

Decoding the Microbiota-Gut-Brain Axis in Major Depressive Disorder: From Molecular Mechanism and Gut Microbiome Dysbiosis to Biomarker Discovery and Precision Therapeutics

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ABSTRACT

The global burden of depression has increased substantially in recent years, making it a major public health problem. Major depressive disorder (MDD) is a multifactorial psychiatric disorder arising from the complex interplay of genetic, environmental, immunological, metabolic, and psychosocial influences. Although the classical monoamine hypothesis has guided antidepressant development for decades, emerging evidence highlights the microbiota-gut-brain (MBG) axis as a pivotal regulator of pathophysiology and a promising target for precision therapeutics. The bidirectional communication between gut microbiota and the central nervous system occurs through interconnected neural, endocrine, immune, and metabolic pathways, influencing emotional regulation, neuroinflammation, and stress responses. Dysbiosis of the gut microbiota is associated with altered microbial metabolites, impaired intestinal barrier integrity, immune activation, and neurotransmitter imbalance, all of which contribute to the onset and progression of MDD. Evidence suggests that altering the gut microbiota will foster the development of effective therapeutic interventions in MDD. Advances in multi-omics technologies have further accelerated the identification of microbiome-derived biomarkers with potential diagnostic, prognostic, and therapeutic value. This article aims to combine mechanistic insights of the MGB axis with clinical applications in MDD to advance biomarker discovery and precision psychiatry.

Keywords: Major depressive disorder, Microbial metabolites, Dysbiosis, Multi-omics technologies, Precision therapeutics, Biomarker discovery

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Introduction

As of 2019, depressive disorders accounted for the greatest percentage of mental disorder disability-adjusted life-years (DALYs) and caused 46.68 million YLDs worldwide, placing second among the top 25 major causes of YLDs at the disorder level. Major Depressive Disorder (MDD), which accounts for 80% of all depressive disorder YLDs, and dysthymia are among these combined causes. In addition to raising the risk of suicide and self-harm, MDD raises the burden of chronic illnesses like diabetes, cancer, and cardiovascular diseases [1]. Our expectations regarding the clinical usefulness of psychotherapies and antidepressant drugs in depression have been lowered in recent years, especially for people who have a history of not responding to multiple standard forms of therapy. This shift became evident as the treatment moved to real-world patients with more inclusion and fewer exclusion criteria, and as intervention delivery became less controlled [2].

MDD is multifactorial, arising from complex interactions of genetics, environmental exposures and psychosocial influences. For many years, the mechanistic framework for MDD was the monoamine hypothesis, which holds that the disorder results from a deficiency of important brain neurotransmitters serotonin, dopamine and norepinephrine. The efficacy of drugs that target these neurotransmitters is limited. A large proportion of patients fail to achieve full recovery, and some patients develop treatment-resistant depression. There is an urgent need to fill this therapeutic gap by exploring new biological frameworks. A novel biological intervention via the microbiota-gut-brain (MGB) axis has paved the way to treat complex MDD. This led to the development of the “microbiota hypothesis of depression”, which suggests that dysbiosis, or disturbance in the healthy balance of microbiota, might disrupt the MGB axis, increasing an individual’s susceptibility to MDD. The most powerful evidence supporting this hypothesis comes from preclinical faecal microbiota transplantation (FMT) studies [3].

The Microbiota-Gut-Brain Axis and its Emerging Role in Major Depressive Disorder

The complex relationship between the gut and brain is playing an important role in the treatment of MDD. There are trillions of bacteria that make up

gut microbiota, which are important for metabolism, immune regulation, and digestion. Moreover, it also influences human behaviour and psychological states through bidirectional communication with the brain via the MGB axis. The comprehensive system of the MGB axis includes gut microorganisms, the gastrointestinal tract, the vagus nerve and the endocrine and immune systems. Research shows that stimuli derived from the gut can directly influence the brain through the vagus nerve. Moreover, metabolic products of gut microbiota can change endocrine balance and neuroinflammation states, thus affecting the brain’s regulation of emotions and cognition [4].

The important neurotransmitters that might be involved in the communication of the MGB axis are dopamine, serotonin, noradrenaline and gamma-aminobutyric acid (GABA). These substances are not only synthesised in the CNS but also in enteroendocrine (EEC) cells under the influence of intestinal peptides and gut microbiota itself. Research shows that gut microbiota have an important impact on the activity of serotonin produced both peripherally and centrally. Specifically, a few members of gut microbiota, including *Candida*, *Streptococcus*, *Escherichia* and *Enterococcus*, can directly produce serotonin. Nevertheless, serotonin significantly affects the composition and activity of gut microbiota.

Research also shows that gut microbiota directly synthesise both dopamine and norepinephrine. Dopamine can be synthesised by the following microorganisms: *Bacillus cereus*, *Bacillus mycoides*, *Bacillus subtilis*, *Escherichia coli*, *Hafnia alvei*, *Klebsiella pneumoniae*, *Morganella morganii*, *Proteus vulgaris*, and *Staphylococcus aureus*. In turn, norepinephrine can be synthesised by *Bacillus mycoides*, *Bacillus subtilis*, *Escherichia coli*, and *Proteus vulgaris*. It has been shown that some types of intestinal bacteria also directly synthesise GABA, mainly *Bifidobacterium* spp. and *Lactobacillus* spp. [5].

Molecular and Cellular Mechanisms Underlying Microbiota-Gut-Brain Axis Dysfunction in Major Depressive Disorder

Gut microbiota communicates with CNS predominantly via dopamine, serotonin, norepinephrine and GABA, but also through intermediate compounds including short-chain fatty acids (SCFAs), tryptophan and secondary bile acids. These neurotransmitters produce signals that are

transported to the brain via afferent VN fibres. In response, the brain sends a signal back to enterochromaffin cells (ECFs) and EECs in the gut wall and mucosal immune system via efferent VN fibres. Activation of VN enhances the gut wall integrity, lowering peripheral inflammation and preventing the release of pro-inflammatory cytokines. Signals produced by the hypothalamus reach the pituitary and adrenal glands and communicate with EECs via the hypothalamic-pituitary-adrenal axis (HPA). The complex regulation of immune responses and enteroendocrine communication maintains a balanced state. If unbalanced, the gut can enter a state of dysbiosis, which may alter intestinal function and the blood-brain barrier, leading to disorders related to the gut and brain [6].

According to recent studies, changes in intestinal permeability are linked to MDD in adolescents according to the lactulose/mannitol change test [7] and found that increased intestinal permeability is linked to translocation of bacteria and their by-products [8]. In addition to a compromised intestinal barrier, increased permeability of the blood-brain barrier (BBB) might be related to MDD and other mental health disorders [9]. Adolescents with early-onset psychosis have been demonstrated to have considerably lower levels of cell adhesion molecules that control BBB permeability [10]. Further studies show that gut microbiota influence neuroinflammation and are involved in the development of depressive symptoms through a mechanism involving the *NLRP3* inflammasome. Th17 cells from the gut infiltrate the CNS, releasing cytokines that cause neuroinflammation by activating neurons, astrocytes, and microglia. This inflammation is associated with stress and mood disorders, which may further affect gut health, creating a feedback loop between the gut and the brain [11].

Dysregulation of microbial metabolites, including short-chain fatty acids (SCFAs), lactate, secondary bile acids, choline metabolites, vitamins, amino acids, estrogen, and tryptophan, is particularly involved in the pathogenesis of MDD. Altered MGB axis, systemic and local inflammation, and epigenetic changes affect multiple brain regions, leading to impaired neurogenesis and neuroplasticity [12]. Mitochondrial dysfunction is also involved in various psychiatric disorders, including depression. Mitochondrial dysfunction in depression, regarding altered genetics and mitochondrial DNA, expression of mitochondrial proteins, oxidative phosphorylation, ATP production, and oxidative stress, can lead to apoptosis and inflammation, decreased neurogenesis, and impaired neurotransmission in neural circuits [13].

Gut Microbiome Dysbiosis in Major Depressive Disorder: Evidence from Preclinical and Clinical Studies

An alteration in the local distribution of microbiota, a change in their functional composition and metabolic processes, or an imbalance in microbial flora, termed dysbiosis, disrupts the natural balance of gut microbiota [14]. The Gut microbiome influences human brain functions through the MGB axis, the bidirectional communication pathway between the brain and gut microbiota, which includes humoral and neural pathways. Animal studies have shown a relationship between gut microbiome dysbiosis (GMD) and abnormal stress response, neuroinflammation and reduced neurogenesis in the host, all of which can contribute to the development of MDD. Experiments using germ-free mice treated with faecal microbiota transplantation (FMT) from MDD patients strongly suggested that gut microbiota contributed to the onset of depressive symptoms. Altered microbial composition in several human studies in a systematic review of 17 studies identified an increase in *eggerthella* and *atopobium* (of the *actinobacteria* phylum), and a decrease in *faecalibacterium* as a common feature. *Faecalibacterium* is a component of butyrate-producing bacteria in the gut, and butyrate has been reported to maintain BDNF and neurogenesis in the hippocampus, improving symptoms. An opposite pattern is identified in the case of *bifidobacterium*, with a lower amount of *Lactobacillus* and *Bifidobacterium* in the gut microbiota of MDD patients compared with healthy controls; a number of animal studies support these findings [15].

A systematic multi-cohort analysis of gut bacteria using a standardized bioinformatics pipeline, identifying and quantifying the prevalence of consistent bacterial markers across cohorts, was conducted. Eight different cohorts with 16s rRNA sequencing data were systematically screened from published journals and combined for analysis. The overall community of depressive-associated gut bacteria was significantly different from healthy controls in terms of Bray-Curtis distance [16]. Recent studies suggest that altering the gut microbiota through probiotics can modulate stress-related behavior and HPA axis activity, with more focus on *bifidobacteria* and *lactobacilli* [17].

Biomarker Discovery and Precision Therapeutics

Microbiota-derived metabolites, including SCFAs, tryptophan metabolites, trimethylamine N-oxide and bile, have emerged as potential biomarkers for depression and anxiety. Human and animal studies indicate that changes in these metabolites are associated with disease severity, progression, and

response to therapy. Microbiota-derived biomarkers in depression and anxiety include butyrate (SCFA), acetate and propionate (SCFAs), kynurenine/tryptophan ratio, and GABA. SCFAs and GABA abundance are reduced in depression and anxiety, while the kynurenine/tryptophan ratio is elevated in depression; it correlates with symptom severity [18]. The possibility of novel microbiota-targeted therapies to restore MGB homeostasis has been thoroughly evaluated. These include probiotic engineering, precision dietary manipulation, bacteriophage therapy, and AI-driven customised medicine [19].

Examining the MGB axis and microbial-based treatment offers a promising way to supplement traditional pharmacotherapies for MDD. Multi-omics approaches, which integrate data from genomics, transcriptomics, proteomics, and metabolomics, provide a comprehensive framework of the molecular mechanisms underlying MDD. Integrated multi-omics has revolutionized our understanding of MDD, from symptom-based descriptions toward molecularly stratified subtypes with convergent dysregulation in synaptic plasticity, immune-inflammatory signaling, HPA-axis modulation, energy metabolism and gut-brain axis. When coupled with AI-driven network modeling and structure-based drug designs, these data offers a roadmap for biomarker-derived biomarker-guided trials and mechanism-based treatments, such as rapid-acting glutamatergic agents, kappa-opioid antagonists, anti-inflammatory interventions, psychedelics and microbiome based strategies. However, significant translational challenges remain [20].

Translational Challenges, Knowledge Gaps and Future Directions

Unfortunately, the signal transduction pathways of the MGB axis, as well as the understanding of inflammation, neurotransmitters, intestinal peptides, and bacterial metabolites, are still not fully understood. Moreover, a large proportion of data on the MGB axis comes from studies on animal models, which, although giving essential information, cannot be directly projected to the human population. Therefore, more studies are required to understand the role of the MGB axis not only in adult organisms, but also in young ones, with the aim of preventing or treating MDD and other mental health problems [21]. Heterogeneity in human clinical trials of microbiota-targeted interventions remains a key challenge in translating MGB axis research to depression treatment. Before being used in clinical settings, microbiota-targeted depression treatments must overcome logistical, safety, and regulatory obstacles.

To address the challenges mentioned above, three research directions are identified to advance the field. First, it is crucial to validate mechanisms in human ex vivo models. Replicating MGB axis signalling in a human-relevant context using 3D coculture systems (such as intestinal organoids paired with brain microvascular endothelial cells) will help validate animal-derived mechanisms (such as SCFA-mediated BBB protection) and lessen reliance on species-mismatched data. Second, it is crucial to develop clinically useful "microbiota typing" tools. This is because routine patient stratification will be made possible by fast and affordable tests (such as PCR-based assays to identify butyrate-producing bacteria like *Faecalibacterium*), which will ensure that interventions are targeted to responders, lower trial heterogeneity, and improve clinical outcomes. Third, testing regimens that combine primary interventions with maintenance strategies to prevent microbiota reversion are a major focus. For instance, a pilot study showed that supplementing FMT with *Akkermansia muciniphila* reduced microbiota reversion by 60% at 12 months, supporting the potential of combination approaches to enhance long-term sustainability [22].

Conclusion

The MGB axis has emerged as a microbiome-based therapeutic opportunity, shifting the paradigm from symptom management to etiological interventions. By elucidating the intricate interplay between brain, immunological, and metabolic pathways and using advancements in synthetic biology and artificial intelligence, we have entered a new era of mental health, where personalized microbiome therapy becomes as common as pharmacotherapy. However, major challenges remain, from the pre-clinical to clinical translatability gap, human research heterogeneity, and safety/regulatory obstacles. In order to address these, interdisciplinary cooperation is needed, combining data science, neuroscience, and microbiology to create stratified long-lasting therapies. The potential of a gut-driven approach is undeniable, but achieving it requires thorough, patient-centered research.

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