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LETTER TO THE EDITOR

Targeting *Dialister*-driven succinate accumulation: A novel strategy for Crohn's disease activity control and recurrence prevention

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Abstract

Crohn's disease (CD) activity and postoperative recurrence significantly affect patients' quality of life, highlighting the need for new treatment and prevention strategies. We read with interest Boronat-Toscano *et al*'s study on *Dialister*-driven succinate accumulation in CD. By analyzing the fecal microbiota, circulating succinate levels, and clinical indices using clinical samples, the researchers explored the roles of *Dialister* and succinate in CD, a previously unaddressed area. They revealed that active CD is characterized by high succinate levels, which are associated with disease severity and inflammatory indicators. The enrichment of *Dialister*, linked to impaired succinate clearance and postoperative recurrence, offers new insights. The study identified succinate and *Dialister* as potential therapeutic

targets, advancing understanding of CD pathophysiology and paving the way for further investigations. Future studies should involve large, multicenter cohorts for validation, explore *Dialister*'s strain-specific metabolic mechanisms, and develop treatments targeting the "succinate axis", thus connecting fundamental research with clinical applications.

Key Words: Crohn's disease; Succinate; Therapeutic targets; Gut microbiota; Inflammatory bowel disease; Postoperative recurrence; *Dialister*

Core Tip: Crohn's disease (CD) greatly affects patients' quality of life, necessitating new treatment strategies. Boronat-Toscano *et al* examined the role of *Dialister* and succinate in CD by analyzing the fecal microbiota, circulating succinate levels, and clinical indices. They found that high succinate levels are linked to active CD and inflammation, with *Dialister* enrichment related to impaired succinate clearance and recurrence. These findings highlight succinate and *Dialister* as therapeutic targets, enhancing understanding of CD and guiding future research. Larger studies should validate these results, explore *Dialister*'s metabolic mechanisms, and develop treatments targeting the "succinate axis" to link basic research to clinical practice.

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TO THE EDITOR

We were intrigued by Boronat-Toscano *et al*'s recent study[1] in *World Journal of Gastroenterology*, which advances our understanding of the interplay among the gut microbiota, metabolic dysregulation, and Crohn's disease (CD) pathogenesis, crucial for improving both biomarkers and targeted therapies for this chronic, relapsing condition. CD is a complex inflammatory bowel disease (IBD) influenced by genetic predisposition, environmental factors, and immune dysfunction. Emerging evidence has highlighted the crucial role of the gut microbiota and its metabolites in CD's pathophysiology. Patients with CD have significantly lower gut microbiota diversity than healthy individuals[2]. Alterations in microbiota structure occur at various taxonomic levels, notably in Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria[3]. *Fusobacterium nucleatum* is more prevalent in patients with CD, and it is associated with disease activity and clinical manifestations through its exacerbation of inflammation *via* the endoplasmic reticulum stress pathway, thereby compromising the intestinal mucosal barrier[4]. Additionally, *Escherichia coli* can evade immune defenses by avoiding neutrophil activation, aiding its growth in the intestine[5]. Gut microbiota metabolites such as the short-chain fatty acid butyrate are significant in managing intestinal inflammation and predicting IBD treatment success. This is especially true in patients with CD treated with azathioprine, in whom butyrate synthesis is linked to clinical remission[6]. Butyrate also activates G protein-coupled receptor 43, enhancing dendritic cell expression of amphiregulin to protect against colitis[7]. Succinic acid, another key intestinal metabolite, is vital in CD for promoting goblet cell proliferation to reduce inflammation and facilitating the conversion of adipose tissue from white to beige, influencing CD pathophysiology[8,9]. Nonetheless, there is an absence of research on how *Dialister*, a slower succinate consumer than genera such as *Phascolarctobacterium*, affects succinate accumulation in CD.

The authors' findings are particularly notable for three key innovations. First, they established circulating succinate as a robust biomarker for CD activity and postoperative recurrence (POR), linking its elevation to core clinical indices and the expression of succinate receptor 1 (SUCNR1). SUCNR1, also known as G-protein-coupled receptor 91, can trigger a cascade of biological processes by binding to succinate in immune cells[10]. Unlike traditional inflammatory markers that capture only isolated aspects of CD pathophysiology, succinate integrates "microbiota-metabolism-inflammation" crosstalk, offering a more holistic view of the disease status. Second, the study redefined the role of *Dialister* in CD. By classifying it as a slow succinate consumer, the authors resolved the apparent paradox of its enrichment in both active and inactive CD. They further linked specific *Dialister* operational taxonomic units (OTUs; *i.e.*, OTU750, OTU745) to POR risk. This moves beyond a binary "beneficial" or "harmful" microbial classification to a function-based framework, which better reflects the complexity of gut microbial ecology. Third, their functional analyses revealed a coordinated metabolic shift within the CD microbiota. This shift is characterized by the upregulation of fumarate reductase, which drives succinate production, and succinate transporters, which facilitate luminal export, alongside the downregulation of nicotinamide adenine dinucleotide dehydrogenase, which impairs oxidative metabolism.

The original study's limitations merit detailed discussion. The study was primarily correlative. Although the authors proposed that *Dialister* is responsible for succinate accumulation, additional experiments, such as colonization studies in germ-free animals, are necessary to firmly establish causation instead of mere correlation. The research might have been

affected by confounding factors. Although univariate analysis was used, these factors might have intricate effects on the microbiome and succinate levels, necessitating strict control in larger studies with multivariate models. Moreover, the small sample size limited statistical power. Although including an independent POR validation cohort partially reduced this limitation, multicenter studies with extensive samples are necessary for stronger significance. Postoperative diet and microbiota changes were not tracked. Conducting a longitudinal study with dynamic data collection could strengthen the findings.

The authors' discoveries provide a mechanistic basis for succinate accumulation and pave the way for broader studies. Larger, multicenter cohorts encompassing diverse ethnicities, regions, and CD phenotypes are needed. Such cohorts will help confirm the link among *Dialister* abundance, succinate levels, and CD outcomes. Longitudinal studies should be conducted to elucidate causality by monitoring changes in *Dialister* and succinate levels before CD flares or POR, rather than relying solely on cross-sectional correlations. This will help determine whether *Dialister* enrichment and succinate accumulation precede disease activity or occur secondary to inflammation. Future studies should stratify cohorts by factors such as diet, smoking, and medication, which this study only assessed *via* univariate analysis, and use multivariate models to strengthen causal inferences. The link between lifestyle interventions and succinate metabolism warrants mechanistic follow-up. The authors reported that regular exercise and a Mediterranean-style diet are associated with lower circulating succinate, but how these relate to *Dialister* abundance or succinate consumption remain unclear. For instance, could the fermentation of dietary fiber by other taxa, such as *Phascolarctobacterium*, a fast succinate consumer with a reduced abundance in CD, affect *Dialister*-related succinate accumulation? Small-scale interventional studies, such as short-term dietary modifications in patients with CD, could test whether such interventions alter the *Dialister*-succinate axis, providing actionable insights for CD management. Additionally, excluding patients with recent antibiotic use, a key confounder of the gut microbiota, is a strength, but future research should examine how CD treatments such as anti-tumor necrosis factor agents and thiopurines influence the *Dialister*-succinate axis, which is crucial for tracking treatment response.

A critical future direction is to dissect the molecular basis of *Dialister*'s slow succinate consumption and its contribution to sustained succinate accumulation in CD. Although this study identified *Dialister* as a slow succinate consumer associated with impaired succinate clearance, the specific metabolic pathways, such as the activity of succinate dehydrogenase or fumarate reductase, differentiating this microbe from fast consumers such as *Phascolarctobacterium* remain unexplored. Furthermore, although the study identified a link between succinate and pro-inflammatory responses through SUCNR1, the downstream cellular processes, such as macrophage polarization, T-cell activation, or epithelial barrier disruption, require mechanistic validation. *In vitro* co-culture models with intestinal epithelial or immune cells could help clarify how *Dialister*-derived metabolic signals influence SUCNR1-dependent cytokine production (*e.g.*, interleukin-1β, tumor necrosis factor-α) or barrier integrity markers (*e.g.*, claudin-1, zonula occludens-1). The study utilized 16S rRNA sequencing and succinate quantification, but integrating multi-omics approaches such as metagenomics, metatranscriptomics, proteomics, or host transcriptomics could offer deeper insights into the gut ecosystem in CD. Metagenomics could identify microbiota genes related to succinate production or consumption, whereas host transcriptomics might uncover the effects of succinate or *Dialister* on host pathways, including hypoxia-inducible factor 1-α signaling and tight junction regulation.

Additionally, therapeutic strategies targeting the *Dialister*-succinate axis warrant exploration. Precision probiotics or synbiotics, such as fast succinate consumers, including *Phascolarctobacterium*, could be used to compete with *Dialister* and lower succinate levels. More rigorous research is required to investigate the competitive effects between other fast succinate consumers and *Dialister*, to gradually build the framework for precision probiotic therapy for CD. These strategies should be evaluated in randomized controlled trials by measuring changes in CD activity and *Dialister* abundance. Fecal microbiota transplantation should be optimized by selecting donors with low *Dialister* and high *Phascolarctobacterium* levels for future randomized controlled trials, and its impact on succinate normalization and recurrence prevention should be examined. Small-molecule therapies, including SUCNR1 antagonists or fumarate reductase inhibitors, should be assessed for their ability to decrease succinate-driven inflammation and microbial succinate production. Furthermore, dietary interventions, particularly involving omega-3 fatty acids, should be explored to influence succinate-metabolizing microbes or host metabolism. These strategies should be tested in preclinical CD mouse models, followed by phase I/II trials in patients with CD.

CD is a chronic IBD with significant effects, underscoring the need for better treatments. Boronat-Toscano *et al*[1] identified succinate and *Dialister* as key factors in CD pathophysiology, suggesting new precision care pathways. Their findings should guide future research on causality, strain-specific roles, and clinical applications to enhance outcomes for patients with CD.

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FOOTNOTES

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REFERENCES

1 **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**: 112618 [*RCA*] [PMID: 41378335 DOI: 10.3748/wjg.v31.i45.112618] [FullText] [Full Text(PDF)]

2 **Sila S**, Jelić M, Trivić I, Tambić Andrašević A, Hojsak I, Kolaček S. Altered Gut Microbiota Is Present in Newly Diagnosed Pediatric Patients With Inflammatory Bowel Disease. *J Pediatr Gastroenterol Nutr* 2020; **70**: 497-502 [*RCA*] [PMID: 31899727 DOI: 10.1097/MPG.0000000000002611] [FullText]

3 **Alam MT**, Amos GCA, Murphy ARJ, Murch S, Wellington EMH, Arasaradnam RP. Microbial imbalance in inflammatory bowel disease patients at different taxonomic levels. *Gut Pathog* 2020; **12**: 1 [*RCA*] [PMID: 31911822 DOI: 10.1186/s13099-019-0341-6] [FullText] [Full Text(PDF)]

4 **Cao P**, Chen Y, Guo X, Chen Y, Su W, Zhan N, Dong W. Fusobacterium nucleatum Activates Endoplasmic Reticulum Stress to Promote Crohn's Disease Development *via* the Upregulation of CARD3 Expression. *Front Pharmacol* 2020; **11**: 106 [*RCA*] [PMID: 32153411 DOI: 10.3389/fphar.2020.00106] [FullText] [Full Text(PDF)]

5 **Moshkovskaya M**, Vakhrusheva T, Rakitina D, Baykova J, Panasenko O, Basyreva L, Gusev S, Gusev A, Mikhalchik E, Smolina N, Dobretsov G, Scherbakov P, Parfenov A, Fadeeva N, Pobeguts O, Govorun V. Neutrophil activation by Escherichia coli isolates from human intestine: effects of bacterial hydroperoxidase activity and surface hydrophobicity. *FEBS Open Bio* 2020; **10**: 414-426 [*RCA*] [PMID: 31961067 DOI: 10.1002/2211-5463.12796] [FullText] [Full Text(PDF)]

6 **Effenberger M**, Reider S, Waschina S, Bronowski C, Enrich B, Adolph TE, Koch R, Moschen AR, Rosenstiel P, Aden K, Tilg H. Microbial Butyrate Synthesis Indicates Therapeutic Efficacy of Azathioprine in IBD Patients. *J Crohns Colitis* 2021; **15**: 88-98 [*RCA*] [PMID: 32687146 DOI: 10.1093/ecco-jcc/jjaa152] [FullText]

7 **Xiu W**, Chen Q, Wang Z, Wang J, Zhou Z. Microbiota-derived short chain fatty acid promotion of Amphiregulin expression by dendritic cells is regulated by GPR43 and Blimp-1. *Biochem Biophys Res Commun* 2020; **533**: 282-288 [*RCA*] [PMID: 32958255 DOI: 10.1016/j.bbrc.2020.09.027] [FullText]

8 **Banerjee A**, Herring CA, Chen B, Kim H, Simmons AJ, Southard-Smith AN, Allaman MM, White JR, Macedonia MC, Mckinley ET, Ramirez-Solano MA, Scoville EA, Liu Q, Wilson KT, Coffey RJ, Washington MK, Goettel JA, Lau KS. Succinate Produced by Intestinal Microbes Promotes Specification of Tuft Cells to Suppress Ileal Inflammation. *Gastroenterology* 2020; **159**: 2101-2115.e5 [*RCA*] [PMID: 32828819 DOI: 10.1053/j.gastro.2020.08.029] [FullText]

9 **Monfort-Ferré D**, Caro A, Menacho M, Martí M, Espina B, Boronat-Toscano A, Nuñez-Roa C, Seco J, Bautista M, Espín E, Megía A, Vendrell J, Fernández-Veledo S, Serena C. The Gut Microbiota Metabolite Succinate Promotes Adipose Tissue Browning in Crohn's Disease. *J Crohns Colitis* 2022; **16**: 1571-1583 [*RCA*] [PMID: 35554517 DOI: 10.1093/ecco-jcc/jjac069] [FullText] [Full Text(PDF)]

10 **Mao H**, Yang A, Zhao Y, Lei L, Li H. Succinate Supplement Elicited "Pseudohypoxia" Condition to Promote Proliferation, Migration, and Osteogenesis of Periodontal Ligament Cells. *Stem Cells Int* 2020; **2020**: 2016809 [*RCA*] [PMID: 32215014 DOI: 10.1155/2020/2016809] [Full Text] [Full Text(PDF)]

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