This is a "preproof" accepted article for *Animal Nutriomics*.
This version may be subject to change during the production process.
10.1017/anr.2024.8

Non-Digestible Carbohydrates and Gut Microbiota: A Dynamic Duo in Host Defense

Xin Zong[a, b], Shuqi Liu[b], Edward C. Deehan[c], Mingliang Jin[a, b*]

[a]Key Laboratory of Molecular Animal Nutrition, Ministry of Education; Ministry of Agriculture and Rural Affairs; Key Laboratory of Animal Feed and Nutrition of Zhejiang Province; Institute of Feed Science, Zhejiang University, Hangzhou 310058, P.R. China

[b]College of Animal Science, Zhejiang University, Hangzhou 310058, P.R. China

[c] Department of Food Science and Technology, University of Nebraska, Lincoln, NE, United States

* Corresponding author: mljin@zju.edu.cn

Abstract:

The sophisticated relationship between the intake of dietary carbohydrates and host immunity is mediated in large part by the gut microbiota. This comprehensive review explores the multifaceted connections linking human gut microbiota with non-digestible carbohydrate metabolism and immune responses, highlighting the critical importance of this symbiotic relationship in maintaining overall host health. Understanding the mechanisms by which gut microbiota act as a bridge between carbohydrate intake and host immunity has significant implications for precision nutrition strategies and the development of therapeutic interventions.

Keywords: Carbohydrates, Gut, Microbiota, Host Immunity

Introduction:

The gastrointestinal tract of humans hosts a complex ecosystem comprising diverse microorganisms, collectively called the gut microbiota [1; 2]. In the context of the gut microbiota and the host, it signifies a harmonious partnership where both the microbial community and the host organism derive advantages from each other. The gut microbiota, consisting of various microorganisms, and the host form a symbiotic relationship that goes beyond mere coexistence; it involves interdependence and cooperation, with each partner playing essential roles in maintaining overall health and functioning. Recent advancements in genomic research have improved the comprehension of these microbial communities and uncovered their remarkable impacts on human health, including complex interactions between the gut microbiota, immune system, and dietary carbohydrates. The symbiotic relationship between carbohydrate metabolism, immunity, and gut microbiota represents an important area of research, providing insights into the delicate balance of host-microbe interactions that influence overall well-being [3].

The gut microbiota, comprising fungi, viruses, bacteria, and archaea, constitutes a dynamic community that adapts to the host's diet and lifestyle [4; 5]. Dietary carbohydrates play a crucial role in shaping this complex symbiosis [6]. Carbohydrates, ranging from simple sugars to complex fibers, function as a major fuel source for the host and, when left undigested by host enzymes, a substrate for microbial fermentation. This relationship has significant implications for the immune system, as the gut provides an interface between immune cells and dietary and microbial antigens. Thus, the gut serves as a vital site for regulating immune responses by balancing host defense and tolerance [7; 8; 9].

This review delves into the intricate interplay among gut microbiota, the immune system, and carbohydrate metabolism, placing particular emphasis on non-digestible carbohydrates. It investigates the dynamic processes by which gut microbiota

https://doi.org/10.1017/anr.2024.8 Published online by Cambridge University Press

modulate host immune responses against carbohydrate-rich diets and, conversely, how immune factors exert influence on both the composition and functionality of gut microbiota. It further discusses the impact of specific carbohydrate types on the delicate balance within this tripartite relationship, including the complex signaling pathways, immune cell modulation, and microbial metabolic activities fundamental to this interdependence. Elucidating how carbohydrates mediate the tripartite interaction between gut microbiota and immunity not only deepens the understanding of fundamental host-microbe interactions but also paves the way for innovative therapeutic strategies. The insights derived from this exploration offer promising avenues for interventions designed to restore and maintain equilibrium in the gut ecosystem. These insights provide novel perspectives on preventive and therapeutic strategies for immune-related disorders and metabolic diseases. In the context of precision medicine, comprehending the complex relationships among gut microbiota, immunity, and carbohydrates is essential for realizing the full potential of personalized healthcare, thereby contributing to the advancement of overall health and well-being.

Carbohydrate Digestion, Absorption, and Metabolism

Carbohydrate digestion, absorption, and metabolism collectively represent a fundamental and intricate process in the human body, essential for extracting energy and supporting various physiological functions[10]. The journey of carbohydrates begins in the mouth, where salivary amylase initiates the breakdown of complex carbohydrates into simpler sugars. However, the primary site of carbohydrate digestion is the small intestine. In the small intestine, pancreatic amylase continues the hydrolysis of starches into oligosaccharides and maltose[11]. The final steps occur at the brush border of absorptive cells, where enzymes like maltase, sucrase, and lactase break down oligosaccharides into monosaccharides such as glucose, fructose, and galactose. These monosaccharides are actively transported across the intestinal epithelium into the bloodstream, facilitating their absorption.

Once absorbed, monosaccharides play a pivotal role in metabolism. Glucose, a central monosaccharide, serves as a primary energy source for cellular activities[12]. It can be

https://doi.org/10.1017/anr.2024.8 Published online by Cambridge University Press

immediately used for energy or stored as glycogen in the liver and muscles for later use. The metabolism of fructose and galactose involves conversion into glucose or intermediates that enter energy-producing pathways[13]. Insulin, a hormone secreted by the pancreas, plays a crucial role in regulating carbohydrate metabolism by facilitating glucose uptake into cells and promoting glycogen synthesis[14]. Additionally, the liver plays a key role in maintaining blood glucose levels by releasing glucose when needed and storing it as glycogen during periods of excess.

Carbohydrate metabolism is intricately linked to overall energy homeostasis, influencing not only immediate energy needs but also long-term storage and utilization. Dysregulation in carbohydrate metabolism can lead to various health issues, including metabolic disorders such as diabetes[15]. Recent research on the role of gut microbiota in carbohydrate metabolism has made significant strides, uncovering intricate mechanisms and shedding light on the profound impact of microbial communities on host physiology. Studies have revealed that the gut microbiota not only participates in the fermentation of complex carbohydrates but also influences the production of metabolites like short-chain fatty acids [16], which play a crucial role in energy regulation and metabolic homeostasis. Furthermore, researchers have identified specific microbial species that exhibit distinct preferences for different types of carbohydrates, highlighting the microbial diversity involved in this intricate process [17; 18]. These findings open up new avenues for understanding and potentially manipulating the gut microbiota to optimize carbohydrate metabolism, offering promising prospects for future therapeutic interventions in metabolic disorders and overall health.

In summary, carbohydrate digestion, absorption, and metabolism represent a tightly regulated and integrated process, ensuring the efficient extraction of energy and supporting the body's diverse physiological functions.

Interply between Non-Digestible Carbohydrates and Gut Microbiota

The interactions between carbohydrates and gut microbiota form a dynamic and symbiotic relationship, carrying substantial implications for the overall health of the host [19]. Within this complex relationship, carbohydrates function as nourishment for

https://doi.org/10.1017/anr.2024.8 Published online by Cambridge University Press

the extensive microbial communities in the gastrointestinal tract and crucial regulators of diverse physiological processes, such as energy metabolism, immune system modulation, and the synthesis of essential biomolecules, highlighting their pivotal role in maintaining overall health and homeostasis.[20]. This section explores the complex interaction between carbohydrates and gut microbiota, emphasizing the critical roles each plays in influencing the dynamics of the other.

1. Carbohydrates as Microbial Fuel: Nourishing the Gut Ecosystem

Carbohydrates, encompassing complex dietary fibers and simple sugars, are the primary energy source for the diverse microorganisms comprising the gut microbiota [21]. While some carbohydrates are absorbed in the upper gastrointestinal tract, a significant portion of carbohydrates found in whole plant foods reach the colon, serving as substrates for microbial fermentation [22].

The fermentation process serves as a metabolic engine, converting complex carbohydrates into metabolic byproducts, which encompass gases and beneficial short-chain fatty acids (SCFAs). This sustains the growth and activity of microbial communities [23]. This section examines the role of carbohydrates as essential fuel sources, detailing how they shape gut microbiota composition and functionality.

Carbohydrate forms: Dietary carbohydrates play a pivotal role in shaping the diversity and composition of the gut microbiota [24]. Opportunistic pathobionts are known to multiply and species that produce SCFAs are known to decrease when simple di- and mono-saccharides are present [25]. On the other hand, gut microbiota ferment undigested and microbiota-accessible carbohydrates (MACs), which increase levels of SCFAs and have beneficial health consequences [26]. For example, Bacteroidota-related species thrive on diverse carbohydrates, whereas Firmicutes-related species specialize in fermenting specific carbohydrates and Proteobacteria-related species efficiently utilize simple sugars [27; 28]. Maintaining a balance between these microbial groups is essential for a harmonious and resilient gut ecosystem (Figure 1).

(1) Complex Carbohydrates:

Sources: Whole grains, fruits, vegetables, legumes, nuts, and seeds.

https://doi.org/10.1017/anr.2024.8 Published online by Cambridge University Press

Effect: Complex non-starch polysaccharides and oligosaccharides that are considered dietary fibers can positively influence putatively health-promoting gut microbes, including *Bacteroides*, *Akkermansia*, *Roseburia*, *Clostridium*, *Fecalibacterium*, *Prevotella*, *Ruminococcus*, *Lactobacillus*, and *Bifidobacterium* [29]. Certain MACs, like galacto-oligosaccharides and fructo-oligosaccharides, are classified as prebiotics. Host microorganisms selectively use these prebiotic substrates to confer health benefits to the host [30]. Complex carbohydrates are first broken down into oligosaccharides and simple sugars, and then into beneficial SCFAs like propionate, acetate, and butyrate. More specifically, butyrate promotes mucosal integrity, regulates inflammation, and keeps the gut lining healthy [31; 32]. Diets high in fiber help promote a healthy gut microbiome by encouraging the expansion of health-promoting bacteria such as *Bifidobacterium* and *Lactobacillus* [33; 34].

(2) Resistant Starch:

Sources: Legumes, unripe bananas, potatoes, and certain whole grains.

Effect: Resistant starches, evading complete digestion and absorption in the small intestine, successfully reach the colon, earning their classification as dietary fibers [35]. They function as substrates for bacterial fermentation in the colon, ultimately yielding the production of short-chain fatty acids (SCFAs). This type of carbohydrate has been associated with promoting beneficial bacteria, such as *Bifidobacterium* and *Agathobacter*, and may contribute to maintaining a healthy gut microbiota [36]. Resistant starches also play a role in enhancing satiety and regulating blood glucose levels [37].

(3) Simple Sugars:

Sources: Caloric sweeteners, sugary snacks, sweetened beverages.

Effect: Simple sugars are comprised of disaccharides, including lactose (glucose and galactose, found in milk), sucrose (fructose and glucose, commonly known as table sugar), and maltose (two glucose molecules), and monosaccharides, like glucose, galactose, and fructose. Diets rich in simple sugars may promote the growth of bacteria related to Proteobacteria and Firmicutes, which efficiently ferment these sugars [38]. This can lead to an imbalanced microbial composition, potentially

https://doi.org/10.1017/anr.2024.8 Published online by Cambridge University Press

promoting the overgrowth of less beneficial bacteria. For instance, certain microbial taxa have been found to predominate in specific dietary forms, like *Clostridium sensu stricto* within a diet rich in saturated fatty acids (short, medium, and long-chain SFAs like palmitic and myristic acids), *Alloprevotella* in a control diet, unclassified *Porphyromonadaceae* in a sugar-centric diet, and unclassified *Ruminococcaceae* in a diet rich in PUFA (n-6 polyunsaturated fatty acids like linoleic acid). *Lactobacillus* have been observed to influence dietary variations, particularly between PUFA- and sugar-rich diets compared to SFA-rich diets [(38)]. Moreover, consuming excessive amounts of simple sugars may lead to a reduction in microbial diversity and an undesirable shift in the gut microbiota, which is associated with dysregulated immunometabolism and the onset of chronic diseases [(39)].

(4) Prebiotics:

Sources: Garlic, onions, leeks, asparagus, chicory root.

Effect: Indigestible fibers play a crucial role in fostering the development and activity of beneficial bacteria, particularly *Bifidobacterium* and *Lactobacillus* [(40)]. Since 2017, the International Scientific Association for Probiotics and Prebiotics (ISAPP) has broadened the concept of prebiotics by refining its definition to encompass "a substrate that is selectively utilized by host microorganisms, conferring a health benefit"[(41)]. Therefore, in addition to fructo-oligosaccharides (FOS, fructans) and galacto-oligosaccharides (GOS), various bioactive compounds or biopolymers can also be classified as prebiotics. Prebiotics offer potential health benefits by modulating gut microbiota and promoting the release of beneficial microbial metabolites, such as SCFAs [(42)], direct contribution to the growth and fermentation of probiotics[(43)], and serving as encapsulating materials for probiotics.

Regular consumption of prebiotics is associated with improved gut health, strengthened immune function, and potential protection against certain gastrointestinal disorders [(44)]. As an example, fructans, which consist of chains of fructose molecules, are recognized as prebiotics and have consistently shown to elevate the abundance of fecal Bifidobacterium in various clinical trials [(45)]. Inulin-type fructans stand out as one of the most frequently employed types of fructans.

https://doi.org/10.1017/anr.2024.8 Published online by Cambridge University Press

Indeed, nutritional intervention with inulin has shown a heightened probability of positive outcomes in the context of metabolic disorders. Elevated abundance of genera including *Arnesiella*, *Bilophila*, *Butyricimonas*, *Victivallis*, *Clostridium XIVa*, *Akkermansia*, *Raoultella*, and *Blautia* has been observed, correlating with metabolic conditions like obesity and hepatic steatosis [46]. GOS, oligosaccharides similar to human milk oligosaccharides [47] display notable stability and solubility. They also exhibit good moisture retention and are resistant to facile hydrolysis by human digestive enzymes.[48]. Upon fermentation by colonic bacteria, galacto-oligosaccharides (GOS) yield short-chain fatty acids (SCFAs), carbon dioxide, and hydrogen. This specific metabolic process serves to stimulate the growth of intestinal *Bifidobacterium* [49]. However, sustained supplementation of GOS could simultaneously enhance the growth of these two bacterial types, thereby reshaping the ecological relationship, diminishing antagonistic effects, and reducing the fluctuation of the intestinal microecology [50].

In summary, the consumption of dietary carbohydrates has a remarkable impact on how the gut microbiota is structured and how it functions. Prebiotics, fibers, including resistant starches, oligosaccharides, and complex non-starch polysaccharides, as well as other bioactive substances, promote microbial diversity and the enrichment of beneficial microorganisms. It aids in the synthesis of metabolites that are beneficial to the digestive tract. Conversely, diets high in simple sugars may lead to imbalances in the gut microbiota, potentially impacting overall well-being and increasing the risk of certain chonic diseases.

https://doi.org/10.1017/anr.2024.8 Published online by Cambridge University Press

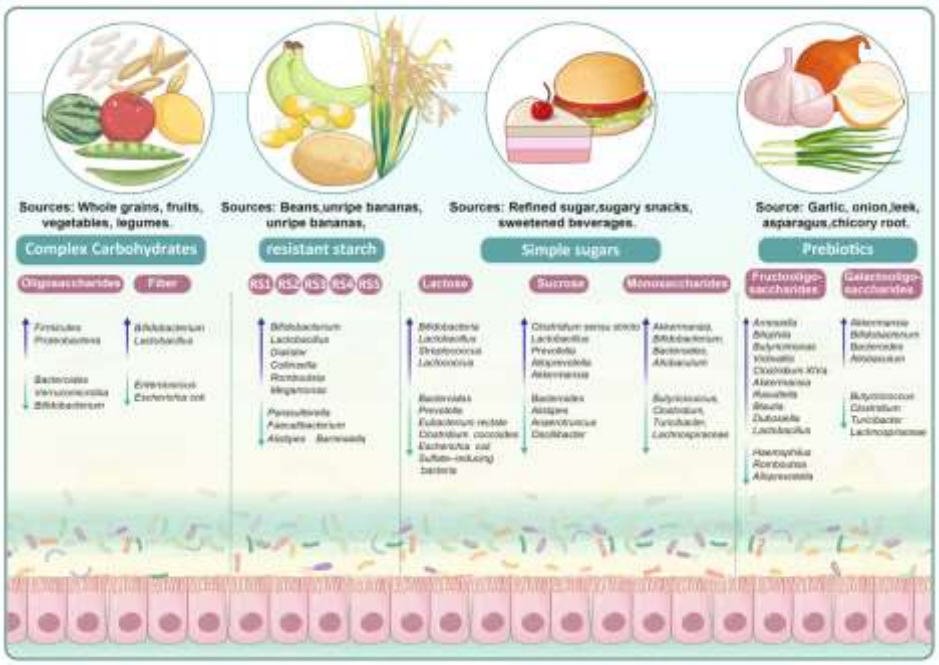

Figure 1. Effects of different types of carbohydrates on the diversity and composition of gut microbiota. This diagram illustrates the sources, classification, and targeting of microorganisms with different types of carbohydrates.

Carbohydrates Over Proteins: Proteases break down the dietary proteins consisting of conserved peptide bonds. Gut bacteria synthesize metallo-, serine-, cysteine-, and aspartic-proteases; however, human cell-derived proteases outweigh these bacterial enzymes in most fecal samples [(51)]. Unlike monosaccharides, the twenty proteinogenic amino acids have more interconversion stages to be integrated into metabolic pathways, so it is unusual for a single bacterial species within the gut microbial community to ferment all amino acids for energy [(52)]. Bypassing the need for amino acid production, the anabolic use of ambient amino acids by microbes saves greater amounts of energy compared to their catabolic usage [(53)]. Therefore, amino acids are generally less efficient as an energy source than carbohydrates for gut microbiota. This explains why the gut microbiota preferentially consumes carbohydrates over proteins, depending on availability [(54)].

Cross-Feeding Dynamics: The gut microbiota, consisting of diverse microbial species, participates in a complex network of cross-feeding and communication facilitated by the availability of carbohydrates. Some bacterial species can utilize by-products of carbohydrate fermentation produced by other species [(55; 56)]. This

https://doi.org/10.1017/anr.2024.8 Published online by Cambridge University Press

dynamic interaction fosters a cooperative environment, influencing the diversity, resilience, and stability of the gut microbiota. For instance, *Bacteroides thetaiotaomicron* has 260 glycoside hydrolases [57], highlighting the evolutionary adaptation required to efficiently utilize various dietary fiber types. However, how the microbial community communicates through signaling molecules, responds to changes in carbohydrate availability, and orchestrates collective responses that influence host physiology still needs further investigation.

2. Microbial Fermentation: A Metabolic Symphony Unleashed

Microbial fermentation transforms carbohydrates into various metabolites within the anaerobic environment of the colon [58]. This process involves the production of short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate. These SCFAs not only act as an energy source for the host but also exert immunomodulatory effects [59; 60]. This section examines the complex metabolic pathways involved in carbohydrate fermentation, emphasizing the diversity of microbial communities contributing to this process. The resulting metabolites are pivotal in maintaining gut homeostasis, influencing immune responses, and impacting overall host health.

(1) Metabolic Pathways in Carbohydrate Fermentation

The fermentation of carbohydrates is a multi-step biological process that often results in the production of energy for microbes via the reduction of carbohydrates to simpler molecules [61]. This complex metabolic pathway highlights the remarkable diversity of microbial communities that contribute to this essential biological function.

Various microbial groups, including bacteria, archaea, and fungi, are at the heart of carbohydrate fermentation, each possessing unique enzymatic capabilities[62]. These microorganisms play pivotal roles in different stages of carbohydrate metabolism, allowing for the use of a wide range of substrates[63]. The diversity within these microbial communities ensures the adaptation to various environmental conditions, nutritional sources, and ecological niches[64].

Carbohydrates, varying from simple sugars to complex polysaccharides, undergo initial enzymatic hydrolysis by a range of glycosidases, amylases, and cellulases [65]. This initial hydrolysis step paves the way for subsequent metabolic transformations.

https://doi.org/10.1017/anr.2024.8 Published online by Cambridge University Press

The breakdown of carbohydrates leads to the formation of intermediary metabolites like pyruvate and acetyl-CoA, which act as central nodes in the complex network of fermentation pathways [66]. The diversity in microbial enzymatic repertoires dictates the fate of these metabolites, resulting in various end products, including organic acids, alcohols, and gases [67]. The metabolic pathways involved are notably diverse, including homolactic, heterolactic, alcoholic, and mixed-acid fermentations, among others [67].

(2) Microbial Diversity and Carbohydrate Fermentation

Notably, the specific pathways employed during carbohydrate fermentation vary among microbial groups. For instance, lactic acid bacteria, including species of *Lactobacillus* and *Streptococcus*, specialize in producing lactic acid through the homolactic fermentation pathway[68]. Meanwhile, yeast species like *Saccharomyces cerevisiae* predominantly utilize the alcoholic fermentation pathway, producing ethanol [69; 70].

The microbial communities involved in carbohydrate fermentation are diverse in their metabolic capabilities and exhibit a high degree of interdependence. Syntrophic relationships are common in anaerobic environments where different microbial species cooperate to accomplish a metabolic task. For example, in the anaerobic degradation of complex carbohydrates like cellulose, bacteria, and fungi work synergistically to hydrolyze, ferment, and metabolize the released sugars [71]. The ecological significance of carbohydrate fermentation extends beyond microbial metabolism [72]. These processes profoundly impact nutrient cycling, carbon fluxes, and the overall balance of ecosystems. Understanding the complex metabolic pathways and the diversity of microbial communities involved in carbohydrate fermentation is crucial for unraveling the complexities of microbial ecology and its implications for various natural and engineered environments [73].

Gut Microbiota-Mediated Metabolism of Carbohydrates in Immune Regulation

The microbial metabolism of dietary carbohydrates is emerging as a crucial factor in immune control, highlighting that the symbiotic interaction between the host and the gut microbiota extends beyond the realm of digestion [74; 75]. The microbial

https://doi.org/10.1017/anr.2024.8 Published online by Cambridge University Press

fermentation of dietary fibers and complex carbohydrates yields SCFAs, including butyrate, propionate, and acetate. SCFAs serve as versatile signaling molecules influencing immune cells through various mechanisms [76]. Butyrate, for example, acts as a histone deacetylase inhibitor, promoting an anti-inflammatory environment and enhancing regulatory T cell (Tregs) differentiation, which is pivotal in immune tolerance [77]. This section elucidates the complex molecular interaction between gut microbiota-mediated carbohydrate metabolites and the host immune system, unveiling how these metabolites shape immune responses and maintain immune homeostasis (Figure 2).

1. Acetate

Acetate, a prevalent SCFA, functions as a nutrient for host cells and has been thoroughly investigated for its involvement in regulating mucosal immunity. Microorganisms commonly secrete acetate and other fermentation acids during growth, and it is well-established that acid accumulation in the growth medium inhibits microbial growth [78]. Beyond serving as an energy source, acetate has been demonstrated to positively affect immune modulation.

To detect ambient acetate, intestinal enterocytes and other cell types contain G-protein coupled receptors (GPCRs), which mediate most of the molecular effects of acetate [79]. One example is the fact that oral acetate may upregulate IFN-stimulated genes in the lung, leading to interferon-β (IFN-β) responses [80]. In mice infected with respiratory syncytial virus, these effects were correlated with a reduction in viral load and lung inflammation [80].

The antiviral activity of acetate in pulmonary epithelial cell lines and its positive effects in RSV-infected animals were substantiated by type 1 interferon (IFN) signaling through the IFN-1 receptor (IFNAR) [80]. Increased blood acetate concentrations stimulate neutrophils in a GPR43-dependent way, promoting phagocytic receptor upregulation, oxidative burst, neutrophil chemotaxis, and cytokine release [81]. Indeed, acetate consistently induces the activation of the NLRP3 inflammasome in intestinal epithelial cells, a mechanism that has been shown to play a key role in protecting against colitis in *nlrp3*$^{-/-}$ mice [82]. Daïen et al. demonstrated

https://doi.org/10.1017/anr.2024.8 Published online by Cambridge University Press

that acetate directly promotes IL-10-producing regulatory B cells (B10 cells) differentiation in mice and humans (both *in vivo* and *in vitro*) [83]. They have observed that the induction of functional B10 cells by acetate effectively facilitates the differentiation of naive T cells to Tregs.

A short-term dietary intervention involving increased fiber intake in women led to elevated plasma acetate levels and a higher proportion of B10 cells, underscoring acetate's efficacy as an inducer of B10 cells [83]. Additionally, acetate priming has been demonstrated to enhance the capability of human neutrophils to eliminate methicillin-resistant strains *Staphylococcus aureus* [81]. The immediate assimilation of acetate also augments the capacity of memory $CD8^+$ T cells to produce interferon-gamma (IFN-γ). [84]. Nevertheless, the potential impact of acetate on modulating the metabolism and function of memory $CD8^+$ T cells during their encounter with pathogens upon re-exposure remains unexplored. Furthermore, acetate plays a role in maintaining intestinal barrier function, aiding wound healing, and effecting changes in the actin cytoskeleton, all crucial aspects of mucosal immunity [85; 86; 87; 88].

2. Propionate

Propionate, also referred to as propionic acid, is a SCFA with three carbon atoms and holds promise in immune regulation. It is produced by commensal gut microbiota within the proximal colon and cecum of mammals. This production occurs through the anaerobic fermentation of oligosaccharides and sugars that originate from enzymatically degraded fibers [89]. In the intestinal tract of humans, propionate is predominantly produced by members of *Firmicutes* and *Bacteroidetes* phyla. These microbial groups generate propionate via the propanediol and succinate pathways, both dependent on a cofactor, vitamin B12 [90; 91].

Various research studies have investigated the effects of propionate on immune modulation. It inhibits histone deacetylases (HDACs), influencing gene expression in immune cells. For instance, a study exploring the function of SCFAs on human basophils found that propionate induces histone acetylation in these cells, and suppression of HDAC activity mimicked propionate's effects [92]. These findings

https://doi.org/10.1017/anr.2024.8 Published online by Cambridge University Press

indicated that propionate may play a complex role in regulating basophil apoptosis, activation, and degranulation via inhibiting HDAC activity [92]. Moreover, engineered propionate-producing bacteria have been shown to attenuate dextran sodium sulfate (DSS)-induced colitis in mice by modulating the immune function of resident macrophages and the production of classic inflammation-related cytokines, suggesting a potential treatment strategy for ulcerative colitis [93]. Consistently, in the gut, propionate supports intestinal epithelial integrity and barrier function [94]. As a signaling molecule, increased levels of gut microbiome-derived propionate are linked to reduced sterile lung inflammation and enhanced bacterial immunity in mice [95]. Additionally, Du et al. discovered that gut microflora influences Th17/Treg cell differentiation in experimental autoimmune prostatitis through propionate [96]. Propionate also acts as a substrate for gluconeogenesis in the liver and colonic epithelium, thereby linking microbial metabolism with systemic metabolic processes that affect immune cell function [78]. Future research is needed to elucidate the underlying molecular mechanisms further and lay the groundwork for clinical studies, potentially broadening the use of propionate as a promising option in combating infections and immune diseases related to metabolic disorders.

3. Butyrate

Butyrate, one of the most extensively studied SCFA, significantly affects immune regulation. Beyond its role as an epigenetic modifier, butyrate boosts the generation and function of Tregs, thereby suppressing inflammatory responses [31]. Through its HDAC inhibiting function, butyrate increases Foxp3 protein acetylation, leading to elevated Foxp3 protein levels in Treg cell cultures [97]. Kespohl et al. investigated the impact of various butyrate concentrations (0.1 mM to 1 mM *in vitro* and 50 mM to 200 mM *in vivo* via oral administration) on T cell-mediated immune responses using $CD4^+$ T cells [98]. They reported that butyrate facilitated the Tregs differentiation *in vivo* and *in vitro* at lower concentrations (0.1 to 0.5 mM). Conversely, butyrate induced the transcription factor T-bet expression at a higher concentration (1 mM), leading to the development of conventional T cells or IFN-γ-producing Tregs [98]; however, conflicting data exist. Other studies using varying doses of butyrate

https://doi.org/10.1017/anr.2024.8 Published online by Cambridge University Press

observed a direct inhibitory effect on B10 cells. These studies speculate that the previously reported induction of B10 cells by butyrate might result from indirect effects mediated by the serotonin-derived metabolite 5-hydroxyindole-3-acetic acid [83].

Butyrate plays a crucial role in reinforcing the integrity of the gut barrier, thereby preventing the translocation of microbial products that could lead to aberrant immune activation. Experimental *in vivo* and *in vitro* models have demonstrated that butyrate supports intestinal integrity. Intestinal cell models [99; 100] under various stress conditions, such as lipopolysaccharide [101] and ethanol [102], show that butyrate treatment protects against intestinal epithelial integrity disruption, as evidenced by measurements of transepithelial electrical resistance (TER) and fluorescein-isothiocyanate (FITC)-dextran permeability. Several mechanisms illustrate butyrate's direct effects on the intestinal epithelial barrier. Butyrate-induced AMP-activated protein kinase (AMPK) activity leads to increased tight junction (TJ) reassembly and TER restoration [103]. In the presence of lipopolysaccharide (LPS), the inhibition of HDAC activity with butyrate not only protects against LPS-induced TER reduction and paracellular permeability but also results in reduced activation of the NLRP3 inflammasome and autophagy [104]. Furthermore, butyrate stabilizes hypoxia-inducible factor (HIF), a transcription factor vital for managing low oxygen levels in the colonic epithelium and regulating intestinal barrier function [105]. Collectively, these findings indicate that butyrate directly benefits intestinal epithelial barrier integrity in a dose-dependent manner.

https://doi.org/10.1017/anr.2024.8 Published online by Cambridge University Press

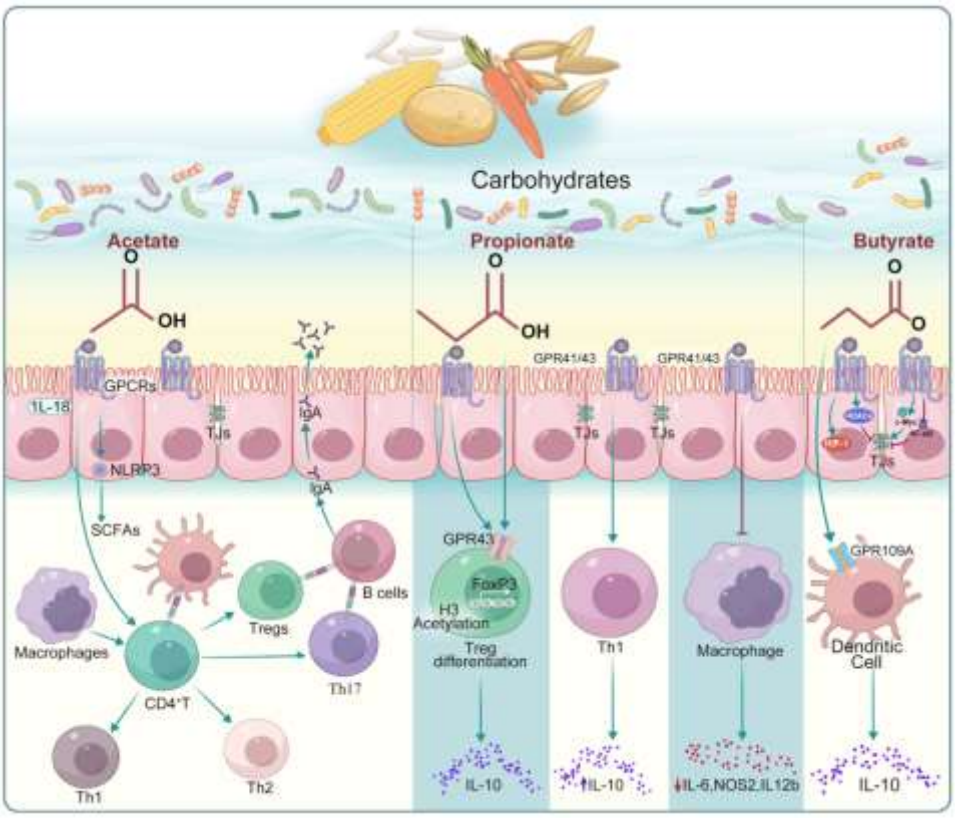

Figure 2. Regulation of the host immune function by short-chain fatty acids (SCFAs) produced by gut microbes that metabolize carbohydrates. Focusing on the three most common short-chain fatty acids (acetate, propionate, butyrate), the figure elucidates their receptors, target cells and related signaling pathways.

Carbohydrate-Derived Microbial Products in Immune Signaling

The complex interaction between carbohydrates and the gut microbiota extends its influence beyond metabolic processes, reaching into host immunity. Carbohydrate-derived microbial products serve as ligands for various pattern recognition receptors (PRRs) expressed on immune cells. TLRs, nucleotide-binding oligomerization domain-containing proteins (NODs), and C-type lectin receptors (CLRs) recognize specific carbohydrate structures, initiating intracellular signaling cascades. This recognition is a pivotal step in immune activation, leading to the production of chemokines, cytokines, and other effector molecules. This section explores the diverse ways in which these microbial products engage in immune signaling, shaping the delicate balance between tolerance and defense (Figure 3).

1. Toll-Like Receptor (TLR) Activation:

https://doi.org/10.1017/anr.2024.8 Published online by Cambridge University Press

TLRs, integral to innate immunity, play a central role in recognizing conserved microbial structures. Carbohydrate moieties, such as LPS and glycolipids, engage TLRs, activating downstream signaling pathways. This activation stimulates the expression of proinflammatory cytokines, shaping the immune response to microbial challenges and contributing to the defense against invading pathogens. For instance, one study demonstrated that pectic heteropolysaccharides selectively cluster with TLR4 during endocytosis, thereby inducing downstream signaling that leads to the phenotypic activation of macrophages [106]. Similarly, research utilizing a high-sugar diet (HSD) model indicated that a diet rich in simple sugars promotes a proinflammatory response through alterations in gut microbiota and TLR4 signaling [107]. Another study investigated the modulatory effects of graminan-type fructans (GTFs) on TLRs, comparing these effects to those of inulin-type fructan I (ITFs) with different chain lengths [108]. They found that GTFs activate NF-κB/AP-1 *via* MyD88 and TRIF pathways, stimulating TLR3, 7, and 9, whereas ITFs activate TLR2 and TLR4. GTFs strongly inhibited TLR2 and TLR4, while ITFs did not inhibit any TLR [108]. These findings highlight the immunomodulatory effects of GTFs *via* TLRs and the attenuation of cytokine production in dendritic cells by both GTFs and long-chain ITFs.

2. NOD Activation:

NOD1 and NOD2 are intracellular receptors that recognize peptidoglycan fragments, including carbohydrate components[109]. NOD proteins are part of the innate immune system and are crucial in recognizing microbial components[110]. These proteins are involved in signaling pathways that trigger immune responses against invading pathogens. Imbalances or dysregulation in the normal functioning of NOD-mediated signaling pathways can lead to abnormal immune responses. NOD1 is a receptor that recognizes meso-diaminopimelic acid-containing peptidoglycan, predominantly found in Gram-negative bacteria [111]. NOD2, on the other hand, serves as a receptor for peptidoglycan from both Gram-negative and Gram-positive bacteria [112; 113]. Activation of NOD2 induces the production of IL-17A in innate lymphoid cells [114]. Furthermore, Paneth cells secrete α-defensins in a NOD2-dependent manner [115]. The

https://doi.org/10.1017/anr.2024.8 Published online by Cambridge University Press

peptidoglycan recognition proteins (PGRPs), including Pglyrp1, Pglyrp2, Pglyrp3, and Pglyrp4, detect peptidoglycan and exert antibacterial activity[116]. NLRC4 functions as a receptor for intracellular flagellin, and its activation triggers caspase-1, inducing IL-1β expression [117]. Mice lacking NLRC4 exhibit severe disease and epithelial injury following DSS treatment [118]. Mortality increases in NLRC4-deficient mice infected with flagellated *Salmonella*, suggesting that NLRC4 enhances immune defense in the intestine. Collectively, these findings underscore the crucial role of these microbial products in influencing the immune system and maintaining immune homeostasis.

In summary, this discussion highlights the complex interplay between NOD-mediated signaling, its dysregulation, and the resultant impact on autoimmune and inflammatory disorders, alongside the role of carbohydrate-derived microbial products in maintaining immune homeostasis. Comprehending these complex relationships is vital for understanding the mechanisms driving immune-related conditions and identifying potential therapeutic approaches.

3. Intracellular Signaling Cascades

Carbohydrate-mediated immune signaling encompasses complex intracellular cascades, notably including the mitogen-activated protein kinase (MAPK) pathways and activation of nuclear factor-kappa B (NF-κB). These pathways converge to regulate gene expression, influencing the production of inflammatory mediators, antimicrobial peptides, and molecules involved in tissue repair. Microbial products like LPS, flagellin, lipoteichoic acid (LPA), and lipopeptide predominantly activate NF-κB, which is known to bind to the promoter region of mucin 2 [119]. Similarly, several inflammatory markers such as TNF-α, interleukins, and Serum amyloid A3activate the NF-κB pathway, stimulating mucin 2 transcription [120], while the Janus Kinase pathway activation exerts inhibitory effects [121]. A study investigating the impact of three different sucrose doses on DSS-induced colitis in mice revealed that varying sucrose consumption levels differentially affect the gut microbiota and the PPAR-γ/MAPK/NF-κB pathway [122].

4. Modulation of Immune Homeostasis

https://doi.org/10.1017/anr.2024.8 Published online by Cambridge University Press

Microbial products derived from carbohydrates directly influence immune cell functions, including phagocytosis, antigen presentation, and the differentiation of various immune cell subsets. By influencing these cellular processes, microbial products actively shape the magnitude and character of the immune response. For instance, under conditions lacking MACs, $CD103^+$ dendritic cells demonstrated a reduced capacity to generate tolerogenic Tregs compared to conditions with high-MAC intake [123]. In a food allergy model, mice on a MAC-free diet showed more severe clinical anaphylaxis than those on a high-MAC diet [123]. Moreover, MACs are critical antibody response regulators in the gut and systemically. Mice on a MAC-free diet displayed impaired homeostatic and pathogen-specific antibody responses [124]. Conversely, mice on a high-MAC diet showed significantly increased IgA production [124]. High-MAC feeding may lead to an improved T follicular helper response, characterized by enhanced germinal center activities in Peyer's patches and a higher IgA^+ B cell presence in the small intestine [123]. These effects are attributed to MAC-induced alterations in gut microbiota composition and SCFA production, which support the production of B cell antibodies through the promotion of plasma cell differentiation [124]. Therefore, dietary interventions combined with beneficial bacterial strain administration could serve as a cost-effective approach to managing various non-communicable diseases associated with Western lifestyles. Further research is required to ascertain (1) which MACs are most effective in microbiota diversification and enhancing SCFA production and (2) the optimal intake of MACs for health maintenance or for treating various inflammatory diseases.

https://doi.org/10.1017/anr.2024.8 Published online by Cambridge University Press

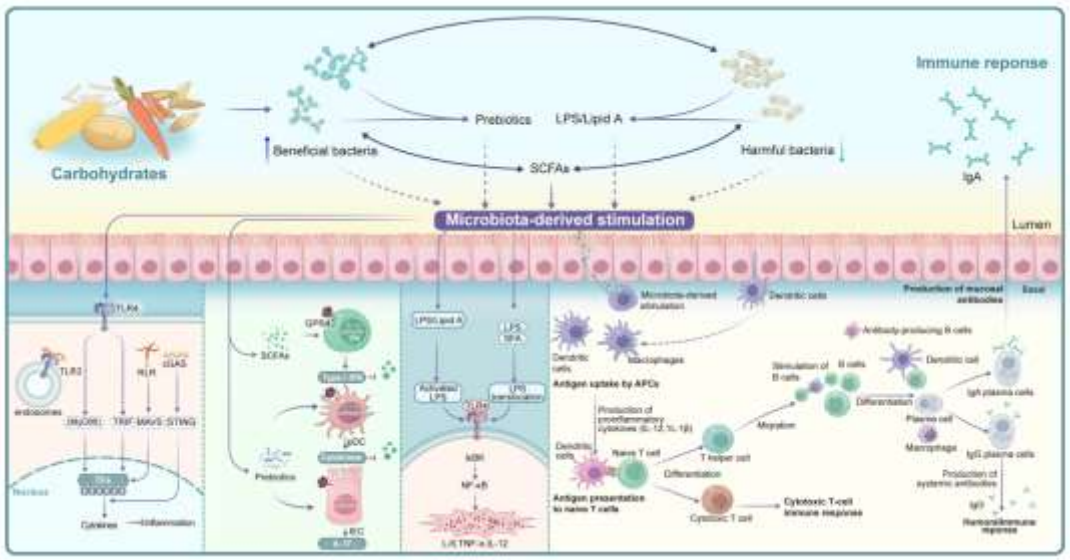

Figure 3. Carbohydrate-derived microbial products regulate host immune function. Carbohydrate-derived microbial products serve as ligands for various pattern recognition receptors, including TLRs, NODs, intracellular signaling cascades, and immune cell homeostasis.

Conclusion

In summary, this review comprehensively explores the intricate relationships between carbohydrates, gut microbiota, and host immunity, emphasizing the pivotal role of the gut microbiota as a bridge in this dynamic relationship. The interaction between carbohydrate-derived microbial products and immune signaling forms a sophisticated network central to host-microbiota interactions. Understanding the nuances of this signaling cascade provides insights into how the immune system interprets and responds to the presence of specific carbohydrates, offering potential targets for therapeutic interventions in immune-related disorders. As research in this field advances, unraveling the complexities of carbohydrate-mediated immune signaling promises to open new avenues for manipulating immune responses for health and disease, including the refinement of precision nutrition approaches and the development of targeted therapeutics based on carbohydrates.

Implications and Future Directions

The review concludes with a forward-looking perspective, highlighting areas for future research to elucidate the complexity of gut microbiota interactions in the

https://doi.org/10.1017/anr.2024.8 Published online by Cambridge University Press

context of carbohydrate metabolism and host immunity. The modulation of gut microbiota-mediated carbohydrate metabolism emerges as a potential avenue for therapeutic interventions in immune-related disorders. Precision nutrition, prebiotics, and probiotics aimed at restoring a balanced microbial community and promoting the production of beneficial metabolites hold promise for influencing immune regulation. Future research should continue to unravel the specific mechanisms by which gut microbiota-derived metabolites impact immune responses, paving the way for personalized approaches to immune modulation.

Abbreviations

SCFAs, short-chain fatty acids; MACs, microbiota-accessible carbohydrates; FOS, fructo-oligosaccharides; GOS, galacto-oligosaccharides; Tregs, regulatory T cell; GPCRs, G-protein coupled receptors; IFN, interferon; HDACs, histone deacetylases; DSS, dextran sodium sulfate; TER, transepithelial electrical resistance; AMPK, AMP-activated protein kinase; TJ, tight junction; HIF, hypoxia-inducible factor; PRRs, pattern recognition receptors; NODs, nucleotide-binding oligomerization domain-containing proteins; CLRs, C-type lectin receptors; HSD, high-sugar diet; GTFs, graminan-type fructans; ITFs, inulin-type fructan I; PGRPs, peptidoglycan recognition proteins; NF-κB, nuclear factor-kappa B; MAPK, mitogen-activated protein kinase; LPA, lipoteichoic acid.

Author Contributions

X.Z. and M.L.J conceived the project, designed the article structure. X.Z wrote the manuscripts. All authors discussed and edited the manuscript.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgments

This work was supported by the National Key Research and Development Project of China (Grant/Award No. 2022YFD1301500, 2023YFD1301101, 2022YFD1300505);

National Natural Science Foundation of China (Grant/Award No. 32372890, 32372889); Fundamental Research Funds for the Central Universities (Grant/Award No. K20230021).

References

1. Zong X, Fu J, Xu BC *et al.* (2020) Interplay between gut microbiota and antimicrobial peptides. *Anim Nutr* **6**, 389-396.

2. Fan LJ, Xia YY, Wang YX *et al.* (2023) Gut microbiota bridges dietary nutrients and host immunity. *Sci China Life Sci* **66**, 2466-2514.

3. Perlman D, Martínez-Alvaro M, Moraïs S *et al.* (2022) Concepts and Consequences of a Core Gut Microbiota for Animal Growth and Development. *Annu Rev Anim Biosci* **10**, 177-201.

4. Martino C, Dilmore AH, Burcham ZM *et al.* (2022) Microbiota succession throughout life from the cradle to the grave. *Nat Rev Microbiol* **20**, 707-720.

5. Parizadeh M, Arrieta MC (2023) The global human gut microbiome: genes, lifestyles, and diet. *Trends Mol Med* **29**, 789-801.

6. Dapa T, Ramiro RS, Pedro MF *et al.* (2022) Diet leaves a genetic signature in a keystone member of the gut microbiota. *Cell Host Microbe* **30**, 183-+.

7. Henneke L, Schlicht K, Andreani NA *et al.* (2022) A metabolic axis in obesity and type 2 diabetes. *Gut Microbes* **14**.

8. Palmer CS (2022) Innate metabolic responses against viral infections. *Nat Metab* **4**, 1245-1259.

9. Pereira AM, de Lurdes Nunes Enes Dapkevicius M, Borba AES (2022) Alternative pathways for hydrogen sink originated from the ruminal fermentation of carbohydrates: Which

microorganisms are involved in lowering methane emission? *Anim Microbiome* **4**, 5.

10. Sanders LM, Zhu Y, Wilcox ML *et al.* (2023) Whole grain intake, compared to refined grain, improves postprandial glycemia and insulinemia: a systematic review and meta-analysis of randomized controlled trials. *Crit Rev Food Sci* **63**, 5339-5357.

11. Shinde VK, Vamkudoth KR (2022) Maltooligosaccharide forming amylases and their applications in food and pharma industry. *J Food Sci Tech Mys* **59**, 3733-3744.

12. Remesar X, Alemany M (2020) Dietary Energy Partition: The Central Role of Glucose. *Int J Mol Sci* **21**.

13. Tian H, Zhao X, Zhang Y *et al.* (2023) Abnormalities of glucose and lipid metabolism in myocardial ischemia-reperfusion injury. *Biomed Pharmacother* **163**, 114827.

14. Rahman MS, Hossain KS, Das S *et al.* (2021) Role of Insulin in Health and Disease: An Update. *Int J Mol Sci* **22**.

15. Nagarajan SR, Cross E, Sanna F *et al.* (2022) Dysregulation of hepatic metabolism with obesity: factors influencing glucose and lipid metabolism. *Proc Nutr Soc* **81**, 1-11.

16. Xie L, Alam MJ, Marques FZ *et al.* (2023) A major mechanism for immunomodulation: Dietary fibres and acid metabolites. *Semin Immunol* **66**, 101737.

17. Wardman JF, Bains RK, Rahfeld P *et al.* (2022) Carbohydrate-active enzymes (CAZymes) in the gut microbiome. *Nat Rev Microbiol* **20**, 542-556.

18. Takeuchi T, Kubota T, Nakanishi Y *et al.* (2023) Gut microbial carbohydrate metabolism contributes to insulin resistance. *Nature* **621**, 389-395.

19. Musso G, Gambino R, Cassader M (2011) Interactions Between Gut Microbiota and Host Metabolism Predisposing to Obesity and Diabetes. *Annu Rev Med* **62**, 361-380.

https://doi.org/10.1017/anr.2024.8 Published online by Cambridge University Press

20. Porter NT, Martens EC (2017) The Critical Roles of Polysaccharides in Gut Microbial Ecology and Physiology. *Annu Rev Microbiol* **71**, 349-369.

21. Rastall RA, Diez-Municio M, Forssten SD *et al.* (2022) Structure and function of non-digestible carbohydrates in the gut microbiome. *Benef Microbes* **13**, 95-168.

22. Tiwari UP, Mandal RK, Neupane KR *et al.* (2022) Starchy and fibrous feedstuffs differ in their in vitro digestibility and fermentation characteristics and differently modulate gut microbiota of swine. *J Anim Sci Biotechno* **13**.

23. Rosli NSA, Abd Gani S, Khayat ME *et al.* (2023) Short-chain fatty acids: possible regulators of insulin secretion. *Mol Cell Biochem* **478**, 517-530.

24. Scott KP, Gratz SW, Sheridan PO *et al.* (2013) The influence of diet on the gut microbiota. *Pharmacol Res* **69**, 52-60.

25. Wagenaar CA, van de Put M, Bisschops M *et al.* (2021) The Effect of Dietary Interventions on Chronic Inflammatory Diseases in Relation to the Microbiome: A Systematic Review. *Nutrients* **13**.

26. Tramontano M, Andrejev S, Pruteanu M *et al.* (2018) Nutritional preferences of human gut bacteria reveal their metabolic idiosyncrasies. *Nat Microbiol* **3**, 514-522.

27. Wexler AG, Goodman AL (2017) An insider's perspective:

as a window into the microbiome. *Nat Microbiol* **2**.

28. Wexler HM (2007) Bacteroides: the good, the bad, and the nitty-gritty. *Clin Microbiol Rev* **20**, 593-+.

29. Zafar H, Saier MH (2021) Gut species in health and disease. *Gut Microbes* **13**.

30. Zhang N, Jin ML, Wang KM *et al.* (2022) Functional oligosaccharide fermentation in the gut:

https://doi.org/10.1017/anr.2024.8 Published online by Cambridge University Press

Improving intestinal health and its determinant factors-A review. *Carbohyd Polym* **284**.

31. Couto MR, Gonçalves P, Magro F *et al.* (2020) Microbiota-derived butyrate regulates intestinal inflammation: Focus on inflammatory bowel disease. *Pharmacol Res* **159**.

32. Gonçalves P, Araújo JR, Di Santo JP (2018) A Cross-Talk Between Microbiota-Derived Short-Chain Fatty Acids and the Host Mucosal Immune System Regulates Intestinal Homeostasis and Inflammatory Bowel Disease. *Inflamm Bowel Dis* **24**, 558-572.

33. Kasahara K, Kerby RL, Romano KA *et al.* (2016) Interactions Between Dietary Fiber and Gut Microbiota Modulate the Development of Atherosclerosis. *Circulation* **134**.

34. Cronin P, Joyce SA, O'Toole PW *et al.* (2021) Dietary Fibre Modulates the Gut Microbiota. *Nutrients* **13**.

35. Jiang F, Du CW, Jiang WQ *et al.* (2020) The preparation, formation, fermentability, and applications of resistant starch. *Int J Biol Macromol* **150**, 1155-1161.

36. Peredo-Lovillo A, Romero-Luna HE, Jiménez-Fernández M (2020) Health promoting microbial metabolites produced by gut microbiota after prebiotics metabolism. *Food Res Int* **136**.

37. Guo JY, Brown PR, Tan LB *et al.* (2023) Effect of resistant starch consumption on appetite and satiety: A review. *J Agr Food Res* **12**.

38. Jamar G, Ribeiro DA, Pisani LP (2021) High-fat or high-sugar diets as trigger inflammation in the microbiota-gut-brain axis. *Crit Rev Food Sci* **61**, 836-854.

39. Arnone D, Chabot C, Heba AC *et al.* (2022) Sugars and Gastrointestinal Health. *Clin Gastroenterol H* **20**, 1912-+.

40. Rezende ESV, Lima GC, Naves MMV (2021) Dietary fibers as beneficial microbiota

https://doi.org/10.1017/anr.2024.8 Published online by Cambridge University Press

modulators: A proposed classification by prebiotic categories. *Nutrition* **89**.

41. Swanson KS, Gibson GR, Hutkins R *et al.* (2020) The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of synbiotics. *Nat Rev Gastro Hepat* **17**, 687-701.

42. Agus A, Planchais J, Sokol H (2018) Gut Microbiota Regulation of Tryptophan Metabolism in Health and Disease. *Cell Host Microbe* **23**, 716-724.

43. Blaser MJ (2016) Antibiotic use and its consequences for the normal microbiome. *Science* **352**, 544-545.

44. Peng M, Tabashsum Z, Anderson M *et al.* (2020) Effectiveness of probiotics, prebiotics, and prebiotic-like components in common functional foods. *Compr Rev Food Sci Food Saf* **19**, 1908-1933.

45. Birkeland E, Gharagozlian S, Birkeland KI *et al.* (2020) Prebiotic effect of inulin-type fructans on faecal microbiota and short-chain fatty acids in type 2 diabetes: a randomised controlled trial. *Eur J Nutr* **59**, 3325-3338.

46. Rodriguez J, Hiel S, Neyrinck AM *et al.* (2020) Discovery of the gut microbial signature driving the efficacy of prebiotic intervention in obese patients. *Gut* **69**, 1975-+.

47. Sangwan V, Tomar SK, Singh RRB *et al.* (2011) Galactooligosaccharides: Novel Components of Designer Foods. *J Food Sci* **76**, R103-R111.

48. Macfarlane GT, Steed H, Macfarlane S (2008) Bacterial metabolism and health-related effects of galacto-oligosaccharides and other prebiotics. *J Appl Microbiol* **104**, 305-344.

49. Canfora EE, van der Beek CM, Hermes GDA *et al.* (2017) Supplementation of Diet With Galacto-oligosaccharides Increases Bifidobacteria, but Not Insulin Sensitivity, in Obese

https://doi.org/10.1017/anr.2024.8 Published online by Cambridge University Press

Prediabetic Individuals. *Gastroenterology* **153**, 87-+.

50. Ma CC, Wasti S, Huang S *et al.* (2020) The gut microbiome stability is altered by probiotic ingestion and improved by the continuous supplementation of galactooligosaccharide. *Gut Microbes* **12**.

51. Vergnolle N (2016) Protease inhibition as new therapeutic strategy for GI diseases. *Gut* **65**, 1215-U1212.

52. Lin R, Liu WT, Piao MY *et al.* (2017) A review of the relationship between the gut microbiota and amino acid metabolism. *Amino Acids* **49**, 2083-2090.

53. Portune KJ, Beaumont M, Davila AM *et al.* (2016) Gut microbiota role in dietary protein metabolism and health-related outcomes: The two sides of the coin. *Trends Food Sci Tech* **57**, 213-232.

54. Geboes KP, De Hertogh G, De Preter V *et al.* (2006) The influence of inulin on the absorption of nitrogen and the production of metabolites of protein fermentation in the colon. *Brit J Nutr* **96**, 1078-1086.

55. Oliphant K, Allen-Vercoe E (2019) Macronutrient metabolism by the human gut microbiome: major fermentation by-products and their impact on host health. *Microbiome* **7**.

56. Zhang SH, Wang JJ, Jiang H (2021) Microbial production of value-added bioproducts and enzymes from molasses, a by-product of sugar industry. *Food Chem* **346**.

57. Xu J, Bjursell MK, Himrod J *et al.* (2003) A genomic view of the human-symbiosis. *Science* **299**, 2074-2076.

58. Petit J, de Bruijn I, Goldman MRG *et al.* (2022) β-Glucan-Induced Immuno-Modulation: A Role for the Intestinal Microbiota and Short-Chain Fatty Acids in Common Carp. *Front*

https://doi.org/10.1017/anr.2024.8 Published online by Cambridge University Press

Immunol **12**.

59. Ranjbar R, Vahdati SN, Tavakoli S *et al.* (2021) Immunomodulatory roles of microbiota-derived short-chain fatty acids in bacterial infections. *Biomed Pharmacother* **141**.

60. Jasim SA, Opulencia MJC, Ramirez-Coronel AA *et al.* (2022) The emerging role of microbiota-derived short-chain fatty acids in immunometabolism. *Int Immunopharmacol* **110**.

61. Panahi HKS, Dehhaghi M, Guillemin GJ *et al.* (2022) Bioethanol production from food wastes rich in carbohydrates. *Curr Opin Food Sci* **43**, 71-81.

62. Zeise KD, Woods RJ, Huffnagle GB (2021) Interplay between Candida albicans and Lactic Acid Bacteria in the Gastrointestinal Tract: Impact on Colonization Resistance, Microbial Carriage, Opportunistic Infection, and Host Immunity. *Clin Microbiol Rev* **34**.

63. Portincasa P, Bonfrate L, Vacca M *et al.* (2022) Gut Microbiota and Short Chain Fatty Acids: Implications in Glucose Homeostasis. *Int J Mol Sci* **23**.

64. Shu WS, Huang LN (2022) Microbial diversity in extreme environments. *Nat Rev Microbiol* **20**, 219-235.

65. Bilal M, Iqbal HMN (2020) State-of-the-art strategies and applied perspectives of enzyme biocatalysis in food sector - current status and future trends. *Crit Rev Food Sci Nutr* **60**, 2052-2066.

66. Francois JM, Lachaux C, Morin N (2019) Synthetic Biology Applied to Carbon Conservative and Carbon Dioxide Recycling Pathways. *Front Bioeng Biotechnol* **7**, 446.

67. Van Treuren W, Dodd D (2020) Microbial Contribution to the Human Metabolome: Implications for Health and Disease. *Annu Rev Pathol* **15**, 345-369.

68. Tian X, Chen H, Liu H *et al.* (2021) Recent Advances in Lactic Acid Production by Lactic

https://doi.org/10.1017/anr.2024.8 Published online by Cambridge University Press

Acid Bacteria. *Appl Biochem Biotechnol* **193**, 4151-4171.

69. da Silva Fernandes F, de Souza ES, Carneiro LM *et al.* (2022) Current Ethanol Production Requirements for the Yeast Saccharomyces cerevisiae. *Int J Microbiol* **2022**, 7878830.

70. Maicas S (2020) The Role of Yeasts in Fermentation Processes. *Microorganisms* **8**.

71. Blair EM, Dickson KL, O'Malley MA (2021) Microbial communities and their enzymes facilitate degradation of recalcitrant polymers in anaerobic digestion. *Current Opinion in Microbiology* **64**, 100-108.

72. Cataldo PG, Villegas JM, de Giori GS *et al.* (2020) Enhancement of γ-aminobutyric acid (GABA) production by

CRL 2013 based on carbohydrate fermentation. *Int J Food Microbiol* **333**.

73. Zimmerman AE, Howard-Varona C, Needham DM *et al.* (2020) Metabolic and biogeochemical consequences of viral infection in aquatic ecosystems. *Nat Rev Microbiol* **18**, 21-34.

74. Daisley BA, Koenig D, Engelbrecht K *et al.* (2021) Emerging connections between gut microbiome bioenergetics and chronic metabolic diseases. *Cell Rep* **37**.

75. Spencer SP, Fragiadakis GK, Sonnenburg JL (2019) Pursuing Human-Relevant Gut Microbiota-Immune Interactions. *Immunity* **51**, 225-239.

76. Kim CH (2023) Complex regulatory effects of gut microbial short-chain fatty acids on immune tolerance and autoimmunity. *Cell Mol Immunol* **20**, 341-350.

77. Salvi PS, Cowles RA (2021) Butyrate and the Intestinal Epithelium: Modulation of Proliferation and Inflammation in Homeostasis and Disease. *Cells-Basel* **10**.

78. Luu M, Visekruna A (2019) Short-chain fatty acids: Bacterial messengers modulating the

https://doi.org/10.1017/anr.2024.8 Published online by Cambridge University Press

immunometabolism of T cells. *Eur J Immunol* **49**, 842-848.

79. Hosmer J, McEwan AG, Kappler U (2023) Bacterial acetate metabolism and its influence on human epithelia. *Emerg Top Life Sci*.

80. Antunes KH, Fachi JL, de Paula R *et al.* (2019) Microbiota-derived acetate protects against respiratory syncytial virus infection through a GPR43-type 1 interferon response. *Nat Commun* **10**.

81. Schlatterer K, Beck C, Schoppmeier U *et al.* (2021) Acetate sensing by GPR43 alarms neutrophils and protects from severe sepsis. *Commun Biol* **4**.

82. Xu MD, Jiang ZY, Wang CL *et al.* (2019) Acetate attenuates inflammasome activation through GPR43-mediated Ca

-dependent NLRP3 ubiquitination (vol 51, 83, 2019). *Exp Mol Med* **51**.

83. Daien CI, Tan J, Audo R *et al.* (2021) Gut-derived acetate promotes B10 cells with antiinflammatory effects. *Jci Insight* **6**.

84. Balmer ML, Ma EH, Thompson AJ *et al.* (2020) Memory CD8+ T Cells Balance Pro- and Anti-inflammatory Activity by Reprogramming Cellular Acetate Handling at Sites of Infection. *Cell Metabolism* **32**, 457-+.

85. Nakano T, Uchiyama K, Ushiroda C *et al.* (2020) Promotion of wound healing by acetate in murine colonic epithelial cell via c-Jun N-terminal kinase activation. *J Gastroen Hepatol* **35**, 1171-1179.

86. Lyu JF, Pirooznia M, Li YS *et al.* (2022) The short-chain fatty acid acetate modulates epithelial-to-mesenchymal transition. *Mol Biol Cell* **33**.

87. Hung KY, Wu SY, Pao HP *et al.* (2022) Acetate, a gut bacterial product, ameliorates

https://doi.org/10.1017/anr.2024.8 Published online by Cambridge University Press

ischemia-reperfusion induced acute lung injury in rats. *Int Immunopharmacol* **111**.

88. Xiong JH, Kawagishi H, Yan Y *et al.* (2018) A Metabolic Basis for Endothelial-to-Mesenchymal Transition. *Mol Cell* **69**, 689-+.

89. Langfeld LQ, Du K, Bereswill S *et al.* (2021) A review of the antimicrobial and immune-modulatory properties of the gut microbiota-derived short chain fatty acid propionate - What is new? *Eur J Microbiol Immunol (Bp)* **11**, 50-56.

90. Louis P, Flint HJ (2017) Formation of propionate and butyrate by the human colonic microbiota. *Environ Microbiol* **19**, 29-41.

91. Morrison DJ, Preston T (2016) Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. *Gut Microbes* **7**, 189-200.

92. Shi YB, Xu MZ, Pan S *et al.* (2021) Induction of the apoptosis, degranulation and IL-13 production of human basophils by butyrate and propionate via suppression of histone deacetylation. *Immunology* **164**, 292-304.

93. Feng Z, Wang X, Kang G *et al.* (2023) Engineered propionate-producing bacteria attenuates murine colitis by modulating the immune function of resident macrophages via histone deacetylase. *J Crohns Colitis* **17**, I174-I177.

94. Shi N, Li N, Duan XW *et al.* (2017) Interaction between the gut microbiome and mucosal immune system. *Military Med Res* **4**.

95. Tian XL, Hellman J, Horswill AR *et al.* (2019) Elevated Gut Microbiome-Derived Propionate Levels Are Associated With Reduced Sterile Lung Inflammation and Bacterial Immunity in Mice (vol 10, 159, 2019). *Frontiers in Microbiology* **10**.

96. Du HX, Yue SY, Niu D *et al.* (2022) Gut Microflora Modulates Th17/Treg Cell

https://doi.org/10.1017/anr.2024.8 Published online by Cambridge University Press

Differentiation in Experimental Autoimmune Prostatitis

the Short-Chain Fatty Acid Propionate. *Front Immunol* **13**.

97. Arpaia N, Campbell C, Fan XY *et al.* (2013) Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. *Nature* **504**, 451-+.

98. Kespohl M, Vachharajani N, Luu M *et al.* (2017) The Microbial Metabolite Butyrate Induces Expression of Th1-Associated Factors in CD4

T cells. *Front Immunol* **8**.

99. Cresci GA, Glueck B, McMullen MR *et al.* (2017) Prophylactic tributyrin treatment mitigates chronic-binge ethanol-induced intestinal barrier and liver injury. *J Gastroen Hepatol* **32**, 1587-1597.

100. Nielsen DSG, Jensen BB, Theil PK *et al.* (2018) Effect of butyrate and fermentation products on epithelial integrity in a mucus-secreting human colon cell line. *J Funct Foods* **40**, 9-17.

101. Feng YH, Wang Y, Wang P *et al.* (2018) Short-Chain Fatty Acids Manifest Stimulative and Protective Effects on Intestinal Barrier Function Through the Inhibition of NLRP3 Inflammasome and Autophagy. *Cell Physiol Biochem* **49**, 190-205.

102. Cresci GA, Bush K, Nagy LE (2014) Tributyrin Supplementation Protects Mice from Acute Ethanol-Induced Gut Injury. *Alcohol Clin Exp Res* **38**, 1489-1501.

103. Eamin EE, Masclee AA, Dekker J *et al.* (2013) Short-Chain Fatty Acids Activate AMP-Activated Protein Kinase and Ameliorate Ethanol-Induced Intestinal Barrier Dysfunction in Caco-2 Cell Monolayers. *J Nutr* **143**, 1872-1881.

104. Siddiqui MT, Cresci GAM (2021) The Immunomodulatory Functions of Butyrate. *J*

https://doi.org/10.1017/anr.2024.8 Published online by Cambridge University Press

Inflamm Res **14**, 6025-6041.

105. Kelly CJ, Zheng L, Campbell EL *et al.* (2015) Crosstalk between Microbiota-Derived Short-Chain Fatty Acids and Intestinal Epithelial HIF Augments Tissue Barrier Function. *Cell Host Microbe* **17**, 662-671.

106. Hyun GH, Cho IH, Yang YY *et al.* (2023) Mechanisms of interactions in pattern-recognition of common glycostructures across pectin-derived heteropolysaccharides by Toll-like receptor 4. *Carbohyd Polym* **314**.

107. Fajstova A, Galanova N, Coufal S *et al.* (2020) Diet Rich in Simple Sugars Promotes Pro-Inflammatory Response via Gut Microbiota Alteration and TLR4 Signaling. *Cells-Basel* **9**.

108. Fernández-Lainez C, Akkerman R, Oerlemans MMP *et al.* (2022) β(2→6)-Type fructans attenuate proinflammatory responses in a structure dependent fashion via Toll-like receptors. *Carbohyd Polym* **277**.

109. Bastos PAD, Wheeler R, Boneca IG (2021) Uptake, recognition and responses to peptidoglycan in the mammalian host. *Fems Microbiology Reviews* **45**.

110. Trindade BC, Chen GCY (2020) NOD1 and NOD2 in inflammatory and infectious diseases. *Immunol Rev* **297**, 139-161.

111. Clarke TB, Davis KM, Lysenko ES *et al.* (2010) Recognition of peptidoglycan from the microbiota by Nod1 enhances systemic innate immunity. *Nat Med* **16**, 228-U137.

112. Kanneganti TD, Lamkanfi M, Núñez G (2007) Intracellular NOD-like receptors in host Defense and disease. *Immunity* **27**, 549-559.

113. Danis J, Mellett M (2021) Nod-Like Receptors in Host Defence and Disease at the Epidermal Barrier. *Int J Mol Sci* **22**.

https://doi.org/10.1017/anr.2024.8 Published online by Cambridge University Press

114. Ermann J, Staton T, Glickman JN *et al.* (2014) Nod/Ripk2 signaling in dendritic cells activates IL-17A-secreting innate lymphoid cells and drives colitis in T-bet-/-.Rag2-/- (TRUC) mice. *P Natl Acad Sci USA* **111**, E2559-E2566.

115. Kobayashi KS, Chamaillard M, Ogura Y *et al.* (2005) Nod2-dependent regulation of innate and adaptive immunity in the intestinal tract. *Science* **307**, 731-734.

116. Liu C, Gelius E, Liu G *et al.* (2000) Mammalian peptidoglycan recognition protein binds peptidoglycan with high affinity, is expressed in neutrophils, and inhibits bacterial growth. *J Biol Chem* **275**, 24490-24499.

117. Franchi L, Amer A, Body-Malapel M *et al.* (2006) Cytosolic flagellin requires Ipaf for activation of caspase-1 and interleukin 1β in salmonella-infected macrophages. *Nat Immunol* **7**, 576-582.

118. Carvalho FA, Nalbantoglu I, Aitken JD *et al.* (2012) Cytosolic flagellin receptor NLRC4 protects mice against mucosal and systemic challenges. *Mucosal Immunol* **5**, 288-298.

119. Paone P, Cani PD (2020) Mucus barrier, mucins and gut microbiota: the expected slimy partners? *Gut* **69**, 2232-2243.

120. Tashiro M, Iwata A, Yamauchi M *et al.* (2017) The N-terminal region of serum amyloid A3 protein activates NF-κB and up-regulates MUC2 mucin mRNA expression in mouse colonic epithelial cells. *Plos One* **12**.

121. Ahn DH, Crawley SC, Hokari R *et al.* (2005) TNF-alpha activates MUC2 transcription via NF-kappaB but inhibits via JNK activation. *Cell Physiol Biochem* **15**, 29-40.

122. Zhang XJ, Zhang BW, Peng B *et al.* (2022) Different Dose of Sucrose Consumption Divergently Influences Gut Microbiota and PPAR-γ/MAPK/NF-κB Pathway in DSS-Induced

https://doi.org/10.1017/anr.2024.8 Published online by Cambridge University Press

Colitis Mice. *Nutrients* **14**.

123. Tan J, McKenzie C, Vuillermin PJ *et al.* (2016) Dietary Fiber and Bacterial SCFA Enhance Oral Tolerance and Protect against Food Allergy through Diverse Cellular Pathways. *Cell Rep* **15**, 2809-2824.

124. Kim M, Qie Y, Park J *et al.* (2016) Gut Microbial Metabolites Fuel Host Antibody Responses. *Cell Host Microbe* **20**, 202-214.

https://doi.org/10.1017/anr.2024.8 Published online by Cambridge University Press