# Postprint: Biological Functions and Mechanisms of Mammalian Target of Rapamycin

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## Abstract

Mammalian target of rapamycin (mTOR) is a highly conserved protein kinase that plays important physiological roles in animal feeding, lipid and protein synthesis, autophagy, and aging, among other aspects, and has become a major focus of current biological research. This article reviews the structure, tissue distribution, physiological functions, and mechanisms of action of mTOR, with the aim of providing a reference for studying the mechanisms of action of the mTOR signaling pathway.

## Full Text

## Mammalian Target of Rapamycin: Biological Functions and Mechanisms

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### Abstract

Mammalian target of rapamycin (mTOR) is a highly conserved protein kinase that plays crucial physiological roles in animal food intake, lipid and protein synthesis, autophagy, and aging, making it a major focus of current biological research. This review summarizes the structure, tissue distribution, physiological functions, and mechanisms of action of mTOR, aiming to provide a valuable reference for studies on mTOR signaling pathway mechanisms.

**Keywords:** mTOR; regulation of food intake; lipid synthesis; protein synthesis; mechanism of action

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Mammalian target of rapamycin (mTOR) is a target protein of rapamycin in animals. Rapamycin is a macrolide compound produced by *Streptomyces hygroscopicus*. In the 1970s, Vezina et al. isolated this bacterium from soil on Easter Island in Chile and reported rapamycin [1]. In 1991, Heitman et al. screened rapamycin-resistant mutant strains of brewer's yeast and identified three related genes, two of which were named target of rapamycin 1 (TOR1) and target of rapamycin 2 (TOR2) after the Spalentor building at their discovery site [2-3]. In 1994, Sabatini first discovered a rapamycin-binding protein in mammals—rats—and named it "mammalian target of rapamycin (mTOR)" because the gene encoding this protein was homologous to yeast TOR1 and TOR2 [4]. Besides mammals, mTOR is widely distributed in other species, such as *Arabidopsis*, fruit flies, and carp [5-7]. Subsequent studies have confirmed that mTOR is a highly conserved serine/threonine protein kinase that integrates signals from upstream factors to exert biological functions. Due to its extensive involvement in biological processes, mTOR has become a research hotspot in biological sciences. This review focuses on the major biological functions and mechanisms of mTOR to provide a reference for fellow researchers.

## 1. mTOR Structure

### 1.1 Gene Structure of mTOR

The mTOR gene has been identified in 315 eukaryotic species. In representative species, the yeast mTOR gene is 7,413 bp long and encodes a protein of 2,470 amino acid residues; its paralogous gene mTOR2 is 7,425 bp long, encoding a protein of 2,474 amino acid residues. The human mTOR gene is located on the short arm of chromosome 1 (1p36.2), with an open reading frame of 7,650 bp encoding 2,549 amino acids and a protein molecular mass of 288.95 kDa. The rat mTOR gene is located on the long arm of chromosome 5 (5q36), with an open reading frame of 8,554 bp encoding 2,549 amino acids and a protein molecular mass of 288.85 kDa. These data demonstrate that the mTOR gene structure is highly conserved, with similar gene fragment sizes and encoded amino acid fragment lengths across species.

### 1.2 Protein Structure of mTOR

mTOR belongs to the phosphatidylinositol kinase-related kinase (PIKK) family. mTOR consists of multiple domains arranged from N-terminus to C-terminus: 20 HEAT repeats, FAT domain, FRB domain, kinase domain, and C-terminal FAT domain. The HEAT domain is a motif of tandem $\alpha$-helical structures found in some cytoplasmic proteins, named after four cytoplasmic proteins [Huntington protein, elongation factor 3, protein phosphatase 2A (PP2A) subunit, and

target of rapamycin (TOR)]. This region is involved in protein-protein interactions and intracellular transport [8]. The FAT domain is a kinase domain (KD) common to the PIKK family, named after three PIKK family proteins (FRAP, ATM, and TRRAP), and is related to mTOR activity. The FRB domain, short for FK506-binding protein rapamycin-binding domain, provides a binding site for mTOR and rapamycin (Fig. 1 [Figure 1: see original paper]) [9].

mTOR has four phosphorylation sites: serine 1261, threonine 2446, serine 2448, and serine 2481, which are closely related to mTOR function. Serine 1261 in the HEAT domain is phosphorylated by insulin signaling, and this phosphorylation promotes further phosphorylation of mTOR downstream targets ribosomal protein S6 kinase (S6K) and eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1). Threonine 2446 is regulated by nutrients and phosphorylated via the adenosine monophosphate kinase (AMPK) pathway. Serine 2448 is phosphorylated by S6K, while serine 2481 is a rapamycin-sensitive site with autophosphorylation activity [10-11].

## 2. Tissue Distribution of mTOR

mTOR is widely distributed in the central nervous system and peripheral tissues of animals. Cota et al. [12] investigated mTOR distribution in rat brain using immunohistochemistry and found that mTOR was widely distributed across various brain regions, with abundant phosphorylated mTOR (at serine 2448) detected in the paraventricular nucleus and arcuate nucleus of the hypothalamus, while less phosphorylated mTOR was found in the lateral hypothalamic area. When examining mTOR mRNA levels in various goat tissues, researchers found higher expression in brain, testis, spleen, kidney, and heart, but lower expression in liver and lung [13]. Makky et al. [14] used in situ hybridization to study the spatiotemporal distribution of mTOR in zebrafish, revealing that mTOR mRNA was first expressed in the brain and subsequently detected in the intestine. Jiang et al. [7] examined mTOR spatiotemporal distribution in carp and found mTOR mRNA expression in heart, muscle, head kidney, spleen, gill, and intestine, with expression levels showing temporal and spatial differences.

## 3. Biological Functions of mTOR

### 3.1 Regulation of Food Intake

mTOR does not directly regulate food intake but participates in feeding control by modulating the expression of downstream appetite-regulating factors in response to energy status and other factors. Studies have shown that mTOR is associated with central appetite-regulating factors such as neuropeptide Y (NPY), agouti-related protein (AgRP), proopiomelanocortin (POMC), and cocaine- and amphetamine-regulated transcript (CART), as well as peripheral appetite-regulating factors including leptin, ghrelin, and nesfatin-1 (a satiety molecule protein). NPY [15], AgRP [16], POMC [17], and CART [18] neural nuclei are located in the hypothalamus—the feeding regulation center—and

exert orexigenic or anorexigenic effects. Leptin [19], ghrelin [20], and nesfatin-1 [21] are appetite-regulating factors in peripheral tissues that also modulate food intake.

Cota et al. [12] first demonstrated that mTOR regulates animal food intake. Central mTOR signaling senses extracellular nutrients and hormone levels to control rat feeding. After feeding, mTOR and downstream target S6K1 phosphorylation levels increased in the arcuate nucleus; after 48 hours of fasting, phosphorylation levels of mTOR and S6K1 decreased, and refeeding after fasting increased phosphorylation levels again, confirming the important role of hypothalamic mTOR in energy sensing. Dietary protein content also affects mTOR signaling expression, as high-protein diets promote mTOR phosphorylation in Landrace pigs [22]. Additionally, mTOR can regulate the expression of other appetite peptides. Studies found that intracerebroventricular injection of leptin increased hypothalamic mTOR phosphorylation levels in rats, while injection of the mTOR inhibitor rapamycin significantly weakened leptin's physiological effects. Subsequent studies showed that mTOR exhibits similar regulatory patterns for many appetite factors. The mTOR signaling pathway mediates the orexigenic effect of peripheral ghrelin in the central nervous system. Martins et al. found that intracerebroventricular injection of ghrelin significantly increased food intake in rats after 2 hours, while also significantly increasing mTOR and S6K1 phosphorylation levels [23]. Hypothalamic mTOR plays a similar role in transducing thyroid hormone signals for feeding regulation [24], where it modulates downstream appetite-regulating factor expression in response to energy status and other factors. Thyroid hormone is an important factor that responds to and regulates energy status; injection of thyroid hormone into the arcuate nucleus of rat hypothalamus significantly increased expression of orexigenic factors NPY and AgRP, decreased expression of anorexigenic factor POMC, and increased food intake. Concurrently, hypothalamic mTOR and downstream factor phosphorylation levels significantly increased, while liver mTOR and downstream factor phosphorylation levels significantly decreased. Correspondingly, intracerebroventricular injection of rapamycin to block mTOR signaling prevented the increase in orexigenic factor expression induced by thyroid hormone, and rat body weight subsequently decreased. This signal transduction role of mTOR in feeding regulation has also been observed in studies of other appetite factors [25-27].

### 3.2 Regulation of Lipid Synthesis

mTOR participates in lipid metabolism processes including lipid synthesis, $\beta$-oxidation, and lipolysis. In lipid synthesis, fatty acid and triglyceride synthesis are key steps involving lipid synthesis enzymes and transcriptional regulators such as acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS), stearoyl-coenzyme A desaturase (SCD), lipin 1, sterol regulatory element-binding protein (SREBP), and peroxisome proliferator-activated receptor-$\gamma$ (PPAR-$\gamma$). Additionally, the activity of enzymes related to lipid oxidation and breakdown,

such as adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL), and monoacylglycerol lipase (MGL), is closely related to lipid synthesis efficiency. Activated by upstream nutrient or insulin signals, mTOR increases expression of SREBP-1c, the most critical transcriptional regulator of lipid synthesis [28], thereby accelerating lipid synthesis. In 2008, mTOR's role in regulating SREBP-1c expression and affecting lipid synthesis was first reported. Treatment of human retinal pigment epithelial cells with 4-hydroxytamoxifen-activated protein kinase B (PKB/AKT) for 4 hours significantly increased nuclear SREBP-1c levels. Since nuclear SREBP-1c increases expression of lipid synthesis-related enzyme genes, fatty acid synthase (FASN) mRNA levels also significantly increased after 4 hours. However, blocking mTOR signaling with rapamycin prevented the AKT-induced increase in nuclear SREBP-1c, and consequently blocked FASN and ATP-citrate lyase (ACLY) mRNA levels [29].

mTOR regulates SREBP-1c through multiple mechanisms, primarily at the mRNA transcription and protein processing levels. In studies of SREBP-1c' s role in lipid synthesis, feeding or insulin stimulation increased SREBP-1c gene expression in liver cells [30-31]. Owen et al. [32] found that rat hepatocytes treated with 100 nmol/L insulin for 15 minutes showed peak nuclear SREBP-1c levels that persisted for 6 hours. Antagonists of phosphoinositide 3-kinase (PI3K), mTOR, and S6K—wortmannin, rapamycin, and LYS6K2—could all block insulin' s effect on nuclear SREBP-1c, indicating that the insulin-PI3K-mTOR-S6K pathway regulates SREBP-1c protein processing. However, while 30-minute rapamycin pretreatment inhibited the insulin-induced increase in SREBP-1c, LYS6K2 did not reduce SREBP-1c mRNA expression. These results suggest that mTOR regulates SREBP-1c mRNA transcription and protein processing through different pathways, though the specific regulatory mechanisms remain unclear. Recent studies have shown that mTOR controls the transport of SREBP-1c from the endoplasmic reticulum to the Golgi apparatus. Han et al. [33] found that inhibiting mTOR blocked SREBP-1c transport to the Golgi. Mutations in the CREB-regulated transcription coactivator 2 (CRTC2) gene increased triglyceride accumulation and elevated mRNA expression of triglyceride synthesis-related genes in mouse hepatocytes, an effect enhanced by high-fat feeding. Meanwhile, immature SREBP-1c outside the nucleus remained unchanged, and SREBP-1c mRNA expression showed no significant difference, while nuclear SREBP-1c increased. Further studies revealed that mTOR plays an important role in this process; activated by elevated energy status, mTOR phosphorylates the 136th amino acid residue of CRTC2, causing CRTC2 to dissociate from the Sec31 subunit of the transport protein COPII. The dissociated Sec31 can then bind to Sec23, transporting immature SREBP-1c from the endoplasmic reticulum to the Golgi apparatus.

### 3.3 Regulation of Protein Synthesis

mTOR stimulates protein synthesis by phosphorylating downstream 4E-BP1 and S6K, thereby enhancing transcription of related genes. This function is

crucial for cell growth and proliferation [34]. 4E-BP1 is a protein that binds to eukaryotic translation initiation factor 4E (eIF4E), which is the cap-binding subunit of the eIF4F translation initiation complex. The 7-methylguanosine "cap" at the 5' end of eukaryotic mRNA is a structure that regulates transcription efficiency, splicing patterns, and nuclear export. Almost all eukaryotic cells require eIF4F to direct ribosomes to this cap structure and initiate mRNA translation, while 4E-BP1 inhibits translation initiation by binding to eIF4E. When mTOR signaling is activated by upstream stimuli, 4E-BP1 is phosphorylated as a downstream factor, causing conformational changes that dissociate it from eIF4E and enhance mRNA translation efficiency [33,35]. Certain branched-chain amino acids are known to activate mTOR signaling [36]. Studies in dairy cows have shown that both L-leucine and L-isoleucine can enhance mTOR and S6K1 phosphorylation levels and promote protein synthesis in mammary epithelial cells [37]. In neonatal piglets fasted for 24 hours, those fed low-protein (LP), low-protein plus leucine (LP+L), or high-protein (HP) diets showed significantly higher mTOR/S6K/4E-BP1 phosphorylation levels and protein synthesis in the LP+L and HP groups compared to the LP group [38]. Columbus et al. [39] conducted similar studies on leucine's effect on protein synthesis in piglets and found that plasma leucine, isoleucine, and valine levels significantly increased in LP+L and HP groups. The LP+L group showed significantly higher phosphorylation levels of 4E-BP1 and eIF4G · eIF4E in the mTOR signaling pathway compared to the LP group, while HP group piglets showed significantly increased body weight and lean mass. Additionally, Yao et al. [40] found that arginine could also activate the mTOR signaling pathway and promote muscle protein synthesis and body weight gain in piglets. Similar results were confirmed in chickens; in arginine-containing culture medium, mTOR, 4E-BP1, and S6K1 mRNA expression significantly increased, while protein synthesis was enhanced and protein degradation decreased in chicken intestinal epithelial cells [41]. These findings indicate that amino acids such as leucine activate the mTOR signaling pathway, increase 4E-BP1 phosphorylation levels, enhance expression of protein synthesis-related genes, and ultimately increase protein synthesis.

### 3.4 Regulation of Autophagy

Autophagy is a general term for the degradation of intracellular components via lysosomes. Triggered by external factors (nutrients, ischemia, hypoxia, growth factor concentrations) and internal factors (metabolic stress, damaged organelles), autophagy degrades damaged organelles and macromolecules to provide raw materials for new protein synthesis, helping maintain protein metabolism balance and intracellular homeostasis. The mechanism by which mTOR regulates autophagy involves controlling the phosphorylation status of the ULK1-Atg13-RB1CC1-Atg101 complex. Under nutrient-rich conditions, mTOR phosphorylates Atg13, which in its hyperphosphorylated state has reduced affinity for Atg1, decreasing Atg1 kinase activity and suppressing autophagy. Conversely, under starvation conditions, mTOR activity is inhibited, Atg13 becomes dephosphorylated and binds tightly to Atg1 kinase,

activating Atg1 and initiating autophagy. Rapamycin can inhibit mTOR activity, facilitating Atg13 dephosphorylation and Atg1 activation to induce autophagy [42-43].

Studies have found that the C-terminal sequence of serine/threonine protein kinase ATM is homologous to the PI3K catalytic domain and can stimulate downstream signals of the LBK/AMPK/TSC2 pathway, thereby inhibiting mTOR. Inhibition of mTOR activates ULK1, which binds to UVRAG and phosphorylates beclin 1 (at serine 14), thereby enhancing the activity of the beclin 1-Vps34-Atg14L complex and initiating autophagy [44-45].

### 3.5 mTOR and Aging Regulation

Aging is the progressive decline of physiological functions in cells, tissues, and organs over time. Aging has long been a research focus, and mTOR has been extensively studied for its role in regulating the aging process. In 2009, a seminal study published in *Nature* first reported the close relationship between mTOR signaling and aging. This study found that adding the mTOR inhibitor rapamycin to the diet of 600-day-old male and female mice increased their lifespan by 13% and 9%, respectively [46]. Subsequently, researchers investigated the relationship between downstream mTOR signals and aging. In the mTOR-S6K1 signaling pathway, both calorie-restricted mice and S6K1 knockout mice showed extended lifespan and reduced age-related diseases [47]. These studies demonstrate that the mTOR signaling pathway participates in organismal aging, though the specific mechanisms remain unclear.

## 4. Conclusion

mTOR is a highly conserved protein that serves as a central sensor for energy metabolism regulation, playing important roles in food intake regulation, lipid metabolism, and protein synthesis. The mTOR signaling pathway can regulate the expression of many genes at transcriptional and translational levels, and its dysregulation can cause systemic disorders. Existing studies have shown that mTOR is closely related to the occurrence of metabolic syndrome, cancer, and other diseases. Therefore, in-depth research on the physiological functions of mTOR will facilitate disease treatment and new drug development. Currently, mTOR research primarily focuses on humans and mice, with relatively few studies on other mammals. Given the powerful physiological functions of mTOR, how to regulate animal production performance through the mTOR signaling pathway will be a future research priority. Since mTOR plays an important regulatory role in protein and lipid synthesis, whether we can improve dietary protein utilization and reduce fat deposition in animals by modulating the mTOR signaling pathway are promising directions for future research, and mTOR is expected to have broad application prospects in animal production.

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