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Opinion

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A model for microbiota-mediated regulation and intervention of intestinal motility

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Introduction

Intestinal motility underpins nutrient absorption, waste excretion, and toxin clearance. Its impairment is a core pathological feature of functional constipation, slow-transit constipation, irritable bowel syndrome, and related disorders. Traditional research has emphasized the intrinsic contractile properties of intestinal smooth muscle and the autonomous rhythmicity of the enteric nervous system (ENS). However, mounting evidence indicates that the gut microbiota and its metabolites are indispensable regulators of intestinal motility [1]. The data indicate that microbiota and intestinal motility form a bidirectional, homeostatic regulatory system: hypothalamic neurons can rapidly remodel the gut microbiota [2]; the microbiota participates in motility regulation via mechanosensitive channels such as Piezo2 [3]; and transit time critically shapes microbial composition and metabolism [4].

In this perspective article, we synthesize recent findings into a model—termed the "Microbiota-Mediated Regulation and Intervention of Intestinal Motility" model. We propose that the core pathological pattern of dysmotility is a vicious cycle of "microbiota dysbiosis→impaired intestinal motility→exacerbated dysbiosis". Specifically, gut microbiota positively drives intestinal motility through a four-axis network of metabolic, neuronal, immunological, and mechanical signaling; impaired motility, in turn, exacerbates microbiota imbalance by prolonging transit time, altering mechanical signals, and disrupting the anaerobic microenvironment; microbiota-based interventions can restore metabolic capacity and signaling pathways, break the vicious cycle, and reestablish intestinal motility homeostasis. The novelty of this model lies in explicitly integrating four self-reinforcing pathological sub-loops and proposing multi-node combination strategies, as well as articulating a threshold-based transition from compensation to decompensation.

Core Model

Basic tenets

The model comprises four core tenets. First, microbial metabolites can positively modulate intestinal motility: butyrate, tryptophan derivatives, and ammonia regulate serotonin (5-HT) synthesis in enterochromaffin (EC) cells, ENS excitability, pacemaker activity of interstitial cells of Cajal, and smooth muscle contractility [1,3]. Second, motility status conversely shapes microbial composition and function: impaired motility prolongs transit, disturbs mechanical signals, elevates intraluminal oxygen tension, and alters pH, thereby influencing microbial composition and metabolism [4]. Third, a self-reinforcing vicious cycle develops under pathological conditions: dysbiosis and reduced motility mutually reinforce each other; we postulate that once a critical threshold (*e.g.*, of transit time or butyrate concentration) is crossed, the system shifts from compensation to decompensation, making spontaneous recovery difficult [3,4]. Fourth, breaking the vicious cycle is the fundamental therapeutic logic: restoring functional microbiota, reconstituting short-chain fatty acid (SCFA) and tryptophan metabolism, and enhancing 5-HT and acetylcholine (ACh) signaling can optimize the microbial colonization environment and restore intestinal motility homeostasis [5,6].

Key regulatory pathways

Butyrate-5-HT pathway

SCFAs, particularly butyrate, are key signaling molecules that regulate 5-HT synthesis in EC cells. Yano *et al.* [1] showed that colonization with butyrate-producing gut commensals in germ-free mice significantly increased colonic and systemic 5-HT levels. Reigstad *et al.* [7] further revealed that SCFAs promote EC cell expression of tryptophan hydroxylase 1, thereby increasing 5-HT production. Butyrate promotes 5-HT synthesis via dual mechanisms: activation of G-protein-coupled receptors free fatty acid receptor 2 (FFAR2)/FFAR3/G protein-coupled receptor 109A and inhibition of histone deacetylases (HDACs) [8]. Commensals such as *Akkermansia muciniphila* further consolidate the butyrate-5-HT axis [9].

Tryptophan-aryl hydrocarbon receptor signaling

Gut microbial metabolism of tryptophan yields indole derivatives (*e.g.*, indole-3-acetate, indole-3-propionate) that activate the aryl hydrocarbon receptor (AhR), thereby modulating mucosal barrier function and immune tolerance [10–12]. Indole-3-acetate from *Lactobacillus* spp. engages the AhR-poly(ADP-ribose) polymerase 1 axis to promote DNA repair [13]. In contrast, indole metabolites from *Fusobacterium varium* upregulate Piezo2, linking tryptophan metabolism to altered motility via Piezo2 [3].

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Microbiota-immune balance regulatory pathway

Microbial metabolites regulate immune homeostasis through multiple routes. SCFAs promote regulatory T cell (Treg) differentiation and suppress T helper 17 cell (Th17)-driven inflammation via G protein-coupled receptor 43 and HDAC inhibition [14–17]; secondary bile acids influence Th17 polarization through farnesoid X receptor/Takeda G protein-coupled receptor 5/pregnane X receptor signaling; tryptophan metabolites modulate the Th17/Treg balance via AhR-IL22 signaling [17]. Moreover, the microbiota can influence ENS neurogenesis through Toll-like receptor 2 signaling, linking immune cues to ENS function [18].

"Microbiota-ammonia-Ach" metabolic compensation pathway

A recent study (currently limited to a single report) reported that, during ACh deficiency and impaired intestinal motility, the gut microbiota upregulates urease activity, increasing ammonia production. The ammonia promotes ACh release by upregulating Cav2.1, thereby driving neuromuscular transmission [19]. The study also found that *Lysinibacillus fusiformis*, isolated from the feces of constipated patients and possessing strong urease activity, significantly elevates ACh levels and restores intestinal motility [19]. We note that this microbiota-ammonia-ACh pathway requires independent replication.

Self-reinforcing pathological loops and multi-node intervention strategies

Within this model, bidirectional interactions between the gut microbiota and intestinal motility can form four self-reinforcing vicious subloops under pathological conditions [3,4]. (1) Butyrate-hypoxia loop. Impaired motility prolongs transit time, reducing luminal oxygen consumption by colonocytes, raising luminal oxygen tension, suppressing strict anaerobes that produce butyrate, further decreasing butyrate and worsening motility [4,20]. (2) Impaired motility and Piezo2-*Fusobacterium* loop. Impaired motility disrupts mechanical signaling and microbial niches, promoting *F. varium* expansion; its indole metabolites upregulate Piezo2, exacerbating motility dysfunction [3]. (3) ENS damage loop. Dysbiosis increases harmful metabolites such as lipopolysaccharide (LPS), damaging ENS neurons, reducing motility and secretion, promoting overgrowth and translocation, and generating more metabolites that worsen ENS injury [18]. (4) Brain-gut axis central loop. Central signaling abnormalities alter gut motility and microbial colonization; microbial metabolites feedback along the brain-gut axis to affect central nervous system function, stabilizing the pathology at a higher level [2]. These loops overlap to form a vicious cycle of "dysbiosis→reduced motility→worsened microenvironment→further dysbiosis", driving disease progression.

Therefore, we propose a multi-node combination intervention strategy: (1) Pathogen clearance with functional probiotic augmentation: selectively remove *F. varium* while concurrently supplementing butyrate-producing and tryptophan-metabolizing strains (*e.g.*, *Bifidobacterium longum*) to restore butyrate production and transit synergy [3]. (2) Combined restoration of butyrate production and motility: coadminister butyrate precursors/prebiotics with prokinetic agents to reestablish butyrate signaling and propulsion, thereby disrupting the butyrate-hypoxia loop [4,20]. (3) Metabolic compensation with neuroprotection: target the microbiota-ammonia-ACh axis by introducing urease-producing strains (*e.g.*, *L. fusiformis*) to achieve metabolic compensation and higher ACh levels, alongside butyrate supplementation to protect ENS function [18,19]. (4) Chronoregulatory approaches: synchronization of host-microbiota diurnal rhythms is critical for maintaining microbial homeostasis. Circadian misalignment can directly exacerbate each of the four loops—for instance, by blunting the diurnal peak of butyrate producers (worsening loop 1) or by altering mechanosensitive gene expression (affecting loop 2). Thus, restoring circadian alignment could be a key adjunct to disrupting pathological loops [21,22].

Limitations and Future Directions

While the proposed model provides an integrative perspective, several limitations should be acknowledged. First, certain pathways —particularly the microbiota-ammonia-ACh axis and Piezo2-*Fusobacterium* loop—currently rest on limited studies and require independent replication. Second, the postulated "critical threshold" for decompensation remains qualitative; quantitative definitions await empirical determination. Third, the model does not fully address contradictory evidence. Although some meta-analyses suggest that probiotics can reduce intestinal transit time overall, the effect size is modest and heterogeneity across studies is substantial [23]. Moreover, germ-free mouse models—while generally showing slower transit and lower 5-HT levels—exhibit variable motility phenotypes, and some motor parameters can be rectified by butyrate alone, suggesting that the microbiota-motility relationship may be partially mediated by specific metabolites rather than requiring complete microbial ecosystems [24]. Additionally, the existence of individuals with significant dysbiosis but normal motility, as well as those with severe dysmotility but relatively preserved microbiota, indicates that the proposed loops are context-dependent and modulated by host genetics, diet, stress, and medications. Fourth, dose-response relationships for key metabolites remain undefined. Future work should test the model through longitudinal cohort studies, interventional designs, and systems modeling to define thresholds and refine intervention strategies.

Conclusion

In conclusion, despite these limitations, this model offers a novel and heuristic construct for understanding microbiota-motility interactions. By integrating bidirectional pathways into a unified framework with four self-reinforcing sub-loops, it provides a testable foundation for multi-node precision therapy of motility disorders. We hope this model stimulates further empirical investigation and, with continued refinement, accelerates translation from mechanistic insight to clinical application [2,4,21,22].

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Conflict of Interest

The author declares no conflict of interest.

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