W J G World Journal of Gastroenterology

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World J Gastroenterol 2025 December 7; 31(45): 112618

DOI: 10.3748/wjg.v31.i45.112618

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Basic Study

Dialister-driven succinate accumulation is associated with disease activity and postoperative recurrence in Crohn's disease

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Specialty type: Oncology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade A, Grade A, Grade C

Novelty: Grade B, Grade B, Grade C

Creativity or Innovation: Grade B, Grade B, Grade C

Scientific Significance: Grade B, Grade B, Grade C

P-Reviewer: Ding H, PhD, China; Kaur A, PhD, Assistant Professor, India

Received: August 1, 2025

Revised: August 29, 2025

Accepted: October 17, 2025

Published online: December 7, 2025

Processing time: 124 Days and 17.8 Hours

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Abstract

BACKGROUND

Succinate, a metabolite produced by both the gut microbiota and the host, has emerged as a key player in chronic inflammation. In patients with Crohn's disease (CD), increased succinate in the intestinal lumen correlates with both dysbiosis and greater disease activity.

AIM

To investigate circulating succinate as a biomarker of CD activity and its associations with gut microbiota, immune, and clinical features.

METHODS

This study with the prospective inclusion of patients with CD in remission, active CD, and non-inflammatory bowel disease controls matched by age, sex, and body mass index. Remission was defined as Harvey-Bradshaw index < 6, C-reactive protein < 0.4 mg/dL, fecal calprotectin < 250 μg/g, and endoscopic activity index Simple Endoscopic Score for CD < 6. Faecal microbiota profiling was performed using 16S rRNA gene sequencing, and demographic, clinical, and treatment variables were recorded along with blood samples (C-reactive protein and succinate) and stool samples.

RESULTS

Succinate levels were significantly elevated in active CD patients compared to inactive patients and non-inflammatory bowel disease controls. These increases were associated with higher Harvey-Bradshaw Index scores, increased expression of the succinate receptor 1 in immune cells, and enrichment of the succinate-producing genus *Prevotella* and the pro-inflammatory phylum Proteobacteria. Conversely, succinate levels negatively correlated with *Odoribacter*, a known succinate consumer. Interestingly, *Dialister*, a slow succinate consumer, was enriched in both active and inactive CD patients and was associated with impaired circulating succinate clearance and increased disease activity as well as postoperative recurrence in a validation cohort. Functional microbial analyses revealed upregulation of fumarate reductase and succinate transporters, alongside reduced NADH dehydrogenase expression, indicating disrupted succinate metabolism.

CONCLUSION

These findings highlight succinate as a promising biomarker for CD activity and progression, suggesting that targeting succinate metabolism or key microbial taxa may offer novel therapeutic opportunities.

Key Words: Crohn's disease; Succinate; *Dialister*; Biomarker; Postoperative recurrence; Inflammatory bowel diseases; Succinic acid; Gut microbiota; *Prevotella*; *Escherichia coli*

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Core Tip: The study reported that circulating succinate, a microbial and host metabolite, are markedly elevated in patients with Crohn's disease. Interestingly, we found that succinate strongly correlates with inflammatory activity and is linked to changes in the gut microbiota, including an increased abundance of the slow succinate consumer genera *Dialister*. Importantly, the presence of the *Dialister* in intestinal tissue was also associated with post-operative recurrence in these patients. These findings highlight succinate as a promising biomarker for disease activity and progression in Crohn's disease and suggest that targeting succinate metabolism or modulating specific microbial taxa could open new therapeutic opportunities.

Citation: Boronat-Toscano A, Queipo-Ortuño MI, Monfort-Ferré D, Suau R, Vañó-Segarra I, Valldosera G, Cepero C, Astiarraga B, Clua-Ferré L, Plaza-Andrade I, Aranega-Martín L, Cabrinety L, Abadia de Barbarà C, Castellano-Castillo D, Moliné A, Caro A, Domènech E, Sánchez-Herrero JF, Benaiges-Fernandez R, Fernández-Veledo S, Vendrell J, Ginés I, Sumoy L, Manyé J, Menacho M, Serena C. *Dialister*-driven succinate accumulation is associated with disease activity and postoperative recurrence in Crohn's disease. *World J Gastroenterol* 2025; 31(45): 112618

URL: https://www.wjgnet.com/1007-9327/full/v31/i45/112618.htm

DOI: https://dx.doi.org/10.3748/wjg.v31.i45.112618

INTRODUCTION

Crohn's disease (CD) is a chronic, relapsing form of inflammatory bowel disease (IBD) that profoundly affects the gastrointestinal tract through a complex interplay of immune dysregulation, genetic predisposition, and environmental influences[1]. Under physiological conditions, the gut microbiota plays a pivotal role in maintaining immune homeostasis and regulating systemic metabolic processes. However, in CD, the gut microbiota exhibits a distinct microbial profile and reduced diversity compared to healthy subjects[2,3]. Despite these findings, it remains unclear whether dysbiosis is a primary driver of inflammation[4,5] or a secondary consequence of the disease[6]. One notable microbial alteration in CD is the enrichment of the phylum Proteobacteria, particularly *Escherichia coli* (*E. coli*), which is frequently found with increased abundance within the intestinal mucosa. Among these, adherent-invasive *E. coli* (AIEC) strains have been strongly implicated in CD pathogenesis due to their ability to adhere to and invade intestinal epithelial cells, evade autophagy, and elicit excessive immune activation[7]. Importantly, the presence of AIEC in resected tissue has also been linked to an elevated risk of endoscopic postoperative recurrence (POR)[8]. In addition to *E. coli*, other members of the Enterobacteriaceae family, such as *Klebsiella pneumoniae* and *Salmonella enterica*, have also been detected in higher abundances in CD patients, potentially contributing to persistent inflammation[9]. Another genus of concern is *Fusobacterium*, particularly *Fusobacterium nucleatum* and *Fusobacterium varium*, which have been shown to disrupt epithelial barrier function and stimulate pro-inflammatory cytokine production, including interleukin-8 and tumour necrosis factor-alpha[10]. Further microbial shifts include increased presence of the *Prevotella* species although their role in CD remains contentious[11]. Some evidence suggests that certain *Prevotella* strains contribute to mucosal inflammation *via* modulation of immune responses or secretion of inflammatory metabolites, while other studies suggest a protective role influenced by dietary patterns, geographical factors, and microbial context[12-14]. Of particular interest is the ability of *Prevotella* species, including *Prevotella copri*, to influence gut metabolite production. Although not major producers of butyrate, these bacteria may impact the broader metabolic output of the microbiota - either promoting succinate accumulation or indirectly affecting butyrate-producing taxa, depending on environmental context and microbial interactions. This highlights how specific taxa may impact CD pathogenesis not only through immune modulation, but also *via* shifts in microbial metabolite profiles. Among microbial metabolites, short-chain fatty acids (SCFAs) such as butyrate, propionate, and acetate play vital roles in maintaining intestinal barrier integrity and promoting immune tolerance[15,16]. Disruptions in their production can result in increased epithelial permeability and immune activation through bacterial translocation. Consequently, changes in microbial composition and function - particularly regarding metabolite output - are now recognised as central to CD pathophysiology. Consequently, key bacterial metabolites like butyrate and its metabolic intermediates are gaining interest as potential biomarkers for disease activity and progression[17]. Succinate, a central metabolite in the tricarboxylic acid (TCA) cycle, is produced by both host cells and the microbiota, and has recently emerged as a metabolite of interest due to its immunoregulatory properties. It exerts its effects through activation of succinate receptor 1 (SUCNR1)[18] and the stabilisation of hypoxia-inducible factor 1-alpha[19]. These effects contribute to macrophage polarisation and amplify cytokine release, creating a feedback loop that sustains inflammation [19]. Succinate's dual role as both a metabolic fuel and a signaling molecule enables it to influence immune responses in diverse, context-dependent ways. In particular, extracellular succinate interacts with SUCNR1 to regulate immune cell activity, thereby fine-tuning inflammatory responses[20]. Although succinate can elicit divergent effects depending on the tissue and disease context[21], its role in amplifying inflammation in CD positions it as a key target for therapeutic intervention. Despite these emerging insights, the dynamic interplay between gut microbiota alterations, succinate metabolism, and systemic inflammation in CD remains incompletely understood. Addressing this gap is essential for the identification of novel disease biomarkers and the development of targeted therapeutic strategies. Recent findings, including data from our group, have further substantiated the role of succinate in CD pathogenesis. We have demonstrated that patients with active CD exhibit significantly higher circulating succinate levels compared to those in remission[22]. In parallel, succinate-producing pathobionts such as AIEC and other Enterobacteriaceae are enriched in the microbiota of CD patients[23,24]. Conversely, beneficial succinate-consuming commensals, such as *Phascolarctobacterium spp.*[25], which help regulate luminal succinate levels, are significantly reduced in this pathogenic environment[26,27]. This highlights a direct link between microbial dysbiosis and altered succinate metabolism. Thus, we propose that systemic succinate accumulation results from a combination of reduced succinate-consuming microbes and an increased abundance of succinate-producing bacteria. In this study, we aim to investigate the interplay between gut microbiota composition, succinate metabolism, and inflammatory activity in CD. Through an integrated approach combining microbial profiling, metabolic quantification, and immunological characterisation, our goal is to elucidate the mechanistic connections between dysbiosis and inflammation, thereby contributing to biomarker discovery and therapeutic innovation in CD.

MATERIALS AND METHODS

Study design and patients

This study included three groups: Active CD patients (n = 10), inactive CD patients (n = 8), and non-IBD individuals (n = 13), recruited between October 2021 and September 2022 at the Joan XXIII University Hospital of Tarragona (HJ23) and IISPV. Inclusion criteria for CD patients were a confirmed diagnosis of CD per European Crohn's and Colitis Organisation criteria, age 18-70 years and signed informed consent. CD remission was defined by a Harvey-Bradshaw Index < 6, C-reactive protein (CRP) < 0.4 mg/dL, fecal calprotectin < 250 μg/g, and Simple Endoscopic Score for CD < 6 (or < 4 if confined to the ileum); patients not meeting these criteria were classified as active CD. Exclusion criteria included severe comorbidities, systemic inflammatory diseases, recent infection, or antibiotic use. Variables assessed included demographics, clinical characteristics, dietary and physical activity questionnaires, routine blood tests (*e.g.*, CRP), and biomarkers (*e.g.*, succinate) as indicated in Table 1. Fecal samples were collected for fecal calprotectin and microbiota analysis. Samples were obtained within two weeks of recruitment.

Isolation of peripheral blood mononuclear cells

Peripheral blood mononuclear cells (PBMCs) were isolated with Pancoll human MSL (Pan Biotech GmbH, Aidenbach, Germany) for all the cohort. Pellets were frozen and stored at -80 °C until RNA extraction.

Real time quantitative polymerase chain reaction gene expression profiling

RNA was extracted from PBMCs using the TriPure Isolation Reagent (Roche, Switzerland). RNA concentration was determined by absorbance at 260 nm, and purity was estimated with a Nanodrop spectrophotometer (Nanodrop Technologies, DE, United States). cDNA was synthesized using SuperScript II reverse transcriptase and random hexamer primers (Invitrogen Life Technologies, CA, United States). Quantitative gene expression was evaluated by real-time polymerase chain reaction (PCR) on a 7900HT Fast Real-Time PCR System using the TaqMan Gene Expression Assay (Applied Biosystems, MA, United States). Genes are listed in Supplementary Table 1.

Validation design of an independent post-surgical recurrence cohort

Inflamed and uninflamed ileal tissues from CD patients (n = 66) undergoing ileocolonic resection were collected. A total of 60 inflamed and 57 non-inflamed ileal samples were included in this study. Demographic and epidemiological features (age, smoking habits, body mass index) and intestinal resection characteristics were recorded in Supplementary Table 2. CD was diagnosed by Lennard-Jones[28] criteria and classified by Montreal classification[29]. To classify patients depending on POR, these were monitored with ileocolonoscopy every six months over a two-year postoperative period. At the end of this follow-up, they were classified as non-recurrent (NR, i0 and i1) or severe recurrent (SR, i3 and i4) based on the Rutgeerts score[30]. These samples were collected at the Germans Trias i Pujol Research Institute for subsequent microbiota analysis at the High Content Genomics and Bioinformatics Unit, IGTP, Badalona, Spain.

Fecal microbiome analysis

Faeces, ileal tissue sample processing, DNA extraction and gut microbiota sequencing. Faeces and ileal tissue samples were processed for DNA extraction and gut microbiota sequencing. DNA was extracted from 200 mg aliquots using the QIAamp Fast DNA Stool Mini kit (Qiagen, Hilden, Germany) for faecal samples and the Nucleospin® Tissue kit (Machery-Nagel, Germany) for ileal tissue samples, which comprised the validation cohort. DNA concentration (A260) and purity (A260/A280 ratio) were assessed using a Nanodrop spectrophotometer (Nanodrop Technologies, Wilmington, DE, United States). For DNA amplification in faecal samples, the Ion 16S Metagenomics kit (Thermo Fisher Scientific, Madrid, Spain) was used, encompassing a primer pool targeting multiple variable regions (V2-4-8 and V3-6, 7-9) of the 16S rRNA gene. Barcoded libraries were generated using the Ion Plus™ Fragment Library Kit (Thermo Fisher Scientific, Madrid, Spain) and sequenced *via* emulsion PCR on an Ion 530 chip using the Ion Torrent S5™ system and Ion 510/520/530 Kit-Chef according to the manufacturer's instructions. For ileal tissue DNA (validation cohort), a modified single-step amplification approach based on the 16S Metagenomic Sequencing Library Preparation kit (Illumina, CA, United States) was used. Dual-index primers targeted the V4 hypervariable region. Amplicons underwent quality control using the Agilent D1000 ScreenTape System, followed by equimolar pooling and purification *via* low-melting agarose gel. Sequencing was performed on the MiSeq System (Illumina, CA, United States) with 15% PhiX control, ensuring > 85% clusters passing filter. Sequencing depth and quality control metrics in the validation cohort were comparable to those of the primary cohort. Preoperative medication use was recorded (Supplementary Table 2) and did not differ between recurrence groups.

Bioinformatics analysis

Faeces samples: Analysis of 16S rRNA amplicons was conducted using QIIME2 (version 2023.7). Quality sequences were processed into amplicon sequence variants (ASVs) using DADA2, with parameters adapted for Ion Torrent data. The ASV obtained through the DADA2 pipeline were merged into a consolidated feature table using the q2-feature-table plugin. Using the q2-vsearch plugin with 97% sequence similarity, all ASVs from the merged feature table underwent clustering into operational taxonomic units (OTUs) employing the Open Reference Clustering method against Greengenes version 13_8, aligning at 97% similarity with OTU reference sequences. Taxonomy assignment to the OTUs was carried out using the q2-feature-classifier classify-sklearn naive Bayes taxonomy classifier. Differential bacteria abundance was analyzed using the DESeq2 (v1.22.2) Bioconductor package with multiple testing correction applied using the Benjamini-Hochberg method, considering a q value of less than 0.05 as significant. Alpha diversity metrics (Shannon

Table 1 Demographic characteristics and clinical data, *n* (%)

	Non-IBD	Inactive CD	Active CD
n	13	8	10
Age, mean ± SD	45.00 ± 10.70	51.62 ± 13.42	39.20 ± 22.19
Gender (male/female)	6/7	3/5	4/6
BMI, kg/m^2, mean ± SD	23.96 ± 3.25	27.02 ± 4.80	23.15 ± 3.64
Smoking status			
Current smoker	4 (30.8)	0 (0.0)	3 (30.0)
Ex-smoker	3 (23.1)	4 (50.0)	4 (40.0)
Never smoker	6 (46.2)	4 (50.0)	3 (30.0)
Years of evolution, mean ± SD	NA	17.38 ± 6.32	5.90 ± 7.32[a]
Surgical resection	NA	1 (12.5)	1 (10)
Corticosteroids	NA	3 (37.5)	0 (0.0)
Thiopurines	NA	3 (37.5)	3 (30)
Anti-TNF treatment	NA	2 (25)	1 (10)
Other biologics	NA	0 (0.0)	0 (0.0)
Antibiotic	NA	0 (0.0)	0 (0.0)
Probiotic	NA	0 (0.0)	0 (0.0)
Age at diagnosis			
A1	NA	2 (25)	2 (20)
A2	NA	3 (37.5)	5 (50)
A3	NA	3 (37.5)	3 (30)
Location			
L1	NA	0	2 (20)
L2	NA	6 (75)	5 (50)
L3	NA	2 (25)	3 (30)
Behaviour			
B1	NA	7 (87.5)	6 (60)
B2	NA	0	0
B3	NA	1 (12.5)	4 (40)
Harvey-Bradshaw index (IQR)	NA	0.00 (0.00, 0.25)	4.50 (3.25, 8.25)[a]
C-reactive protein (IQR), mg/dL	NA	0.40 (0.40, 0.48)	1.20 (0.72, 1.80)[a]
Calprotectin (IQR), μg/g	NA	35.75 (27.00, 45.45)	464.90 (215.95, 667.50)[a]
SES-CD, mean ± SD	NA	0.80 ± 1.79	12.22 ± 6.59[a]
Succinate, μM, mean ± SD	104.38 ± 10.72	124.76 ± 39.19[a]	156.71 ± 28.94[a,b]

[a]$P < 0.01$, significant differences compared with non-inflammatory bowel disease.
[b]$P < 0.05$, significant differences compared with inactive disease.
Age at diagnosis: A1 < 16 years; A2 17-40 years; A3 > 40 years; location: L1 = ileal; L2 = colonic; L3 = ileocolonic; behavior: B1 = non-stenotic, non-fistulizing Crohn's disease; B2 = stenotic Crohn's disease; B3 = fistulizing Crohn's disease. IBD: Inflammatory bowel disease; CD: Crohn's disease; BMI: Body mass index; TNF: Tumor necrosis factor; IQR: Interquartile range; SES-CD: Simple Endoscopic Score for Crohn's disease; NA: Not available.

and Chao1), beta diversity metrics (Bray-Curtis dissimilarity), and principal coordinate analysis were computed using the q2-diversity plugin. Significance of alpha diversity was determined using the Kruskal-Wallis test, while significance of beta diversity was assessed using the non-parametric ANOSIM test.

Ileal samples: The microbiome analysis was conducted also using QIIME2, following a standard workflow to process and

analyze 16S rRNA gene sequences[31]. Before using QIIME2, data was trimmed using TrimGalore software and quality checked with MultiQC software. Subsequently, the samples were processed as described above.

Circulating succinate measurement

Fluorimetric method: Circulating serum/plasma succinate levels were measured using the EnzyChromTM Succinate Assay Kit (BioAssay Systems, Hayward, CA, United States). The assay sensitivity was 12 μmol/L and the intra- and inter-assay co-efficients of variance were less than 3.5% and 6.95%, respectively.

Sample stratification by Dialister or Phascolarctobacterium succinotypes

Although many intestinal bacteria possess the metabolic capacity for succinate utilization, the genera *Dialister* and *Phascolarctobacterium* have been identified as the primary succinate consumers in the human gut microbiome[32]. Building on the succinotype stratification framework first established by Anthamatten *et al*[32], we followed the previously described methodology[32,33] to investigate whether our succinotypes are associated with disease activity and POR exploring their correlation with circulating succinate levels. To classify samples based on succinotype, we first classified on the genus level as either *Dialister* or *Phascolarctobacterium* using the assign Taxa function from the DADA2 package. Then, the relative *Dialister* ratio was stablished as rD = nD/(nD + nP), being n the read counts of *Dialister* (D) and *Phascolarctobacterium* (P), respectively. After that, a clear *Dialister*-phenotype (D-phenotype) was assigned to a sample when rD > 0.9 and a clear *Phascolarctobacterium*-phenotype (P-phenotype) was assigned if rD < 0.1 of *Phascolarctobacterium vs Dialister*, or *vice versa*. Samples with fewer than 10 combined *Dialister* and *Phascolarctobacterium* counts were not considered.

Statistical analysis

Statistical analyses were carried out using SPSS software version 15.0 (SPSS Inc., Chicago, IL, United States) and R version 3.3.3. Clinical and anthropometric variables following a normal distribution are expressed as mean ± SD, whereas non-normally distributed variables are presented as median with interquartile range (25th-75th percentile). Comparisons between groups for normally distributed variables were conducted using Student's *t*-test with Bonferroni correction. For non-parametric data, the Kruskal-Wallis test followed by Dunn's *post hoc* test was applied. Categorical variables were compared using the χ^2 test. For microbiota data, differences between groups were assessed using the unpaired Mann-Whitney *U* test. Microbiota comparisons across three or more groups were additionally analysed using two-way ANOVA followed by Kruskal-Wallis test. Lifestyle and medication variables (dietary habits, physical activity, smoking, and medication use) were recorded and examined in univariate analyses. Given the limited sample size and the large number of potential covariates, robust multivariate modelling was not feasible without risking model overfitting and unstable estimates. Functional metagenomic and metabolomic differences were visualised using hierarchical clustering and heatmap representations. Graphs and visualisations were generated with GraphPad Prism version 6.0 (GraphPad Software Inc., San Diego, CA, United States). Pearson's correlation coefficients, adjusted with Bonferroni correction, were used to assess associations between clinical, biochemical and microbiome variables. To determine variables independently associated with circulating succinate levels, multiple linear regression analyses with stepwise forward selection were performed. All variables significantly associated in univariate analysis were included in the models. A $P < 0.05$ was considered statistically significant. Artificial intelligence (OpenAI ChatGPT) was used for data visualization code generation (Supplementary Figures 1 and 2). All scripts were subsequently reviewed, manually edited, and executed by the authors using Google Colab.

RESULTS

Alterations in microbial diversity and composition in active and inactive CD patients

Baseline demographic variables (sex, age, and body mass index) did not differ significantly among groups (Table 1). We next evaluated differences in microbial diversity. A significant reduction in alpha diversity was observed in the inactive CD group compared with the non-IBD group, as measured by the Fisher index ($P = 0.036$) and the Shannon index ($P = 0.015$) (Figure 1A). Alpha diversity was also significantly lower in the active CD group than in the non-IBD group across all four indices assessed: Fisher ($P = 0.0015$), Shannon ($P = 0.0032$), Chao1 ($P = 0.019$), and ACE ($P = 0.038$) (Figure 1A). Although a consistent trend towards reduced alpha diversity was observed in active *vs* inactive CD, none of the four indices reached statistical significance (Figure 1A). Beta diversity measured using the Jaccard and Bray-Curtis indices, also revealed a significant shift, as indicated by global ANOSIM ($r = 0.1915$, $P < 0.002$), suggesting distinct clustering of specific samples from the rest (Figure 1B). At the phylum level, Campylobacteriota, Fusobacteriota, and Proteobacteria were significantly more abundant in the active CD group compared with the non-IBD group. In contrast, Verrucomicrobiota levels were markedly lower in the active CD group, while Fusobacteriota abundance was also reduced in the inactive group relative to the non-IBD group (Figure 1C). At the genus level, notable differences were observed among groups. The active CD group exhibited a marked increase in *Escherichia*, *Fusobacterium*, and *Campylobacter* abundances compared with the non-IBD group. Meanwhile, the inactive CD group showed a significant increase in *Prevotella* relative to non-IBD patients (Figure 1D). Furthermore, when comparing inactive and active CD patients, *Prevotella* species were significantly more abundant in the inactive group, whereas *Fusobacterium* and *Campylobacter* were markedly reduced. Finally, at the species level, our results revealed a significant increase in the relative abundance of pathobiont species and strains in the active CD group, including *E. coli*, *Campylobater concisus*, *Dialister pneumosintes*, *Prevotella buccae*, and *Fusobacterium nucleatum* (Figure 1E). In contrast, we observed a marked decrease in the relative abundance of previously

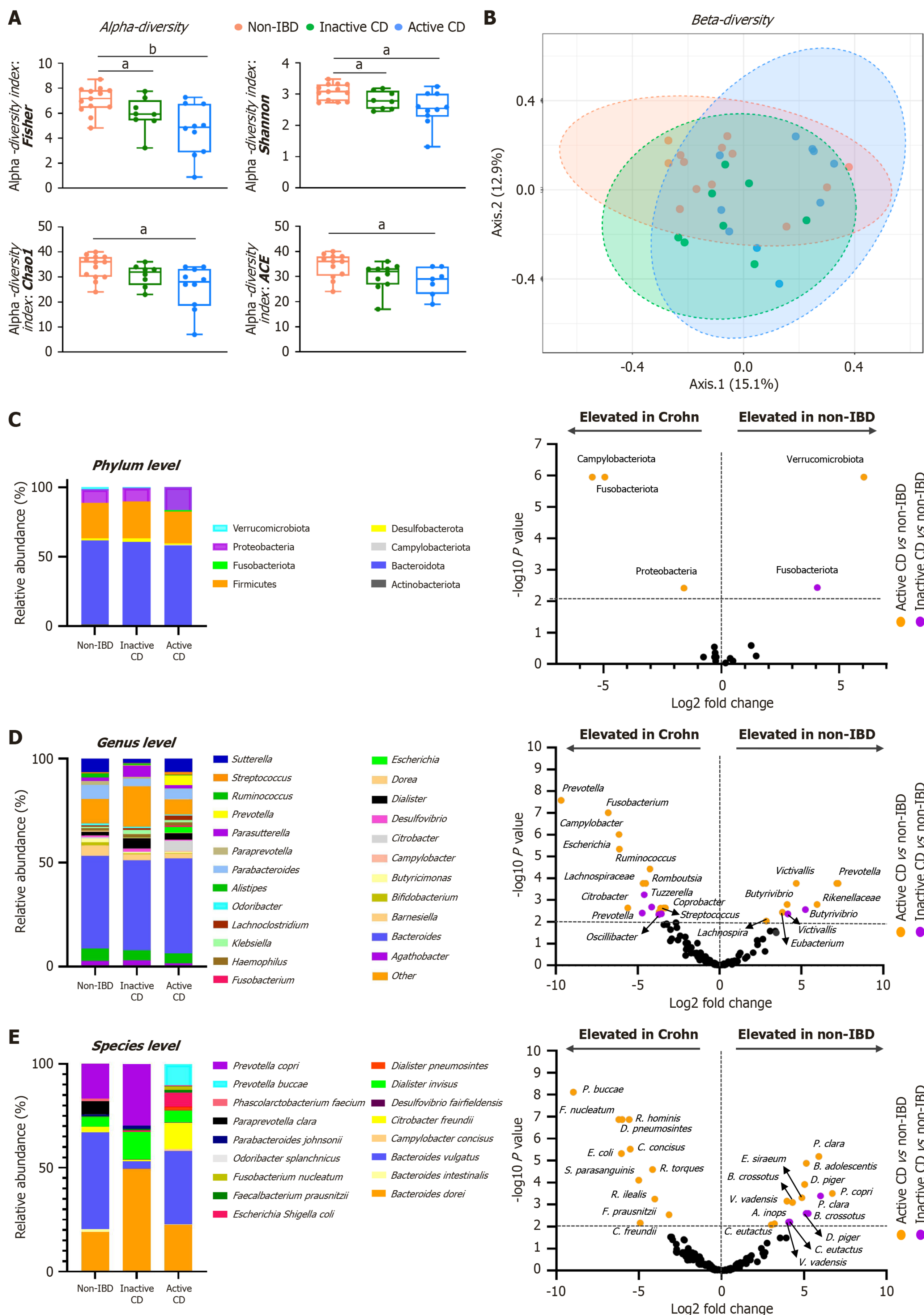

Figure 1 Microbiota composition and diversity in active and inactive Crohn's disease and non-inflammatory bowel diseases subjects. A: Alpha diversity analysis using the Fisher, Shannon, Chao1, and ACE diversity indices for each 16S rRNA dataset. Statistical significance was determined using the

Kruskal-Wallis test followed by the Mann-Whitney *U* test. $^{a}P < 0.05$; $^{b}P < 0.01$; B: Principal coordinates analysis based on the Bray-Curtis dissimilarity index, illustrating beta diversity differences among study groups; C-E: Taxonomic differences between groups: Bar charts (left panels) represent the mean relative abundances of amplicon sequence variants, while volcano plots (right panels) highlight significantly different taxa between Crohn's disease patients and non-inflammatory bowel diseases individuals at various taxonomic ranks: Phylum (C), genus (D), and species (E) levels. CD: Crohn's disease; IBD: Inflammatory bowel diseases.

identified as beneficial species such as *Bifidobacterium adolescentis*, *Prevotella copri*, *Eubacterium siraeum*, and *Paraprevotella clara* in the active CD group compared to both non-IBD and inactive CD groups (Figure 1E). This shift in microbial composition underscores the potential role of these specific species in disease pathogenesis and highlights the importance of microbial balance in the management of CD.

Circulating succinate levels are elevated in CD patients and associate with inflammation

In line with previous observations[22], plasma succinate levels were significantly higher in both active and inactive CD patients, compared to non-IBD individuals ($P < 0.0001$ and $P = 0.0077$, respectively). Notably, active CD patients exhibited significantly higher succinate levels than inactive CD patients ($P = 0.0203$) (Supplementary Figure 1A and Supplementary Table 3). Circulating succinate levels showed a positive correlation with the Harvey-Bradshaw Index ($r = 0.3008$, $P = 0.018$) and with the gene expression of its receptor, SUCNR1, in PBMCs ($r = 0.526$, $P = 0.007$) (Supplementary Figure 1B). Conversely, circulating succinate levels correlated negatively with the gene expression of toll-like receptor 4 in PBMCs ($r = -0.52$, $P = 0.008$). Interestingly, *SUCNR1* gene expression in PBMCs was positively associated with the levels of pro-inflammatory markers such as high sensitivity CRP ($r = 0.72$, $P = 0.002$) and fecal calprotectin ($r = 0.2957$, $P = 0.036$), which are biological activity biomarkers commonly used in clinical practice for IBD treatment (Supplementary Figure 1B). Lifestyle and dietary factors were also linked to circulating succinate levels. Regular physical exercise and a history of never smoking were associated with lower succinate concentrations (Supplementary Figure 1C). Additionally, individuals with a diet rich in fish and olive oil displayed significantly lower succinate levels (Supplementary Figure 1C).

Circulating succinate levels correlates with a specific microbial signature

Circulating succinate levels were specifically associated with distinct gut microbiota taxa. Notably, we observed a positive correlation between succinate levels and the phyla Proteobacteria ($r = 0.70$, $P = 1.49 \times 10^{-5}$) and Campylobacteriota ($r = 0.52$, $P = 0.012$). At the genus level, significant associations were found with *Prevotella* ($r = 0.38$, $P = 0.010$), *Flavonifractor* ($r = 0.42$, $P = 0.012$), *Streptococcus* ($r = 0.6$, $P = 0.002$) and *Oscillobacter* ($r = 0.4$, $P = 0.037$). Finally, at the species level, succinate levels correlated positively with *Prevotella buccae* ($r = 0.46$, $P = 0.009$), *Campylobater concisus* ($r = 0.51$, $P = 0.012$) and *E. coli* ($r = 0.50$, $P = 0.012$) (Figure 2A and B). Given these observations, we classified the significant bacterial species identified in the study cohort as either succinate producers or consumers across groups (Table 2). Notably, we observed a marked increase in the succinate-producing species *Prevotella buccae*, *Fusobacterium nucleatum*, *Campylobacter concisus*, and *E. coli* in active CD patients compared to non-IBD subjects, along with a decrease in the succinate-consuming species *Odoribacter splanchnicus*. This aligns with the elevated circulating succinate levels found in active CD patients. Conversely, we detected an increase in the succinate-consuming species *Dialister pneumosintes*. Although this may seem contradictory, *Dialister pneumosintes* is a slow succinate consumer, which may contribute to the sustained elevated succinate levels observed in active CD patients. The succinate producing species *Fusobacterium nucleatum*, *E. coli* and *Prevotella buccae*, abundance was significantly higher in active CD patients compared with non-IBD and inactive CD patients who also exhibited a significant higher abundance of these species compared with the non-IBD group. Similarly, in inactive CD patients, we observed a significant increase in the succinate-producing species *Paraprevotella clara*, *Bacteroides* intestinal and *E. coli* compared to non-IBD subjects. Conversely, the succinate-consuming species *Phascolarctobacterium faecium* was significantly decreased. These findings suggest that even in inactive CD, an altered succinate metabolism persists, potentially influencing the gut microbial balance and host metabolic responses. Finally, when comparing active and inactive CD patients, we observed a significant increase in the succinate-producing species *Prevotella buccae*, *Prevotella copri*, *Fusobacterium nucleatum*, *Campylobacter concisus*, *E. coli*, *Bacteroides vulgatus*, *Citrobacter freundii*, and *Parabacteroides johnsonii* in the active CD group. Lastly, in our cohort, the succinate-producing genus *Prevotella* and *Prevotella buccae* species exhibited a positive correlation with succinate levels, *SUCNR1* gene expression as well as CD activity biomarkers such as PCR and fecal calprotectin together with the Harvey-Bradshaw Index, suggesting a potential key inflammatory role in CD patients (Figure 2C and Supplementary Figure 2). Moreover, *Prevotella* genus and *Prevotella buccae* also showed a positive correlation with some phyla: Proteobacteria, Fusobacteriota, and Campylobacterota, genus: *Streptococcus* and *Suturella*, and species: *Campylobater concisus*, *Citrobacter freundii* and *E. coli*, further emphasizing their involvement in succinate metabolism and inflammatory processes. To note, *Prevotella buccae* exhibited a negative correlation with relative gene expression of nucleotide-binding oligomerization domain containing 2 and toll-like receptor 4 in PBMCs, being both of them key receptors involved in bacterial clearance (Supplementary Figure 2).

Dialister-succinotypes correlate with circulating succinate levels associate with disease activity

Recent studies have identified *Dialister* as slow succinate consumer compared to other succinate-consuming genera, such as *Phascolarctobacterium*[32,33]. In our cohort, we observed a higher prevalence of D-phenotype compared to P-phenotype in both non-IBD individuals and CD patients (70% and 85.7%, respectively), with CD patients exhibiting a greater proportion of D-phenotype individuals than non-IBD controls (Figure 3A). Moreover, *Dialister* abundance in D-phenotype individuals positively correlated with circulating succinate levels ($r = 0.2892$, $P = 0.0213$). Notably, the

Table 2 Significant bacterial species identified as succinate producers or consumers in the study cohort

Non-IBD *vs* inactive CD	*P* value	Non-IBD *vs* active CD	*P* value	Active *vs* inactive CD	*P* value
Succinate-producers					
Paraprevotella clara	6.09E-06	*Prevotella buccae*	1.18E-10	*Prevotella buccae*	5.76E-07
Bacteroides intestinalis	3.95E-03	*Roseburia hominis*	6.15E-09	*Prevotella copri*	2.01E-06
Escherichia coli	3.01E-02	*Fusobacterium nucleatum*	8.20E-09	*Fusobacterium nucleatum*	7.22E-06
Parabacteroides johnsonii	3.37E-02	*Campylobacter concisus*	2.29E-07	*Campylobacter concisus*	2.50E-05
Faecalibacterium prausnitzii	4.38E-02	*Escherichia coli*	4.32E-04	*Escherichia coli*	6.09E-03
		Paraprevotella clara	6.91E-07	*Bacteroides vulgatus*	9.25E-03
		Bifidobacterium adolescentis	1.58E-06	*Citrobacter freundii*	9.26E-03
		Prevotella copri	5.58E-05	*Parabacteroides johnsonii*	9.89E-03
		Faecalibacterium prausnitzii	7.51E-04		
		Citrobacter freundii	1.89E-03		
Succinate-consumers					
Phascolarctobacterium faecium	4.46E-03	*Dialister pneumosintes*	6.72E-09	*Dialister pneumosintes*	6.25E-06
Dialister invisus	2.80E-02			*Phascolarctobacterium faecium*	1.73E-03

CD: Crohn’s disease; IBD: Inflammatory bowel disease.

clustering of D-phenotype individuals based on their *Dialister* abundance and circulating succinate levels aligned with disease activity status, effectively distinguishing between active and inactive CD patients as well as non-IBD individuals (Figure 3B). Indeed, *Dialister* abundance was significantly higher in both active and inactive CD patients compared to non-IBD subjects (Figure 3C). Furthermore, we observed a significant negative correlation between *Dialister* and *Phascolarctobacterium* abundances within our cohort (Figure 3D), suggesting that the balance between these two succinate-consuming bacteria may determine whether succinate accumulates or is efficiently cleared. Given that *Dialister* is a slow succinate consumer, its higher abundance correlates with increased succinate levels (Figure 3B), whereas *Phascolarctobacterium*, as a fast consumer, may contribute to lower succinate concentrations when more prevalent as happens in non-IBD subjects. Interestingly, we also identified a significant negative correlation between *Phascolarctobacterium* abundance and *SUCNR1* gene expression in PBMCs (Figure 3E), suggesting that the rapid succinate clearance facilitated by *Phascolarctobacterium* may prevent SUCNR1 stimulation in systemic circulation. Taken together with our findings linking succinate levels to established CD clinical activity biomarkers, these results suggest that *Dialister* succinotype and *Dialister* abundance may serve as potential microbiome-based biomarkers associated with inflammation and CD activity.

Dialister presence in the intestinal mucosa may be POR indicator in CD patients

Considering other authors suggested *Dialister* succinotypes in CD patients are potentially associated with a higher frequency of relapses[33] and given the observed association between *Dialister* abundance and CD activity in our cohort, we aimed to explore whether *Dialister* presence in the intestinal mucosa could predict POR in CD. To explore this, we performed a microbiome analysis of inflamed and uninflamed ileal tissue biopsies collected prospectively from an inception cohort of 34 adult CD patients at the time of surgery. Patients were subsequently followed and monitored *via* IC every six months over a two-year postoperative period. Based on their Rutgeerts score[30], they were classified at the end of the follow-up period into three groups: NR (i0-i1), mild recurrent (MR, i2), or SR (i3-i4). Interestingly, we observed a significant increase in the abundance of *Dialister* OTU 750 in R (MR + SR) CD patients compared to NR patients, in the non-inflamed and inflamed mucosa (P = 0.034 and P = 0.043, respectively; Figure 3F). This suggests that *Dialister*, specifically OTU 750, may serve as a potential indicator of POR in CD patients. Additionally, analysis of OTU 745 revealed its potential to differentiate SR patients from those with NR and MR, with significant differences observed among these groups in inflamed mucosa (P = 0.001 and 1.86×10^{-6}, respectively; Figure 3G) and in uninflamed mucosa between NR and MR (P = 0.005; Figure 3G). These findings indicate that OTU 745 may help stratify CD patients based on recurrence severity, further supporting the role of *Dialister* as a microbiome-based predictor of CD progression.

Functional analysis identifies succinate as a key player in CD

Metabolic pathway analysis revealed a significant enrichment of carboxylic acid biosynthesis pathways in CD samples (false discovery rate = 1×10^{-44}), with succinate emerging as a central metabolite (Figure 4A). Functional profiling of microbial gene expression in faecal samples from CD patients, compared to non-IBD individuals, identified key alterations in metabolic processes associated with succinate production and export (Figure 4B). Specifically, a significant downregulation of NADH dehydrogenase was observed in bacteria from CD patients, suggesting impaired electron transport chain activity and consequent intracellular accumulation of NADH. In parallel, increased expression of

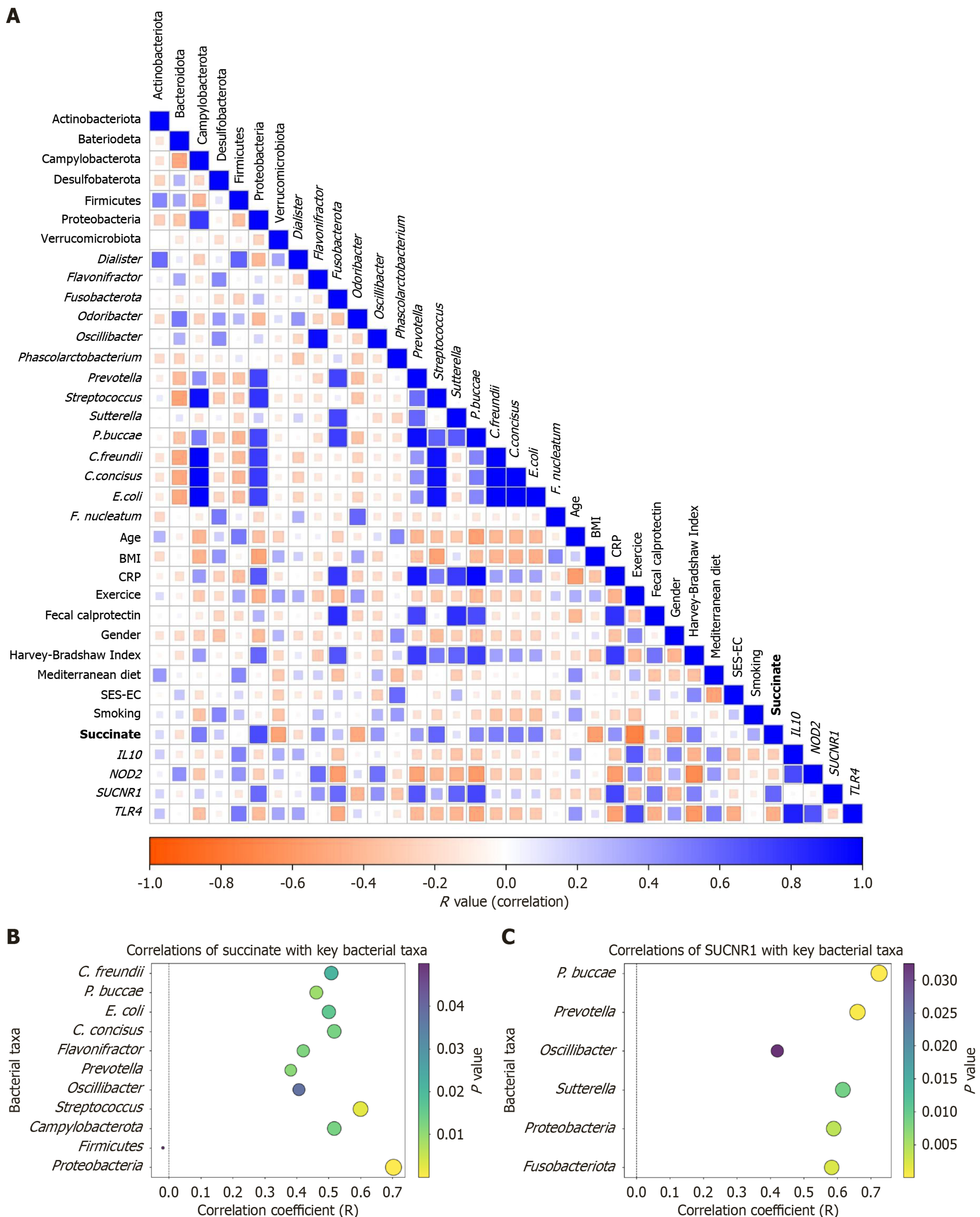

Figure 2 Correlation between gut microbiota metabolite succinate, microbial composition, and inflammatory markers. A: Correlogram displaying Pearson's correlation coefficients among succinate levels, microbial relative abundances, and clinical and biological parameters in the study cohort (*n* = 31); B: Correlation between circulating succinate levels and specific microbial taxa; C: Correlation between the succinate receptor 1 and specific microbial taxa. SUCNR1: Succinate receptor 1.

glycolytic enzymes and key TCA cycle enzymes - such as citrate synthase and isocitrate dehydrogenase - points to enhanced metabolic flux through pathways that generate NADH and intermediate metabolites. This pattern is consistent with an incomplete or truncated TCA cycle, commonly observed in strict anaerobes, where certain oxidative steps are bypassed or absent. The resulting NADH excess may be redirected towards fermentative processes characteristic of strict anaerobes in the colonic environment. In this context, fumarate reductase - a key enzyme in anaerobic respiration and

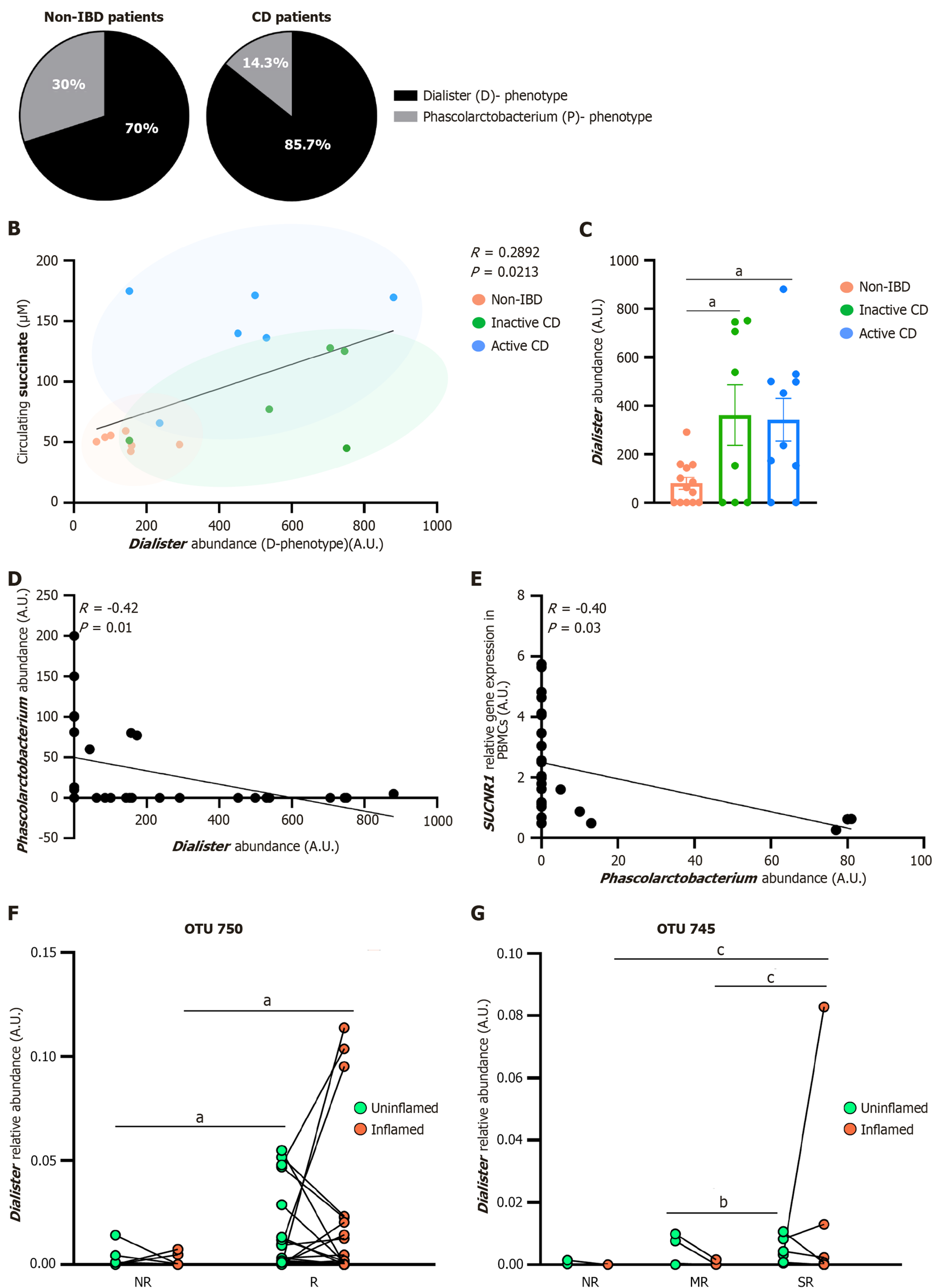

Figure 3 *Dialister* abundance associates with disease activity and postoperative recurrence in Crohn's disease. A: Classification of individuals into distinct "succinotypes" based on the relative abundances of *Dialister* and *Phascolarctobacterium* in Crohn's disease (CD) and non-inflammatory bowel diseases (IBD) subjects; B: Significant negative correlation between plasma succinate levels and *Dialister* abundance, a slow succinate-consuming genus (Pearson's ρ, *P*

value indicated in the figure); C: Comparison of *Dialister* abundance across active CD, inactive CD, and non-IBD subjects. [a]P < 0.05 *vs* non-IBD. Statistical analysis: Kruskal-Wallis test followed by pairwise Mann-Whitney U tests; D: Negative correlation between *Dialister* and *Phascolarctobacterium* abundances within the cohort (Pearson's ρ); E: Negative correlation between *Phascolarctobacterium* abundance and succinate receptor 1 gene expression in peripheral blood mononuclear cells (Pearson's ρ); F: Mucosal *Dialister* operational taxonomic unit 750 levels distinguish non-recurrent from recurrent CD patients in uninflamed tissue from the validation cohort; G: Mucosal *Dialister* (operational taxonomic unit 745) abundance in inflamed mucosa differentiates among non-recurrent, mild-recurrent, and severe recurrent CD patients. Statistical significance was assessed using DESeq2 on non-transformed count data: [a]P < 0.05; [b]P < 0.01; [c]P < 0.001, as indicated in the panels. CD: Crohn's disease; IBD: Inflammatory bowel diseases; OTU: Operational taxonomic unit; SUCNR1: Succinate receptor 1; NR: Non-recurrent; R: Recurrent; MR: Mild-recurrent; SR: Severe recurrent.

succinate fermentation - was significantly upregulated, promoting the conversion of fumarate into succinate as an alternative electron sink. Finally, succinate transport was also markedly elevated, with L-citrate/succinate and L-tartrate/ succinate transporters upregulated in bacteria from CD patients, facilitating the export of succinate into the gut lumen. Together, these findings suggest a coordinated metabolic shift in strict anaerobic bacteria within the CD gut microbiota, in which disrupted oxidative phosphorylation leads to increased fermentative succinate production and its active secretion. Succinate thus emerges not only as a key metabolic by-product, but also as a potential mechanistic contributor and biomarker of CD activity.

DISCUSSION

Succinate, a central metabolite of the TCA cycle, is not only a byproduct of microbial fermentation but also a potent pro-inflammatory signal[19]. Elevated succinate levels have been implicated in various chronic inflammatory diseases including hypertension[34], ischemic heart disease[35], obesity[36] and type 2 diabetes mellitus[37-39]. Under these conditions, extracellular succinate signals thought its receptor SUCNR1 and stabilizes of hypoxia-inducible factor 1-alpha, thereby promoting macrophage polarization and cytokine release[19]. In previous studies, we detected a significant upregulation of *SUCNR1* gene expression in the mesenteric adipose tissue surrounding the inflamed intestinal region in active CD patients, also known as creeping fat[22]. Initially, this tissue serves as a protective barrier, preventing transmural bacterial translocation from the damaged intestinal epithelium to the bloodstream in the early stages of the disease[40,41]. However, as the disease progresses, creeping fat becomes increasingly pro-inflammatory[42]. Together with the inflamed mucosa, it creates a self-perpetuating inflammatory cycle that exacerbates CD pathogenesis. Recent evidence has further highlighted succinate as a key immunomodulatory metabolite in intestinal inflammation. It signals *via* SUCNR1 in epithelial and immune cells, influencing T cell responses and the production of pro-inflammatory cytokines[43,44]. Moreover, strain-level variation in microbial succinate production and consumption has been shown to modulate susceptibility to inflammation and to shape gut microbial composition[44,45]. In parallel, microbiota-targeted therapeutic strategies are gaining increasing attention: Notably, a recent randomised controlled trial demonstrated the efficacy of oral lyophilised faecal microbiota transplantation in ulcerative colitis[46]. These findings strengthen both the mechanistic and translational context of our study. In this study, we provide novel insights into the role of succinate metabolism and its relationship with the gut microbiota, specifically examining both succinate-producing bacteria and those with distinct succinate-consumption dynamics (fast and slow consumers). We observed a significant reduction in alpha diversity and compositional shifts in the gut microbiota of patients with active CD compared to both non-IBD controls and those with inactive CD. These findings are consistent with previous studies linking dysbiosis to disease activity[47]. A reduction in microbial diversity is a well-documented feature of IBD, with lower microbial richness correlating with inflammation and disease progression[48]. Furthermore, decreased microbial diversity has been associated with increased intestinal permeability and immune activation, suggesting a potential role in disease exacerbation[17]. Our findings demonstrate that circulating succinate levels are significantly elevated in CD patients, particularly those with active disease, and correlate with key inflammatory markers, including the Harvey-Bradshaw Index and *SUCNR1* gene expression in PBMCs. Moreover, succinate levels positively correlate with the abundance of pro-inflammatory bacteria, such as members of the phylum Proteobacteria and succinate-producing species like *E. coli*, *Fusobacterium nucleatum*, and *Prevotella buccae*. These results align with previous studies showing that an increase in *E. coli*, particularly AIEC, contributes to gut inflammation through epithelial invasion and immune modulation[24,49]. Unfortunately, we were unable to distinguish the AIEC phenotype in our samples only using 16S RNA sequencing. *Fusobacterium nucleatum* has been implicated in pro-inflammatory responses and colorectal carcinogenesis[50,51], suggesting that its increased abundance in CD patients may exacerbate mucosal inflammation. Collectively, these findings reinforce the growing body of evidence that succinate is not merely a metabolic byproduct but an active mediator of inflammatory processes in CD. Furthermore, our results revealed significant associations between circulating succinate levels and the Harvey-Bradshaw Index, as well as the gene expression of its receptor SUCNR1 in PBMCs, which positively correlates with commonly used clinical markers of inflammation in CD, such as faecal calprotectin and PCR. These findings support the hypothesis that succinate acts as a metabolic link between gut dysbiosis and systemic inflammation in CD. Notably, the substantial reduction in circulating succinate levels observed in patients with inactive CD suggests that metabolic dysregulation may normalize with disease remission, highlighting succinate as a potential dynamic biomarker of disease activity. The comparative analysis of succinate-producing and succinate-consuming bacterial species across study groups reveals critical insights into the microbial contributions to succinate metabolism in CD. In our cohort, distinct differences were observed between controls, inactive CD, and active CD groups, emphasizing the dynamic interplay of microbial

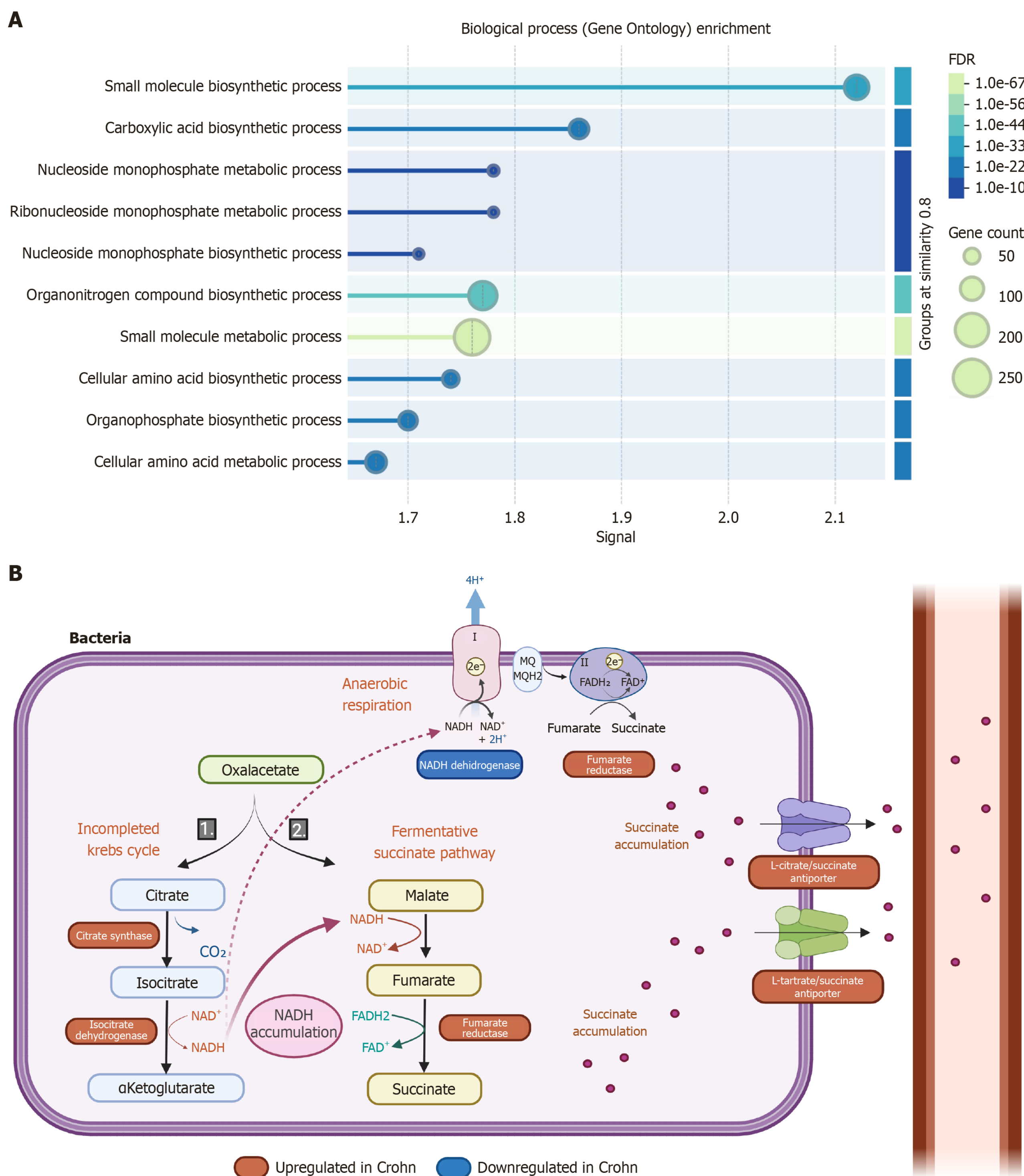

Figure 4 Functional analysis reveals succinate as a key metabolite associated with microbial dysbiosis in Crohn's disease. A: Gene Ontology enrichment analysis of microbial functions reveals a significant increase in carboxylic acid biosynthesis pathways in faecal microbiota from active Crohn's disease (CD) patients compared with non-inflammatory bowel diseases controls (false discovery rate = 1×10^{-44}), with succinate emerging as a central metabolite; B: Schematic representation of the main metabolic pathways active in strict anaerobic gut bacteria in CD patients. These bacteria exhibit upregulation of glycolytic enzymes and of specific enzymes of the (incomplete) tricarboxylic acid cycle - namely citrate synthase and isocitrate dehydrogenase - leading to increased NADH production. In the context of reduced NADH dehydrogenase activity, the excess NADH is diverted towards fermentative and anaerobic respiratory pathways, favouring succinate production. Fumarate reductase, an enzyme responsible for reducing fumarate to succinate, is also upregulated. Additionally, transporters such as L-citrate/succinate and L-tartrate/succinate are significantly increased, promoting succinate export from the bacterial cell. This metabolic reprogramming reflects adaptations typical of strict anaerobes and may contribute to the accumulation of microbial-derived succinate observed in CD. Figure created with BioRender.com. FDR: False discovery rate.

functions during disease progression. Conversely, succinate producers, including *E. coli*, *Fusobacterium nucleatum*, and *Prevotella copri*, were significantly enriched in active CD patients compared to controls and inactive CD patients. These species are known for their pro-inflammatory potential, producing succinate as a metabolic byproduct that can amplify systemic inflammation *via* SUCNR1 activation[52]. Notably, *Fusobacterium nucleatum* and *E. coli* are established pathobionts linked to epithelial invasion and immune activation in CD, further underscoring their pathogenic role in the disease[10,24]. The positive correlation between succinate levels and pro-inflammatory microbial taxa suggests that these species may be key contributors to succinate accumulation and subsequent immune activation. Elevated succinate has been implicated in macrophage polarization towards a pro-inflammatory M1 phenotype, further contributing to tissue damage and immune dysregulation in CD[19]. Regarding succinate consumers, *Odoribacter* correlates negatively with circulating succinate levels in our cohort. Odoribacteraceae is one of two succinate-consuming bacterial families associated with circulating succinate[36]. Interestingly, extracellular vesicles of *Odoribacter spanchnicus* have been shown to exhibit anti-inflammatory properties *in vitro*[53], anti-colorectal cancer activity[54], and alleviate IBD by modulating gastrointestinal inflammation and intestinal barrier function *via* the nucleotide-binding oligomerization domain-, leucine-rich repeat-, and pyrin domain- containing receptor 3 inflammasome suppression in a mice model[55]. Additionally, the presence of *Odoribacter* within a well-balanced gut microbiota is primarily associated with its ability to produce SCFAs, which play a crucial role in maintaining intestinal health. Commensal bacteria ferment dietary fiber and resistant starch into SCFAs, which serve as an essential energy source for intestinal epithelial cells[56]. Among these metabolites, butyrate is particularly significant due to its diverse health benefits contributing to gut homeostasis by reinforcing the intestinal barrier, modulating immune responses, and exerting anti-inflammatory effects within the intestinal mucosa, playing a key role in reducing the production of proinflammatory cytokines and thereby supporting overall gut health and immune regulation[57]. Additionally, oral administration of *Odoribacter*, based on its ability to reduce succinate levels, has been shown to improve glucose tolerance and the inflammatory profile in two independent models of obesity (db/db mice and diet-induced obese mice)[58]. Surprisingly, other succinate consuming species, such as *Dialister invisus* and *Dialister pneumosintes*, were enriched in fecal samples of CD patients and active CD patients, respectively. However, it is essential to distinguish between fast and slow succinate consumers within the microbiota. While the specific succinate metabolism of each detected genus remains unclear, previous studies have classified *Phascolarctobacterium* as a fast succinate consumer and *Dialister* as a slow succinate consumer and have further stratified microbial communities into *Dialister*-based succinotypes[32]. Following this methodology, we stratified our cohort and observed that the *Dialister*-enriched succinotype was more prevalent in CD patients than in non-IBD controls, and positively correlated with circulating succinate levels. This correlation suggests that an increased presence of slow succinate consumers, such as *Dialister*, may contribute to reduced succinate clearance, leading to succinate accumulation. Furthermore, the higher prevalence of *Dialister* succinotypes in CD patients supports the notion that microbial metabolic shifts favoring slow succinate consumers may play a key role in sustaining the pro-inflammatory environment in CD. These findings highlight the potential for microbiota-targeted therapeutic strategies, such as fecal microbiota transplantation[59] or targeted metabolite supplementation, to mitigate succinate-driven inflammation and restore gut homeostasis. Additionally, the *Dialister* succinotype in patients with CD has previously been associated with a higher frequency of disease relapses per year, suggesting its potential link to relapse frequency[33]. Notably, our study is the first to propose, to our knowledge, that it *Dialister* relative abundance in intestinal mucosa might be an interesting prediction tool for POR and to discriminate between different recurrence statuses - NR, recurrent, and SR - considering both inflamed and non-inflamed ileal regions. Specifically, we observed that *Dialister* OTU 750 abundance was significantly increased in recurrent (MR + SR) CD patients compared to NR patients, while OTU 745 distinguished SR patients from NR and MR patients in both inflamed and non-inflamed mucosa. These observations suggest that strain-level variation within *Dialister spp.* may influence succinate metabolism and recurrence risk, highlighting its potential utility as a microbiome-based biomarker for CD progression. However, future studies incorporating multi-omic approaches and functional validation will be necessary to confirm these findings. Several studies have already shown that some species such as *Faecalibacterium prausnitzii* abundance is reduced in resected CD patients in comparison with those without resection[60,61]. However, it is still not clear whether this shift is a consequence of these patients featuring a more acute disease or if it is due to the surgery procedure itself. Here, we were able to stablish for first time to our known, a link between *Dialister* abundance, CD activity and higher risk of POR in CD patients. However, future studies incorporating multi-omic approaches validating these findings might be necessary. These findings highlight the need to further explore *Dialister* and succinate as potential biomarkers for both disease activity and POR in CD. Moreover, future studies should assess their potential utility in monitoring long-term treatment efficacy and evaluating how different therapies may influence *Dialister* abundance in the gut microbiota. The functional analysis of microbial metabolism in fecal samples of CD and non-IBD patients further supports a dysregulated succinate metabolism. Patients with CD exhibit increased expression of fumarate reductase, an enzyme that, under anaerobic conditions, reverses the fumarate-to-succinate conversion, leading to intracellular succinate accumulation. Simultaneously, the upregulation of succinate transporters (L-citrate/succinate antiporter and L-tartrate/succinate antiporter) facilitates succinate export[62], further increasing extracellular succinate levels. This metabolic shift may contribute to CD pathogenesis by promoting a pro-inflammatory microbial environment and disrupting host-microbe metabolic interactions. Curiously, we observed a decrease in NADH dehydrogenase in bacteria from CD patients which provoke an altered electron transport chain, which could further drive dysbiosis and inflammatory signaling. This metabolic reprogramming aligns with previous research demonstrating that microbial succinate metabolism is intricately linked to host metabolic pathways, influencing both local and systemic immune responses[52,63]. These findings highlight the dual impact of microbial dysbiosis in CD: A diminished capacity for succinate consumption and an increased burden of succinate production. This imbalance reinforces the role of succinate as a central metabolic signal linking dysbiosis to inflammation in CD. Therapeutic strategies restoring succinate-consuming microbes or reducing succinate-producing bacteria combined with targeted modulation of succinate

pathways (*e.g.*, SUCNR1 antagonists) may offer targeted approaches to mitigate inflammation and improving gut health in IBD[64]. It is important to note that these functional insights are predicted from 16S rRNA gene sequencing using PICRUSt2 and therefore represent inferred, not directly measured, microbial functions. Validation of these predictions through shotgun metagenomics or targeted metabolomics will be necessary to confirm the observed functional shifts and further elucidate their role in CD pathogenesis, which we propose as a priority for future studies. Our study has several additional limitations. First, its cross-sectional design precludes the establishment of causal relationships between microbial alterations, succinate metabolism, and disease activity; thus, our findings should be interpreted as associations rather than causal links. Another limitation is that potential confounders - such as diet, lifestyle, and medication use - were assessed only in univariate analyses. Given the modest sample size relative to the number of covariates, inclusion in multivariate models would have carried a substantial risk of overfitting and unstable estimates. Future studies with larger, adequately powered cohorts will be needed to formally address these factors using multivariate approaches. In addition, factors including diet, medication use, and genetic background, all of which may influence microbial composition and metabolism, should be carefully accounted for. Longitudinal and mechanistic studies will also be essential to confirm whether succinate metabolism and microbiota alterations play a causal role in CD pathogenesis and to delineate the metabolic pathways underlying succinate-driven inflammation. Second, the primary cohort size (n = 31) is relatively small, reducing statistical power, particularly given the high interindividual variability of the gut microbiome. Although no formal power analysis was performed due to feasibility constraints, effect sizes for succinate differences and microbial shifts were consistent across groups. The inclusion of an independent validation cohort for POR (n = 66) partially mitigates this limitation. Third, in the validation cohort, postoperative changes in diet and microbiome composition were not formally monitored, which could influence recurrence risk. Preoperative medication use was recorded and did not differ between recurrence groups (Supplementary Table 2). Future studies should incorporate longitudinal monitoring of diet, microbiome dynamics, and medication changes to better assess their impact on POR and validate these findings.

CONCLUSION

Our study underscores the role of microbiota-driven succinate dysregulation as a significant contributor to systemic inflammation in CD, with strong links to disease activity. These findings open the door to novel diagnostic and therapeutic approaches that target both microbial and metabolic pathways in this complex disease.

ACKNOWLEDGEMENTS

We wish to particularly acknowledge the patients and the BioBank IISPV (PT17/0015/0029) integrated in the Spanish National Biobanks Network for its collaboration. We would like to thank Dr. M Mañosa for providing the validation study cohort from Hospital Germans Trias i Pujol. The authors thank Olga Soler and Laia Cabré, biochemistry students, for their assistance with the experimental work and for preparing the images and tables, respectively.

FOOTNOTES

Author contributions: Boronat-Toscano A, Monfort-Ferré D, Suau R, Vañó-Segarra I, Clua-Ferré L, Astiarraga B, and Ginés I conducted the experiments; Valldosera G, Cepero C, Cabrinety L, Abadia de Barbarà C, Moliné A, Domènech E, Caro A, and Menacho M contributed to the selection of the study population and the processing of human samples; Queipo-Ortuño MI, Suau R, Plaza-Andrade I, Aranega-Martín L, Castellano-Castillo D, Benaiges-Fernandez R, Sánchez-Herrero JF, and Sumoy L performed microbiota experiments and data analysis; Queipo-Ortuño MI, Vañó-Segarra I, Benaiges-Fernandez R, Sánchez-Herrero JF, Sumoy L, and Serena C carried out the statistical analyses; Boronat-Toscano A, Monfort-Ferré D, Fernández-Veledo S, Vendrell J, Menacho M, and Serena C conceptualized the study, interpreted the data; Boronat-Toscano A and Serena C drafted the manuscript; Queipo-Ortuño MI, Sumoy L, Manyé J, and Serena C reviewed the manuscript; Serena C serves as the guarantor of this work.

Supported by the grant from I Clinical GETECCU_Galapagos (to Menacho M and Serena C); the grant from the Ministerio de Ciencia, Innovación y Universidades, PID2023-146315OB-I00 (to Manyé J and Serena C); the grant by the Instituto Salud Carlos III, PI20/00420 (to Manyé J) and PI22/01498 (to Domènech E and Sumoy L), co-funded by the European Union; and the grant, PI-AGAUR 2022-B00577 (to Boronat-Toscano A).

Institutional review board statement: This study was approved by the Ethics Committee of the Hospital Universitari Joan XXIII (Approval No. PI21/00011).

Conflict-of-interest statement: Fernández-Veledo S, Vendrell J, and Serena C are co-inventors of a patent (WO2019141780A1) licensed to SUCCIPRO S.L. In addition, Fernández-Veledo S and Vendrell J are co-founders of this company. The authors declare that these relationships have neither influenced nor biased the design, execution, or interpretation of the present work. All authors further declare that they have no other financial or personal relationships that could be perceived as potential conflicts of interest.

Data sharing statement: The 16S rRNA gene sequencing data generated in this study have been deposited in the NCBI Sequence Read

Archive. Data from the HJ23 cohort are available under BioProject accession number PRJNA1250964 (http://www.ncbi.nlm.nih.gov/bioproject/1250964) and PRJNA1241201 (http://www.ncbi.nlm.nih.gov/bioproject/1241201) for the validation cohort at IGTP. These datasets will be made publicly available upon publication. Functional profiling results presented in the manuscript were obtained through computational analysis (PICRUSt2) of the HJ23 cohort 16S rRNA data and are therefore fully reproducible using the deposited sequences. Quantitative PCR data from PBMCs and circulating succinate levels from the HJ23 cohort are provided in Supplementary Table 3.

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S-Editor: Wang JJ
L-Editor: A
P-Editor: Lei YY

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