REVIEW

Mechanistic Target of Rapamycin Complex 1: From a Nutrient Sensor to a Key Regulator of Metabolism and Health

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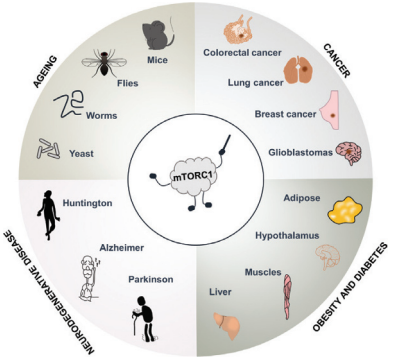
ABSTRACT

Mechanistic target of rapamycin complex 1 (mTORC1) is a multi-protein complex widely found in eukaryotes. It serves as a central signaling node to coordinate cell growth and metabolism by sensing diverse extracellular and intracellular inputs, including amino acid–, growth factor–, glucose-, and nucleotide-related signals. It is well documented that mTORC1 is recruited to the lysosomal surface, where it is activated and, accordingly, modulates downstream effectors involved in regulating protein, lipid, and glucose metabolism. mTORC1 is thus the central node for coordinating the storage and mobilization of nutrients and energy across various tissues. However, emerging evidence indicated that the overactivation of mTORC1 induced by nutritional disorders leads to the occurrence of a variety of metabolic diseases, including obesity and type 2 diabetes, as well as cancer, neurodegenerative disorders, and aging. That the mTORC1 pathway plays a crucial role in regulating the occurrence of metabolic diseases renders it a prime target for the development of effective therapeutic strategies. Here, we focus on recent advances in our understanding of the regulatory mechanisms underlying how mTORC1 integrates metabolic inputs as well as the role of mTORC1 in the regulation of nutritional and metabolic diseases. *Adv Nutr* 2022;13:1882–1900.

Statement of Significance: Herein, we review recent advances of the regulatory mechanisms underlying how mTORC1 integrates metabolic inputs. Our review provides recent advances of the role of mTORC1 in the development of nutritional and metabolic diseases.

GRAPHICAL ABSTRACT



Keywords: mTORC1, nutrient, signal transduction, metabolism, metabolic diseases

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Introduction

In early 1975, Sehgal and colleagues (1, 2) identified a secondary metabolite of *Streptococcus hygroscopicus* called rapamycin, a compound with antifungal, immune-suppressive, and antitumor activity. Then, in 1991, Heitman J and coworkers (3) identified the target molecule of this compound in a rapamycin-resistant yeast mutant. Sabatini et al. (4) later identified the direct target of rapamycin in mammals and named the molecule RAFT1 [rapamycin and FK506-binding protein 1A (FKBP12) target 1]/FRAP (FKBP-rapamycin associated protein)/mTOR (mechanistic/mammalian target of rapamycin). Amino acid sequence analysis showed that mTOR was the mammalian ortholog of yeast TOR (5, 6). Subsequent investigations revealed that the TOR-coding gene is ubiquitous among eukaryotes. mTOR has become the focus of increasing attention given its role in integrating nutrient, growth, and stress signals in the regulation of cell growth and metabolism (7).

mTOR is an atypical serine/threonine-protein kinase belonging to the phosphatidyl inositol-3-kinase (PI3K)–related protein kinase (PKK) family. Biochemical studies have shown that mTOR exerts its physiological functions via 2 distinct protein complexes, known as mTOR complex 1 (mTORC1) and mTORC2 (8). mTORC1 plays a crucial role in the regulation of cell size, cell proliferation, and autophagy through ribosomal S6 kinase (S6K) 1 (S6K1), sterol regulatory element-binding protein (SREBP), peroxisome proliferator-activated receptor-γ (PPARγ), hypoxia-inducible factor 1, subunit α (HIF1α), or unc-51-like autophagy activating kinase (ULK) 1 (ULK1) (9, 10), whereas mTORC2 is involved in various physiological processes, such as cell metabolism, proliferation, and autophagy through protein kinase B (AKT1), protein kinase C (PKC), and serum/glucocorticoid regulated kinase 1 (SGK1) (9, 11). mTORC1 and mTORC2 are not independent cellular signaling pathways. The phosphorylation of AKT by mTORC2 is important for the activation of mTORC1. However, it is worth noting that mTORC2 is not essential for mTORC1 activation: for instance, nutrients (amino acid), energy (ATP), and hypoxia can activate mTORC1 in a mTORC2-Akt–independent manner (12, 13). Furthermore, the negative feedback catalyzed mTORC1 pathway indirectly inhibits the activation of mTORC2 through phosphorylating growth factor receptor bound protein 10 (GRB10) and insulin receptor substrate 1 (IRS1) (14–16).

As a central regulator of growth and metabolism, the mTORC1 pathway is involved in sensing nutritional signals, including those related to amino acids, growth factors, glucose, nucleotides, mechanical stress, and even pH. Hypo- or hyperactivation of mTORC1 is closely related to metabolic dysregulation, which may have pathological consequences, including the development of metabolic diseases such as obesity and type 2 diabetes, as well as cancer, neurodegenerative disorders, and aging (8). In this review, we focus on recent advances in our understanding of the regulatory mechanisms underlying the functions of mTORC1 and emphasize the role of this kinase complex in nutrient sensing and the regulation of cellular metabolism.

Components of the mTOR Complexes

mTORC1 and mTORC2 can be distinguished by their subunit composition, different sensitivities to rapamycin, and unique downstream effectors and functions. The components of the mTOR complexes are listed in **Table 1**. mTORC1 is allosterically inhibited by rapamycin. Mechanistically, rapamycin forms a gain-of-function complex with FKBP12, and then directly binds to FRB domain of mTOR to inhibit mTORC1 kinase activity (17). Notably, regulatory-associated of mTOR (Raptor) binds to mTOR, generating the rapamycin-sensitive mTORC1, while rapamycin-insensitive companion of mTOR (Rictor) associates with mTOR, yielding the rapamycin-insensitive mTORC2 (7). As no specific inhibitor of mTORC2 has been identified to date, most studies investigating mTOR have focused on how mTORC1 is regulated and its physiological function. Fortunately, with the use of genetic approaches, deciphering the biological significance of mTORC2 is no longer a considerable challenge.

Upstream Regulation of mTORC1 Signaling

In mammals, both fasting and feeding affect the circulating concentrations of nutrients and growth factors that regulate glycogen synthesis, lipid uptake or lipolysis, protein synthesis or breakdown, and gluconeogenesis in various tissues, thereby maintaining systemic metabolic homeostasis. The mTOR pathway has attracted considerable research attention due to its role as a key regulator linking nutrients, growth factors, and metabolism. It is widely believed that the activation of mTORC1 is tightly coupled to the Rag GTPase-mediated lysosomal localization and the tuberous sclerosis

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Abbreviations used: Aβ, amyloid-β peptide; acetyl-CoA, acetyl-coenzyme A; AD, Alzheimer disease; AKT, protein kinase B; AMPK, AMP-activated protein kinase; ARF, ADP-ribosylation factor; CASTOR, cellular arginine sensor for mTORC1; CR, caloric restriction; eIF4, eukaryotic translation initiation factor 4; ENO, enolase; FKBP12, FK506-binding protein 1A; GAP, GTPase-activating protein; GATOR, GAP activity toward Rags; GDH, glutamate dehydrogenase; GLS, glutaminase; GLUT1, glucose transporter 1; GPI, glycosylphosphatidylinositol; GRB10, growth factor receptor bound protein 10; HD, Huntington's disease; HFD, high-fat diet; HIF1α, hypoxia-inducible factor 1, subunit α; HK, hexokinase; IRS, insulin receptor substrate; IRS1, insulin receptor substrate 1; KO, knockout; LDHA, lactate dehydrogenase A; LRS1, leucyl-tRNA synthetase 1; MTHFD2, methylenetetrahydrofolate dehydrogenase (NADP-dependent) 2, methenyltetrahydrofolate cyclohydrolase; mTOR, mechanistic/mammalian target of rapamycin; mTORC1, mTOR complex 1; mTORC2, mTOR complex 2; PD, Parkinson's disease; PFK, phosphofructokinase; PFKFB, phosphofructokinase, fructose-2,6-bisphosphatase; PGAM, phosphoglycerate mutase; PI3K, phosphatidyl inositol-3-kinase; PKC, protein kinase C; PKG, protein kinase G; PKM, pyruvate kinase M; PPARγ, peroxisome proliferator-activated receptor γ; PRAS40, proline-rich AKT substrate 40 kDa; PTEN, tensin homologue deleted on chromosome 10; Raptor, regulatory-associated of mTOR; RHEB, Ras homolog enriched in brain; Rictor, rapamycin-insensitive companion of mTOR; S6K, ribosomal S6 kinase; SAM, *S*-adenosylmethionine; SAMTOR, SAM sensor upstream of mTORC1; SLC38A9, solute carrier family 38 member 9; SREBP, sterol regulatory element-binding protein; TFEB, transcription of transcription factor EB; TM4SF5, transmembrane 4 L 6 family member 5; TSC, tuberous sclerosis complex; ULK, unc-51-like autophagy activating kinase; WAT, white adipose tissue; α-KG, α-ketoglutarate; 4EBP1, eukaryotic initiation factor 4E binding protein 1.

TABLE 1 Components of mTORC1 and mTORC2[1]

mTORC1		mTORC2	
Name	**Function**	**Name**	**Function**
mTOR	Provides the kinase activity of the complex	mTOR	Provides the kinase activity of the complex
Raptor	Regulating the assembly of mTORC1, and its lysosomal localization (205)	Rictor	Coordinate with mTORC2 to phosphorylate substrates (206)
mLST8	Stabilizing the kinase activity of the complex (207)	mLST8	Stabilizing the kinase activity of the complex (207)
PRAS40	An inhibitory protein of the complex (61)	mSin1	Regulating the assembly of mTORC2, and its membrane localization (208)
DEPTOR	An inhibitory protein of the complex (209)	DEPTOR	An inhibitory protein of the complex (209)
Tel2	Regulating the assembly and stability of mTORC1 (210)	PROTOR1/2	Promote the kinase activity of the complex (211, 212)
Tti1			

[1]DEPTOR, DEP-domain–containing mTOR-interacting protein; mLST8, mammalian lethal with SEC13 protein 8; mSin1, mammalian stress-activated protein kinase interacting protein 1; mTOR, mechanistic/mammalian target of rapamycin; mTORC1, mTOR complex 1; mTORC2, mTOR complex 2; PRAS40, proline-rich protein kinase B (AKT) substrate 40kDa; PROTOR1/2, protein associated with Rictor 1 or 2; Raptor, regulatory-associated of mTOR; Rictor, rapamycin-insensitive companion of mTOR; Tel2, telomere maintenance 2; Tti1, Tel two interacting protein 1.

complex (TSC)–governed Ras homolog enriched in brain (RHEB) activation (18, 19) (**Figure 1**).

Regulation of mTORC1 signaling by amino acids

Amino acids also are dynamic regulators of mTORC1 to coordinate cellular status and functions (20). Compelling evidence indicates that mTORC1 is activated by an array of regulatory molecules in response to fluctuations in amino acid concentrations and is recruited to the lysosomal surface via the Rag GTPase axis (21); the key components of the Rag GTPase axis are listed in **Table 2**. As reported, arginine, leucine, glutamine, and methionine are the best examples of stimulating the activity of mTORC1, while other amino acids have also been recently identified as mTORC1 activators (22) (**Figure 2**).

Arginine, leucine, and methionine activate the mTORC1 signaling pathway through the Rag GTPase axis. In particular, cellular arginine sensor for mTORC1 (CASTOR)1 has been identified as the intracellular arginine sensor. Saxton RA and Chantranupong L et al. (23, 24) showed that arginine can block the inhibitory effect of CASTOR1 on GTPase-activating protein (GAP) activity toward Rags (GATOR)2, which is essential for the activation of Rag GTPase and mTORC1. The intracellular level of leucine is sensed by Sestrin 1/2, transmembrane 4 L 6 family member 5 (TM4SF5), leucyl-tRNA synthetase 1 (LRS1), and secretion-associated Ras-related GTPase 1B (SAR1B) (25–31). Moreover, LRS1 can also activate mTORC1 via its catabolite acetyl-coenzyme A (acetyl-CoA), which mediates Raptor acetylation through EP-300 (32).

Leucine is transported into the cell via SLC7A5/SLC3A2 to help maintain glutamine levels (33). Glutamine has been shown to activate mTORC1 through Rag GTPase or ADP-ribosylation factor (ARF) GTPase. Glutamine is converted to α-ketoglutarate (α-KG) through the activity of glutaminase (GLS) and glutamate dehydrogenase (GDH). α-KG can promote the conversion of inactive RagB-GDP to RagB-GTP. Furthermore, the direct binding of leucine to GDH has been shown to enhance glutaminolysis and α-KG production. Thus, glutamine and leucine collaboratively activate mTORC1 by regulating the activation of RagB (34). Glutamine can also activate mTORC1 independently of α-KG and Rag GTPase. For instance, the small G protein ARF1 can recruit mTORC1 to the lysosome in response to glutamine stimulation (35) (Figure 2).

Methionine is reported to activate the mTORC1 signaling pathway through *S*-adenosylmethionine (SAM) sensor upstream of mTORC1 (SAMTOR) (36), which is a SAM sensor and connects methionine and one-carbon metabolism to the mTORC1 signaling pathway (Figure 2). Besides arginine, leucine, glutamine, and methionine, other amino acids that are involved in regulating mTORC1 activity are continuously being identified. CystIine reportedly activates the mTORC1 pathway through Rag GTPase (37). Meanwhile, asparagine is a key molecule that connects mitochondrial respiration to mTORC1 (38). Threonine activates mTORC1 in a manner that is dependent on threonyl-tRNA synthetase 2 (TARS2), which promotes the GTP loading of RagA (39) (Figure 2). In addition to cytoplasmic amino acids, lysosomal amino acids such as leucine and arginine can also regulate mTORC1 signal transduction through their interaction with the lysosome positioning protein TM4SF5 and solute carrier family 38 member 9 (SLC38A9) (30, 40). SLC38A9 not only acts as an amino acid sensor in the lysosome but also enables the cholesterol-mediated activation of mTORC1 independently of its arginine-sensing function (40–42) (Figure 2).

It is widely believed that mTORC1 activation due to fluctuating amino acid concentrations is mediated by the Rag GTPase. However, a recent study revealed that amino acids derived from exogenous proteins (obtained through macrocytosis) activate mTORC1 in a Rag GTPase-independent manner with the aid of the homotypic fusion and protein sorting (HOPS) complex. Interestingly, the Rag GTPase negatively regulates mTORC1 activation in response to macrocytosis-derived amino acids (43). These observations

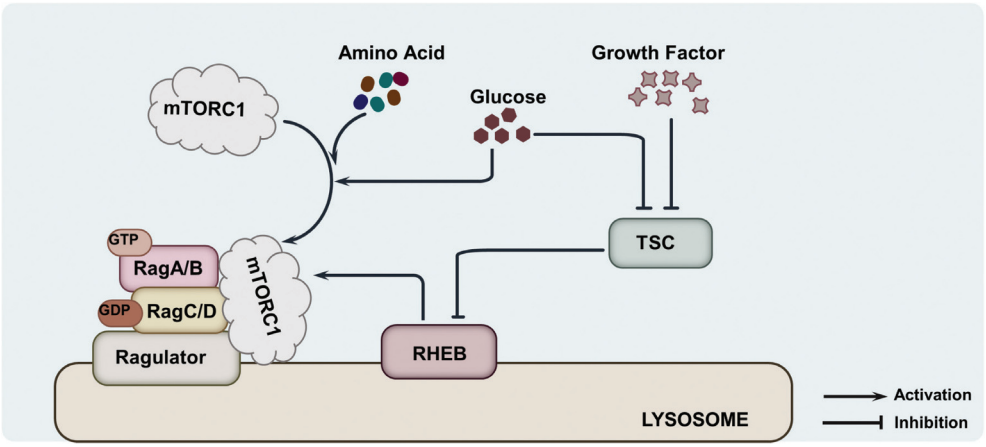

FIGURE 1 Rags and RHEB GTPases control the activation of mTORC1. GDP, guanosine diphosphate; GTP, guanosine triphosphate; mTORC1, mechanistic target of rapamycin complex 1; RHEB, Ras homolog enriched in brain; TSC, tuberous sclerosis complex.

highlight that amino acids from distinct sources exert different regulatory effects on the activity of mTORC1.

Therefore, amino acids, including arginine, leucine, methionine, glutamine, cI(e)ine, threonine, etc., induce the activation of mTORC1 via distinct mechanisms that involve Rag GTPase (44), and several findings also highlight that glutamine and asparagine mediate mTORC1 lysosomal localization and activation in a Rag GTPase-independent manner (35, 45, 46). Moreover, α-KG and acetyl-CoA, the metabolite of glutamine and leucine, also increase mTORC1 activity (32, 34); whether the metabolites of other amino acids have a more direct role on mTORC1 activation and the mechanisms remains to be investigated in the future.

Regulation of mTOR signaling by growth factors

mTORC1 is a downstream mediator of several growth factor–dependent signaling pathways. Unlike with amino acid stimulation, growth factor signals are sensed through the AKT/RHEB/TSC axis (**Figure 3**). The interaction between

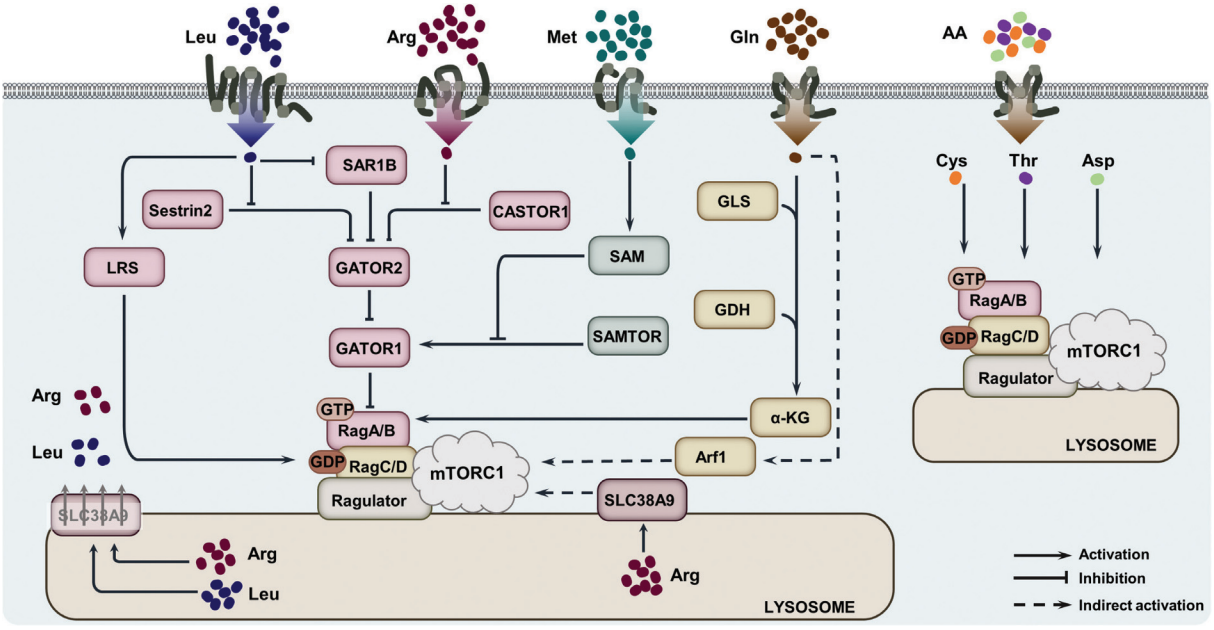

FIGURE 2 Amino acid regulation of mTORC1 signaling. AA, amino acid; Arf1, ADP-ribosylation factor 1; CASTOR, cellular arginine sensor for mTORC1; GATOR, GTPase-activating protein (GAP) activity toward Rags; GDH, glutamate dehydrogenase; GDP, guanosine diphosphate; GLS, glutaminase; GTP, guanosine triphosphate; LRS, leucyl-tRNA synthetase; mTORC1, mechanistic target of rapamycin complex 1; SAM, *S*-adenosylmethionine; SAMTOR, SAM sensor upstream of mTORC1; SAR1B, secretion-associated Ras-related GTPase 1B; SLC38A9, solute carrier family 38 member 9; α-KG, α-ketoglutarate.

TABLE 2 Summary of the key components of the Rag GTPase axis[1]

	Function
Rag GTPase	Facilitating the translocation of mTORC1 to the lysosomal surface (213)
GATOR1/2	GAP for RagA/B (182)
Ragulator	GEF for RagA/B (213)
CASTOR1/2	The intracellular arginine sensor (23, 24)
Sestrin 1/2	The intracellular leucine sensor (25–27)
KICSTOR	Recruiting GATOR1/GATOR2 to the lysosome (214)
LRS1	The intracellular leucine sensor (28, 29)
SAR1B	The intracellular leucine sensor (31)
TM4SF5	The intracellular leucine sensor (30)
GDH/GLS	Enhancing glutaminolysis and α-KG production (34)
SAMTOR	The intracellular methionine or SAM sensor (36)
SLC38A9	The lysosomal arginine and cholesterol sensor (40)

[1]CASTOR, cellular arginine sensor for mTORC1; GAP, GTPase-activating protein; GATOR, GAP activity toward Rags; GDH, glutamate dehydrogenase; GEF, guanine nucleotide exchange factor; GLS, glutaminase; LRS1, leucyl-tRNA synthetase 1; SAR1B, secretion-associated Ras-related GTPase 1B; SAM, *S*-adenosylmethionine; SAMTOR, SAM sensor upstream of mTORC1; SLC38A9, solute carrier family 38 member 9; TM4SF5, transmembrane 4 L 6 family member 5; α-KG, α-ketoglutarate.

growth factors and the mTORC1 pathway is exemplified by insulin, and accumulating evidence has indicated that many proteins are involved in insulin pathway (47) (see **Table 3**).

TSC2, the hub that integrates signals for mTORC1 regulation, functions as a GAP of RHEB GTPase and inhibits RHEB GTPase and mTORC1 activation (48, 49). Several studies have demonstrated that TSC is regulated by several protein kinase signaling pathways (Table 3). The activation of AKT modulates the phosphorylation of TSC2 at multiple sites, which either inactivates TSC2 or leads to its dissociation from the lysosomal surface, subsequently leading to increased mTORC1 activation (50–52). Insulin/PI3K signals also activate mTORC1 through other AGC kinases. Evidence has shown that PKC-δ and protein kinase G (PKG) phosphorylates TSC2 to modulate mTORC1 activity (53, 54). Besides the IRS/AKT pathway, the Ras-ERK1/2 (-extracellular regulated protein kinase 1/2), Wnt-GSK3 (-glycogen synthase kinase-3), and TNFα-IKKβ (-inhibitor of nuclear factor κB kinase β subunit) pathways are also involved in regulating the phosphorylation and activation of TSC2 (55–57) (Figure 3 and **Table 4**). Moreover, a recent study identified a novel upstream regulatory protein of the TSC complex, GAP SH3 binding protein 1/2 (G3BP1/2), which resides at the lysosomal surface and is responsible for recruiting the TSC complex to the lysosome and inhibiting the activation of mTORC1 (58).

In addition to TSC2, there is some evidence that mTOR is phosphorylated at Ser2448 by AKT or S6K, which promotes the activation of mTORC1 (59, 60), while the phosphorylation of proline-rich AKT substrate 40 kDa (PRAS40) at Thr246 by AKT relieves the inhibitory effect of PRAS40 on mTORC1 (61). Taken together, these results demonstrate that multiple signaling kinases regulate the mTORC1 activation status through the phosphorylation of TSC2 and other substrates (Figure 3).

Regulation of mTOR signaling by glucose

mTORC1 is a key hub for glucose-sensing pathways. However, the mechanism underlying how glucose availability is sensed and regulated by mTORC1 is poorly understood. It is well documented that information regarding glucose availability and energy levels are transmitted to mTOR by AMP-activated protein kinase (AMPK), a core regulator of intracellular metabolic homeostasis that directly senses cellular energy fluctuations (62). Studies have suggested that AMPK regulates the mTORC1 pathway by targeting multiple substrates, including TSC2, mTOR, and Raptor, in response to glucose signals. Under energy-depleted conditions, AMPK phosphorylates TSC2, thereby promoting its GTPase activity and inhibiting the activation of RHEB and mTORC1 signaling (63). AMPK can also directly regulate the mTORC1 pathway through phosphorylating Raptor (64), a key component of mTORC1, thereby inhibiting its kinase activity and, consequently, the whole mTORC1 pathway. However, it is reported that AMPK activates mTORC2 by phosphorylating Ser1261 on mTOR and unidentified site(s) on Rictor (65). Moreover, studies have demonstrated that glucose is involved in amino acid–mediated mTORC1 activation by inhibiting the regulatory functions of AMPK on the v-ATPase/Ragulator complex or LRS1, which enhances mTORC1 targeting to the lysosome surface by promoting the activity of Rag GTPase (66, 67). In addition, aldolase can control the formation of a lysosomal complex containing Ragulator, liver kinase B1 (LKB1), axis inhibitor protein (AXIN), and AMPK, thereby modulating mTORC1 activation in response to fluctuations in glucose concentrations (68). However, a recent study identified dihydroxyacetone phosphate (DHAP), a metabolite of aldolase, as a key activator of mTORC1 via the GATOR/Rag GTPase signaling axis in a manner that is independent of AMPK (69). Collectively, these findings highlight that glucose participates in both the amino acid– and growth factor–mediated activation of the mTORC1 via both AMPK-dependent and -independent mechanisms (**Figure 4**).

Regulation of mTOR signaling by nucleotide, mechanical stress, and pH

The localization and activation of mTORC1 are thought to coordinate signals relating to fluctuations in amino acid, growth factor, and glucose concentrations in the control of cell growth (7). However, mTORC1 is also involved in sensing adenine, mechanical or energetic stress, and pH signals. The mTORC1 pathway senses changes in adenine concentrations in a manner similar to how it senses amino acid availability, while the depletion of intracellular guanine stocks inhibits mTORC1 by suppressing RHEB activation (70). Both pressure overload and energetic stress can inhibit mTORC1 activity by promoting PKG1 or receptor-interacting protein kinase 1 (RIPK1)–mediated phosphorylation of TSC2 at Ser1364/1365 or Ser1387, respectively (54, 71). Moreover, acidification triggered by circadian rhythms drives the rearrangement of the lysosome, which separates mTORC1 from RHEB, thereby inhibiting the activity of the

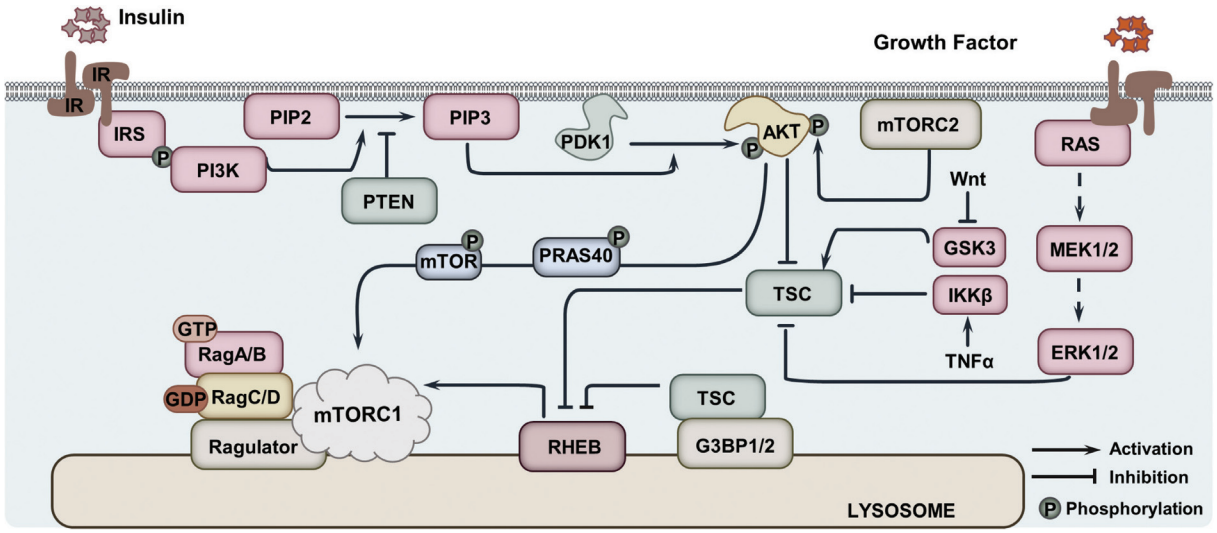

FIGURE 3 Growth factor regulation of mTORC1 signaling. AKT, protein kinase B; ERK1/2, extracellular regulated protein kinase; G3BP1/2, GAP SH3 binding protein 1/2; GDP, guanosine diphosphate; GSK3, glycogen synthase kinase-3; GTP, guanosine triphosphate; IKKβ, inhibitor of nuclear factor kappa B kinase beta subunit; IR, insulin receptor; IRS, IR substrate; MEK1/2, mitogen-activated protein kinase 1/2; mTOR, mechanistic target of rapamycin; mTORC1, mechanistic target of rapamycin complex 1; mTORC2, mechanistic target of rapamycin complex 2; P, phosphorylation; PDK1, phosphoinositide-dependent protein kinase-1; PI3K, phosphatidyl inositol-3-kinase; PIP2, phosphatidylinositol-4,5-bisphosphate; PIP3, phosphatidylinositol-3,4,5-trisphosphate; PRAS40, proline-rich AKT substrate 40 kDa; PTEN, tensin homologue deleted on chromosome 10; RHEB, Ras homolog enriched in brain; TSC, tuberous sclerosis complex.

former (72). Furthermore, the core clock protein period 2 (PER2) recruits TSC1 to mTORC1, thereby specifically suppressing the activity of the mTORC1 pathway (73) (**Figure 5**).

Regulation of mTOR signaling by other upstream regulators

In addition, it was found that exogenously added phosphatidic acid (PA), the metabolic product of phospholipase D (PLD) (74), could activate the mTORC1 pathway by directly stimulating mTORC1 activation (75), competitively inhibiting binding of rapamycin and mTOR (76), or specifically displacing DEP-domain-containing mTOR-interacting protein (DEPTOR) (77–79). Oxygen levels can also directly regulate mTORC1 through multiple pathways (80). Hypoxia directly regulates mTORC1 by DNA damage response 1 (REDD1), which activates TSC1/2 by disrupting the interaction between TSC2 and 14–3–3 proteins (81–83). Moreover, hypoxia reduces mTORC1 signalingthrough transcriptional regulation of Bcl-2/adenovirus e1B 19 kDa-interacting protein 3 (BNIP3), which can interfere with the interaction between mTOR and its positive regulator RHEB (84, 85). Additionally, studies demonstrate that mTORC1 can not only sense folate but also regulate the expression of folate transporter, which has broad biological significance, including metabolic reprogramming, tumorigenesis, and tumor metastasis (86–90).

The above data provide ample evidence that the mTORC1 pathway senses oscillations in nutrient concentrations as well as other environmental changes via 2 pathways—namely, the Rag GTPase and TSC/RHEB signaling axes, which respectively control mTORC1 intracellular localization and the activation of the mTORC1 pathway (Figure 1). Although

TABLE 3 Overview of the key components of the insulin pathway[1]

Name	Function
IRS	Recruiting PI3K to the plasma membrane
PI3K	Converting the PIP2 to PIP3
PIP3	Recruiting PDK1, mTORC2, and AKT to plasma membrane
PDK1	Phosphorylating AKT at Thr308 (215)
mTORC2	Phosphorylating AKT at Thr473 (216)
PTEN	Conversion of PIP3 to PIP2 (217)
TSC2	GAP of RHEB GTPase (48, 49)

[1] GAP, GTPase-activating protein; IRS, insulin receptor substrate; mTORC2, mechanistic/mammalian target of rapamycin complex 2; PI3K, phosphatidyl inositol-3-kinase; PIP2, phosphatidylinositol-4,5-bisphosphate; PIP3, phosphatidylinositol-3,4,5-trisphosphate; PDK1, phosphoinositide-dependent protein kinase-1; PTEN, tensin homologue deleted on chromosome 10; RHEB, Ras homolog enriched in brain; TSC2, tuberous sclerosis complex 2.

TABLE 4 Overview of TSC2 phosphorylation[1]

Kinase	Phosphorylation site of TSC2
AKT	Ser939, Ser981, and Thr1462 (50–52)
PKC-δ	Ser932/939 (53)
PKG	Ser1364/1365 (54)
Ras-ERK1/2	Ser540/664/1798 (56)
Wnt-GSK3	Ser1341/1337 (55)
TNFα-IKKβ	Ser487/511 (57)

[1] PKC, protein kinase C; PKG, protein kinase G; ERK1/2, extracellular regulated protein kinase; GSK3, glycogen synthase kinase-3; IKKβ, inhibitor of nuclear factor kappa B kinase β subunit; TSC2, tuberous sclerosis complex 2.

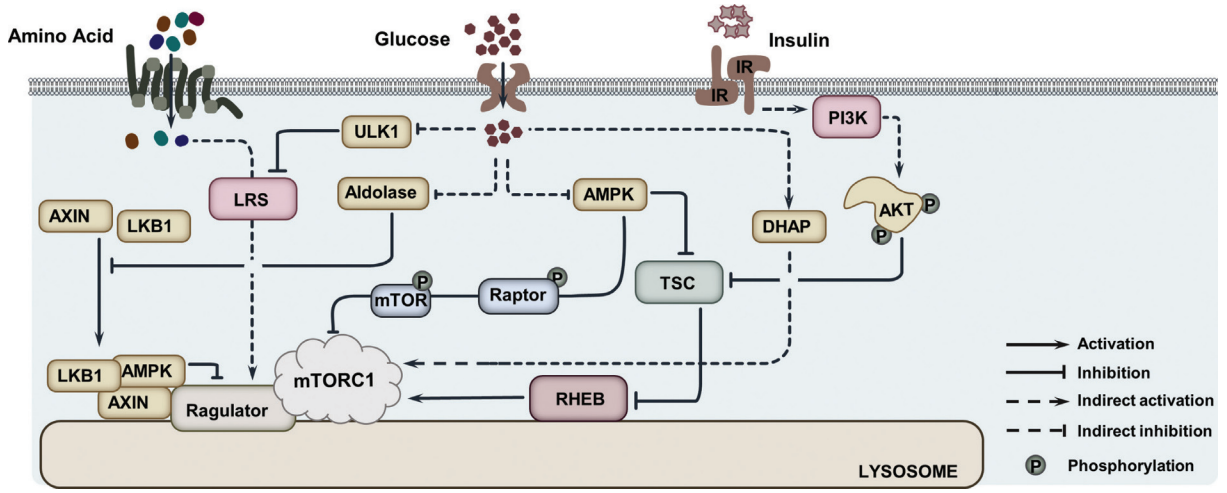

FIGURE 4 Glucose regulation of mTOR signaling. AMPK, AMP-activated protein kinase; AXIN, axis inhibitor protein; DHAP, dihydroxyacetone phosphate; IR, insulin receptor; LKB1, serine/threonine kinase 11/liver kinase B1; LRS, leucyl-tRNA synthetase; mTOR, mechanistic target of rapamycin; mTORC1, mechanistic target of rapamycin complex 1; Raptor, regulatory-associated of mTOR; RHEB, Ras homolog enriched in brain; TSC, tuberous sclerosis complex; ULK1, unc-51 like autophagy activating kinase 1.

the AKT/TSC/RHEB signaling axis is essential, mTORC1 cannot be fully activated under amino acid starvation, even in TSC knockout cells (91). The mTORC1 pathway requires both sufficient nutrients and a signal from growth factors for full activation.

mTORC1 as a Regulator of Metabolic Pathways

mTORC1 has been reported to control both biomass accumulation and metabolism by modulating key cellular metabolic processes, including protein, lipid, nucleic acids, and autophagy. Thus, mTORC1 has profound effects on health, aging, and the lifespan.

Regulation of protein synthesis

The regulation of protein synthesis is one of the best-characterized cellular functions of the mTORC1 pathway. The activation of mTORC1 leads to a dramatic increase in the translation of specific mRNAs. mTORC1 regulates transcription and translation processes via phosphorylating 2 well-characterized substrate proteins—that is, eukaryotic initiation factor 4E binding protein 1 (4EBP1) and S6K (**Table 5**). The phosphorylation of 4EBP1 by mTORC1 results in the dissociation of 4EBP1 from eukaryotic translation initiation factor 4 (eIF4) E (eIF4E), which promotes the assembly of the eIF4F complex and, consequently, translation initiation (92). S6K, a conserved substrate of mTORC1, regulates protein synthesis at both the transcriptional and

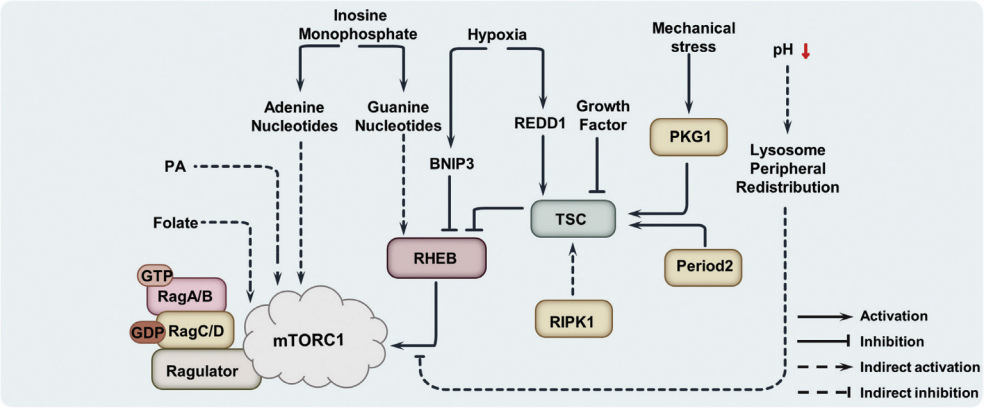

FIGURE 5 Nucleotide signals, mechanical stress, pH, and other upstream factors regulation of mTORC1 signaling. BNIP3, Bcl-2/adenovirus e1B 19 kDa-interacting protein 3; GDP, guanosine diphosphate; GTP, guanosine triphosphate; mTORC1, mechanistic target of rapamycin complex 1; PA, phosphatidic acid; Period2, period circadian regulator 2; PKG1, protein kinase G1; REDD1, DNA damage response 1; RIPK1, receptor-interacting protein kinase 1; TSC, tuberous sclerosis complex.

TABLE 5 Overview of mTORC1 pathway in regulating cellular metabolism[1]

Substrate	Function
The mTORC1 pathway regulates protein synthesis	
4EBP1	Promoting the assembly of the eIF4F complex and resulting in translation initiation (92)
S6K	Regulating protein synthesis by phosphorylating EIF4B (93), PDCD4 (94), SKAR (95), EEF2K (96), CBP80 (97), and S6 (98)
The mTORC1 pathway regulates lipid synthesis	
SREBP1	Regulating the expression of lipogenic enzymes (116)
CRTC2	Inhibiting the maturation of SREBP1 (114)
Lipin-1	Regulating the activation SREBP activity (115)
PPARγ	Regulating the expression of lipogenic enzymes (117–120)
SRPK2	Controls the expression of lipogenic enzymes (123)
EPRS	Facilitating the uptake of long-chain fatty acids (124)
HMGCR	Promoting the cholesterol biosynthesis (125)
ATGL	Promoting adipocyte lipolysis (127)
CPT1	Regulating fatty acid oxidation (128)
Histones	Regulating the expression of the lipogenic gene (129)
The mTORC1 pathway regulates nucleotides synthesis	
SREBP1/G6PD	Increase the production of nucleotides (109)
MTHFD2	Provides one-carbon unit for purine synthesis (132)
CAD	Promoting pyrimidine ribonucleotide synthesis (133)
The mTORC1 pathway regulates glucose metabolism	
HIF1α	Inducing the expression of glycolytic enzymes (136, 140)
C-Myc	Inducing the expression of glycolytic enzymes (7, 136)
The mTORC1 pathway regulates autophagy	
ATG13	Regulating the initiation of autophagy (143–145)
ULK1/2	Regulating the initiation of autophagy (143–146)
AMBRA1	Regulating nucleation of autophagosomes (147, 148)
ATG14L	Regulating autophagosome formation (150)
TFEB	Regulating lysosomal biogenesis and autophagy (153)
UVRAG	Regulating autophagosome and autolysosome formation (157)
Pacer	Regulating autophagosome maturation (158)
WIPI2	Controlling autophagy flux (159)
p300	Regulating autophagy (160)

[1] AMBRA1, autophagy and beclin 1 regulator 1; ATG13, autophagy-related gene 13; ATGL, adipose triglyceride lipase; ATG14L, atg14-like protein; CBP80, nuclear cap-binding protein subunit 1, 80 kDa; CAD, carbamoylphosphate synthetase II, aspartate transcarbamoylase, and dihydroorotase; CPT1, carnitine palmitoyltransferase I; CRTC2, CREB regulated transcription coactivator 2; EEF2K, eukaryotic initiation factor 2 kinase; EIF4B, eukaryotic translation initiation factor 4B; EPRS, glutamyl-prolyl-tRNA synthetase; G6PD, glucose-6-phosphate dehydrogenase; HIF1α, hypoxia-inducible factor 1, subunit α; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; MTHFD2, methylenetetrahydrofolate dehydrogenase (NADP-dependent) 2, methenyltetrahydrofolate cyclohydrolase; mTORC1, mechanistic/mammalian target of rapamycin complex 1; PDCD4, programmed cell death 4; PPARγ, peroxisome proliferator-activated receptor γ; SKAR, S6K1 Aly/REF-like target; SREBP, sterol regulatory element-binding protein; SRPK2, SR protein kinase 2; S6K, ribosomal protein S6 kinase 1; TFEB, transcription of transcription factor EB; ULK1/2, unc-51-like autophagy activating kinase 1/2; UVRAG, UV radiation resistance-associated gene protein; WIPI2, WD repeat domain, phosphoinositide interacting 2; 4EBP1, eukaryotic initiation factor 4E binding protein 1.

translational levels. S6K enhances protein synthesis by phosphorylating multiple downstream substrates, including EIF4B (93), programmed cell death 4 (PDCD4) (94), S6K1 Aly/REF-like target (SKAR) (95), eukaryotic initiation factor 2 kinase (EEF2K) (96), and nuclear cap-binding protein subunit 1, 80 kDa (CBP80) (97). Moreover, the activation of S6K1 results in the phosphorylation of ribosomal protein S6 on Ser235 and Ser236 (98), and the phosphorylation of both residues has a positive influence on protein synthesis at the translation level (99), while the role of phosphorylation of ribosomal protein S6 in regulating global rates of protein synthesis is controversial. For example, neither knock-inhosphorhospho-deficient S6 variant nor knockout of both S6K1 and S6K2 have significant effects on global rates of protein synthesis (100–104). Together, these observations imply that mTORC1 positively regulates protein translation through the combined phosphorylation of S6K and 4EBP1 in response to favorable growth conditions. Moreover, mTORC1 promotes cellular amino acid uptake and protein synthesis through the ubiquitin ligase neural precursor cell expressed, developmentally down-regulated 4–2 (Nedd4-2)–mediated degradation of system A amino acid transporter isoform (SNAT2) and system L amino acid transporter isoform (LAT1) (105) (**Figure 6**).

The mTORC1 pathway regulates lipid synthesis

The critical role of mTORC1 in lipid metabolism is mediated via the major transcriptional regulator, SREBP, which is a master regulator of lipid metabolism–related genes, including fatty acid synthase (*FASN*), acetyl-CoA carboxylase (*ACC*), and stearoyl-CoA desaturase 1 (*SCD1*). SREBP is synthesized in the endoplasmic reticulum as

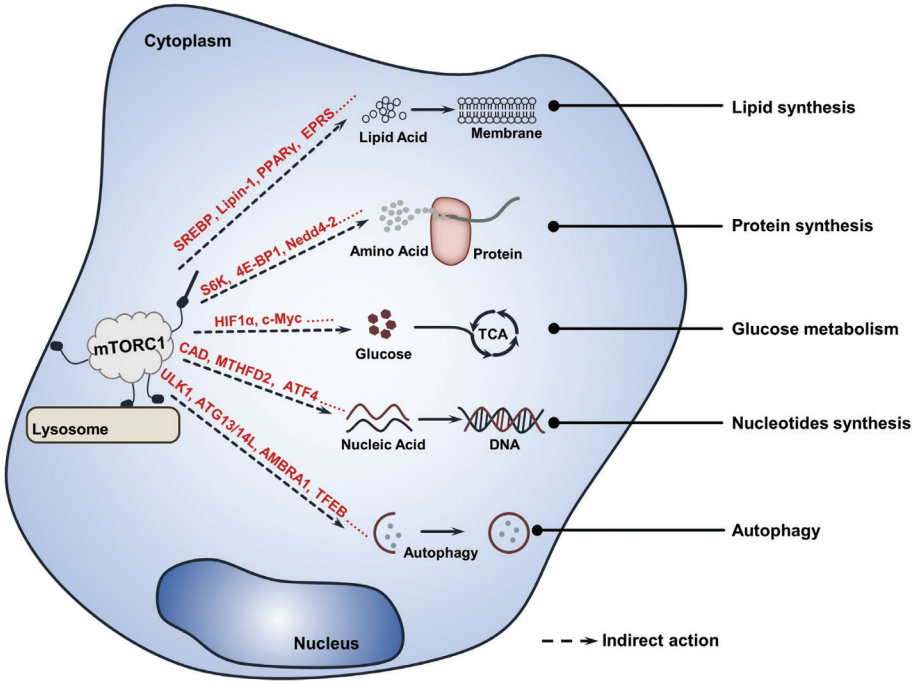

FIGURE 6 mTORC1 as a regulator for metabolic pathways. AMBRA1, autophagy and beclin 1 regulator 1; ATF4, activating transcription factor 4; ATG13, autophagy related 13; CAD, carbamoyl-phosphate synthetase 2, aspartate transcarbamylase, and dihydroorotase; EPRS, gamylprolyl-tRNA synthetase; HIF1α, hypoxia-induced factor 1α; MTHFD2, methylenetetrahydrofolate dehydrogenase (NADP-dependent) 2, methenyltetrahydrofolate cyclohydrolase; mTORC1, mechanistic target of rapamycin complex 1; Nedd4-2, neural precursor cell expressed, developmentally downregulated 4–2; PPARγ, peroxisome proliferator-activated receptor γ; S6K, ribosomal S6 kinase 1; SREBP, sterol regulatory element-binding protein; TCA, tricarboxylic acid; TFEB, transcription of transcription factor EB; ULK1, unc-51 like autophagy activating kinase 1; 4E-BP1, eukaryotic initiation factor 4E binding protein 1.

inactive precursors, followed by processing in the Golgi and translocation to the nucleus to induce the expression of genes involved in cholesterol and fatty acid synthesis (106–108). Accumulating evidence has shown that mTORC1 is necessary for the maturation and activation of SREBP (109–113). The processing of SREBP1 in the Golgi is increased in TSC-deficient cells (109, 111), and the S6K1-mediated activation of SREBP involves inhibition and phosphorylation of CREB regulated transcription coactivator 2 (CRTC2) at Ser136, which attenuates its inhibitory effect of cytoplasmic coat protein complex II (COPII)-dependent maturation of SREBP (114, 115). mTORC1 also regulates the SREBP transcriptional network through modulation of Lipin-1 nuclear localization. Activated mTORC1 can phosphorylate Lipin-1 and keep it in the cytoplasm, promoting SREBP binding to SRE-containing lipogenic genes (115). Moreover, the stability of SREBP1 is also controlled by mTORC1-S6K1 (116). Thus, mTORC1 controls lipogenesis by regulation of SREBP at the level of maturating, transcription, and stability.

Furthermore, several reports revealed that mTORC1 plays a fundamental role in adipogenesis by modulating the activity of PPARγ (117–120). However, the mechanism by which mTORC1 activates PPARγ is still not fully elucidated. One study observed that mTORC1 regulates the translation of PPARγ (121). Another report suggests that the transactivation capability of PPARγ is promoted by mTORC1 (118). It is also shown that mTORC1 could activate PPARγ through SREBP1-mediated production of PPARγ ligands (122). Moreover, mTORC1 promotes lipid biogenesis via the phosphorylation of the Ser494 residue (123). In addition, the mTORC1/S6K pathway facilitates the cellular uptake of long-chain fatty acids through phosphorylating glutamyl-prolyl-tRNA synthetase (EPRS) at Ser999 (124). Recent findings also highlight the role of mTORC1 in modulating the stability of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), the rate-limiting enzyme in the cholesterol biosynthesis pathway, by promoting the phosphorylation of Ser132 and Ser134 in ubiquitin-specific peptidase 20 (USP20) (125) (Figure 6 and Table 5).

In addition, mTORC1 inhibits lipolysis through early growth response protein 1 (Egr1)–adipose triglyceride lipase (ATGL) (126, 127), and inhibition of mTORC1 promotes fatty acid oxidation by regulating the activity of carnitine palmitoyltransferase I (CPT1) (128). mTORC1 can also regulate the expression of the lipogenic gene through epigenetic modification of histones (129) (Table 5). Consistent with the role of mTORC1 in cellular lipid metabolism, the expression of active AKT induces lipid synthesis in an mTORC1-dependent manner (113). Defects in TSC2 regulate de novo lipid biosynthesis by activating mTORC1 signaling (109). Likewise, expression of constitutively active RHEB increases de novo adipogenesis (130), while inhibition of mTORC1

via ablation of Raptor in the liver strongly supports the requirement of mTORC1 in adipogenesis (131).

The mTORC1 pathway regulates the synthesis of nucleotides

In addition to protein and lipids synthesis, mTORC1 plays a key role in nucleic acid production. mTORC1 regulates the pentose phosphate pathway through mTORC1/SREBP1/glucose-6-phosphate dehydrogenase (/G6PD), which leads to an increase in the production of nucleotides (109). Methylenetetrahydrofolate dehydrogenase (NADP-dependent) 2, methenyltetrahydrofolate cyclohydrolase (MTHFD2), a key component of the mitochondrial tetra hydrogen folic acid cycle, provides a one-carbon unit for purine synthesis and is a key regulatory protein for nucleic acid synthesis. mTORC1 reportedly enhances the expression of *MTHFD2* through activating transcription factor 4 (ATF4) (132). Moreover, phosphoproteomics and metabolomics studies have revealed that mTORC1 can stimulate pyrimidine ribonucleotide synthesis through mediating carbamoylphosphate synthetase II, aspartate transcarbamoylase, and dihydroorotase (CAD) phosphorylation at Ser1859 (133, 134). Additionally, mTOR also regulates cellular folate uptake by modulating plasma membrane localization of folate receptor-α (FR-α) and reduced folate carrier (RFC) to control the synthesis of nucleotides (135) (Figure 6 and Table 5).

The mTORC1 pathway regulates glucose metabolism

It has been reported that mTORC1 is involved in glycolysis and the TCA cycle via regulating the expression of HIF1α and Myc; both of these proteins can promote glucose uptake by mediating the expression of glucose transporter 1 (GLUT1), as well as hexokinase (HK), phosphofructokinase (PFK), fructose-2,6-bisphosphatase (PFKFB), glycosylphosphatidylinositol (GPI), phosphoglycerate mutase (PGAM), enolase (ENO), pyruvate kinase M (PKM), and lactate dehydrogenase A (LDHA), thus facilitating glucose metabolism (136–138).

HIF1α.

HIF1α is a transcription factor induced by hypoxia, and its translation can be enhanced by mTORC1 through the phosphorylation and inhibition of 4EBP1 in response to normoxic conditions (109, 139), thereby inducing the expression of glycolytic genes, including *HK2*, *PFK*, *PFKFB*, *LDHA*, and *PKM2*, to increase glycolytic flux. In addition to glycolysis, HIF1α also controls the activation of pyruvate dehydrogenase (PDH) complex by increasing the expression of pyruvate dehydrogenase kinase 1 (PDK1), which can inhibit the production of acetyl-CoA and negatively regulate the TCA cycle (136, 140).

C-Myc.

C-Myc is another crucial transcription factor known to regulate glucose metabolism. S6K1 enhances C-Myc translation efficiency by modulating the phosphorylation of eukaryotic initiation factor EIF4B (141). The increase in the C-Myc level leads to the expression of a large number of glycolytic enzymes, including LDHA, PFK, GPI, PGAM, and ENO. Moreover, C-Myc also regulates glutamine metabolism and glucose uptake by controlling the expression of alanine, serine, cysteine-preferring transporter 2 (ASCT2)/GLS, and GLUT1, thereby involved in glycolysis and the TCA cycle (7, 136) (Figure 6 and Table 5).

The mTORC1 pathway regulates autophagy

mTORC1 has been extensively studied in the context of autophagy (142), and the specific mechanism by which mTORC1 exerts its effects on autophagy has been gradually clarified. Studies demonstrate that mTORC1 regulates autophagy in at least 4 ways. First, mTORC1 phosphorylates and inactivates the initiation of autophagy by phosphorylating ULK complex components, including autophagy-related gene 13 (ATG13) and ULK1/2 (143–146). mTORC1 phosphorylates ULK1 at Ser758 and restricts the phosphorylation of ULK1 at Ser317/Ser777 by AMPK, resulting in the inhibition of ULK1 activity (146). Second, mTORC1 inhibits the activation of ULK1 through directly phosphorylating autophagy and beclin 1 regulator 1 (AMBRA1) (147), thereby inducing the nucleation of autophagosomes (148, 149). Third, mTORC1 also inhibits autophagosome formation by directly phosphorylating ATG14L at Ser3, Ser223, Thr233, Ser383, and Ser440 (143–145, 150, 151). Last, mTORC1 inhibits autophagy by regulating the transcription of transcription factor EB (TFEB) (152), which is the major transcriptional regulator of lysosomal biogenesis and autophagy genes (153). The phosphorylation of TFEB at Ser142 and Ser211 by mTORC1 promotes the interaction of TFEB with 14–3–3 to keep it in the cytoplasm, thereby inhibiting the transcription of genes required for lysosomal biogenesis and autophagy (152, 154–156). As a critical kinase complex, mTORC1-mediated UV radiation resistance-associated gene protein (UVRAG) phosphorylation can lead to the disruption of autophagosome and autolysosome formation under nutrient-replete conditions, thereby inhibiting autophagy (157). Moreover, mTORC1 also inhibits autophagy by phosphorylating Pacer at Ser157 (158); WD repeat domain, phosphoinositide interacting 2 (WIPI2) at Ser395 (159); and p300 at 4 serine residues in the C-terminal region (160) (Figure 6 and Table 5).

In addition to autophagy, mTORC1 can also influence genomic instability by phosphorylating superoxide dismutase 1 (SOD1) and ring finger protein 168 (RNF168) and enhancing cancer cell survival and tumor formation (70, 161). Overall, these data imply that lysosomal mTORC1 coordinates a variety of physiological and biochemical processes in cells, such as protein, lipid, nucleotide, and glucose metabolism, as well as DNA damage repair, to maintain cellular and physiological homeostasis; in contrast, mTORC1 pathway dysregulation is associated with diseases such as diabetes, cancer, and aging.

mTORC1 as a Regulator of Health and Aging

Evidence for the importance of mTOR function in vivo lies in that the lack of multiple key components in this pathway contributes to embryonic lethality (162, 163). Moreover, a study in mice has shown that long-term feed deprivation poses a risk of death for animals expressing RagA-GTP (a constitutively active form of RagA), in which mTORC1 signaling is uncontrolled (164), while a similar effect is also observed in sestrin knockout (KO) mice (165). This indicates that balanced mTORC1 activation is a prerequisite for maintaining organismal survival.

Obesity and diabetes

Maintaining optimal mTOR activation is essential for sustaining energy/metabolic homeostasis. Excessive nutrient and cytokine availability contributes to persistent mTORC1 activation, which leads to the degradation of IRS1 and blocks signal transduction in the insulin pathway, thereby triggering insulin resistance, blocking glucose absorption, aggravating obesity, and increasing the risk of type 2 diabetes (14). The consumption of a high-fat diet (HFD) leads to the continuous production of cytokines, nutrients, and hormones, forcing the mTORC1 pathway to maintain a persistent "on" state, which disrupts the insulin pathway by activating GRB10 (15, 16). Frequently, branched-chain amino acids (BCAAs) are involved in type 2 diabetes and insulin resistance via mTORC1 and mTORC2 pathways (166–168). A recent study suggested that mTORC1 controls postembryonic development by sensing leucine-derived monomethyl branched-chain fatty acid (169). Collectively, these data demonstrate that mTORC1 activation may be a biomarker for the development of insulin-resistant disease, and dysregulated mTORC1 signaling also accounts for the unbalanced metabolic cycles seen in a variety of tissues.

Hypothalamus.

Studies have shown that mTOR regulates leptin- and insulin-related anorexia through the hypothalamus, which is the center for sensing and integrating signals relating to hormone and nutrient availability, as well as controlling food intake, glucose metabolism, and lipid homeostasis (170, 171). However, the link between mTORC1 activation in the hypothalamus and food intake behavior remains controversial, and future research should reveal the precise mechanisms underlying mTOR signaling-mediated regulation of food intake and how this signaling can be manipulated to treat type 2 diabetes and obesity.

Adipose.

The biogenesis of white adipose tissue (WAT), the largest energy storage organ in the body, is regulated by the mTORC1 pathway. mTORC1 boosts energy storage by promoting the synthesis and deposition of triglycerides in WAT. However, mice that specifically lack mTORC1 in adipose tissue are lean and resistant to obesity induced by an HFD (172).

Liver.

Ketone bodies are used as energy by peripheral tissues and fasting can promote the production of ketone bodies in the liver by inhibiting the activity of the mTORC1 pathway. However, feed deprivation does not promote the production of ketone bodies in mice exhibiting constitutive activation of mTORC1 (173).

These results strongly suggest that the mTORC1 pathway plays a fundamental role in controlling glucose, lipid, and ketone body metabolism across various tissues. Meanwhile, dysregulated mTORC1 signaling can lead to the development of metabolic diseases, such as insulin resistance, diabetes, and obesity (**Figure 7**).

Cancer

Accumulating evidence has implicated obesity and diabetes as important mechanisms underlying the occurrence and development of numerous cancers. For instance, obesity-induced liver steatosis could lead to hepatocellular carcinoma, whereas the antidiabetic drug metformin can reduce the risk of cancer through the mTORC1 pathway. Metformin is one of the most prescribed antidiabetic medicines and has shown other benefits such as reductions in body weight, antiaging, and anticancer (174, 175). Metformin can inhibit mitochondrial respiratory chain complex I (176, 177), which further decreases the level of ATP and increases AMP levels, thus resulting in the activation of AMPK (178). Moreover, metformin also binds to presenilin enhancer 2 (PEN2) to activate AMPK (179) and inhibit mTORC1 by phosphorylating the TSC and Raptor subunit of mTORC1 (63, 64). It is also known that metformin acts to suppress mTORC1 in the absence of TSC1/2 or AMPK, while Rag GTPase protects the mTORC1 pathway from inhibition by metformin, indicating that metformin inhibits mTORC1 in an AMPK-independent and Rag GTPase-dependent manner (180).

The mTOR pathway is closely related to tumorigenesis, not only because of its important role in obesity and diabetes but also because of its crucial involvement in regulating the cell cycle, proliferation, and growth, as well as protein synthesis and glucose metabolism. Tumor occurrence and development are usually accompanied by the hyperactivation of the mTORC1 pathway, which is induced by mutations in mTOR, GATOR1, PI3K, AKT, and tensin homologue deleted on chromosome 10 (PTEN), among other factors; hyperactivation of the mTORC1 pathway promotes the development of cancers such as colorectal cancer, lung cancer, breast cancer, and glioblastomas (181, 182). The mTOR pathway is estimated to be dysregulated in nearly 30% of all cancers (172, 181).

Liver-specific PTEN-KO or TSC1-KO mice exhibit increased mTORC1 activity and metabolic abnormalities, including glucose and lipid metabolism disorders, and subsequently develop hepatocellular carcinoma (172). Moreover, mTORC1 promotes the translation of mRNA encoded by genes that regulate processes such as cell survival, cell cycle progression, angiogenesis, and energy metabolism through

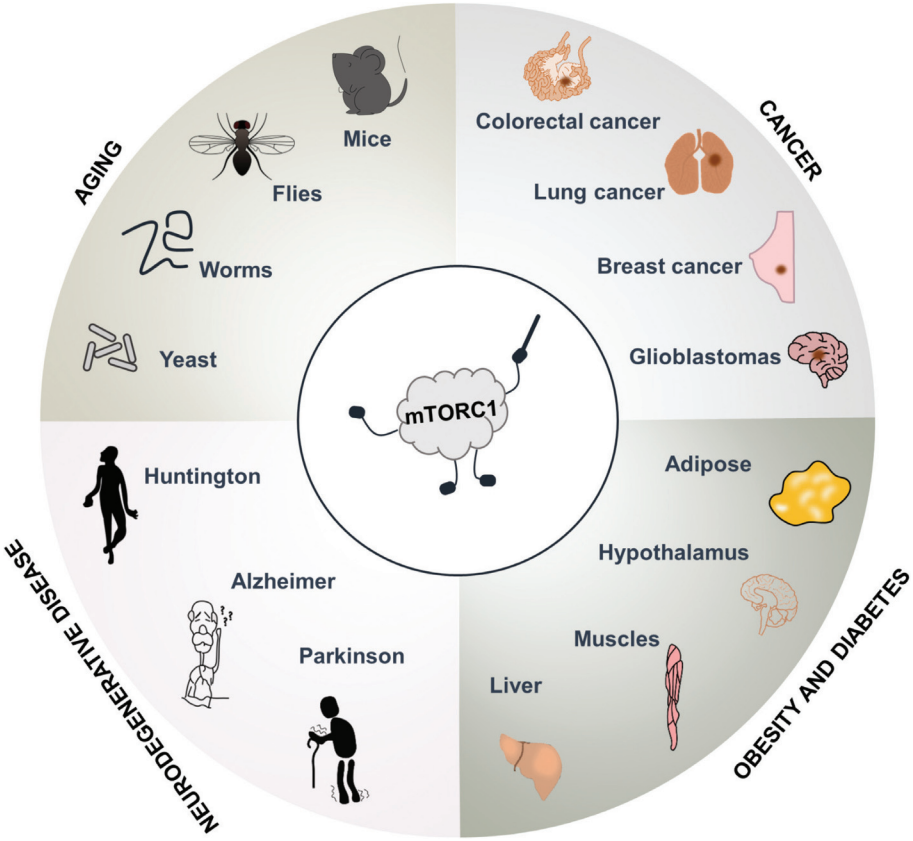

FIGURE 7 mTORC1 as a regulator for health and aging. mTORC1, mechanistic target of rapamycin complex 1.

4EBP, thereby impacting cell proliferation and tumorigenesis. In addition, mTOR activation promotes ribosome biosynthesis through S6K, thereby helping to maintain a high level of cancer cell growth (181). Drugs targeting the mTORC1 pathway, including temsirolimus (CCI-779), everolimus (RADD001), and ridaforolimus (AP23573), are currently used in the treatment of a variety of solid tumors and hematological malignancies, while a variety of mTORC1 inhibitors, including rapamycin and its derivatives, are undergoing both preclinical and clinical assessments (181).

Taken together, these results show that the mTORC1 pathway can increase nutrient availability for the production of a large number of macromolecular metabolites, which provides favorable conditions for the rapid growth and proliferation of cancer cells. Identifying biomarkers and understanding the nutritional requirements of tumor cells will allow for the development of more specific mTOR-targeted drugs with better therapeutic effects and improved safety profiles.

Aging

Emerging evidence has shown that the inhibition of the mTORC1 pathway via gene KO, rapamycin treatment, or caloric restriction (CR) can increase the lifespan of yeast, worms, flies, and mice (183–186), highlighting the importance of mTORC1 in biological aging. CR, defined as a reduction in nutrient intake without malnutrition, plays an important role in regulating lifespan-enhancing partly mediated by decreased mTORC1 signaling (187). CR reduces the activation of mTORC1 in paneth cells to abolish the intestinal stem cell–augmenting effects of the niche (188). Feeding with a CR diet did not extend the lifespan of yeast or worms when mTORC1 is inhibited, indicating that CR prolongs lifespan through mTORC1 signaling (187, 189, 190). However, the role of mTORC1 and CR in regulating lifespan is also controversial, as the inhibition of mTORC1 activity synergized with CR to promote lifespan extension in flies (191). Rapamycin does not delay aging in flies that express a constitutively activated form of S6K or harbor null alleles of 4EBP, while the knockdown of ATG5, which is required for autophagosome formation, inhibits the life-prolonging effect of rapamycin (192). These data indicate that mTORC1 may regulate lifespan extension through controlling protein synthesis (mRNA translation) and autophagy. However, it is not yet clear to what extent mRNA translation or autophagy contributes to the life-prolonging effect of rapamycin.

mTORC1 promotes protein synthesis and inhibits autophagy, which can foster cellular stress (protein aggregation, organelle dysfunction) and lead to the accumulation of cell damage, thereby promoting the occurrence of aging-related disorders, including Alzheimer disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) (8) (Figure 7).

The clinical features of AD include the progressive loss of short-term memory and the onset of cognitive dysfunction. AD is positively correlated with age, and its mechanism is related to the pathological spreading of amyloid-β peptide (Aβ) and tau protein. Aβ deposits and tau hyperphosphorylation have been detected in the brains of AD model mice and mTORC1 activation was found to be increased in brain regions containing Aβ deposits. Interestingly, feeding mice rapamycin inhibited this increase in mTORC1 activity, reduced Aβ and tau pathology, and ameliorated learning and memory deficits. Importantly, a similar increase in mTORC1 activation is also found in affected brain regions of AD patients, further indicating the importance of mTORC1 in the progression of this disorder (192).

The beneficial effects of rapamycin on the brain may not be limited to AD as rapamycin administration has been shown to improve pathological markers in PD and HD. PD is a neurological disease characterized by progressive motor dysfunction resulting from the gradual degeneration of central and peripheral nervous system neurons. The accumulation of toxic proteins and impaired autophagy in the brain may contribute to the development of the disease. Over the last decade, numerous studies have shown that inhibiting mTORC1 with rapamycin promotes the autophagic degradation of aggregate-prone proteins in vitro and reduces the severity of neurodegeneration in several in vivo models by slowing protein synthesis (193, 194). In particular, rapamycin induces autophagy in an mTORC1-dependent manner and also exerts a protective effect against HD (195, 196).

Given its central role in integrating a variety of signals relating to nutrient availability and regulating multiple physiological processes, including protein synthesis and autophagy, mTORC1 is expected to represent a therapeutic target for delaying aging and treating neurodegenerative diseases; however, much remains to be learned about the effects of mTORC1 in these processes. For instance, we do not know the exact mechanism by which mTORC1 exerts its beneficial effects; it will be of great interest to learn whether metabolic reprogramming, such as insulin sensitivity, is involved in mTORC1-mediated lifespan extension.

Conclusions and Perspectives

The mTORC1 network of signaling pathways integrates nutrient-related information on a cellular, tissue, and organism level to coordinate nutrient availability and anabolic processes that allow for either cell growth or cancer development and progression (7). However, compared with pathways such as the Hippo, Wnt, and TGF-β pathways, relatively little is known about mTORC1, a complex that was discovered approximately only 25 y ago. Nevertheless, the information gathered to date on factors acting upstream of mTORC1 and the identification of key components in this pathway have begun to provide an outline of the role of mTORC1 signaling in cellular, physiological, and pathological processes.

We now have a clearer understanding of the network of signals (such as amino acids, glucose, growth factors, and fatty acids) that activate mTORC1 (8). However, our understanding of how and which vitamins, minerals, and trace elements activate the mTORC1 pathway remains limited. Additionally, although the GAP for RHEB is known (the TSC complex) (48), which factor acts as the guanine nucleotide exchange factor (GEF) for RHEB remains to be established. Moreover, further in-depth research is required to clarify the connection between the upstream signals that regulate the cross-talk between amino acid– and glucose-dependent pathways, as well as between amino acid– and growth factor–dependent pathways (66, 197). mTORC1 lysosomal localization is known to be essential for its activation; however, recent studies have shown that the site of mTORC1 activation is not limited to the lysosomal surface, and can also occur on the Golgi apparatus and in the nucleus (198–200). Accordingly, it becomes interesting to know whether mTORC1 can be activated in other subcellular locations and whether amino acids in different cellular compartments can activate mTORC1.

Alongside this, relatively few of the 20 amino acids are known to be sensed by mTORC1 (7, 43). Although cyst(e)ine, threonine, and asparagine have recently been reported to activate mTORC1 (37–39), whether the remaining amino acids similarly activate mTORC1 is unknown. TFEB phosphorylation is strictly dependent on amino acid–mediated activation of RagC and RagD GTPases but is not sensitive to growth-induced RHEB activity. The mechanism plays a crucial role in Birt–Hogg–Dubé syndrome caused by mutations in the RagC and RagD activator folliculin (FLCN) (201). However, whether mTORC1 responds to various stimuli through the differential phosphorylation of specific substrates remains to be determined.

Given that mTORC1 dysregulation is an important factor leading to metabolic diseases, it is tempting to infer that inhibiting this key node may lead to the reversal of obesity and diabetes. Importantly, metformin, a drug used for the treatment of type 2 diabetes, has been shown to effectively inhibit mTORC1 (202). The ablation of S6K1, an mTORC1 substrate, can also improve insulin sensitivity and prevent obesity (203). However, patients receiving rapamycin treatment have severe side effects related to insulin resistance, possibly because long-term rapamycin treatment not only inhibits mTORC1 activity but also disrupts the integrity of mTORC2, thereby weakening the AKT-dependent insulin response (204). To avoid these adverse effects, inhibitors that specifically target mTORC1 must be developed.

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Data Availability

Data sharing is not applicable to this article.

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