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Bacteroides thetaiotaomicron in Gut Homeostasis: Genomic Adaptation, Metabolic Function, and Immune Modulation

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Abstract: *Bacteroides thetaiotaomicron*, a member of the gut commensal flora, is highly versatile and an important part of gut homeostasis in humans. Despite growing interest in its diverse biological functions, no previous review has comprehensively integrated its established roles in gut homeostasis with its emerging implications for gut–brain axis signaling, cancer immunomodulation, and future microbiome-based therapeutics. This review will fill this gap by offering an integrated and mechanistic review of these mutually connected functions. Specifically, this review focuses on the core biological functions of *B. thetaiotaomicron*, including genomic adaptation and regulatory plasticity, polysaccharide metabolism, nutrient recycling, outer membrane vesicle-mediated host immune modulation, maintenance of intestinal barrier integrity, microbiota homeostasis, colonization resistance, and its potential as a next-generation probiotic. We further discuss two emerging translational areas: its production of neuroactive metabolites involved in gut–brain communication and its role in shaping responses to cancer immunotherapy through the toll-like receptor 4/interleukin-12/T helper 1 axis in combination with immune checkpoint blockade primarily shown in murine models and observational human studies. Finally, we highlight current limitations, including reliance on animal models, lack of clinical validation, incomplete metabolite characterization, and a lack of understanding of microbiome–immune interactions, and provide a blueprint for future directions in multi-omics, microbial engineering with clustered regularly interspaced short palindromic repeats, and synthetic biology for precision microbiome medicine.

Keywords: *Bacteroides thetaiotaomicron*, gut microbiota, live biotherapeutics, gut–brain, CRISPR

1. Introduction

The human gastrointestinal tract harbors a dense metabolically active microbial community that is the basis of host physiology and immunologic homeostasis [1]. Over the past decade, the accumulating evidence has introduced the gut microbiota as one of the most significant modulators of intestinal barrier integrity, nutrient metabolism, and immune system formation [2]. A wide variety of disorders have been linked to maladaptation of this complex ecosystem, such as inflammatory bowel disease, metabolic syndrome, autoimmune diseases, and chronic low-grade inflammation [3, 4]. Among *Bacteroides* spp., one of the most abundant and genetically stable genera in the healthy human gut, *Bacteroides thetaiotaomicron* was the first to have its genome sequenced and has become one of the most common commensals, employed in host–microbe interaction studies. It is a high-profile anaerobic gram-negative bacterium that belongs to the phylum Bacteroidetes with a large repertoire of loci of polysaccharide utilization enabling it to degrade a diverse range of dietary and host-derived glycans [5, 6]. Besides the metabolic roles mentioned, recent studies have highlighted its possible role in the regulation of mucosal immunity, changing epithelial barrier activity, and also stability of the microbial communities [7]. Despite substantial progress in characterizing *B. thetaiotaomicron*'s metabolic and immunological roles, several critical knowledge gaps persist: the mechanistic basis of its gut–brain signaling, its species-specific contribution to cancer immunotherapy, and standardized frameworks for its clinical application remain insufficiently synthesized. This review addresses these gaps by providing an integrated mechanistic overview of *B. thetaiotaomicron* across gut homeostasis and neuroimmunological and oncological contexts, thereby delineating a translational roadmap for its application in precision microbiome medicine.

2. Genomic Features and Adaptation Mechanisms

B. thetaiotaomicron can thrive in the post-weaning intestine because of its highly dynamic genome, enabling metabolic adaptation and condition-specific expression of genes. This *B. thetaiotaomicron* genome has been estimated to encode 226 glycoside hydrolases and 15 polysaccharide lyases and can hydrolytically degrade the polysaccharides that we cannot process in our own bodies because we also lack the required enzymes (e.g., *B. thetaiotaomicron* expresses 64 arabinosidases, xylanases, and pectate lyases) [8, 9].

It constitutes the most detailed 16S rRNA sequence enumeration of adult human colonic microflora published to date. This

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genetically manipulable organism served as a model to understand the effects of constituents of the microflora on gut gene expression [7]. The *B. thetaiotaomicron* genome is highly plastic and contains condition-specific genes with the assistance of which it adapts to the gut. The extensive metabolic specialization was functionally linked to over 600 genes and the identification of major loci in a genome-wide fitness profiling study. It is characterized by an extremely large repertoire of polysaccharide utilization loci (PULs), which cleave a large range of dietary and host glycans, in most instances in a cooperative and substrate-selective way. The bacterium uses non-canonical pathways to synthesize arginine and has the capacity to respond to changes in nitrogen metabolism by switching to alternative enzymes using ammonium sensitivity, indicating that the bacterium regulates its metabolism in vivo based on the diet. Other adaptations include glycosaminoglycan usage, a bile salt-inducible efflux system, which is stress-tolerant, and a novel 3-keto-intermediate-based metabolite pathway of disaccharide-degrading activity, all of which ensure ecological fitness and gut colonization [10].

In addition to having a large PUL repertoire, *B. thetaiotaomicron* undergoes rapid in vivo genomic diversification, which facilitates gut adaptation. The reversible genomic configurations produced by the phase-variable shufflons, especially the BT2262-BT2269 locus, are involved in increasing mucus association and colonization fitness. The high rate of occurrence of de novo polymorphisms and clonal interference, which goes with gut colonization, suggests that there is intense selection that is still going on. Hybrid two-component system regulators are incredibly enriched with mutations, demonstrating that regulatory rewiring of PUL expression and nutrient sensing is a major adaptive response, and recurring mutations in TonB-dependent transporters show that their efficient acquisition of host glycans is selected. Niche-specific evolutionary forces are also further evidenced by spatially greater diversity in the small intestine [11–13]. Along with the previously described genomic diversification, transcriptome-scale independent component analysis (BtModulome) has determined the global regulatory structure of *B. thetaiotaomicron*, clarifying 110 autonomously regulated sets of genes that describe the majority of the transcriptional variation. This system demonstrates multilayered regulation of PUL expression, bile salt-responsive modules, and networks of regulation, including several hitherto uncharacterized ECF-σ factors. These sigma factors are involved in the coordination of important adaptive activities such as oxidative and redox stress response, nutrient uptake, capsular polysaccharide regulation, and stringent response-mediated in vivo fitness. Interestingly, SigW-1 will suppress a number of PUL genes in trans, which refutes the classical paradigm of locus-restricted PUL regulation. The modular iModulon organization also offers a systems-scale foundation for functional prediction and strain engineering of this gut commensal [14, 15]. All these observations reiterate the importance of genome plasticity and regulatory modularity in the process of niche-specific adaptation and in vivo fitness. The key genomic determinants underlying *B. thetaiotaomicron* adaptation to the gut environment, along with their functional roles and adaptive significance, are summarized in Table 1.

2.1. *B. thetaiotaomicron* in polysaccharide metabolism

The *Bacteroides species*, especially *B. thetaiotaomicron* in particular, is a significant component of the human gut microbiome because it has adapted to degrading more complex carbohydrates in the diet that cannot be degraded by the host [16–18]. These bacteria use PULs, modular genetic systems that encode glycoside hydrolases (GHs), susD-like binding proteins, and TonB-dependent transporters (TBDTs) to degrade polysaccharides into oligosaccharides and monosaccharides, which are then fermented to short-chain fatty acids (SCFAs) like acetate and propionate, as illustrated in Figure 1 [19, 20]. Recent articles highlight the importance of numerous TonB homologs in *B. thetaiotaomicron* in enhancing its ability to uptake carbohydrates, and mutants show impairment of growth on a wide variety of glycans including levan, which highlights strain-specific variations in the utilization of plant-derived fibers as an energy source [19]. Similarly, *Bacteroides* spp. including *B. ovatus, B. uniformis, B. fragilis,* and *B. thetaiotaomicron* actively ferment purified polysaccharide of Fuzhuan brick tea (FBTPS-3), upregulating GH28 family enzymes of rhamnogalacturonan I breakdown and generating SCFAs to enhance colonic health [21].

Table 1. Genomic determinants of gut adaptation in *B. thetaiotaomicron*

Feature	Key examples	Primary role	Adaptive significance	Reference
CAZymes	226 GHs, 15 PLs	Glycan degradation	Dietary niche expansion	[8, 9]
PULs	susC/D, CAZymes	Polysaccharide utilization	Nutrient versatility	[10]
HTCS regulators	BT2391, BT3172	PUL regulation	Glycan sensing in vivo	[11–13]
TonB transporters	TBDTs	Glycan uptake	Competitive fitness	[11–13]
Phase variation	BT2262–BT2269	Reversible gene expression	Mucus colonization	[11, 12]
Genome diversification	SNPs, clonal interference	Rapid evolution	Environmental selection	[11–13]
Nitrogen switch	DapL/Ddh; CarAB/CarB2	Ammonium response	Diet-dependent metabolism	[10]
Arginine pathway	N-succinyl route	Amino acid biosynthesis	Nutrient limitation survival	[10]
GAG utilization	CS, HA systems	Host glycan use	Mucus persistence	[10]
Bile resistance	BT2792–2795	Efflux pump	Stress tolerance	[10]
Disaccharide pathway	3-keto intermediate	Sugar metabolism	Substrate expansion	[10]
iModulons	110 modules	Global regulation	Coordinated adaptation	[14]
ECF-σ factors	SigH-1, SigW-1	Stress and CPS control	In vivo fitness	[14]
Spatial adaptation	Small intestine diversity	Niche selection	Ecological flexibility	[11–13]

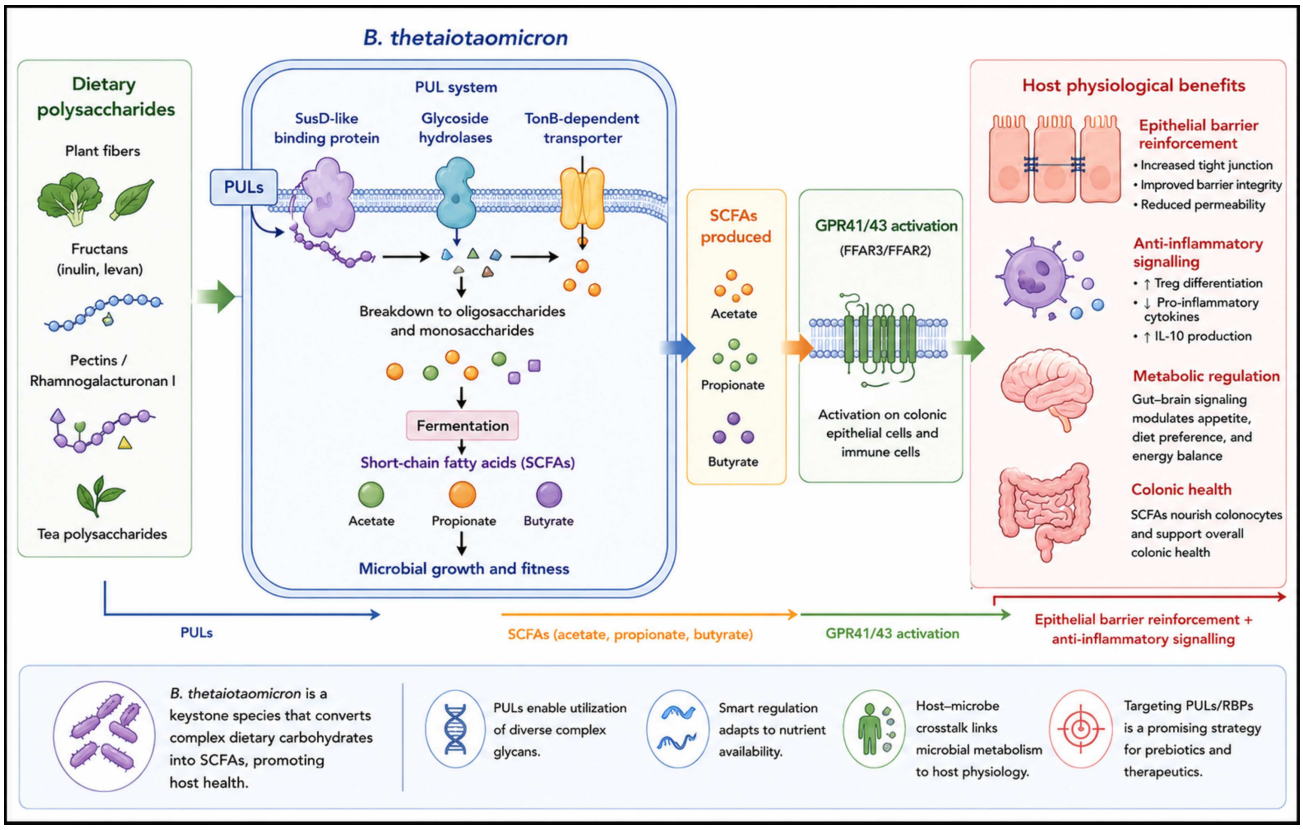

Figure 1. Role of *Bacteroides thetaiotaomicron* in polysaccharide metabolism and host benefits. *B. thetaiotaomicron* degrades complex dietary polysaccharides through polysaccharide utilization loci (PULs), producing short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate. These metabolites contribute to epithelial barrier integrity, immune regulation, metabolic balance, and overall colonic health, highlighting its role as a key gut symbiont

2.2. The utilization-molecular regulation

These PULs are regulated by complex post-transcriptional processes that entail the binding of these PULs by RNA-binding proteins (RBPs). Global RBP RbpB in *B. thetaiotaomicron* attaches to single-stranded RNA sequences in PUL operons and capsular polysaccharide loci to control expression in response to nutrient changes; RbpB mutants have a growth defect on raffinose-family oligosaccharides, and its involvement in coordinating microbial fitness has been demonstrated [22]. Another new family of RBPs also regulates polysaccharide metabolism and binds mRNAs to stabilize or destabilize transcripts according to the abundance of glycans, as shown in genetic screens involving these regulators in metabolic reprogramming [23]. Comparative proteomics in response to changing diets, including fucose versus mucin-O-glycans, shows dynamic fucosylation of glycoproteins, including two-component signal transduction systems and ammonium transporters, which respond to changing pol [20].

2.3. Host–microbial crosstalk and physiological effects

Besides microbial metabolism, *Bacteroides* carbohydrate metabolism affects host physiology. Preferential degradation of fructans by fructan-fermenting *Bacteroides* strains in gnotobiotic mouse models controls host food intake and preference for non-fermentable diets, which is mediated by post-intestinal reward signaling and hypothalamic stimulation, therefore linking the composition of the microbiota to the regulation of appetite and energy homeostasis [24]. This communication is extended to immune homeostasis and protection, where fermentation by PUL improves the integrity of the epithelia and suppresses inflammation in the presence of SCFAs. A combination of these findings of 2021–2025 studies makes *Bacteroides* a keystone species in gut ecology, which can be designed in prebiotics as a way to target PULs/RBPs to optimize host metabolic and immune functioning [21–24].

3. Interaction with the Host Immune System

B. thetaiotaomicron communicates with the host immune system in several ways that allow the intestinal microbiota to interact with immune cells and influence mucosal homeostasis. One of the key processes is the formation of outer membrane vesicles (OMVs), which carry bacterial elements through the barrier of the intestinal mucus. They possess bacterial antigens and bioactive molecules that can be delivered to host immune cells without having to invade the bacteria directly. It has been experimentally proven that antigens of *B. thetaiotaomicron* can travel to host immune cells via OMVs, which depends on sulfatase, permitting the antigens of microbes to enter antigen-presenting cells within tissues of the intestines [25]. This research has shown that the activity of sulfatase aids in the penetration of the OMV across the mucus layer, where the antigens of the bacteria are detected by the host immune system and hence contribute to the process of immune recognition. The mechanism emphasizes the interaction that exists between commensal bacteria and host immunity, whereby the delivery of antigens is controlled, with the bacteria remaining within the luminal intestines.

B. thetaiotaomicron OMVs also modulate the reaction of immune cells, especially in immune regulation. Research on human immune cells has found that vesicles of this bacterium have the capability of provoking regulatory dendritic cell responses in healthy conditions [26]. The immunoregulatory properties of these dendritic cells facilitate the tolerance of the immune system within the intestinal tract. Nevertheless, it was also stated in the same research that this regulatory effect is distorted in people with inflammatory bowel disease (IBD), and consequently, this vesicle-mediated host-microbiota communication might be impaired in the case of intestinal inflammation [26]. Further studies have also shown that extracellular vesicles released by *B. thetaiotaomicron* can prime innate immune cells and induce anti-inflammatory responses, meaning that vesicle-associated molecules influence the immune signaling mechanisms in the gut [27]. Moreover, transcriptomic studies have revealed that these vesicles may have a type-specific effect on host immune pathways; that is, various populations of immune cells react in different ways to vesicle-associated cues [28]. All of this suggests that vesicle-mediated signaling is a major activity through which *B. thetaiotaomicron* can communicate with host immune cells.

B. thetaiotaomicron possesses some bacterial components in addition to the vesicle-mediated interactions, which mediate immune signaling. The polysaccharide capsules on the surface of this bacterium take part in the process of regulating the host immune system by presenting and recognizing bacterial antigens in the intestine. Experimental studies have reported that the capsules allow the bacterium to precisely tune immune responses in the presence of an existing intestinal antigen, indicating that the capsular structures are involved in the regulation of host immunologic recognition of bacterial components [29]. The capsular polysaccharides enable the bacteria to react to the host immune system and stabilize a symbiotic relationship in the intestines by controlling the availability of antigens in the bacterium.

Various studies have also been able to identify bacterial genes and metabolic systems that contribute to the immunomodulatory effect of *B. thetaiotaomicron*. One of them is the BT1549 gene, which has been known to organize the bacteria to mediate the synthesis of the anti-inflammatory cytokine interleukin-10 (IL-10) in vitro [30]. This study has defined the bacterial component as having a role in the IL-10 stimulatory effect that is associated with *B. thetaiotaomicron*, indicating that the specific bacterial genes can influence the host defenses. Similarly, the Na+-translocating NADH:quinone oxidoreductase has been identified as important in the immune-modulating properties of the bacterium [31]. Alteration of this complex alters the ability of the bacterium to modulate immune reactions, and it is claimed that the metabolic activities that are maintained by bacteria contribute to the immune relations between the microbe and the host.

Besides these molecular interactions, *B. thetaiotaomicron* has also been identified to influence the adaptive immune responses involving intestinal inflammation. Experimentally, it has been established that this bacterium can alleviate colon inflammation through activation of the aryl hydrocarbon receptor (AhR) signaling pathway and maintenance of homeostasis in the CD4+ T cells [32]. AhR signaling also participates in the regulation of immune response in the intestinal environment, and the study has reported that *B. thetaiotaomicron* stimulates AhR signaling to regulate the ratio of CD4+ T cells that are involved in the inflammatory process in the intestine. Such findings also paint a picture of commensal bacteria mediating immune responses by engaging with host immune signaling pathways.

Comprehensively, the existing data indicate that *B. thetaiotaomicron* interacts with the host immune system via a complex of complementary activities, including the ability to deliver antigens to the dendritic cell and innate immune system, regulation of dendritic cell and innate immune responses, regulation of cytokine production, and stimulation of T-cell homeostasis signaling in relation to the interaction with the host immune system. In such mechanisms, an important gut commensal has been shown to specifically interact with immune communication in the intestinal environment. Emerging cell-resolved and multi-omics approaches used to elucidate *B. thetaiotaomicron* host interactions and their biological relevance are summarized in Table 2.

Table 2. Emerging cell-resolved approaches for elucidating *Bacteroides thetaiotaomicron*–host interactions

Emerging approach	Major findings	Relevance to *B. thetaiotaomicron* biology	References
Cell type-specific transcriptomics	Transcriptomic profiling demonstrated that *B. thetaiotaomicron*-derived extracellular vesicles differentially regulate immune signaling pathways across distinct host immune-cell populations, with altered responses observed in inflammatory bowel disease.	Provides mechanistic insight into immune-cell-specific host responses to *B. thetaiotaomicron*.	[28]
Integrated multi-omics (genomics, transcriptomics, proteomics and metabolomics)	Multi-omics integrates microbial composition, metabolic activity, and host responses to identify regulatory pathways and disease-associated microbial functions.	Enables systems-level understanding of *B. thetaiotaomicron* metabolism, immune modulation, and host interactions.	[33–35]
Machine learning-assisted transcriptomic network analysis	Identification of 110 independently regulated transcriptional modules (iModulons) controlling nutrient sensing, stress adaptation and polysaccharide utilization.	Reveals regulatory networks governing adaptation and functional plasticity of *B. thetaiotaomicron*.	[14]
Cell-resolved immune profiling	Gut microbiota regulate systemic inflammation through specific immune-cell subsets, including $PF4^+$ macrophages, highlighting cell-specific host responses.	Suggests future application of cell-resolved immune profiling for dissecting *B. thetaiotaomicron*-mediated immunomodulation.	[36]

(*Continued*)

Table 2. (*Continued*)

Emerging approach	Major findings	Relevance to *B. thetaiotaomicron* biology	References
Spatial transcriptomics	Highly multiplexed spatial transcriptomics enables visualization of bacterial spatial organization and gene expression within complex microbial communities.	Provides a promising platform to map *B. thetaiotaomicron* localization and spatial host–microbe interactions within intestinal tissues.	[37]
Single-cell and spatial multi-omics in cancer	Single-cell sequencing and spatial transcriptomics are transforming understanding of microbiome-mediated tumor immunity and treatment response.	May facilitate investigation of *B. thetaiotaomicron*-mediated immune modulation during cancer immunotherapy.	[38–40]
Future direction	Integration of single-cell RNA sequencing, spatial transcriptomics, and multi-omics will enable cell-specific and spatial mapping of epithelial, stromal, and immune-cell responses to *B. thetaiotaomicron*.	Expected to improve mechanistic understanding and precision microbiome therapeutics.	[14, 37, 38]

4. *B. thetaiotaomicron* and the Gut–Brain Axis

B. thetaiotaomicron is one of the commensal gut bacteria that have been implicated in central nervous system (CNS) function and whose activity is mediated by overlapping metabolic, immunological, and neuroactive channels, all of which have an overall influence on neuropsychiatric and neurodegenerative outcomes. Experimental evidence suggests that *B. thetaiotaomicron* may influence brain physiology through the production of neuroactive metabolites. The *Bacteroides* species of the gut intestines, such as *B. thetaiotaomicron*, have been reported to produce gamma-aminobutyric acid (GABA), the main neurotransmitter of the mammalian CNS, whose production is controlled in response to the conditions of acid stress in the gut lumen [41]. In addition to GABA, commensal gut microbes exhibit species-specific abilities to produce a rich repertoire of neuroactive metabolites—such as indoles, tryptophan catabolites—which have region-specific effects on brain chemistry and behavior [42]. The metabolites produced by microbiomes do not operate independently but instead interact with various mechanistic pathways to regulate neurodegeneration and do so by targeting aspects of blood–brain barrier integrity, glial activation, and synaptic homeostasis [43]. The local particularity of the effects of *B. thetaiotaomicron* was directly identified in a murine monocolonization model, which found that this one species induces unique, brain-region-specific changes in the characteristics of Alzheimer's disease, highlighting the specificity with which a single commensal can model neuropathological development [44].

Adding to these metabolite-induced processes is an equal degree of immunological aspects of gut–brain communication. The intestinal immune environment—especially T helper (Th) cell differentiation—is a key interface between microbial cues and neurobiological performance. Microbial communities vary in strain-level diversity in modulating depressive-like behavior via a gut–Th1/Th17–brain axis, with strain-level variation in microbial communities diversifying peripheral immune polarization, which is ultimately transduced into changes in CNS activity [45]. This neural-immune crosstalk is not just incidental but signifies an organized signaling pathway, spanning a spectrum of homeostatic regulation to overt neuropathology, in which Th cell subsets are important transducers that convert luminal microbial signals into neuroinflammatory or neuroprotective brain parenchyma [46].

Interventional data also add to the relevance of these overlapping pathways, which have a translational component. Using a rationally constructed microbial consortium in a *Drosophila melanogaster* model of Parkinson's disease, directed microbial community engineering was demonstrated to reduce neurodegradation—a proof-of-concept result that confirms the mechanistic model of links between particular microbial species and neurodegradation-modulatory functions [47]. Collectively, preclinical evidence suggests that *B. thetaiotaomicron* is not just a passive gut commensal but an active contributor to gut–brain axis signaling, with the ability to impact neurological health via the coordinated action of neuroactive metabolites, immune-cell regulation, and region-specific molecular reorganization of brain tissue. Specificity of these effects at the species-level and even strain-level has important implications on the design of microbiome-targeted therapeutics in neuropsychiatric and neurodegenerative diseases. The involvement of *B. thetaiotaomicron* across major disease conditions, including its functional mechanisms, associated host outcomes, and available evidence, is summarized in Table 3.

5. *Bacteroides thetaiotaomicron* in Cancer Immunotherapy

One such biologically important modulator of antitumor immunity in the gut microbiome-tumor microenvironment (TME) axis has become a dominant symbiotic anaerobe of the human gut, *B. thetaiotaomicron*, which is a dominant symbiotic anaerobe of the human gut. The intestinal microbiome has its ways of influencing systemic immune responses through a complex network of microbial–host interactions, where commensal bacteria actively shape the functional tone of tumor-infiltrating lymphocytes, dendritic cell maturation, and cytokine milieus, ultimately determining the outcomes of immunotherapy [39, 48]. In this context, *B. thetaiotaomicron* fits into a mechanistically relevant niche owing to its ability to interact with innate immune signaling cascades that mediate mucosal immunity to antitumor responses.

5.1. TLR4/IL-12/Th1 pathway activation

One of the key regulatory uses of *B. thetaiotaomicron* to regulate antitumor immunity is the activation of the toll-like receptor 4 (TLR4) signaling axis. TLR4 on dendritic cells and macrophages in the gut-associated lymphoid tissue can be

Table 3. Overview of the involvement of *Bacteroides thetaiotaomicron* across major disease conditions, summarizing disease-associated status, principal functional mechanisms, host phenotypic outcomes, available evidence, and representative references

Disease/condition	*B. thetaiotaomicron* status	Major functional alteration and mechanism	Host outcome/phenotype	Evidence level and model	Key references
Inflammatory bowel disease/colitis	Depleted (reduced abundance vs healthy controls)	Impaired outer membrane vesicle-mediated regulatory dendritic cell induction; loss of interleukin-10 stimulation; disrupted tight junction regulation via aryl hydrocarbon receptor (AhR) signaling	Increased intestinal permeability, exaggerated mucosal inflammation, loss of epithelial immune homeostasis	Human observational studies, *in vitro* studies, and murine experimental models	[26, 30, 32, 49, 50]
Type 2 diabetes mellitus, obesity, and metabolic syndrome	Reduced abundance; functionally altered polysaccharide utilization loci activity	Reduced propionate production, dysregulated arginine and nitrogen metabolism, impaired goblet cell differentiation	Insulin resistance, intestinal inflammation, hepatic lipid accumulation	Animal models, *in vitro* studies, limited human observational studies	[2, 50–52]
Colorectal cancer	Enriched in immune checkpoint inhibitor (ICI)-responsive patients; functionally active in immunostimulatory capacity	Toll-like receptor 4-interleukin-12 (IL-12)-T helper 1 (Th1) activation, short-chain fatty acid (SCFA)-mediated histone deacetylase inhibition, increased cluster of differentiation 8-positive ($CD8^+$) T-cell infiltration	Enhanced anti-tumor immunity and improved response to ICIs	Human cohorts, murine models, and fecal microbiota transplantation (FMT) studies	[33, 39, 40, 53]
Immune checkpoint inhibitor (ICI) response	Enriched in responders; positively correlates with objective response rate, progression-free survival (PFS), and overall survival (OS)	Enhanced dendritic cell activation, IL-12 production, Th1 polarization, reduced regulatory T cells (Tregs), and FMT-mediated immune restoration	Improved objective response, PFS, and OS	Human cohorts, murine models, and FMT studies	[14, 39, 40, 54, 55]
Neuropsychiatric disorders	Strain-level variation in abundance; functionally altered neuroactive metabolite production	Gamma-aminobutyric acid production, tryptophan metabolites, gut–brain immune signaling	Depression- and anxiety-like behavior, altered brain chemistry	Animal models, *in vitro* studies, limited human data	[41–46]

(*Continued*)

Table 3. (*Continued*)

Disease/condition	*B. thetaiotaomicron* status	Major functional alteration and mechanism	Host outcome/phenotype	Evidence level and model	Key references
Neurodegenerative diseases	Present in murine models with region-specific neuropathological effects; human abundance data limited	Brain molecular remodeling, blood–brain barrier modulation, neuroactive metabolites	Altered Alzheimer's disease-related traits and reduced Parkinson's disease neurodegeneration	Animal models	[42–44, 47]
Diarrheal disease/intestinal barrier dysfunction	Depleted or functionally impaired; restoration associated with recovery	AhR-nuclear factor erythroid 2-related factor 2 (Nrf2) activation, SCFA signaling, restoration of epithelial barrier	Reduced diarrhea severity and improved intestinal barrier integrity	Animal models and *in vitro* studies	[56–59]
Hepatic steatosis/nonalcoholic fatty liver disease	Reduced abundance in steatotic models; colonization therapeutically beneficial	Gut–liver axis regulation, folate metabolism, unsaturated fatty acid biosynthesis	Reduced hepatic lipid accumulation and improved metabolic health	Murine models	[50]

stimulated by lipopolysaccharide and other microbe-associated molecular patterns that are released by *Bacteroides* species [48]. The key immunostimulatory cytokine is interleukin-12 (IL-12), which promotes the differentiation of naïve CD4 + T cells toward a Th1 phenotype, characterized by robust interferon-gamma secretion, which in turn enhances TME priming and effector functions of CD8 + T lymphocytes [60]. This circuit is further reinforced by microbial metabolites produced by *B. thetaiotaomicron*, such as SCFAs and succinate that further amplify this immunostimulatory circuit by regulating the activity of histone deacetylase in T cells and thereby sustaining the expression of tumor cell killing programs [53]. The net effect of this TLR4/IL-12/Th1 axis activation is a change in the intratumoral immune environment between an immunosuppressive, tolerogenic, and an inflammatory, cytotoxic, immune-mediated tumor clearance [40]. It has synergy with CTLA-4 and PD-1/PD-L1 blockade.

The best example of the relevance of *B. thetaiotaomicron* is exhibited in the context of immune checkpoint inhibitor (ICI) therapy. Significant research by Vétizou et al. [54] established that the efficacy of anti-CTLA-4 blockade critically depended on the presence of select *Bacteroides* species, including *B. thetaiotaomicron* and *B. fragilis*, which demonstrated in both murine models and human patients that these commensals were required to promote optimal therapeutic responses to ipilimumab. Mice lacking these taxa (i.e., germ-free and antibiotic-treated) had significantly attenuated responses to blockade of CTLA-4, and colonization with *B. thetaiotaomicron* restored antitumor activity—an effect mechanistically connected to increased production of dendritic cell IL-12 and Th1 polarization at tumor sites [54]. More recently, this synergy has been extended to the PD-1/PD-L1 axis; *Bacteroides*-enriched microbiome setups have been linked with augmented CD8+ T-cell infiltration, reduced regulatory T-cell (Treg) accumulation, and favorable modulation of the PD-L1 expression landscape within tumors [39, 40]. The immunological mechanism behind this synergy is likely due to the ability of *B. thetaiotaomicron* to maintain systemic Th1 immune tone, thus making the TME more receptive to checkpoint disinhibition by alleviating the suppressive dominance of the PD-1/PD-L1 and CTLA-4 co-inhibitory pathways [53, 60].

5.2. Clinical implications to predict immune checkpoint inhibitor (ICI) responder

The mechanistic eminence of *B. thetaiotaomicron* in regulating checkpoint immunotherapy has potential clinical implications, especially to stratify patients who are likely to respond to ICI regimens. The concept of pre-treatment fecal microbiome composition as a predictive biomarker of ICI response is supported by emerging evidence that *Bacteroides* abundance—especially *B. thetaiotaomicron*—positively correlates with objective response rates, progression-free survival, and overall survival across various types of cancer, including melanoma, non-small cell lung cancer, and urothelial carcinoma [39, 40]. Lin et al. [55] also highlight the translational aspect of such a relationship by reporting that the enriched non-responder immunological competence by fecal microbiota transplantation (FMT) of ICI responders was reported to enhance therapeutic outcomes. The application of metagenomic profiling of *B. thetaiotaomicron* in clinical practice presents a manageable opportunity to refine the patient selection criteria for ICI therapy, minimize immune-related adverse events related to treatment in unlikely responders, and guide adjunctive microbiome-targeted interventions such as dietary modulation, probiotic supplementation, or FMT to optimize the immunological substrate on which checkpoint blockade acts [40, 55]. Overall, *B. thetaiotaomicron* is not just a passive commensal, as its abundance and immunostimulatory activity have been correlated with ICI responsiveness in observational human studies, and it could be a clinically actionable biomarker that requires further interventional validation.

6. Role of *B. thetaiotaomicron* in Maintenance of Intestinal Barrier Integrity

B. thetaiotaomicron is a significant commensal bacterium within the human gut and a key factor in maintaining human intestinal homeostasis of the barrier. This organism was shown to use communication with host epithelial cells and the mucosal immune system to control the effects of inflammatory responses and epithelial integrity. *B. thetaiotaomicron* is also an example of commensal mucin-degrading bacteria, which have the ability to prevent inflammation of the intestinal epithelium and to regulate tight junction proteins, enhancing the functionality of the intestinal lining barrier and preventing its excessive permeability, as illustrated in Figure 2 [57]. These bacteria promote a normal intestinal microenvironment, which helps the host to avoid injury by inflammation through their maintenance of tight junctions and control of epithelial immune signaling. The evidence of the barrier-protective effect of *B. thetaiotaomicron* is also supported by several experimental studies. Administration of *B. thetaiotaomicron* has been found to control the gut microbiota composition and host immune response and improve intestinal mucosal protection in animal models. Protective responses to necrotic enteritis in broiler chickens induced by the dose-dependent action of *B. thetaiotaomicron* incorporated enhancement of gut immunity and microbial balance, and it is evident that *B. thetaiotaomicron* can strengthen gut defense and aid in preserving the integrity of the epithelial barrier [57]. Likewise, an analysis of disease models of metabolic disease has shown that *B. thetaiotaomicron* can alter the expression/composition of intestinal inflammatory genes and the host intestinal microbiota, implying that it can suppress intestinal inflammation and enhance metabolic and immune homeostasis in the host, which is directly associated with the stability of the intestinal barrier [51].

The diet-dependent barrier can also be safeguarded by *Bacteroides* species. Fucoidin of *Undaria pinnatifida* supplemented in fiber-deficient mice enhanced the strength of *Bacteroides* in the anti-inflammatory response and acted as a preservative of the intestinal barrier integrity. The protective effect described was associated with a shift in the gut microbial flora and an enhancement in mucosal barrier functioning, and it was found that the diet, commensal bacteria (*B. thetaiotaomicron*), and epithelial barrier preservation are interrelated [61]. In addition, extracellular vesicles produced by *B. thetaiotaomicron* have been shown to communicate with host intestinal cells. These vesicles can penetrate epithelial layers and can communicate with immune-related cells in multicellular models of the intestine, indicating a potential route by which this bacterium communicates with host tissues and controls mucosal immune responses that contribute to barrier protection [58].

The intestinal barrier integrity is strongly dependent on the composition of gut microbiota and its microbial metabolites. Analyses on intestinal permeability describe commensal bacteria that also include *Bacteroides* species as playing a significant role in the maintenance of tight junctions of the epithelium, immune signaling, and mucosal defense mechanisms that work together to offer stability to the barrier [62]. *B. thetaiotaomicron* regulates inflammatory reactions, the activation of mucus layer processes, and the interaction with epithelial cells to support the integrity of the gut barrier and avoid intestinal diseases associated with dysbiosis.

7. Microbiota Homeostasis and Colonization Resistance

B. thetaiotaomicron is a significant gut commensal, which plays major roles in the stability of microbiota and the protection of a host against pathogen intruders. Colonization resistance is one of the main mechanisms by which the gut microbiota can establish homeostasis: in this case, resident microbes exclude the establishment of pathogens by means of competition for nutrients, metabolic activity, and immune regulation. Gut microbiota, such as *Bacteroides* species, maintain ecological balance in the intestine through occupying metabolic niches and generating metabolites that inhibit the growth of pathogens and promote the health of the epithelia [63, 64].

Colonization resistance is mainly determined by the metabolic activities of commensal bacteria. It has been shown that SCFAs are the dietary products created by microbial fermentation,

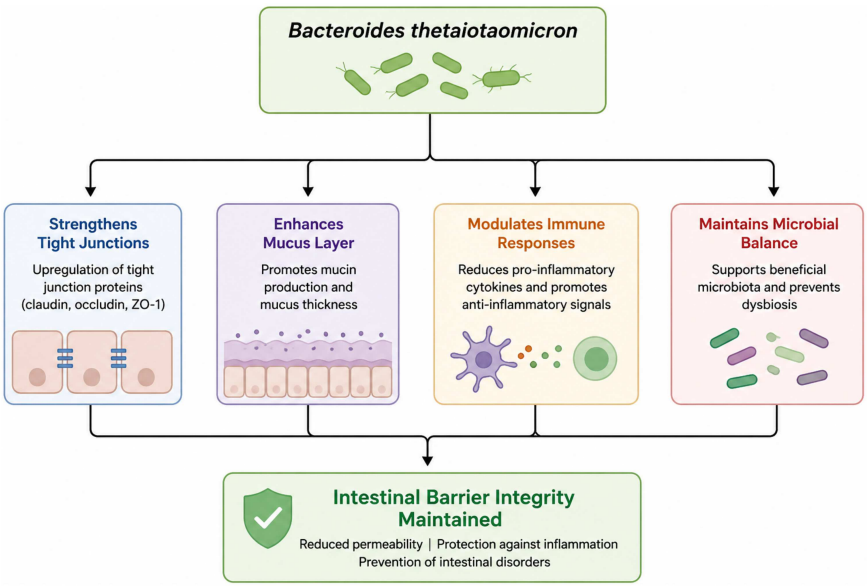

Figure 2. Role of *Bacteroides thetaiotaomicron* in maintaining intestinal barrier integrity through strengthening of tight junctions, enhancement of the mucus layer, modulation of immune responses, and maintenance of microbial balance

which inhibit the growth of pathogenic Enterobacteriaceae and other opportunistic bacteria. SCFAs change the intestinal pH, disrupt the bacterial metabolic processes, and provide a poor environment in which the pathogens can thrive, which enhances the microbial-mediated protective mechanisms [64, 65]. Moreover, there are certain metabolic pathways that occur in *Bacteroides* that lead to the homeostasis of the host intestines, such as in *Bacteroides* species, which have a metabolism requiring methylmalonyl-CoA mutase, which facilitates the synthesis of propionate, a major SCFA that can support intestinal goblet cell differentiation and mucus secretion. Goblet cell hyperactivity increases the barrier of the mucosa, curbing the adherence of pathogens and leading to intestinal immune homeostasis [52].

Gut microbe–host immune signaling pathway interactions also increase colonization resistance. Host pattern recognition receptors, such as TLRs, interact with microbial molecules and metabolites and are charged with the responsibility of regulating immune reactions and ensuring the stability of mucosal barriers. Regulated stimulation of these pathways through commensal microbiota leads to balanced immune responses, inhibits overreaction to inflammation, and maintains mechanisms against pathogen protection [66]. The bidirectional interaction of intestinal microbes and host immunity is necessary to uphold intestinal homeostasis.

B. thetaiotaomicron exhibits an extraordinary degree of genetic adaptability in addition to metabolic and immune interactions, enabling it to survive in the competitive intestinal ecosystem. It is known that this bacterium experiences dynamic changes in its genetic and transcriptional activities during colonization that have increased its ability to exploit a wide array of nutrients and endure environmental stress in the gut [67]. This versatility enables *B. thetaiotaomicron* to preserve its niche in the environment and make the microbial community stable. Moreover, the *Bacteroidales* order members are involved in interbacterial competition that is characterized by secretion systems and antimicrobial factors, which help the members to suppress other competing microbes and stabilize the balanced microbial communities in the gut environment [68].

Taken together, these processes, such as metabolic competition, SCFA generation, immune regulation, and genetic plasticity, allow *B. thetaiotaomicron* to be an important component of microbiota homeostasis and fortification of the colonization-protective response to enteric pathogens.

8. Probiotics and Therapeutic Potential of *B. thetaiotaomicron*

B. thetaiotaomicron is a recently spotted next-generation probiotic candidate with the ability to control the gut microbiota composition, host metabolism, and immune systems. The next-generation commensals, such as *B. thetaiotaomicron*, are indigenous to the human gut microbiota and have unique metabolic abilities that enable them to be in close contact with host physiology and intestinal ecologies, unlike traditional probiotics like *Lactobacillus* and *Bifidobacterium*. They exhibit these properties, which are promising for therapeutic effects (prevention or treatment) of a variety of gastrointestinal and metabolic disorders [69].

The protective effect of *B. thetaiotaomicron*, particularly in IBD, is seen in a number of studies. Experimental studies indicate that the abundance of this bacterium in the gut can be used to treat colitis by altering the structure of the microbial community, as well as suppressing intestinal inflammation. As an example, the administration of *Houttuyniae herba* was demonstrated to target the growth of *B. thetaiotaomicron* that results in a better balance of gut microbiota and excellent anticolitic activity in experimental animals [49]. On the same note, plant microRNA-enriched exosomes derived from garlic were claimed to remodel the gut microbiome and augment the proportion of *B. thetaiotaomicron*, which led to the reduction of murine colitis and enhanced intestinal immune homeostasis [50].

In addition to IBD, *B. thetaiotaomicron* demonstrates therapeutic prospects in diarrheal illnesses and the dysfunction of the intestinal barrier. Luo and colleagues showed that the bacterium can reduce diarrhea by modulating the ecological networks of the gut microbes and tryptophan metabolism. This interaction of the metabolism induces host AhR and Nrf2 signaling pathways, which are important to maintain intestinal barrier integrity, antioxidant defense, and mucosal immunity [56]. These mechanisms point to the ability of the bacteria to connect to microbial metabolism and the host signaling pathways to achieve intestinal homeostasis.

There is also an emerging indication that *B. thetaiotaomicron* can be beneficial in the amelioration of other metabolic disorders extraintestinal to the gut. Colonization of a murine model of hepatic steatosis with *B. thetaiotaomicron* changed gut microbial composition and regulated gut-liver metabolic pathways including folate metabolism and unsaturated fatty acid biosynthesis. Such changes in metabolism decreased the lipid content of the liver and positively affected the metabolic parameters, which indicates that this bacterium can be used as a therapeutic agent in metabolic liver disease [50].

B. thetaiotaomicron has physiological characteristics that are beneficial to its effect as a probiotic bacterium besides treatment of diseases. It has been demonstrated that the bacterium can increase tolerance to oxidative stress due to the rhamnose-dependent metabolic processes that could help it to survive and endure the stresses of the intestinal environment [70]. These adaptation processes play a significant role in stabilizing colonization and activity of the host gut microbiome.

The recent developments in synthetic biology and microbial engineering also increase the therapeutic potential of commensal bacteria like *B. thetaiotaomicron*. The designed engineered live bacterial therapeutics may express therapeutic molecules, regulate immune responses, or provide beneficial metabolites into the gastrointestinal tract. Synthetic biology and systems biology are thus being utilized to create engineered commensals as directed therapies to complicated illnesses, such as inflammatory and metabolic syndromes [71].

Altogether, the existing data suggest a high potential in *B. thetaiotaomicron* as a next-generation probiotic with wide therapeutic applications. This bacterium can provide an interesting target for future microbiome-based therapies, which could be achieved through the modulation of microbial communities, host immune signaling, and metabolic interactions with the host and resilience to intestinal stress.

9. Cutting-Edge Technologies in *B. thetaiotaomicron* Research

The latest development of high-throughput technologies has greatly contributed toward our knowledge of the biology of *B. thetaiotaomicron* and its role in the interaction between the host and microbiome. The application of multi-omics (e.g., genomics, transcriptomics, proteomics, and metabolomics) is becoming common in the study of *Bacteroides* group members. Such combined studies give the researcher a chance to discover metabolic processes, regulatory connections, and host–microbe interactions

that lead to bacterial adaptations and functional action in the intestinal environment [35]. The use of multi-omics is especially useful in connecting microbial composition and functional outcomes, as is the case with microbiome studies of diseases that include multiple analyses of metagenomic and metabolomic data to delineate microbial metabolic changes and their relationship with disease phenotypes [34].

Microbiota-mediated therapeutic responses have also been studied by the application of metagenomic and metabolomic technologies. As an example, the results of integrated omics analyses have shown that microbial community structure and metabolic patterns can impact the outcome of treatment of colorectal cancer therapies, highlighting the importance of microbiome-derived metabolites and microbial interactions play a crucial role in modulating host immune responses [33]. These methods give information on the functional roles of the most crucial commensal species, such as *B. thetaiotaomicron*, in complicated microbial communities.

Another technological frontier in microbiome studies that is developing very fast is synthetic biology and engineered microbial systems. Controlled experimental models, "synthetic microbial communities," are establishing a new model for investigating microbiota–host interactions and metabolic disease mechanisms. The systems have enabled scientists to develop simplified microbial ecosystems, which provide an opportunity to study microbial cooperation, competition, and host metabolic responses in detail under predetermined conditions [33]. Simultaneously, systems-wide studies of microbiome–host interactions are elucidating the role of microbial metabolites in regulating host gene expression and epigenomic regulation as well as revealing a more in-depth understanding of the mechanisms of microbial control over human health and disease [72].

The genetic engineering technologies also allowed direct manipulation of *Bacteroides* species. The clustered regularly interspaced short palindromic repeats (CRISPR)-based genome editing systems have been extended to *Bacteroides*, enabling functional studies and modification of genes targeted to study the microbial pathways. Effective CRISPR-based base-editing systems have been created to permit specific genomic alterations in gut *Bacteroides* species that allow much better study of gene functionality and metabolic activities in these microorganisms [73]. Besides that, molecular mechanisms, which help bacteria to survive in the gastrointestinal environment, have been presented by CRISPR-based screening strategies to identify regulatory small RNAs that determine bile tolerance in *B. thetaiotaomicron* [74].

Beyond genome editing, engineered commensal bacteria are being explored as programmable living therapeutics. Initial research has shown that *B. thetaiotaomicron* is capable of genetic programming to detect certain environmental signals within the gut and then trigger preprogrammed engineered genetic circuits. This potential will allow creating microbial biosensors and therapeutic delivery systems that can detect disease-related signals and generate relevant biological reactions in the intestinal environment [75]. More recent studies suggest that CRISPR-assisted probiotic reengineering might be used to prioritize the reengineering of gut microbial functions in situ, which may allow the curing of metabolic disorders by specific manipulation of microbiota pathways [76]. Taken together, these new technologies, such as multi-omics of *B. thetaiotaomicron*, synthetic microbial communities, CRISPR-mediated genome editing, and programmable commensal bacteria, as summarized in Figure 3, are changing the study of *B. thetaiotaomicron*. The mentioned strategies not only enhance our knowledge of the molecular processes that

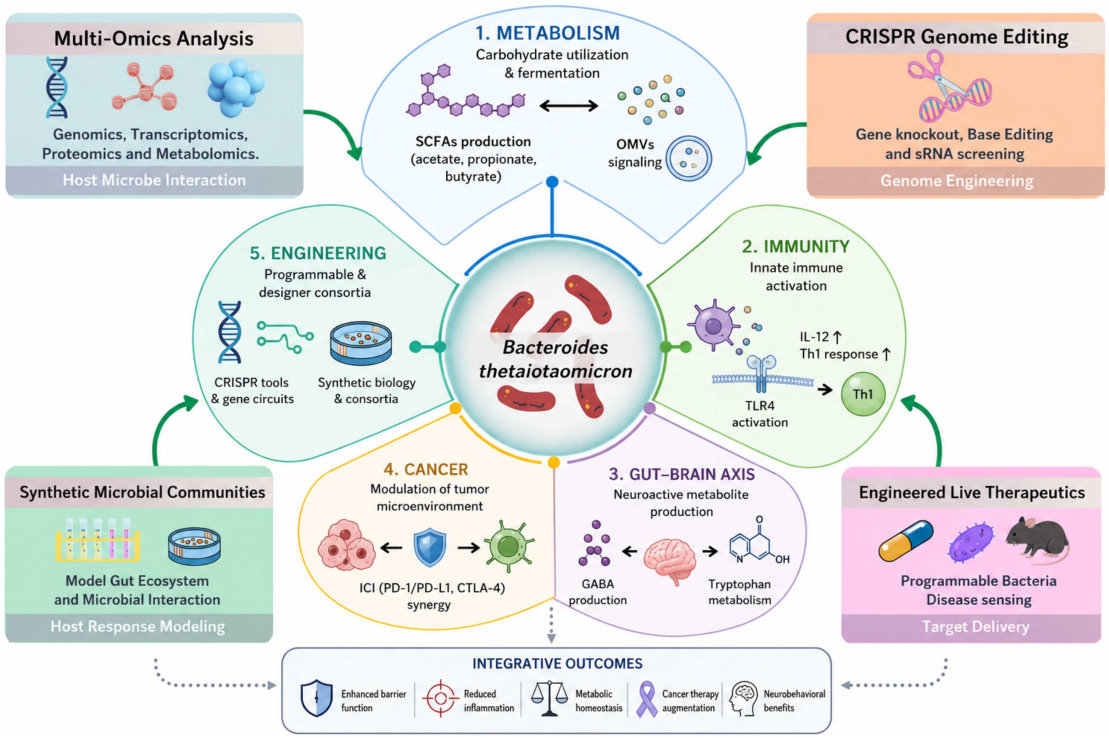

Figure 3. Integrative overview of the biological functions and translational potential of *Bacteroides thetaiotaomicron*. The schematic depicts *B. thetaiotaomicron* as a central node connecting metabolism, immune regulation, gut–brain communication, cancer immunotherapy, and microbiome engineering (CRISPR and synthetic biology), alongside enabling platforms including multi-omics, synthetic microbial communities, and engineered live therapeutics

underlie host–microbe interactions but also open the path to microbiome-based therapeutic interventions.

10. Conclusion and Future Perspectives

B. thetaiotaomicron has firmly established itself as an important functional symbiotic member of the gut ecosystem whose focus goes beyond nutritional ecology. Its broad polysaccharide utilization capability, genomic plasticity, and immunomodulatory potential are all part of its ability to maintain host metabolic stability, integrity of the mucosal barrier, and resistance to colonization. This review builds on that knowledge, adding a new, frontier dimension, gut–brain axis signaling, and cancer immunotherapy, which largely enhances its translational value. In neurologic contexts, *B. thetaiotaomicron* establishes and alters the neurologic environment via brain region-specific molecular remodeling, CNS neuroactive metabolites, and Th1/Th17 immune transduction. An important question yet to be answered is whether this organism has deterministic and reproducible effects on neuropsychiatric phenotypes, and via which predominant metabolic, immunological, or neuroendocrine pathway? It elevated activation of the TLR4/IL-12/Th1 pathway and, combined with the checkpoint inhibitors, makes it a highly viable microbiome-based prognosis of ICI response in oncology. However, it is not known whether the number of *B. thetaiotaomicron* is predictive of immunological competence or if immunological competence is selected for *B. thetaiotaomicron*. Whether increases in *B. thetaiotaomicron* abundance correlate with increases in immunological competence, or whether immunity selects for *B. thetaiotaomicron*, remains unclear, with profound implications for therapeutic measures. In both areas, shared gaps require urgent action. Restriction of dependence on the murine model restricts clinical translation. Patient stratification and standardized microbiome profiling thresholds do not exist. The complete bioactive metabolite profile is not characterized. In addition, less studied is the architecture of host genomes, especially HLA haplotypes and germline immune variants, which are other axes that contribute to interindividual variability. However, engineering tolerance of resilient live biotherapeutic delivery in treatment-exacerbated dysbiotic gut environments continues to elude a solution. Moving forward, three priorities need to be addressed in designing future research: mechanistic resolution via integrated multi-omic study design; causal establishment via controlled interventional trial designs with targeted FMT of *B. thetaiotaomicron* (or a defined live biotherapeutic dosing); and clinical standardization of *B. thetaiotaomicron* quantitative profiling frameworks. These are important lacunae to address to maximize its potential usage as a commensal symbiont pathway and, beyond that, as a manageable target within precision microbiome medicine.

However, the priorities listed must be viewed in the context of these limitations of this present synthesis. The literature used for this review was not gathered in a systematic, protocol-driven way and, as a result, was not subject to inclusion criteria or to any formal quality appraisal tools and, therefore, may be biased toward studies reporting positive or novel findings. Some of the sources for the gut–brain axis and cancer immunotherapy conversations are preprints or early online publications, and therefore, the findings should be interpreted as preliminary. The underlying mechanistic evidence, especially related to neuroactive metabolite signaling and ICI-modulating activity, is also largely obtained from murine model systems such as monocolonization and gnotobiotic models in vitro, which are not suitable to reflect the diversity of humans, their gut ecology, or strains. Combined, these limitations indicate that the picture of translation that emerges in this work should be regarded as hypothesis-generating, and the priorities listed above as steps to corroborating, clinically informed evidence.

Ethical Statement

This study does not contain any studies with human or animal subjects performed by any of the authors. The authors confirm that this manuscript has not been published or is under review in any journals. This manuscript represents entirely review work, and if work and/or words of others have been used, this has been appropriately cited. Generative AI and AI-assisted technologies have not been utilized in the writing process.

Conflicts of Interest

Indra Mani is the Editorial Board Member for Medinformatics and was not involved in the editorial review or the decision to publish this article. The authors declare that they have no conflicts of interest to this work.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Author Contribution Statement

Dishi: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Indra Mani:** Conceptualization, Writing – original draft, Writing – review & editing, Supervision, Project administration.

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