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Review

## The gut microbiota at the service of immunometabolism

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## 19 Summary

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

28

29 *Keywords: Immunometabolism, Metabolism, Microbiota, Immunity*

## 30 Introduction

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

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

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

## 60 1- Immunometabolism: energy architecture to promote immunity

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

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

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

78 The **TCA cycle** (or Krebs or citric acid cycle), which takes place in mitochondria in eukaryotes,  
79 is a crucial engine in energy generation. Its primary substrate is acetyl-CoA produced either  
80 from pyruvate by oxidative decarboxylation at the end of glycolysis or from FA oxidation. It is  
81 estimated that the TCA cycle produces approximately 30 molecules of ATP from one molecule  
82 of glucose, including the consumption of the NADH and FADH<sub>2</sub> molecules produced by  
83 **oxidative phosphorylation** (OXPHOS) in mitochondria.

84 **FA synthesis** is required for the biosynthesis of the cell membrane, energy storage, and the  
85 generation of signaling molecules. This pathway is tightly dependent on mTOR (mammalian  
86 target of rapamycin) signaling and principally uses acetyl-CoA and other molecules provided  
87 by glycolysis, the TCA cycle and the PPP. **Beta-oxidation** is the main metabolic pathway for  
88 FA degradation. It leads to the production of acetyl-CoA, NADH and FADH<sub>2</sub> and then to a high  
89 amount of energy through the TCA cycle and OXPHOS. **Cholesterol** is an essential precursor  
90 of several biomolecules, including steroid hormones, vitamin D, oxysterols, and bile acids. **Bile**  
91 **acids** (BAs) are produced through the oxidation of cholesterol. These molecules are a good  
92 example of co-metabolism, as they are synthesized as primary and conjugated BAs by the  
93 liver (Fiorucci et al., 2018); they reach the intestine through the bile duct and are converted by  
94 gut microbiota enzymes into unconjugated secondary BAs. Most of the BAs are reabsorbed in  
95 the terminal ileum and go back to the liver, completing their entero-hepatic cycle. Beyond their  
96 role in lipid digestion, BAs are signaling molecules impacting many immune cell types through

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

99 Besides their building blocks role for proteins, some **AAs** are also precursors of bioactive  
100 molecules that contribute to the maintenance of signaling pathways and metabolism (Liu et al.,  
101 2020). Glutamine and aspartate are involved in nucleotide synthesis (Cory and Cory, 2006;  
102 Gots, 1971). Glutamine can also feed the TCA cycle to produce energy or be a substrate for  
103 FA synthesis. Metabolites of other AAs, such as arginine and tryptophan, are involved in cell  
104 proliferation and growth processes (Badawy, 2019; Milner, 1985). For example, tryptophan  
105 can be metabolized into a myriad of active molecules through three major pathways: the  
106 kynurenine pathway, the serotonin pathway, and the indole pathway. While the first two  
107 pathways occur in mammalian cells, the last pathway takes place in the gut microbiota and  
108 leads to the production of aryl hydrocarbon receptor (AhR) agonists that exhibit  
109 immunomodulatory effects (Agus et al., 2018). The production of serotonin from  
110 enterochromaffin cells in the gut is under the influence of the microbiome. It is well established  
111 as a direct immunomodulatory factor, with seven receptor isoforms expressed on immune and  
112 non-immune cell types (Shajib and Khan, 2015).

## 113 2- Key roles of the microbiota in immune cells metabolism

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

### 116 **Epithelial cells**

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

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

139 Among the different IEC types, enterochromaffin (EC) cells are responsible for the production  
140 of serotonin (5-HT), which has major effects on immune cells (see below). Serotonin production  
141 in the colon is largely modulated by the gut microbiota and particularly spore-forming bacteria  
142 metabolites. The mechanisms are not fully elucidated, but it has been shown that upregulation  
143 of Tph1 expression, the rate-limiting enzyme in serotonin production, can be achieved by  
144 SCFAs (butyrate and propionate) and some secondary bile acids, such as deoxycholate  
145 produced by microbial biotransformation of cholate (Yano et al., 2015). Even if further  
146 investigations are needed, this data suggest that modulating the gut microbiota composition or  
147 directly administrating microbial metabolites could allow manipulating the production of  
148 serotonin from a therapeutic perspective.

149

## 150 **Macrophages**

151 Macrophages are in the first line during the immune response but also sense and respond to  
152 the microbiota to control it without initiating a detrimental inflammatory response. During the  
153 pathogenic response, the metabolic profile of activated macrophages varies as a function of  
154 the situation. In pro-inflammatory M1 macrophages, the TCA cycle is disrupted, leading to the  
155 accumulation of itaconate and succinate and a shift to glycolysis (Rodríguez-Prados et al.,  
156 2010; Tannahill et al., 2013). Itaconate is a major actor in immunometabolism that exhibits  
157 immunomodulatory and antimicrobial effects. It is also involved in the accumulation of  
158 succinate, as it directly inhibits its oxidation by blocking the activity of succinate dehydrogenase  
159 (SDH) (Lampropoulou et al., 2016). Succinate exhibits a pro-inflammatory effect through its  
160 oxidation that generates mitochondrial ROS (Reactive Oxygen Species) and leads to IL-1 $\beta$   
161 production (Mills et al., 2016). Conversely, M2 macrophages have an intact TCA cycle and rely  
162 mostly on OXPHOS (Huang et al., 2014; Vats et al., 2006). The gut microbiota modulates  
163 these processes, notably through SCFAs. Butyrate, but not acetate or propionate, reprograms  
164 macrophage metabolism toward OXPHOS and lipid metabolism leading to an anti-  
165 inflammatory M2 phenotype (Scott et al., 2018). The detailed mechanisms are not identified  
166 but involve the up-regulation of genes involved in OXPHOS (such as mitochondrial ATP  
167 synthase and NADH dehydrogenase) and lipid metabolism (such as lipoprotein lipase)  
168 pathways. As an illustration, the impaired production of butyrate induced by antibiotics  
169 promotes the pro-inflammatory polarization of the intestinal macrophages, leading to a global  
170 dysfunction of the immune response (Scott et al., 2018). This might play a role in the  
171 association between antibiotics intake and the emergence of inflammatory and metabolic  
172 diseases (Cox et al., 2014; Hviid et al., 2011).

## 173 **Innate lymphoid cells (ILCs)**

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



177 O'Sullivan, 2020). Transcriptomic analysis suggests that ILC1s use mTOR signaling, ILC2s  
178 depend on sphingolipid and amino acid metabolism, and ILC3s rely on glycolysis (Gury-BenAri  
179 et al., 2016). The gut microbiota profoundly impacts ILCs function as demonstrated by the  
180 dramatic effects of antibiotics on the transcriptomic program of ILC1s, ILC2s and ILC3s (Gury-  
181 BenAri et al., 2016). ILC3 is the main type of ILC present in the gastrointestinal tract. These  
182 cells express ROR $\gamma$ t, can produce IL-17 and IL-22, and are crucial regulators of inflammation,  
183 infection, microbiota composition, and metabolism (Klose and Artis, 2016). ILC3 functions,  
184 such as maintenance of the intestinal epithelium defense, depend on circadian signals  
185 mediated by the circadian regulator ARNTL (Aryl Hydrocarbon Receptor Nuclear Translocator  
186 Like). Light-dark cycles are key factors in this process, but the gut microbiota, which is known  
187 to be an actor in diurnal rhythmicity (Thaiss et al., 2016), also had some impact (Godinho-Silva  
188 et al., 2019). This signaling circuit connecting the gut microbiota, ILC3 and the intestinal  
189 epithelial clock is also involved in the regulation of the local and systemic lipid metabolism  
190 (Wang et al., 2017).

191 Gut microbiota-derived butyrate modulates ILC2 functions, inhibiting their uncontrolled  
192 activation and, consequently, their negative role in lung inflammation and asthma. The  
193 mechanism is not determined. Yet, the involvement of intracellular metabolism is supported by  
194 the induction of changes in mROS production and glycolysis by butyrate (Lewis et al., 2019).  
195 Moreover, the preferential use FAs over glucose by ILC2 to maintain their function in infection  
196 or nutritional stress suggest that butyrate might directly fuel the TCA (Wilhelm et al., 2016).  
197 Succinate, produced in the gut by protists and specific bacteria, stimulates the secretion of IL-  
198 13 by ILC2, through an indirect action on Tuft cells and IL-25 (Schneider et al., 2018). The role  
199 of succinate of other origin and its direct impact on ILC2 remains to be explored.

200

201 **T cells**

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

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

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

230 2016). Although these phenomena were described with host cell-derived acetate, they are  
231 likely triggered, at least in the gut, by the massive amount of acetate produced by the gut  
232 microbiota.

233 SCFAs also exhibit significant effects on CD4+ T cells, notably regarding the generation of T  
234 helper (Th) 17, Th1 (Park et al., 2015), and regulatory T cells (Furusawa et al., 2013; Smith et  
235 al., 2013). The mechanisms involve the inhibition of HDACs and regulation of the mTOR  
236 pathway (a master regulator of cell growth and metabolism). This link has been recently shown  
237 with pentanoate (also known as valerate), a subdominant microbiota-produced SCFA that can  
238 stimulate the production of the anti-inflammatory cytokine IL-10 by providing additional acetyl-  
239 CoA for histone acetyltransferases and enhancing glycolysis and mTOR activity (Luu et al.,  
240 2019). Two mechanisms have been suggested regarding the activation of mTOR by SCFA  
241 (Figure 2). Through their action on energy production pathways, SCFAs induce the production  
242 of ATP and the depletion of AMP, which are inhibitor and activator of AMP-activated protein  
243 kinase (AMPK), respectively. Consequently, the inhibitor activity of AMPK on mTOR is  
244 repressed, thus leading to mTOR activation (Kim et al., 2016; Luu et al., 2019; Zhou et al.,  
245 2018). The second potential mechanism involves the HDAC inhibition activity of SCFAs.  
246 SCFAs, in association with P300/CBP (E1A binding protein p300/ CREB-binding protein),  
247 promote acetylation of the Ribosomal protein S6 kinase beta-1 (S6K1), which is a downstream  
248 target of mTOR, leading to more robust activation of the pathway (Park et al., 2015). Another  
249 layer of complexity has been indicated recently by showing that the effects of SCFAs on T cell  
250 metabolism are dependent on the inflammatory context (Trapecar et al., 2020).

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

257 In the colon specifically, BAs act through the bile acid receptor Breg to regulate the function of  
258 ROR $\gamma$ <sup>+</sup> Treg cells, which are significant players in the maintenance of colonic homeostasis  
259 (Song et al., 2020).

## 260 **B cells**

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

275 B cells have a critical role in tolerance toward the gut microbiota through the production of  
276 immunoglobulins and the action of IL-10-producing Bregs (regulatory B cells). In Bregs, Rosser  
277 and colleagues recently showed that butyrate could divert tryptophan metabolism toward the  
278 serotonin pathway and the production of 5-hydroxyindole-3-acetic acid (5-HIAA) (Rosser et al.,  
279 2020). Surprisingly, 5-HIAA was shown to activate AhR in these cells, mediating the  
280 suppressive effect of butyrate supplementation in a rheumatoid arthritis model *in vivo*.

## 281 3- Consequences for disease pathogenesis

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

## 288 **Infections**

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

309 important actors in response to *C. rodentium*, notably through the production of IL-22 and IL-  
310 17A, which occur in an mTOR dependant way. The activation of mTOR complex 1 (mTORC1)  
311 leads to metabolic reprogramming of ILC3 characterized by enhanced glycolysis and mROS  
312 production. Mechanistically, mTORC1 activates HIF1 $\alpha$  that supports ROR $\gamma$ t and stimulates  
313 glycolysis. The downstream produced mROS contribute to stabilize HIF1 $\alpha$  and to reprogram  
314 ILC3 metabolism toward the response to bacterial pathogens (Di Luccia et al., 2019).

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

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

### 327 **Inflammatory Bowel Disease**

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

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

351 Previous studies have also shown a link between mitochondrial dysfunction and IBD. The  
352 expression of prohibitin 1 (PHB1), an inner mitochondrial membrane component, is decreased  
353 in colonic biopsies from IBD patients (Hsieh et al., 2006; Theiss et al., 2007). Moreover,  
354 mitochondrial dysfunction in IECs and notably in Paneth cells can induce ileal inflammation in  
355 mouse models (Jackson et al., 2020). Interestingly, Paneth cell abnormalities in patients with  
356 Crohn's disease correlate with alterations in both microbiota composition and oxidative  
357 phosphorylation in ileal tissue (Liu et al., 2016). Mechanistically, mitochondrial respiration  
358 impairment forces IECs to acquire a dysfunctional Paneth cell phenotype, leading to metabolic  
359 imbalance and inflammation (Khaloian et al., 2020). Moreover, mitochondrial impairment in  
360 Crohn's patients also involves a decrease in H<sub>2</sub>S detoxification, while the relative abundance  
361 of H<sub>2</sub>S-producing microbes is increased in the gut microbiota. The amount of *Atopobium*  
362 *parvulum*, a keystone microbiota species for H<sub>2</sub>S production, correlated with Crohn's disease

363 severity (Mottaweia et al., 2016). Overall, the net increase in H<sub>2</sub>S due to increased microbiota  
364 production and decreased mitochondrial detoxification is involved in intestinal inflammation  
365 pathogenesis.

## 366 Conclusion

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

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



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

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## 399 Author Contributions

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

## 401 Declaration of Interests

402 The authors declare no competing interests.

403

## 404 Figure legends

### 405 **Figure 1. Influence of the gut microbiota on immunometabolism**

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

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

432

### 433 **Figure 2. Mechanism of activation of the mTOR pathway by SCFA**

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

442

443 **Figure 3. Immunometabolism and the microbiota in diseases**

444 **Infections.** Upon infection with *Salmonella*,  $\gamma\delta$  IEL behavior changes are associated with  
445 activation of OXPHOS and anaerobic glycolysis and boost epithelial barrier protection. This  
446 response is dependent on mTOR and microbiota signals. Metabolic changes are also  
447 observed in IECs in response to *Citrobacter rodentium*, with downregulation of the TCA cycle  
448 and OXPHOS. In parallel, IECs present a dysregulation of cholesterol homeostasis. During  
449 this infection, pathogen-induced Th17 cells rely on glycolysis and OXPHOS, while commensal  
450 microbe-induced Th17 cells rely mostly on OXPHOS. ILC3 are other important actors in  
451 response to *C. rodentium*, notably through mTORC 1 activation (mTORC1) that leads to HIF1 $\alpha$   
452 activation that supports ROR $\gamma$ t and stimulates glycolysis. In parallel, the downstream produced  
453 mROS contribute to stabilizing HIF1 $\alpha$ . Metabolic reprogramming of ILC3 permits to produce  
454 IL-22 and IL-17A to sustain immune response. These differences in bioenergetic profiles are  
455 associated with different mitochondrial morphologies. During the response to infection and  
456 sepsis, T cells generate NOX2-mediated ROS. Acetate can restore the oxidant-antioxidant  
457 balance in T cells in this setting and likely through the upregulation of HDAC activity. During  
458 pathogen infection, TLR engagement in macrophages induces the recruitment of TRAF6 to  
459 mitochondria, leading to an increased production of ROS that is involved in response to  
460 intracellular pathogens. In SIV- and HIV-infected individuals, the intestinal epithelium presents  
461 altered PPAR $\alpha$  signaling and FA  $\beta$ -oxidation, which correlates with an alteration in the  
462 intestinal epithelial barrier that can be restored by microbiota-derived factors.

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

469 inflammatory H<sub>2</sub>S is observed in IBD. It is connected to the increased H<sub>2</sub>S production by the  
470 abnormal microbiota associated with the impairment in mitochondrial detoxification. *Atopobium*  
471 *parvulum* is a keystone microbiota species for the production of H<sub>2</sub>S.

472

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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.

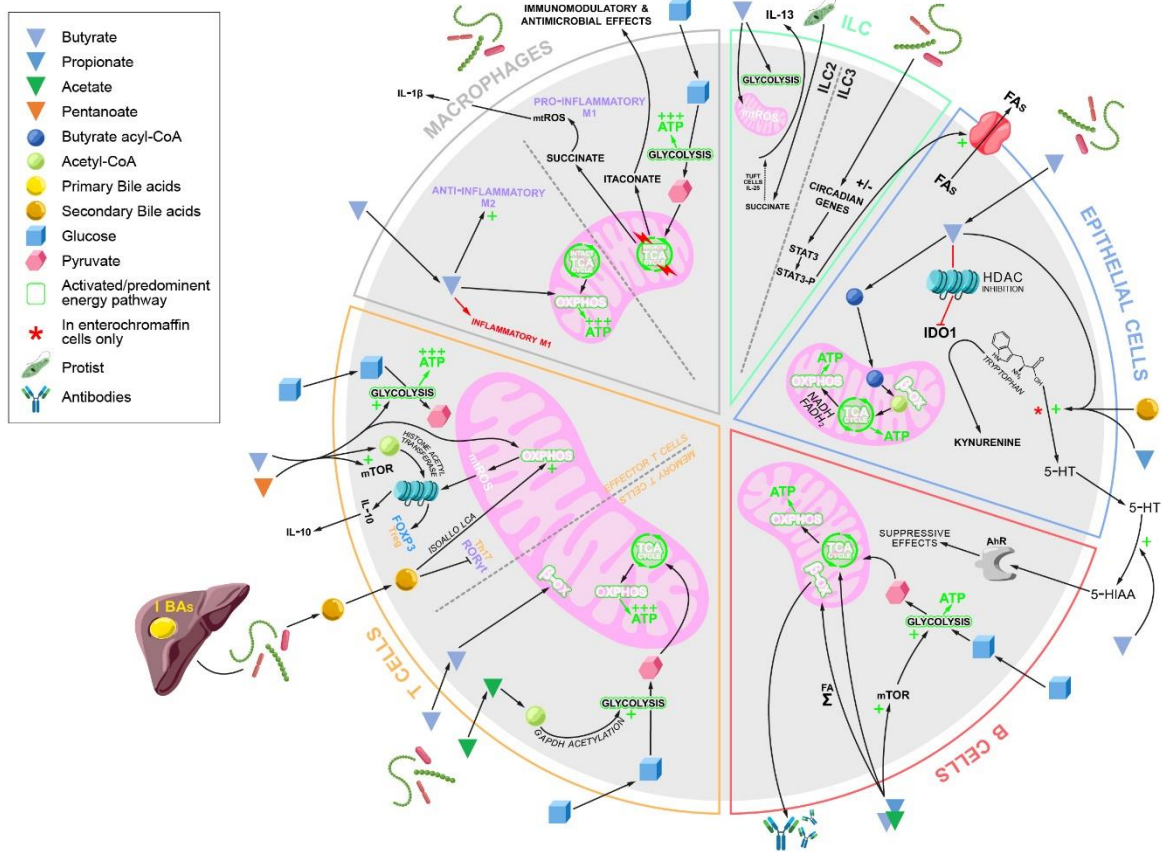


Figure 1. Influence of the gut microbiota on immunometabolism

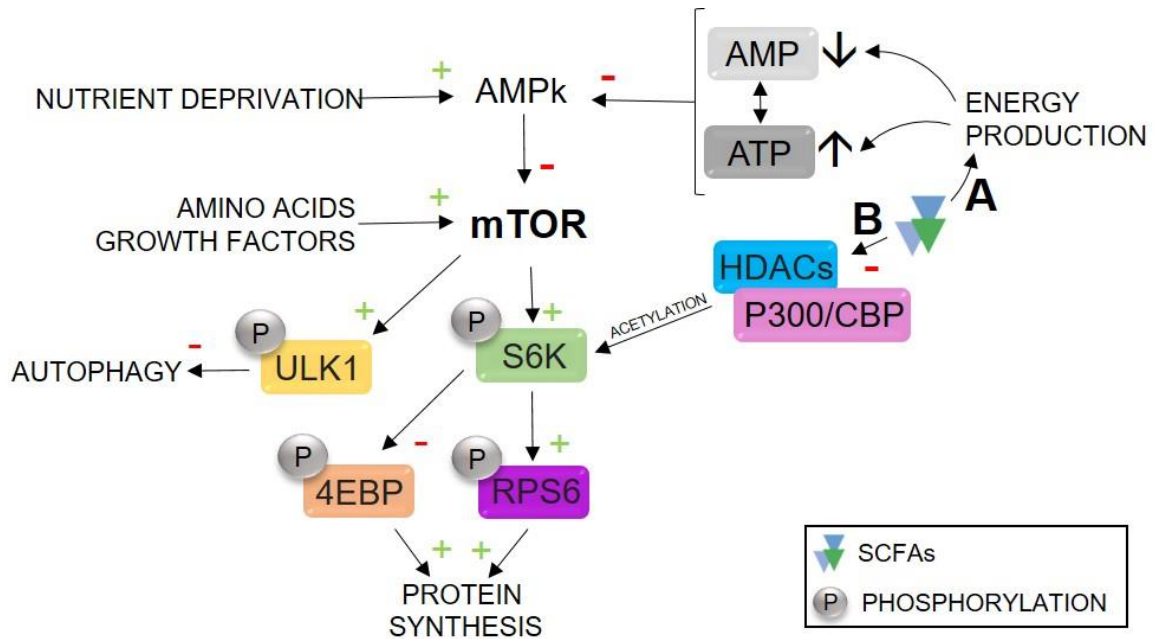


Figure 2. Mechanism of activation of the mTOR pathway by SCFA

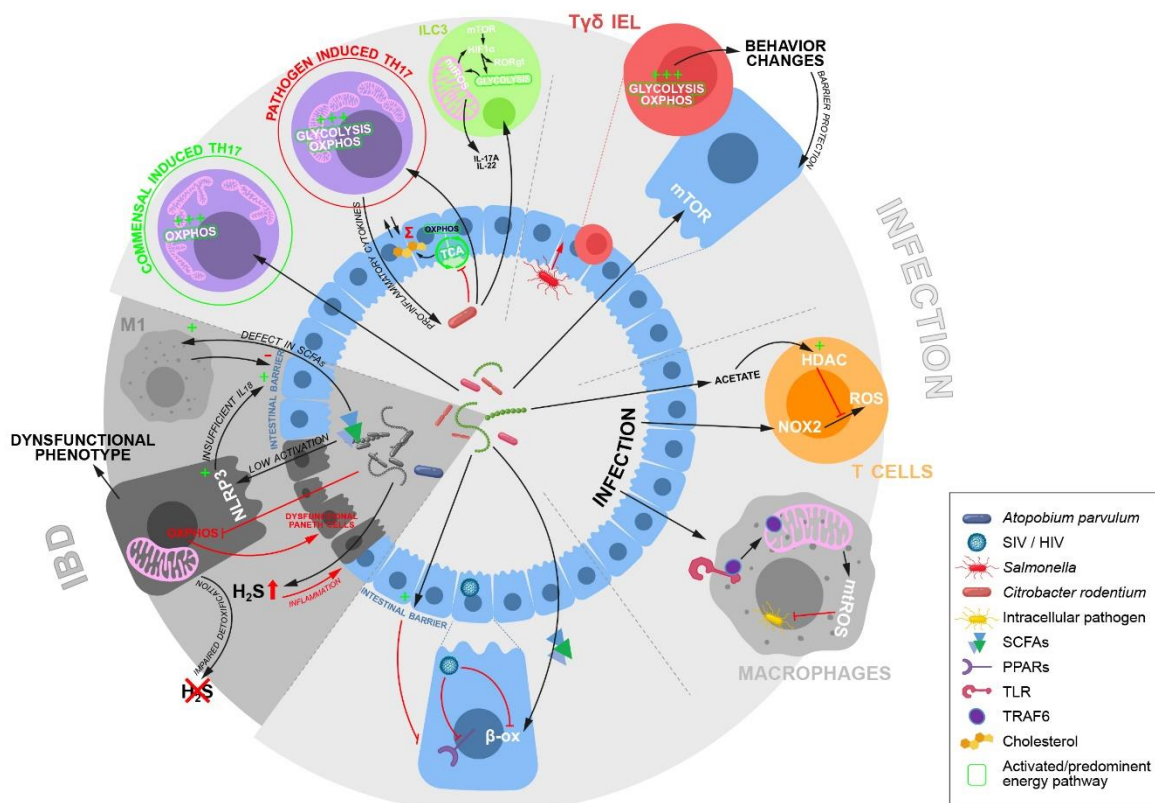


Figure 3. Immunometabolism and the microbiota in diseases