



Letter to the Editor: Deciphering macrophage heterogeneity and optimizing probiotics *via* spatial multi-omics

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Abstract

We read the paper published in *World Journal of Gastroenterology* by Yang *et al* on how *Bifidobacterium* species alleviate colitis by modulating deoxycholic acid (DCA) levels and macrophage polarization, which provides important insights into the microbiome-immune axis. However, the classic M1/M2 polarization model oversimplifies the plasticity of macrophages and fails to account for the spatial heterogeneity of the intestinal microenvironment. Therefore, we propose integrating spatial transcriptomics and spatial metabolomics to resolve the intricate correlations between DCA distribution and specific macrophage subsets. Building upon this, we further discuss the transition from broad-spectrum probiotic supplementation to mechanism-driven precision probiotic strategies, emphasizing the future need to develop engineered strains capable of spatial awareness and metabolic pathway remodeling. This spatial multiomics-guided precision intervention framework holds promise for advancing colitis treatment toward approaches with greater mechanistic depth.

Key Words: Macrophage plasticity; Spatial transcriptomics; Spatial metabolomics; Deoxycholic acid; Precision probiotics; Colitis

Core Tip: In colitis, macrophage phenotypes extend beyond the simple M1/M2 dichotomy, and their functions are shaped by the spatial microenvironment wherein they reside. Although existing spatial omics studies have delineated the cellular distributions within inflammatory regions, whether the spatial enrichment of key metabolites (such as deoxycholic acid) across distinct mucosal layers drives divergent macrophage transcriptional programs remains unclear. Spatial multiomics offers the potential to resolve the issue of metabolite-immune spatial specificity, thereby providing a reference for developing precise probiotic therapies with well-defined targets of action.

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TO THE EDITOR

We read with great interest the study by Yang *et al*[1] published in *World Journal of Gastroenterology*, which elucidated how *Bifidobacterium* species alleviate high fat diet induced colitis by reducing fecal deoxycholic acid (DCA) levels and inhibiting M1-type macrophage polarization. This work provides valuable evidence for understanding the link among diet, microbial metabolism, and immune dysregulation and highlights potential avenues for probiotic intervention.

LIMITATIONS OF THE M1/M2 MODEL: ABSENCE OF SPATIAL AND METABOLIC INFORMATION

Although the M1/M2 model has long been used to describe macrophage functional states, the central challenge in the field is no longer simply to negate this dichotomy but to determine how high-dimensional single-cell transcriptomic data can be integrated and interpreted within their true tissue spatial context. Macrophages exhibit high plasticity, and their phenotypes exist along a continuous functional spectrum that is dynamically shaped by complex signals within the local microenvironment, including specific metabolites[2,3]. However, in the absence of spatial tissue information, these subsets are often discussed separately from their microbial exposure and metabolic contexts, which limits our understanding of their actual biological functions.

Recently, spatial transcriptomics has been applied to map the distribution of immune cells within intestinal tissues; however, existing studies have predominantly focused on the spatial localization of cell types or states, with direct analysis of the heterogeneous tissue distribution of metabolites and their influence on local immune responses remaining scarce[4-6]. In particular, whether the distribution of bile acids, such as DCA, is significantly different across distinct anatomical layers of the colonic mucosa (*e.g.*, regions adjacent to the epithelium *vs* deeper areas of the lamina propria) and whether these differences correspond to distinct transcriptional signatures of functionally divergent macrophage subsets remain largely understudied.

KEY VALUE OF SPATIAL MULTI-OMICS: PROPOSING A TESTABLE PREDICTION

Against this background, integrating spatial transcriptomics with spatial metabolomics holds promise for providing more direct evidence to elucidate the relationship between bile acids and local immune responses. Such an integrated approach not only preserves the spatial location information of immune cells but also helps to simultaneously visualize the distribution of key metabolites within tissues, thereby preventing the dissociation of metabolic signals from their actual functional contexts[7,8]. Guided by this rationale, we propose a testable hypothesis: In colitis models, DCA enrichment near the epithelial region might more frequently co-localize with macrophages, exhibiting a transcriptional profile associated with chemotaxis regulation and barrier maintenance; conversely, localized elevation of DCA levels in deeper lamina propria may correlate more strongly with gene expression patterns linked to enhanced inflammatory responses and tissue damage. If this hypothesis is confirmed, it would help clarify that bile acids may exert distinct immunological effects within different tissue microniches.

ADVANCING TOWARD MECHANISM-DRIVEN PRECISION PROBIOTIC THERAPY

A deeper understanding of the spatial relationship between bile acids and immune cells would also facilitate the re-evaluation of probiotic application strategies in colitis. In this context, precision probiotics refer not only to the selection and supplementation of specific strains but also to the targeted modulation of gut microbial functions based on well-defined metabolic pathways and precise tissue localization[9]. Beyond simply enhancing bile salt hydrolase activity, future research may explore more sophisticated strategies, such as engineering bacteria capable of sensing and responding to local bile acid levels or inflammatory signals or modulating multiple bile acid-related pathways to

influence host immune responses, thereby improving the specificity of interventions[10,11].

Notably, application of spatial metabolomics to intestinal tissues is limited by technical challenges, including those related to metabolite signal stability, spatial resolution, and integration methods for multiomics data[12,13]. Therefore, currently, such research is more suited for elucidating biological questions rather than directly guiding clinical practice. Nevertheless, full acknowledgment of these practical challenges may lay the groundwork for subsequent technological advancements and translational research in this field.

CONCLUSION

In summary, Yang *et al*[1] opened a crucial avenue for exploration. We believe that the key to the next breakthrough lies not in whether spatial technologies are adopted but in leveraging spatial multiomics to clarify the immune-instructive roles of metabolites within distinct tissue niches, thereby enabling the development of truly mechanism-driven precision probiotic strategies. By focusing on this underexplored spatial-metabolic-immune interface, this approach might open pathways for substantive advances in both fundamental research and therapeutic innovation for colitis.

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FOOTNOTES

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Author contributions: Meng D performed the literature investigation and synthesis, developed the central scientific arguments (macrophage spatial heterogeneity and spatial multi-omics-guided precision probiotics), and drafted the original manuscript. Zhang BB and Zhao JN jointly conceptualized the overall framework of the Letter to the Editor, defined the key scientific positioning and scope, and provided methodological and mechanistic guidance to ensure the proposed hypotheses were coherent, testable, and aligned with current spatial multi-omics and microbiome-immune research. Zhang BB and Zhao JN carried out substantive critical revision throughout, strengthening the logical structure and academic rigor, refining the key messages, and improving clarity, accuracy, and

coherence across all sections. Zhang BB and Zhao JN served as co-corresponding authors because they shared primary senior responsibility for the work from conception to submission, jointly supervised and directed the manuscript's scientific trajectory, and took final decision-making authority on content and framing. They also provided complementary expertise and cross-disciplinary oversight that was essential to integrate the microbiome–bile acid–macrophage axis with spatially resolved multi-omics reasoning and translational interpretation, and they jointly assumed accountability for the integrity of the work, including verification of key statements, consistency of interpretation, and approval of the final version. In addition, they coordinated submission-related tasks and communication with the journal, responded to editorial/reviewer queries, and ensured that all revisions were implemented accurately and on time. All authors read and approved the final manuscript.

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