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Review

The gut microbiota at the service of immunometabolism

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Summary

The gut microbiota is implicated in immune system functions. Regulation of the metabolic processes occurring in immune cells is crucial for the maintenance of homeostasis and immunopathogenesis. Emerging data demonstrate that the gut microbiota is an actor in immunometabolism, notably through the effect of metabolites such as short-chain fatty acids, bile acids, and tryptophan metabolites. In this review, we discuss the impact of the gut microbiota on the intracellular metabolism of the different subtypes of immune cells, including intestinal epithelial cells. Besides the effects on health, we discuss the potential consequences in infection context and inflammatory bowel diseases.

Keywords: Immunometabolism, Metabolism, Microbiota, Immunity

Introduction

Metabolism involves cellular mechanisms to sustain life during physiological or pathological processes. More generally, it is about energy; the utilization of metabolic substrates, notably glucose, fatty acids (FAs), and amino acids (AA); and the balance between catabolism and anabolism that maintain cellular homeostasis. Metabolism is impacted by lifestyles and dietary habits, as illustrated by the increased rate of infection in malnourished populations (Blanton et al., 2016; Hashimoto et al., 2012) and the metabolic syndrome-related disease outbreak in overfed populations living in developed countries (Khare et al., 2020). In 2002, immunometabolism, a new branch of metabolism, was brought to light with the discovery of the link between CD28 activation and glycolysis in T cells (Frauwirth et al., 2002, p. 2). This field notably aims to understand the impact of immune cells on metabolism and, conversely, the metabolic needs of immune cells during homeostasis and pathological settings.

The microbiome is a major contributor to health, contributing to several development processes, homeostatic states and responses to pathogenic situations. Although the human

microbiome is composed of several microbiotas colonizing different niches (e.g., lung, skin, mouth, and vagina), the most studied is that in the gastrointestinal tract. It is composed of diverse microbial communities, approximately 100 trillion microorganisms (Sarin et al., 2019; Sender et al., 2016) and 150,000 microbial genomes (Pasolli et al., 2019). The gut microbiome is composed of bacteria, fungi, viruses, and protists (Iliev and Leonardi, 2017; Richard and Sokol, 2019; Shkoporov and Hill, 2019), and following millions of years of concomitant evolution, it is in symbiosis with its host. The gut microbiome plays a role in the modulation of both metabolism and immunity. Indeed, microbiome-derived molecules, either produced or transformed by microorganisms, are major actors in the dialogue with immune cells (Bäckhed et al., 2004; Cavallari et al., 2020; Lavelle and Sokol, 2020). Given the key role of the gut microbiome in physiological processes, any alteration in its composition or function could induce or participate in a disease (Pigneur and Sokol, 2016). The global role of the gut microbiota in immunity has been extensively reviewed (Honda and Littman, 2016; Rooks and Garrett, 2016). Here, we specifically discuss the effects of the gut microbiota on immunometabolism, and more precisely, on the intracellular metabolism of immune cells, in health and the potential consequences in diseases.

1- Immunometabolism: energy architecture to promote immunity

Immune system development/activation typically involves changes in the expression of large numbers of genes and results in the acquisition of new functions, such as high production of cytokines, lipid mediators, tissue-remodeling enzymes, ~~and toxic gases,~~ and the ability to migrate through tissues and/or undergo cellular division. Immune cells use the same pathways as other cell types to generate energy and ensure their effective functioning. The main metabolic pathways involved in immunometabolism are glycolysis, the TCA (tricarboxylic acid) cycle, the pentose phosphate pathway (PPP), FA oxidation, FA synthesis, and AA metabolism. Among the microbiome metabolism pathways impacting the metabolism of the immune cells, we will notably discuss short-chain fatty acid (SCFA) production, tryptophan metabolism, lipid metabolism and bile acid transformation. We present here the main actors we will discuss and

refer the reader to recent extensive reviews on this topic for more details (Bantug et al., 2018; Goodpaster and Sparks, 2017; O'Neill et al., 2016).

Glycolysis is a relatively inefficient way to generate energy, as the breakdown of one unit of glucose produces only 2 ATP molecules (Lunt and Vander Heiden, 2011). However, it is a source of intermediate molecules for other pathways, including the PPP, AA and FA metabolism pathways, and it can be swiftly activated, which is particularly relevant for proliferating cells such as T cells.

The **TCA cycle** (or Krebs or citric acid cycle), which takes place in mitochondria in eukaryotes, is a crucial engine in energy generation. Its primary substrate is acetyl-CoA produced either from pyruvate by oxidative decarboxylation at the end of glycolysis or from FA oxidation. It is estimated that the TCA cycle produces approximately 30 molecules of ATP from one molecule of glucose, including the consumption of the NADH and $FADH_2$ molecules produced by **oxidative phosphorylation** (OXPHOS) in mitochondria.

FA synthesis is required for the biosynthesis of the cell membrane, energy storage, and the generation of signaling molecules. This pathway is tightly dependent on mTOR (mammalian target of rapamycin) signaling and principally uses acetyl-CoA and other molecules provided by glycolysis, the TCA cycle and the PPP. **Beta-oxidation** is the main metabolic pathway for FA degradation. It leads to the production of acetyl-CoA, NADH and $FADH_2$ and then to a high amount of energy through the TCA cycle and OXPHOS. **Cholesterol** is an essential precursor of several biomolecules, including steroid hormones, vitamin D, oxysterols, and bile acids. **Bile acids** (BAs) are produced through the oxidation of cholesterol. These molecules are a good example of co-metabolism, as they are synthesized as primary and conjugated BAs by the liver (Fiorucci et al., 2018); they reach the intestine through the bile duct and are converted by gut microbiota enzymes into unconjugated secondary BAs. Most of the BAs are reabsorbed in the terminal ileum and go back to the liver, completing their entero-hepatic cycle. Beyond their role in lipid digestion, BAs are signaling molecules impacting many immune cell types through

several membranes and nuclear receptors, such as G protein-coupled bile acid receptor 5 (TGR5), farnesoid X receptor (FXR) and vitamin D receptor (VDR).

Besides their building blocks role for proteins, some **AAs** are also precursors of bioactive molecules that contribute to the maintenance of signaling pathways and metabolism (Liu et al., 2020). Glutamine and aspartate are involved in nucleotide synthesis (Cory and Cory, 2006; Gots, 1971). Glutamine can also feed the TCA cycle to produce energy or be a substrate for FA synthesis. Metabolites of other AAs, such as arginine and tryptophan, are involved in cell proliferation and growth processes (Badawy, 2019; Milner, 1985). For example, tryptophan can be metabolized into a myriad of active molecules through three major pathways: the kynurenine pathway, the serotonin pathway, and the indole pathway. While the first two pathways occur in mammalian cells, the last pathway takes place in the gut microbiota and leads to the production of aryl hydrocarbon receptor (AhR) agonists that exhibit immunomodulatory effects (Agus et al., 2018). The production of serotonin from enterochromaffin cells in the gut is under the influence of the microbiome. It is well established as a direct immunomodulatory factor, with seven receptor isoforms expressed on immune and non-immune cell types (Shajib and Khan, 2015).

2- Key roles of the microbiota in immune cells metabolism

Several recent studies highlighted newly discovered mechanisms by which the gut microbiota manipulates immunometabolism pathways in specific immune cell types (Figure 1).

Epithelial cells

The gastrointestinal epithelium is a highly relevant actor in host-microbiome interactions; it is one of the first players in the immune response, and intestinal epithelial cells (IECs) are now considered immune cells (Allaire et al., 2018). The energy metabolism of IECs, particularly in the colon, is largely dependent on the gut microbiota. Early in life, before adaptive immune system maturation, unidentified microbiota-derived molecules activate intraepithelial lymphocytes (IELs) and ILC3 through STAT3 phosphorylation in an IL-23 and IL-22 dependent

manner. In the absence of adaptive immunity, the IL-23-ILC3-IL-22-IEC circuit allows to control the gut microbiota, but the overactivated IL-22 production leads to an abnormal lipid metabolism with reduced expression of key lipid transporters (*e.g.* CD36, Fabp1/2), and reduction of triglycerides and free FA in serum (Mao et al., 2018). In germ-free mice, colonocytes exhibit an energy-deprived state with decreased activity of enzymes of the TCA cycle, β oxidation, and pyruvate dehydrogenase complex (Donohoe et al., 2011). Autophagy is induced by the energetic stress to maintain homeostasis in colonocytes. The SCFA butyrate produced by the gut microbiome in the colon is indeed the only source of carbon for colonocytes. After being transformed into butyryl-CoA, it diffuses passively into the mitochondria, undergoes β-oxidation, and feeds the TCA cycle and OXPHOS to produce energy and dampen autophagy activation (Donohoe et al., 2011). IECs are massively exposed to gut microbes and produce mucus and antimicrobial peptides to maintain a safety distance. Butyrate also promotes intestinal homeostasis by downregulating IDO1 expression and the kynurenine pathway in human IECs (Martin-Gallausiaux et al., 2018). The mechanisms involve a reduction in signal transducer and activator of transcription (STAT) 1 expression and HDAC (histone-deacetylase) inhibition.

Among the different IEC types, enterochromaffin (EC) cells are responsible for the production of serotonin (5-HT), which has major effects on immune cells (see below). Serotonin production in the colon is largely modulated by the gut microbiota and particularly spore-forming bacteria metabolites. The mechanisms are not fully elucidated, but it has been shown that upregulation of TpH1 expression, the rate-limiting enzyme in serotonin production, can be achieved by SCFAs (butyrate and propionate) and some secondary bile acids, such as deoxycholate produced by microbial biotransformation of cholate (Yano et al., 2015). Even if further investigations are needed, this data suggest that modulating the gut microbiota composition or directly administrating microbial metabolites could allow manipulating the production of serotonin from a therapeutic perspective.

Macrophages

Macrophages are in the first line during the immune response but also sense and respond to the microbiota to control it without initiating a detrimental inflammatory response. During the pathogenic response, the metabolic profile of activated macrophages varies as a function of the situation. In pro-inflammatory M1 macrophages, the TCA cycle is disrupted, leading to the accumulation of itaconate and succinate and a shift to glycolysis (Rodríguez-Prados et al., 2010; Tannahill et al., 2013). Itaconate is a major actor in immunometabolism that exhibits immunomodulatory and antimicrobial effects. It is also involved in the accumulation of succinate, as it directly inhibits its oxidation by blocking the activity of succinate dehydrogenase (SDH) (Lampropoulou et al., 2016). Succinate exhibits a pro-inflammatory effect through its oxidation that generates mitochondrial ROS (Reactive Oxygen Species) and leads to IL-1β production (Mills et al., 2016). Conversely, M2 macrophages have an intact TCA cycle and rely mostly on OXPHOS (Huang et al., 2014; Vats et al., 2006). The gut microbiota modulates these processes, notably through SCFAs. Butyrate, but not acetate or propionate, reprograms macrophage metabolism toward OXPHOS and lipid metabolism leading to an anti-inflammatory M2 phenotype (Scott et al., 2018). The detailed mechanisms are not identified but involve the up-regulation of genes involved in OXPHOS (such as mitochondrial ATP synthase and NADH dehydrogenase) and lipid metabolism (such as lipoprotein lipase) pathways. As an illustration, the impaired production of butyrate induced by antibiotics promotes the pro-inflammatory polarization of the intestinal macrophages, leading to a global dysfunction of the immune response (Scott et al., 2018). This might play a role in the association between antibiotics intake and the emergence of inflammatory and metabolic diseases (Cox et al., 2014; Hviid et al., 2011).

Innate lymphoid cells (ILCs)

There are different types of innate lymphoid cells (ILCs) characterized by the expression of specific membrane markers, transcription factors, and cytokine signatures. During their activation, ILCs change their energy metabolism profoundly to fit their new functions (Rolot and

O'Sullivan, 2020). Transcriptomic analysis suggests that ILC1s use mTOR signaling, ILC2s depend on sphingolipid and amino acid metabolism, and ILC3s rely on glycolysis (Gury-BenAri et al., 2016). The gut microbiota profoundly impacts ILCs function as demonstrated by the dramatic effects of antibiotics on the transcriptomic program of ILC1s, ILC2s and ILC3s (Gury-BenAri et al., 2016). ILC3 is the main type of ILC present in the gastrointestinal tract. These cells express RORγt, can produce IL-17 and IL-22, and are crucial regulators of inflammation, infection, microbiota composition, and metabolism (Klose and Artis, 2016). ILC3 functions, such as maintenance of the intestinal epithelium defense, depend on circadian signals mediated by the circadian regulator ARNTL (Aryl Hydrocarbon Receptor Nuclear Translocator Like). Light-dark cycles are key factors in this process, but the gut microbiota, which is known to be an actor in diurnal rhythmicity (Thaiss et al., 2016), also had some impact (Godinho-Silva et al., 2019). This signaling circuit connecting the gut microbiota, ILC3 and the intestinal epithelial clock is also involved in the regulation of the local and systemic lipid metabolism (Wang et al., 2017).

Gut microbiota-derived butyrate modulates ILC2 functions, inhibiting their uncontrolled activation and, consequently, their negative role in lung inflammation and asthma. The mechanism is not determined. Yet, the involvement of intracellular metabolism is supported by the induction of changes in mROS production and glycolysis by butyrate (Lewis et al., 2019). Moreover, the preferential use FAs over glucose by ILC2 to maintain their function in infection or nutritional stress suggest that butyrate might directly fuel the TCA (Wilhelm et al., 2016). Succinate, produced in the gut by protists and specific bacteria, stimulates the secretion of IL-13 by ILC2, through an indirect action on Tuft cells and IL-25 (Schneider et al., 2018). The role of succinate of other origin and its direct impact on ILC2 remains to be explored.

T cells

T cell metabolic plasticity is necessary to fit the permanently dynamic immune environment. The gut microbiota actively participates in this programming via ROS, SCFA, and BA production and REDOX signaling modification (Skelly et al., 2019). Effector and memory T cells have very different functions and needs and thus exhibit different metabolism. It is dominated by aerobic glycolysis in effector T cells and by FA oxidation and OXPHOS in memory T cells. Mitochondrial dynamics are evidence of these differences, with fused mitochondrial networks in memory T cells and punctate mitochondria in effector T cells (Buck et al., 2016). In addition, mitochondria are a critical component of T cell activation, mainly through ROS production (Sena et al., 2013). T cells stimulation via CD3 induces calcium influx that stimulates the function of pyruvate dehydrogenase and TCA enzymes. TCA cycling activates the mitochondrial electron transport chain and leads to the production of ROS, which are required for T cell activation. ROS act in synergy with calcium influx to elicit IL-2 expression, likely in an NF-κB and AP-1 dependent manner (Kaminski et al., 2010).

Microbiota-derived SCFAs boost $CD8^+$ T cell effector functions by modifying their cellular metabolism (Trompette et al., 2018). SCFAs produced by the metabolism of dietary fibers by the gut microbiota stimulate OXPHOS and mitochondrial mass in CD8+ T cells as well as their glycolytic capacity. The mechanisms are not yet fully understood, but a part of these changes depend on GPR41 activation. Besides, SCFAs can diffuse into the cytoplasm and serve as a substrate for FAO, leading to the production of Acetyl-CoA that fuel TCA and then OXPHOS. In activated CD8+ T cell, SCFAs, particularly butyrate, boosts the uptake and oxidation of FA, leading to a disconnection of the TCA cycle from glycolytic input and favoring OXPHOS through FA catabolism and glutamine utilization. This butyrate-induced cellular metabolism adaptation is required for the differentiation to memory T cells (Bachem et al., 2019).

In stress situations, a massive amount of acetate is released into the extracellular space via hydrolysis from acetyl-CoA. Acetate uptake by memory $CD8^+$ T cells expands the acetyl-CoA pool though TCA cycle and ATP citrate lyase activity and triggers the acetylation of GAPDH (Glyceraldehyde 3-phosphate dehydrogenase), a key enzyme in glycolysis. The prompt stimulation of glycolysis allows the rapid recall capacity of $CD8^+$ memory T cells (Balmer et al.,

2016). Although these phenomena were described with host cell-derived acetate, they are likely triggered, at least in the gut, by the massive amount of acetate produced by the gut microbiota.

SCFAs also exhibit significant effects on CD4+ T cells, notably regarding the generation of T helper (Th) 17, Th1 (Park et al., 2015), and regulatory T cells (Furusawa et al., 2013; Smith et al., 2013). The mechanisms involve the inhibition of HDACs and regulation of the mTOR pathway (a master regulator of cell growth and metabolism). This link has been recently shown with pentanoate (also known as valerate), a subdominant microbiota-produced SCFA that can stimulate the production of the anti-inflammatory cytokine IL-10 by providing additional acetyl-CoA for histone acetyltransferases and enhancing glycolysis and mTOR activity (Luu et al., 2019). Two mechanisms have been suggested regarding the activation of mTOR by SCFA (Figure 2). Through their action on energy production pathways, SCFAs induce the production of ATP and the depletion of AMP, which are inhibitor and activator of AMP-activated protein kinase (AMPK), respectively. Consequently, the inhibitor activity of AMPK on mTOR is repressed, thus leading to mTOR activation (Kim et al., 2016; Luu et al., 2019; Zhou et al., 2018). The second potential mechanism involves the HDAC inhibition activity of SCFAs. SCFAs, in association with P300/CBP (E1A binding protein p300/ CREB-binding protein), promote acetylation of the Ribosomal protein S6 kinase beta-1 (S6K1), which is a downstream target of mTOR, leading to more robust activation of the pathway (Park et al., 2015). Another layer of complexity has been indicated recently by showing that the effects of SCFAs on T cell metabolism are dependent on the inflammatory context (Trapecar et al., 2020).

BAs also have an essential impact on T cells. A derivative of lithocholic acid (LCA), 3-oxoLCA, inhibits the differentiation of Th17 cells by directly interacting with the transcription factor RORγt (Hang et al., 2019). Conversely, another derivative of LCA, isoalloLCA, promotes the differentiation of Treg cells. The mechanism involves the stimulation of OXPHOS and the production of mitochondrial ROS, which leads to the increased expression of FOXP3 by increasing the levels of histone (H3K27) acetylation in the Foxp3 promoter (Hang et al., 2019).

In the colon specifically, BAs act through the bile acid receptor Breg to regulate the function of RORγ+ Treg cells, which are significant players in the maintenance of colonic homeostasis (Song et al., 2020).

B cells

B cell differentiation into plasma cells and the production of antibodies require a massive amount of energy and a global change in cellular metabolism. Gut microbiota-derived SCFAs contribute to fuel the cellular energy engine at different levels for these processes and to boost antibody production. SCFAs are converted into acetyl-CoA that is integrated into the mitochondrial TCA cycle leading to the production of ATP. SCFAs also stimulate glycolysis in B cell via mTOR activation. SCFAs-derived acetyl-CoA is also a substrate in FA (particularly palmitic acid) synthesis, which is crucial for plasma cell differentiation and stimulates antibody production (Kim et al., 2016). Using an elegant strategy based on genetically engineered *Clostridium sporogenes* in germ-free mice, it has recently been shown that branched SCFAs, such as isobutyrate or isovalerate, can also modulate B cells functions. The absence of branched SCFAs production in manipulated mice led to an increased frequency of IgA+ plasma cells in the small intestine and increased levels of IgA bound to the surface of innate immune cells such as neutrophils, macrophages and dendritic cells (Guo et al., 2019). The mechanisms underlying these effects are not yet known.

B cells have a critical role in tolerance toward the gut microbiota through the production of immunoglobulins and the action of IL-10-producing Bregs (regulatory B cells). In Bregs, Rosser and colleagues recently showed that butyrate could divert tryptophan metabolism toward the serotonin pathway and the production of 5-hydroxyindole-3-acetic acid (5-HIAA) (Rosser et al., 2020). Surprisingly, 5-HIAA was shown to activate AhR in these cells, mediating the suppressive effect of butyrate supplementation in a rheumatoid arthritis model *in vivo*.

3- Consequences for disease pathogenesis

Immunometabolism at steady-state promotes homeostasis. However, the energy requirement of immune cells during inflammatory and infectious diseases is much higher, and their whole metabolism is altered. These processes are involved in both the pathogenesis of nonseptic inflammatory disorders and in the resolution of infection (Zmora et al., 2017). As seen above, the gut microbiota modulates immunometabolism and thus can have positive or negative effects on these pathological events (Figure 3).

Infections

Innate immune cells are the first bulwark against bacterial infection. TCRγδ (T cell receptor) IELs are key players in the initial response to intestinal pathogens. Their location within the intestinal epithelium and their motility, which are dependent on the gut microbiota, allow effective surveillance of the mucosal surface (Hoytema van Konijnenburg et al., 2017). Upon infection with Salmonella, the change in γδ IEL behavior is associated with the activation of OXPHOS and anaerobic glycolysis. These metabolic changes are dependent on mTOR and microbial cues in IECs. These data highlight a complex 3-partner system in which the gut microbiota, through action on IECs, induces the metabolic reprogramming of γδ IELs to boost their mucosal surveillance capacity (Hoytema van Konijnenburg et al., 2017). Metabolic changes are also observed in IECs in response to infection. In the early steps of infection with the mouse pathogen *Citrobacter rodentium*, downregulation of the TCA cycle and OXPHOS is observed in parallel with perturbations of cholesterol homeostasis. Cholesterol synthesis and import are activated simultaneously with cholesterol efflux suggesting either an atypical cholesterol metabolism regulation in IECs during stress or the manipulation of cholesterol homeostasis by *C. rodentium* (Hopkins et al., 2019). Starting on the second week following infection with *C. rodentium*, the Th17 cell response is activated and required to resolve the infection. These pathogen-induced Th17 cells rely on anaerobic glycolysis and OXPHOS, while commensal microbe-induced Th17 cells rely mostly on OXPHOS. These differences in bioenergetic profiles are associated with different mitochondrial morphologies and a pro-inflammatory phenotype in pathogen-induced Th17 cells (Omenetti et al., 2019). ILC3 are other

important actors in response to *C. rodentium*, notably through the production of IL-22 and IL-17A , which occur in an mTOR dependant way. The activation of mTOR complex 1 (mTORC1) leads to metabolic reprogramming of ILC3 characterized by enhanced glycolysis and mROS production. Mechanistically, mTORC1 activates HIF1α that supports RORgt and stimulates glycolysis. The downstream produced mROS contribute to stabilize HIF1α and to reprogram ILC3 metabolism toward the response to bacterial pathogens (Di Luccia et al., 2019).

During the response to infection and sepsis, T cells generate NOX2 (NADPH oxidase 2)-mediated ROS. Acetate can restore the oxidant-antioxidant imbalance in T cells during sepsis independently of GPR43 (G-protein-coupled receptor) and likely through upregulation of HDAC activity (Al-Harbi et al., 2018).

Mitochondrial FA metabolism in the intestinal epithelium is impaired in SIV-infected rhesus macaques and HIV (human immunodeficiency viruses)-infected patients. The underlying mechanisms involve altered PPARα (peroxisome proliferator-activated receptor) signaling and impaired FA β-oxidation of short- and medium-chain FAs, which correlate with an alteration in the intestinal epithelial barrier. Interestingly, these phenomena are modulated by the gut microbiome, as mitochondrial FA metabolism and intestinal barrier function can be rapidly restored by the administration of the probiotic *Lactobacillus plantarum*, independent of any effect on CD4+ T cells (Crakes et al., 2019).

Inflammatory Bowel Disease

The prominent role of the gut microbiota in the pathogenesis of inflammatory bowel disease (IBD) has been demonstrated by both human and animal studies (Britton et al., 2019; Lavelle and Sokol, 2020). The first actors in the interaction with the gut microbiota in IBD are epithelial cells. Alterations in the metabolism and functions of IECs are involved in IBD and lead to an impaired intestinal barrier and the translocation of microbial molecules, resulting in overactivation of the gut immune system. Some studies are now linking the gut microbiota to defective IEC metabolism in intestinal inflammation, notably through the Nod-like receptor (NLR) family. NLRX1 (nucleotide-binding oligomerization domain, leucine-rich repeat

containing X1) is a mitochondria-associated NLR with potential anti-inflammatory effects in colitis settings (Leber et al., 2018). NLRX1 is required to maintain balanced glutamine metabolism and barrier functions in IECs. The mechanisms are not clearly demonstrated, but it is suggested that NLRX1 may support the glutamine input into the TCA cycle through its metabolism into glutamate and α-ketoglutarate. The impaired glutamine metabolism in IECs leads to changes in AA availability for the gut microbiota, inducing changes in composition. Interestingly, the altered gut microbiota exhibits a pro-inflammatory effect by itself, as demonstrated by fecal microbiota transfer experiments (Leber et al., 2018). NLR-associated inflammasomes are also involved. SCFAs induce the activation of NLRP3 (NOD-like receptor family, pyrin domain containing 3) via their receptors GPR43 and GPR109a, inducing ion (K^+ and Ca^{2+}) efflux, and promoting epithelial repair in colitis setting through IL-18 maturation and release (Macia et al., 2015). The impact of SCFAs on macrophage polarization is also relevant in IBD. SCFAs depletion, for example, induced by antibiotics, favors an M1 hyperresponsive phenotype leading to an overproduction of pro-inflammatory cytokines and to the promotion of intestinal inflammation (Scott et al., 2018).

Previous studies have also shown a link between mitochondrial dysfunction and IBD. The expression of prohibitin 1 (PHB1), an inner mitochondrial membrane component, is decreased in colonic biopsies from IBD patients (Hsieh et al., 2006; Theiss et al., 2007). Moreover, mitochondrial dysfunction in IECs and notably in Paneth cells can induce ileal inflammation in mouse models (Jackson et al., 2020). Interestingly, Paneth cell abnormalities in patients with Crohn's disease correlate with alterations in both microbiota composition and oxidative phosphorylation in ileal tissue (Liu et al., 2016). Mechanistically, mitochondrial respiration impairment forces IECs to acquire a dysfunctional Paneth cell phenotype, leading to metabolic imbalance and inflammation (Khaloian et al., 2020). Moreover, mitochondrial impairment in Crohn's patients also involves a decrease in H_2S detoxification, while the relative abundance of H_2S-producing microbes is increased in the gut microbiota. The amount of *Atopobium parvulum*, a keystone microbiota species for H_2S production, correlated with Crohn's disease

severity (Mottawea et al., 2016). Overall, the net increase in H_2S due to increased microbiota production and decreased mitochondrial detoxification is involved in intestinal inflammation pathogenesis.

Conclusion

The effects of the gut microbiome on host immune cells is often examined with classical host-microbes interaction concepts, relying on the recognition of conserved microbial motifs by innate immunity sensors, or on the effect of microbial molecules on a host cell receptors. Despite the crucial role of the cellular metabolism in the ability to mount an appropriate immune response, the studies investigating how the gut microbiota directly affects it, remain scarce. Yet, the gut microbiota has a special relationship with metabolism, notably via the mitochondria due to their common origin. Mitochondria share a large part of their genome with bacteria, so communication and regulation can be evoked between these entities, which are only separated by the cell membrane (Lin and Wang, 2017). Host cell and gut microbiota are tightly connected in an inter-kingdom metabolic network that allows the proper functioning of mammalian meta-organisms. Each pathway is modulated by or depends on metabolites from others. It takes the collapse of only one path to compromise the normal operation. These processes are even more critical for immunometabolism, as immune cells need to react to stimuli rapidly and to reprogram their metabolism to exercise their functions. Gut microbiota-derived metabolites are genuinely represented in immunometabolism, with a particularly important role of SCFAs, BAs, and AA metabolites. Deciphering all the ins and outs resulting from the action of the microbiota on immunometabolism is highly challenging. Part of the complexity lies in the final effects of the microbial products, which can be different depending on the context or the cell types. The intrinsic diversity of the actors within the gut microbiota and the immune system brings an additional level of difficulty in the exploration of these interactions.

The next step in the understanding of host-microbiota cross-talk is to decipher more precisely the bidirectional impact of each metabolism on that of the partner in health and disease. This

effort is crucial to identify therapeutic targets that will be actionable through metabolic modulation. These innovative treatments may take several forms. The modulation of the gut microbiota to favor beneficial metabolite-producing bacteria is one possibility. However, an even more attractive strategy is to precisely impact host-microbiota metabolism by accurately supplementing a missing metabolite and/or inhibiting an overactivated pathway simultaneously on both sides of the interkingdom cross-talk.

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Author Contributions

C.M. and H.S. wrote the paper.

Declaration of Interests

The authors declare no competing interests.

Figure legends

Figure 1. Influence of the gut microbiota on immunometabolism

In **epithelial cells**, after being transformed into butyrate-CoA, butyrate diffuses passively in the mitochondria, undergoes β-oxidation, and feeds the TCA cycle and OXPHOS to produce energy. Butyrate also repress IDO1 via HDAC inhibition. In enterochromaffin cells, the metabolism of tryptophan into serotonin (5-HT) is stimulated by butyrate, propionate and bile acids. The production of 5-HIAA from 5-HT is stimulated by butyrate, and 5-HIAA binds AhR in Breg cells, inducing suppressive effects. SCFAs also increase glycolysis and mTOR activity in **B cells**. SCFAs-derived acetyl-CoA are also substrate in FA synthesis and β-oxidation, which is crucial for antibody production.. In **memory T cells**, butyrate activates β-oxidation,

while acetate-derived acetyl-CoA stimulates glycolysis through acetylation of GAPDH. In **effector T cells**, the secondary bile acid isoalloLCA stimulates OXPHOS and the production of mtROS, which leads to the upregulation of FOXP3 through histone acetylation in its promoter region, resulting in Treg differentiation. Another secondary bile acid, 3-oxoLCA, interacts directly with RORγt and inhibits the differentiation of Th17 cells. Pentanoate stimulates glycolysis and mTOR activity and leads to the production of acetyl-CoA, which feeds histone acetyltransferase activity and IL-10 production. SCFAs also boost $CD8^+$ T cell effector function via an increased glycolytic capacity, OXPHOS and mitochondrial mass. In **macrophages**, butyrate promotes OXPHOS activation and the anti-inflammatory M2 phenotype. The impaired production of butyrate can be involved in the pro-inflammatory polarization of the intestinal macrophages, leading to a global dysfunction of the immune response. In M1 macrophages, the TCA cycle is broken, succinate and itaconate accumulate, and glycolysis dominates energy production. The accumulation of succinate generates mtROS and leads to IL-1β production. Itaconate exhibits immunomodulatory and antimicrobial effects. In **ILC3s**, the gut microbiota influences circadian gene expression, which favors STAT3 phosphorylation during development and modulates FA transport in IECs. Succinate, produced in the gut by protists and specific bacteria, stimulates the secretion of IL-13 by **ILC2**, through an indirect action on Tuft cells and IL-25.

Figure 2. Mechanism of activation of the mTOR pathway by SCFA

A. Through their action on energy production pathways, SCFAs induce the production of ATP and the depletion of AMP, which are inhibitor and activator of AMP-activated protein kinase (AMPK), respectively. Consequently, the inhibitor activity of AMPK on mTOR is repressed, thus leading to mTOR activation. **B.** SCFAs, in association with P300/CBP, promote acetylation of the Ribosomal protein S6 kinase beta-1 (S6K1), which is a downstream target of mTOR, leading to more robust activation of the pathway with RPS6 (Ribosomal Protein S6) phosphorylation and inhibition of 4EBP (Translation initiation factor 4E binding protein) phosphorylation. ULK1: Unc-51 Like Autophagy Activating Kinase 1).

Figure 3. Immunometabolism and the microbiota in diseases

Infections. Upon infection with *Salmonella*, γδ IEL behavior changes are associated with activation of OXPHOS and anaerobic glycolysis and boost epithelial barrier protection. This response is dependent on mTOR and microbiota signals. Metabolic changes are also observed in IECs in response to *Citrobacter rodentium*, with downregulation of the TCA cycle and OXPHOS. In parallel, IECs present a dysregulation of cholesterol homeostasis. During this infection, pathogen-induced Th17 cells rely on glycolysis and OXPHOS, while commensal microbe-induced Th17 cells rely mostly on OXPHOS. ILC3 are other important actors in response to *C. rodentium*, notably through mTORC 1 activation (mTORC1) that leads to HIF1α activation that supports RORgt and stimulates glycolysis. In parallel, the downstream produced mROS contribute to stabilizing HIF1α. Metabolic reprogramming of ILC3 permits to produce IL-22 and IL-17A to sustain immune response. These differences in bioenergetic profiles are associated with different mitochondrial morphologies. During the response to infection and sepsis, T cells generate NOX2-mediated ROS. Acetate can restore the oxidant-antioxidant balance in T cells in this setting and likely through the upregulation of HDAC activity. During pathogen infection, TLR engagement in macrophages induces the recruitment of TRAF6 to mitochondria, leading to an increased production of ROS that is involved in response to intracellular pathogens. In SIV- and HIV-infected individuals, the intestinal epithelium presents altered PPARα signaling and FA β-oxidation, which correlates with an alteration in the intestinal epithelial barrier that can be restored by microbiota-derived factors.

IBD. The altered microbiota produces an insufficient amount of SCFAs, leading to defective activation of NLRP3 and, subsequently, to inadequate production of IL-18 that normally promotes epithelial repair. Defect in SCFAs promotes M1 polarization leading to the production of pro-inflammatory cytokines promoting intestinal inflammation. An alteration in the metabolism and functions of IECs, notably Paneth cells, is observed in IBD. It is linked to altered microbiota signals leading to inhibition of OXPHOS. The accumulation of pro-

inflammatory H_2S is observed in IBD. It is connected to the increased H_2S production by the abnormal microbiota associated with the impairment in mitochondrial detoxification. *Atopobium parvulum* is a keystone microbiota species for the production of H_2S.

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Highlights and eTOC blurb

The gut microbiota is implicated in immune system functions. Regulation of the metabolic processes occurring in immune cells is crucial for the maintenance of homeostasis and immunopathogenesis. Michaudel & Sokol focused on emerging data demonstrating that the gut microbiota is an actor in immunometabolism, notably through the effect of metabolites.

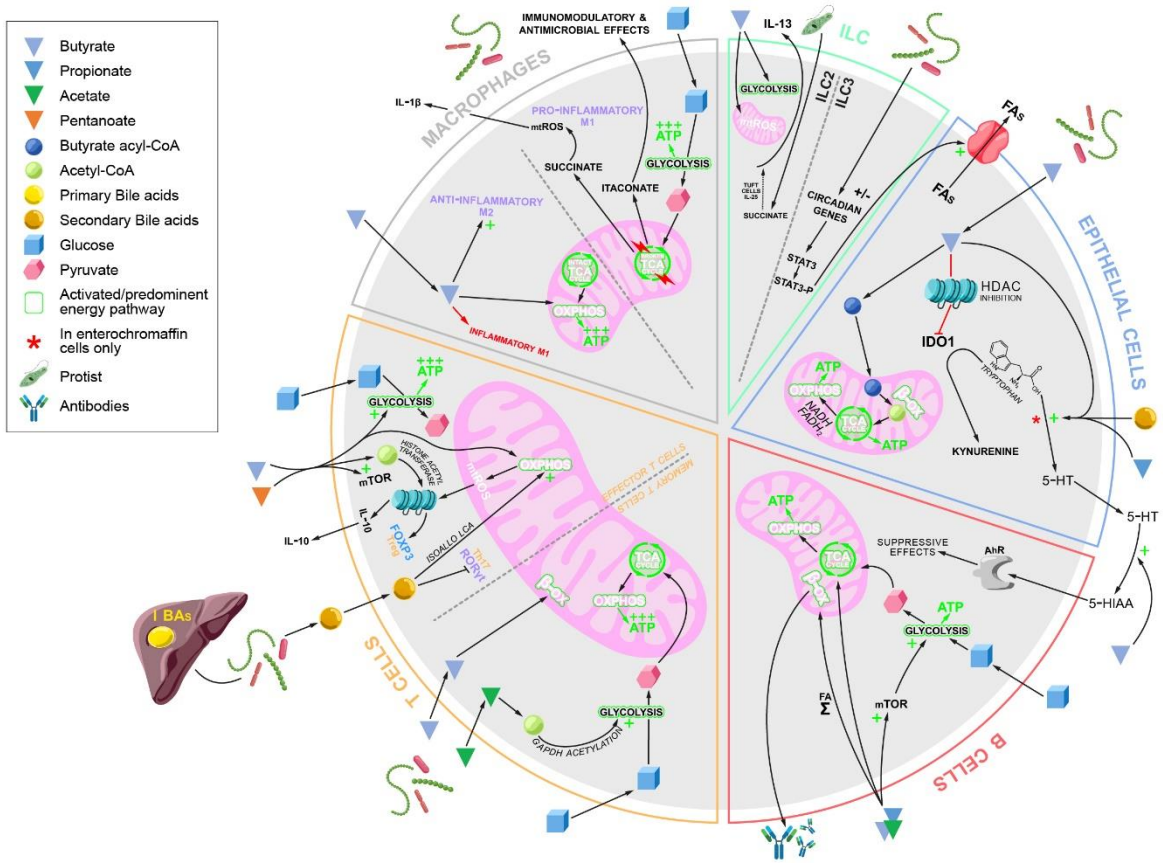

Figure 1. Influence of the gut microbiota on immunometabolism

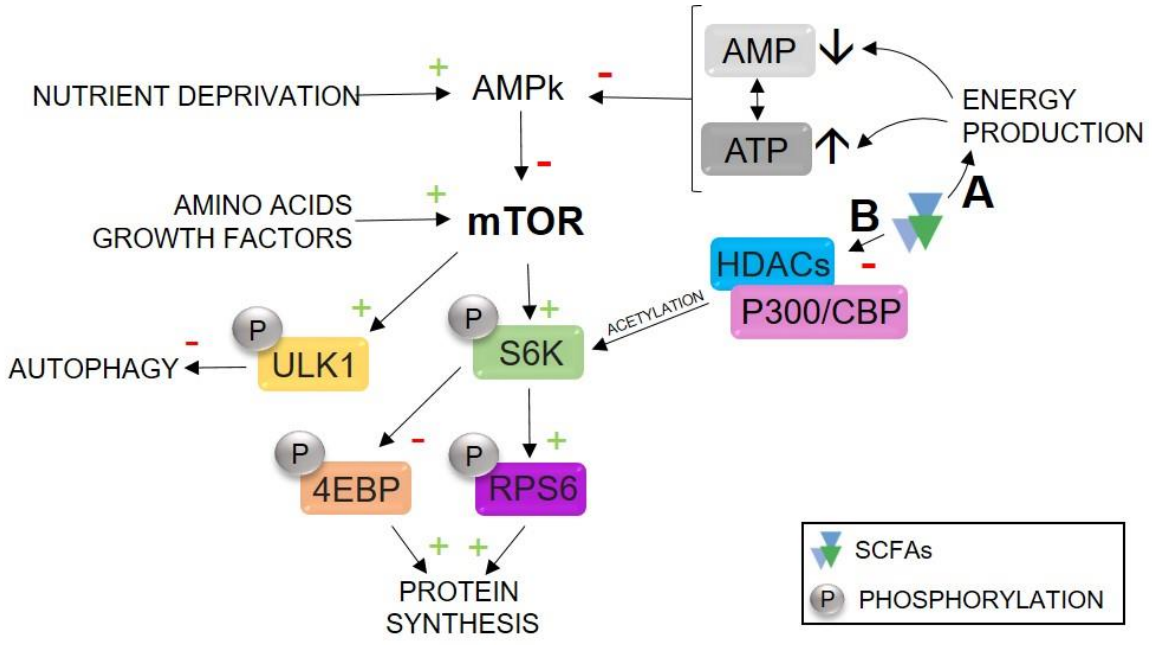

Figure 2. Mechanism of activation of the mTOR pathway by SCFA

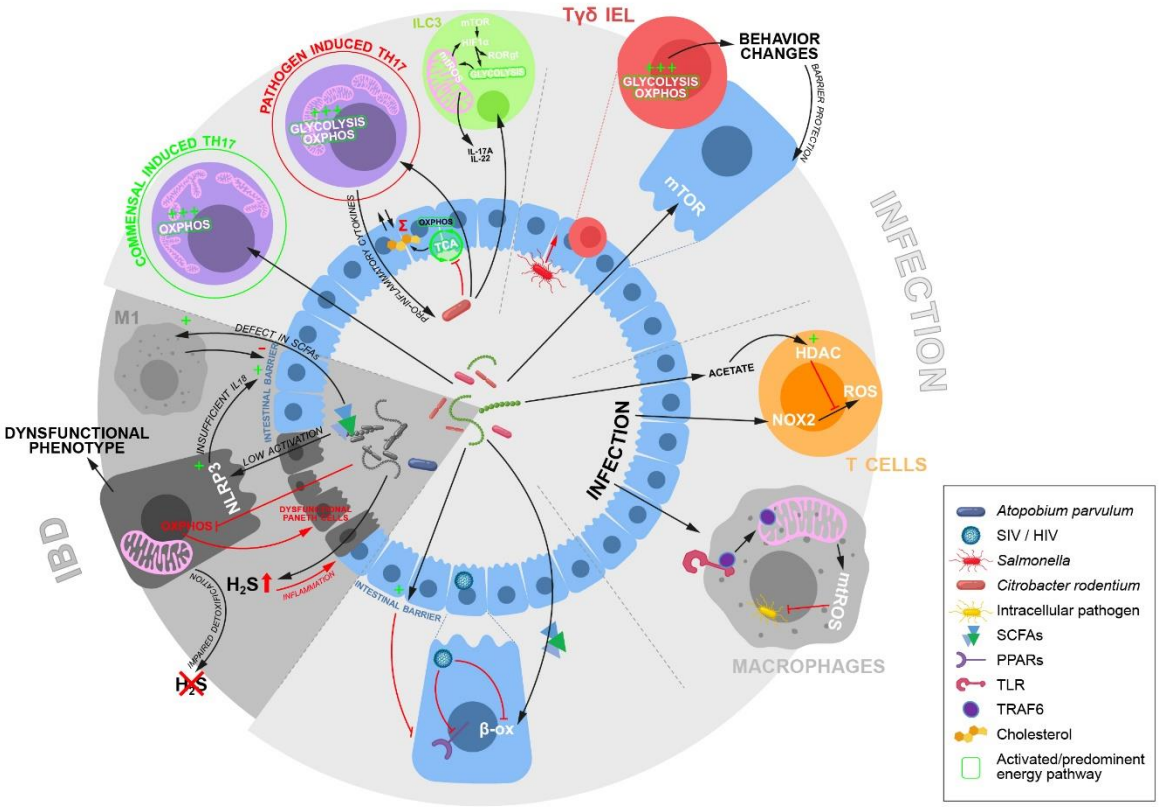

Figure 3. Immunometabolism and the microbiota in diseases