Arh. farm. 2023; 73: 484 – 514 *Review article/Pregledni rad*

Crosstalk between vitamin status and Gut Microbiota: the key to maintaining immune homeostasis in the gut

Marija Rakić[1#], Jelena Repac[1#], Tanja Lunić[1], Bojan Božić[1], Biljana Božić Nedeljković[1]*

University of Belgrade, Faculty of Biology, Institute of Physiology and Biochemistry "Ivan Djaja", Group of immunology. Studentski trg 16, 11000 Belgrade, Serbia

[#]Equally contributed

*Corresponding author: Biljana Božić Nedeljković; e-mail: biljana@bio.bg.ac.rs

Abstract

The human gut microbiota is a diverse ecosystem that harbours a variety of microorganisms, including proteobacteria, bacteria, viruses, fungi, protists, and archaea. These microorganisms are collectively involved in several vital functions, including nutrient metabolism, vitamin synthesis, immune system regulation, neurotransmitter production, drug metabolism, and communication with the central nervous system. Dysbiosis within the gut microbiota has been shown to be a critical factor in the development of chronic disease. Investigating the effects of gut microbiota composition on overall health holds promise for the treatment of inflammatory diseases and the development of new therapeutic interventions. One notable aspect of the functionality of the gut microbiota is its involvement in the production of essential B vitamins. These vitamins exert a significant influence on immune responses and the composition of the gut microbiota. Competition may occur between the host and the gut microbiota for B vitamins, which some bacteria obtain from food or from synthesis by other gut bacteria. Thus, the availability of B vitamins in the diet has the potential to influence the composition of the gut microbiota and thus immune homeostasis. The profile of the gut microbiota varies individually, with diet proving to be an important modulator of both its composition and functional properties. However, further extensive research efforts are needed to understand the complex interplay between the gut microbiota, vitamins, and immune response mechanisms. Such investigations have the potential to develop innovative therapeutic strategies for a spectrum of inflammatory diseases, opening new avenues for improved patient outcomes.

Key words: Gut microbiota, Dysbiosis, Immune system, B Vitamins, Homeostasis

doi.org/10.5937/arhfarm73-46395

Gut Microbiota ecosystem

The gastrointestinal system (GIT) is the anatomical site that is regularly exposed to multiple environmental stimuli through food intake, which is why the lumen of GIT is considered the richest source of antigens in the human body. Accordingly, the microbial community inhabiting the human GIT represents a complex and well-structured ecosystem that provides its host with important metabolic (breakdown of indigestible nutrients, synthesis of vitamins) and immunomodulatory functions, and also acts as a dynamic barrier against colonization by pathogenic species (1, 2). The seemingly separate aspects of gut microbiota (GM) function, food digestion and immune modulation are in fact highly intertwined, as byproducts of microbial metabolism act as messengers for epithelial barrier maintenance and drivers of phenotypic changes in local immune cells (Figure 1). Moreover, competition with pathogens for the same ecological niche hinders excessive immune activation and thus also contributes to a more balanced physiological state (3, 4). In addition to dietary components, the GM is also involved in the degradation of xenobiotics, which significantly affects the bioactivity and bioavailability of ingested drugs (5-7). In view of this, experimental attempts aimed at *ex vivo* capturing the drug-metabolism ability of gut microbes at a community-level (8) and machine-learning based approaches for discovering the GM status as a biomarker of medical treatment outcome are starting to emerge (9, 10).

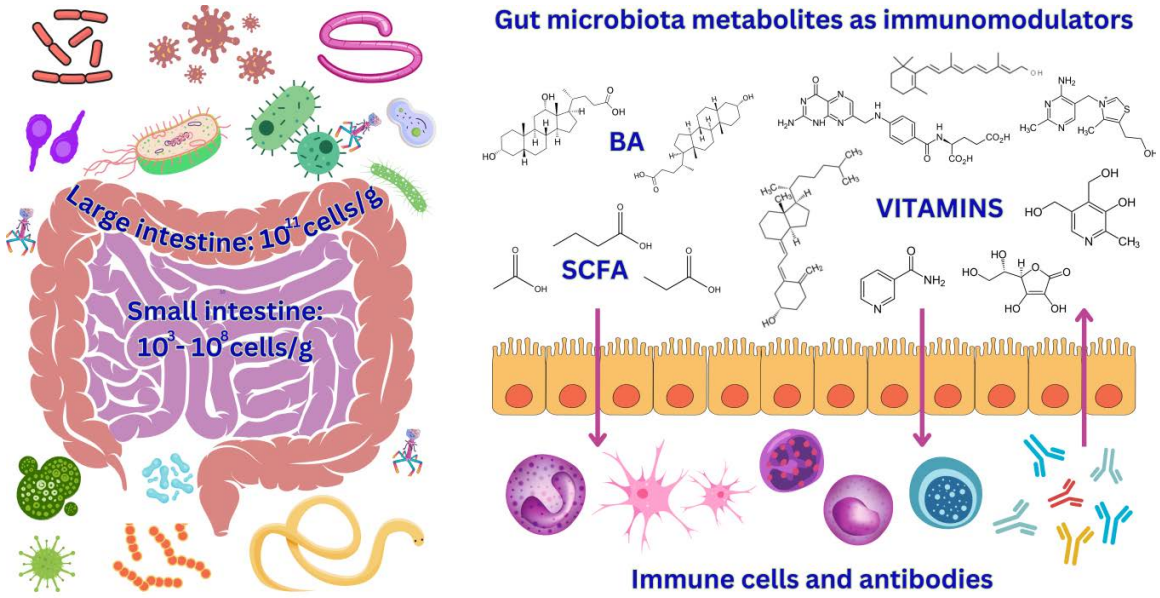

Figure 1. **Gut microbiota composition and cross-talk between microbial-derived metabolites and neighboring immune cell populations**

Slika 1. **Sastav mikrobiote creva i uticaj produkovanih metabolita na populacije rezidentnih imunskih ćelija**

The ratio of symbiotic microorganisms to human host cells is approximately 1:1 (11), mainly due to the high density of microorganism populations along the distal segments of GIT (12). More specifically, the estimated number of bacterial cells per gram of feces is 10^{10}-10^{11}, which is also true for viruses (11, 13). The most abundant gut-associated bacterial phyla are *Firmicutes* (represented by more than 200 genera) and *Bacteroidetes*, which together account for nearly 90% of the richness of the gut community (1, 14, 15). Less common but also functionally very relevant phyla are *Actinobacteria*, *Proteobacteria*, *Fusobacteria*, and *Verrucomicrobia* (1). In addition to the predominant prokaryotic communities (bacteria and viruses), the intestinal microbiota is also composed of microscopic species classified as Eukarya (fungi, helminths and protists) and Archaea (16, 17); however, with lower community richness at the species level. The estimated abundance of archaeal cells per gram of feces is nearly two orders of magnitude lower than that reported for bacteria and viruses (approximately 10^9), while estimates for mycobiome abundance are even lower (10^2-10^6) (13).

The human intestine contains predominantly hydrogentrophic archaea that convert byproducts of bacterial metabolism to methane. Some of these methanogenic species (*Methanobrevibacter smithii* and *Methanosphaera stadtmanae*) are ubiquitous but highly specific representatives of the human GM (18, 19), owing to pronounced adaptability to variable conditions in the habitat. For Western civilization, ubiquitous distribution has also been reported for the fungal genera *Candida*, *Saccharomyces*, and *Malassezia* (16). Interestingly, at the time of initial gut colonization, fungal diversity and abundance correlate negatively with bacterial community richness, and in adulthood this is observed as a fungal bloom in response to antibiotic treatment when a massive depletion of bacterial communities occurs.

The opportunistic drug-induced spread of otherwise harmless commensals implies that both reciprocal and host interactions are highly context-dependent for components of the GM, sometimes complicating the correct positioning of underexplored taxa. For example, the gut-colonizing protist *Blastocystis*, characterized as “the most common eukaryotic organism reported in human fecal samples” (20), has been described as both pathogenic and commensal (21), which may be due in part to a looser definition of commensalism for protists/helminths that implies only a long-lasting tolerance of the immune system under undisturbed conditions (22). Although seemingly of no benefit to the host, *Blastocystis* has also been designated as a block-forming agent essential for the maintenance of the gut ecosystem due to a long history of association with humans (demonstrated in coprolites) and a positive correlation with bacterial community richness and alpha diversity (16, 17). Accordingly, the lower abundance and species richness of intestinal bacteria in industrialized (more sanitized) environments was causally inferred as an indirect effect of the slimming of protozoan and helminths communities in the gut (17). This has also been confirmed by a recent study (23) showing that antibiotic treatment leads to a massive reduction in *Blastocystis* abundance. Remarkably, the dense interaction network of microbial communities in the gut goes beyond the presumed multilevel trophic stratification (24) and also explains the rapid intrahost evolution of its

members due to the high rate of horizontal gene transfer (13). This process plays a prominent role in shaping the gut resistome (collection of genes conferring resistance to antimicrobial drugs), which can be seen as a form of community adaptation to the nowadays widespread use of antibiotics (25).

Apart from antimicrobial drugs, GM also responds to many other conditions/factors in the environment and is probably influenced by the genetic background of the host (11, 26). Accordingly, the human GM is characterized by a high degree of inter- and intra-individual variability. Moreover, primary colonization of the gut is largely stochastically controlled (27), while *sensu stricto* inheritance of the maternal microbiota accounts for only a few species transmitted directly at birth (11). The actual diversification of primary communities occurs in early childhood, most intensely after weaning, when new dietary patterns begin to shape the environmental landscape in the gut. This period correlates with a profound influence of the GM on the education/maturation of the immune system and is often referred to as a "window of opportunity" for major interventions in the composition of the GM. As a proxy of dietary regime, transit time and stool consistency also strongly affect the composition of GM, as stool retention favors the overgrowth of fast-growing microbial taxa, sometimes with pathological consequences in the form of small intestine bacterial overgrowth (SIBO) syndrome (28-30). In addition, drug intake (especially antibiotics and proton pump inhibitors), stress, lack of sleep, high body mass index, and other factors that (negatively) affect host homeostasis and immunity modulate gut microbial communities, but also lifestyle in a modern (highly sanitized) environment characterized by a low parasite burden (16). Consequently, it is unusual to speak of a healthy microbiota, but rather of eubiosis, which refers to the spectrum of different microbial community states capable of balancing their commensal interactions with the host.

Gut Microbiota enterotypes

Despite constant exposure to a highly dynamic environment, the distinctive structural complexity of the gut microbial ecosystem (which correlates with species richness/diversity) provides inherent resilience to perturbation and favors stratified rather than continuous shifts in community composition (31). The stability of the GM in adulthood has been shown to persist over a period of more than 10 years, and the abundance rather than the composition of various microbial species is influenced by environmental stressors (32). Interestingly, the stability of the GM was also confirmed at the level of individual strains (33). Accordingly, pioneering research in this field already attempted to identify characteristic eubiotic states of the GM, leading to the concept of enterotypes – recurrent patterns of GM composition dominated by particular bacterial taxa – that correlate most strongly with long-term dietary habits (31, 34).

In early childhood, *Bifidobacteria* and *Proteobacteria* generally serve as community organizers for primary gut ecosystems, whereas the GM in adulthood is characterized by the prevalence of *Bacteroides*, *Prevotella*, or *Ruminococcus* (and rarely other *Firmicutes* genera) (1). The three major adult stage enterotypes have been widely

validated in the context of different ethnicities, geographies, and lifestyles (rural *vs.* industrial environments), demonstrating diet as the core environmental factor shaping the gut community landscape (14, 35-37). The enterotype dominated by *Prevotella* correlates with a diet rich in complex carbohydrates, due to the high efficiency of the hydrolytic enzymes of *Prevotella* in degrading plant fibers (1). Likewise, the *Bacteroides*-dominated enterotype is a form of GM adaptation to the high-fat animal (Western) diet (14, 38-40), while the *Ruminococcus*-enterotype is best adapted to a diet rich in plants and fermented products (41). The enterotypes dominated by *Bacteroides* and *Ruminococcus* also share the ability to degrade mucin glycoproteins, which affects the turnover rate and stability of the intestinal mucosal barrier(1).

Although rather simple, the concept of enterotyping (40) could have clinical application in diagnostics and prediction of disease susceptibility/medical treatment outcomes, as the dimensionality reduction of the complex GM to a small number of (core) community descriptors facilitates the discovery of medically relevant covariates (38, 42). A year-long cohort study in Sweden (43) has shed light on the long-term enterotype stability (32) and significant intraindividual variation in the GM (44). The study identified three main patterns of variability for GM constituents highlighting stable, bimodal, and variable species. By elucidating ecosystem dynamics, this research supports the concept of core community taxa and offers guidelines for the development of algorithms to predict the evolution of the gut community in response to various (stochastic and tailored) environmental factors.

Gut Microbiota fluctuations along the gastrointestinal system

The concept of enterotypes is a proxy for the composition of GM along the colon only. First, noninvasive methods like fecal DNA sequencing reveal colon microbial communities, while characterizing small intestine microbiota is challenging due to invasive methods prone to artifacts (cross-contamination) and is also unsuitable for healthy subjects (45, 46). Ileostomy samples offer a unique exception to cross-contamination issues, enabling valuable studies of dynamic small intestine microbial communities. However, limitations include a limited study population and the impact of altered ileal anatomy. Secondly, the large intestine hosts microbes 100 times more abundantly than other body compartments, including the small intestine, which lags by 4 times. (31). The density of microbial load along the small intestine (proximal duodenum to terminal ileum) increases from 10^3 to 10^8 cells/g, whereas the microbial load of the large intestine (bacterial only) was estimated to be approximately 10^{11} cells/g of luminal contents (13, 47).

Clearly, GM in the small intestine can only be characterized involving strategies that bypass any type of sampling from the colon, like standard/routine feces collection procedure. Breakthroughs in this area are urgently needed to fully comprehend the effects of various chemical gradients along the GIT – that generate highly specialized microenvironments – on the composition and metabolic variations of the GM, greatly impacting the function of neighboring immune system components. In general, acidity,

concentration of digestive enzymes, bile acids, gasses (pO_2, pCO_2, and pH_2), and dietary antigens decrease from the duodenum to the colon, while the mucus thickness and the total microbial load increase due to the less harsh environment in the distal segments of the GIT (47-49).

In contrast to the dense communities of obligate anaerobes favored in the hypoxic environment of the colon, aerobic bacteria and facultative anaerobes, predominantly from the phyla *Firmicutes*, *Proteobacteria*, and *Actinobacteria*, colonize the small intestine, the most common genera being *Lactobacillus*, *Clostridium*, *Staphylococcus*, *Streptococcus*, *Bacteroides*, *Veillonell*a, *Gemella*, *Actinomyces*, and *Escherichia* (1, 47, 50). Proximally to distally, microbial communities differ more in the lumen, likely due to more uniform conditions in the mucosal environment, which is also protected from rapid digesta flow rates (3-5 h) (1). The proximal luminal communities of the small intestine are particularly dynamic, in response to the rhythmicity of daily food intake and the associated concentration and activity of digestive enzymes. In addition, these communities are severely impacted by proton pump inhibitors, which alter not only gastric, but also the pH of the duodenal compartment. Remarkably, a significant overlap was observed between the GM in the proximal small intestine and the oral microbiota, probably due to the daily influx of more than 1 L of saliva containing about 10^{12} bacteria (51).

How variable transit times alter the biology of bacterial communities from the small intestine is best illustrated by the SIBO syndrome, in which pathological overgrowth of fast-growing taxa occurs in response to slow peristalsis. This has been shown to affect the turnover rate of essential micronutrients functionally related to small intestinal physiology. For example, SIBO is one of the causative factors for cobalamin (vitamin B12) deficiency and malabsorption in the ileum (49), as it is overused by the overgrown bacterial communities for their own metabolic purposes. Similar effects were reported for thiamine (vitamin B1) and nicotinamide (vitamin B3) deficiency, in contrast to the observed increased availability of folate (vitamin B9), probably as a result of biosynthesis mediated by the overgrown microbiota along the small intestine, predominantly the ileal compartment (50). In addition to the synthesis and absorption of B vitamins, the ileum is also characterized by a high turnover rate of vitamins C, D, K, and other micronutrients (Se, Mg, and Mn) (49, 52). Moreover, considerable amounts of bile acids (BAs) and short-chain fatty acids (SCFAs) (53, 54) are produced in the ileum, especially by abundant representatives of various *Clostridiales* genera from the thick mucosal layer. The microbes residing in the ileum, but also duodenum and jejunum, rapidly metabolize simple carbohydrates from the nutrient-rich environment (46), demonstrating once again that the (availability of) dietary components most directly shape(s) highly dynamic microbial communities in the small intestine.

The cross-talk between Gut Microbiota and immunity

In the previous chapter, we saw how specialized microenvironments along the GIT form networks for the establishment of characteristic microbial ecosystems. This regional specialization of the commensal microbiota is primarily reflected in its communication

with neighboring components of the immune system, whose anatomical (and functional) organization is also determined by the anatomy of the associated GIT compartments, including unique organization of the gut-associated lymphoid tissue (GALT) and the presence of a decreasing gradient of pro-inflammatory cytokine concentration along the GIT (48, 55). The structure (maturation) of GALT is also shaped by the composition of GM and this influence extends beyond the local compartment by virtue of soluble immune modulators, targeting extraintestinal lymphoid and non-lymphoid tissues (56). The impact of this extremely close connection between the gut anatomy, resident microbiota, and associated immune system on the host well-being is illustrated by a recent bibliometric analysis of original research articles on the GM for the period between 2010 and 2021 (57). The results of this analysis show that, in addition to microbiology journals, numerous articles were published in clinical medicine journals, with the most frequently cited ones examining the relationship between the GM and human health/disease status.

The defense mechanisms provided by the components of the immune system, located mainly in the lamina propria of the GIT, are largely complemented by a thick mucus layer produced by specialized epithelial cells (goblet cells), which prevents the extraintestinal translocation of microbes and largely isolates the immune cells from the contents of the lumen, enriched with commensals, food components, and transiting microbes (4, 58). The mucosal barrier network is predominantly composed of highly O-glycosylated proteins – mucins, mixed with antimicrobial peptides (cathelicidins and defensins) and secretory immunoglobulin A (IgA), which protect against and opsonize microbes that come into contact with them. This represents the first line of defense in the gut and is also a way to mitigate excessive immune activation, which is achieved mainly by redirecting immune activity to tolerogenic processes (59). The mucosal barrier is further reinforced by tight junctions in the epithelial lining that severely restrict paracellular permeability and the access of microbes and their metabolites to the blood and lymphatic circulation. On the luminal side, the protective role of the intestinal barrier is complemented by the activity of bacteriocins, natural antimicrobial peptides produced by commensals, and the influence that some commensals exert on mucosal renewal by stimulating the production of mucins in goblet cells (58, 60-62).

When microorganisms, or at least their antigens, manage to breach through the mucosal barrier, thanks to the specialized transcytotic activity of epithelial microfold cells (M cells), immune processes are initiated in the GALT, which is one of the largest lymphoid organs of the body, rich in isolated and aggregated lymphoid follicles (48). More specifically, the initiation of immune responses relies on the uniquely organized GALT structures along the ileum – Peyer`s patches, particularly rich in B cell follicles with differentiated germinal centers and antigen-sampling dendritic cells (63). B cell follicles are covered by an epithelium containing M cells specialized for transporting antigens of the intestinal microbiota from the lumen to dendritic cells, which initiate the cascade of adaptive immune responses by presenting antigens to naïve T lymphocytes. GALT, and also the gut-draining lymph nodes, harbor different subsets of dendritic cells biasing the downstream activity of T cells to tolerogenic or pro-inflammatory responses,

which makes them a signaling hub for the maintenance of intestinal homeostasis. In addition to dendritic cells and T lymphocytes (regulatory and effector subsets), immune responses in the gut also depend on the activity of mucosa-associated invariant T lymphocytes (MAIT cells), specialized intraepithelial T lymphocytes (IELs, unconventional γδT cells), innate lymphoid cells (ILCs), natural killer (NK) cells, neutrophils, and macrophages, all of which have distinct surface markers reflecting their functional specialization and gut-homing patterns of recirculation. Under undisturbed conditions, the small intestine is particularly rich in IELs, Th17 subset of $CD4^+$ T cells, ILC2 and ILC3 cells, while the Tregs specific for commensal microbes predominate in the colon (49).

In different compartments of the GIT immune cells are orchestrated to provide either protection from pathogenic invaders or tolerance to recurrent commensals/food components. Tolerance to food antigens is maintained mainly in proximal segments along the GIT, which is the primary site for nutrient absorption. Establishment of food tolerance in the small intestine is controlled in part by diurnal rhythms of major histocompatibility complex (MHC) class II expression on resident epithelial cells that depend on food intake (which in turn causes shifts in local microbial community composition). The function of resident epithelial cells is closely related to the activity of highly mobile IELs, which serve immune surveillance, form the layer along the basolateral side of the epithelium, and also reinforce the integrity of the intestinal barrier (47, 64). The role of IELs in the pathogenesis of celiac disease, which is characterized by abnormal sensitivity to gliadin antigens from cereals, supports the tolerance-promoting effect of IEL to foods (64). Conversely, tolerance to commensal microbes in the colon relies on the regulatory phenotype of $CD4^+$ T cells (65), the induction of which can be influenced by the GM itself (*Akkermansia muciniphila* is a well-characterized trigger of the $ROR\gamma t^+$ regulatory T cell phenotype) or the corresponding microbial metabolites, such as SCFAs, which are abundantly produced in the colon (3).

The choice of inflammation over tolerance and *vice versa* depends on the context of antigen presentation to the immune system, i.e., the balance between pro-inflammatory and anti-inflammatory signals in the surrounding milieu, which is controlled primarily by the GM itself. In this context, the GM functions both as an object and as a modulator of local immune activity. These interactions are especially important in early childhood, when critical processes of immune system education occur and the maturing lymphocytes acquire the ability to discriminate between their own and foreign and between harmless and pathogenic microbial species for proper establishment of regulatory mechanisms (58). Recent evidence shows that the microbiota begins to communicate with the body *in utero*, as metabolites of the maternal microbiota are represented in the fetal metabolome (66, 67) and typical gut microbes, such as representatives of *Firmicutes*, *Actinobacteria*, and *Proteobacteria*, have been detected at the maternal-fetal interface (placenta and umbilical cord) (3). Since the education of the human immune system also begins during intrauterine development (the first trimester) (68), this could be influenced in part by the exposure of maturing T lymphocytes to the colonizing maternal microbiota

or its metabolites. A possible avenue for mediating microbial effects on *in utero* immune system maturation could be epigenetic reprogramming, as a recent study in mice shows that even mild maternal infections cause IL-6 dependent imprinting of the fetal GIT tissue with resulting long-term susceptibility to increased intestinal inflammation in adulthood (69). Consequently, a shift in the balance of immune system activity from a tolerogenic to a pro-inflammatory state in response to altered GM can adversely affect the host health. The persistence of a local pro-inflammatory milieu has systemic effects and, depending on the host's genetic background and lifestyle, can result in a number of different diseases – metabolic, autoimmune, inflammatory, neurological, and even various psychiatric disorders have all been linked to perturbed gut microbial communities (1, 114, 134, 142).

Gut Microbiota Metabolites as Essential Messengers to the Immune System

Communication between gut microbes and the immune system can be mediated either through direct recognition of microbial structures or indirectly *via* metabolites that GM abundantly produce (49). Normally, the recognition of gut microbes is initiated by the cells of innate immunity, since the immune surveillance of the intestinal luminal contents is based on the activity of IECs, whereas the same activity in the lamina propria is predominantly carried out by dendritic cells and macrophages. Common to these cell types is the expression of receptors with specificity for common microbial structures (patterns) – pattern recognition receptors (PRRs), with Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain receptors being two overrepresented classes (70, 71). Upon activation, PRRs activate downstream signaling pathways and ultimately alter gene expression of immune-related (soluble and membrane-bound) mediators, primarily cytokines, chemokines, and several classes of immune receptors. The outcome depends on the specific cascade and target genes being utilized. It can lead to either the promotion of tolerance or the triggering of inflammatory/protective responses. In both cases, adaptive immunity cells, such as effector or regulatory lymphocytes, are also involved. The precise mechanism of differentiation between commensal and pathogenic bacteria remains unclear, as both types of bacteria contain microbial patterns recognized by PRRs; however, there are data supporting the hypothesis of TLR-dependent priming of dendritic cells by intestinal commensal bacteria, in part due to fine-tuning of receptor surface expression (3, 4, 56, 58). Although pattern sharing complicates distinguishing between pathogens and commensals, it is consistent with the dynamic, context-dependent interactions between gut microbes and the host, where a given species may act as both a pathogen and commensal depending on environmental conditions.

The priming of dendritic cells for tolerogenic activity by commensal bacteria and many other immunomodulatory functions of the GM are probably mediated by abundant microbial metabolites, especially in the colon. Some of these metabolites are not produced by the host and are formed exclusively as by-products of microbial metabolism during the breakdown of certain dietary components. Advances in high-throughput omics

technology, particularly metabolomics and metagenomics, have contributed significantly to our understanding of the complex interplay between the immune system and nutrition. The metabolites of the GM act as critical signaling hubs for communication, with the immune system contributing significantly to the maintenance of homeostasis (4). Depending on the starting material, metabolites of the GM can be divided into those derived from ingested materials, host-generated metabolites, or those synthesized *de novo* (72). Based on chemical composition, the major classes of metabolites of the GM include short-chain fatty acids (SCFAs) as byproducts of microbial fermentation, secondary bile acids (BAs), choline metabolites such as trimethylamine N-oxide, tryptophan, and indole derivatives, as well as vitamins, neurotransmitters, and various lipids (73), of which SCFAs and secondary BAs have been repeatedly confirmed as key regulators of intestinal immunity that also affect systemic immunity.

BAs are metabolites derived from cholesterol, primarily synthesized as cholic acid and chenodeoxycholic acid in the liver and conjugated to taurine and glycine before excretion (74). More than 95% of the (conjugated) BAs that reach the intestine are absorbed and recycled to the liver, while the remaining portion undergoes transformation dependent on the intestinal microbiota, mainly by deconjugation but also by oxidation, epimerization, dehydroxylation, and esterification. The deconjugation depends on the activity of specific hydrolases encoded mainly by the genomes of the gram-positive bacterial genera *Clostridium*, *Enterococcus*, *Bifidobacterium*, and *Lactobacillus*, and partially by the gram-negative members of the *Bacteroidetes*. Dehydroxylation is predominantly carried out by abundant Clostridia, whereas oxidation and epimerization depend heavily on bacterial representatives of the genera *Bacteroides*, *Eubacterium*, *Peptostreptococcus*, *Ruminococcus*, *Bifidobacterium*, *Egghertella*, *Enterobacter*, and *Escherichia* in addition to Clostridia (75, 76). The abundance of possible enzymatic biotransformations allows for the formation of a highly diverse pool of secondary BAs in the gut that reflects the composition of the microbial community (76). At physiological concentrations, BAs derived from bacteria, such as deoxycholic acid and lithocholic acid, directly modulate intestinal immunity by affecting immune cell differentiation and activity (77, 78). The best-characterized targets of secondary BAs are Tregs and Th17 cells, and these metabolites also largely influence the balance between Th17 cells and Tregs in the GALT. Indeed, a derivative of lithocholic acid attenuates Th17 cell differentiation by interacting with the nuclear receptor RAR-related orphan receptor gamma (RORγt). Conversely, it also stimulates the differentiation of Tregs *via* upregulation of the *Foxp3* gene transcription in conjunction with another nuclear receptor, NR4A1, thereby establishing a tolerance-promoting milieu, which is in contrast to the pro-inflammatory activities of many other secondary BAs and their derivatives (76, 79).

It was found that BAs affect other lymphocyte subsets, in addition to Tregs and Th17 cells, such as cytotoxic T lymphocytes, B cells, Th1 and Th2 subsets of $CD4^+$ T cells, and also innate immunity cells, such as dendritic cells, macrophages, and NK cells (74). The pleiotropic effect depends on the binding of BA to several classes of receptors, of which binding to the farnesoid X receptor (FXR), G protein-coupled

receptor-1 (TGR5/GPBAR1; GPCR), pregnane X receptor (PXR), and vitamin D receptor (VDR) have been most extensively studied to date (76). The FXR receptor is abundantly expressed by macrophages, dendritic cells, and NK cells, so its overall activation has a major impact on gut innate immunity (80, 81). Activated FXR functions as a transcriptional regulator by binding to promoter regions of target genes in complex with the retinoid X receptor. Interestingly, FXR receptor expression is modulated by TLR9, a member of the PRR receptor class that senses microbes by recognizing their genetic material (82). The expression of GPBAR1 on immune cells largely overlaps with the expression pattern of FXR (81), whereas high expression of TGR5 is characteristic of lymph nodes (83). Signaling downstream of TGR5 is cAMP-dependent and interferes with the NF-κB and AKT-mTOR LIP pro-inflammatory signaling pathways, as well as STAT3 signaling in gastric cancer proliferation, which is an inflammation-coupled process. The PXR-dependent anti-inflammatory effect also interferes with NF-κB signaling (84), which is generally known as the most common target of various anti-inflammatory agents/metabolites.

The attenuation of the pro-inflammatory NF-κB pathway is also a prominent role of SCFAs produced by the GM, especially in the proximal segments of the colon (85). The term SCFAs refers to carboxylic acids with aliphatic tails of up to six carbon atoms, with the best-known representatives being acetate, propionate, butyrate, pentanoate, and malonate. These compounds are formed as by-products of microbial fermentation, which usually occurs in the final phase of metabolism of dietary fibers and also proteins (85, 86). The most abundant and biologically active are acetate (C2), propionate (C3), and butyrate (C4), with a 3:1:1 ratio of production in the intestine. Here, the production of acetate and propionate is mainly carried out by the representatives of the bacterial phylum *Bacteroidetes* (especially the genera *Bacteroides*, *Prevotella*, *Parabacteroides*, and *Alistipes*), while the representatives of the phylum *Firmicutes* are devoted to the production of butyrate, the most efficient species being *Faecalibacterium prausnitzii*, *Eubacterium rectale*, and *Eubacterium hallii*. Butyrate is also abundantly produced by the *Becteroidetes* species *Roseburia intestinalis* and *Anaerostipes butyraticus* (4, 87, 88).

In terms of immunomodulation, SCFAs are probably the most potent and pleiotropic class of metabolites of the GM, having as final targets the key mediators of intestinal homeostasis maintenance (the intestinal barrier, cells of innate and adaptive immunity), due to their distinct ability to influence not only the life cycle (proliferation, growth, differentiation, apoptosis), but also the activity of target cells (secretory phenotype, chemotaxis, metabolism) (85-87, 89, 90). The integrity of the intestinal barrier is modulated by SCFAs both structurally and functionally through several mechanisms. First, the barrier stability is enhanced by SCFAs, particularly butyrate, *via* upregulation of tight junction protein (occludin, zonulin, claudin) expression (72, 91, 92). SCFAs also promote the production of the mucus layer and antimicrobial substances such as defensins, cathelicidins, and C-type lectins by specialized epithelial cells, as well as bacteriocins by representatives of the GM (90). In parallel with stimulation of their

differentiation from monocytes, SCFAs also stimulate the synthesis of antimicrobial peptides in macrophages (87). While this process in intestinal epithelial cells depends on the activation of G protein-coupled receptor 43 (GPR43) and downstream signaling *via* the cell growth pathway involving the mitogen-activated protein kinase cascade, stimulation of defense peptides in macrophages occurs in response to metabolic reprogramming initiated by epigenetic changes in gene expression (93).

In epithelial cells, SCFAs also function as an energy source leading to ATP synthesis by β-oxidation in mitochondria (4, 94). This leads to significant oxygen consumption, which contributes to a hypoxic environment in the colon that favors the growth of obligate anaerobic commensals. Stimulation of hypoxia in response to SCFAs also occurs *via* the stabilization of the transcription factor Hypoxia-inducible factor, with many anti-inflammatory functions in the intestinal tract, particularly at the level of barrier integrity and innate immunity cells (neutrophils, macrophages, dendritic cells) regulation (4, 95-98).

Additionally, SCFAs also act on many other cell populations of innate immunity, such as ILCs, NK cells, eosinophils, and basophils, mainly by activating membrane-embedded GPCRs (88). One such example is the GPCR-dependent activation of the NLPR3 inflammasome leading to the production of IL-18, an important soluble mediator that regulates intestinal barrier turnover and stability (99). Neutrophil recruitment is also influenced by binding of SCFAs to GPCRs. On endothelial cells, this binding event leads to thr production of the chemoattractants CXCL1 and CXCL8, whereas the activation of GPCRs on neutrophils triggers chemotactic movements (100). Further on, in response to SCFA binding to GPCR, ILC3 subset proliferation is upregulated, but also the production of IL-22 *via* downstream AKT/STAT3 signaling cascade (101, 102). Interestingly, the binding of butyrate, but also of vitamin B3, to GPCR109A on antigen-presenting cells promotes the tolerogenic phenotype, leading to an increased proportion of IL-10-producing Tregs in the colon (103). SCFA-binding GPCRs in the gut predominantly include GPR43, GPR41, GPR109A, and OR51E2, which are constitutively (and abundantly) expressed on intestinal epithelial, innate inflammatory (activated macrophages, different ILC subsets, eosinophils) and tolerogenic antigen-presenting cells (88). Depending on the aliphatic side chain length, SCFAs differentially activate these receptors. For example, GPR43 has the largest affinity for acetate (C2) and propionate (C3), while butyrate readily activates GPR41 and GPR109A receptors (104).

Although GPCRs are abundantly expressed on innate immune cells under basal and inflammatory conditions, they are rarely found on lymphocytes. For example, only low expression of GPR43 has been detected on Tregs (88). However, SCFAs undoubtedly exert multiple effects on lymphocyte function, including effector, regulatory, and memory phenotypes (105). For example, in response to butyrate, differentiation of $CD4^+$ T cells into $Foxp3^+$ Tregs occurs, associated with increased expression of anti-inflammatory cytokines IL-10 and transforming growth factor-β (TGF-β). The secretory activity of $CD8^+$ cytotoxic T lymphocytes is also influenced by SCFAs, through the upregulation of CD25, IFNγ, TNF-α, and granzyme B expression (56, 85). In addition,

the differentiation and growth of the $CD4^+$ T cell subsets Th1 and Th17 can be induced by acetate and propionate acting on naïve T cells (72). In this regard, the differentiation of pro-inflammatory $CD4^+$ T cell phenotypes has been widely demonstrated under specific polarizing conditions and in response to elevated SCFA concentrations. Finally, important aspects of B cell functioning, such as differentiation to effector and regulatory phenotypes, IgA antibody production, and control of immunoglobulin class switching and somatic hypermutation, are also responsive to SCFAs, particularly butyrate and propionate, and in a concentration- and context-dependent manner (85). This wide variety of immunomodulatory effects of SCFAs on cells of adaptive immunity have epigenetic reprogramming as a common denominator. Indeed, SCFAs have recently been recognized as a new class of regulators of enzymes that perform acetylation (histone acetyltransferases, HAT) and deacetylation of histones (histone deacetyltransferases, HDAC). At target genes, SCFAs promote histone acetylation and act as potent inhibitors of HDAC, leading to overall chromatin decondensation facilitating transcriptional activation. For example, through HDAC inhibition in T cells, acetate readily promotes T cell growth and differentiation *via* mTOR-S6K kinase pathway (72). In addition to histone modifications, SCFAs were found to affect DNA methylation status, and this was the first pathway ever reported for an effect of SCFAs at the epigenome level (85).

The fact that the catalytic activity of DNA- and chromatin-modifying enzymes (various methyl- and acetyltransferases) crucially depends on the availability of substrates in the milieu is strongly exploited by the intestinal microbiota, which besides SCFAs also produces other classes of metabolites that serve as substrate reservoirs (methyl/acetyl group donors) for epigenetic modification reactions (85, 106). In this sense, B vitamins derived from the GM have been recognized as very potent modulators of epigenome status due to their involvement in folate and one-carbon metabolism (especially B2, B6, and B12), which generates the universal methyl donating intermediate S-adenosylmethionine (SAM) (107, 108). In particular, commensal species belonging to the genera *Lactobacillus* and *Bifidobacterium* are known to produce folate and other B-group vitamins in large quantities (109), which is one of the properties that promotes their use as probiotics. Additionally, vitamins A, D and C are recognized as regulators of host epigenome status.

The role of vitamins and Gut Microbiota in modulating immunity

Vitamins are essential micronutrients that play a key role in many physiological and biochemical reactions. They act as coenzymes and cofactors in numerous processes, including cellular function, energy metabolism, antioxidant protection, neurological function, and immune response. As humans lack the ability to biosynthesize most vitamins, they must be supplied exogenously through a balanced diet (110). However, some vitamins (from B and K group) can be synthesized by the members of GM and consequently absorbed in the colon. Recent studies have revealed a substantial link between vitamins and the GM composition, highlighting the significance of this relationship for immune system functioning and human health (111, 112). Namely, the

interplay between the GM and a host's immune systems is crucial for restraining inflammation and upholding intestinal homeostasis. This interaction not only governs the immune system within the intestines, but also has a significant impact on broader systemic immune mechanisms. The GM role in shaping both innate and adaptive immunity is pivotal in achieving immune homeostasis and maintaining overall health (113). Furthermore, a strong correlation between vitamin deficiency and microbiota dysbiosis has been established, which, in turn, has been associated with a range of pathological conditions (114). Inadequate levels of certain vitamins may prompt alterations in gut composition, fostering the excessive growth of pathogenic strains, ultimately giving rise to persistent inflammatory conditions (115). Although it is not yet fully understood whether the GM is the cause or an outcome of the disease, it has become evident that changes in communities of gut microbes can disrupt immune balance, potentially resulting in the development of various inflammatory conditions, including autoimmune diseases.

Vitamins can be categorized into two groups: fat-soluble vitamins (comprising A, D, E, and K) and water-soluble vitamins (including vitamin C and B vitamins). Vitamin A (retinol, retinal, retinoic acid) is a fat soluble vitamin whose key biological roles encompass vision support, growth promotion, and preservation of epithelial and mucous tissues. Vitamin A plays a pivotal role in the regulation of immunological functions. It influences the differentiation, maturation, and function of both the innate and adaptive immune system. This includes the regulation of macrophage and neutrophil functions, NK T cells, homeostasis of processes in bone marrow, and the proliferation of thymocytes (116). A deficiency of vitamin A may lead to changes in the microbial community, ultimately increasing vulnerability to GIT infections (117). In one study, retinoic acid supplementation hindered Norovirus replication in a murine model. This study showed that retinoic acid treatment increased *Lactobacillus sp.* presence during Norovirus infection (118). Moreover, retinoic acid administration elevated levels of *Allobaculum*, *Aggregatibacter*, *Bifidobacterium*, *Dialister*, and *Enhydrobacter* (112, 115). Additionally, vitamin A supplementation has been linked to reduced mortality and morbidity from infectious gastrointestinal diseases, possibly by altering the GM (117).

Vitamin D (cholecalciferol) has an important role in regulating calcium levels and in promoting bone mineralization. There are numerous studies proving a significant relation of the active form of vitamin D (1,25-dihydroxyvitamin D3) and the immune system (119). Actually, it was demonstrated that the nuclear vitamin D receptor (VDR) is expressed in many immune cells. These findings make vitamin D a potent immunomodulator, having a role in the modulation of pro-inflammatory T cells function and promotion of regulatory T cells. Therefore, vitamin D has been shown to be of crucial significance in the pathophysiology of autoimmune diseases, such as insulin-dependent type 1 diabetes mellitus (T1D), multiple sclerosis (MS), inflammatory bowel disease (IBD), systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA) (120). In addition, roles of vitamin D and the VDR in relation to the GM have also been explored. Several studies have found microbiome-modulatory effects of vitamin D and its potential

in maintaining immune homeostasis through interactions with the GM (112). For instance, in a particular study, the provision of weekly vitamin D supplementation (50,000 IU of ergocalciferol) over a span of 12 months led to elevated levels of SCFA in feces and an increased presence of SCFA-producing genera such as *Ruminococcus*, *Fecalibacterium*, and *Dialister* (115). Moreover, additional research demonstrated that vitamin D supplementation (a single dose of 40,000 IU once weekly for eight weeks) correlated with diminished intestinal inflammation in patients afflicted with active ulcerative colitis (UC) and Crohn's disease (CD). These findings strongly imply that the administration of vitamin D could potentially yield positive effects on a range of autoimmune disorders. This effect could be attributed to the alteration of the composition of intestinal bacteria, thereby increasing the abundance of potentially beneficial bacterial strains (117).

Vitamin E (tocopherol) is a fat-soluble vitamin that is well known for its antioxidant effects. It plays a role in controlling the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), while also influencing signal transduction processes (121). Vitamin E has also shown immunomodulatory effects on the development, functioning, and regulation of dendritic cells, macrophages, NK cells, T, and B cells. Natural antioxidants have been shown to influence the composition of the GM by scavenging excess free radicals and altering the GIT redox potential. Thereby, vitamin E can potentially reshape the GM community towards an anti-inflammatory state, thus helping to alleviate mucosal inflammation. A noteworthy correlation was observed between vitamin E intake and an elevated relative proportion of *Bacteroidetes*, accompanied by a reduction in *Firmicutes* at the phylum level. Additionally, increased vitamin E consumption was linked to a decline in *Proteobacteria*, a phylum housing various pathogens and exhibiting pro-inflammatory characteristics (112, 115, 122). This suggests that vitamin E intake might contribute to cultivating a more favorable GM composition by fostering the proliferation of beneficial bacteria.

Vitamin K (phylloquinone - K1, menaquinone - K2) is a fat-soluble vitamin that has a crucial role in blood coagulation and bone metabolism. Additionally, it can serve as a co-factor for certain plasma proteins, influencing immune responses, especially those modulated by T cells (123). Dietary vitamin K is mainly present in the phylloquinone form, yet it can also be in the form of menaquinones present in fermented foods or synthesized by GM. The menaquinone synthesized *de novo* by GM can serve as a co-factor for specific microbes that need it or its derivatives for growth, benefiting both the host and these microbes (112). This indicates that vitamin K promotes bacterial diversity and acts as a mediator in interactions between diet, GM, and the dynamics of the GM community. Apart from its established functions in blood coagulation and bone health, ongoing research is uncovering the potential of vitamin K to enhance intestinal well-being (124). Vitamin K has been linked to mitigating intestinal inflammation and oxidative stress, promoting the development of intestinal epithelial cells and modulating GM composition and its metabolites. These findings propose a potential utilization of vitamin K as an adjuvant in treating various intestinal disorders, such as IBD.

Vitamin C (ascorbic acid) plays a crucial role as both an antioxidant and a cofactor. Vitamin C acts as free radical scavenger, protecting cellular components from oxidative stress. Moreover, vitamin C promotes the absorption of iron and is essential for the synthesis of collagen, carnitine, and norepinephrine, which are fundamental for various physiological processes in the body. Due to the inability of humans to synthesize vitamin C, it is essential to obtain this vitamin through dietary sources. Furthermore, vitamin C plays a vital role in supporting and regulating the immune system (125, 126). In recent years, there has been significant research on its immunomodulatory properties and its impact on the GM, particularly in the context of oxidative stress. Overall, vitamin C exerts a diverse range of positive effects on cellular functions in both the innate and adaptive immune systems. It influences various components of the immune system, such as epithelial barriers, phagocytes, B and T lymphocytes, and inflammatory mediators (126). Additionally, as an essential vitamin for collagen synthesis, vitamin C plays a crucial role in maintaining the integrity of epithelial barriers. Moreover, it enhances keratinocyte differentiation, fibroblast proliferation, migration, and accelerates the wound healing process. Vitamin C exerts both anti-inflammatory and anti-microbial properties. It aids in promoting neutrophil migration to infection sites, facilitating efficient phagocytosis, and enhancing microbial killing. This multi-faceted role of vitamin C contributes significantly to the adequate immune response and defense against various respiratory and systematic infections. Several studies have shown that vitamin C has the capacity to modulate GM composition (127). In one study, it was demonstrated that vitamin C supplementation increased the alpha diversity (a measure of the diversity or richness of microorganisms within a specific sample or environment) and the SCFA levels (112). As an antioxidant, vitamin C also has a role in preventing oxidative damage within the intestinal tract, increasing the integrity of the epithelial barrier, and thus preventing the infiltration of harmful bacteria and toxins into the bloodstream. It also contributes to the gut homeostasis by promoting the growth and activity of beneficial bacteria, and may play a preventive role in gut-related disorders (127).

B vitamins

Vitamin B1 (thiamin) serves as a cofactor for several enzymes and it is required for the synthesis of nucleic acids, fatty acids, steroids, and aromatic amino acids. Its role is thoroughly described in energy metabolism and is linked to immune cells function. Particularly, it was showed that naïve B cells in Peyer's patches need vitamin B1 for ATP generation and differentiation to IgA-producing B cells, which play the main role in the GALT (128). Several gut bacteria (*Bacteroides fragilis*, *Prevotella copri*, *Clostridium difficile*, some Lactobacillus spp., *Ruminococcus lactaris*, and Bifidobacterium spp.) generate vitamin B1 in both free thiamine and thiamine pyrophosphate form, which play a crucial role in energy metabolism within the colon (128, 129). In addition, these findings indicate that thiamine synthesized by the GM plays a distinct role in shaping the composition or functionality of the GM.

Vitamin B2 (riboflavin), along with its active derivatives flavin adenine dinucleotide and flavin mononucleotide, serves as a cofactor in various enzymatic processes which are integral to the energy-producing reactions involved in metabolizing carbohydrates, fats, and proteins (130). Riboflavin is linked to the regulation of immune cell differentiation and generation of ROS, which represent crucial effector molecules in inflammation and immune responses. In addition, it was shown that riboflavin derivatives are important for the activation of MAIT cells. This population of T cells performs antigen-presentation and production of inflammatory cytokines like IFNγ and IL-17, and therefore takes part in the host defense against pathogens, but is also involved in the development of autoimmune and inflammatory diseases (128). Metagenomic analysis of GM suggests that certain bacteria like *Lactobacillus plantarum, L. fermentum*, *Bacteroides fragilis, Prevotella copri*, *Clostridium difficile*, and *Ruminococcus lactaris* can produce riboflavin, highlighting its potential role in the modulation of GM composition and function of the immune system.

Vitamin B3 (niacin/nicotinic acid/nicotinamide) is a precursor of nicotinamide adenine dinucleotide, a coenzyme which is crucial for a range of metabolic functions, primarily as a redox cofactor (130). Vitamin B3 displays anti-inflammatory characteristics, effectively diminishing the levels of pro-inflammatory cytokines including IL-6, IL-1, and TNF-α. Furthermore, vitamin B3 influences the differentiation of regulatory T cells, thus playing a role in maintaining immunological homeostasis (128). Various intestinal bacteria can synthesize vitamin B3, including *Bacteroides fragilis*, *Prevotella copri*, *Ruminococcus lactaris*, *Clostridium difficile*, *Bifidobacterium infantis*, *Helicobacter pylori*, and *Fusobacterium varium*. Therefore, vitamin B3 can influence the composition of the GM and also contribute to the functioning of colonic epithelial cells, thus aiding in the maintenance of the intestinal epithelial barrier. Through the suppression of inflammatory cytokine production in the colon, vitamin B3 has the potential to effectively mitigate inflammation observed in gastrointestinal disorders like IBD and CD (112).

Vitamin B5 (pantothenic acid) plays a crucial role as a necessary precursor for coenzyme A (CoA), which is a vital component in the synthesis of acetyl-CoA. This compound is pivotal in a range of metabolic pathways, including the citric acid cycle, the synthesis of neurotransmitters, and the oxidation of fatty acids (129, 130). Vitamin B5 contributes to the body's defense mechanisms by enhancing both innate and adaptive immunity. It was demonstrated that vitamin B5 triggers phagocytosis and the production of pro-inflammatory cytokines, such as IL-6 and TNF-α, and thereby induces Th1 and Th17 responses (128). A comprehensive genomic analysis of the human GM has highlighted that the ability for *de novo* synthesis of pantothenic acid is notably restricted within the genomes of *Bacteroidetes* and *Proteobacteria*. Various intestinal bacteria, including *Bacteroides fragilis*, *Prevotella copri*, *Escherichia coli*, *Corynebacterium glutamicum*, *Salmonella typhimurium*, and *Helicobacter pylori* can synthesize vitamin B5, suggesting its important role in the composition of GM.

Vitamin B6 (pyridoxine, pyridoxal, and pyridoxamine) is the precursor of the pyridoxal phosphate and pyridoxamine phosphate, which are important coenzymes that play essential roles in diverse cellular functions. In addition to its role in amino acid synthesis and breakdown, it also participates in the metabolism of fatty acids and carbohydrates (130). Vitamin B6 also plays a significant role in intestinal immune regulation by influencing the metabolism of the sphingosine 1-phosphate, the crucial lipid mediator that controls the gut-homing of lymphocytes (128). Within the mammalian GIT, bacteria engage in the synthesis of vitamin B6 utilizing *de novo* routes or salvage pathways. Comprehensive metagenomic investigations have revealed that certain bacteria possess the capacity for vitamin B6 biosynthesis, such as *Bacteroides fragilis, Prevotella copri*, *Bifidobacterium longum*, *Collinsella aerofaciens*, and *Helicobacter pylori*. Vitamin B6 deficiency is associated with the development of inflammatory diseases such as allergy, RA, and IBD. Research has revealed that a lack of vitamin B6 disrupts the balance between Th1 and Th2 responses, while also causing modifications in microbiota diversity, as well as in gut microbiota metabolites (128, 129).

Vitamin B7 (biotin) is a crucial coenzyme for various biochemical processes, contributing to glucose, amino acid, and fatty acid metabolism. Vitamin B7 also participates in the regulation of epigenetic mechanisms, specifically in the gene expression of the nuclear factor kappa B (NF-κB), a pivotal signaling molecule engaged in the generation of pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6 (130). In response to a deficiency in vitamin B7, the activation of nuclear transcription of NF-κB is triggered, suggesting that vitamin B7 inhibits the NF-κB activation and restrains the expression of genes linked to pro-inflammatory cytokines. Through metagenomic analysis, it has been revealed that certain bacteria, namely *Bacteroides fragilis, Prevotella copri*, *Fusobacterium varium*, and *Campylobacter coli* possess a biosynthesis pathway for vitamin B7 (128). Studies revealed that insufficient biotin levels result in disruptions to GM balance and the excessive proliferation of *Lactobacillus murinus*, ultimately contributing to the onset of alopecia (129, 131).

Vitamin B9 (folate) functions as a coenzyme in various metabolic reactions, including the synthesis of DNA and amino acids. Vitamin B9 is pivotal in cerebral methylation processes, preserving neuronal and glial membrane lipids, and influencing neurotransmitter metabolism such as serotonin and dopamine (130). Furthermore, vitamin B9 contributes to maintaining immune equilibrium by influencing the function of Treg and MAIT cells, thereby preventing the occurrence of excessive inflammatory responses (128). It has been determined that *Bacteroides fragilis*, *Prevotella copri*, *Clostridium difficile*, *Lactobacillus plantarum*, *L. reuteri*, *L. delbrueckii subsp bulgaricus*, *Streptococcus thermophilus*, *Fusobacterium varium*, and *Salmonella enterica* possess a biosynthesis pathway for folate. Thus, folate deficiency can significantly alter GM diversity.

Vitamin B12 (cobalamine) is a complex, cobalt-containing vitamin involved in various metabolic processes. Its active forms, methylcobalamin and adenosylcobalamin, are important methyl donors crucial for nucleic acid synthesis and protein and lipid

metabolism. It also acts as a cofactor for methionine synthesis by facilitating the recycling of the amino acid homocysteine to methionine. In addition, cobalamin is essential for the proper functioning of the central nervous system, as well as for the formation of erythrocytes (130). Studies have revealed that vitamin B12 operates as an immunomodulator, influencing immune responses via $CD8^+$ T cells and NK T cells (128). In the human gut, only a limited number of bacteria have the capability to synthesize vitamin B12 (around 20% of gut bacteria) (130). Metagenomic analysis has predicted the presence of a vitamin B12 biosynthesis pathway in certain bacteria, including *Bacteroides fragilis*, *Prevotella copri*, *Clostridium difficile*, *Faecalibacterium prausnitzii*, *Ruminococcus lactaris*, *Bifidobacterium animalis*, *B. infantis*, *B. longum*, and *Fusobacterium varium*. An inadequate or excessive intake of dietary vitamin B12 could potentially impact the composition of GM. Notably, vitamin B12 supplementation in humans has led to an increase in the relative abundance of *Prevotella*, while decreasing the abundance of *Bacteroides*.

B vitamins and inflammation-related disorders

The interplay of vitamins, the immune system, and the GM is a complex and dynamic relationship. The overlapping effects in epigenome reprogramming between different gut-microbiota derived metabolites (SCFAs and vitamins), but also the possibility that they bind to the same class of receptors (GPCRs), point to a degree of inherent redundancy in signaling networks at the interface between the GM and immune system in host homeostasis. Any deviation from the delicate functioning of the GM ecosystem disrupts this hub of immune signaling and sets the stage for the initiation of multifaceted pathogenetic pathways. In this context, vitamins from both food intake/supplementation and GM exert a profound immunomodulatory influence on the composition and functionality of the GM (112). This, in turn, positions vitamins as crucial agents in maintaining the gut homeostasis and overall health status. Consequently, deficiencies in vitamins have been linked to various inflammatory disorders (132).

Gastrointestinal disorders encompassing IBD, UC, and CD are characterized by an ongoing and chronic GIT inflammation, reflecting on mucosal immune dysregulation and changes in the composition of the GM (133). A study showcased significant differences in the gene abundance profile related to B vitamins between individuals with IBD and healthy controls (112). Persistent inflammation of the intestinal tract, accompanied by increased levels of pro-inflammatory cytokines, has been demonstrated to induce alterations in the absorptive capabilities of the epithelium (134). As a result, discernible differences in the GM composition seem to be present among IBD patients, who are frequently susceptible to deficiencies in essential vitamins, including B vitamins (135). Disruptions in vitamin absorption have resulted in significantly reduced vitamin B2 levels among individuals with IBD. Additionally, perturbations in vitamin B6 and B12 are frequently observed in IBD patients (132, 135). Given the common occurrence of vitamin insufficiencies among individuals with IBD, it becomes crucial to underscore the particular importance of B vitamins. Furthermore, the assessment of vitamin status in

individuals with CD revealed heightened depletion of vitamins B1, B2, B6, and B9 (135). Additionally, a link was identified between CD and decreased expression of microbial genes responsible for generating vitamins B1, B2, and B9 (112, 136). Another study demonstrated that vitamins B3 and B5 exhibited notable reductions in the feces of individuals with CD, possibly stemming from a diminished population of bacteria that produce these vitamins (136). The diminished levels of this vitamin were directly linked to a decrease in the presence of *Faecalibacterium*, known for its role in preventing mucosal inflammation (137). Inadequacies of B vitamins in GIT inflammatory conditions could stem from hindered absorption due to inflammation, a decrease in the surface area available for absorption, and changes in the composition of gut bacteria responsible for B vitamin production. Consequently, B vitamins might offer a viable adjunctive approach for addressing gut inflammatory disorders, given their potential to display anti-inflammatory properties, foster the growth of beneficial gut bacteria, and re-establish gut-immune homeostasis (138).

Members of the B vitamin group are crucial for the proper functioning of the nervous system, and their deficiency has been linked to various neurodegenerative disorders (139). Studies have shown that the GM influence has systemic effects as well, including the central nervous system (CNS) (140). This bidirectional gut-brain axis enables communication between the GM and the CNS, influencing the blood-brain barrier's permeability and, consequently, homeostasis within the CNS (141). Due to the fact that B vitamins serve as cofactors in various metabolic pathways for the GM, changes in B vitamin levels could potentially result in gut dysbiosis. As a result, this dysbiosis could disrupt immune homeostasis, creating an environment conducive to the colonization of pathogenic strains. Consequently, the modification of GM using B vitamins might offer an additional avenue for therapeutically addressing autoimmune diseases, such as MS (142, 143). This approach could entail enhancing anti-inflammatory responses, thus leading to a subsequent reduction of CNS inflammation. In a recent study (144), authors examined the alterations in microbiota composition within an animal model of multiple sclerosis, experimental autoimmune encephalomyelitis (EAE). This study involved both animals that did not receive any treatment and animals that were treated with a B vitamin complex (VBC) containing B1, B2, B3, B5, B6, and B12, where a clear change in the gut microbiota (GM) caused by EAE was shown, with the most significant change being a decrease in the abundance of *Prevotellaceae* compared to the healthy control animals. Numerous studies have highlighted a deficiency in *Prevotella* abundance among MS patients when compared to healthy individuals, indicating a potential role of *Prevotella* in promoting anti-inflammatory responses (140). At the peak of the EAE course, *Prevotella* abundance was notably higher in VBC-treated animals when compared to non-treated animals, indicating a potential effect of B vitamins in shaping the GM composition (144). Nevertheless, additional research is required to thoroughly investigate how GM communities interact with B vitamins in influencing the development of MS and EAE disease progression.

One study (145) proposed that an underlying disruption in vitamin B6 metabolism constitutes the fundamental biochemical basis for symptoms associated with Attention-deficit hyperactivity disorder (ADHD). The large intestine's normal microbiota plays a significant role in synthesizing vitamin B6, and key neurotransmitters such as norepinephrine, tryptophan, serotonin, dopamine, and gamma aminobutyric acid are processed or synthesized by enzymes reliant on the coenzyme pyridoxal phosphate, which represents the active form of vitamin B6. These findings may indicate a potential link between ADHD and vitamin B6 production by gut bacteria. Furthermore, reduced levels of serum vitamin B12 are linked to an elevated risk of Alzheimer's disease, Parkinson's disease, and mild cognitive impairment (143, 146). Vitamin B12 acts as a coenzyme for methionine synthase, an enzyme that converts homocysteine into methionine. Elevated plasma homocysteine levels are associated with various clinical manifestations, particularly affecting the CNS (147, 148). The disruption of homocysteine catabolism might stem from deficiencies in vitamin B6, B9, or B12. Additionally, the microbiota composition has the potential to impact circulating homocysteine levels, thereby playing a role in various neurodegenerative disorders. Studies indicate that increasing the consumption of these B vitamins could potentially decrease the risk of such conditions by reducing plasma homocysteine levels (149). B vitamins can potentially affect both the composition and operation of the GM by, among other mechanisms, promoting the metabolism of specific bacteria and inhibiting the colonization of others.

Conclusion

The GM encompasses a variety of microorganisms, including proteobacteria, bacteria, viruses, fungi, protists, and archaea, which are involved in multiple functions, including nutrient metabolism, vitamin production, immune system function, neurotransmitter production, drug metabolism, and brain-gut communication. Consequently, GM dysbiosis may play an essential role in the development of chronic diseases, so that research on the effects of the composition of GM on general well-being could help in the treatment of various inflammatory diseases and in the formulation of new therapeutic strategies. As primary vitamins produced by GM, B vitamins play a role in influencing immune responses and the composition of GM. Because certain bacteria rely on B vitamins from food or vitamins synthesized by other intestinal bacteria, competition for B vitamins may occur between the host and GM. The availability of dietary B vitamins has the potential to influence the composition of the GM and consequently modulate immune homeostasis. Although the profile of GM varies from person to person, diet can alter both its composition and function. However, more in-depth research is needed to fully understand the complex interplay between the GM, vitamins, and mechanisms of immune response to pave the way for innovative therapeutic strategies targeting a range of inflammatory diseases.

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Interakcija vitamina i mikrobiote creva kao ključni faktor u održavanju imunske homeostaze u gastrointestinalnom traktu

Marija Rakić[1#], Jelena Repac[1#], Tanja Lunić[1], Bojan Božić[1], Biljana Božić Nedeljković[1*]

Univerzitet u Beogradu, Biološki fakultet, Institut za fiziologiju i biohemiju „Ivan Đaja“, Grupa za imunologiju. Studentski trg 16, 11000, Beograd, Srbija

[#]Jednak doprinos

*Autor za korespondenciju: Biljana Božić Nedeljković; e-mail: biljana@bio.bg.ac.rs

Kratak sadržaj

Mikrobiota creva predstavlja raznovrstan ekosistem mikroorganizama uključujući proteobakterije, bakterije, viruse, gljive, protiste i arheje. Ovi mikroorganizmi učestvuju u sintezi vitamina, regulaciji imunskog sistema, produkciji neurotransmitera, metabolizmu lekova, kao i komunikaciji sa centralnim nervnim sistemom. Nedavna istraživanja pokazala su da dizbioza mikrobiote creva može dovesti do razvoja različitih hroničnih bolesti kod ljudi. Ispitivanje uticaja sastava mikrobiote creva na opšte zdravlje pruža uvid u nove pristupe u lečenju inflamatornih bolesti i razvoj inovativnih terapeutika. Jedna od ključnih uloga mikrobiote creva ogleda se u sintezi vitamina B grupe, za koje je pokazano da ispoljavaju imumodulatorna svojstva. S druge strane, određene bakterije mikrobiote creva metabolišu vitamine B grupe direktno iz hrane, što ih u potrebi za B vitaminima stavlja u konkurentni odnos sa ćelijama domaćina. Zbog toga, dostupnost vitamina B u ishrani može uticati na sastav mikrobiote creva, a samim tim i na održavanje imunske homeostaze. Ishrana predstavlja ključni modulator kako sastava, tako i funkcionalnih svojstava mikrobiote creva čiji se profil značajno razlikuje među individuama. Međutim, neophodna su dodatna istraživanja kako bi se razumela kompleksna interakcija između mikrobiote creva, B vitamina i mehanizama imunskog odgovora. Ovaj tip istraživanja može doprineti razvoju inovativnih terapeutskih strategija za širok spektar inflamatornih bolesti ljudi.

Ključne reči: Mikrobiota creva, Dizbioza, Imunski sistem, B vitamini, Homeostaza