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REVIEW

The Role of Butyric Acid and Microorganisms in Chronic Inflammatory Diseases and Microbiome-Based Therapeutics

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Abstract: Butyric acid, produced by gut microbiota fermentation, has gained significant attention over the past decade. It shows strong therapeutic potential in both experimental and clinical treatments for inflammatory diseases across multiple systems. However, factors such as the host's environment, genetics, and microbial lineage transmission influence gut microecology and butyric acid metabolism, resulting in variable and sometimes opposing, therapeutic effects. Consequently, precise personalized medicine is essential for diseases related to microbes and butyric acid. This review first introduces the fundamentals of butyric acid, focusing on its immune mechanisms and its effects on early-life microbiota. It then summarizes how microbes and butyric acid contribute to the treatment of systemic inflammatory diseases (eg, autoimmune diseases (AIDs), asthma, metabolic syndrome) and discusses the concept of Microbial Precision Therapy (MPT). Understanding butyric acid provides deeper insight into managing inflammatory diseases and supports precise medication and personalized therapy. This approach may offer more effective and safer strategies for multi-system inflammatory disorders.

Keywords: butyric acid, inflammatory diseases, microbial precision therapy, intestinal flora

Introduction

Gut microbiota and their metabolites play a central role in maintaining host health, particularly in immune regulation. Butyrate, a major short-chain fatty acid primarily produced by *Firmicutes* through dietary fiber fermentation,[1] has received significant attention due to its strong anti-inflammatory and immunomodulatory properties.[1] It serves as the primary energy source for colonic epithelial cells and is absorbed via passive diffusion and monocarboxylate transporters (MCT1/SMCT1).[2] Only trace amounts enter the systemic circulation and are metabolized in the liver via the portal vein.[2,3] Butyrate regulates immune cell function mainly by activating G protein-coupled receptors (GPCRs) and inhibiting histone deacetylases (HDACs),[4] showing therapeutic potential for chronic inflammatory diseases. However, its effects depend on concentration and microenvironment, and are significantly influenced by host genetics, environmental factors, and inter-individual differences in microbiota. Therefore, addressing individual variability and the paradoxical effects of butyrate to enable precise interventions remains a key research challenge (Figure 1).

Despite substantial progress in both basic and clinical research on butyrate, and the emergence of microbiome-based therapies (eg, specific probiotics, engineered bacteria, fecal microbiota transplantation (FMT), butyrate supplements, and nanoparticle delivery), further investigation is needed to translate these findings into effective personalized treatment strategies. This review first explains the immune regulatory mechanisms of butyrate and its interactions with early-life microbiota. It then summarizes its diagnostic and therapeutic roles in multi-system inflammatory diseases (eg, intestinal, respiratory, and circulatory systems). Finally, it discusses integrated precision microbiome strategies involving dietary modulation, probiotics, FMT, butyrate, and its precursors.

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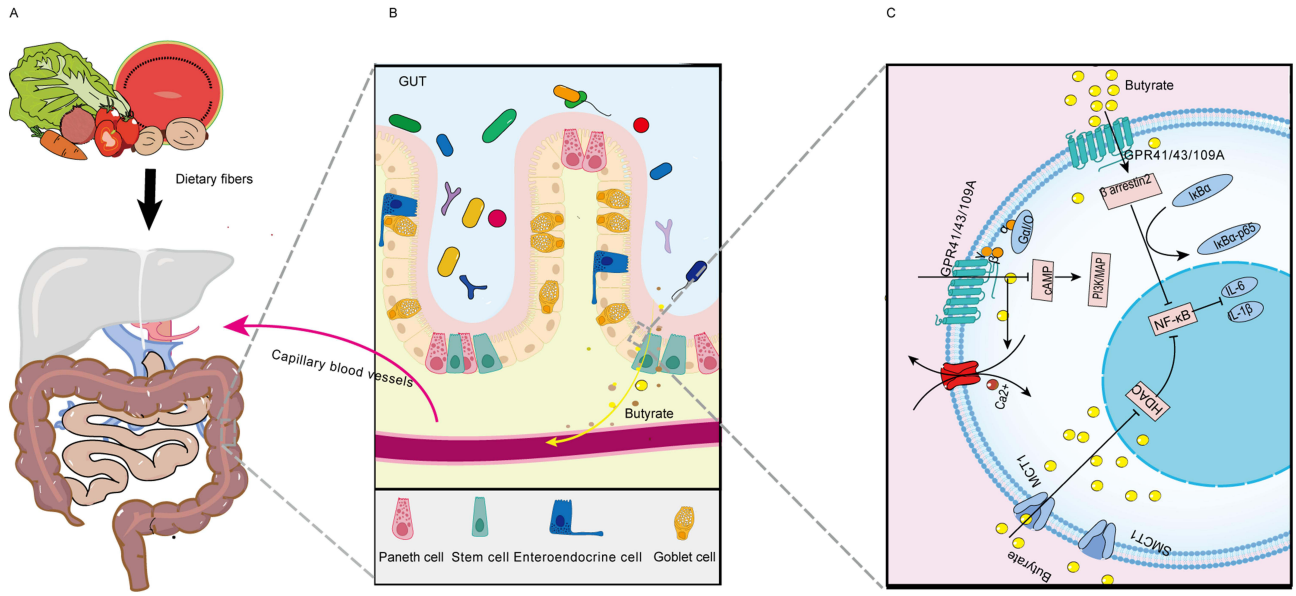

Figure 1 (**A** and **B**) Butyric acid production, transport in the body, and absorption. Reproduced from Sepich-Poore GD et al. The microbiome and human cancer. Science. 371(6536). doi:10.1126/science.abc4552, 2021, AAAS.[5] (**C**) Butyric acid acts by activating GPR41, GPR43, and GPR109A and inhibiting HDAC.

Mechanism of Action of Butyric Acid

Butyrate primarily functions in the intestinal tract.[6] The action of butyric acid depends upon the modulation of butyric acid by several key host receptors, primarily the activation of G protein-coupled receptors (GPCRs) (GPR41, GPR43, and GPR109A)[4] and the inhibition of HDAC, which are involved in immunomodulation, lipid metabolism, and energy homeostasis. GPR41, GPR43, and GPR109A are distributed widely across multiple tissues and organs, including adipose tissue, colonic epithelium, and immune cells.[7–9] All bind to heterotrimeric G proteins (GαI/O), causing changes in the ligand structure,[10] inhibiting the production of cyclic adenosine monophosphate (cAMP), elevating Ca^{2+} and K^{+} fluxes, and enhancing the downstream PI3K/MAP kinase pathway.[11] The GPCR signal molecule β-arrestin2 also binds to GPR41, GPR43, and GPR109A, and is involved in immune signal transduction. The physical combination of β-arrestin2 and the IκBα-p65 complex stabilizes the spatial structure of IκBα, inhibits the inflammatory pathway NF-κB, and proinflammatory cytokines such as interleukin 6 (IL-6), IL-8, and IL-1β.[12] Furthermore, each GPCR receptor has distinct characteristics and functions. GPR41 is more easily activated by butyric acid and is extensively expressed in immune cells, including B and T cells, Dendritic Cells (DCs), and neutrophils. It is also highly expressed in pancreatic β-cells[13] and white adipose tissue,[14] which raises leptin levels, increases energy expenditure, and alleviates metabolic diseases such as diabetes and obesity. In the nervous system, GPR41 is most abundant in sympathetic ganglia. Direct modulation of the sympathetic nervous system (SNS) by GPR41 can increase myocardial norepinephrine (NE) release and regulate energy homeostasis,[15] while also reducing sympathetic projections to the heart during embryonic life and promoting sympathetic neurodevelopment.[16] GPR43 is highly expressed in immune cells (neutrophils, eosinophils, mast cells, basophils, and monocytes) and controls immune balance, specifically innate immunity.[17] It is also expressed by intestinal epithelial cells, L cells, and adipocytes. It is involved in the regulation of peptide YY (PYY), glucagon-like peptide-1 (GLP-1), and leptin, as well as the treatment of metabolic diseases.[11] Another GPR109A, is highly specific and sensitive to butyrate. Among short-chain fatty acids (SCFAs), only butyric acid activates GPR109A with a low threshold. When combined, butyric acid has anti-inflammatory effects in various tissue cells throughout the body by activating GPCRs and regulating metabolism and neurons. The functions of butyrate can also be mediated through the inhibition of HDACs. HDACs are widespread epigenetic regulatory enzymes present in nearly all tissues of the body.[18,19] As early as 1977, butyric acid was discovered as an endogenous inhibitor of HDAC.[20] It can inhibit Zn^{2+}-dependent class I (HDAC1, HDAC2, HDAC3, and HDAC8) and class II (HDAC4, HDAC5, HDAC7, HDAC9, HDAC6, and HDAC10) HDACs, as well as regulate inflammation and adaptive immunity.[21] As an HDAC inhibitor, in the immune system, butyric acid inhibits proinflammatory mediators and inflammatory pathways like TNF-α, Th17, and NF-κB. This increases the

expression of anti-inflammatory mediators, such as IL-10, and promotes the development of Treg cells. Furthermore, the inhibition of HDAC by butyric acid is directional. An animal study found that transplanting butyric acid-producing *Faecalibacterium* into germ-free mice reduced the expression of HDAC receptors in intestinal epithelial cells.[22] Furthermore, butyrate inhibits HDAC, reshapes the chromatin conformation of target gene promoters, indirectly activates Aryl Hydrocarbon Receptor (AHR), increases the production of regulatory B cells (Bregs), IL-10, and reduces the differentiation of germinal center (GC) B cells and plasma cells.[23] It has recently been demonstrated that butyric acid binds to the peroxisome proliferator-activated receptor (PPAR), which is highly expressed in adipose tissue, immune cells, and intestinal epithelial cells. It plays roles in maintaining intestinal barrier integrity, regulating metabolism, and exerting anti-inflammatory actions.[24] The diversity of butyrate receptors has a significant impact on regulating gut microbiota and host functions. Therefore, further studies are needed to determine the pathways and mechanisms of action of these receptors in various tissues throughout the body, as well as to investigate whether it is possible to target and precisely activate the receptors by adjusting the route and dosage of butyric acid administration based on one's conditions.

Butyric Acid and the Early-Life Microbiota

With the advancement of modernization and urbanization, the evolution of the human living environment, and health level had a dramatic effect on the vaginal early-life microorganisms and the change in the human disease spectrum, from the mother's health status during pregnancy to the mode of delivery (such as vaginal delivery and cesarean section), feeding methods (such as breastfeeding and artificial feeding), and other changes in the mother's bacteria lineage transmission method, changes in lifestyle,[25] and antibiotic use have a direct impact on the composition of the microflora in early life,[26] and this series of interfering factors may last for many years and even increase the risk of metabolic disorders and autoimmune diseases in adulthood.[27] Butyric acid, a key compound produced by bacterial fermentation, plays a major role in the developmental trajectory of early-life microbial communities.

From the embryonic stage, the microbial community influences the host immune system. Bacterial lineage transmission from the mother during pregnancy provides a "window of opportunity" for immune shaping and development in offspring. The uterus is generally thought to be sterile,[28] with few microorganisms detectable Because the fetus does not have direct access to the mother's microbiota during pregnancy, microbial metabolites are transferred to the fetus as the primary mode of action. Butyric acid can directly affect immune cell maturation, and research has indicated that it can cross the placental barrier,[29,30] activate GPR41 in the thymic microenvironment, increase the expression of autoimmune regulatory factors (Aire), influence the production of Treg and immune tolerance, and can lower children's risk of developing allergic disorders.[31]

Delivery mode serves as a critical pathway for vertical transmission of the maternal-neonatal microbiome. In contrast to cesarean (CS) infants, who primarily acquire microorganisms from the maternal skin and environment, vaginally delivered babies inherit the maternal vaginal microbiota.[32] This results in a higher abundance of beneficial flora, where *Bifidobacterium* and *Lactobacillus* contribute to increased butyrate production and reduced colonization by opportunistic pathogens.[32,33] A large Danish cohort study found that children born via cesarean section had an increased susceptibility to developing chronic inflammatory disorders (CID), for example, Inflammatory Bowel Disease (IBD), diabetes mellitus (DM), and rheumatoid arthritis (RA). Despite this, some studies have reached different conclusions. For example, studies on type 1 diabetes indicate no disease linkage to CS microbiota transfer.[34] Confounding factors such as preterm birth, feeding practices, antibiotic use, and insufficient data validity may explain these inconsistencies. Therefore, more cross-regional, multicohort clinical trials with long-term follow-up are needed to determine the effect of CS on disease development. The most significant impact of cesarean section on infants is the delayed colonization of microbes such as Bacteroides and Bifidobacterium, which is associated with an increased risk of childhood allergic diseases.[35,36] The interaction between butyric acid and the microbial community is bidirectional. Butyric acid can influence the composition of the microbial community by elevating butyrate levels and promoting the growth of beneficial bacteria, including Lactobacillus, Bifidobacterium, and Ruminococcus.[37] It increases the abundance of bacterial flora in cesarean-born infants, reduces delays in microbiota colonization, and lowers the risk of allergic diseases in early life. Furthermore, butyric acid inhibits HDAC, promotes forkhead box protein P3 (FOXP3) expression and Treg cell differentiation, thus

lowering the risk of immune diseases in children. In addition to butyric acid supplementation, clinical research has evidence that fecal microbiota transplantation (FMT)[23] and vaginal microbiota transplantation (VMT),[38] which transfer maternal fecal or vaginal microorganisms, respectively (with FMT potentially via breast milk), aid in the recovery and remodeling of microorganisms following cesarean section. Additional clinical and basic research is required to improve and develop these treatments.

Breastfeeding is also an important mode of vertical transmission of the mother-infant microbiome. Breastfeeding during infancy has a significant impact on forming the infant's immune and microbiota development. Compared to formula feeding, breastfed children have a lower risk of autoimmune diseases, and their infant intestinal flora contains more *Bifidobacterium, Actinomycetes*, and *Firmicutes*.[39] Furthermore, transmitting the bacterial flora, the carbon in breast milk source oligosaccharides can act as a substrate for microbiota,[40] causing them to produce SCFAs like butyrate, which activate GPCR receptors and influence the regulation and shaping of immune tolerance.[41] Breast milk also contains other microbial metabolites that regulate immunity, such as antibodies, antimicrobial peptides, lipopolysaccharides, and innate immune factors (such as Toll-like receptor 2(TLR2), TLR4, and Cluster of Differentiation 14 (CD14), which promote the baby's passive immunity.[29] Maternal transfer of SIgA maintains mucosal homeostasis in the infant, coats commensal microorganisms,[42] neutralizes pathogens via pIgR-mediated transcytosis,[43] and maintains host-microbe mucosal immune homeostasis.[44] The role of IgA is not limited to early life but continues throughout life. It is the primary line of defence for intestinal antigen-specific immunity.[45] Short-chain fatty acids, such as butyric acid, can boost IgA levels by activating GPR43 and supporting intestinal immunity.[46]

In addition to the transmission of the mother's flora, antibiotic use has a substantial impact on the composition of the microbiome during early life. Antibiotics can disrupt children's microbiota for months or even into adulthood, with varying types of antibiotics having variable effects on the gut microbiome.[47] Furthermore, antibiotic use can influence the synthesis of microbial metabolites by interfering with the enrichment of butyrate and acetate synthesis genes in infants during the third week of life, inhibiting butyrate production and increasing the prevalence of childhood metabolic disorders, asthma, and IBD, among others.[48] Therefore, antibiotic use must be precise and short-term concerning the child's condition, with special attention paid to restoring the child's flora following antibiotic use.

Butyric Acid Regulation of Host Barriers and the Immune System

Butyrate and the Intestinal Barrier

The gut barrier divides the abdominal organs and the luminal environment[49] and is a critical site for human body material exchange, intestinal flora, and food immune tolerance.[50] The intestinal barrier is associated with the following gastrointestinal diseases (IBD and celiac disease), metabolic diseases (diabetes and obesity), and autoimmune diseases, which are all associated with inflammation. Intestinal barrier disruption, known as "leaky gut",[51] causes the translocation of intestinal microbiota and luminal inflammatory mediators and is a major cause of local and systemic inflammation.[52] Butyrate is significant in several closely related major layers of the intestinal mucosa, helping to preserve the intestinal barrier's integrity. Butyric acid protects physical barriers via several pathways. First and foremost, butyrate, as intestinal cells' primary source of energy,[53] promotes the regeneration of intestinal epithelial goblet cells, increases the synthesis of MUC2 mucin, an essential constituent of the mucosal lining of the intestinal layer, and protects the integrity of the physical barrier. As a preferred energy source for colonic cells, the beta-oxidation process of butyrate in the cellular mitochondria consumes oxygen, thereby activating hypoxia-inducible factor (HIF),[54] which promotes the expression of tight junction proteins such as occludin, Zonula occludens-1 (ZO-1), and Claudin-1, enhances transepithelial electrical resistance (TEER), and reduces Claudin-2 expression.[55] Butyrate can also regulate the actin-related protein synaptopodin (SYNPO) by inhibiting HDAC, promoting the expression of α-actinin-4 (ACTN4), restoring intestinal barrier function, and maintaining the integrity of the intestinal mucosa.[56] In addition to physical barriers, studies have shown that butyrate activates mammalian target of rapamycin signaling pathway (mTOR) and STAT3 by binding to GPR43 in IEC, leading to increased expression of RegIIIγ, β-defensin, and cathelicidin-related antimicrobial peptide (CRAMP). To maintain chemical barriers and adjust the ecological balance of microbiota.[57] At the immune barrier level, butyric acid regulates immune cells, reduces proinflammatory mediators, exerts anti-inflammatory effects, and restores intestinal immune barrier function. The intestinal flora is considered

to be part of the biological barrier. Certain bacteria can regulate the intestinal barrier. The interaction between butyric acid and intestinal flora is bidirectional. Butyric acid can promote the growth of helpful bacteria in the intestines while also suppressing the growth of dangerous bacteria. The microbiome, by producing butyric acid, it inhibits the colonization resistance of pathogenic bacteria (like *Salmonella, Shigella*,[58] and *Candida albicans*[59]), limits their spread to the surrounding environment, and alleviates clinical symptoms caused by harmful bacteria. In contrast, an animal study found that feeding mice a high-fiber diet (HFD) resulted in elevated levels of butyrate in the intestines as well as levels of the receptor Gb3 for Shiga toxin-producing E. coli (STEC).Contributing to the colonization of Shiga toxin-producing *E. coli*, in addition to the effect of butyric acid, other factors associated with HFD (such as increased levels of acetic acid and propionic acid) and the host's immunity may increase susceptibility to STEC infection.[60] Furthermore, butyric acid is capable of traversing both the placental barrier and the blood-brain barrier (BBB), increasing the expression of BBB's tight junction proteins claudin-5 and ZO-1, and restoring and protecting the barrier.[61] Butyrate preserves the structural integrity of the gut barrier through multiple mechanisms. However, high levels of butyric acid change the osmotic pressure inside and outside the membrane, causing cell apoptosis and destroying the mucosal barrier.[62] Therefore, excessive butyric acid supplementation is not permitted. A treatment plan should be created based on your specific situation; otherwise, it will be ineffective (Figure 2).

Butyric Acid and Immunity

Innate immunity, adaptive immunity, and microorganisms work together to maintain immune homeostasis and effectively resist and eliminate invading pathogens. Butyrate, a microbially derived short-chain fatty acid, is crucial in immune regulation. Innate immune cells such as macrophages, granulocytes, dendritic cells, etc, are all affected by butyric acid. Macrophages are the first line of defence for innate immunity and can engulf and kill immunogenic substances.[64] Reported studies have suggested that butyrate inhibits HDAC activation and induces macrophage differentiation, reduces macrophage glycolysis pathway, increases adenosine monophosphate (AMP) expression, inhibits mTOR signal, and causes the LC3-related autophagy pathway, enhances the expression of calprotectin (S100A8 and S100A9) mRNA, effectively strengthens macrophage antibacterial activity, and prevents the spread of inflammation.[65] Butyric acid also inhibited autophagy and NLRP3 inflammasome activation by inhibiting the PI3K/Akt/NF-κB pathway, reducing oxidative stress, inflammation, and metabolic dysfunction in the PI3K-dependent autophagy pathway in human monocyte–macrophage-derived THP-1 cells.[66]

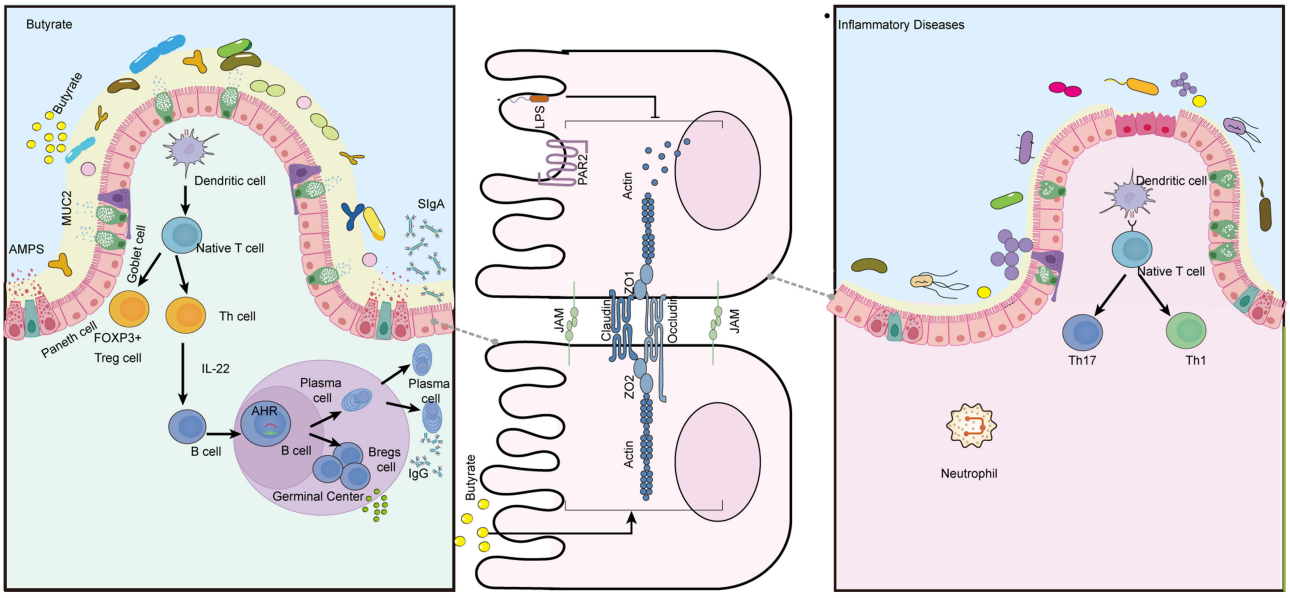

Figure 2 Butyric acid maintains the integrity of the intestinal barrier by restoring the physical barrier (restoring cuprates, tight junction proteins), chemical barrier (restoring the function of Paneth cells, increasing the level of AMPS), immune barrier (anti-inflammatory), and biological barrier (inhibiting harmful bacteria) to combat the diffuse spread of inflammation. Reprinted from Rungrasameviriya P, Santilinon A, Atichartsintop P, Hadpech S, Thongboonkerd V. Tight junction and kidney stone disease. Tissue Barriers. 2024;12(1):2210051. doi:10.1080/21688370.2023.2210051. Reprinted bypermission of the publisher (Taylor & Francis Ltd, http://www.tandfonline.com).[63]

Furthermore, butyrate can regulate the M1/M2 polarization balance of macrophages, inhibit M1 cell polarization, promote M2 cell polarization, and prevent inflammation from arising or spreading. Neutrophils are the first responders of immune cells. During the acute phase of inflammation, butyrate inhibits HDAC, limiting the recruitment of neutrophils, reducing neutrophil-derived expression of Chemokine (C-C motif) ligand 3 (CCL3), CCL4, and IL-8, reducing neutrophil extracellular trap (NET) formation, and limiting the inflammatory response.[67] Allergic effector cells (eosinophils, basophils, mast cells, and innate lymphocytes 2) are the essential cells for the development and progression of allergic diseases. Butyric acid treats allergic diseases by inhibiting a wide range of allergic cells. Yingzi Cong team's research shows that whether administered systemically or locally, butyrate inhibits HDAC in a dose-dependent manner, inhibiting the GATA3 gene, reducing the number of Group 2 innate lymphoid cells (ILC2), lowering the concentration of IL-5, IL-13 cytokines, and improving AHR and Eosinophil-induced airway inflammation, all of which alleviate allergic asthma.[23] In eosinophils, butyric acid activates caspase-3/7, decreases the expression of Bcl-2 family members (Bcl-xL and Mcl-1), induces the intrinsic apoptotic pathway, and inhibits the expression of the adhesion molecules CD44, CD49d, and eosinophilic chemotactic protein-2 (eotaxin-2), and its receptor Chemokine Receptor 3 (CCR3). Regulates eosinophil survival, migration, and adhesion.[68] In contrast, however, one study found that butyric acid activation of GPR43 promotes secretion of IL-5 and IL-13 by Th2 cells, increases the number of eosinophils, exerts a positive feedback effect in the immune system, amplifies the Th2 cell effect, and exacerbates asthma in a mouse model.[69] This could be due to the various concentrations, durations, and routes of administration of butyric acid. Therefore, more work is necessary to confirm the effect of butyrate on eosinophils. The complex mechanism of butyric acid's action on immune cells is not only evident in eosinophils, but its mechanism of action in basophils is also unclear. Butyric acid inhibits HDAC-induced apoptosis in basophils and lowers IL-4 levels; at the same time, it promotes IL-3 secretion-induced increase in CD69, stimulates activation and proliferation of basophils and Th2 cells, and activates IgE-mediated degranulation of surface CD63 basophils, leading to the release of a significant quantity of inflammatory mediators (eg, histamine, leukotrienes).[70] The precise function of the butyric acid in allergic effector cells remains unclear. More research is needed to combine the etiology, location, and duration of the patient's disease with the frequency and mode of butyric acid administration to guide more precise and effective butyric acid administration in allergic diseases.

Butyric acid is important in the interaction between adaptive immune T cells and B cells. The anti-inflammatory Treg cell/pro-inflammatory Th17 cell balance is essential for intestinal microcosmic immune homeostasis. Treg cells come from two distinct individual lineages of origin: Thymus-derived Treg (tTreg) cells and peripherally-derived Treg (pTreg) cells. Most commensal bacteria and their metabolites affect the production of extra-thymic (pTreg) cells, as the proportion of Treg cells in the feces is significantly reduced in mice treated with broad-spectrum antibiotics or germ-free (GF) mice. Nicholas Arpaia and his team found that butyrate promotes the differentiation of Tregs due to peripheral induction, rather than an increase in thymic output.[40] Butyrate is dependent on the intronic enhancer (CNS1) to induce Forkhead box P3 (FOXP3), which promotes the production of T regulatory cells (Tregs), increases the secretion of transforming growth factor-β (TGF-β) and (IL-10, and inhibits the differentiation of IL-17-producing Th17 cells, which maintain immune homeostasis. On the other hand, butyrate induces Breg cell differentiation by inhibiting HDAC, mediates B lymphocyte-induced maturation protein 1 (Blimp-1) production of IL-10, and increases IgA and IgG release.[71]

Butyric Acid Immunity Duality

Butyric acid is an immune regulator. Many studies have shown that butyric acid has anti-inflammatory properties. However, butyric acid exhibits proinflammatory properties under certain conditions. The immunomodulatory mechanism of butyric acid is difficult to define. Butyric acid's immune duality is strongly influenced by its concentration. Low concentrations of butyric acid inhibit IL-8 release and suppress inflammatory responses, whereas higher concentrations of butyrate increase IL-8 expression and secretion, resulting in pro-inflammatory effects.[72] Results of an animal study, low concentrations of butyrate (0.2–1 mM) activated AHR receptors in RA model mice, increased Breg, reduced inflammation, and improved RA in mice. In contrast, in CIA model rats, high concentrations of butyrate (20–30 mM) increased lipopolysaccharide (LPS), produced proinflammatory T cells (Th1, Th17), increased proinflammatory factors (IL-1, IL-17), promoted inflammation, and exacerbated RA in rats. Different species of experimental animals in this experiment have different thresholds of butyric acid, which could explain why butyric acid has a dual nature. Clinical observations indicate that butyrate

concentrations in the stools of full-term infants are typically below 100 mmol/L.[73–75] This level supports intestinal barrier integrity and suppresses the production of inflammatory cytokines. However, in preterm infants, factors such as intestinal immaturity, early initiation of enteral feeding, and impaired gastrointestinal motility may lead to excessive accumulation of butyrate in the gut, with concentrations rising significantly (up to 200–300 mmol/L).[74] Such elevated levels can damage the intestinal mucosa and increase the risk of necrotizing enterocolitis (NEC).[76] Neonatal rat models have confirmed mucosal damage caused by high butyrate concentrations.[77] Therefore, supplementation with substrates for short-chain fatty acid (SCFA) production, including dietary fiber—particularly for pregnant women and infants—requires careful evaluation based on individual conditions and should be administered judiciously to avoid indiscriminate intake. Butyrate has also demonstrated duality in colorectal cancer (CRC) HT-29 cells and Caco-2, with one study finding that it inhibits inflammation by decreasing IL-8 release in Caco-2 cells, while increasing IL-8 secretion in HT-29 cells.[78,79] These paradoxical effects of butyrate may be dose and/or formulation-dependent, as butyrate has a dose-specific effect on colon cell proliferation in vitro. At low doses, butyrate promotes colonocyte proliferation.[80] At higher doses, butyrate can cause cell cycle arrest and apoptosis in vitro and ex vivo,[81] as well as inhibit the proliferation of human colon epithelial cells. Given studies indicating the dose-dependent anti-inflammatory effects of butyrate, a systematic and individualized research framework is required. Basic Research should establish gradient dose models (in vitro) to elucidate the dual immunomodulatory mechanisms across energy metabolism, immune responses, and signaling pathways, identifying the threshold for the anti-inflammatory to pro-inflammatory transition. For clinical translation, real-time monitoring of intestinal pH (eg, PillTrek smart capsules[82]), periodic metagenomic/metabolomic profiling, and colon-targeted drug delivery systems are needed to maintain stable luminal butyrate concentrations and circumvent upper GI tract interference.

Microbiota and Butyrate in Chronic Inflammatory Diseases

Chronic inflammatory diseases (CID)—such as inflammatory bowel disease (IBD), multiple sclerosis (MS), asthma, type 2 diabetes (T2D), atherosclerotic cardiovascular disease (ACVD), and nonalcoholic fatty liver disease (NAFLD)—share a common pathological basis: immune dysregulation and persistent inflammation. Butyrate, a core microbial metabolite derived from the fermentation of dietary fiber, exerts immunomodulatory effects that help mitigate the progression of CID through multiple mechanisms (Figure 3 and Table 1).

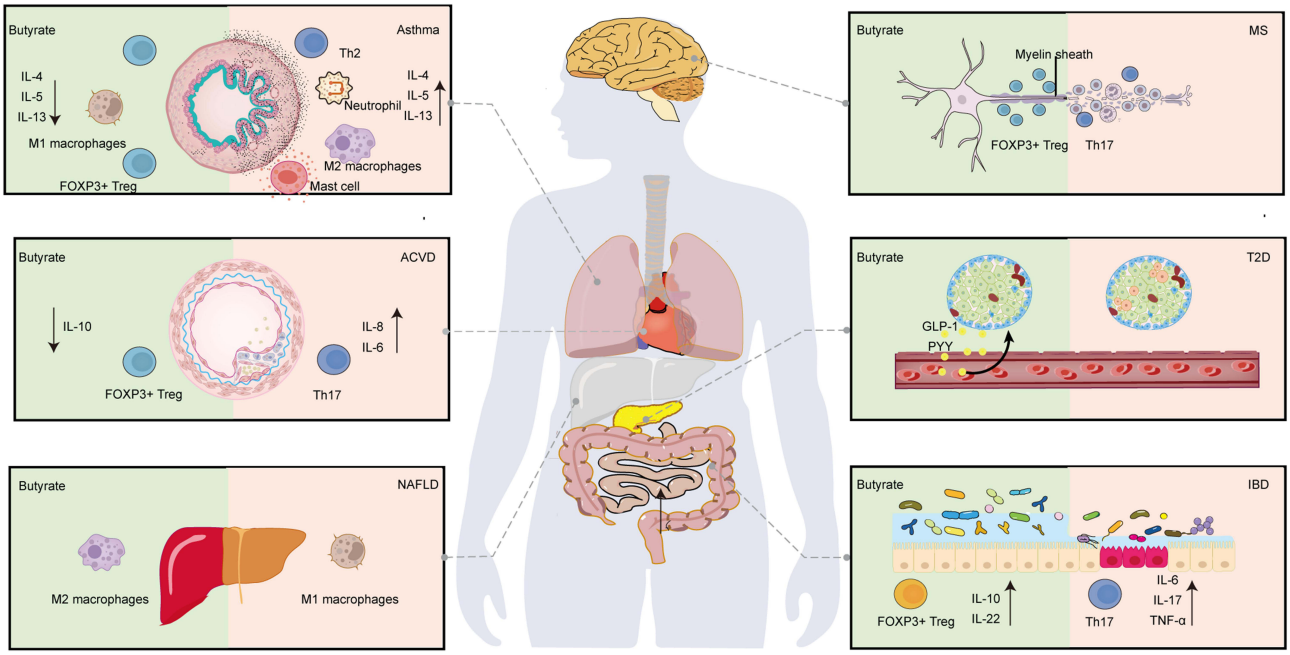

Figure 3 Mechanism of action of butyric acid on various systemic diseases. Butyric acid exerts positive effects on the respiratory, cardiovascular, endocrine, and digestive systems.

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Table 1 Regulatory Mechanisms of Butyric Acid in Multiple Chronic Inflammatory Diseases

Disease	Model	Butyrate Administration	Molecular Mechanisms/Pathways
IBD	C57BL/6 mice	Tributyrin (1.5 g/kg BW)	↓ LPS expression; preserved TJ structure; ↑ IL-10 and JNK mRNA[83]
	HIF-1α$^{\Delta IEC}$mice[a]	Sodium butyrate (2% in drinking water)	↑ HIF-1 expression; restored intestinal autophagy; ↓ TNF-α, IL-1β, and IL-6 expression[54]
	Treg and Th17 cells	In vitro butyrate treatment	↑ PPARγ; ↑ OXPHOS; ↓ glycolysis → ↑ Treg differentiation; ↓ Th17 differentiation[84]
	IBD patients	Fecal butyrate (GC-MS[b] quantification)	↑ M2 macrophage polarization; activated WNT-ERK1/2 axis; ↑ goblet cell mass and mucin formation[66]
MS	Cuprizone-induced demyelination[c] (C57BL/6J mice)	Sodium butyrate (200 mM in drinking water)	↓LPC-induced demyelination; ↑ remyelination; ↑ oligodendrocyte differentiation[85]
PSS	PSS patients	↑ Butyrate-producing bacteria (16S rDNA)	↓ IL-6, IL-12, IL-17, TNF-α; ↑ IL-10 and FOXP3 mRNA; ↑ Treg cell levels[86]
Obesity	HFD mice (60% fat)	Sodium butyrate (5% w/w diet)	↑ ABCA1, ABCA8, LCAT1 expression; ↑ immunometabolic signatures; ↓ inflammation; attenuated ER stress; corrected defective autophagy → improved adipose tissue microenvironment[87]
	3T3-L1 adipocytes and RAW264.7 macrophages	In vitro butyrate treatment	↓ TNF-α, MCP-1, IL-6, FFAs; ↓ MAPK phosphorylation; ↓ NF-κB activity; ↓ adipocyte lipase activity[88]
Diabetes	Mouse islet cells and INS-1E β-cells	Sodium butyrate treatment	Improved β-cell function; prevented cytokine-induced impairment of GSIS[89]
NAFLD	HFD-fed mice	Sodium butyrate (5 mM)	↓ HDAC2 → ↑ GLP-1R in HepG2 cells; ↑ hepatic p-AMPK/p-ACC; ↑ insulin receptor/IRS-1 expression[90]
	HFD mice	Sodium butyrate (200 mg/kg)	↑ GPR43/GPR41 → ↑ LKB1-AMPK-Insig pathway; ↓ hepatic lipogenesis[91]
Asthma	Human peripheral eosinophils	Butyrate (10 μmol/L)	↓ eosinophil infiltration; promoted inflammation resolution via reduced surviva[68]
CRC	EG7 tumor-bearing mice	Sodium butyrate (30 mM in drinking water)	Enhanced ID2-dependent IL-12 signaling → regulated anti-tumor CD8+ T cell responses; promoted anti-cancer immunity[92]

Notes: [a]HIF-1α$^{\Delta IEC}$ mice: Intestinal epithelial cell (IEC)-specific HIF-1α knockout mice. [b]GC-MS: Gas chromatography-mass spectrometry. [c]Cuprizone-induced demyelination: Mice fed 0.2% cuprizone diet for 3 weeks.

Autoimmune Disease

Inflammatory Bowel Disease

IBD is a widespread chronic inflammatory disease of the gastrointestinal tract that includes ulcerative colitis (UC) and Crohn's disease (CD).[93,94] Unlike ulcerative colitis, which manifests as chronic inflammation with lesions limited to the colon, CD manifests as segmental inflammation with lesions affecting any part of the gastrointestinal tract.[95] IBD may be caused by genetic factors, environmental changes, immunity, and other factors,[83] but the exact cause is unknown. Intestinal inflammation and intestinal barrier destruction have been clinically observed during IBD attacks. Butyrate has been shown to possess intestinal barrier-protective properties and anti-inflammatory effects; it is a popular research topic for the treatment of IBD. The earliest documented records of butyrate treating IBD date back decades. Butyrate lowers intestinal permeability by increasing epithelial tight junctions. In CD, butyrate inhibits LPS, heals ileal microvillus damage, and increases tight junction (TJ) expression, as confirmed in vivo,[96] protects intestinal barrier integrity, and

slows disease progression. Genome-wide association studies (GWAS) have shown that autophagy-related genes are closely linked to IBD,[84] and deletion of intestinal epithelial (IEC) HIF-1α significantly reduces autophagy., resulting in disruption of intestinal barrier integrity and increased susceptibility to dextran sulfate sodium (DSS)-induced IBD. Butyrate can increase the oxygen consumption of intestinal epithelial cells, maintain "physiological hypoxia" in the intestinal epithelium, enhance the expression of HIF-1, and restore intestinal autophagy.[54] Butyrate modulation of immune cells and counteracting the inflammatory response are also important modalities in the treatment of IBD, such as butyrate regulating the Treg/Th17 balance. Clinical observations have shown that the pro-inflammatory cytokine IL-17 is elevated in the intestinal mucosa of IBD patients.[97] Butyrate stimulates the production of IL-10 and IL-22 by regulating the Treg transcription factor FOXP3.[23] Butyrate can also activate peroxisome proliferator-activated receptor γ (PPARγ), which in vivo shifts mitochondrial energy metabolism from Th17-dependent glycolysis to Treg-dependent Oxidative Phosphorylation (OXPHOS). This metabolic reprogramming promotes the conversion of Th17 cells to Treg cells, maintains Treg/Th17 balance, regulates intestinal immune homeostasis, and reduces intestinal inflammation.[98] However, an animal experiment demonstrated that butyric acid treatment reduced the levels of Tregs and Th17 simultaneously.[99] The dominance of Th17 in animals may lead to the secretion of IL-6, which inhibits Tregs and increases TNF-α and IL-17A. Th17 is metabolized via glycolysis, which inhibits Treg production. Furthermore, different feeding concentrations and animal models may produce varying results. Reducing toxic mediators is also a pathway of butyrate in the treatment of IBD. Overexpression of inducible nitric oxide Synthase (iNOS), which produces nitric oxide (NO), can worsen symptoms in patients with IBD. In the DSS mouse model, butyrate inhibits the NF-κB pathway, inhibits the expression of iNOS, and reduces the production of cytotoxic NO, reducing inflammation and alleviating the symptoms of IBD.[100]

Multiple Sclerosis (MS)

MS is a chronic neurological disease characterized by demyelination and immune cell infiltration in the central nervous system,[101] and its pathogenesis is unknown. Among them, Th1 and Th17 cells proliferate and secrete the proinflammatory factor IL-17, which is important in the pathogenesis of MS.[102] More than a decade ago, the intestinal microbiota was discovered to play a major role in developing MS in experimental autoimmune encephalomyelitis model mice.[103] MS patients' feces contain more *Methanobrevibacter* and *Akkermansia muciniphila* than those of healthy people's feces.[101,104] *Methanobrevibacter* is a methane-producing archaea that can lower butyric acid levels.[105] *A. muciniphila* stimulates proinflammatory T cells,[85] which are involved in the development of MS. On the contrary, *Parabacteroides distasonis* and *Clostridium cluster* XIVa are reduced.[104] Both intestinal bacteria can induce Treg cells and suppress the inflammatory response to MS. Among them, the *C. cluster*, in particular, activates GPR41 and GPR43, which increases IL-10 production and strengthens TJs, reduces intestinal permeability, downregulates inflammation, and alleviates MS. Butyrate has been shown in animal studies to promote myelination regeneration.[106] However, more randomized and controlled trials are required to eliminate confounding factors, investigate the therapeutic effect of intestinal flora, particularly its metabolite butyric acid, on MS, and seek more effective treatment methods.

Primary Sjögren's Syndrome

Primary Sjögren's syndrome (PSS) is an autoimmune disorder marked by chronic inflammation of exocrine glands such as the lacrimal and salivary glands.[107] In addition to genetic factors, infections and environmental factors can all increase the risk of PSS. PSS is characterized by elevated proinflammatory cytokines, serum autoantibodies, and infiltration of T and B cells. Clinical studies have found an increase in the intestinal flora *Escherichia coli*, Shigella, and Streptococcus compared to healthy people, and several bacterial genera can cause infection and worsen PSS.[108] Butyric acid can impede the colonization of harmful bacteria like *E. coli* and *Shigella. Bacteroidetes, Parabacterium*, and *Prevotella* are less common within the gut microbiome of PSS patients, and multiple bacterial genera can induce Treg cells and inhibit PSS inflammation. *Prevotella* and *Parabacterium* can cause an increase in butyrate levels. Butyrate inhibits the NF-κB signaling pathway, IL-6, and TNF-α by activating GPR43 and GPR41. It also regulates Treg cell differentiation and reduces the expression of IL-17, inhibiting inflammatory responses and mitigating PSS.[86]

Microbiota and Butyrate in Metabolic Disease

Obesity

In recent years, due to changes in living conditions and eating habits, the global prevalence of obesity has risen dramatically. Obesity is expected to reach 42% of the global population by 2030, and it is frequently accompanied by type 2 diabetes, nonalcoholic fatty liver disease, metabolic syndrome, and cardiovascular disease, all of which pose serious threats to public health security.[109] Effective and consistent obesity management is urgent. Lifestyle intervention, which includes reasonable exercise and dietary patterns, is an effective way to lose weight. Jeffrey I Gordon et al separated obese twins' (OB) feces from lean twins' (LN) feces and transplanted them into germ-free mice, discovering that the butyrate concentration in mice transplanted with LN feces was significantly higher.[110] However, some studies showed the contrary, with obese patients clinically observed to have higher fecal butyrate levels than lean individuals, which could be attributed to species and individual differences in microbiota.[111,112] Thus, the mechanism and effect of butyric acid on obesity remain unknown. However, multiple studies have found that butyric acid combats obesity by regulating appetite, energy metabolism, and inhibiting inflammatory responses. Butyric acid activates vagus nerve signal (an intracerebral neural circuit), inhibits the expression of appetite neuropeptide Y (NPY) in the hypothalamus, and decreases the concentration of the nucleus of the solitary tract and the dorsal vagal complex, resulting in a sense of satiety. Butyric acid can also stimulate the digestive system to secrete GLP-1,[87,113] which activates hypothalamic signaling either through the gut-brain neural circuit or directly via the circulatory system, thereby suppressing appetite and reducing food intake. In addition to suppressing appetite, butyrate can activate the vagus nerve, stimulating the SNS controlled by the hypothalamus, activating brown adipose tissue to consume triglycerides (TG), and promoting fatty acid oxidation and energy consumption.[114] Systemic inflammation, particularly visceral inflammation, is an important marker of obesity. Butyric acid inhibits HDAC, inhibits proinflammatory M1 cells, increases anti-inflammatory M2 cells,[88] decreases circulating endotoxin, and inhibits lipopolysaccharide (LPS). The activated inflammatory cascade reaction reduces Nuclear Factor Kappa B Subunit 1 (NFKB1) and RELA Proto-Oncogene (RELA) gene expression, inhibits proinflammatory pathways and proinflammatory mediators like NF-κB, MAPK, and TNF-α, and inhibits the inflammatory response of obesity.[115,116] Furthermore, obesity is closely associated with central appetite dysregulation. Although lifestyle interventions may offer short-term weight loss, they frequently result in relapse and demonstrate limited long-term effectiveness. Therefore, individualized treatment strategies combining pharmacotherapy and bariatric surgery should be guided by clinical evaluation.

Diabetes

With the advancement of microbial genomics research, microbiota changes in diabetes have received widespread attention. The Human Microbiome Project (HMP) and the T2D Metagenomic-wide Association Study (MWAS) have shown that opportunistic pathogenic bacteria in the intestinal flora of diabetes patients (such as *Clostridium*, various *E. coli*), with an increased abundance of *Veillonella*, are one prevalent characteristic of visceral obesity and significant insulin resistance.[117] Decreased plentiful beneficial bacteria, particularly butyric acid-producing bacteria such as Roseburia intestinalis, *E. faecalis,* and *C. perfringens*, were significantly reduced,[118] prompting the question of whether butyric acid has the potential to be a drug and biological aim for diabetes treatment. Regardless of the HFD, GPR43$^{-/-}$ mice are obese, which is a risk factor for developing diabetes. Butyric acid activates GPR43 in adipocytes, increasing the levels of GLP-1 and PYY, reducing insulin resistance and alleviating diabetes.[89] Inflammation is a major pathway in prediabetes and persists throughout the disease. Butyric acid in vivo activates GPR43 and GPR41 receptors, stimulates intestinal epithelial Paneth cells, enhances the secretion of β-defensins, helps restore the intestinal chemical barrier,[57] and increases the expression of the tight junction proteins, Claudin-1, Claudin-4, and ZO-1, thereby improving the function of the intestinal physical barrier.[119] It prevents microbial translocation and inflammatory dissemination. Additionally, it suppresses the pro-inflammatory cytokine IL-1β, thereby protecting pancreatic β-cells.[120] Furthermore, butyrate *clinically* inhibits harmful bacteria and restores flora balance in diabetic patients.[121]

Diabetes is a chronic disease. Long-term or even lifelong medication presents a significant challenge for diabetic patients and the medical system. Metformin is the first-line treatment for T2D. Metformin treatment increases the number

of positive correlations between *Proteobacteria* and *Firmicutes*.[122] Metformin treatment raises the probability of increased propionate and butyrate concentrations in patients[123] De Vadder et al discovered that increased SCFAs levels in the intestine stimulate gluconeogenesis (IGN) via various complementary mechanisms, particularly propionate and butyrate. Butyrate indirectly increases cAMP, which activates IGN in intestinal cells, while propionate, a substrate for IGN, activates the GPR43 receptor, triggering gluconeogenesis, which converts to glucose.[124] A clinical study shows that, compared to placebo, WBF-011 (*Akkermansia muciniphila, Anaerobutyricum hallii, Clostridium beijerinckii, Clostridium butyricum, Bifidobacterium infantis, and inulin*) significantly improves postprandial blood glucose and HbA1c levels while reducing gastrointestinal side effects in metformin-treated T2D patients.[125] Thus, probiotics containing butyrate-producing bacteria and *Akkermansia muciniphila* may serve as adjuncts to metformin therapy. However, the mechanism of SCFAs (short-chain fatty acids) in T2D remains unclear. Large-scale clinical cohort studies that account for genetic, racial, gender, and age differences are needed to support precision diabetes treatment.

Nonalcoholic Fatty Liver Disease

Nonalcoholic Fatty Liver Disease(NAFLD) is the world's most common chronic liver disease, affecting 25% of the adult population,[126] and the prevalence of it is rising due to lifestyle and metabolic disorders like obesity and Diabetes Mellitus (DM). NAFLD is not a single disease, but rather a histological spectrum of the liver that progresses from isolated steatosis (non-NASH) with an inflammatory cascade to nonalcoholic steatohepatitis (NASH) with increased liver fibrosis, cirrhosis, and even hepatocellular carcinoma (HCC).[127,128] Currently, the US Food and Drug Administration (FDA) has not approved any medications. And effective treatments are urgently needed. The microbiota and its metabolite butyric acid are intimately linked to the liver and play an important role in the prevention, diagnosis, and treatment of NAFLD. Prevention of NAFLD is most effective when initiated early in life. Maternal metabolic diseases during pregnancy, as well as HFD, are significant risk factors for NAFLD. Ching-Chou Tsai's team discovered that *Lactobacillus reuteri* and butyrate reduced hepatic steatosis in HFD pregnant rats, altered the mother's intestinal and placental microbiota, and prevented metabolic diseases like NAFLD.[90] A higher abundance of Aspergillus and Enterobacteriaceae and a lower output of butyric acid-producing thick-walled bacteria such as *E. faecalis* and *B. Prevotella* were seen during the development of NAFLD compared to healthy individuals.[129] It demonstrates that the microbiome and butyrate can be used as noninvasive diagnostic tools for NAFLD. Combining existing diagnostic methods, larger cohort studies, metagenomics combined with machine learning, and the gut-liver axis connection are required to achieve a precise and accurate diagnosis. Furthermore, butyric acid can treat and prevent NAFLD progression. Inhibiting glucose and lipid metabolism disorders, and inflammation, is essential for preventing NAFLD from developing and progressing.[91] Butyrate inhibits HDAC, boosts GLP-1R expression, and enhances its sensitivity.[130] Furthermore, butyrate activates GPR43 and GPR41 receptors, activating the Liver Kinase B1 – AMP-activated Protein Kinase – Insulin-induced Gene Protein (LKB1-AMPK-Insig) signal pathway, inhibiting hepatic fat metabolism,[131] and slowing the progression of NAFLD; several investigations have demonstrated that inflammation plays a significant part in the onset and progression of NAFLD. Butyric acid can also inhibit proinflammatory mediators like the NF-κB pathway, and M1 macrophages, while promoting anti-inflammatory M2 macrophage recruitment.[132] It also stimulates the secretion of a variety of antimicrobial peptides (AMPs) by Paneth cells to restore the chemical barrier and inhibit the inflammatory response. However, in vitro studies demonstrate that due to the "butyric acid paradox",[133] immune and metabolic dysregulation, excessive butyric acid creates a pro-inflammatory and protumor microenvironment, resulting in cholestasis and even HCC.[131,134] Therefore, dietary fiber supplementation should not be taken at face value, and a personalized nutritional strategy should be developed based on one's specific situation.

Atherosclerotic Cardiovascular Disease

Atherosclerotic cardiovascular disease (ACVD) is characterized by the accumulation of plaque in arteries and the thickening of arterial walls, which can lead to narrowing or even blockage of arteries. It is the primary cause of cardiovascular disease and among the primary reasons for mortality of the world's population, particularly the elderly.[135] Diabetes, hyperlipidemia, hypertension, obesity, etc, are all risk factors for atherosclerosis. The Purna C Kashyap team discovered a decrease in the diversity of intestinal flora in patients with ACVD, particularly in the

abundance of butyric acid-producing bacteria like *Clostridium, Faecalibacterium*, and *Roseburia*.[136] Butyric acid levels are lower in ACVD patients, and butyric acid reduces ACVD by inhibiting the adhesion subunit (VCAM-1), an induced chemokine (IL-8), through inhibition of HDACs/JNK or p38MAPK/IL-33/NF-κB signal pathways.[137] Butyric acid can also activate GPR109a on macrophages, reduce the amount of pro-inflammatory mediators: cytokines IL-6 and Th17 cells, increase the levels of anti-inflammatory mediators: Treg cells and cytokines IL-10, and reduce vascular inflammation.[138]

Butyric Acid and Microorganisms in Allergic Disease

Asthma

Asthma is a respiratory allergy, a frequent illness of the respiratory system that affects more than 300 million children worldwide.[139] It is characterized by chronic airway inflammation and lung hyperresponsiveness. Asthma is most common after exposure to allergens, climate change, and air pollution. There is mounting evidence to suggest that the development of asthma is strongly related to the composition of the gut flora, with asthmatics having lower fecal butyrate concentrations than healthy people.[140] Butyrate has numerous benefits for asthma. Th2 cell activation is a critical factor in asthma. Butyrate can activate the transcription factorFOXP3 in T cells, induce the production of Tregs, reduce Th2 cells, and inhibit IL-13, IL-5, and IL-4, alleviating asthma.[141] Macrophages are the most abundant immune cells in the lungs, and an M1/M2 imbalance plays an essential part in the onset and progression of asthma. Chunrong et al discovered that butyric acid can inhibit M2 polarization and reduce airway hyperreactive inflammation. Butyrate induces eosinophil apoptosis, inhibits mast cell degranulation, and disables key allergy effector cells.[23,68] Furthermore, butyric acid increases the expression of the TJ protein occludin, which maintains the integrity of the airway and intestinal barriers, inhibits the colonization of pathogens like *Staphylococcus aureus, Streptococcus pneumoniae*, as well as respiratory syncytial virus, slows the spread of inflammation, and lowers the risk of asthma triggers.[142,143]

Colorectal Cancer

Colorectal cancer (CRC), ranks as the third most prevalent cancer globally,[92] and its incidence and mortality rates are increasing year after year. In addition to familial inheritance, the environment, and a high-fat, low-fiber diet have been identified as risk factors for CRC,[144] and IBD is a precancerous lesion of CRC due to its chronic inflammatory nature. Butyric acid, a fermentation product of dietary fibre that inhibits rectal cancer cell proliferation while resisting inflammatory responses, is expected to be developed as a drug to slow the progression of CRC. First, reduced butyric acid concentrations have been observed in CRC patients and high-risk colorectal cancer patients. Butyric acid could be used as a noninvasive biomarker in conjunction with other assays for CRC screening to aid in early detection, diagnosis, and treatment.[145] Butyrate can also inhibit glycolysis and tumor growth by blocking glucose metabolism in CRC and lowering metabolic precursors and energy supply. Butyrate inhibited HDAC3 activity, reduced vascular endothelial growth factor expression, blocked Akt1 phosphorylation, and inhibited ERK1/2, reducing the migration and invasion capabilities of cancer cells. Recent biological studies have found that butyrate increases CD8+T number and antitumor capacity via Inhibitor of DNA binding 2 (ID2)-dependent activation of the IL-12 pathway.[146] However, this research was carried out in a mouse model, and further clinical studies are needed to confirm the role of butyrate in patients with CRC, as well as the relevance and combination therapy of butyrate with other antitumor therapies such as radiotherapy and chemotherapy.

Treatment Method

From diet, fecal microbiota transplantation (FMT), probiotics, etc. to specifically or nonspecifically changing the intestinal flora and increasing the abundance of butyrate-producing bacteria, to directly increasing butyrate concentration in different dosage forms and administration methods, all may be beneficial to human health, and the advantages and disadvantages of these treatment patterns, the actual situation of the patient should be comprehensively considered during clinical applications, and the most appropriate treatment should be selected (Figure 4).

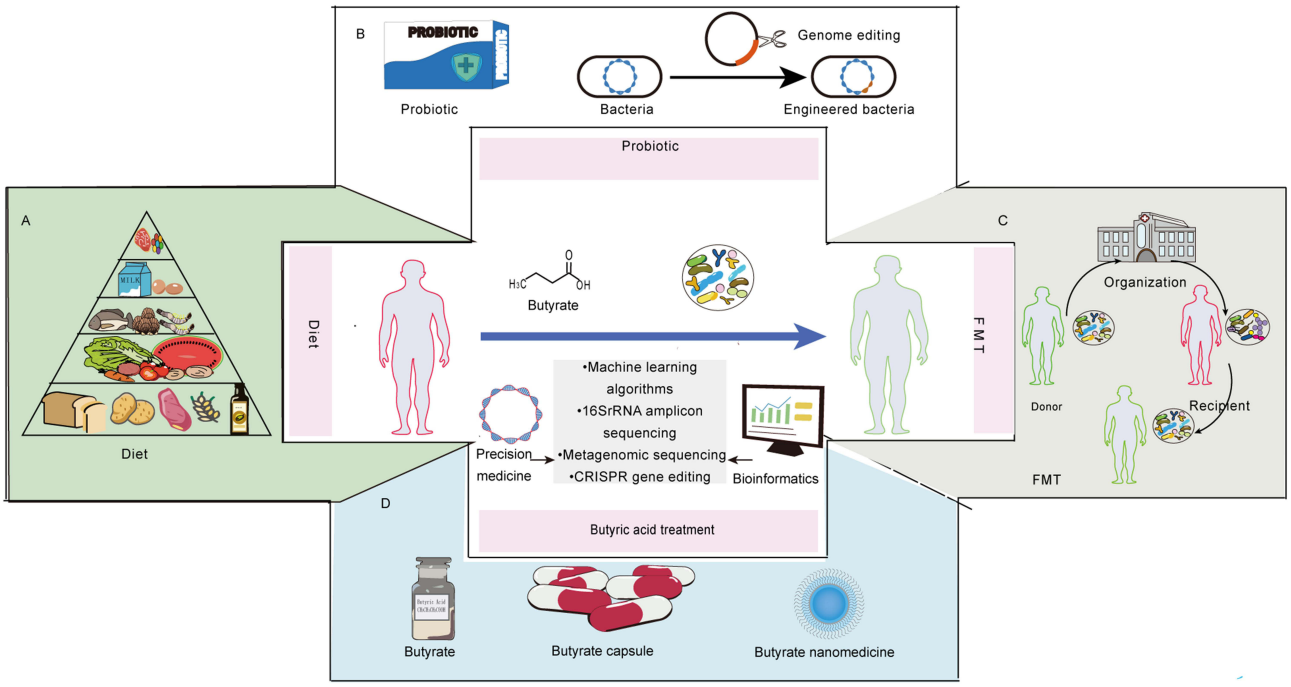

Figure 4 Microbial therapy of gut flora and butyric acid (**A**) Healthy diet. (**B**) Probiotics, engineered bacteria. (**C**) Fecal microbial transplantation. (**D**) Oral butyrate therapy includes butyrate salts, butyrate capsules, butyrate nanomedicines. Precise microbial therapies can be formulated by combining precision medicine and bioinformatics to increase butyric acid levels, restore the balance of intestinal flora, and restore human health.

Diet

Diet is a significant factor in determining the makeup and structure of the intestinal microbiota. As their living standards have improved, people's dietary structure has changed, as have intestinal microorganisms and butyric acid. The dietary pattern characteristic of the Western diet (high sugar, high fat, with large amounts of saturated fat) and excessive nutrition leads to increased use of dietary emulsifiers. This reduces the alpha diversity and stability of the gut microbiota,[147] decreases expression of the butyrate-producing gene (butyryl-CoA:acetate CoA-transferase(bcoA)), lowers butyrate concentration,[148] enhances intestinal barrier permeability, and facilitates translocation of endotoxin lipopolysaccharide (LPS) into systemic circulation – thereby exacerbating inflammatory progression. In addition, high-sugar and high-fat diets cause insulin resistance and dyslipidemia, which exacerbate metabolic diseases like obesity and diabetes.[149] In contrast, most dietary recommendations include whole plant foods like vegetables, fruits, and whole grains.[150] As the sole natural origin of dietary fiber, a whole plant diet can act as a carbon source for SCFAs like acetic acid and butyric acid, increasing their concentration. SCFAs can influence microbiota, maintain intestinal energy homeostasis, and regulate host immunity and metabolism function.[151] Consider the Mediterranean diet (MedDiet) pattern (high intake of whole plant foods and olive oil, moderate intake of fish and other meats, and low intake of sugars, fats, and refined grains), for instance.[152] Increase the abundance of butyric acid-producing bacteria such as *Faecalibacterium prausnitzii* and *Roseburia*, resulting in gut microbes mutually that benefit the host. The symptoms of diabetes and NAFLD can be improved. Reduce the prevalence of cardiovascular and cerebrovascular disorders.[123] As a result of the plasticity of the gut microbiome and the vast individual differences among hosts, one-size-fits-all dietary guidelines cannot meet the diverse dietary needs of individuals. Precision nutrition (personalized nutrition) is required to predict the dietary response to intestinal microbiome intervention based on individual characteristics, resulting in precise dietary recommendations for various groups of people to preserve human health.[153–155] Precision nutrition first requires collaboration between microbiomes and nutrition, using microbial sequencing and dietary testing to collect data, combined with a person's characteristics (eg, genetics, lifestyle, baseline metabolism, and drug use), and using machine learning algorithms, mediation analysis,[156] Bayesian network,[157] and Structural Equation Models.[158] This methodological integration establishes evidence-based causal relationships between microbiome dynamics and human health outcomes under dietary interventions, ultimately generating personalized nutritional recommendations. Second, the

implementation of large-scale precision nutrition recommendations faces a significant challenge. Based on numerous large-scale participant cohort studies, implementation departments, regulatory authorities, and professional societies must be established to achieve standardization and the best results for precision nutrition.

Fecal Microbiota Transplantation

FMT is a treatment method in which intestinal microorganisms from a healthy donor are transferred into the patient through different means (enemas, nasoduodenal tubes, or colonoscopy).[159] It was first introduced as early as 1700. Previously, Huanglong Tang was recorded as the prototype of fecal transplantation in Ge Hong's "Zhou Hou Bei Ji Prescriptions".[160] FMT was initially employed to treat *C. difficile* infection (CDI) with great success. According to studies, the cure rate of FMT in treating CDI is up to 90%,[161,162] which is higher than the first-line treatment for CDI vancomycin. In the face of relapsed and refractory CDI, FMT has excellent results and effectively reduces patient mortality.[163] FMT primarily treats CDI by restoring the gut microbiota, enhancing bacterial diversity, increasing butyrate-producing *Bacteroides* and *C. clusters* IV/XIVa, while reducing *Proteus*. Increased butyric acid concentration activates HIF-1, increases the expression of its target gene Hif1a, restores the integrity of IEC connections and intestinal barrier integrity,[164] reduces inflammatory response and inflammation spread, and inhibits *Salmonella typhimurium*, including *Shigella* of pathogenic bacteria to treat CDI.[58] Although FMT is far less effective in treating UC than CDI, it remains a viable microbial therapy. Clinical observations have shown that patients with UC have low efficacy and a high recurrence rate in FMT treatment, as well as fewer *C. cluster* IV *and* XIVa microbiota and that if there are many *Bacteroidetes* and *Proteobacteria*,[165] and the change in butyric acid concentration is not obvious. On the contrary, if the recipient has a large number of butyric acid-producing bacteria, or if the donor provides butyric acid-producing bacteria, the butyric acid concentration will rise, causing anti-inflammation and increasing the cure rate of UC. Furthermore, FMT can treat other diseases (like stroke) by increasing the quantity of bacteria that produce butyrate and the amount of butyrate.[166] However, the action pathway of butyric acid in FMT therapy is still unknown. Although this approach holds significant potential, FMT personalized therapy requires continuous refinement—particularly regarding donor screening, donor-recipient matching, and standardized protocols throughout treatment—when individualized microbiota variations are pronounced and host-microbiota interactions remain unclear. Firstly, before fecal transplantation, a comprehensive fecal bank should be established, and donors should be screened using a combination of complete blood and fecal pathogenic testing as well as questionnaires to eliminate adverse effects caused by infectious diseases, mental illness, lifestyle, etc.[167] At the same time, it can also be used to save the feces of the recipient before illness or during the remission period of a healthy diet for autologous fecal microbiome transplantation (aFMT), thereby improving the safety, colonization rate, and efficiency of FMT. The selection of donors and recipients is essential for FMT's success. Donor–recipient matching is crucial for successful FMT. By using bioinformatics tools such as 16S rRNA amplicon sequencing and shotgun metagenomics, combined with machine learning methods (eg, Random Forest), we can predict post-FMT microbiome composition. By comparing the donor and recipient microbiota and identifying microbial deficiencies in the recipient, compatible donors with matching enterotypes can be selected. This strategy improves formulation accuracy and enhances FMT efficacy and clinical success.[168] Furthermore, the recipient's immunological status and antibiotic interventions critically determine the success of FMT therapy. In an animal model, FMT failed to restore gut microbiota or resolve persistent CDI in mice with Foxp3$^+$ Treg deficiency, demonstrating that host immunity is a fundamental determinant of treatment efficacy. Nicola Segata et al discovered that patients who received antibiotics or antibiotic pretreatment before FMT more effectively received the donor strain and had lower colonization tolerance.[168] There are many forms of antibiotics with different antibacterial mechanisms. According to studies, different antibiotics have different, if not opposite, effects on FMT's effectiveness. Using FMT in the therapy of IBD, metronidazole treatment increases beneficial bacteria while inhibiting iNKT cells. Increase IL-10 levels and resist inflammatory responses, whereas vancomycin treatment increases the inflammatory infiltration of immune cells, activates iNKT cells, increases proinflammatory Th1/Th17 cells, and promotes inflammation.[169] Furthermore, the pathogenic characteristics of the disease and pathogens are important considerations. The research team of Christian L. Hvas demonstrated that the usage of antibiotics has an important impact on the effectiveness of FMT in the treatment of CDI, and the use of antibiotics should be limited and discontinued at least one week before FMT.[170] Therefore, patients should carefully

choose donors and antibiotics based on the characteristics of their microbiota, health status, and disease before FMT. During FMT, the basic dosage unit should be developed, the patient's basic situations should be considered, the appropriate route of administration should be chosen, and the recipient should be given the optimal dosage and frequency. Post-FMT is an important period for microbial colonization. Patients should use endoscopy, proteomics, and metagenomic sequencing to determine treatment efficacy, as well as microbial markers to predict future outcomes following FMT. Additionally, patients should focus on cultivating and maintaining a healthy lifestyle, as well as stabilizing the flora.

Probiotics

The International Scientific Association for Probiotics and Prebiotics defined probiotics as "live microorganisms when administered in adequate amounts, confer a health benefit on the host".[171] This concept first appeared as early as 1974 and has evolved to the present day. Unlike FMT, probiotics regulate the bacterial flora more specifically. For example, *C. butyricum* was first discovered by Kinji Miyairi in 1933. According to one animal experiment, *C. butyricum* produces butyric acid, which lowers the pH of the intestinal lumen to inhibit *C. difficile*, activates FOXP3 to produce Treg cells, triggers an anti-inflammatory mechanism, diminishes inflammation in the intestines, and preserves a balanced immune system.[172] *Lactobacillus rhamnosus* (LGG) was isolated from healthy human feces for the first time in 1983 by Sherwood Gorbach and Barry Goldin. Oral administration of LGG has been shown to increase butyric acid concentrations in the intestinal mucosa and serum, activate Treg cell activation in bone marrow (BM) CD8+T cells to up-regulate the expression of the Wnt ligand, Wnt10b, and increase bone formation, thereby preventing osteoporosis-induced fractures.[173] The effectiveness of probiotics and intestinal mucosal colonization has been debated. However, analysis of indigenous microbiota composition combined with baseline hosts through microbiome and genome sequencing to establish efficient microbial prediction models and algorithms to predict individualized use of probiotics is beneficial in eliminating resistance to colonization.[29] Probiotic surface modifications involving covalent coupling, in situ polymerization, surface coating, and membrane encapsulation are all effective methods for improving probiotic delivery and colonization.[174] Microbial–host studies are mostly genus-based and also consider interactions with other strains. A meta-analysis found that different probiotic blends and single-strain probiotics were more effective in reducing late-onset sepsis in preterm babies.[175] Therefore, in addition to single-strain probiotics, probiotic formulas should also be developed for the interspecies network of human intestinal microbiota (NJS16) as well as the microbiome network to improve the effectiveness and accuracy of probiotic therapy.[176,177] The probiotic formulation (Ecologic®825) contains 9 probiotic species, including *Bifidobacterium lactis* W51 and *B. bifidum* W23. Dynamic metabolic network and multivariate analyses revealed that the probiotic formulation increased the content of N-acyl amino acids in the adult small intestinal stoma and significantly increased butyrate vs propionate concentrations.[178,179] Engineered microorganisms have received a lot of attention, from Escherichia coli Nissle 1917 to CRISPR-engineered microorganisms due to differences in baseline hosts (race, age, gender, mode of production, lifestyle, etc), which result in unique microbial compositions of individuals and the need to develop individualized microbial therapies.[180,181] Integrating multi-omics data (eg, genomics, metabolomics) with AI-driven machine learning models (eg, Genetic Algorithms, artificial neural networks (ANNs), Random Forest (RF)) enables strain identification and screening, biomarker prediction, early diagnosis, and metabolic profiling. This integration supports the development of personalized and precise probiotic therapies.[182] Nonetheless, because of the genetic modification of strains by engineered microorganisms, biosafety and medical ethics must be considered when conducting R&D and clinical trials, as well as morality.[183]

Butyric Acid Treatment

Butyrate is a low molecular weight compound formed during the fermentation of anaerobic bacteria. It is unstable, has poor pharmacokinetics, has a short half-life, and is prone to off-target effects.[184] It also has a low pH in the stomach. It produces an unpleasant rancid butter smell. The intestines have difficulty absorbing the original *n*-butyrate,[96] which is also degraded by upper gastrointestinal enzymes. Therefore, oral butyrate is difficult to transport to the intestines to perform its function.[185] To improve patient acceptance and more efficient use of butyrate, new methods must be developed. The first step is to coat butyrate. Butyrate is housed in a sustained-release capsule.[186] When taken, it prevents

butyrate from being affected by the pH of the upper gastrointestinal tract and transports it to the intestines, where it can perform its function. Furthermore, butyrate microencapsulation is a superior coating method, using a lipid base and buffer compounds (carbonate and bicarbonate) to coat core butyrate granular products. Butyrate can be protected against strong acids. Environmental factors can cause specific intestinal enzymes to degrade lipid structure, releasing and functioning in the intestine.[187] However, actual observations have shown that this only solves a portion of the problem. Even if it is wrapped, some butyrate is still degraded in the stomach, and the odor remains unpleasant. In recent years, research and development of nanocarriers for butyric acid has also been successful. Yukio Nagasaki's research team used butyric acid as the ester part and an amphiphilic block polymer (PEG-b-PV(Bu)) to assemble polymer micelles (BNP of butyric acid-based nanoparticles). The action of digestive tract esterase slowly hydrolyzes BNP, which remains in the intestine at a constant concentration for at least 48 hours. The covalent binding of its main chain reduces the mop effect of butyric acid, inhibits the generation and spread of unpleasant odors, and protects the gastrointestinal tract, ultimately improving its efficacy. The animal experiments revealed that when compared to oral administration of butyrate, BNP significantly reduced blood sugar in diabetic model mice, improved glycolipid homeostasis, and protected pancreatic beta cells.[184] Coincidentally, Cathryn R Nagler and his team developed a butyrate micelle (ButM). ButM is an amphiphilic block copolymer with a high concentration of butyric acid linked to a hydrophobic block in its core band via ester bonds. Micelles formed by salts, which are neutrally and negatively charged polymers, can transport butyrate to the appropriate receptor site more accurately. (Electrically neutral substances act in the ileum, while negatively charged substances target the cecum). In addition, the unpleasant odor of butyrate can be concealed.[188] Animal studies have shown that ButM is effective in treating peanut allergies. In the mouse peanut allergy model, ButM increased intestinal microbial diversity, butyric acid-producing bacteria like *C. cluster* XIVa, decreased Major Histocompatibility Complex (MHC II) and costimulation on Antigen - Presenting Cell (APC cells). The molecule CD86 inhibits Th2-induced allergic reactions,[188,189] reduces the production of IL-4, IL-13, IL-5, lowers IgE concentration, inhibits mast cell degranulation, and lowers the allergic bioactive substance histamine and mast cells' Protease-1 (mMCPT-1) secretion.[186] Furthermore, because oral administration of butyrate has a low systemic circulation concentration and utilization rate, local administration may be considered for extraintestinal disease treatment.

Conclusion

Advances from the Human Microbiome Project (HMP) have intensified microbiota research, positioning butyric acid as a key metabolite of growing interest. Numerous animal and clinical studies have confirmed its role in regulating immune function, demonstrating therapeutic effects in infectious diseases, chronic inflammatory disorders (eg, IBD, asthma, MS), and metabolic conditions (eg, obesity, diabetes, NAFLD). Although insights into microbiome–butyrate interactions have accumulated over the past decade, the precise mechanisms remain unclear. Personalized microbial ecosystems result from complex host–microbiota–butyrate interactions and individual variability, yet butyrate-based precision therapies are still underdeveloped. While animal models provide valuable mechanistic insights, the lack of standardized models and inherent genetic and physiological differences between species limit clinical translation. Microbial therapies—including dietary interventions, fecal microbiota transplantation (FMT), probiotics, and metabolites (eg, butyric acid, bile acids)—require metagenomic screening to address microbiota variations associated with race, geography, age, disease state, lifestyle, and production methods. Large-scale longitudinal cohorts are needed to validate their clinical efficacy. Ongoing debates concern optimal strain selection, long-term impacts on native microbiota, and sustained mucosal colonization, as current studies often focus on short-term outcomes rather than microbial persistence and disease progression. Clinical implementation should consider patient-specific factors, including disease characteristics (etiology, location, progression), behavioral patterns (eg, exercise, sleep), and individual microbiota profiles, to guide the development of personalized diets, donor matching, targeted probiotics, and standardized metabolite formulations (eg, dosage forms, concentrations, and administration frequency). Ultimately, machine learning–driven databases may enable the delivery of highly precise, individualized microbial therapeutics.

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