Current Opinion in Microbiology

The Role of Microbial Succinate in the Pathophysiology of Inflammatory Bowel Disease: Mechanisms and Therapeutic Potential

--Manuscript Draft--

Manuscript Number:	
Full Title:	The Role of Microbial Succinate in the Pathophysiology of Inflammatory Bowel Disease: Mechanisms and Therapeutic Potential
Article Type:	83a. HMI: Bacteria (February 2025)
Short Title:	Microbial Succinate in Inflammatory Bowel Disease
Keywords:	succinate; inflammatory bowel disease; dysbiosis; SUCNR1; gut microbiome; inflammation
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Abstract:	Inflammatory bowel disease (IBD) is a chronic condition linked to gut microbiota dysbiosis and altered bacterial metabolite production, particularly succinate, which plays a key role in both microbial metabolism and human mitochondrial energy processes. In IBD, succinate levels are elevated due to an increase in succinate-producing bacteria, driving inflammation and disease progression. Succinate acts as a signaling molecule via its receptor SUCNR1, regulating metabolic responses, but when dysregulated, it promotes inflammation and fibrosis. The dysbiotic gut microbiota in IBD patients contributes to elevated succinate levels, exacerbating IBD symptoms and increasing susceptibility to complications like Clostridioides difficile infection. Research suggests that manipulating succinate metabolism through dietary fiber, prebiotics, probiotics, or targeted therapies (e.g., SUCNR1 antagonists, SDH inhibitors) could restore microbial balance, reduce inflammation, and offer new therapeutic avenues for IBD management.
Author Comments:	As agreed with Scientific Editor Lachlan Beckingham, we are submitting the manuscript without completing the General Information tab, as the pop-up with classifications is not functioning correctly (the correct terms are not appearing, we selected all in order to build the PDF). We await further instructions regarding this matter.

The Role of Microbial Succinate in the Pathophysiology of Inflammatory Bowel Disease: Mechanisms and Therapeutic Potential

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ABSTRACT

Inflammatory bowel disease (IBD) is a chronic immune-mediated condition linked to gut microbiota dysbiosis and altered production of bacterial metabolites, including succinate, which is also a key intermediate in human mitochondrial energy metabolism in human cells. Succinate levels in the gut are influenced by microbial community dynamics and cross-feeding interactions, highlighting its dual metabolic and ecological importance. Extracellular succinate acts as a key signaling metabolite linking microbial metabolism to host physiology, with transient rises supporting metabolic regulation but chronic elevations contributing to metabolic disorders and disease progression. Succinate signals through the its cognate receptor SUCNR1, which mediates adaptive metabolic responses under normal conditions but drives inflammation and fibrosis when dysregulated.

IBD patients display a dysbiotic gut microbiota characterized by an increased prevalence of succinate-producing bacteria, contributing to elevated succinate levels in the gut and circulation. This imbalance drives inflammation, worsens IBD severity, and contributes to complications like *Clostridioides difficile* infection and fibrosis. Emerging evidence highlights the potential of intestinal and systemic succinate levels as indicators of microbial dysbiosis, with a bidirectional relationship between microbial composition and succinate metabolism. Understanding the factors influencing succinate levels and their interaction with dysbiosis shows promise in the development of therapeutic strategies to restore microbial balance. Approaches such as dietary fibre enrichment, prebiotics, and probiotics to enhance succinate-consuming bacteria, combined with targeted modulation of succinate pathways (e.g. SDH inhibitors, SUCNR1 antagonists) hold promise for mitigating inflammation and improving gut health in IBD.

KEYWORDS: succinate, inflammatory bowel disease, dysbiosis, SUCNR1, gut microbiome, inflammation.

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic, immune-mediated condition characterized by inflammation of the gastrointestinal (GI) tract [1]. The two main forms of IBD, Crohn's Disease (CD) and Ulcerative Colitis (UC), lead to a variety of symptoms including abdominal pain, diarrhoea, fatigue, and weight loss, which greatly impact their quality of life. Although the precise cause of IBD is still unclear, it is thought to result from a disruption in the balance between gut-resident microbiota and the mucosal immune system. This imbalance is driven by a combination of genetic and environmental factors, such as diet and stress [2]. Despite there are several treatments available, still there are up to 50% of patients that do not have a sustained response to current therapies [3,4], highlighting the need for a deeper understanding of its pathophysiology.

There is substantial evidence linking IBD to microbial metabolites, which play a crucial role in modulating intestinal health and immune responses [5]. Several studies have demonstrated that IBD patients exhibit alterations in gut microbiota composition, or dysbiosis, which leads to reduced microbial diversity and disruptions in metabolite production. This altered microbial metabolome is increasingly recognized as a potential marker for disease severity and as a target for therapeutic intervention [6–8]. A common trait across both CD and UC is a decrease in beneficial short-chain fatty acid (SCFA)-producing bacteria, such as those that produce butyrate and propionate [9]. These SCFAs have anti-inflammatory properties and are essential for maintaining the integrity of intestinal barrier [10]. However, despite these shared characteristics, UC and CD present distinct microbial and metabolome signatures [11]. Alterations in secondary bile acids [12], tryptophan-derived metabolites, and microbial-derived polyamines and indole compounds [13], all linked to immune modulation, are implicated in IBD. Among these, succinate stands out as a central player in host and microbial processes [14,15].

This review examines succinate's dual role in IBD as a metabolic and signalling molecule, highlighting its contribution to chronic inflammation, gut barrier dysfunction, and fibrosis. It discusses microbial succinate's role in perpetuating inflammation and dysbiosis, evaluates therapeutic strategies targeting succinate, and explores emerging approaches to reduce succinate levels and modulate the microbiota for improved IBD management

REGULATION OF GUT SUCCINATE: BIOCHEMICAL PATHWAYS, MICROBIAL CONTRIBUTIONS, AND THE IMPACT OF DYSBIOSIS

Succinate, a dicarboxylic acid central to energy metabolism, is produced via distinct pathways in human cells and bacteria (Figure 1). In **human cells**, succinate serves as a key intermediate in the TCA cycle within mitochondria. It facilitates electron transfer by reducing FAD to $FADH_2$, which feeds into oxidative phosphorylation to drive ATP production. This mitochondrial pathway situates succinate as a crucial intermediary in cellular respiration, highlighting its role in maintaining energy homeostasis [16]. In addition to the TCA cycle, in the central nervous system, succinate can also be

synthesized through the gamma-aminobutyric acid (GABA) shunt. This alternative metabolic pathway bypasses two steps of the TCA cycle and serves as a link between neurotransmitter metabolism and cellular energy production [17].

Microbial cells, particularly those residing in the gastrointestinal tract, also contribute to succinate production, using distinct anaerobic fermentation pathways that differ from those in human cells (Figure 1). In the GI tract, especially in the distal sections such as the colon, microbial fermentation plays a major role in metabolizing undigested carbohydrates and dietary fibres. This anaerobic fermentation process generates a variety of metabolites, predominantly SCFAs [18], but also gases such as hydrogen and carbon dioxide [19], and organic acids including succinate [14,15,20].

The production of succinate, a metabolite synthesized by multiple bacterial taxa, is highly influenced by interspecies interactions and the dynamics of cross-feeding within microbial communities [21,22]. Within the Bacteroidetes phylum, key succinate producers include the Prevotellaceae and Veillonellaceae families, as well as other species such as *Bacteroides fragilis* and *Bacteroides vulgatus* [23]. Additionally, succinate production is observed among the Firmicutes, such as *Faecalibacterium prausnitzii*, which is notably abundant in IBD [24]. These bacteria rely on anaerobic fermentation pathways, converting substrates like fumarate into succinate. This non-mitochondrial pathway serves as a terminal electron sink in anaerobic conditions, enabling energy conservation and redox balance. Under normal physiological conditions, succinate concentrations in the gut lumen remain low due to rapid utilization by succinate-consuming bacteria, which are distributed across multiple phyla. While Bacteroidetes were initially believed to metabolize succinate into propionate, evidence suggests they predominantly export succinate as an intermediate, likely due to the low energy yield of its conversion to propionate [20,21]. In contrast, genera such as Dialister, Veillonella [25] and Phascolarctobacterium [26], from the Firmicutes family, are recognized as efficient succinate consumers. Therefore, a critical factor that determines the levels of succinate in the gut lumen is the composition and balance of microbial communities. A notable example of this delicate balance is the interaction between *Phascolarctobacterium faecium* and *Bacteroides thetaiotaomicron* in the human gut. While this interaction can promote the beneficial conversion of succinate into propionate, *B. thetaiotaomicron* may also contribute to the proliferation of *Clostridioides difficile* [22,27], highlighting the complexity of these microbial dynamics.

Dietary composition is a critical factor influencing succinate levels in the gut. The availability of fermentable substrates, including complex carbohydrates and fibres, significantly impacts microbial fermentation pathways responsible for succinate production. For example, mice fed a diet supplemented with purified fructooligosaccharides showed elevated cecal succinate levels [28], whereas low concentrations of succinic acid were observed in the cecum of mice fed with fermentable dietary fibre [29]. Moreover, supplementation with refined inulin has been shown to induce abnormal succinate accumulation in the intestinal lumen, which partially contributes to the promotion of colon inflammation and tumorigenesis [30].

Antibiotic use is also a prominent factor contributing to the disruption of succinate production and consumption dynamics within the gut. Broad-spectrum antibiotics can

disrupt microbial balance by disproportionately reducing populations of succinate-consuming bacteria while allowing succinate-producing species to dominate. This microbial imbalance can result in transient succinate accumulation, which may promote pathogenic inflammatory responses and disrupt gut homeostasis. For instance, antibiotic-induced succinate increases in mice have been shown to favour *Clostridioides difficile* proliferation in the disrupted intestine. Furthermore, recent evidence suggests that succinate enhances biofilm formation and help persistence of *C. difficile* [31].

While further research is required, current evidence suggests that both intestinal and systemic succinate levels could serve as potential indicators of microbial dysbiosis [15]. Notably, this relationship between microbial composition and succinate levels appears to be bidirectional. A recent study in mice demonstrated that oral succinate administration promotes intestinal dysbiosis and trends toward increased mucosal inflammation and impaired gut barrier function. These effects become significantly pronounced under LPS-induced inflammatory conditions [32], highlighting the complex interplay between succinate metabolism, microbial dynamics, and host inflammatory responses.

Understanding factors influencing succinate levels and their interaction with dysbiosis is key to developing therapies for restoring microbial balance. As discussed in subsequent sections, interventions such as dietary fibre enrichment, prebiotics, and probiotics to enhance succinate-consuming bacteria, and targeted modulation of succinate pathways show promise in reducing inflammation and improving gut health in IBD.

SUCCINATE: A KEY EXTRACELLULAR SIGNALING MOLECULE AS A GPCR LIGAND

Extracellular succinate accumulation has emerged as a critical link between microbial metabolism and host physiology. Circulating succinate levels transiently rise during physiological contexts such as exercise [33], cold exposure [34], and food intake [35], acting as an endocrine-like signal to regulate metabolic homeostasis [36]. However, chronically elevated succinate levels in pathological conditions contribute to disease progression and metabolic dysregulation. Metabolic disorders, including obesity and type 2 diabetes (T2D), are associated with increased succinate levels, linked to dysbiosis and a distinct succinate-related microbiome [37]. Similarly, as detailed later, substantial evidence demonstrate that IBD is associated with elevated circulating succinate levels, correlating with dysbiosis and disease activity [23,38,39]. Furthermore, aberrant succinate release occurs in other pathological conditions, such as cardiovascular disease [40], rheumatoid arthritis [41], and certain cancers [42], although its potential connection to dysbiosis in these contexts remains unexplored.

In the extracellular space, succinate primarily acts through the SUCNR1 receptor. SUCNR1 exhibits context-dependent signalling, promoting adaptive metabolic responses during physiological conditions but driving inflammation and pathology when succinate levels are dysregulated. This GPCR, located on the plasma membrane of various cell types [43–45], activates intracellular signalling via different G protein subunits. While SUCNR1 was initially thought to function only in pathological states

with chronic succinate elevation, it is now known to regulate physiological processes, including the renin-angiotensin system in the kidney [46], leptin and insulin secretion by adipose tissue and the pancreas, respectively [35,36], and muscle remodelling [34]. In pathological conditions, succinate-SUCNR1 dysregulation contributes to fibrosis and chronic inflammation, as extensively reviewed elsewhere [47].

SUCCINATE AND THE GUT MICROBIOME IN IBD

Patients with IBD often exhibit a dysbiotic microbiota profile characterized by a reduction in beneficial commensal bacteria, such as *Firmicutes* and *Bacteroides*, alongside an increased abundance of Enterobacteraceae [7,48]. Specifically, a marked decreased in *Faecalibacterium prausnitzii* and *Prevotella* sp. has been observed, coupled with an increased prevalence of potentially pathogenic bacteria such as *Enterococcus faecium*, *Enterococcus faecalis*, and *Escherichia coli* [24]

Recent studies have shown that the disruption in the balance between succinate-producing and succinate-consuming bacteria is reflected in the accumulation of succinate in feces and circulation [23]. An overrepresentation of succinate-producing bacteria, such as *Bacteroides fragilis* and *B. vulgatus,* has been reported in the colon of patients with UC and in mouse models of colitis induced by DSS or TNBS [23]. Conversely, a reduced abundance of succinate-consuming bacteria, such as *Phascolarctobacterium succinatutens,* has been observed in the intestine of CD patients [23].

Gut microbiota-derived succinate promotes *Clostridioides difficile* infection [27], which is more frequent in IBD patients [49]. Although *C. difficile* is a succinate-consumer, its overgrow in IBD is facilitated by elevated succinate availability, exacerbating intestinal inflammation [27]. A recent study identified two bacterial genera, *Phascolarctobacterium* and *Dialister*, as fast and slow succinate-consumers, respectively, leading to the proposed microbiome classification “succinotype”. Notably, the *Dialister* succinotype, more prevalent in IBD patients, reinforces the connection between succinate metabolism and IBD pathophysiology [50].

Despite clear imbalances between succinate producers and consumers in IBD, the reported succinate levels from intestinal tissue and faeces remain inconsistent. While some studies indicate increased levels [23,38], others show no significant changes in succinate levels among IBD patients [50,51], likely due to methodological differences in sample handling, storage and analysis, complicating fecal TCA metabolite detection and interpretation [52].

Conversely, targeted metabolomics consistently report increase plasma [39] or serum succinate [23,38] in UC and CD patients relative to healthy controls. Disrupted intestinal transepithelial succinate transport [23] and increased gut permeability during IBD, suggest systemic succinate accumulation stems, at least partly, from elevated intestinal levels. Since succinate activates inflammatory pathways in peripheral organs, elevated circulating levels may contribute to the extra-intestinal manifestations commonly observed in IBD.

THE SUCCINATE-SUCNR1 AXIS IN IBD: INFLAMMATION, BARRIER INTEGRITY, AND FIBROSIS

Elevated succinate levels, driven by microbial dysbiosis and altered host metabolism, results in excessive SUCNR1 activation, which modulates key IBD processes, including inflammation, impaired intestinal barrier integrity, and tissue remodelling.

Inflammation. The succinate-SUCNR1 axis plays a dual role in IBD by acting on macrophages and tuft cells, where SUCNR1 is highly expressed. SUCNR1 activation contributes to both acute inflammation and resolution [53]. However, in pathological contexts, such as IBD, aberrant SUCNR1 signalling perpetuates inflammation and exacerbates disease progression. SUCNR1 knockout mice with chemically induced colitis show reduced pro-inflammatory cytokine production (e.g. IL-1β and IL-6) and are protected against colitis [38]. Furthermore, *in vitro* studies demonstrated that increased luminal succinate uptake by macrophages activated with LPS sustains inflammation [23]. Microbial succinate activates SUCNR1 in tuft cells of the intestinal epithelium by microbial succinate promotes type 2 immune responses, epithelial cell proliferation, and antimicrobial peptides production by Paneth cells. These processes help resolve inflammation and reshape the microbiota, to prevent invasion by pathogens [54–56]. Consistently, inflamed ileal tissues from IBD patients and mouse models show reduced tuft cell numbers compared to healthy individuals [57,58]. In a mice model of IBD, tuft cell expansion has been reported to reduced chronic intestinal inflammation.

Barrier Integrity. Compromised barrier integrity is central to IBD pathogenesis [47], with conflicting evidence regarding succinate's role. In healthy rats, succinic acid infusion impaired colonic cell proliferation and reduced crypt size [59], suggesting a detrimental effect. Conversely, in obesity models, dietary succinate restored mucosal barrier function, promoted goblet cell differentiation, and improved dysbiosis [60]. Similarly, in pigs, orally-administered succinate enhance epithelial integrity but also induced inflammatory cytokine expression [61]. These findings underscore the context-dependent effects of succinate on barrier function, necessitating further investigation.

Fibrosis. Elevated succinate and SUCNR1 overactivation drive fibrosis in chronic IBD, as observed in other pathological conditions like MASLD [62]. Fibrosis involves TGF-β production, inflammatory cell recruitment, and myofibroblast activation [38]. SUCNR1 activation promotes profibrotic factors (e.g. TGF-β , α-SMA, Col1a1) [38] and triggers epithelial-to-mesenchymal transition via Wnt signaling [63]. Fibrosis in CD is typically transmural, causing strictures and obstructions, while in UC, fibrosis is rare and limited to the mucosa [64]. Further studies are needed to clarify the succinate/SUCNR1 axis's specific role in fibrosis.

THERAPEUTIC POTENTIAL OF TARGETING GUT MICROBIOTA-RELATED SUCCINATE PATHWAYS

Targeting the gut microbiota and its metabolites offers a multifaceted strategy for IBD management. Prebiotics and probiotics have been extensively studied, but discrepancies remain between findings in animal models and human studies [65]. Regarding microbiota-derived succinate, the probiotic *Clostridium butyricum* reduces intestinal succinate levels in mouse models of intestinal inflammation caused by

Clostridioides difficile infection, increasing succinate-consuming bacteria, decreasing succinate producers, and reducing intestinal inflammation [66]. In DSS-induced colitis models, *C. butyricum* enhances anti-inflammatory macrophages [67], reduces pro-inflammatory macrophages, and enhances barrier function via its probiotic effects and extracellular vesicles, leading to decrease disease activity [68,69]. A biotherapeutic consortium of multiple *Clostridia* strains (VE202) promotes colonic regulatory T (Treg) cells and shows efficacy in colitis models [70], which Phase I trials indicating good tolerance in humans [71].

Certain dietary interventions also reduce succinate levels. For example, a hypocaloric Mediterranean diet combined with exercise decreases the succinate producer-to-consumer ratio and succinate levels in patients with obesity [37]. Similarly, fermented rice bran supplementation lowers succinate in diet-induced obesity models [72], though none of these interventions has been tested in IBD.

Fecal Microbiota Transplantation (FMT) shows promise in IBD but suffers from limited research, low success rates, lack of standardized protocol [73], and insufficient statistical significance, likely due to poor mechanistic understanding and procedure optimization [74].

Antibiotics, though widely used in IBD management, present risks, including treatment intolerance, increased susceptibility to *Clostridioides difficile* infection, and antibiotic resistance [75]. Long-term antibiotic use and low dietary fibre intake disrupt host-microbiota symbiosis, positioning antibiotics as a potential risk-factor for IBD [76].

Pharmacological strategies targeting the succinate/SUCNR1 axis also offer promise. SDH inhibitors reduce succinate accumulation and show efficacy in cancer models [77], while SUCNR1 antagonists might block succinate signalling to reduce inflammation and fibrosis. Although these approaches hold potential, they remained unexplored in the context of IBD [78,79].

FUTURE RESEARCH DIRECTIONS

Future research is essential to clarify how microbiota-derived succinate contributes to dysbiosis and drives IBD pathogenesis, and to identify effective therapeutic strategies. Approaches like SDH modulation and SUCNR1 inhibition remain untested in IBD, with SUCNR1 blockade potentially causing adverse effects by disrupting its physiological functions. Reducing circulating succinate alone may be insufficient if intestinal succinate remains the primary driver of metabolic dysfunction [80]. FMT has shown limited success, likely due to patient heterogeneity, emphasizing the need for more specific microbiota-based targets [73]. Targeted therapies focusing on microbial succinotypes capable of metabolizing succinate more effectively could improve outcomes Future strategies may include dietary interventions, prebiotics or probiotics to increase succinate-consuming bacteria. Innovative approaches such as blocking agents (e.g., peptides or antibodies) or modulation of microbial enzymes involved in succinate metabolism hold promise for IBD and other conditions with elevated succinate, including metabolic and cardiovascular diseases.

ACKNOWLEDGEMENTS

We thank all past and present members of the DIAMET lab for their valuable contributions and insightful discussions.

FUNDING

Research is supported by grants from the Spanish Ministry of Science and Innovation MCIN/AEI/10.13039/ 501100011033 (RTI2018-093919-B-100 and PID2021-122480OB-100 and PDC2022-133164-I00 to SF-V; PTQ2022-012572 to C. G-B and PTQ2023-012978 to S.N), co-financed by the European Regional Development Fund (ERDF), and from CIBER -Consorcio Centro de Investigación Biomédica en Red (CB07708/0012), Instituto de Salud Carlos III, Ministerio de Ciencia e Innovación. Work also received financial support by "La Caixa" Foundation through grant agreement LCF/TR/CI23/56000014 (CI23-20043 to I. H-R), and grant agreement LCF/PR/HR20/52400013 (ID 100010434 to SF-V). SF-V acknowledge support from the Agency for Management of University Research Grants of the Generalitat de Catalunya (2021 SGR 01409).

We also acknowledge funding support from ACCIO, the public agency for the competitiveness of Catalan enterprise (ACE052/22/000049) and the CDTI (SNEO-20231359).

Author's relationships and activities SF-V and IH-R are co-founders of SucciPro, S.L. No aspect of this article has been influenced by this relationship, nor is there any perceived influence on the work. All authors declare that there are no relevant relationships or activities that could bias, or be perceived to bias, their research efforts.

Contribution statement SF-V designed and conceived the outline of this review. SF-V, IH-R, CG-B, and SN wrote the original draft, reviewed and edited the manuscript. CG-B prepared and designed the figures. All authors approved the final manuscript.

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Declaration of Interest Statement

Author's relationships and activities SF-V and IH-R are co-founders of SucciPro, S.L. No aspect of this article has been influenced by this relationship, nor is there any perceived influence on the work. All authors declare that there are no relevant relationships or activities that could bias, or be perceived to bias, their research efforts.

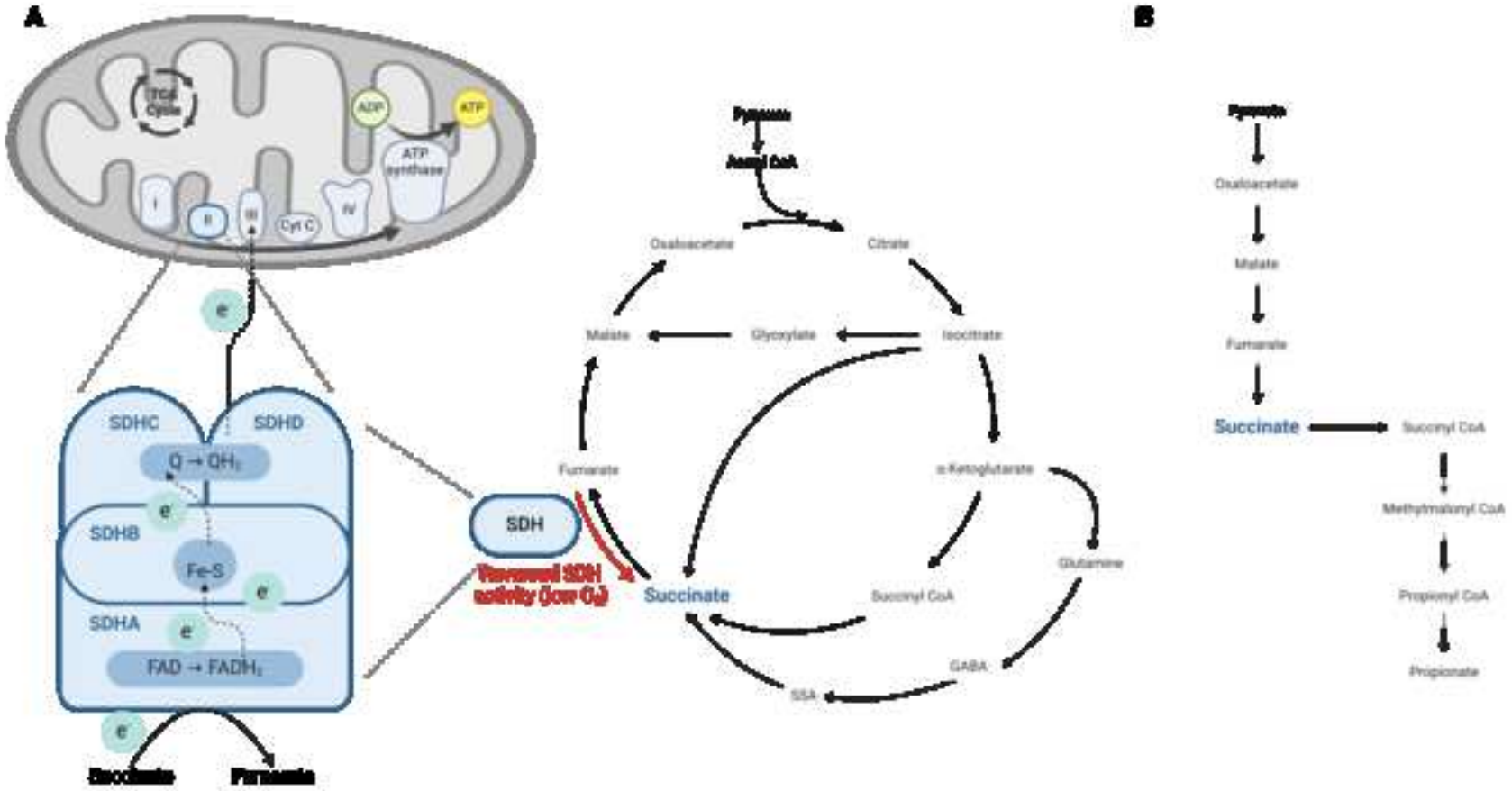
Contribution statement SF-V designed and conceptualized the outline of this review. SF-V, IH-R, CG-B, and SN wrote the original draft, reviewed and edited the manuscript. CG-B prepared and designed the figures. All authors approved the final manuscript.

Figure captions

Graphical abstract. Effects of succinate on IBD. Succinate plays a key role in the progression of Inflammatory Bowel Disease (IBD) by contributing to chronic inflammation, fibrosis, and dysbiosis. The mechanisms linking IBD and dysbiosis remain poorly understood. However, its development is influenced by genetic predisposition, immune dysregulation, intestinal barrier dysfunction, and environmental factors. Dysbiosis appears to function both as a driver and a consequence of IBD, sustaining inflammation and microbiota-host imbalances through a bidirectional feedback loop. In IBD, an imbalance between succinate-producing and succinate-consuming microbes in the microbiota is often observed. This imbalance leads to increased succinate production in the gut lumen, where it exerts multiple effects. Within the epithelial barrier, succinate activates the SUCNR1 receptor on Tuft cells, which activates Type 2 immunity, which its cell count is reduced in IBD. Additionally, succinate activates SUCNR1 on epithelial cells, triggering the pro-fibrotic factor TGF-1β and Wnt signalling pathways, which promote epithelial-to-mesenchymal transition (EMT) and fibrosis. Succinate can also cross the epithelial barrier, either through transport mechanisms or via epithelial injury, activating SUCNR1 in pro-inflammatory macrophages and stimulating the release of pro-inflammatory cytokines. This combination of inflammatory and fibrotic responses creates a vicious cycle that amplifies disease progression. Figure created with BioRender. https://BioRender.com/d73i553.

Figure 1. Succinate production pathways in host cells and gut microbiota. (A) In host mitochondria, succinate serves as an intermediate metabolite within the tricarboxylic acid (TCA) cycle. It is generated through the conversion of succinyl-CoA and subsequently oxidized by succinate dehydrogenase (SDH) to produce fumarate. SDH plays a dual role in mitochondrial respiration and the TCA cycle by transferring electrons (e^-) from succinate to flavin adenine dinucleotide (FAD), iron-sulfur clusters (Fe-S), and ubiquinone (Q) through its four subunits: SDHA, SDHB, SDHC, and SDHD. As part of mitochondrial complex II, SDH links the TCA cycle to the electron transport chain, facilitating ATP production. Additionally, succinate can be synthesized via the γ-aminobutyric acid (GABA) shunt from succinic semialdehyde (SSA) or through the glyoxylate shunt from isocitrate. Under low oxygen conditions, succinate may accumulate due to the reversal of SDH activity. (B) In microbial fermentation, succinate is primarily produced via the reversal of specific TCA cycle reactions. Pyruvate is carboxylated to generate oxaloacetate, which is subsequently reduced to malate, fumarate, and finally succinate. The metabolic fate of succinate, including its conversion to propionate, is determined by bacterial species and environmental conditions. Figure created with BioRender. https://BioRender.com/f34e123.

Figure 1


A
TCA Cycle
ATP
ATP
ATP synthase
I
II
III
Cyt C
IV
e
SDHC
SDHD
Q → QH2
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SDHB
Fe-S
e
SDHA
e
FAD → FADH2
e
Succinate
Fumarate
SDH
Reversed SDH activity (low O2)
Pyruvate
Acetyl CoA
Oxaloacetate
Citrate
Isocitrate
Glyoxylate
Malate
Fumarate
α-Ketoglutarate
Glutamine
Succinyl CoA
Succinate
GABA
SSA
B
Pyruvate
Oxaloacetate
Malate
Fumarate
Succinate
Succinyl CoA
Methylmalonyl CoA
Propionyl CoA
Propionate

HIGHLIGHTS

- Succinate links microbial activity with host health through metabolic and community interactions.
- Elevated succinate levels drive inflammation and disease progression in IBD via SUCNR1 receptor dysregulation.
- Increased succinate-producing bacteria in IBD patients worsens inflammation.
- Intestinal and systemic succinate levels indicate microbial dysbiosis and IBD severity.
- Prebiotics, probiotics, and targeting succinate pathways (e.g., SDH inhibitors, SUCNR1 antagonists) may reduce inflammation and improve gut health

Graphical Abstract