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Implication of the Gut Microbiota in Metabolic Inflammation Associated with Nutritional Disorders and Obesity

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Scope: More than a decade ago, the concept of "metabolic endotoxemia" is elaborated on the fact that some bacterial components, classified as microbial associated membrane pathogens (MAMPs) can pass through the gut barrier and create a systemic low tone inflammation.

Methods and results: The translocation of lipopolysaccharides and its contribution to systemic inflammation are largely studied in murine models of obesity, allowing to unravel the molecular pathways involved in the process. Many different pathological contexts evoke the loss of gut barrier as an event contributing to inflammation and thereby driving metabolic and behavioral alterations.

Conclusion: This review describes the role of nutrition as a modulator of metabolic regulation and focuses on the contribution of the gut microbiota in the process of the production of a large diversity of bioactive metabolites. The two first sections of the review will be dedicated to the impact of nutritional disorders on both the gut microbiota composition and on metabolic inflammation. The last and more prominent section will describe the role of different nutrient-derived gut metabolites on the gut barrier integrity, metabolic inflammation, and peripheral tissue alterations during obesity or associated complications.

1. A Gut Microbial Dysbiosis is Associated with Nutritional Disorders

The gut microbiota composition and function can be influenced by many internal and external factors including genetic background, age, lifestyle, diet, or drugs use.[1] In this current review, we focus specifically on nutrition as a key environmental factor influencing both the gut microbes and the host health. Therefore, the first part describes the various gut bacterial signatures associated with the most well-known pathologies linked to nutritional disorders. Indeed, obesity is commonly associated with a set of pathologies including diabetes, liver diseases, or cardiovascular disorders (CVD).[2] Inflammation is one of the drivers of obesity-related complications.[3,4] Gut microbial changes (alterations of gut microbiota composition and/or function) have been associated with metabolic and inflammatory disorders, leading to a "dysbiotic state".[4] It is undeniable that dysbiosis occurs during obesity-related comorbidities, like hepatic diseases,[5] type 2 diabetes (T2D),[6,7] and CVD such as atherosclerosis, hypertension, and vascular dysfunction.[8] However, the characterization of the dysbiosis appears to be disease-specific, some diseases being associated with the presence of potentially pathogenic microbes, whereas others are characterized by a depletion of health-associated bacteria.[9]

In the context of hepatic diseases, a role for gut barrier dysfunction linked to dysbiosis is often proposed. Increased intestinal permeability may lead to the translocation of microorganisms or microbial components (like lipopolysaccharides [LPS]) that reach the liver through the portal vein. Indeed, circulating LPS, at a level much lower than the one observed in severe infection, can trigger low-grade inflammation and induce liver fat accumulation.[3] Interestingly, the abundance in *Bacteroides*, *Clostridium*, *Desulfovibrio*, or *Atopobium* spp. are positively correlated with LPS concentrations in the plasma and the liver, whereas some other bacteria (among them *Akkermansia* spp. or *Lactobacillus intestinalis*)[10] are negatively correlated with LPS levels. In addition, *Bacteroides* or *Ruminococcus* increase whereas *Prevotella* decreases in patients with non-alcoholic steatohepatitis (NASH).[5] NASH can progress to more serious disease stages, such as advanced fibrosis, a condition that has been associated with higher levels of *Bacteroides vulgatus* and *Escherichia coli*.[11] Actually, the presence of advanced fibrosis in non-alcoholic fatty liver disease (NAFLD) in the patients from this study is associated with a decrease of Gram-positive Firmicutes and an increase of Gram-negative Proteobacteria (including *E. coli*).[11]

Another example of obesity-related comorbidities associated with a dysbiotic microbiota is T2D. Accurately, the gut microbiota of T2D patients was also characterized by a decrease of several butyrate-producing bacteria and enrichment of op-

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portunistic pathogens including, *Bacteroides* spp., *Clostridium* spp., *Eggerthella lenta*, and *E. coli*[7,12] (for review, see ref. [13]). A mathematical model based on metagenomics profiles identified *Roseburia* spp. and *Faecalibacterium prausnitzii* as highly discriminant bacteria for T2D.[12] The reported anti-inflammatory properties of these bacteria and their benefits on the intestinal homeostasis prove the interest to modulate the gut microbiota as a means to regulate the inflammatory processes.[14,15] On this basis, the manipulation of the microbiome can be a therapeutic tool for the management of inflammation during obesity-associated metabolic alterations. It can be achievable through nutrients and dietary phytochemicals, or through treatment or promotion of certain bacterial metabolites.

2. Nutritional Disorders Drive Metabolic Inflammation during Obesity and Related Pathologies

The second part of this review summarizes the mechanistic studies demonstrating how nutritional disorders can drive metabolic inflammation through the gut microbiota and gut barrier alterations.

2.1. Gut Barrier Alterations Lead to Metabolic Endotoxemia

In 2007, Cani and collaborators showed that mice fed a high-fat diet (HFD) had higher blood LPS levels resulting in inflammation, fatty liver, and insulin resistance development.[3] The authors defined this condition as "metabolic endotoxemia" and tied its onset to the gut microbiota. The implication of intestinal bacteria in LPS-induced metabolic dysfunction was demonstrated in studies depleting the gut microbiota.[16,17] The precise mechanism by which the gut microbiota influence metabolic endotoxemia and obesity is not entirely deciphered. However, there is a consensus that gut microbial changes in response to unhealthy diets disturb homeostatic interaction between microbiota and the host.[18]

This interplay occurs at the gut barrier interface, which is composed of chemical and physical components. Antimicrobial peptides and secretory immunoglobulin A confer the chemical protection, and the physical barrier consists of a mucus layer and cell junctions sealing the paracellular space between epithelial cells.[19] Furthermore, the gut barrier is heavily laden with non-epithelial cells, like lymphocytes or macrophages, responsible for mediating an immune-type response.[20] All these elements participate to keep an adequate gut barrier function and integrity, and their alterations can lead to a number of disease states.[19] Indeed, increased gut permeability and reduced expression of genes encoding for tight junction proteins have been proposed as the trigger event for metabolic endotoxemia.[21] This hypothesis is reinforced by observational studies in humans, in which impairments in the tight junction are found in severely obese subjects.[22]

2.2. TLRs and NOD Participate in the Metabolic Inflammation in Obesity

The contact between microbiota and intestinal cells dictates which signals are sensed and which reactions are subsequently initiated. This dialog occurs through the so-called microbial-associated molecular patterns (MAMPs) that can specifically bind to pattern recognition receptors (PRRs) expressed in epithelial and immune cells.[23] PRRs can also recognize damage-associated molecular patterns (DAMs) released from the host cells.[23] PRRs are part of the innate immune response and, as such, control inflammatory and immunological responses. The best PRRs examples are the toll-like receptors (TLRs) and NOD-like receptors (NLRs).

One well-studied signaling pathway is the TLR4/MyD88/NF-κB triggered by LPS. In 2007, Cani et al. showed that 4-week LPS infusion was sufficient to trigger HFD-induced metabolic diseases such as obesity and diabetes, demonstrating the role of circulating LPS per se in metabolic dysfunction.[3] By using tools for gene deletion, it was confirmed that TLR4 deletion in HFD-fed mice exerts a protective effect against adipose tissue inflammation and insulin resistance.[24–26] In line with these results, mice deficient in CD14 (a key molecule in TLR4 signaling) turned to be resistant to inflammation upon a HFD or chronic LPS administration.[3] TLRs signaling also modulate tight junction proteins, thereby indirectly influencing host metabolism. In the case of TLR4, its activation has been associated with an increased intestinal permeability.[27]

Other TLRs with links with metabolic health are TLR2 and TLR5. The first binds LPS, lipoteichoic acids, and saturated fatty acids.[28] The role of TLR2 in metabolic dysfunction was evidenced by using TLR2-deficient mice, these mice being protected from insulin resistance and beta cell dysfunction induced by an obesogenic diet.[29] Besides, TLR2 also regulates the intestinal barrier function. Specifically, TLR2 deficiency triggers early tight junctions disruption, whereas therapy with TLR2 agonists restore gut barrier function in a murine model of colitis.[30] Regarding TLR5, the first evidence pinpointed that it may protect against metabolic syndrome as genetically deficient TLR5 mice exhibited hyperphagia and developed the main features of metabolic syndrome.[31] However, these results could not be reproduced by other authors.[32,33] Even if the studies discussed so far, particularly those related to TLR2 and TLR4, reported a detrimental response to their signaling, not all the studies point in this sense. Indeed, as it is forward presented, certain metabolites, like indole-3-propionic acid and proteins of probiotic bacteria are also ligands for TLR2 and TLR4, but in this case, their recognition has been linked with a protective response.[34,35] Thus, the TLRs signaling seems not to be a black or white matter, but instead a much more complex issue encompassing health and disease outcomes.

Lastly, the proteins NOD1 and NOD2 are members of the nucleotide-binding oligomerization domain-like receptors (NLRs) and induce inflammatory signals in response to bacterial peptidoglycan (PGN). Interestingly, mice deficient in NOD1 and NOD2 receptors are protected from the inflammation and insulin intolerance induced by an obesogenic diet.[36] The same study also showed that injections with mimetics of PGN activate NOD1 and cause acute systemic insulin resistance.[36]

2.3. The Endocannabinoid System Contributes to Metabolic Alterations and Inflammation

Several studies suggest that the interaction between gut microorganisms and the endocannabinoid system could participate

in the development of fat mass, inflammation and, gut barrier dysfunction (for review, see ref. [37]). The endocannabinoids present different affinities for the cannabinoid receptor 1 (CB1) and CB2, that are G-protein-coupled membrane receptors. Besides, endocannabinoids might act upon non-CB1, non-CB2 receptors.[38] For instance, endocannabinoids also interact with peroxisome proliferator-activated receptor-α (PPAR-α) and PPAR-γ, as well as with other G-protein-coupled receptor (GPR) or the transient receptor potential cation channel subfamily V member 1 (TRPV1; also known as vanilloid receptor 1).[37,38] Some compounds belonging to a large group of bioactive lipids, such as AEA (*N*-arachidonoylethanolamine), have been described as "gate openers" and contribute to gut permeability. AEA is a CB1 agonist and activates TRPV1.[37] In contrast, "gate keepers," such as PEA (*N*-palmitoylethanolamine), 2-AG (2-arachidonoylglycerol), 2-OG (2-oleoylglycerol), 2-PG (2-palmitoylglycerol) or PGD2-G (glycerol ester of prostaglandin D2) contribute to gut barrier and reduce intestinal inflammation.[37] PEA can activate PPAR-α whereas others, like 2-OG, can activate GPR119.[37]

LPS is able to regulate the production of endocannabinoids by immune cells, demonstrating a link between bacterial components and the endocannabinoid system.[39,40] In RAW264.7 macrophages, LPS decreases PEA biosynthesis by suppressing *N*-acylphosphatidylethanol-amine-specific phospholipase D (NAPE-PLD) transcription[39] and selectively stimulates AEA synthesis through interaction with the cell surface CD14.[40]

2.4. Some Specific Bacteria, or Their Membrane Components, Regulate the Metabolic Inflammation Observed upon Nutritional Disorders

Some probiotics have been shown to regulate the PRRs and the endocannabinoid system, thus resulting in beneficial effects on health. Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. Indeed, several strains of *Lactobacillus* and *Bifidobacterium* have shown metabolic benefits, most likely by affecting glucose homeostasis and reducing inflammation and hepatic steatosis. Also, new probiotics strains like *Bacteroides uniformis* 7771, *Pediococcus pentosaceus* LP28, or *Saccharomyces boulardii* have demonstrated an anti-obesity effect.[41–44] However, most of the studies describe the effects without analyzing the molecular mechanisms and signaling pathways involved in the beneficial effects of probiotics. For instance, it has been reported that *Lactobacillus plantarum* ameliorates the effects of an obesogenic diet in mice, through a mechanism that involves a bacteriocin that restores the intestinal epithelium.[45] Still, the precise signaling pathways activated by *L. plantarum* resulting in increased ZO-1 production (one tight junction protein) must be deciphered.

In addition to the effects reported with some specific strains, it has been demonstrated that bacterial components can also impact metabolic inflammation and disorders. In this way, Cavallari et al. showed that muramyl dipeptide (MDP, peptides derived from bacterial peptidoglycan) limits metabolic inflammation and reduces insulin resistance via NOD2 signaling.[46] Interestingly, they also demonstrated that MDP injections decrease adipose inflammation of mice fed a HFD.[46] Since MDP can be found in the wall of many bacteria, the authors proposed a MDP-based postbiotics approach in the context of metabolic inflammation. This approach consists to test secreted factors, cellular components or bacterial metabolites that can exhibit biological effects in the host.

The same concept is supported by recent data relating the interest of *Akkermansia muciniphila*. The first observations described how the oral administration of *A. muciniphila* restored the mucus layer thickness in mice on a HFD and reversed the diet-induced metabolic disorders[41]. The bacterium also contributed to the production of antimicrobial and increased the number of mucin-producing goblet cells.[47,48] Interestingly, *A. muciniphila* also influenced the endocannabinoid system since its administration in HFD-fed mice increased the levels of the so-called "gate keepers," an effect associated with improved gut barrier function and decreased metabolic endotoxemia.[47] Knowing that the pasteurized form of *A. muciniphila* was as or even more efficacious than the live bacteria, it was described that the Amuc_1100* proteins from the membrane of *A. muciniphila* interact with TLR2 and, most interestingly, that their administration in mice partially recapitulates the effects of *A. muciniphila* against obesity, insulin resistance, and gut barrier alteration.[34] Similarly, the polysaccharide A (PSA) from the capsule of *Bacteroides fragilis* has also reported beneficial effects in mice as it prevents intestinal inflammation by inducing IL-10 production in T cells.[49] Like *A. muciniphila*, the PSA from *B. fragilis* activates the TLR2 on CD4+ T cells to establish host-microbial symbiosis and suppress immune reaction.[50] These are two good examples that illustrate that TLR signaling can be associated with a beneficial health outcome.

In conclusion, nutritional disorders drive several mechanisms that can lead to metabolic inflammation and metabolic alterations in the whole body. Moreover, some bacteria, or their membrane component, seem also important to regulate these processes. As a consequence, we will address in the last part of this paper how secondary metabolites produced by the gut microbiota from different food can also affect the metabolic inflammation as well as the development and progression of metabolic complications.

3. Nutrients-Derived Metabolites Can Be Important Modulators of Metabolic Inflammation and Disorders

In this last part, we reveal how the production of specific nutrient-derived bacterial metabolites by the gut microbiota plays a role in the regulation of both metabolic inflammation and host metabolism. Indeed, the fermentation of some nutrients by the gut microbes produces a huge and diverse panel of metabolites having an impact on host physiology.[51] Emerging evidence demonstrated that metabolic disorders are characterized by alterations in the intestinal microbiota composition and its metabolites, as recently summarized in an elegant review.[52] At the molecular level, several mechanisms linking the activation of inflammatory pathways and impaired insulin action come into play. In this part, we report the metabolites produced by the gut microbiota from specific nutrient with a particular focus on their effect on inflammatory response altering the gut barrier integrity or inducing a metabolic response (summarized in **Figure 1**).

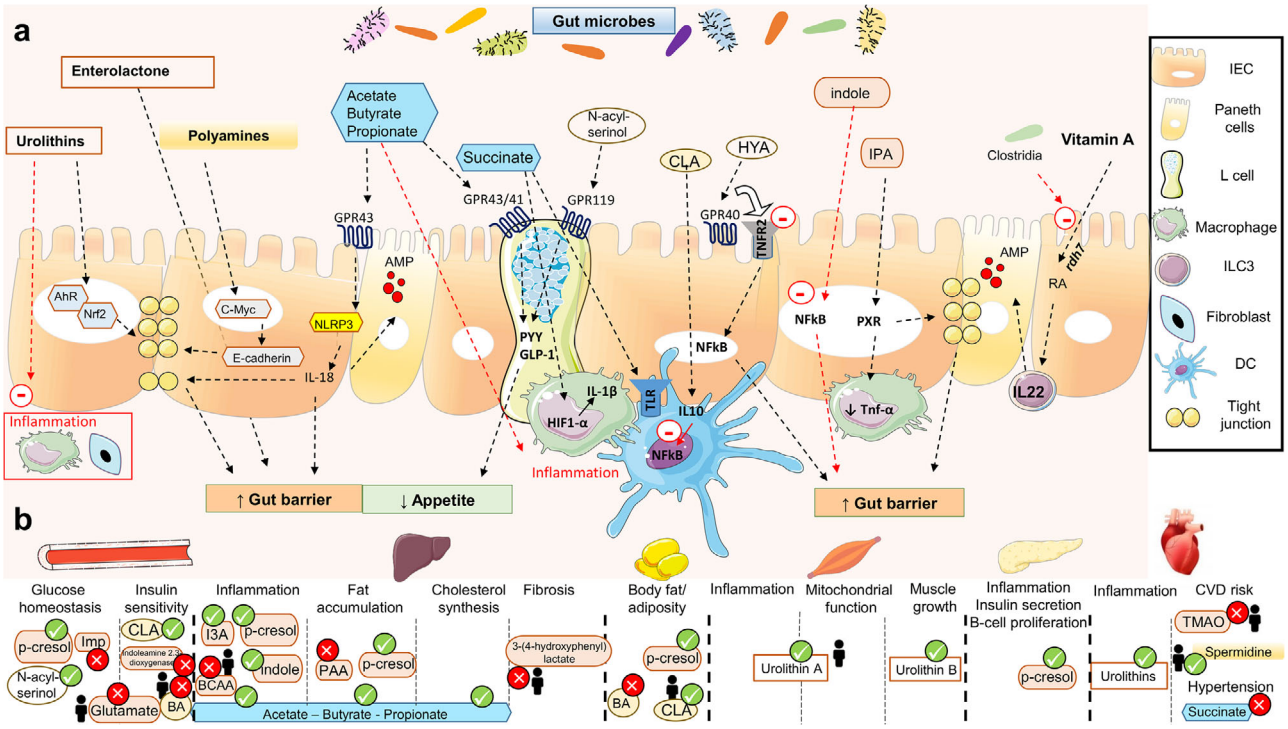

Figure 1. Molecular mechanisms driven by bacterial metabolite to regulate the gut barrier integrity, metabolic inflammation, and peripheral tissue alterations. a) Bacterial metabolites participate in the inflammatory response altering the gut barrier integrity and inducing peripheral metabolic alterations. From polyphenols, production of enterolactone could be beneficial for the gut barrier integrity, and urolithins synthesis can reduce intestinal inflammation. From carbohydrates, gut bacteria can produce SCFA that can modulate the gut barrier function, the intestinal inflammation or the production of gut peptides involved in the regulation of food appetite. However, succinate could enhance the intestinal inflammation. From fatty acids, gut microbes can produce metabolites (*N*-acyl-serinol, CLA or HYA); these ones can participate in the regulation of both gut inflammation and gut peptides synthesis for the regulation of food appetite. From phenols, gut microbes can produce some metabolites (such as indole or IPA) able to regulate the gut inflammation through NF-κB or PXR proteins, thus leading to the improvement of gut barrier function. Finally, gut bacteria can also modulate the production of vitamin-derived metabolite such as retinoic acid and in this way, participate in the regulation of antimicrobial peptides production. b). This part shows the reported beneficial or detrimental effects of bacterial metabolites on metabolism in various tissues. IEC, intestinal epithelial cells; ILC3, type 3 innate lymphoid cells; DC, dendritic cells; BA, bile acids; BCAA, branched-chain amino acids; CLA, conjugated linoleic acids; HYA, 10-hydroxy-*cis*-12-octadecenoic acid; Imp, imidazole propionate; IPA, indole 3-propionic acid; I3A, indole-3-acetate; PAA, phenylacetic acid; PXR, pregnane X receptor; CVD, cardiovascular disease; SCFA, short chain fatty acids; TMAO, trimethylamine-*N*-oxide. ↑ increased; ↓ decreased; beneficial effect; detrimental effect; human study. The figure was produced using Smart Servier Medical Art under the terms of the Creative Commons Attribution 3.0 Unported (CC BY 3.0).

3.1. Non-Digestible Carbohydrate-Derived Metabolites

Short-chain fatty acids (SCFA, mostly acetate, propionate, and butyrate) are well-known metabolites that can be produced upon fermentation of dietary fibers. SCFA target the GPR receptors present at the surface of intestinal epithelial cells (IEC). These compounds are the most widely investigated metabolites produced by the gut microbiota that influence host metabolism, as recently reviewed.[53] As a proof of causality, it has been demonstrated that supplementation of acetate, propionate, or butyrate to animals reduces hepatic inflammation and fat accumulation, cholesterol synthesis, and regulates appetite.[53] In co-cultures of adipocytes and macrophages, butyrate reduces the levels of pro-inflammatory cytokines, like does propionate on human adipose tissue explants.[54,55] SCFA also modulates the function of intestinal macrophages by reducing the levels of pro-inflammatory cytokines in LPS-treated macrophages or neutrophils through a down-regulation of histone deacetylases.[56,57] Consistently, sodium butyrate alleviated HFD-induced NAFLD in rats through activation of PPAR-α, that coincided with reduced content of histone deacetylases and the suppression of NF-κB-mediated inflammation.[58] In line with all these observations, mice deficient in a receptor coupled to GPR43 have an exaggerated inflammatory response in models of colitis, arthritis, and asthma.[59] In addition, the activation of GPR43 by acetate and propionate contributes to limit the expansion of adipose tissue in animals fed a HFD.[60] Moreover, acetate, propionate, and butyrate stimulate the secretion of the satiety hormones glucagon-like peptide 1 (GLP1) and peptide YY (PYY) through GPR41 and GPR43 receptors.[53]

Besides, the binding of these three SCFA to GPR43 on colonic epithelial cells leads to NLRP3 (NOD, LRR and, pyrin domain-containing protein 3) inflammasome activation.[61] This response enhances the production of IL-18 in IEC that ultimately improves the epithelial barrier integrity.[62] However, other authors have reported opposite findings on the regulation of NLRP3 inflammasome during obesity, that led them to collectively conclude that the NLRP3 inflammasome is a central player in the obesity-induced inflammation.[63,64] This conclusion is based on observations performed on mice deficient in Nlrp3

that were resistant to the development of HFD-induced obesity and were protected from obesity-induced insulin resistance.[63] Thereby, the expression of tight-junction has been linked with the production of SFCA.[65] Accordingly, some human studies have corroborated these observations. For example, the administration of arabinoxilo-oligosaccharides (AXOS) in overweight subjects produced dose-related changes in bacterial taxa and increased the fecal concentration of acetate, propionate, and butyrate that might explain the up-regulation of claudin-3 and 4 in colonic biopsies.[66]

However, some intermediate metabolites of SCFA synthesis pathway are not playing a beneficial role facing inflammation. For example, succinate is a metabolic-end product of some bacteria and a key intermediate in microbial propionate synthesis.[67] Succinate can stabilize the hypoxia-inducible factor-1a (HIF-1a) transcription factor in activated macrophages and in this way, increases the inflammation through an up-regulation of pro-inflammatory cytokine IL-1β.[68] In dendritic cells, succinate induces migratory responses and acts in synergy with TLRs for the production of pro-inflammatory cytokines.[69] Interestingly, elevated succinate was detected in rodent models of hypertension and metabolic diseases.[70]

3.2. Fatty Acid-Derived Metabolites

The interaction between dietary lipids and the gut microbiota has been recently summarized.[71] Long-chain fatty acids (LCFA) provided by the diet can be used as a precursor for the production of bioactive lipids. Some conjugated linoleic acids (CLAs) are first identified as microbial lipid metabolites generated by commensal lactic acid bacteria in the intestine of ruminants. However, the production of *trans* and conjugated metabolites from LCFA can also occur in the murine or human gut and could be associated with a potential effect on host lipid composition and metabolism.[72–75] Some CLA reduce adiposity, improve insulin sensitivity, and exert anti-inflammatory properties.[76] For instance, 10-hydroxy-*cis*-12-octadecenoic acid (HYA), a gut microbial metabolite of CLA, has a protective effect on epithelial barrier integrity by down-regulating the expression of TNFR2, through the GPR40-MEK-ERK pathway in Caco-2 cells treated with pro-inflammatory cytokines and a murine model of colitis.[77] In the same way, the *cis*-9, *trans*-11 isomer of CLA suppresses NF-kB activation and IL-12 production in dendritic cells through ERK-mediated IL-10 induction.[78] These data suggest the anti-inflammatory properties of some CLA that can be interesting in the context of metabolic diseases.[78]

In addition, the administration of a mixture of probiotic strains (VSL#3) modulated gut microbial diversity by producing CLA in the colon. The CLA target PPAR-Υ in macrophages suppressing the inflammatory response in a mouse model of colitis.[79] In humans, the potential interest of CLA in the management of metabolic disorders has been investigated. Indeed, 6 months supplementation with CLA in healthy, overweight, and obese adults induced a fat mass decrease in the legs and reduced the waist-hip ratio.[80]

Interestingly, functional metagenomics screening for NF-kB activators identified another metabolite produced by the human gut microbiome called commendamide (or *N*-acyl-3-hydroxypalmitoylglycine).[81] Commendamide resembles long-chain *N*-acyl-amides (a group of endogenous lipids) and activates GPRs, G2A/GPR132 that is implicated in disease models of autoimmunity and atherosclerosis. Moreover, based on bioinformatics analysis, Cohen and collaborators identified a microbial lipid, *N*-acyl-serinol, that is a GPR119 agonist able to regulate both metabolic hormones production and release from L-cells and glucose homeostasis.[82]

3.3. Cholesterol-Derived Metabolites

Bile acids (BA) are endogenous steroid molecules derived from cholesterol. The important role of BA in the context of obesity, T2D, dyslipidemia, and NASH is well described.[83] Primary BA are first produced in hepatocytes and converted into secondary BA by gut microbiota. So, microbes are responsible for the intestinal modification of BA but also for the regulation of hepatic enzymes involved in BA synthesis. Reabsorbed BA (95%) can return into the liver, and a small amount of BA escaping hepatic capture reaches the peripheral tissues via the systematic circulation. The animal studies available so far have shown that BA affect metabolism and energy expenditure, although the mechanisms are not entirely clear, and some conflicting results exist (for a review, see ref. [84]). BA are ligands for the nuclear receptors farnesoid X receptor (FXR) and the membrane-bound Takeda G protein-coupled receptor (TGR) 5, and coordinately regulate both metabolism and inflammation. The modulation of BA pool by gut-microbiota-based therapeutic strategies can be a tool for the treatment of inflammation associated with metabolic disorders.

In addition, human studies show that total BA concentrations increase in obese patients and correlate with body mass index.[83,85] Moreover, insulin resistance was associated with increased total BA concentrations, fasting tauro-conjugated BA, and glyco-chenodeoxycholic acid.[86] The gut microbiota transforms BA present in the intestines by different mechanisms, including the hydrolysis of conjugated BA by bile salt hydrolases (BSH).[83] For instance, BSH is active in *Lactobacillus, Bifidobacterium, Firmicutes, Enterococcus, Clostridium*, and *Bacteroides*, some of these bacteria being regulated during metabolic disorders.[83] Several studies describe changes in BA pool composition upon following nutritional intervention in obesity. Indeed, total fecal BA levels decreased by 26% after a weight-loss intervention based on very low calorie diet in obese postmenopausal women.[87] Following weight loss, the authors observed negative correlations between Clostridiaceae and lithocholic acid (LCA), and between isolithocholic acid and Clostridiaceae and *Ruminococcus*. On the contrary, *Eubacterium* positively correlated with LCA and isolithocholic acid, *Oscillospira* with cholic acid and *Faecalibacterium* with ursodeoxycholic and murocholic acids.[87] Another study reports that total fecal BA, cholic acid (CA), chenodeoxycholic acid (CDCA), and BA synthesis were higher in patients with NASH compared to healthy subjects.[88] In this paper, *Clostridium leptum* was positively correlated with fecal unconjugated lithocholic acid and inversely with unconjugated CA and unconjugated CDCA.[88] However, despite some correlation analysis, the causal relationship between obesity or metabolic disorders and BA pool is not established, large inter- and intra-individual variability in BA composition and diurnal variations

complexifying the interpretation of the data.[86] Studies in humans are needed to understand the directionality of interaction between BA and the gut microbiota during metabolic alterations.

3.4. Phenol-Derived Metabolites

A substantial amount of undigestible proteins can escape enzymatic digestion, undergo proteolysis by the gut microbiota, and thereby lead to the production of numerous bacterial metabolites. Among them, the phenolic compounds phenol, p-cresol, and indoles (including indole-3-acetate (I3A), indole-3-propionic acid (IPA), indole) are the major metabolites of bacterial fermentation of tyrosine, phenylalanine, and tryptophan.[89]

An emerging picture points toward the action of these metabolites as key metabolism modulators. In obesity, there is an increase in the intestinal indoleamine 2,3-dioxygenase activity, which shifts tryptophan metabolism from indole and IL-22 production toward kynurenine.[90] The knock-down of indoleamine 2,3-dioxygenase in mice improves insulin sensitivity and preserves the gut barrier, and decreases endotoxemia, and inflammation.[90] Our team has recently shown that the indole metabolite decreases the mRNA expression of pro-inflammatory mediators (IL-1β, Ccl2, and Cd14) in precision cut-liver slices (PCLS) from *ob/ob* mice, a model of NAFLD associated with chronic liver inflammation.[91] These findings were consistent with previous data demonstrating the beneficial impact of indole from *E. coli* in the IEC response to gastrointestinal tract pathogens.[92] These specific effects of indole were highlighted by the ability of the compound to attenuate NF-kB activation and to improve epithelial cell barrier properties.

Moreover, 1 mM of p-cresol, another metabolite produced by gut microbes from aromatic amino acid tyrosine, also prevented the LPS-induced up-regulation of the pro-inflammatory cytokines (*Ccl2* and *Il-1β*) in vitro in PCLS from *ob/ob* mice, after 4 h of incubation.[91] However, this result was to be considered with some caution since at higher concentrations and for a longer incubation (1.6 or 3.2 mM during one day), p-cresol appeared to be genotoxic for colonocytes by increasing DNA damage.[93] Other authors observed that chronic administration of p-cresol in HFD-fed mice reduced adiposity and fat liver accumulation, improved glycemic control, and stimulated insulin secretion and β-cell proliferation.[94] Interestingly, p-cresol reduced the expression of *tnf-α* and *il-6* in the pancreas of HFD-mice and up-regulated the expression of sirtuin-1 (a molecule associated with improving insulin sensitivity).[94] The authors hypothesized that the effects of p-cresol could be mediated, partly through a down-regulation of dual-specificity tyrosine phosphorylation regulated kinase (DYRK1A) involved in the stimulation of β-cell proliferation.[94]

Indole-3-acetate (I3A) and tryptamine, two tryptophan-derived metabolites, depend on the microbiota and are depleted under a HFD in mice.[95] Both metabolites limited the accumulation of fatty acids and the LPS-stimulated production of pro-inflammatory markers in macrophages. In hepatocytes, I3A beneficially regulated the inflammatory response under lipid loading through activation of aryl hydrocarbon receptor (AhR), demonstrating that gut microbiota can influence inflammatory response in the liver through this metabolite.[95] In vivo, intraperitoneal injection of indole-3-acetic acid ameliorated the HFD-induced systemic insulin resistance. This was associated with an improvement of oxidative and inflammatory stress in the liver. Notably, indole-3-acetic acid treatment limited the HFD-induced increases in mRNA expression of several markers involved in lipid metabolism in the liver.[96] IPA is also important for maintaining intestinal epithelial barrier integrity and regulating inflammation through the xenobiotic sensor called pregnane X receptor (PXR). IPA synthesis was linked to the presence of *Clostridium sporogenes*, and IPA served as a likely physiologic ligand for PXR and down-regulated enterocyte-mediated inflammatory cytokine TNF-α while up-regulating junctional protein-coding mRNAs.[35] The same authors exposed TLR4$^{+/+}$ and TLR4-deficient mice to the indomethacin (an anti-inflammatory drug) induced intestinal injury and showed that the presence of TLR4 is required for mediating the protective effects of IPA against the changes in permeability defects by indomethacin.[35]

Other metabolites are of interest in the context of metabolic diseases, and especially the progression of hepatic steatosis such as phenylacetic acid derived from the microbial degradation of phenylalanine.[97] Indeed, this bacterial compound induced liver steatosis and branched-chain amino acids (BCAA) use in primary human hepatocytes and mice. In addition, it was associated with a more pro-oxidant and immune stimulated status, but the molecular mechanisms remain to be investigated.[98] Interestingly, patients with steatosis enrolled in the FLORINASH study have low microbial gene richness, hepatic inflammation, elevated BCAA, and an imbalance in the aromatic amino acids and BCAA metabolism.[97]

Untargeted metabolome profiling also highlighted a significant association between 3-(4-hydroxyphenyl)-lactate metabolite, derived from tyrosine metabolism, and liver fibrosis in a human cohort.[99] However, there is no indication regarding a potent action of these metabolites on inflammatory markers.

3.5. Amino Acid-Derived Metabolites

Another metabolite produced by the gut microbiota is imidazole propionate, which is elevated in the context of metabolic alterations such as T2D.[100] This metabolite is produced from histidine and impairs the glucose tolerance and insulin signaling at the level of insulin receptor through the activation of p38ϒ Mitogen Activated Protein Kinase (MAPK).[100]

Glutamate has also been proposed a potentially harmful microbially modulated metabolite. Serum metabolomics analysis performed in a cohort of lean and obese subjects showed that glutamate, among all amino acids, was the most increased in obese individuals.[101] This change was explained by the abundance of *Bacteroides thetaiotaomicron*, a glutamate-fermenting commensal that was markedly decreased in obese individuals and was inversely correlated with serum glutamate concentration.[101] In addition, *B. thetaiotaomicron* reduced plasma glutamate concentration and alleviated diet-induced body-weight gain and adiposity in mice. Finally, the reduced circulating glutamate concentration was associated with the improvement of hyperglycemia, insulin resistance, and serum concentration of leptin and inflammation markers such as hsCRP after bariatric surgery.[101]

3.6. Amines-Derived Metabolites

Biogenic amines are small organic nitrogen compounds. They are formed by the decarboxylation of amino acids or by amination and transamination of aldehydes and ketones during normal metabolic processes in living cells (humans and microorganisms). Among the biogenic amines of interest are amines like trimethylamine and polyamines (such as putrescine, spermine or spermidine). The high levels of polyamines present in the intestinal tract may originate from the diet or be produced de novo by host cells and intestinal bacteria.[102] The analysis of colonic luminal metabolome in germ-free mice revealed that intestinal luminal concentrations of putrescine and spermidine, but not of spermine, are mainly dependent on colonic microbiota.[103] In addition, the concentration of polyamines may be regulated by some dietary fermentable fibers such as pectin, guar gum or fructans in the lower part of the gut.[104,105] An in vitro study showed that polyamines enhance E-cadherin transcription by activating c-Myc, thus promoting the function of the epithelial barrier.[106] Polyamines appear to be also interesting in the context of metabolic diseases in humans, since the intake of dietary spermidine inversely correlated with the incidence of cardiovascular disease.[107] The mechanisms of action underlying the beneficial effects of spermidine remained unclear, but some studies related an autophagy-dependent mechanism and potentially autophagy-independent processes through the regulation of arginine bioavailability and nitric oxide production, as reviewed by Madeo et al.[108]

Trimethylamine present in red meat is also a precursor for the trimethylamine-*N*-oxide (TMAO), produced by intestinal microbiota and exhibiting detrimental effects on host physiology.[109,110] Apoe−/− mice supplemented with TMAO showed enhanced macrophage levels of CD36 and SR-A1 (two macrophage scavenger receptors implicated in atherosclerosis).[110] This bacterial metabolite seems to promote atherosclerosis and is associated with a higher risk of cardiovascular disease in humans by regulating the cholesterol and sterol metabolism in macrophages.[109]

3.7. Polyphenol-Derived Metabolites

The gut-derived metabolites urolithins are produced from the natural polyphenol ellagic acid by *Gordonibacter* species and are reported to have anti-inflammatory properties in a wide range of tissues.[111] For instance, urolithin A (uroA) ameliorates TNF-α-induced inflammation in human colon fibroblasts,[112] and improves LPS-induced impairment of tight junction protein and inflammatory response in Caco-2 cells.[113] An elegant study strongly demonstrated the high potential of uroA to restore the gut barrier function and inflammation through direct activation of AhR by using a preclinical colitis model.[114] In a rat model of early diabetes, both uroA or uroB isoforms administration prevents the initial inflammatory response of myocardial tissue to hyperglycemia, by counteracting the increase of fractalkine (CX3CL1).[115] Also, uroA, uroB, and uroC improved inflammation in LPS challenged murine macrophages.[116] In mice, uroA attenuated the TNF-α-induced muscle mass loss by preventing the NF-kB signaling activation[117] whereas uroB enhanced the muscle growth and could reduce the muscle loss observed in some patho-physiological conditions, probably by targeting on the androgen receptor.[118] A first-in-human clinical trial recently showed that uroA administration to humans is safe and promotes skeletal muscle health by improving mitochondrial function.[119] However, its beneficial impact on the inflammation remained to be evaluated in humans.

Equol is an isoflavone metabolite that is produced from daidzin by several species (e.g., *Enterococcus faecium, Lactobacillus mucosae, Bifidobacterium* spp., *Coriobacteriaceae* spp., *Eggerthella* spp.).[51] This metabolite demonstrates a high affinity for the estrogen receptor β (ERβ). However, not all individuals produce equol from isoflavone, and it seems that only the equol producers metabotype could benefit from the potential health advantage of the compound. For instance, acute isoflavones intake improved carotid-femoral pulse-wave velocity, a marker of arterial stiffness, only in equol producer men.[120] Similarly, in postmenopausal women with metabolic syndrome, 8 weeks of a diet enriched with soy protein and aglycone isoflavones significantly improved the levels of C-reactive protein (CRP) only in equol producer women.[121]

In addition to isoflavones, lignans are another class of phytoestrogens, that could be metabolized into enterodiol or enterolactone by several gut bacteria (including *Enterococcus faecalis, Eggerthella lenta, Blautia producta, Eubacterium limosum, Clostridium scindens,* and *Lactonifactor longoviformis*).[51] In vitro, enterolactone protected intestinal barrier integrity after an inflammatory insult.[122] However, the impact of these metabolites on peripheral metabolic inflammation remains to be evaluated.

3.8. Vitamin-Derived Metabolites

Vitamin A is metabolized by IEC, which operates in an intimate association with microbes and immune cells. Indeed, the concentration of retinoic acid, a vitamin A metabolite, is modulated by *Clostridia* commensal bacteria that are able to suppress the expression of retinol dehydrogenase 7 (*Rdh7)* gene involved in the conversion of retinol into retinoic acid.[123] In addition, the deletion of *Rdh7* in IEC in genetic mouse models diminished retinoic acid signaling in immune cells and reduced the IL-22-dependent antimicrobial response.[123]

This part of the review highlights that the gut microbiota, through the production of several nutrient-derived metabolites can control the metabolic inflammation and metabolism in different organs. However, we are only at the onset of the identification of the whole panel of gut-derived metabolites and of the mechanism involved in the regulation of inflammation and metabolic disturbances occurring upon obesity.

4. Conclusion and Perspectives

The emergence of new studies linking nutrition, gut microbiota, and host health, highlights the key role of gut-related metabolites or bacterial components. Indeed, the gut microbiota can control energy metabolism and metabolic inflammation in peripheral tissues through the production of bacterial metabolites and/or by releasing bacterial components passing through the intestinal wall to reach the systemic circulation.

In addition to their impact on host metabolism and metabolic inflammation, some gut-derived metabolites can also play a crucial role in the control of cerebral functions, including the regulation of food intake, energy expenditure, brain development, or cognitive functions. This raises the interest to study the impact of dietary intervention, and gut-derived metabolites, in the management of psychological alterations that are also often present or associated with metabolic disorders.[124]

Additionally, other factors deserve more attention in future investigations, like for instance, the impact of physical activity. Indeed, the recent discovery that the microbiome of professional athletes differs from sedentary subjects in terms of composition and metabolites production raises the interest to study the impact of physical activity on gut microbiota in the context of metabolic diseases.[125] Further investigations based on metabolomics aiming to identify the diversity of compounds produced by gut microbiota are needed to better understand the host-nutrient-microbes interactions during metabolic disorders.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

Research data are not shared.

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