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## Reciprocal interactions between gut microbiota and autophagy

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### Abstract

A symbiotic relationship has set up between the gut microbiota and its host in the course of evolution, forming an interkingdom consortium. The gut offers a favorable ecological niche for microbial communities, with the whole body and external factors (e.g., diet or medications) contributing to modulating this microenvironment. Reciprocally, the gut microbiota is important for maintaining health by acting not only on the gut mucosa but also on other organs. However, failure in one or another of these two partners can lead to the breakdown in their symbiotic equilibrium and contribute to disease onset and/or progression. Several microbial and host processes are devoted to facing up the stress that could alter the symbiosis, ensuring the resilience of the ecosystem. Among these processes, autophagy is a host catabolic process integrating a wide range of stress in order to maintain cell survival and homeostasis. This cytoprotective mechanism, which is ubiquitous and operates at basal level in all tissues, can be rapidly down- or up-regulated at the transcriptional, post-transcriptional, or post-translational levels, to respond to various stress conditions. Because of its sensitivity to all, metabolic-, immune-, and microbial-derived stimuli, autophagy is at the crossroad of the dialogue between changes occurring in the gut microbiota and the host responses. In this review, we first delineate the modulation of host autophagy by the gut microbiota locally in the gut and in peripheral organs. Then, we describe the autophagy-related mechanisms affecting the gut microbiota. We conclude this review with the current challenges and an outlook toward the future interventions aiming at modulating host autophagy by targeting the gut microbiota.

**Key Words:** Gut microbiota; Autophagy; Probiotic; Brain; Liver; Muscle

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**Core Tip:** We are now aware that maintaining a fine equilibrium between the host and its gut microbiota is a prerequisite to maintain host homeostasis and promote long-term health. Several host and microbial processes interact dynamically to respond to external stresses. Among these processes, host autophagy acts as a cytoprotective mechanism responsive to a wide range of stress conditions, including metabolic, immune, and microbial stimuli. Autophagy was initially described as a degradative process active upon nutrient starvation. However, this process fulfils a wide range of other functions that are essential to host homeostasis. We discuss herein reciprocal interactions of autophagy with the gut microbiota in health and disease conditions.

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## INTRODUCTION

The commensal microbiota living in the human gut is a unique ecosystem that has co-evolved with human to establish a symbiotic relationship. This microbial community is estimated to encompass about  $10^{14}$  resident microorganisms, dominated by bacteria, but containing also populations of archaea, fungi, protozoa, and viruses[1]. The host provides nutrients and a favorable environment (*i.e.*, ecological niches) for its microbial inhabitants. In return, the gut microbiota plays multiple roles that contribute to the host whole-body homeostasis, in particular by metabolizing dietary nutrients, by preventing colonization by enteric pathogens, and by regulating the host immune system and metabolism. The gut microbiota is, for instance, essential for the synthesis of vitamins (*e.g.*, K and B-group vitamins) and the fermentation of dietary fibers and carbohydrates, which generate short-chain fatty acids (SCFAs). These fermentation products are used as energy source by organs and are also involved in the regulation of various cellular processes (*e.g.*, intestinal barrier integrity, mucus production, and inflammation)[2,3].

Through their interactions with the host, gut microbes and their derived products are involved not only in the physiological regulation of the gut mucosa but also in that of organs located at distance from the gut mucosa, as illustrated by the studies detailing molecular features of the gut-microbiota-brain axis[4-6]. Keeping the mutualistic relationship between the gut microbiota and the host throughout host's life is thus essential to maintain the health status of the host[7]. Deleterious shifts in the composition of the gut microbiota, called dysbiosis, can unbalance its functions, leading to the disruption of host homeostasis. This is particularly well illustrated by the ability of fecal microbiota transplantation (FMT) to transmit detrimental metabolic and/or pro-inflammatory traits from a sick donor to healthy recipient mice[8-10]. In addition to environmental stresses, the symbiotic equilibrium of the gut microbiota and the host can also be broken by dysfunctions/alterations in the host metabolism and immune system, which are conditions that can contribute to dysbiosis[8,11,12]. In this context, the roles of autophagy in strengthening the intestinal barrier and in maintaining host metabolic and inflammatory balance position it as the cornerstone of the symbiotic relationship between the gut microbiota and the host[4,13].

Macroautophagy/autophagy is an intracellular and multistep process starting with the formation of a membranous cup-shaped structure, called phagophore, which engulfs portions of the cytoplasm. The phagophore elongates and finally closes to form a sealed double-membraned vacuole, called autophagosome, whose maturation ends by its fusion with lysosomes[14-16]. Autophagy was initially described as a lysosomal catabolic process occurring under starvation that degrades and recycles cytoplasmic macromolecules (*e.g.*, proteins, lipids, and carbohydrates) for the biosynthesis of essential cellular components and to restore energy balance[17]. Nowadays, autophagy process and autophagy-related proteins are recognized as key cellular components whose roles are not restricted to the regulation of energy balance[18,19]. These roles include, but are not limited to, the regulation of the inflammatory response, the cytoprotection by preventing the accumulation of intracellular waste (*e.g.*, damaged organelles and misfolded or aggregated proteins), the protection against

intracellular pathogens (*e.g.*, bacteria, fungi, or viruses), the membrane dynamic (*e.g.*, transport or secretion), and the regulation of cell differentiation and survival. Autophagy also regulates specific functions related to the features of organs. For example, at the gut mucosa - the first tissue at the interface between the gut microbiota and the host - autophagy is involved in the regulation of the functions of the secretory cells and of the intestinal stem cell[4]. In the central nervous system, autophagy plays roles in neuronal development and survival and other various functions[20]. The central role of autophagy in maintaining homeostasis, and thus the health status, is supported by the observed embryonic or neonatal lethality of mice deficient for most autophagy-related (*Atg*) core genes (*Becn1*, *Vps34*, *Atg9a*, *Ulk1/2*, *Atg3*, *Atg5*, *Atg7*, and *Atg16l1*) as well as association of numerous diseases and disorders with autophagy defects[19,21].

Of note, a growing number of recent studies highlight that most of the proteins of the autophagy machinery also mediate autophagy-independent functions, including phagocytosis, exocytosis, cytokinesis, DNA repair, or innate and adaptive immune signaling[22]. To exert their numerous functions, the machineries involving autophagy proteins are intricately with molecular sensors specialized in the detection of various stimuli such as microbial sensors [*e.g.*, Toll-like receptors (TLR) and Nod-like receptors (NLR)], stress sensors (*e.g.*, HMGB1, Sestrins, ER-stress sensor proteins, P2XR, and cGAS-STING pathway), or energy status sensors (*e.g.*, AMPK and mTOR pathways) [23-29].

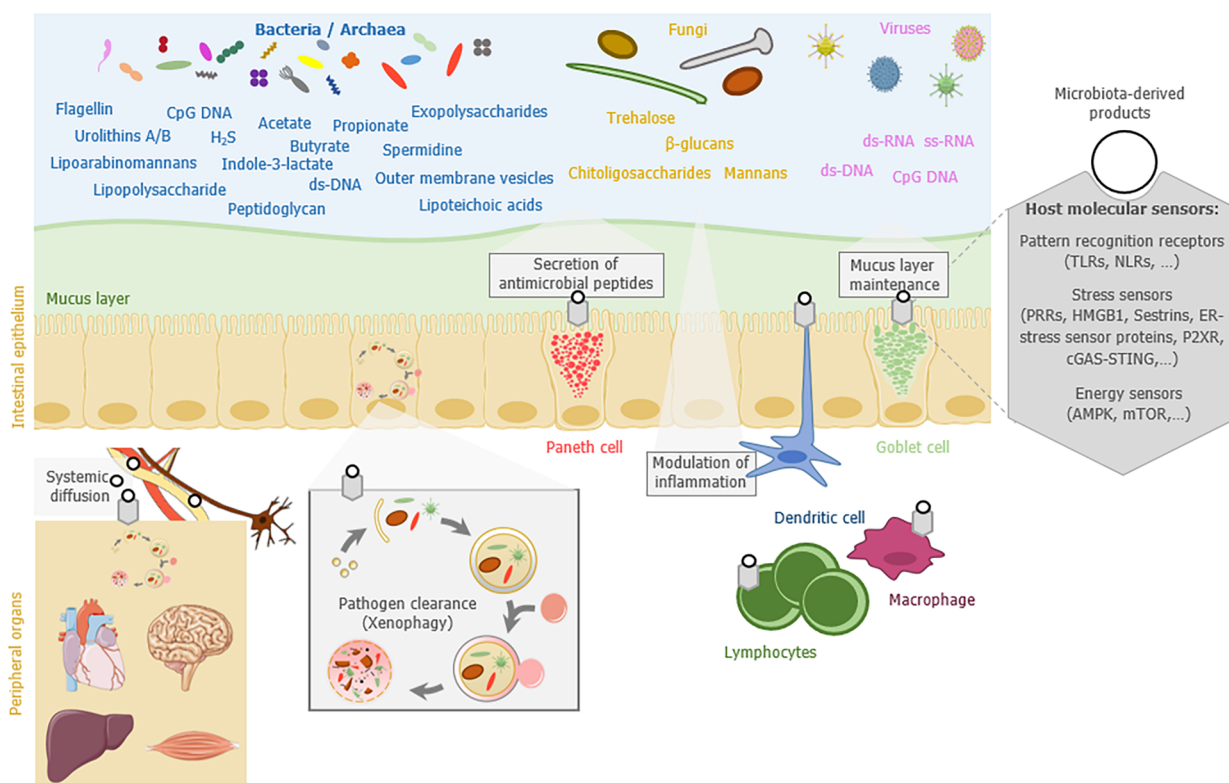
In this review, we summarize the current knowledge on how the gut microbiota influences host autophagy locally in the gut mucosa or remotely in peripheral organs (brain, heart, liver, or muscles), and how autophagy or autophagy-related proteins can reciprocally shape the gut microbiota composition and modify its functions (Figure 1). We finally discuss the potential of targeting the gut microbiota as a strategy to modulate autophagy or restore its functionality in pathological context.

## INFLUENCE OF THE MICROBIOTA ON GUT AUTOPHAGY

A first clue that points out a direct implication of the gut microbiota in the regulation of host autophagy has been provided by analyzing autophagy in germ-free mice (*i.e.*, mice lacking microorganisms and bred in isolators without any microbial exposure). Basal autophagy was decreased in the colonic epithelium of germ-free mice compared to conventionally raised mice, suggesting that the gut microbiota influences intestinal autophagy in physiological condition[30]. The increase in basal activity of autophagy in germ-free mice was attributed to an energy-deprived status of colonocytes. Treatment of these cells with butyrate, a SCFA generated by some gut bacteria and serving as main energy source for colonocytes, was sufficient to reverse the phenotype. *In vivo*, colonization of germ-free mice with the butyrate-producing bacterial strain *Butyrivibrio fibrisolvens* was sufficient to restore autophagy steady state. In addition to butyrate, other bacteria-derived metabolites may have the ability to reduce basal autophagy in the colon. They include indole-3-lactate, which is a tryptophan metabolite produced notably by the bacteria belonging to the *Lactocaseibacillus*, *Lactobacillus*, *Bifidobacterium*, *Megamonas*, *Roseburia*, or *Ruminococcus* genus[31,32].

Pathogen-associated molecular patterns (PAMPs), which are conserved microbial molecules, are also able to modulate autophagy usually by stimulating the process [23]. These effects have been particularly well described for pathogens. PAMPs mainly act by interacting with specific host cell receptors that belong to the TLR and NLR families. This has been illustrated by the ability of the lipopolysaccharide (LPS) from Gram negative bacteria to stimulate autophagy through its binding to TLR4[33], or the peptidoglycan (PGN) from Gram positive bacteria through NOD1-, NOD2-, and TLR2-associated signaling[34,35]. Besides those of bacteria, fungal PAMPs can also mobilize components of the autophagy machinery. This is true for  $\beta$ -glucans that are found in fungal cell walls and stimulate autophagy-related processes through their binding to the host receptor Dectin-1[36,37]. Trehalose, a non-reducing disaccharide produced by bacteria and fungi, is also a potent autophagy inducer, for which the ability to stimulate colonic autophagy during colitis in mice has been described[38,39]. In addition, in-depth studies of the infectious cycle of some pathogenic bacteria have shed the light on the existence of secreted bacterial effectors able to activate (*e.g.*, Ats-1 protein from *Anaplasma phagocytophilum*) or inhibit (*e.g.*, RavZ protein from *Legionella pneumophila*) autophagy at various stages of the process[40,41]. It is not excluded that some commensal microorganisms in the gut express such proteins that influence host autophagy.





**Figure 1 Complex interplay between gut microbiota and autophagy.** The interactions between the gut microbiota and autophagy are bidirectional. Autophagy is involved in the regulation of several mechanisms (grey boxes) that shape the gut microbiota. Reciprocally, some bacterial- (blue), fungal- (orange), or viral-derived (pink) compounds are able to modulate autophagy in the gut mucosa as well as in distant organs through systemic pathways (circulatory system, nervous system ...). Modulation of autophagy by the gut microbiota involves microbiota-derived products such as microbial compounds (lipopolysaccharide, peptidoglycan ...), microbial derived-compounds (short chain fatty acids, secondary biliary acids ...), or signaling molecules (cytokines, hormones ...). They stimulate a wide range of host molecular sensors (pattern recognition receptors, stress sensors, and energy sensors; grey hexagons) located in the gut or peripheral organs. PRR: Pattern recognition receptor; TLR: Toll-like receptor; NLR: Nod-like receptor.

Given the influence of gut microbiota-related factors on autophagy, one could expect that alterations in the composition of the gut microbiota would affect autophagy in the gut mucosa. Indeed, an increase in the expression of some autophagy-related proteins (FoxO1, FoxO3, GABARAP, and ATG7) and LC3-II/LC3-I ratio and a decrease in AKT activation have been reported in newborn piglets receiving FMT[42]. In addition, alteration of the gut microbiota resulting from the administration of a cocktail of broad-spectrum antibiotics increased the basal activity of autophagy as well as the expression of some autophagy-related proteins (ATG16L1, ATG5, and IRGM1) in the ileal mucosa of mice[43,44]. Interestingly, oral administration of a single bacterial species (*e.g.*, *Desulfovibrio* spp., *Fusobacterium nucleatum*, or *Escherichia coli*) in conventional mice can also be sufficient to modulate gut autophagy [42,44,45]. Altogether, these studies suggest that autophagy regulatory network is sensitive to changes in the gut microbiota.

## SYSTEMIC EFFECTS OF THE GUT MICROBIOTA ON HOST AUTOPHAGY

Microbial-derived metabolites (*e.g.*, PAMPs), compounds that are issued from the gut microbiota metabolism (*e.g.*, neuroactive compounds and SCFAs) and host bioactive molecules that are produced in response to its interaction with the gut microbiota (*e.g.*, cytokines), can have large systemic effects and modulate the physiology of organs that are distant from the gut. Influence of the gut microbiota on the brain is a well-documented example of such effects[6]. Several communication routes (immune system, autonomic nervous system, neuroendocrine system, hypothalamic – pituitary – adrenal axis, and other metabolic pathways) between the microbiota and the brain have been identified[6]. It is very likely that similar pathways and microbiota-derived players, or at least some of them, modulate as well the physiology of other organs in the body. Evidence is accumulating on the modulation of autophagy by the gut



microbiota in distant organs and several of these are presented below (Table 1).

### Modulation of autophagy in nervous tissues

Although few studies are available on this emerging topic, they suggest that the gut microbiota could influence autophagy in the brain throughout life in both physiological and pathological conditions.

Diet is a key environmental factor that drives the composition and metabolic functions of the gut microbiota[46,47]. In particular, maternal diet can influence post-natal gut microbiota and neurological development of the offspring[48]. In a recent study, Wang and colleagues reported that feeding mothers with a high sugar and high fat (HSHF) diet, a condition that modifies the gut microbiota of the offspring, modulates also the expression of neuronal and autophagy markers in the brain during early life stage[49]. Particularly, they observed that the LC3A and LC3B levels were modified in the brain of the offspring in the HSHF group compared to controls before 28 d of age, and then decreased, meaning that autophagy may be differentially regulated in HSHF offspring[49].

Aging is associated with a decline of host autophagy including in the brain[50]. Influence of the gut microbiota on brain autophagy in aging has been evidenced in *in vivo* models. Alteration of autophagy has been reported in the brain of D-gal-treated mice, a model of accelerated aging[51,52]. These alterations were characterized by decreases in the LC3-II/LC3-I ratio and in the expression of ATG7 and SIRT1, as well as by increased phosphorylation of the master negative regulator of autophagy mTOR (S2448) and expression of p62 in the hippocampus tissue of D-gal-induced aging mice [52]. Interestingly, the administration of urolithin A (UA), a bioactive metabolite generated by the gut microbiota, was efficient in rescuing these autophagy-related defects. To note, UA administration also allowed to reverse increases in the LC3-II/LC3-I ratio, the expression of p62, and the phosphorylation of mTOR (S2448), as well as the decreased expression of Sirt-1 and ATG7 observed in the hippocampus of 12-mo-old mice[52].

Autophagy defect is thought to play a role in neurodegenerative processes associated with numerous diseases, including Alzheimer's disease (AD)[53]. Interestingly, although a causal relationship remains to be demonstrated, a few studies suggest that dysbiosis associated with AD could influence brain autophagy[54]. Decreased Beclin-1 expression and increased expression of p62 have been observed in the brain of old 3xTg-AD mice (a transgenic mouse model of AD) compared to young control mice, indicating alterations in autophagy[55]. Interestingly, in addition to modifying the composition and predicted function of the gut microbiota, oral supplementation of old 3xTg-AD mice with a combination of nine probiotic strains (*Streptococcus thermophilus*, *Bifidobacterium longum*, *B. breve*, *B. infantis*, *Lactobacillus acidophilus*, *Lactiplantibacillus plantarum*, *Lactocaseibacillus paracasei*, *Lactobacillus delbrueckii* subsp. *bulgaricus*, and *Levilactobacillus brevis*; SLAB51 formulation) also partially restored defects in autophagy[55]. Moreover, SLAB51 was also effective in restoring the impaired expression level and activity of SIRT1, a positive regulator of autophagy, in the brain of 3xTg-AD mice[56,57].

In another context, changes in the composition of the fecal microbiota have been reported in patients with acute ischemic stroke (AIS), a common cerebrovascular disease caused by sudden loss of blood circulation in a specific brain area[58,59]. Interestingly, anal administration of the fecal supernatant obtained from an AIS patient to antibiotics-treated mice resulted in increased expression of genes encoding Beclin-1, ATG12, and LC3 as well as increased expression of Beclin-1 at the protein level and an increased level of LC3-II in brain tissue compared to antibiotics-treated mice that received the fecal supernatant of healthy controls[59].

The retina, which is the light sensitive neural tissue that lines the back of the eyes, displays numerous similarities with the brain either anatomically or functionally[60]. Neurodegenerative conditions that affect the brain seem to compromise the retina, and *vice versa*[60-62]. Similarly to the brain, the retina is also highly sensitive to nutritional variations[63]. Retina autophagy[64,65] as well as modifications in the gut microbiota [66-69] is suspected to contribute to retinal diseases such as diabetic retinopathy, age-related macular degeneration, and glaucoma. Although no causal relationship has been yet established, one can assume that, as in the brain, the gut microbiota might influence retinal autophagy and that changes in its composition might alter retinal autophagy and contribute to the development of retinopathies.

### Modulation of liver autophagy

Evidence of the influence of the gut microbiota on liver autophagy came from studies in gut microbiota-deprived mouse models. Comparison of germ-free mice and altered

**Table 1** Data supporting the existence of a systemic regulation of autophagy by the gut microbiota

Ref.		Impact on autophagy		
		Brain	Liver	Muscles
[49,74-76]	Diet-induced changes in the gut microbiota	Feeding of mother mice with an HSHF diet: Changes in the expression levels of LC3A-I/LC3A-II/ LC3B-I/LC3B-II in the offspring.	Feeding mice or rats with an HF diet: Changes in the expression levels of LC3, p62, mTOR, and p-AKT and modulation of the LC3-II amount.	
[55,56,59,70]	Mice with specific gut microbiota	AD mice <sup>1</sup> : Modulation of the lysosomal activity (Cathepsin L) and SIRT1 activity and changes in the expression levels of Beclin-1, p62, and SIRT1.  FMT from patients with AIS to mice: Changes in the expression levels of <i>Becn1</i> , <i>ATG12</i> , and <i>LC3</i> expression and in the amount of LC3-II.	ASF colonized mice: Changes in the expression of a set of genes related to autophagy/membrane trafficking ( <i>Uvrags</i> , <i>Atg14</i> , <i>Becn1</i> , <i>Bcl2l1</i> , and <i>Pik3c3</i> ) and lysosomal functions ( <i>Chmp4c</i> and <i>Chmp2a</i> ) compared to germ-free mice.	
[71,79]	Germ free or antibiotic-treated animals		Antibiotic treatment of mice fed a normal diet: Alteration of the basal expression of LC3 compared to controls.	Germ free piglets: Changes in the expression levels of LC3A, LC3B, and <i>Becn1</i> and of mTOR, p-mTOR, AKT, and p-AKT levels compared to normal and/or FMT piglets.
[55,56,75,76,78]	Probiotics	SLAB51 <sup>2</sup> : Modulation of SIRT1 activity and changes in the expression levels of Beclin-1, p62, and SIRT-1 as well as in the LC3-II amount in AD mice <sup>1</sup> .	<i>Limosilactobacillus reuteri</i> : Modulation of the expression levels of mTOR and p-AKT in HFD-fed rats.	<i>Lactocaseibacillus rhamnosus</i> , <i>Pediococcus acidilactici</i> , <i>Bifidobacterium adolescentis</i> : Changes in the expression levels of LC3 and ATG7 in rats fed a high-calorie diet.
[52,71,74,77,80]	Gut microbiota-derived products	UA: Modulation of LC3-II/LC3-I and p-mTOR/mTOR ratio and changes in the expression levels of ATG7 and p62 in mouse models of aging <sup>3</sup> .	SCFAs: Activation of the PPAR $\gamma$ -UCP2-AMPK pathway, and induction of autophagy flux and lysosomal activity in mouse hepatocyte AML-12 cells.  FXR and TGR5 <sup>4</sup> : Involved in autophagy modulation.	UA: Induction of mitophagy in <i>Caenorhabditis elegans</i> and in rodents.  UB: Modulation of LC3-II/LC3-I, p-mTOR/mTOR and p-ULK1/ULK1 ratio and change in the expression level of p62 in a rat model of ischemia/reperfusion injury.

<sup>1</sup>AD mice: Mouse model of Alzheimer's disease (3xTg-AD mice).<sup>2</sup>SLAB51: A combination of nine probiotic strains (*Streptococcus thermophilus*, *Bifidobacterium longum*, *B. breve*, *B. infantis*, *Lactobacillus acidophilus*, *Lactiplantibacillus plantarum*, *Lactocaseibacillus paracasei*, *Lactobacillus delbrueckii* subsp. *bulgaricus*, and *Levilactobacillus brevis*).<sup>3</sup>D-gal-treated mice and 12-mo-old mice.<sup>4</sup>FXR and TGR5: Bile acid receptors.

HSHF diet: High sugar and high fat diet; HF diet: High fat diet; FMT: Fecal microbiota transplantation; SCFAs: Short chain fatty acids (propionate and butyrate); AIS: Acute ischemic stroke; ASF: Altered Schaedler's flora; UA: Urolithin A; UB: urolithin B.

Schaedler's flora (a community of eight bacterial species) colonized mice revealed that absence of the gut microbiota altered hepatic expression of genes involved in autophagy and lysosomal functions[70]. In another study, a decrease in the expression of LC3 at the protein level has been reported in the liver of mice deprived from gut microbiota as a consequence of chronic treatment with antibiotics (ampicillin and neomycin) compared to control mice[71]. In addition, those authors showed that microbial-derived SCFAs (propionate and butyrate) activated autophagy, induced lysosomal activity, and increased autophagy flux *in vitro* in mouse hepatocyte AML-12

cells[71]. The mechanism involves the activation of the PPAR $\gamma$ -UCP2-AMPK pathway [71].

Primary bile acids are synthesized from cholesterol in the liver and are converted into secondary bile acids by the gut microbiota[72]. Bile acids are signaling molecules that can activate nuclear hormone receptors including FXR and TGR5 (also known as GPBAR1), which is a cell-surface receptor of the G protein-coupled receptor family [73]. These two bile acid receptors have been described to modulate autophagy in the liver and adipose tissue in fed and fasted states[74].

Several alterations of autophagy, including a decreased amount of LC3 mRNA and LC3-II and an increased amount of p62, have been observed in the liver of mice fed a high-fat diet (HFD), a potent inducer of dysbiosis[74]. Chronic exposure of rats to an HFD can lead to NASH (non-alcoholic fatty steatohepatitis). Development of this liver disease has been associated with dysbiosis and alterations in autophagy, particularly increased expression of hepatic mTOR and p-AKT[75,76]. Interestingly, supplementation of an HFD with a probiotic strain (*Limosilactobacillus reuteri*) and/or treatment of NASH mice with antibiotics (metronidazole) tended to normalize the hepatic content of these two autophagy-related proteins, as well as SCFAs and *Firmicutes* and *Bacteroidetes* fecal contents, thus suggesting a role of the gut microbiota in the modulation of hepatic autophagy[75,76]. To note, some data suggest a role for TGR5 in the regulation of autophagy in response to HFD[74].

### Modulation of autophagy in muscle tissues

An induction of autophagy, characterized by decreased phosphorylation of mTOR (S2448) and ULK1 (S757), an increased amount of LC3-II, and decreased expression of p62, has been reported in a rat model of ischemia/reperfusion injury[77]. Interestingly, intraperitoneal injection of urolithin B (UB), a gut microbiota-derived metabolite, was able to reverse this phenotype[77]. The inhibitory effect of UB on autophagy is thought to activate the Nrf2-related antioxidant response by increasing p62 accumulation and favoring p62-Keap1 interaction[77]. Another argument that suggests the influence of the gut microbiota on heart autophagy has been provided by changes in the expression levels of LC3 and ATG7 observed in heart tissue of rats fed a high-calorie diet supplemented with probiotics (*Lactocaseibacillus rhamnosus*, *Pediococcus acidilactici*, and *Bifidobacterium adolescentis*)[78].

In addition to the heart, autophagy might be regulated by the gut microbiota in other muscles. Recently, high-throughput RNA-seq analysis revealed that the expression levels of autophagy-related genes (*LC3A*, *LC3B*, and *Beclin-1*) were modulated in the skeletal muscles of germ-free piglets compared to control piglets [79]. Moreover, germ-free piglets harbored decreased expression of mTOR and AKT and their phosphorylated forms, phospho-mTOR (S2448) and phospho-AKT (S473), respectively, compared to control piglets[79]. FMT of germ-free piglets with stools collected on healthy donors pigs was effective in restoring the amounts of phospho-AKT and mTOR to a level similar to that of controls[79]. Some microbial-derived metabolites able to influence the muscle autophagy have been identified. For example, a role of UA as a mitophagy (selective degradation of mitochondria by autophagy) inducer in the muscle tissue has been described in the model organism *Caenorhabditis elegans* and in rodents[80].

## SHAPING OF THE GUT MICROBIOTA BY AUTOPHAGY

As developed in the first part of this review, the gut microbiota is able to influence host autophagy by several pathways and through complex regulatory networks governing the autophagy machinery. Reciprocally, autophagy and autophagy-related proteins can shape the gut microbiota (Figure 1). This is particularly well illustrated by changes in the gut microbiota composition observed in mice conditionally deficient for autophagy (*Atg5*<sup>-/-</sup>, *Atg7*<sup>-/-</sup>, and *ATG16L1* T300A knock-in) in the gut[81-83]. Interestingly, alterations of autophagy in peripheral organs such as the liver have been shown to influence the composition of the gut microbiota[84].

A first overall reason that would explain why autophagy activity in the gut mucosa can modulate the abundance of gut microorganisms is that this process is essential to maintain homeostasis of their ecological niche. Indeed, basal autophagy is crucial to maintain the integrity of Lgr5-positive intestinal stem cells that give rise to all differentiated lineages of the intestinal epithelium throughout life[85]. In addition, autophagy contributes to the maintaining of intestinal barrier integrity, particularly by regulating proteins involved in tight junctions (*e.g.*, Claudin-2 and Occludin) on the apical side of



intestinal epithelial cells and by promoting cell survival upon various stress (*e.g.*, bacterial or viral infection, inflammation, or chemical stress)[4,86-88].

The main cellular mechanisms by which host autophagy shapes the gut microbiota (including pathosymbionts) are described below.

### Clearance of pathogens

Autophagy mediates the bulk or selective lysosomal degradation of cellular components. In selective autophagy, selective autophagy receptors (SARs) recognize and bind specific cargoes to promote phagophore formation around them, ultimately leading to their degradation into a mature autolysosome. These specific cargoes can be for instance mitochondria (mitophagy), lipid droplets (lipophagy), protein aggregates (aggrephagy), or peroxysomes (pexophagy)[89]. A selective form of autophagy termed xenophagy is dedicated to the elimination of intracellular pathogens (*e.g.*, bacteria, viruses, fungi, or protozoa) and is supported by the expression of several SARs including NDP52, Optineurin, p62, TAX1BP1, Galectin 8, and TECPR1[90]. Xenophagy has been shown to restrict or avoid the intracellular persistence and the replication of various human pathogenic or pathosymbiotic bacteria, residing either in damaged vacuoles [*e.g.*, *Salmonella* Typhimurium or adherent-invasive *Escherichia coli* (AIEC)] or free in the host cytosol (Group A *Streptococcus*)[91-93]. Thus, by limiting the dissemination of invasive pathogens from the gut lumen to extra-intestinal sites, autophagy also restrains their persistency in the gut microbiota[94,95]. Defects in xenophagy are thought to contribute to the etiology of Crohn's disease (CD) an inflammatory bowel disease (IBD) characterized by chronic and severe intestinal inflammation associated with dysbiosis[96]. In particular, a coding polymorphism (Thr300Ala) in the autophagy-related gene *ATG16L1* that confers an increased risk for the development of CD has been shown *in vitro* and *in vivo* to alter the xenophagy process, thus favoring persistency of the CD-associated AIEC bacteria[92,97,98]. CD risk polymorphisms have also been identified in other autophagy-related genes, including core autophagy genes (*IRGM*, *ULK1*, *ATG4a*, and *ATG4d*) and genes involved more specifically in xenophagy (*NOD2* and *NDP52*)[99-101].

One important point is that, besides xenophagy, non-canonical autophagy such as LC3-associated phagocytosis (LAP) can also contribute to the clearance of intracellular pathogens. This specific form of phagocytosis requires an important set of core autophagy proteins (UVRAG, BECN1, VPS34, LC3, ATG3, ATG4, ATG5, ATG7, ATG12, and ATG16L1), but some other proteins involved in canonical autophagy remain dispensable (ATG14, ULK1, FIP200, and AMBRA1). LAP also distinguishes from canonical autophagy by the formation of single-membrane vacuoles called LAPosomes[102]. Efficiency of LAP to increase clearance of pathogens such as *Listeria monocytogenes* or *Aspergillus fumigatus* has been shown[103,104].

### Mucus layer maintenance

A mucus layer composed of highly glycosylated proteins (mucins) overlays the gut epithelium and represents an important physical barrier limiting the contact of luminal microbes with the epithelium, thus avoiding their potential translocation into underlying tissues[105]. The mucus layer differs between the small and large intestine in terms of physicochemical properties (*e.g.*, thickness, density, and composition) and it is under the influence of numerous factors, including the gut microbiota and the diet [106-108]. Whereas in the small intestine the mucus is non-attached and constitutes a discontinuous layer, it is organized in two layers - the inner and outer mucus layers - in the large intestine. Compared to the intestinal lumen, only few bacterial species are able to live and to persist in the mucus layer. This is partly due to the important amount of various antimicrobial compounds (*e.g.*, IgA, lysozyme, defensins, REG3γ, and phospholipase A2-IIA) found in the mucus layer, particularly in the small intestine. However, some commensal bacteria are molecularly equipped to bind, degrade the mucus glycans, and/or harvest the oligosaccharides, giving them a selective advantage in colonizing this particular ecological niche[109]. Among others, mucin-degrading specialists include species belonging to the genera *Bacteroides* (*e.g.*, *B. thetaiotaomicron* and *B. fragilis*), *Ruminococcus* (*e.g.*, *R. gnavus* and *R. torques*), and *Akkermansia* (*e.g.*, *A. muciniphila*). Interestingly, *A. muciniphila*, a bacterial species belonging to the phylum Verrucomicrobia, is considered as a healthy marker of the intestine since its presence in high abundance is associated with a healthy mucosa whereas reduction of its abundance is associated with intestinal disorders (*e.g.*, obesity and IBD)[110,111]. Studies suggest that the composition of mucus-associated microbiota differs depending on the intestinal segment or the mucus layer (outer or inner layer) that is considered[105]. Bacteria belonging to the phylum Firmicutes have been found in higher abundance in the mucus layer than Bacteroidetes, both in

humans and in rodents[105].

Mucus plays a critical role in the maintenance of the symbiotic relationship between the host and the gut microbiota[112]. Deletion of the *Muc2* gene in mice results in changes in the gut microbiota composition characterized in particular by an increase in the abundance of potential pathobionts (*e.g.*, *Desulfovibrio*, *Escherichia*, and *Erysipelotrichaceae*), and the reduction of beneficial bacteria (*e.g.*, *Lactobacilli*) and *Lachnospiraceae* [112]. In addition to ensuring an habitat and energy sources for a specific part of the gut microbiota, the mucus constitutes a protective layer against pathogen invasion and infection, although some pathogenic bacteria have developed efficient strategies to colonize this special environment and reach the intestinal epithelium (*e.g.*, *Shigella flexneri* and AIEC)[113,114]. Thus, modifications in mucus layer structure or composition by genetic and environmental factors, such as diet, can modify the gut microbiota[105]. These changes can be beneficial when they strengthen the mucus barrier properties, but they can also be deleterious by favoring emergence of pathobionts, by bringing harmful bacteria closer to the epithelial barrier and by destabilizing the symbiotic relationship between the gut microbiota and the host, at the gut mucosa as well as at systemic levels[107].

Mucus secretion into the gut lumen is achieved by specialized secretory cells, the goblet cells. Mucins, the proteins forming the mucus, are packed into secretory granules that are localized on the apical side of the goblet cells and constitutively secreted by fusion of the granules with the plasma membrane. Proteins belonging to the core autophagy machinery (ATG5, ATG7, and LC3B) are critical in mice for the release of these secretory granules by supporting the generation of reactive oxygen species[115].

The NLRP6 inflammasome has been identified, among others roles, as a key factor involved in autophagy-induced regulation of goblet cell secretory functions[116,117]. NLRP6-deficient mice exhibit defective autophagy in intestinal cells including in goblet cells, a phenotype that is associated with impaired mucus layer formation. This mucus alteration may contribute, together with the other NLRP6-related defects, to modulating the composition of the gut microbiota and abnormally bring microbes closer to the epithelial barrier in NLRP6-deficient mice. Analyses of the gut microbiota in NLRP6-deficient mice revealed an abnormal representation of the bacterial phyla Bacteroidetes (*Prevotellaceae*) and Saccharibacteria (formerly known as TM7)[116]. In addition, alteration of the mucus layer in NLRP6-deficient mice enables *Citrobacter rodentium*, a mouse-specific pathogen, to penetrate deeper into the crypts and be more invasive[117]. The role of autophagy in shaping the gut microbiota through the regulation of mucus layer maintenance is also supported by observations made in *Atg7*-deficient mice. Secretion of mucins from goblet cells was diminished in colonic-epithelial cell-specific *Atg7* knock-out mice[82]. This phenotype was associated with an abnormal composition of the gut microbiota characterized in particular by an increased abundance of *Clostridia* and *Prevotellaceae* in *Atg7*-deficient mice. In addition, those authors observed an increased bacterial burden in the colon, a phenotype that could contribute to the exacerbated sensitivity to experimental colitis observed in *Atg7* knock-out mice. Interestingly, stimulation of the autophagy-related process, either by a beneficial bacterial strain (*Bifidobacterium dentium*) or by a polyphenol (oxyresveratrol), has been shown to enhance mucin production by goblet cells in *in vivo* and *in vitro* models[118,119].

### Secretion of antimicrobial compounds in the gut lumen

Autophagy and autophagy-related proteins can also affect the composition of the gut microbiota by regulating the secretion of some antimicrobial compounds released into the gut lumen by enterocytes, Paneth cells, or immune cells. Among them, immunoglobulins of the A class (IgAs) are daily released in huge amount (several grams per day) into the gut lumen and shape the composition of the gut microbiota. Alterations of the gut microbial ecosystem have been reported in the absence of hypermutated intestinal IgA in mice with deficiency of activation-induced cytidine deaminase[120-122]. Changes in the gut microbiota were particularly characterized by expansion of anaerobic bacteria in the small intestine, with a domination by segmented filamentous bacteria[121]. Several other studies in mouse models support the role of IgAs in regulating the diversity and composition of microbiota[123,124]. Data obtained in humans showed that selective IgA-deficiency (sIgAd) is associated with a mild intestinal dysbiosis, characterized by expansion of pro-inflammatory bacteria (*e.g.*, *E. coli*, *Prevotella*), reduction of anti-inflammatory commensals (*e.g.*, *Faecalibacterium*), and perturbation of bacterial dependency association network[125]. In addition, Catanzaro and colleagues reported also a trend toward a decreased alpha diversity and shifts in the relative abundance of some taxa (*e.g.*, increase in *Eubacterium dolichum* and *Rumino-*

*coccus bromii* and decrease in *Paraprevotellaceae*) in human sIgA subjects compared to controls[126]. IgAs are produced by gut-resident antibody-secreting plasma cells (PCs) that display important metabolic adaptations and endoplasmic reticulum expansion to cope with the stress of producing very large amounts of IgAs[127]. Some studies suggest that autophagy is required for sustainable production of immunoglobulins by PCs since mice with conditional deficiency of *Atg5* in B cells had defective antibody responses, with an increased sensitivity of PCs to cell death[128]. In addition, mice deficient for *Atg5* in B cells harbored a decreased number of IgA-secreting PCs isolated from the gut-associated lamina propria, Peyer's patches, and mesenteric lymph nodes in comparison to control mice[129].

Another important antimicrobial compound to which commensal bacteria are directly exposed in the gut lumen is the lysozyme secreted by Paneth cells, which are secretory epithelial cells located at the bottom of the crypts in the small intestine. This antimicrobial protein is also produced by macrophages and neutrophils in the lamina propria. Three types of lysozyme have been described so far across the animal kingdom[130]. Lysozyme causes bacterial lysis by hydrolyzing bacterial cell wall PGN, but it can also induce cationic killing of bacteria by inserting into and forming pores into the lipid bilayer of the bacterial cell membrane. This is the case with c-type lysozyme expressed in human[130]. Not all bacteria are equally sensitive to lysozyme and some pathogenic bacteria have developed strategies to escape its antimicrobial activity[130]. The contribution of lysozyme in shaping the gut microbiota is illustrated by the dysbiosis observed in lysozyme-deficient mice (*Lyz1*<sup>-/-</sup> mice) that is characterized by the expansion of some mucolytic bacteria such as *Blautia gnavus* (formerly known as *Ruminococcus gnavus*)[130,131]. No change in luminal bacterial load and alpha-diversity was observed in the cecum- and mucosal-associated bacteria in the ileum and the colon of *Lyz1*<sup>-/-</sup> mice[131]. However, changes occurred in the composition of the fecal microbiota (expansion of *Dorea formicigenerans* and reduction of *Candidatus Arthromitus*) as well as the ileal microbiota (expansion of *B. gnavus* and *D. formicigenerans* and reduction of *C. Arthromitus*) in *Lyz1*<sup>-/-</sup> mice[131].

Alpha-defensins (also called crypt defensins or cryptdins) are another example of antimicrobial factors that are produced by Paneth cells, whose roles in host defense against enteric pathogens and regulation of the composition of the gut indigenous microbiota have been described[132]. Interestingly, abnormal packaging and secretion of antimicrobial compounds by Paneth cells have been reported in mice harboring Paneth cells deficient for the autophagy-related genes *Atg5*, *Atg7*, and *Atg16l1* and in patients with CD-associated *NOD2* and *ATG16L1* variants[133-135]. Of note, this defect in lysozyme packaging in autophagy-deficient mice required an infectious (viral or bacterial) trigger[136,137].

Even if canonical autophagy is considered as a degradative process, some infectious agents such as *Salmonella* Typhimurium can trigger a secretory autophagy resulting in the formation of LC3-positive, double-membraned lysozyme granules[136]. These autophagosome-like vacuoles are not directed for the fusion with the lysosomes but instead reach the plasma membrane for the release of their content into the gut lumen. Thus, the autophagy machinery participates in the unconventional protein secretion of lysozyme, thereby affecting the composition of the gut microbiota by counter-selecting the lysozyme-sensitive bacteria. In this context, it has been suggested that vitamin D, via binding to the vitamin D receptor expressed by Paneth cells, can sustain autophagy activities in these cells[138]. To note, several studies suggest that expression and secretion of other antimicrobial peptides than lysozyme, such as the defensins and cathelicidins, would be regulated by autophagy. However, the exact molecular mechanisms remain to be determined[82,139].

### Modulation of inflammation

Cell stimulation by microorganisms (*e.g.*, invasive pathogens) or danger signals (*e.g.*, extracellular ATP, uric acid, or HMGB1) are usually associated with the triggering of inflammatory processes through the release of cytokines and chemokines. Inflammation is a protective response that results in tissue repair. However, this response needs to be tightly regulated in order to avoid excessive and/or chronic inflammation that could be detrimental for host tissues. In the gut mucosa, immune tolerance toward the resident gut microbiota should be maintained to avoid chronic gut inflammation and sustain homeostasis[140]. Unbalanced inflammatory responses can also alter the gut microbiota as shown in mouse models of colitis that mimic human IBD, in which inflammation induces microbial dysbiosis[141,142]. Chronic inflammatory state was also suggested to contribute to dysbiosis in IBD patients[143]. This inflammation-driven bacterial dysbiosis is commonly characterized by an overall decrease in bacterial diversity, especially in Firmicutes (*Clostridium* groups) and an overgrowth of



species belonging to *Enterobacteriaceae*[143,144].

Autophagy machinery and autophagy-related proteins are key contributors to the regulation of the inflammatory processes. Thus, one could assume that modulation of inflammation by autophagy could influence the composition of the gut microbiota. Autophagy is usually considered as an anti-inflammatory process, particularly since it controls activation of inflammasomes that are multimeric protein complexes involved in the maturation of pro-inflammatory cytokines[145]. Mice deficient for *Atg16l1* in haematopoietic cells have been shown to be highly sensitive to chemically-induced colitis and produce increased levels of IL-1 $\beta$  and IL-18, two cytokines processed by inflammasomes[146]. *Atg16l1*-deficient macrophages that were stimulated by LPS also produced higher amounts of these cytokines compared to wild-type macrophages. Autophagy can alleviate activation of inflammasomes, at least by removing stimuli that induced them (*e.g.*, intracellular infectious agents) and by degrading some inflammasome components (*e.g.*, NLRP1, NLRP3, AIM2, or pro-CASP1)[147]. Interestingly, alterations of the gut microbiota (*e.g.*, increased abundance of Bacteroidetes) as well as enhancement of the local Th1 and Th17 immune responses have been reported in mice with dextran sodium sulfate (DSS) colitis that express the CD risk allele *ATG16L1* T300A - a genetic context known to impair some autophagy-related functions - compared to DSS-treated wild-type mice[81]. Similar observations have been made in gnotobiotic mice expressing the CD risk allele *ATG16L1* T300A and inoculated with human stools from active CD patients[81]. These data illustrated how a subtle polymorphism in an autophagy-related gene could deeply impact the equilibrium between immune responses and the gut microbiota.

Autophagy is also able to modulate signaling of interferons, notably by degrading key players of type-I interferon responses (*e.g.*, RIG-I, STING, MDA5, IRF3, MAVS, and cGAS)[148]. Abnormal regulation of interferon signaling can lead to alterations of the gut microbiota as described in knock-out mice and viral infection models[149]. Interestingly, the gut microbiota has been described to stimulate intestinal autophagy *via* the induction of the type-II interferon, and this microbiota-mediated activation of autophagy has been shown to protect the host against infection by the protozoan parasite *Toxoplasma gondii* by limiting the deleterious production of the pro-inflammatory cytokine TNF- $\alpha$ [150]. Autophagy has also been described to limit the production and the secretion of various cytokines including TNF- $\alpha$ , IL-1 $\beta$ , IL-23, IL-6, TGF- $\beta$ , and MIF[151,152]. However, the molecular mechanisms by which autophagy regulates their expression remain elusive. In many cases, autophagy reduces secretion of cytokines by simply alleviating cellular stress that triggers the inflammatory responses.

## CONCLUSION

Given its crucial role in regulating homeostasis at both cell and tissue levels, it is not surprising that alterations of autophagy are connected to a large number of disorders (*e.g.*, IBD, cancers, and neurodegenerative diseases). To assume its various functions, autophagy activation is tightly regulated and the gut microbiota has recently emerged as a contributor in its regulatory networks in both the gut mucosa and other tissues. This advance in the understanding of the molecular mechanisms supporting this highly integrated cellular process that tip the balance between health and disease offers new opportunities to develop preventive or therapeutic tools. Indeed, the gut microbiota appears as a promising target to restore functional autophagy or to prevent its alterations in various disease conditions. The growing interest that was aroused from the discovery of such a hub position occupied by the gut microbiota in maintaining physical and mental health status has led to the conceptualization, development, and/or examination of various tools to manipulate the gut microbiota (probiotics, prebiotics, synbiotics, postbiotics, FMT, Crispr/Cas9, diet...). In the era of personalized medicine, such a toolbox could constitute a key element that could be integrated in the therapeutic strategies. However, further explorations of the interplay between the gut microbiota and autophagy are needed. Important advances have been made in understanding the local dialogue between the gut microbiota and autophagy at the level of the gut mucosa, but less is known about how and in which extent they communicate at the systemic level. Bi-directionality of the interactions between the gut microbiota and the autophagy network, plasticity and complexity of the gut microbiota and its multiple effects on host, as well as pleiotropy of the functions of autophagy are all factors that increase the level of complexity of the system. Better characterization of the cellular and molecular actors from both sides - the gut

microbiota and autophagy - that contribute and regulate the framework of their interactions to maintain homeostasis constitutes a prerequisite to propose new preventive and therapeutic tools in pathological conditions associated with dysbiosis and/or autophagy dysfunction.

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