Review

mTOR and gut microbiota in various disorders: mechanisms and potential drugs

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Abstract: The mammalian or mechanistic target of rapamycin (mTOR) integrates multiple intracellular and extracellular upstream signals involved in the regulation of anabolic and catabolic processes in cells, and plays a key regulatory role in cell growth and metabolism. Activation of the mTOR signaling pathway has been reported to be associated with a wide range of human diseases. A growing number of in vivo and in vitro studies have demonstrated that the gut microbes and its complex metabolites can regulate host metabolic and immune responses through the mTOR pathway, and result in disorders of host physiological functions. In this review, we summarize the regulatory mechanisms of gut microbes and mTOR in different diseases, and discuss the crosstalk between gut microbes and their metabolites and mTOR in the disorders in gastrointestinal tract, liver, heart and other organs. We also discuss the promising application of multiple potential drugs that can adjust the gut microbiota and mTOR signal pathways. Despite the limited findings between gut microbes and mTOR, elucidating their relationship may provide new clues for the prevention and treatment of various diseases.

Keywords: mTOR; gut microbes; metabolites; therapy

1. Introduction

The mammalian or mechanistic target of rapamycin (mTOR) is a conserved serine/threonine kinase with two structurally similar but functionally distinct protein complexes named mTOR complex1 (mTORC1) and 2 (mTORC2). mTOR is sensitive to different environmental factors, such as energy and nutrient availability, and is involved in regulating cellular activities such as cell proliferation, cell growth, protein synthesis and autophagy[1-3]. Dysregulation of mTOR signaling has been reported in manydiseases such as cancer, diabetes, heart disease, and neurological disorders[2, 4, 5].

Commensal microorganisms in human body have gained more and more attentions in recent years. The vast majority of commensal microorganisms colonize in the gut and differ between individuals due to genetic background, age, sex, diet, and other factors. It has been found that gut microbiota are involved in the regulation of various diseases such as intestinal diseases, liver diseases, heart diseases, obesity[6], diabetes[7] and Alzheimer's disease[8], and are associated with physiological processes such as immunity and autophagy.

In the present review, we discuss mTOR signaling in detail and review recent evidence that gut microbes and mTOR are involved in multiple diseases and the underlying mechanisms. We also discuss the potential therapeutic drugs currently available to regulate gut microbes and mTOR signaling pathway indifferent disorders.

2. Mechanistic target of rapamycin (mTOR)

2.1. mTORC1 and mTORC2 structure

mTOR is a member of the phosphoinositide 3-kinase(PI3K)-related protein kinase (PIKK) family, which has serine/threonine protein kinase activity[9, 10]. In mammals, mTOR combines with different subunits to form two macromolecular complexes, mTOR complex 1 (mTORC1) and 2 (mTORC2).

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Some subunits exist in both complexes, while others are specific components in only one complex[5].

mTORC1 is composed of mTOR, mammalian lethal with SEC13 protein 8 (mLST8) and regulatory-associated protein of mTOR (RAPTOR) as core components, forming a dimeric structure[11-13]. RAPTOR is the defining subunit of mTORC1, which is responsible for recruiting substrates and its subcellular localization[14]. Proteins proline-rich AKT substrate of 40 kDa (PRAS40), DEP domain-containing mTOR-interacting protein (DEPTOR), and the Tti1/Tel2 complex are the remaining component of mTORC1[1]. Specially, both PRAS40 and DEPTOR are endogenous repressor proteins of mTORC1[15, 16].

The mTORC2-specific combinatorial proteins include rapamycin-insensitive companion of mTOR (RICTOR)[17], protein observed with RICTOR 1/2 (PROTOR 1/2)[18], mammalian stress-activated protein kinase-interaction protein 1 (mSIN1)[19], and some common subunits of mTOR kinase, such as mLST8, DEPTOR, Tel2 and Tti1 with mTORC1[2]. RICTOR and mSIN1 are the defining subunits of mTORC2. The N-terminal of mSIN1 is embedded in RICTOR and binds to mLST8 to maintain the stability of mTORC2[20]. Meanwhile, mSIN1 ensures substrate recruitment[21] and plays an important role in plasma membrane localization and inhibition of mTORC2[22, 23].

2.2. Upstream regulation of mTORC1

mTORC1 is more well-characterized of the two complexes. It integrates multiple intracellular and extracellular upstream signals including growth factors, energy inputs, and nutrients. The activation and localization of mTORC1 requires upstream signals of two groups of small G proteins, that is, Ras homolog enriched in the brain (Rheb) and Ras-related GTPases (Rags)[19-21]. mTORC1 is recruited from the cytoplasm to the lysosome by Rags and activated by Rheb in the GTP-bound state on the lysosome when the cellular environment contains sufficient cytokines, nutrients, endocrine signals and energy[22].

mTORC1 is regulated by growth factors and other mitogens, and the tuberous sclerosis complexes (TSC)1/2 plays an important role in this process. TSC1/2 acts as a GTPase-activating protein (GAP) on lysosomal Rheb, converting it to an inactive GDP-bound state to inhibit mTORC1[20, 23]. TSC1/2 transmits multiple upstream signals that affect mTORC1. Insulin and insulin-like growth factor 1 (IGF1) phosphorylate TSC2 via the PI3K/AKT pathway, which dissociates TSC from the lysosomal surface and activates mTORC1[24-26]. AKT stimulates phosphorylation of the endogenous repressor of the mTORC1 complex, PRAS40, to promote Rheb-driven mTORC1 activation in a TSC1/2 non-dependent manner[10, 27]. Pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), phosphorylate TSC1 via IκB kinase β (IKKβ), leading to TSC1/2 inhibition[28]. Classical Wnt signaling activates mTORC1 by inhibiting glycogen synthase kinase 3 (GSK3), and GSK3 phosphorylates TSC2 by initiating phosphorylation in an AMPK-dependent manner[29]. In addition, TSC is inhibited by regulation of ERK and P90 ribosomal S6 kinase (RSK)[30, 31].

mTORC1 is inactive when the environment is in low oxygen and energy,in which the cellular synthetic response is inhibited. When ATP production is poor, AMP-activated protein kinase (AMPK) activation is sensitive to AMP and ADP [32]. AMPK inhibits the mTORC1 complex during energy stress via a twin mechanism: AMPK act directly on mTORC1 to phosphorylate Raptor[33]; it also phosphorylates TSC2 and increase its GAP activity on Rheb, indirectly inhibiting mTORC1[34]. When oxidative stress is enhanced, thioredoxin 1 (Trx1) in cardiomyocytes interacts directly with mTORC1 to maintain its kinase activity[35]. Hypoxia induces transcriptional regulation of DNA damage response 1 (Redd1) expression to activate TSC1/2[36, 37]. Notably, DNA damage also induces the expression of various p53 target genes, including phosphatase and tensin homolog deleted on chromosome 10，TSC1/2 and AMPK, which deliver signal to mTORC1[38, 39]. However, in cardiomyocytes, DNA-damage-inducible transcript 4-like (DDiT4L) inhibits mTORC1 but activates mTORC2 activity[40]. Additionally, Cellular hypoglycemic conditions inhibit the binding of hexokinase-II (HK-II) to mTORC1[41]. Other cellular stresses such as amino acid deficiency, hyperosmolarity, and PH stress induce TSC2 recruitment to the lysosome, thereby negatively regulating mTORC1[42].

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mTORC1 can be activated by amino acids, a process that is dependent on the involvement of Rag GTPases. Mammals have four species ranging from Rag-A to Rag-D, while Rag-A or Rag-B form obligate heterodimers with Rag-C or Rag-D, respectively. The active conformation of RAG is related to the loading state of the nucleotide, when in the "on" state, RagA/B binds to GTP and RagC/D binds to GDP. At this point, mTORC1 is recruited into the lysosome by RAG and is then activated by Rheb. In the presence of sufficient nutrients, the Rag in the "on" state interacts with RAPTOR to ensure the activation of mTORC1[43]. When amino acid is exhausted, Folliculin (FLCN) relocalizes to the lysosome and prevents the exchange of GDP with GTP in Rag-A[44].

mTORC1 perceives amino acid concentrations in lysosomes and envelopes through multiple mechanisms, and these processes require different complexes to deliver amino acid signals to the Rag[45]. Several well-characterized amino acid sensors have been identified. Sestrin2 is a cytoplasmic leucine sensor of the mTORC1 pathway[46]. Under leucine starvation conditions, Sestrin2 binds and inhibits GATOR2; after restoring leucine levels, leucine binds to Sestrin2 and dissociates GATOR2 to activate mTORC1[47]. Similar to Sestrin2, GTPase-activating protein activity toward Rags-1 (CASTOR1), a cytoplasmic arginine sensor. Arginine binds directly to CASTOR1 and relieves the inhibition of GATOR2[46]. SLC38A9, a lysosomal arginine sensor, transmits state information of amino acids to mTORC1. SLC38A9 interacts with the Rag GTPase-Ragator complex, which is localized to the lysosome, mediating the transport of leucine-based essential amino acids and activating mTORC1 in an arginine-dependent manner[48-50]. S-adenosylmethionine (SAM) sensor upstream of mTORC1(SAMTOR), the upstream sensor of SAM, binds to GATOR1 and negatively regulates mTORC1 when methionine is starved or SAM is at low levels [51]. In addition, vesicular H^+-adenosine triphosphate ATPase (v-ATPase) is required for amino acid activation of mTORC1[52].

2.3. Substrates and functions of mTORC1

Once activated by different inputs, mTORC1 responds by acting on different substrates. It not only promotes anabolic synthesis such as protein, nucleic acid and lipid synthesis, cellular metabolism and energy expenditure, but also inhibits catabolic processes, including autophagy.

Firstly, mTORC1 phosphorylates eukaryotic initiation factor 4E-binding proteins (4E-BPs) and p70 S6 kinase 1 (S6K1) thereby promoting protein synthesis[24]. Phosphorylation of 4E-BP1 releases eukaryotic translation initiation factor 4E (eIF4E) and promotes the formation of its complex, thereby derepressing the translation process. Phosphorylated S6K1 phosphorylates its eponymous target ribosomal protein S6 to participate in controlling the transcriptional process during ribosome genesis[25]. In addition, S6K1 augments protein synthesis through activation of eIF4B and degradation of programmed cell death 4 (PDCD4)[26, 27]. Although both are involved in the control of translation, the role of 4E-BP1 is more prominent[3].

Secondly, mTORC1 controls the synthesis of lipids and nucleic acids required for cell proliferation. To a large extent, mTORC1 acts through the transcription factors sterol regulatory element binding protein 1/2 (SREBP1/2), a substrate that controls the expression of multiple lipid genes. Transcription of SREBP1/2 can be regulated by mTORC1 through modulating phosphorylation of lipin 1 or S6K1-dependent manner.mTORC1 inhibition reduces SREBP1/2 expression impairing its function and decreasing lipid synthesis[28-30]. Phosphorylation of mTORC1 also increased the expression level of peroxisome proliferator-activated receptor γ (PPAR-γ) to promote adipogenesis[31, 32]. In addition, mTORC1 promotes lipid biosynthesis by regulating SR protein kinase 2 (SRPK2) to stabilize lipid biosynthetic enzymes[33].

mTORC1 controls the synthesis of new pyrimidines and purines in different cellular models to enrich the nucleotide pool for nucleic acid synthesis, which is essential to maintain DNA replication and RNA synthesis. De novo synthesis of pyrimidines of mTORC1 is mediated by S6K1 promoting the enzymatic activities of carbamoyl-phosphate synthetase 2, and aspartate transcarbamoylase, dihydroorotase (CAD)[34, 35]. mTORC1 stimulates activating transcription factor 4 (ATF4) and mitochondrial tetrahydrofolate cycle enzyme methylenetetrahydrofolate dehydrogenase 2 (MTHFD2) to promote purine synthesis[36].

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Moreover, mTORC1 also actively regulates cellular metabolism and ATP production to. mTORC1 increases the expression of glycolytic enzymes by activating the transcription and translation of hypoxia-inducible factor 1α (HIF1α), while the activation of SREBPsenhances the pentose phosphate pathway[29]. It has been shown that mitochondrial biogenesis is regulated by mTORC1 through promoting the binding action of transcription factor yin–yang 1 (YY1) with PPARγ coactivator-1a (PGC1-a)[37]. mTORC1 enhances mitochondrial activity through 4E-BP to increase ATP production[38].

In addition to its positive effects on anabolism, mTORC1 negatively regulates catabolism, especially autophagy, to promote growth. Autophagy is the process of degradation of intracellular components, which is considered essential for the organism's starvation response as well as for organelle renewal. Unc-51-like autophagy-activating kinase 1 (ULK1) and ATG13 form in complex with 200 kDa FAK family interacting protein (FIP200) and ATG101 to promote the autophagy[39]. mTORC1 phosphorylates and inhibits ULK1 and A TG13 to negatively regulate autophagy[40-42]. mTORC1 can also bind and phosphorylate UVRAG thereby enhancing the antagonistic effects of autophagic vesicle maturation in a nutrient-rich environment[43]. When mTORC1 is repressed, nuclear translocation of transcription factor EB (TFEB) and transcription factor E3 (TFE3) are promoted, facilitating the expression of multiple genes associated with autophagy and lysosomes[44-47]. Recent studies have shown that mTORC1 directly phosphorylates VAMP8 blocking STX17-SNAP29-VAMP8 SNARE complex formation and inhibiting autophagosome-lysosome fusion[48]. mTORC1 may also affect autophagy by regulating effectors such as death-associated protein 1 (DAP1)[49] and WIPI2[50].

2.4. Upstream regulation of mTORC2

mTORC2 is activated by growth factors such as insulin through PI3K. The PH domain in mSIN1 can combine with phosphatidylinositol 3,4,5-trisphosphate (PIP3), upon PI3K activation, and result in mTORC2 activation[23]. Stimulated by PI3K signaling, the ribosome binds to mTORC2, which is essential for mTORC2 activation[51]. mTORC2 activation also requires the interaction with TSC1/2 independent on Rheb, but the mechanism remains unclear[52].

mTORC2, in addition to being regulated by PI3K/AKT, is also regulated through the mTORC1 negative feedback loop. Degradation of IRS1 induced by mTORC1 and its effector S6K inhibits insulin/PI3K/AKT signaling[53-55]. Growth factor receptor-bound protein 10 (Grb10), which negatively regulates insulin/IGF-1 signaling, is activated by mTORC1 and mediates the inhibition of PI3K[56, 57]. In addition, SK6 promotes RICTOR and mSIN1 activity, respectively, thereby inhibiting mTORC2[58, 59]. In contrast, AMP-activated protein kinase (AMPK) directly phosphorylates the complex of mTORC2 and RICTOR and promotes AKT signaling, a process that is independent on mTORC1-mediated negative feedback[60].

Compared with mTORC1, the cellular localization of mTORC2 is more diverse and can localize on the plasma membrane, endoplasmic reticulum, mitochondria, and mitochondria-associated ER membranes (MAM)[61]. However, it remains to be unrevealed how mTORC2 is stimulated at these sites.

2.5. Substrates and functions of mTORC2

mTORC2 regulates a variety of important cellular functions，such as cell structure, metabolism, survival, and proliferation, by regulating members of the AGC family including AKT, serum, glucocorticoid-induced protein kinase 1 (SGK1) and protein kinase C-α(PKC-α). mTORC2 can phosphorylate its terminal hydrophobic motif Ser473 to directly activate AKT[62]. Deletion of AKT-Ser473 phosphorylation impaired only forkhead box O1/3a (FoxO1/3a) and did not affect TSC2 and GSK3-β[63, 64]. mTORC2 activates SGK1 and its substrate N-myc downstream regulated gene 1 (NDRG1) to promote cell survival in hypoxic conditions, which is similar to the effect of FOXO3a[65-67].In addition, mTORC2 mediates cell survival by inhibiting mammalian sterile 20-like kinase (MST1) of the hippo pathway[68, 69]. PKC-α is the third AGC kinase activated by mTORC2, which is involved in the regulation of cytoskeleton and structure together with RHO GTPases[17, 70].

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3. Gut microbiota

Trillions of microorganisms have adapted to inhabit the human intestine and form a complex ecological community, which is an indispensable part of the human body[71]. The microbiota obtained at birth developed synchronously with the development of host, and maintains its stability and diversity after adulthood[72]. Because microorganisms are distributed in different regions with the host, diversity is determined by the local environment including diet[73], high altitude and other extreme weather[74, 75].

The gastrointestinal tract (GI) is composed of stomach, small intestine(SI) and large intestine(LI).Specific microbiota reside in the unique microenvironment of each section[72]. Five categories of microbiota reside in the stomach of healthy people, including *Firmicutes, Bacteroidetes, Actinobacteria, Fusobacteria and Proteobacteria*[76]. *Gram-positive bacteria* and *facultative anaerobic bacteria* are mainly found in the SI, such as *Lactobacilli, Enterococci* and *Streptococci*, which is benefical to food digestion and nutrition absorption[77]. *Firmicutes* and *Bacteroidetes*, mainly settle in the large intestine[78].

In addition to the number, species and composition of the gut microbes, the metabolites of the microbes have attracted more attention these years. Undigested carbohydrates in the SI are fermented by microorganisms in the LI to produce single chain fatty acids (SCFAs), namely acetate, propionate and butyrate.

Gut microbiota contribute to the defens of intestinal pathogens, nutrition and energy absotption from the diet, and maintainace of normal immune function[79]. Disregulation of the normal balance between gut microbiota and host is involved in many disorders, such as obesity[80], aging[81], inflammatory bowel disease[82], neurological diseases[83], and the occurrence and development of tumors[84]. Recent studies have found that intestinal microorganisms are more closely related to mTOR signaling pathway (as shown in Figure 1).

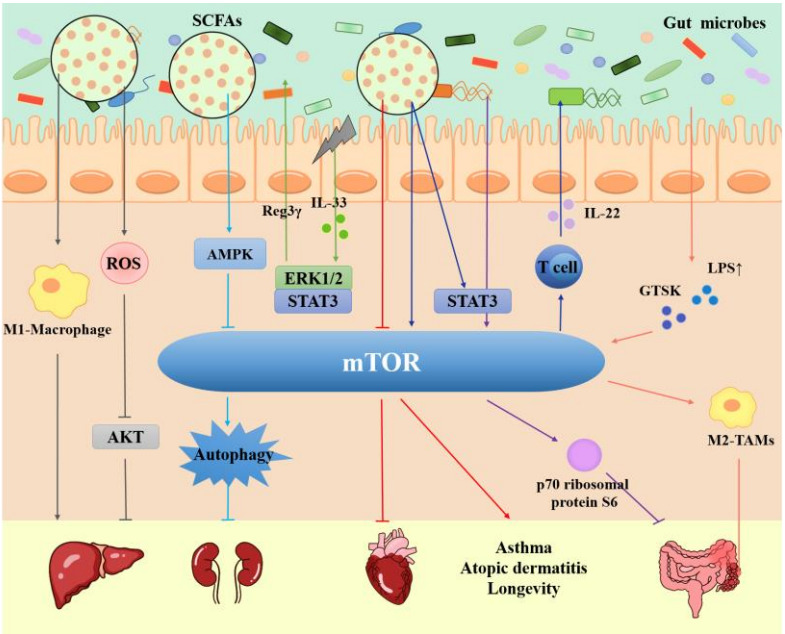

Figure 1. Schematic representation of crosstalk between gut microbes and mTOR signaling pathway in different diseases. Gut microbes directly or indirectly stimulate mTOR through changes in their own abundance or metabolites (mainly SCFAs), integrating intra- and extracellular signals, which in turn influence disease development. A detailed description of these interactions is provided in the main text. Arrows represent activation and horizontal lines indicate inhibition. The different coloured lines represent different regulatory mechanisms. Abbreviations: AMPK: AMP-activated protein kinase, ERK1/2: Extracellular signal–regulated kinases 1/2, ROS: Reactive oxygen species, SCFAs: Short chain fatty acids, IL33: Interleukin-33, IL-22: Interleukin-22, CTSK: Cathepsin K, LPS: lipopolysaccharide, TAMs: Tumor-associated macrophages.

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3.1. Gut microbiota, mTOR and Intestinal Diseases

Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), is a chronic recurrent intestinal inflammatory disease mediated by immunity. The most common symptoms of these diseases are abdominal pain, diarrhea and weight loss, and the incidence rate is increasing worldwide[85-87]. Intestinal inflammation caused by western diet is accompanied by the activation of mTOR, which is contingent on microbial derived pathogen-associated molecular patterns, in intestinal epithelial cells (IEC), such as endotoxin, poly (I: C) and flagellin[88]. It is worth noting that IL-33 can activate the mTOR pathway of intestinal epithelial cells and promote the induction of REG3γ to faciliate the symbiosis of intestinal microflora[89]. Short chain fatty acids (SCFAs), a metabolite of intestinal microorganisms, can promote the production of IL-22 by $CD4^+$ T cells and IEC. In particular, butyrate can accelerate the phosphorylation of STAT3 and mTOR to up regulate the expression of IL-22 to maintain the stability of the intestinal environment[90].In addition, extra-intestinal activation of microbiota-specific $CD4^+$ T cells and concomitant inhibition of mTOR metabolism can remove $CD4^+$ T memory (TM) cells thereby preventing colitis[91].

Chronic inflammation is a characteristic of IBD and the driving force of human colon cancer. Studies have shown that the microbial composition of mouse colon induced by dextran sodium sulfate (DSS) and/or azomethane (AOM) is significantly different from that of the control group. It is worth noting that the abundance of Clostridium and Staphylococcus aureus is increased. Meanwhile, PI3K/AKT/mTOR, fatty acid metabolism and oxidative phosphorylation signals were found to be upregulated in DSS / AOM mice by gene expression profiling[92]. *Clostridium butyricum* promotes the upregulation of AKT/mTOR and downstream molecule p70 ribosomal protein S6 kinase expression and alters the production of anti-inflammatory cytokines to exert a protective effect on intestinal barrier function[93]. In contrast, *Lactobacillus X12* inhibited the growth of colorectal cancer cells by inhibiting mTOR and regulating cell cycle-associated proteins p27 and E_1[94]. In the genesis and development of colon cancer, the imbalance of gut microbiota is accompanied by the release of endotoxin lipopolysaccharide (LPS)[95]. With the increase of LPS level, Cathepsin K (CTSK), a metastasis-related secretory protein, secreted by tumor can interact with macrophage membrane receptor Toll-like receptor 4 (TLR4) to activate mTOR pathway. The TLR4-mTOR-dependent pathway accelerates the M2 polarization of tumor associated macrophages to promote the progression of colorectal cancer[96].

3.2. Gut microbiota, mTOR and Liver Diseases

The gut microbiota and mTOR signaling pathways have been shown to play an important role in liver diseases[97-99]. Inoculation of mice treated with high-fat diet with feces from patients with nonalcoholic fatty liver disease (NAFLD) result in aggravated liver injury[100]. Recently, study has shown that NF73-1, an *E. coli* isolated from the intestines of NASH patients, can enter the liver through TLR2/NLRP3, induce M1 macrophages, and finally promote the development of NAFLD，with the activation of mTOR-S6K1-SREBP-1/PPAR-α[101].In fact, the abundance of microbiota is low and diversity is less in mice with NAFLD. Interestingly, Alisol B 23 acetate (AB23A) could rebalance the gut microbiota, especially reducing the abundance of *Firmicutes*/*Bacteroidaeota* and *Actinobacteriota*/*Bacteroidaeota*. During this process, AB23A plays the role of probiotics on NAFLD by inhibiting activity of mTOR, TLR4 and NF-κB[102]. Similarly, *Lactobacillus rhamnosus*, which is considered to be one of the most extensive probiotic, has also been revealed in the role of alcoholic fatty liver. The combination therapy of *Lactobacillus rhamnosus* culture supernatant and bone marrow mesenchymal stem cells (BMMSCs) can accelerate autophagy and improve alcoholic fatty liver disease by inhibiting PI3K/mTOR pathway[103].In hepatocellular carcinoma cell line Huh-7, Pant et al. found that butyrate, a short chain fatty acid produced by gut microbiota during anaerobic fermentation, inhibited the phosphorylation of AKT and mTOR by inducing reactive oxygen species (ROS), thereby inducing autophagy of liver cancer cells[104]. In general, the disregulation of the gut microbiota and mTOR signal will promote the progression of liver diseases, in which autophagy and immune cells are also involved.

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3.3. Gut microbiota, mTOR and Heart disease

The gut microbes and mTOR signaling pathways are both involoved in heart disease. Butyrate, a metabolite of gut microbiota, significantly inhibits PI3K/AKT/mTOR pathway while enhancing ATG5 mediated autophagy in the murine STC-1 enteroendocrine cell line[105]. When mTOR is activated by PI3K and AKT, it can inhibit autophagy by regulating the activity of ULK1[106]. Urolithin B(UB), a metabolite of gut microbiota, can inhibit autophagy through AKT/mTOR/ULK1 pathway to play a protective role in myocardial ischemia-reperfusion injury in rats. More specifically, the p62/Keap1/Nrf2 signaling pathway protects against oxidative stress and caspase 3-dependent apoptosis[107]. Similarly, this protective effect was also confirmed in the mouse model of myocardial infarction (MI). UB inhibits cardiomyocyte apoptosis by activating AKT/mTOR pathway and simultaneously suppresses NF-κB to reduce the occurrence of arrhythmia after hypoxia[108].

3.4. Gut microbiota, mTOR and Other Diseases

The interaction of gut microbiota and mTOR is also reported in other diseases, in which autophagy, energy metabolism and immunity are involved.

AMP activated protein kinase (AMPK), a key energy receptor, can inhibit the formation of auto phagosomes caused by mTOR[42]. Sodium butyrate can activate the phosphorylation of AMPK in the renal tissue of diabetic mellitus (DM) rats to inhibit mTOR and increase the number of auto phagosomes, thus aggravate the kidney injury of DM rats[109]. In the rat model of diet induced obesity (DIO), Xiexin Tang (XXT) promotes the production of SCFAs by intestinal flora and the expression of AMPK to inhibit the activation of mTOR signal pathway, to adjust the disorder of lipid metabolism and reduce systemic inflammatory response[110]. In addition, both IL-37 and alanylglutamine can increase the expression of AMPK and reduce the expression of mTOR to alleviate chronic inflammation in the mouse models of allergic asthma and atopic dermatitis (AD), respectively. In this process, the diversity and metabolites of intestinal microorganisms are regulated. The difference is that IL-37 increases autophagy related IC3B, decreases autophagy related ubiquitinated protein p62, and the NF-κB and STAT3 signaling pathways may be involoved in the treatment of alanylglutamine[111, 112].A recent study showed that environmental low-dose radiation (LDR) compromises the intestinal barrier and increases PA in the organism. This is accompanied by increased expression of PYCR1 in the liver and inhibition of the IRS-1/AKT/mTOR axis, and an accompanying increase in *Parabacteria* in the gut microbiota, leading to impairment of HFD-induced obesity and insulin resistance[113]. In the mouse models of high-fat diet, simultaneous inhibition of mTORC1 and mTORC2 could aggravate intestinal inflammation and destroy blood glucose homeostasis, while specific inhibition of mTORC1 could alleviate intestinal inflammation and improve glucose tolerance. Interestingly, the chronic inhibition of mTORC2 contributed to the changes of gut microbiota caused by high fat, such as *Turicibacter* and unclassified *Marinilabiliaceae*[114]. Long term inhibition of mTOR can prolong the life span of mice and mildly change intestinal metagenes, which are related to immune cells[115]. Moreover, *Prevotella Copri* obtained from pig intestines can promote chronic inflammatory response and fat deposition through TLR4 and mTOR signaling pathways after its inoculation in mice[116].

3.5. Gut microbes and mTOR in the analysis of big data

The human intestinal microbes are so numerous and diverse that they have been called the "second genome". The microbial census began with 16s rRNA gene sequencing, and PCR is applied to amplify 16s rRNA and then two to three times sanger sequencing is utilized to complete the gene sequencing. In order to make the sequencing more accurate, second-generation sequencing and third-generation technologies were developed to make the study of microbiota genomics more efficient and rapid[117].

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In order to understand the impact of gut microbes on human health, researchers analyzed 124 human-derived feces by macro genome sequencing to create a genomic catalog of the human gut microbiome, covering most of the prevalent gut microbial genes in humans[118]. More studies are delving into the role of microbiota in different health and disease conditions through transcriptomic and metabolomics. Analysis of microorganisms in feces by 16S rRNA sequencing revealed a relative decrease in bacterial abundance in mice with colorectal cancer[119]. In addition, analysis of colonic tissues by whole transcriptome profiling revealed that enhanced PI3K-AKT-mTOR signaling in colorectal cancer mice was accompanied by a significant increase in the expression level of phosphorylated S6 ribosomal protein (a downstream target of the mTOR pathway)[92]. In 129 stool samples from NAFLD patients consuming high carbohydrate (HC), alterations in intestinal microbial species were found, with a significant increase in the abundance of *Enterobacteriaceae* and a significant decrease in the abundance of *Ruminococcaceae* compared to 75 normal samples. Meanwhile, analysis of 90 liver transcripts revealed that the expression of SREBF2 and mTOR increased with the enhancement of NAFLD activity[120].

4. Application of multiple drugs affecing gut microbes and mTOR in the treatment of different diseases

In recent years, further studies on, the direct or indirect interaction between gut microbiota and mTOR in various diseases have been revealed. The significance of a variety of physiological activities in the body, including metabolic response, autophagy, immune response and so on, is also shown above. Many kinds of drugs have demanstrated promising evidence in preclinical studies in different diseases as shown in Table 1. More effective treatment methods need further evaluation one effectiveness and safety in clinical trials.

4.1. Treatment of Intestinal diseases

Mu Xia Li et al. revealed the mechanism of Huangqin decoction (HQD) in the treatment of gastrointestinal diseases such as UC. As a traditional Chinese medicine therapy, HQD could improve the clinical performance of DSS induced UC model, inhibit the inflammatory response in vivo and rebalance the gut microbiota. HQD treatment activated PI3K/AKT/mTOR signaling by up regulating amino acid metabolism, andimproved the barrier function of intestinal epithelial[121, 122]. Dandan Wang et al. found that a polysaccharide was isolated from Panax ginseng (GP) reduced the intestinal injury of DSS induced colitis in rats. GP treatment increased microbial community diversity, improved the compositions of gut microbiota，reduced the phosphorylation level of mTOR and activated autophagy to inhibit inflammation[122]. In addition, SCFAs and metformin (MTF) can regulate intestinal immunity to prevent colitis, and have potential therapeutic applications[90, 123]. Theabrownin (TB) inhibited the development of CRC by decreasing *Bacteroidceae* and *Bacteroides* associated with CRC and increasing the production of SCFAs, thereby inhibiting cell proliferation through suppression of PI3K/AKT/mTOR phosphorylation[5].

4.2. Treatment of Liver Diseases

In the HFD-induced rat model of NAFLD, fecal levels of *Firmicutes* and *Bacteroidetes* and short chain fatty acids returned to normal in the treatment with *L. reuteri* + MTZ alone or in combination with MTF More precisely, combined therapy prevented steatosis and the progression of liver injury by inducing autophagy by p-AKT/mTOR/LC-3II pathways in the liver[124]. Fan Xia et al. found that AB23A not only reduced the abundance of *Firmicutes*/*Bacteroidaeota* and *Actinobacteriota* /*Bacteroidaeota*, but also decreased the activities of mTOR and TLR4 to prevent the progress of NAFLD[102]. Besides, the combined LGG-s and BMMSC treatment also inhibited PI3K/mTOR signal to accelerate autophagy, which has the potential to alleviate alcoholic steatohepatitis[125].Interestingly，in the HFD-induced metabolic syndrome, Zhenzhen Deng et al. found that low molecular weight fucoidan

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fraction LF2 and MTF have similar effects on gut microbiota, increasing the proportion of *Verrucomicrobia* and enriching the abundance of *Akkermansia muciniphila*. LF2 promoted the phosphorylation of PI3K and AKT in a dose-dependent manner, but reversed the over activation of mTOR, thereby improving lipid metabolism[126].

According to the report, the gut microbiota can regulate the immune response of hepatocellular carcinoma (HCC), thus readjust the gut microbiota could be a potential option for HCC treatment[127]. Butyrate, considered as a potential candidate drug for the treatment of liver cancer, could inhibit the phosphorylation of AKT and mTOR through reactive oxygen species, resulting in the up regulation of autophagy proteins beclin 1, ATG 5, LC3-II, thereby promoting the formation of autophagy bodies[104]. Curcumin can significantly sensitize hepatoma cells to 5-FU cytotoxicity and increased the apoptosis rate through synergistic effects. The gut microbiota facilitates oral utilization of curcumin in vivo and enhances chemo-sensitivity of hepatocellular carcinoma cells to 5-FU by blocking PI3K/AKT/mTOR signaling pathway in vitro[128].

4.3. Treatment of Other Diseases

Probiotics regulate PI3K/AKT/mTOR signaling pathway, which is beneficial to coordinate immune response. Probiotics fermentation technology (PFT) activated PI3K/AKT signal transduction pathway but inhibited glycogen synthase kinase-3β (GSK-3β) and mTOR signal, its potential role in the treatment of Alzheimer's disease was parallel to that of pioglitazone[129]. Additionally, there are reports that *Aronia melanocarpa* polysaccharide (AMP) activated PI3K/AKT/mTOR signaling pathway and its downstream apoptotic protein family, inhibitd brain cell apoptosis and enriched intestinal beneficial bacteria to delay aging, which had similar function to MogrosideV and its metabolite 11-oxo-mogrol[130, 131]. In contrast to the mechanism of action of AMP, Xiexin Tang (XXT) ameliorates obesity by promoting the activity of key enzymes for SCFAs synthesis and inhibiting AMPK while activating mTOR signaling[110].

Ophiopogonin D (OPD) could increase the abundance of *Bacteroidetes*, reduce the relative abundance of *Firmiuts*, inhibit the phosphorylation of mTOR and the expression of SREBP1 and SCD1 to alleviate fat metabolism, and result in to prevention of atherosclerosis and metabolic syndrome[132]. The mechanism that β-hydroxyβ-methylbutyrate(HMB) functions through Bacteroidetes-acetic acid-AMPKα axis to reduce the lipid metabolism of Bama Xiang mini-pigs was somewhat similar[133]. By the way, *Flammulina velutipes* polysaccharide (FVP) affected the abundance of gut microbiota, especially Bacteroidetes phylum and Muribaculaceae family, and up regulated mTOR signal pathway in cardiac tissue[134]. However, the specific mechanism remains to be determined.

Oral administration of bruceae Frutus oil (Bo) under the influence of gut microbiota inhibited breast cancer. At the same time, Bo changed the dominant strains of gut microbiota and promoted mTOR activity, leading to the inhibition of autophagy[135]. In contrast, 20(s)-ginsenoside Rh2 (grh2) played an anti-tumor role by inhibiting PI3K/AKT/mTOR signal[136]. Both Engineered resistant-starch (ERS) diet and ketogenic diet (KD) reduced mTOR phosphorylation and regulated microorganisms[137, 138]. Diet may serve as a synergistic approach to improve the treatment of diseases.

The direct interaction between mTOR and intestinal microorganisms provides potential ideas for treatment. Firstly, microencapsulated rapamycin (eRapa), the best pharmacological mTOR inhibitor studied in the study of life span and health extension, had strong immune effects and can gently change intestinal metagenes, which was worthy of further study[139]. Then, resveratrol, a specific inhibitor of mTOR complex 1, alleviated the changes of intestinal microflora in diet induced obese mice[114]. Furthermore, The microflora metabolite SCFAs activated mTOR and STAT3 of IEC to produce antimicrobial peptides to balance the intestinal environment[140].

Overall, in view of the limitations of current treatment, more drugs can only be used as a potential choice for disease treatment, which has broad clinical application prospects in the future.

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Table 1. List of drugsaffecting microbiota and mTOR signal pathway in different disorders.

Name	Disease	Pathway affected	Changes of gut microbiota	Cell response
HQD [121]	UC	↑PI3K/AKT/mTOR	↑*Firmicutes*, *Bacteroidetes*,	↑amino acid metabolism, p-S6 and p-4EBP1 ↓Apoptosis
P.ginseng [122]	IBD	↓mTOR, TLR4, NF-kB	↓Gram-negative bacteria	↑Autophagy ↓p62
SCFAs [90]	CD and UC	↑mTOR, STAT3	against enteric infection of *Citrobacter rodentium*	↑HIF1α, AhR, IL-22 ↓Gpr41, HDAC
TB [141]	CRC	↓PI3K/AKT/mTOR	↓Bacteroidceae and Bacteroides ↑Prevotellaceae and Alloprevotella	↑cyclin D1 protein, cleaved caspase 3
SCFAs [140]	——	↑mTOR, STAT3	——	↑AMP, RegIIIγ, β-defensins
L. reuteri + MTZ[124]	NAFLD	↓mTOR, AKT	↑*Akkermansia muciniphila*, *Firmicutes*, butyrate	↑Autophagy, LC-3II ↓LPS, NF-kB, TNF-α
AB23A [102]	NAFLD	↓mTOR, TLR4, NF-kB	↓*Firmicutes/Bacteroidaeota*, *Actinobacteriota/Bacteroidaeota*	↑ZO-1, occludin
LGG-s and BMMSC [125]	Alcoholic liver disease	↓PI3K/mTOR, PI3K/NF-kB	——	↑Autophagy ↓NKB cells, TFH cells
LF2 [126]	METS	↓PI3K/AKT/mTOR	↑*Verrucomicrobia*, *Akkermansia muciniphila*	↓SREBP-1c, PPARγ
Butyrate [104]	HCC	↓mTOR, AKT	——	↑ROS, Autophagy: beclin 1, ATG 5, LC3-II
Curcumin [128]	HCC	↓PI3K/AKT/mTOR	↑family Helicobacteraceaeorder, order Campylobacterales, and genus Helicobacter and Campylobacteria	↑apoptosis
PFT [129]	AD	↑PI3K/AKT ↓mTOR, GSK-3β	——	↓oxidative stress, inflammation
AMP [130]	Brain aging	↑PI3K/AKT/mTOR ↓AMPK/SIRT1/NF-κB	↑*Bacteroides* ↓*Firmicutes*	↓apoptosis, NLRP3
MogV and 11-oxo-mogrol [131]	neuronal damages	↑AKT/mTOR	——	↑neurite outgrowth ↓apoptosis, $[Ca^{2+}]_i$ release
OPD [132]	atherosclerosis	↓mTOR/SREBP1/SCD1	↑*Bacteroidetes*, *Faecalibaculum* ↓*Firmicutes*, *Ileibacterium*	↑insulin resistance ↓lipid metabolism

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HMB [133]	Obesity	↑AMPKα, Sirt1, and FoxO1 ↓mTOR	↑*Bacteroidetes*, acetic acid	↓lipid metabolism
XXT [110]	Obesity	↑AMPK ↓mTOR	↑key synthetic enzymes of SCFAs	↑energy expenditure:PGC-1α, UCP-2 ↓energy intake
FVP [134]	Heart	↑mTOR, etc ↓AMPK, PI3K-Akt, etc	↑*Bacteroidetes*, *Muribaculaceae*	↑Immunity
BO [135]	TNBC	↑mTOR	↑*Candidatus Melainabacteria* bacterium *MEL.A1*, *Ndongobacter massiliensis*, *Prevotella ruminicola*	↓Autophagy Regulate amino acid metabolism
GRh2 [136]	T-ALL	↓PI3K/AKT/mTOR	↑*Bacteroidetes*, *Verrucomicrobia* ↓*Firmicutes*, *Proteobacteria*	↑Immunity, tight junction proteins, antimicrobial peptides, IgA
ERS Diet [137]	PC	↓mTOR, ERK1/2	↑diversity of microbiota ↑Formate, Lactate ↓Propionate	↓Proliferation
Resveratrol [114]	Obesity and Diabetes	↓mTOR	↓*Lactococcus*, *Clostridium* XI, *Oscillibacter*, and *Hydrogenoanaerobacterium*	↑insulin resistance
ERapa [115]	Longevity	↓mTOR	Alteration of gut metagenomes	Regulate T, B, myeloid, and innate lymphoid cells

[1] Arrows indicate up-regulation or down-regulation.

5. Conclusions and Future Perspective

mTOR signal pathway plays a significant role in various physiological processes in the cell. The gut microbiota and its complex metabolites regulate a wide range of host functions, including autophagy, fatty acid metabolism, oxidative phosphorylation, and immune response. Dysregulation of the gut microbiota is associated with various disorders, such as cancers, diabetes, and inflammatory diseases, in which the mTOR signal pathway is also involoved.. In the present review, we introduced mTOR signal pathway, the correlation between gut microbes and mTOR, their function the mechanisms in multiple diseases (the crosstalk between the two is shown in Figure 1), and the possible treatments utilizing microbiota and mTOR inhibitors in these diseases.

Currently, there are still unsolved problems remain to be elucidated regarding the study of the gut microbiota and mTOR. Most existing studies suggest a phenomenal association between gut microbes and mTOR, with disease development causing composition changes in the gut microbiota or regulation of its metabolites, accompanied by inhibition or activation of mTOR.

The translation of basic mTOR and microbiota studies to the clinical setting remains challenging. Most studies focus on the evidence in animal models, few is known about mTOR in clinical trials. More data needs to be verified in clinical conditions. As inhibition of mTOR does not always lead to protective effects, it may also be controversial. Furthermore, due to the complexity of the organism, mTOR activity is increased in some pathological conditions and decreased by others, making it difficult to estimate the exact effects of therapeutic intervention. More in-depth systematic studies are in

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great need to elucidate how mTOR is associated with gut microbes, to produce more conclusive and valid results, and to further explore new drug candidates for the treatment of relevant diseases.

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Abbreviations

4E-BPs	4E-binding proteins
AB23A	Alisol B 23-acetate
AD	Alzheimer's disease
AMP	Aronia melanocarpa polysaccharide
AMPK	AMP-activated protein kinase
AMPK	AMP-activated protein kinase
AOM	Azomethane
ASD	Autism spectrum disorder
ATF4	Activating transcription factor 4
BMMSCs	Bone marrow mesenchymal stem cells
BMMSCs	Bone marrow mesenchymal stem cells
BO	Bruceae fructus oil
CASTOR1	GTPase-activating protein activity toward Rags-1
CD	Crohn's disease
CTSK	Cathepsin K
DAP1	Death-associated protein 1
DDiT4L	DNA-damage-inducible transcript 4-like
DEPTOR	DEP domain-containing mTOR-interacting protein
DSS	Dextran sodium sulfate
eIF4E	Eukaryotic translation initiation factor 4E
ERS	Engineered Resistant-Starch
FLCN	Folliculin
FoxO1/3a	Forkhead box O1/3a
FVP	Flammulina velutipes polysaccharide
GAP	GTPase-activating protein
GI	Gastrointestinal tract
Grb10	Growth factor receptor-bound protein 10
GSK3	Glycogen synthase kinase 3
HCC	Hepatocellular Carcinoma
HK-II	Hexokinase-II
HMB	β-hydroxy-β-methylbutyrate
HQD	Huangqin decoction
IBD	Inflammatory bowel disease
IEC	Intestinal epithelial cells
IGF1	Insulin and insulin-like growth factor 1
IKKβ	IκB kinase β

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L. reuteri	Lactobacillus reuteri DSM 17938
LGG-s	Lactobacillus rhamnosus culture supernatant
LI	Large intestine
LPS	Lipopolysaccharide
METS	Metabolic syndrome
mLST8	Mammalian lethal with SEC13 protein 8
MogV	MogrosideV
mSIN1	Mammalian stress-activated protein kinase interacting protein 1
MST1	Mammalian sterile 20-like kinase
MTF	Metformin
MTHFD2	Methylenetetrahydrofolate dehydrogenase 2
mTOR	The mammalian or mechanistic target of rapamycin
mTORC	mTOR complex
NAFLD	Nonalcoholic fatty liver disease
NDRG1	N-myc downstream regulated gene 1
NKB	Natural killer B cell
OPD	Ophiopogonin D
P. ginseng	Polysaccharides from Panax ginseng C. A. Meyer
PC	Pancreatic cancer
PDCD4	Programmed cell death 4
PFT	Probiotics fermentation technology
PGC-1α	Proliferator-activated receptor gamma coactivator 1-alpha
PI3K	Phosphoinositide 3-kinase
PIKK	Phosphoinositide 3-kinase related protein kinase
PKC-α	Protein kinase C-α
PPAR-γ	Peroxisome proliferator-activated receptor γ
PRAS40	Proline-rich substrate of 40 kDa
PROTOR1/2	Protein observed with RICTOR 1/2
Rags	Ras-related GTPases
RAPTOR	Regulatory-associated protein of mTOR
Redd1	Regulation of DNA damage response 1
Rheb	Ras homolog enriched in the brain
ROS	Reactive oxygen species
RSK	Ribosomal S6 kinase
S6K1	S6 kinase 1
SAM	S-adenosylmethionine
SCFAs	Short chain fatty acids
SGK1	Serum and glucocorticoid-induced protein kinase 1
SI	Small intestine
SREBP1/2	Sterol regulatory element binding protein 1/2
SRPK2	SR protein kinase 2
STZ	Streptozotocin
T-ALL	T-cell acute lymphoblastic leukemia
TB	Theabrownin
TFH	Follicular helper T cell
TLR4	Toll-like receptor 4
TNBC	Triple-negative breast cancer
TNF-α	Tumor necrosis factor-α
Trx1	Thioredoxin 1
TSC	Tuberous sclerosis complexes
UC	Ulcerative colitis
UCP-2	Uncoupling protein-2
ULK1	Unc-51-like autophagy-activating kinase 1

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