases.^{143–145} Iron ions as Fe^{3+} bind to transferrin (Tf) and are internalized through Tf receptor 1 (TfR) located in the cell membrane, facilitating their transport from the extracellular environment into the cell. Within the cell, they are reduced to Fe^{2+} .^{146,147} Fe^{2+} is stored in the labile iron pool (LIP) or ferritin (FT). FT is the primary intracellular iron storage protein, composed of FT heavy and light chains. Alternatively, Fe^{2+} can be exported from the cell via Ferroportin1 (FPN).^{148,149} FPN is an important iron transport protein that mainly facilitates the outward transport of non-heme iron absorbed from the intestine and stored iron, maintaining iron homeostasis in the body by regulating iron flow. It plays a significant role in the process of ferroptosis. Decreased FPN activity leads to iron accumulation, triggering iron ferroptosis. Excessive Fe^{3+} and Fe^{2+} induce the Fenton reaction, generating ROS. ROS damage lipids, proteins, and DNA, ultimately causing ferroptosis. Therefore, maintaining cellular iron homeostasis is essential to prevent oxidative damage, cytotoxicity, and cell death. Polyunsaturated fatty acids (PUFA) are converted to PUFA-CoA by long-chain acyl-CoA synthase-4 (ACSL4), binding to membrane phospholipids (PLs) via lysophosphatidylcholine acyltransferase 3. Subsequently, under the influence of lipoxygenases, non-toxic PL-PE-OH converts to toxic PL-PE-OHO, a reaction reversible by GSH peroxidase 4 (Gpx4). Excessive lipid peroxidation damages cell membrane PLs and alters the nature of the cell membrane lipid bilayer, ultimately accelerating ferroptosis.

Another critical feature of ferroptosis is glutathione depletion and reduced Gpx4 levels. GSH, an important endogenous antioxidant, scavenges ROS, maintaining intracellular redox balance and reducing oxidative damage, with cysteine being the rate-limiting substrate for its synthesis. Cystine/glutamate antiporter (System Xc⁻), comprising SLC7A11 and SLC3A2 proteins, transports cysteine into cells for conversion to cysteine.

In essence, a close connection exists between ferroptosis and macrophages, which is crucial for iron homeostasis maintenance and immunomodulation. Macrophages regulate iron homeostasis by recognizing and adhering to senescent red blood cells through surface receptors and transporting them intracellularly via vesicles. This process is facilitated by heme oxygenase-1 (HO-1), generating free iron, carbon monoxide, and biliverdin.¹⁵⁰ HO-1 can decrease intracellular iron storage and suppress the inflammatory response of macrophages by inhibiting M1 polarization.¹⁵¹ In cases of intracellular iron overload in macrophages, the Fenton reaction occurs, generating large amounts of ROS and ultimately leading to ferroptosis. Therefore, comprehensively studying the interactions between macrophages and ferroptosis is crucial to unraveling the molecular mechanisms underlying the immune response and iron homeostasis. This exploration is important for identifying new therapeutic targets for related diseases (Figure 3).

The Characteration of Ferroptosis in Macrophages Polarization

Impaired iron metabolism can trigger ferroptosis and macrophage polarization. Iron overload disrupts the balance between M1/M2 macrophage polarization and promotes M1 macrophage polarization.¹³⁴ RSL3 is an inducer of iron apoptosis, inhibiting iron-related cell death and controlling inflammatory progression by increasing *Nrf2* expression.¹⁵² *NRF2*, an antioxidant transcription factor, upregulates GPX4 expression. Under inflammatory conditions, *NRF2* expression is reduced in ferroptotic macrophages, leading to increased ROS levels and exacerbating cell death.¹⁵³ Additionally, ROS can activate Chk2, promoting M1 macrophage polarization.¹⁵⁴ GPX4 plays a role in inhibiting iron-related cell death. Gpx4-deficient macrophages can be induced to undergo ferroptosis in response to IL-4 stimulation.¹⁵⁵ M2 macrophages co-activate the ERK-cPLA2-ACSL4 pathway to induce ferroptosis and further exacerbate mucosal damage in UC.¹⁵⁶ In DSS-induced UC, macrophages undergo iron-related cell death and can be activated by β -caryophyllene to activate the type 2 cannabinoid receptor, which inhibits iron-induced cell death.¹⁵⁷ Regulating iron-related cell death in macrophages has important implications for inflammatory responses and tissue damage. A more comprehensive understanding of the mechanisms of macrophage ferroptosis in IBD pathogenesis could facilitate the development of novel therapeutic agents and strategies.

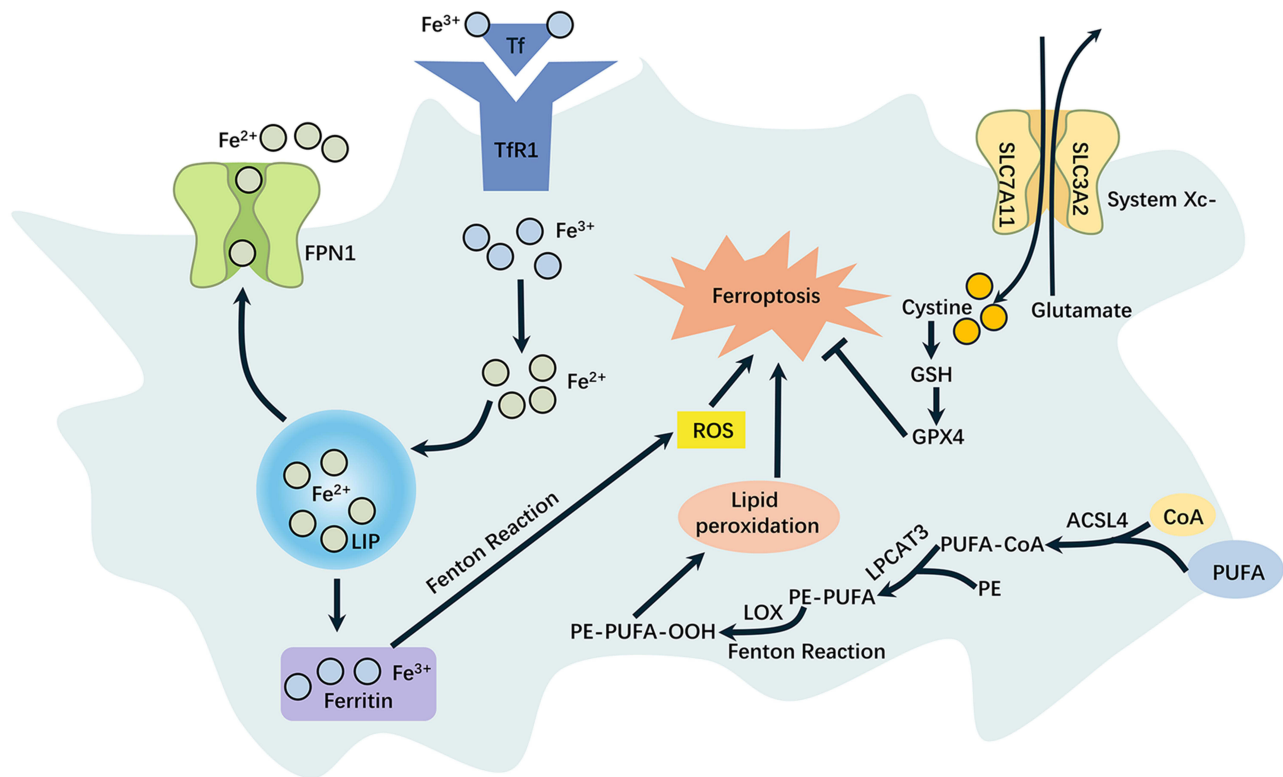


Figure 3 Macrophage ferroptosis in IBD. Fe³⁺ binds to transferrin and is transported to the cell through TfR1, where it is reduced to Fe²⁺, which is partially stored in the labile iron pool. Excessive intracellular accumulation of Fe³⁺ and Fe²⁺ can cause the Fenton reaction, which produces ROS and eventually leads to ferroptosis.

Macrophage Metabolic Reprogramming in the Treatment of IBD

Traditional Therapeutic Drugs

In the 20th century, significant advances were made in IBD treatment. Initially, treatment measures for colitis were mainly bed rest and colonic irrigation due to the limited understanding of the disease at that time.¹⁵⁸ As research progressed, more effective treatment options emerged, such as salicylates, corticosteroids, immunosuppressive drugs, and biologics. Mild-to-moderate UC is commonly treated with 5-aminosalicylic acid to alleviate inflammation. For left-sided UC, combined enema therapy is often recommended.¹⁵⁹ However, some patients may experience non-responsiveness or intolerance to 5-ASA. Acute 5-ASA intolerance syndrome can increase the risk of colectomy and further worsen symptoms.^{160–162} Combining 5-ASA with Fer-1 treats UC and improves the colonic mucosal barrier by promoting M2 macrophage polarization.¹⁵⁶ Corticosteroids effectively alleviate acute moderate-to-severe IBD symptoms by suppressing the immune response and decreasing intestinal permeability to improve the patient's condition. Short-term corticosteroid use in high doses is linked to adverse effects, such as hyperglycemia and hypertension, making it unsuitable for maintenance therapy.¹⁶³ Traditional immunosuppressive agents include mercaptopurine, methotrexate, and 6-mercaptopurine, which are primarily utilized in treating corticosteroid-refractory or corticosteroid-dependent IBD cases. These drugs effectively retard the progression of IBD by modulating immune system activity, offering patients a long-term treatment option.¹⁶⁴ When patients fail to respond adequately to conventional therapies, biologics such as TNF antibodies (infliximab), anti- α 4 β 7 integrin monoclonal antibodies (vedolizumab), and Janus kinase (JAK) inhibitors (upadacitinib) can be considered as alternative treatments. However, approximately 30% of patients do not respond to biologics during initial treatment, and 50% experience reduced efficacy or non-responsiveness with long-term use.¹⁶⁵ Prolonged use of biologics may lead to the development of anti-drug antibodies or increase the risk of cancer.¹⁶⁶ Research in the 20th century on IBD treatment has made significant progress through continuous drug innovation and progressive refinement of therapeutic strategies. However, the efficacy and safety of current drugs remain significant challenges. Therefore, the development of new, safer targeted therapies and drug delivery systems is urgently needed.

Current Research Status on Macrophage Immuno-Metabolic Therapy

Approaches targeting macrophages for treating IBD include pharmacotherapy and drug delivery systems. In pharmacological treatment, current research focuses on modulating macrophage function and phenotype to promote inflammation abatement and tissue repair.

New drugs can alleviate inflammation by inhibiting inflammatory signaling pathways, modulating macrophage polarization, and inducing anti-inflammatory cell phenotypes. For example, isosteviol sodium attenuates DSS-induced chronic colitis by inhibiting NF- κ B/P65-regulated macrophage polarization.¹⁶⁷ D-mannose, a monosaccharide, significantly inhibits macrophage production of IL-1 β , reduces lactate and succinate levels in macrophages, and prevents the activation of HIF-1 α , protecting mice from UC.¹⁶⁸ Shikonin, a *PKM2* inhibitor, binds to the *PKM2* protein in macrophages, thereby ameliorating colitis symptoms in mice.⁵¹ Bergenin binds to PPAR- γ , promotes PPAR- γ nuclear translocation and transcriptional activity, inhibits macrophage activation, and ameliorates colitis in mice.¹⁶⁹ Dioscin has an anti-inflammatory effect and can reduce UC symptoms in DSS-induced mice. The mechanism is suggested to regulate the signal transduction between mTOR, HIF-1 α , and PPAR- γ , thereby affecting macrophage polarization.¹⁷⁰ Notably, these interventions are primarily supported by murine studies; human IBD validation is ongoing.

Another approach is altering drug delivery to increase drug concentrations within macrophages, improving therapeutic efficacy and reducing systemic side effects. For example, nanoparticles or targeting agents can increase drug delivery efficiency within macrophages. This approach has achieved certain success in treating tumor-associated macrophages and holds potential for IBD treatment. Turmeric-derived nanovesicles (TNVs) significantly attenuate DSS-induced UC pathological injury by a mechanism that promotes M2 macrophage polarization. Additionally, TNVs target sites of inflammation and macrophages.¹⁷¹ Thalidomide, a drug for IBD treatment, mainly inhibits angiogenic activation and has anti-inflammatory properties.¹⁷² However, its use is restricted due to high systemic adverse effects. Meng et al developed polydopamine-coated thalidomide nanocrystals, which alleviated colitis symptoms in mice by increasing Thalidomide concentration in inflamed intestinal tissue and inducing M2 macrophage polarization.¹⁷³

Critical Evaluation of Key Studies and Translational Challenges

While the studies discussed herein provide valuable insights into macrophage metabolic reprogramming in IBD, it is crucial to acknowledge their strengths and limitations, as well as the reasons for inconsistent findings across different models. Mouse models of colitis, such as those induced by dextran sulfate sodium (DSS), 2,4,6-trinitrobenzene sulfonic acid (TNBS), or genetic deficiencies (eg, IL-10 knockout), have been instrumental in elucidating the pathogenic mechanisms of IBD. These models offer the advantage of controlled genetic and environmental conditions, enabling the dissection of specific pathways, such as the roles of HIF-1 α , PPAR- γ , and ferroptosis in macrophage function.^{51,52,60,68,77,156} However, a key limitation is that these models do not fully recapitulate the complex etiology and chronicity of human IBD, which involves polygenic susceptibility (eg, APC gene mutations), environmental triggers, and dynamic host-microbiome interactions.^{4,30} For instance, the DSS model primarily induces epithelial damage and acute inflammation, but human IBD is characterized by chronic relapse and persistent microbial stimulation.^{174–176} Moreover, while certain genetic manipulations in mice (eg, *TRPA1* deletion) exacerbate tumorigenesis, human data show that low *TRPA1* expression in colorectal cancer is associated with poor survival, highlighting fundamental differences in molecular pathology.¹⁷⁴ Additionally, the microbiome in mouse models is more malleable and responds markedly to interventions (eg, *Blautia hominis* LYH1 or *Alistipes finegoldii* OMVs alleviating inflammation), whereas human IBD features complex, persistent dysbiosis with species-specific adaptations (eg, *Malassezia*'s oxygen-dependent fitness in the human gut) that are not replicated in mice.^{177–179} Consequently, therapeutic interventions that show efficacy in mouse models, such as targeting *PKM2* or PPAR- γ , may not always translate to human patients.^{51,68,169}

While Pan et al provided an excellent dissection of microbiota-metabolite crosstalk in macrophage glycolysis, and Bittencourt et al broadly surveyed immune cell metabolism, our work advances the field through two critical contributions.^{16,18} Firstly, establishing ferroptosis as an amplifier of macrophage-driven inflammation in IBD, a mechanistic axis underdeveloped in prior syntheses. Secondly, delivering a critical appraisal of nanotherapy that transcends preclinical data summaries by explicitly addressing scalability challenges and IBD-specific delivery barriers.

Crucially, our framework resolves longstanding controversies, including HIF-1 α 's dual roles in inflammation/tissue repair and PPAR γ 's pro-tumorigenic risks, thereby identifying actionable therapeutic niches.

The heterogeneity in HIF-1 α function underscores a paradigm shift in macrophage immunometabolism: metabolic regulators are not intrinsically “pro-inflammatory” or “anti-inflammatory” but are dynamic sensors of microenvironmental stress. This explains why therapies like HIF stabilizers succeed in resolution-phase colitis but may fail in acute flares. Consequently, biomarker-driven patient stratification is essential for targeted metabolic therapy. Nanotechnologies offer promise but require optimization for human IBD microbiome and immune landscapes. The paradoxical functions of PPAR- γ in IBD-associated carcinogenesis highlight the context-dependent nature of metabolic regulators, which may vary between acute injury models and chronic human disease.^{71,72} Furthermore, immune responses in mice are often more tractable; for example, compounds like RTA-408 can readily inhibit T cell proliferation and enhance Treg frequency, and *FATS* can degrade *HIF-1 α* to suppress M1 macrophage polarization.^{176,180} However, human IBD involves a more intricate network of immune cells, including diverse innate lymphoid cells (ILCs) whose differentiation and recruitment are multi-factorial, a complexity not fully captured in mouse models.¹⁸¹ Moreover, while ferroptosis has been implicated in macrophage-driven inflammation in mouse models (eg, via Pannexin-1), its relevance in human IBD macrophages remains to be fully established.¹⁵⁶ Differences in barrier repair mechanisms also contribute to inconsistencies: mouse models show inducible barrier restoration (eg, via Hyperoside-induced autophagy or *Hymenolepis nana* ESPs activating tuft cell/IL-13 signaling), but human IBD barrier defects involve sustained epigenetic regulation (eg, *IGF2BP2*-mediated m6A modification of CBR1, impacting the PI3K/Akt pathway) that is only partially modeled in mice.^{182–184}

Another critical consideration is the inherent differences between murine and human macrophage biology. For example, human intestinal macrophages exhibit distinct developmental pathways and phenotypic markers compared to their murine counterparts.^{175,184} These differences may account for discrepancies in metabolic responses observed in mouse models versus human studies. Additionally, therapeutic translation faces hurdles: drugs effective in mice (eg, piroxicam analogs inhibiting MEK/ERK/NF- κ B or dendritic cell biohybrid modulators) often encounter resistance in human IBD, where biomarkers like *IGF2BP2* are needed to predict anti-TNF response, reflecting clinical heterogeneity absent in mouse models.^{183,185,186} Detection methods also differ, with mouse studies employing techniques like NIR-II imaging for microplastic tracking, while human IBD relies on biomarker assays (eg, MMP-9 detection via VHH-SPR probes).^{187,188} Furthermore, mouse models typically focus on acute pathology, whereas human IBD involves systemic long-term complications (eg, reproductive endocrine dysregulation) and diverse infectious etiologies (eg, *Clostridioides difficile* strains with variable toxin profiles) that are not fully represented.^{189,190} Therefore, future research should prioritize human macrophage studies, including those using organoids, patient-derived cells, and multi-omics approaches, to validate findings from animal models and bridge the translational gap.

Conclusions

Immunometabolic studies have identified significant metabolic differences between M1-type and M2-type macrophages in IBD development and progression. Therefore, targeted modulation of macrophage metabolic reprogramming processes may offer a novel therapeutic approach.¹⁹¹

This review highlighted how disruptions to intracellular nutrient metabolism affect macrophage polarization and function in IBD, and the interactions between ferroptosis and macrophages. Additionally, it summarizes conventional therapeutic agents for IBD and potential drugs targeting macrophage immuno-metabolic reprogramming. Despite recent advances, the mechanisms linking macrophage metabolism to IBD are incompletely defined and require further human validation.¹⁹² Therefore, further exploration of the effects of microenvironmental stimuli on macrophage metabolism in IBD is necessary. Mechanisms and effects at the cellular level have been the primary focus of most studies; however, exploration into the clinical importance and application of these findings is lacking. Further studies could establish correlations between these findings and clinical diseases. However, we emphasize that the mechanistic evidence discussed herein primarily derives from preclinical models (eg, murine colitis, in vitro systems), which may not fully recapitulate human IBD pathophysiology. Key hypotheses—such as ferroptosis-driven macrophage inflammation or nanoparticle-based targeting—require rigorous validation in human cohorts. Future studies must prioritize human macrophage multi-omics, longitudinal tissue analyses, and clinical trials to bridge this translational gap.

Abbreviations

IBD, Inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; APCs, antigen-presenting cells; GSH, glutathione; *NOD2*, domain-containing 2; *ATG16L1*, autophagy-related 16-like 1 gene; *TGF- β 1*, transforming growth factor β 1; *IL23R*, interleukin 23 receptor; *TLR4*, toll-like receptor 4; LPS, Lipopolysaccharide; IL-4, interleukin-4; TCA, tricarboxylic acid cycle; PPP, the pentose phosphate pathway; *HIF-1 α* , hypoxia-inducible factor 1 α ; OXPHOS, oxidative phosphorylation; *IRG1*, immune response gene 1; DSS, dextran sodium sulfate; EVs, Extracellular vesicles; PPAR, peroxisome proliferator-activated receptor; DSS, dextran sulfate sodium; Treg, regulatory T; PGE2, prostaglandin E2; FAO, fatty acid oxidation; CPT2, Carnitine palmitoyltransferase 2; SREBPs, sterol regulatory element binding proteins; ACC, acetyl-CoA carboxylase; FAS, fatty acid synthase; PDH, pyruvate dehydrogenase; Arg, Arginine; NO, nitric oxide; iNOS, inducible NO synthase; Arg-1, arginase-1; Trp, Tryptophan; IDO1, indoleamine 2,3-dioxygenase 1; XANA, xanthurenic acid; KYNA, kynurenic acid; AABA, α -aminobutyric acid; D-Ala, D-alanine; SEPP1, selenoprotein P; 15-PGDH, 15-hydroxyprostaglandin dehydrogenase; ROS, reactive oxygen species; Tf, Transferrin; TfR, Tf receptor 1; LIP, labile iron pool; FT, ferritin; FPN, Ferroportin1; PUFA, Polyunsaturated fatty acids; ACSL4, long-chain acyl-CoA synthase-4; PLs, phospholipids; Gpx4, GSH peroxidase 4; HO-1, heme oxygenase-1; TNVs, Turmeric-derived nanovesicles.

Data Sharing Statement

Data will be made available on request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; 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.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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