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Mammalian target of rapamycin
Hitting the bull's-eye for neurological disorders

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The mammalian target of rapamycin (mTOR) and its associated cell signaling pathways have garnered significant attention for their roles in cell biology and oncology. Interestingly, the explosion of information in this field has linked mTOR to neurological diseases with promising initial studies. mTOR, a 289 kDa serine/threonine protein kinase, plays an important role in cell growth and proliferation and is activated through phosphorylation in response to growth factors, mitogens and hormones. Growth factors, amino acids, cellular nutrients and oxygen deficiency can downregulate mTOR activity. The function of mTOR signaling is mediated primarily through two mTOR complexes: mTORC1 and mTORC2. mTORC1 initiates cap-dependent protein translation, a rate-limiting step of protein synthesis, through the phosphorylation of the targets eukaryotic initiation factor 4E-binding protein 1 (4EBP1) and p70 ribosomal S6 kinase (p70S6K). In contrast, mTORC2 regulates development of the cytoskeleton and also controls cell survival. Although closely tied to tumorigenesis, mTOR and the downstream signaling pathways are significantly involved in the central nervous system (CNS) with synaptic plasticity, memory retention, neuroendocrine regulation associated with food intake and puberty and modulation of neuronal repair following injury. The signaling pathways of mTOR also are believed to be a significant component in a number of neurological diseases, such as Alzheimer disease, Parkinson disease and Huntington disease, tuberous sclerosis, neurofibromatosis, fragile X syndrome, epilepsy, traumatic brain injury and ischemic stroke. Here we describe the role of mTOR in the CNS and illustrate the potential for new strategies directed against neurological disorders.

Introduction

Mammalian target of rapamycin (mTOR) is a serine/threonine protein kinase and has been known to play its role in cell growth and proliferation. mTOR is activated by phosphorylation in response to growth factors, mitogens and hormones.[1-4] Rapamycin is a macrolide antibiotic from Streptomyces hygroscopicus that specifically inhibit the activity of mTOR. To foster its inhibitory effect on mTOR, rapamycin binds to immunophilin FK-506-bidining protein 12 (FKBP12) to attach to mTOR, which prevents mTOR from phosphorylation.[5] The function and regulatory pathway of mTOR have been extensively investigated and is gaining more broad attention in cancer research, development, metabolism and the central nervous system (CNS) diseases.

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The mTOR protein is a 289 kDa kinase that contains multiple protein domains. The carboxy-terminal acid terminal has a conserved sequence with homology to the catalytic domain of phosphoinositide-3-kinase (PI 3-K) family.[6] The domain contains phosphorylation sites, such as threonine 2446, serine 2448 and serine 2481, which function to regulate mTOR activity. The phosphorylation of serine 2481 is an autocatalytic target of mTOR.[7,8] The residue serine 2448 is the target of Akt (protein kinase B), another serine/threonine kinase and p70 ribosomal S6 kinase (p70S6K), while threonine 2446 is phosphorylated by AMP activated protein kinase (AMPK) and p70S6K.[9-11] The C-terminal also contains FKBP12-rapamycin-associated protein (FRAP), ataxia-telengiectasia (ATM) and transactivtion/transformation domain-associated protein domain (FAT). The FKBP12-rapamycin binding domain (FRB) is adjacent to the FAT domain and is the site of interaction between mTOR and FKBP protein bound to rapamycin.[12] The N-terminal of mTOR contains a tandemly repeated HEAT (Huntingtin, Elongation factor 3, A subunit of Protein phosphatase-2A and TOR1) motif, which provide protein interaction between mTOR complex with regulatory-associated protein with mTOR (Raptor) or rapamycin-insensitive companion of mTOR (Rictor) and has been associated with multimerization of mTOR.[13]

The mTOR exerts its functions mainly through two mTOR complexes: mTORC1 and mTORC2,[14] in which mTOR associates with its regulatory proteins. In acute setting, rapamycin dominantly inhibits the activity of mTORC1. The mTORC2 is relatively resistant to rapamycin and prolonged treatment is required for rapamycin to inhibit the activity of mTORC2.[15]

The components of mTORC1 currently include (1) mTOR. mTOR is the catalytic subunit of the complex. (2) Raptor. Raptor is an essential component of the complex and functions to recruit mTOR substrate to the mTORC1 complex.[16,17] Raptor is a 150 kDa mTOR binding protein that also binds to 4EBP1 and p70S6K. The binding of Raptor to mTOR is necessary for the mTOR-catalyzed phosphorylation of 4EBP1 in vitro, and it strongly enhances the mTOR kinase activity toward p70S6K.[16]

Table 1. The components of mTOR complex (mTORC) and their function

Components	Function
mTOR	Catalytic subunit of mTORC1 and mTORC2
Raptor	An essential component of mTORC1, recruits mTOR substrates to mTORC1and promotes the activity of mTORC1 to 4EBP1 and p70S6K
Rictor	Promotes the assembly and the activity of mTORC2, stabilizes mSIN1
PRAS40	An mTORC1 binding partner and negatively regulates the activity of mTORC1 by binding to mTORC1
mSIN1	A necessary component of mTORC2, promotes the assembly and the activity of mTORC2 to phosphorylate Akt at serine 473
mSLT8	A necessary component for the stability of Rictor-mTOR interaction and activity of mTORC2
Deptor	Negatively regulates the activity of both mTORC1 and mTORC2
Protor-1	A Rictor binding subunit in mTORC2

4EBP1, eukaryotic initiation factor 4E-binding protein 1; Deptor, DEP domain-containing mTOR-interacting protein; mLST8, mammalian lethal with Sec13 protein 8; mSIN1, mammalian stress-activated protein kinase interacting protein; mTOR, mammalian target of rapamycin; p70S6K, p70 ribosomal S6 kinase; PRAS40, proline-rich Akt substrate 40 kDa; Protor-1, protein observed with Rictor-1; Raptor, regulatory-associated protein of mTOR; Rictor, rapamycin-insensitive companion of mTOR.

(3) Proline rich Akt substrate 40 kDa (PRAS40). PRAS40 is an mTORC1 binding partner that direct competitively inhibits the binding of mTORC1 substrate to Raptor.[18] Upon activation, mTOR can directly phosphorylate PRAS40 resulting in the dissociation of PRAS40 with mTORC1.[19] Phosphorylation of PRAS40 on serine183 and serine 221 by mTORC1, and threonine 246 by Akt leads to its dissociation from mTORC1, and its binding to 14-3-3 protein.[20] Phosphorylation of PRAS40 on serine 221 and 183 but not serine-212 is sensitive to rapamycin treatment.[19] (4) Mammalian lethal with Sec13 protein 8 (mLST8). The function in mTORC1 is not clear. (5) DEP-domain-containing mTOR-interacting protein (Deptor). Deptor may negatively regulate the activity of mTORC1 and loss of Deptor activates mTORC1,[21] (**Table 1**).

Similarly, mTORC2 consists of six different proteins (1) mTOR. (2) Rictor. Rictor is beneficial to the assembly and promotes the activity of mTORC2.[22] Rictor is also essential for mTORC2 to activate Akt.[23] The Rictor-mTOR complex directly phosphorylates Akt/PKB on serine 473 in vitro and facilitates threonine 308 phosphorylation by phosphoinositide-dependent kinase 1 (PDK1).[23] (3) Mammalian stress-activated protein kinase interacting protein (mSIN1). mSIN1 is necessary for the assembly of mTORC2 and for its capacity to phosphorylate Akt.[24] Genetic ablation of *msin1* abolishes Akt-serine 473 phosphorylation and disrupts Rictor-mTOR interaction but maintains threonine 308 phosphorylation, suggesting that mSIN1-Rictor-mTOR complex in necessary for Akt serine 473 phosphorylation, which is required for TORC2 to support cell survival.[25] (4) mLST8. mLST8 is necessary for the Rictor-mTOR interaction and for the stability and activity of mTORC2 complex.[26] (5) Protein observed with Rictor-1 (Protor-1). Protor-1 is a Rictor-binding subunit of mTORC2.[27] Rictor and mSIN1 have been shown to stabilize each other to form the structural foundation of mTORC2 and is required for Akt phosphorylation.[25] (6) Deptor. Deptor also negatively regulates the activity of mTORC2.[21]

Activation of mTOR Complex

Growth factor and mTORC1. Growth factors activate G-protein coupled receptors and receptor tyrosine kinase and then stimulate mTORC1 by inhibiting tuberous sclerosis complex1 (TSC1)/TSC2 through phosphoinositide 3 kinase (PI 3-K)-Akt and Ras-extracellular signal-regulated kinase (ERK) mediated pathways (**Fig. 1**).

TSC1 (hamartin)/TSC2 (tuberin) complex is a negative regulator of mTORC1. TSC2 functions as a GTPase-activating protein (GAP), converting a small G protein Ras homologue enriched in brain (Rheb) to the inactive GDP-bound form.[28] The active GTP-bound Rheb can directly interact with Raptor and activate mTORC1 complex. Rheb also regulates the binding of 4EBP1 with mTORC1.[29] The decreased activity of TSC1/TSC2 complex is mediated through the phosphorylation of TSC2 by Akt, ERK or p90 ribosomal S6 kinase 1 (RSK1).[28,30-32] Rheb also can regulate mTOR through FKBP38, a member of FKBP family that is structurally related to FKBP12. FKBP38 is an endogenous inhibitor of mTOR and reduces the activity of mTOR through association with mTORC1. Rheb interacts directly with FKBP38 and prevents its association with mTOR in a guanosine 5'-triphosphate (GTP)-dependent manner.[33]

Activation of Akt is dependent on PI 3-K.[34-39] The activation of the receptor tyrosine kinase (RTK) and the G protein-coupled receptor (CPCR) are required to activate PI 3-K. PI 3-K is composed of a catalytic p110 subunit and a regulatory p85 subunit. Growth factors or cytokines, can stimulate the recruitment of PI 3-K to the plasma membrane. Following activation, PI 3-K phosphorylates membrane glycerophospholipid phosphatidylinositol 4,5-bisphosphate [PI (4,5)P_2] resulting in the production of phosphatidylinositol 3,4,5-trisphosphate (PIP_3) and phosphatidylinositol 3,4-disphosphate (PIP_2). The critical step for activation of Akt is its transition from the cytosol to the plasma membrane by the binding of Akt to PIP_2 and PIP_3 through its PH domain. As a result of this sequence of events, Akt becomes available for phosphorylation by several upstream kinases.[40,41]

There may exist TSC1/TSC2 dependent and independent Akt signaling pathways to mTORC1. In the TSC1/TSC2 dependent pathway, activated Akt directly phosphorylates TSC2 on multiple sites resulting in the destabilization of TSC2 and disruption of its interaction with TSC1.[28,42] The phosphorylation of TSC2 at the residues of serine 939 and 981 can result in its sequestration in the cytosol, where it is bound to the anchor protein 14-3-3, leading to the activation of Rheb and mTORC1.[30] In the TSC1/TSC2 independent pathway involves the mTORC1 binding protein PRAS40. Activated Akt phosphorylates PRAS40 and dissociates its binding to Raptor of the mTORC1 complex and releases

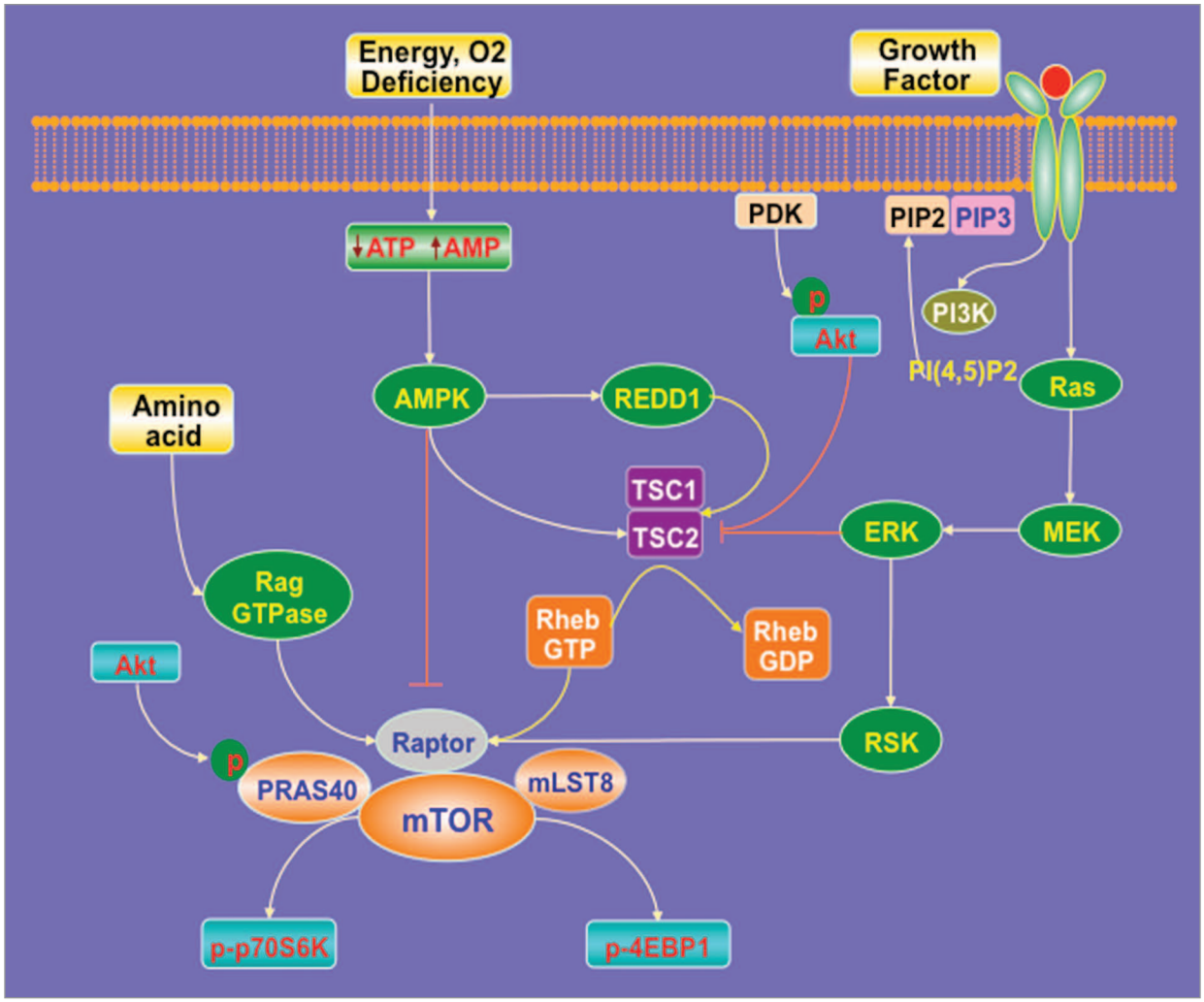

Figure 1. Activation of mammalian target of rapamycin complex 1 (mTORC1). Growth factors activate mTORC1 through both phosphoinositide 3 kinase (PI 3-K)-Akt and Ras-extracellular signal-regulated kinase (ERK) mediated pathways. Activation of Akt is dependent upon PI 3-K. Growth factors or cytokines, can stimulate the recruitment of PI 3-K to the plasma membrane. Following activation, PI 3-K phosphorylates membrane glycerophospholipid phosphatidylinositol-4,5-bisphosphate [PI (4,5)P_2] resulting in the production of phosphatidylinositol-3,4,5-trisphosphate (PIP_3) and phosphatidylinositol-3,4-disphosphate (PIP_2). Akt is translocated from the cytosol to the plasma membrane through the binding to PIP_2 and PIP_3 through its PH domain. As a result of this sequence of events, Akt becomes available for phosphorylation by its upstream kinases, such as phosphoinositide-dependent kinase 1 (PDK1). Activated Akt can phosphorylate tuberous sclerosis complex-2 (TSC2), resulting in the disruption of its interaction with TSC1, activation of Ras homologue enriched in brain (Rheb) and subsequent activation of mTORC1. Akt can also directly phosphorylate proline rich Akt substrate 40 kDa (PRAS40) and reduce its binding to regulatory associated protein of mTOR (Raptor) and release its suppression of mTORC1. In the ERK mediated mTORC1 activating pathway, ERK is activated upon Ras induced activation of mitogen activated kinase/ERK kinase (MEK) and then phosphorylation of TSC2 ensues. ERK also can activate the ribosomal S6 kinase (RSK), which phosphorylates Raptor resulting in the activation of mTORC1. Oxygen deprivation or hypoxia reduces cellular ATP level and stimulates AMP activated protein kinase (AMPK) which may induce the expression of transcriptional regulation of DNA damage response 1 (REDD1), releasing TSC2 from the binding to protein 14-3-3 and inhibiting mTORC1 activity. Similarly, cellular energy deficiency also activates AMPK, which phosphorylates TSC2 promoting its GTPase activating protein activity and turning Rheb-GTP into Rheb-GDP and subsequent inhibits mTORC1 activity. AMPK induced phosphorylation of Raptor on serine 722 and 792 also results in the inhibition of mTORC1 activity. Amino acids can induce relocalization of mTORC1 and activate Rag GTPase, which binds to Raptor and activates mTORC1. Upon activation, mTORC1 phosphorylates its two major downstream targets p70 ribosome S6 kinase (p70S6K) and eukaryotic initiation factor 4E-binding protein 1 (4EBP1).

mTORC1 from the suppression by PRAS40,[18,43-46] facilitating the activation of mTORC1.

In the insulin induced Akt-mTORC1 activated signaling pathway, a negative feedback loop has been found. Downstream of Akt activation is the mTORC1 activated signaling event, which reversely repress insulin PI 3-K-Akt axis. The underlying mechanism may involve the insulin receptor substrate 1 (IRS1). Following activation, mTORC1 phosphorylates and activates its downstream target p70S6K, which then phosphorylates and inhibits IRS1, the upstream of PI 3-K.[47]

In addition to PI 3-K/Akt signaling pathway, Ras-ERK signaling has also been associated with the activation of mTORC1

in response to growth factors. In the ERK mediated mTORC1 activating pathway, ERK is activated upon Ras induced activation of mitogen activated kinase/ERK kinase (MEK) and then the phosphorylation of TSC2 ensues. ERK-dependent phosphorylation on serine 664 of TSC2 leads to TSC1-TSC2 dissociation and impairment of TSC2 ability to inhibit mTOR signaling, suggesting that the Ras/MAPK pathway upstream of the TSC complex and that ERK may modulate mTOR signaling pathway and contribute to disease progression through phosphorylation and inactivation of TSC2.[31]

The phosphorylation of Raptor also regulates the activity of mTORC1. Activation of the Ras-ERK pathway leads to high Raptor phosphorylation on RXRXXpS/T consensus motifs and RSK 1 and 2 are required for Raptor phosphorylation. Importantly, Raptor mutants lacking RSK-dependent phosphorylation sites markedly reduces mTOR phosphotransferase activity, suggesting that RSK-mediated phosphorylation of Raptor is important for mTORC1 activation through the Ras-ERK pathway.[48] Rheb overexpression also increases phosphorylation on Raptor serine 863 as well as on the five other identified sites (serine 859, 855, 877, 696 and threonine 706). In addition, Raptor serine 863 phosphorylation functions as a master biochemical switch that modulates hierarchical raptor phosphorylation (phosphorylation on serine 863 is required for phosphorylation on serine 859 and serine 855). Moreover, Raptor defect leads to a reduced activity of mTORC1.[49] Upon activation, mTOR also phosphorylates Raptor in vitro and in vivo, which is stimulated by insulin and inhibited by rapamycin. More importantly, the site-directed mutation of Raptor on serine 863 reduces mTORC1 activity.[50] Consequently, manipulating the phosphorylation of Raptor mediates the activation of mTORC1.

Cellular energy deficiency and mTORC1 activation. The energy and nutrient level of the cells can also modulate the activity of mTORC1. The lowered cellular energy status downregulates the activity of mTORC1[51,52] through AMPK mediated cell signaling pathway.[53] AMPK serves as a sensor for cellular energy status and can be activated by increased level of AMP or AMP/ATP ratio.[54] Upon activation, AMPK phosphorylates TSC2 at the residue of serine 1387 (human) or serine 1345 (rat), promoting its GAP activity to turn Rheb-GTP into Rheb-GDP and thereby inhibiting the activity of mTORC1.[53] While in TSC2 null cells, activation of AMPK still partially inhibits mTORC1, suggesting that there exists an alternative pathway for AMPK signals to mTORC1.[55] The mTORC1 component Raptor have been identified as a direct substrate of AMPK and demonstrate that AMPK directly phosphorylates Raptor at two conserved serine sites: serine 722 and serine 792, resulting in the binding of Raptor to a cytoplasmic dock protein 14-3-3 and resulting in the inhibition of mTORC1.[53,56]

Upstream of AMPK is the LKB1, a tumor suppressor. LKB1 is a serine/threonine kinase and a major kinase that phosphorylates AMPK under the condition of cellular energy deficiency.[54] LKB1 phosphorylates AMPK at threonine 172 resulting in AMPK activation followed by inhibition of mTORC1.[57] Recently, the tumor suppressor p53 has been demonstrated to activate AMPK under oxidative and genotoxic stress.[58] Two p53 target genes, *sestrin 1* and *sestrin 2*, have been identified to suppress mTORC1. verexpression of Sestrin1 and Sestrin 2 activates AMPK, which phosphorylates TSC2 and stimulates its GAP activity and thus inhibits the activity of mTORC1.[58]

Oxygen deprivation and mTORC1 activation. Hypoxia reduces ATP level and activates AMPK, which then downregulates the activity of mTORC1 through activating TSC1/2 complex.[59] Hypoxia also induces the inhibition of mTORC1 through a mechanism that involves transcriptional regulation of DNA damage response 1 (REDD1).[60-62] Hypoxia induced reduction in mTORC1 activity correlates with increased expression of the hypoxia-inducible REDD1 gene. Disruption of REDD1 abrogates the hypoxia-induced inhibition of mTOR. In contrast, REDD1 overexpression is sufficient to downregulate mTORC1 activity in a TSC1/TSC2-dependent manner.[60] Further study indicates that hypoxia and REDD1 suppress mTORC1 activity by releasing TSC2 from its inhibitory binding to protein 14-3-3 induced by growth factors. Endogenous REDD1 is required for hypoxia induced dissociation of endogenous TSC2/14-3-3 and subsequent inhibition of mTORC1.[61] Interestingly, AMPK inhibition prior to hypoxia prevents REDD1 expression and thereby sustains mTOR activity in neck squamous cell carcinoma,[63] suggesting that AMPK activation after hypoxia may be crucial in regulating REDD1 expression to control the mTOR activity. In addition, hypoxia induced expression of REDD1 may also be dependent on hypoxia inducible factor 1α (HIF-1α) activation.[64,65]

Amino acid and mTORC1 activation. Amino acid level is also a strong stimulant that regulates the mTORC1 activity. Amino acids, especially leucine, an essential amino acid, are required for mTORC1 activation. Amino acid starvation results in rapid inhibition of mTORC1 signaling.[66-72] Cellular uptake of L-glutamine and its subsequent rapid efflux followed by influx of essential amino acids has been proposed to be the rate-limiting step that activates mTOR.[73] Interestingly, in $TSC^{-/-}$ cells, amino acid deprivation still impairs the mTORC1 signaling, suggesting that amino acid regulate the activity of mTORC1 through a mechanism that is independent of TSC1/TSC2 complex.[74]

The two human proton-assisted amino-acid transporters (PATs), PAT1 and PAT4, have been identified to be required for amino acid induced the activation of mTORC1 in starved HEK-293 cells. PAT1 is highly concentrated in intracellular compartments in HEK-293 cells, including endosomes.[75] Recent study has shown that the presence of amino acids relocate the dispersed cytoplasmic mTOR to endosomal compartments around which Rheb accumulates in HEK-293 cells.[76] PATs could have a role in transmitting the amino-acid signal from the cortical cytoplasm to mTORC1.[75]

Recently, Rag proteins have been linked to amino acid sensing and the regulation of mTORC1 signaling.[76-78] Rag proteins are a family of four related guanosine phosphatases (GTPases). The expression of a Rag mutant that is constitutively bound to GTP within cells results in the resistance of the mTORC1 pathway to amino acid deprivation and conversely, expression of a GDP-bound Rag mutant prevents stimulation of mTORC1 by amino acids.[76]

In mammalian cells, the RagA or RagB forms heterodimers with either RagC or RagD and the resulting heterodimers strongly bind to Raptor. The binding of Rag GTPases to Raptor, is necessary and sufficient to mediate amino acid signaling to mTORC1, and mediates the amino acid induced re-localization of mTORC1 within the endomembrane system of the cell. mTORC1 is generally distributed throughout the cytoplasm but with amino acid stimulation it is rapidly relocalized to the perinuclear region that contains the mTORC1 activator Rheb.[76] Recent study indicates that amino acids induce translocation of mTORC1 to lysosomal membranes, where the Rag proteins reside. The complex Regulator encoded by the *MAPKSP1*, *ROBLD3* and *c11orf59* genes interacts with the Rag GTPases, recruits them to lysosomes leads to mTORC1 activation. Thus, Rag-Ragulator-mediated translocation of mTORC1 to lysosomal membranes is the key event in amino acid signaling to mTORC1.[78]

Activation of mTORC2. Compared to mTORC1, the signaling pathway to activate mTORC2 is far from elucidation. The TSC1/2 complex has been associated with regulation of mTORC2 activity, however, in contrast to inhibiting the activity of mTORC1, TSC1/2 complex seems to promote the activity of mTORC2.[79] Lack of functional TSC1/TSC2 complex in cells results in the loss of the mTORC2 kinase activity in vitro. The study indicates that TSC1/2 complex can physically associate with mTORC2 to enhance the activity of mTORC2 using a mechanism that is independent of its GAP activity toward Rheb.[79] Further study indicates that TSC1/2 complex can directly stimulate the in vitro kinase activity of mTORC2 may through the interaction between the N-terminal region of TSC2 and the C-terminal region of the mTORC2 essential component Rictor.[80]

To regulate the activity of mTORC2, there may exist interaction between mTORC1 and mTORC2. The essential mTORC2 component Rictor is phosphorylated on the residue of threonine 1135 by growth factors that is sensitive to rapamycin and is downstream of mTORC1. The activated p70S6K1, the downstream activating target of mTORC1, appears to be the candidate in the mTORC1 signaling pathway that can phosphorylate Rictor.[81] The Rictor phosphorylation does not affect mTORC2 integrity or in vitro kinase activity, however, phosphorylation of this site modulates the binding of Rictor and mTORC2 with protein 14-3-3, which is rapamycin sensitive.[82] The expression of a site mutant of Rictor (T1135A) in either wild-type or Rictor null cells causes an increase in the mTORC2-dependent phosphorylation of Akt on serine 473, suggesting that Rictor-T1135 phosphorylation by mTORC1-dependent mechanisms regulates the activation of mTORC2.[81,83]

The Function of mTOR Complex

In response to growth factor, mitogen, nutrient and stress, mTORC1 has been well established to regulate cell growth and cell proliferation. Induction of protein and lipid synthesis has been considered the driving factor for mTORC1 to promote cell growth.[13,84,85] The mTORC1 initiates cap-dependent protein translation, a rate-limiting step of protein synthesis, through phosphorylating its two major downstream targets p70S6K and 4EBP1.[86] Multiple phosphorylation sites have also been found on the serine and threonine residues of p70S6K, however, phosphorylation of threonine 389 residue by mTOR is critical for p70S6K activation and serves as a marker for mTOR activity.[87] Upon activation, mTORC1 is recruited to the eukaryotic initiation factor3 (elF3) translation initiation complex at the 5'-methylguanosine cap of mRNAs, where p70S6K is bound, and then directly phosphorylates p70S6K,[88] resulting in its dissociation with elF3 complex, activation and subsequent phosphorylation of its translational targets. In contrast, phosphorylation of 4EBP1 (threonine 37/46, serine 65 and threonine 70) results in its inactivation and the loss of its ability to bind to an initiation factor elF4E, enabling cap-dependent translation.[89-91] In addition, mTORC1 can also regulate growth factor induced activation of mitogen-activated protein kinase (p44/42) through protein phosphatase 2A (PP2A).[84] The critical roles of p44/42 in growth factor mediated transcription, DNA replication and protein translation have been well recognized.

The cytoskeleton organization regulation is the primary function of mTORC2.[92] mTORC2 has also been involved in the regulation of cells survival and cell cycle progression.[22,93-98] mTORC2 may signal to the actin cytoskeletin through protein kinase C (PKC) by phosphorylating and activating PKC[99] and also may through Akt signaling pathway involving Rho GTPase.[23,92,100] Expression of constitutive active forms of the Rho GTPases promotes organization of the actin skeleton and prevents the actin defect due to loss of mTORC2 function.

The Role of mTOR Complex in the Nervous System

Synaptic plasticity. In the CNS, mTOR has been involved in synaptic plasticity. Synaptic plasticity is the alteration of the strength of connections among neurons, which is considered as the mechanism for memory storage in the CNS. Synapse is the basic unit that is essential for the communication between neurons and can be potentiated by repeated activity or response. Synaptic transmission between axons and dendrites in neurons is a measure of communication at synapses. Two forms of lasting synaptic plasticity, long-term potentiation (LTP) and long-term depression (LTD) of excitatory synaptic transmission, are widely expressed at excitatory synapse in the mammalian brain. In the long lasting forms of synaptic plasticity, altered translational control and protein synthesis play a critical role in synaptic plasticity.[9,101]

As a principal modulator of translation, mTOR has been associated with the regulation of synaptic plasticity. The target proteins of mTOR, 4EBP1 and eukaryotic initiation factor-4E (eIF4E), have been detected in the cell bodies and dendrites in cultured hippocampal neurons and their distribution completely overlaps with a postsynaptic density protein-95 (PSD-95) at synaptic sites, suggesting that the postsynaptic localization of these proteins. Rapamycin application results in a reduction of late-phase LTP expression and also blocks the synaptic potentiation induced by brain-derived neurotrophic factor (BDNF).[102] Downstream of BDNF, mTOR mediated mRNA translation and synaptic glutamate receptor (GluR)1 expression that is required for memory consolidation.[103]

The study demonstrates that consolidation of inhibitory avoidance long-term memory (IALTM) in rats entails mTOR activation in the dorsal hippocampus after training increase in AMPA receptor GluR1 subunit expression, which is inhibited by mTOR inhibitor rapamycin. In addition, either pre- or post-training, administration of anti-BDNF antibodies into dorsal CA1 impairs IALTM retention and abolishes the learning-induced biphasic activation of mTOR and p70S6K and blocks GluR1 expression, suggesting that mTOR signaling has a role downstream of BDNF in controlling fear-memory consolidation.[103]

Activation of the PI 3-K/Akt-mTOR signaling pathway has been involved in fear memory retention. High-frequency stimulation induces LTP, resulting in the phosphorylation of Akt (at the serine 473 residues), mTOR, p70S6K and 4EBP1, which is inhibited by the infusion of PI 3-K inhibitors (wortmannin and LY294002) and an mTOR inhibitor (rapamycin) into the medial prefrontal cortex, a crucial neural locus for the control of cognition and emotion. Inhibition of PI 3-K and mTOR also interferes with the long-term retention of trace fear memory but not with short-term trace fear memory and object recognition memory.[104] Systemic inhibition of mTOR by rapamycin also weakens the traumatic fear memory reconsolidation and inhibits the contextual fear memory,[105,106] suggesting the potential application of mTOR inhibition for posttraumatic stress disease and other acquired anxiety. Physical stress evoked by tail shock in rats induces a profound and prolonged phosphorylation of PDK1, Akt, mTOR, p70S6K and eIF4B in hippocampal CA1 homogenate, which is prevented by the PI 3-K inhibitor.[107] Further study indicates that stress also upregulate the dendritic scaffolding protein PSD-95, which is involved in the formation of LTP and LTD, in an mTOR-dependent manner. These results suggest a key role of PI 3-K/mTOR signaling in mediating the stress induced modification of hippocampal synaptic plasticity may through invoking the protein expression of PSD-95.[107]

Neuroendocrine. The role of mTOR in the regulation of neuroendocrine through the hypothalamic axis has also been described. Hypothalamic mTOR signaling regulates food intake and acts as a cellular fuel sensor to energy status.[108] mTOR signaling is controlled by energy status in the arcuate nucleus of the hypothalamus. Central administration of leucine increases hypothalamic mTOR signaling and decreases food intake and body weight. The hormone leptin that has proanorectic effect increases hypothalamic mTOR activity, the inhibition of which by rapamycin reduces leptin's anorectic effect. Central mTOR also controls gonadotropic axis and the onset of puberty.[109] Central activation of mTOR can stimulate leuteinizing hormone secretion and the blockade of central mTOR signaling by rapamycin causes inhibition of the gonadotropic axis at puberty, revealing delayed vaginal opening, decreased LH and estradiol levels and ovarian and uterine atrophy. Inactivation of mTOR also blunts the positive effects of leptin on puberty onset in food-restricted females. The gonadotropic effects of mTOR may acquire through the regulation of Kiss1 expression in the arcuate nucleus of the hypothalamus.[109] The expression of Kiss1 has been suggested to regulate the hypothalamic reproductive axis and puberty.[109-111] Inhibition of mTOR evokes a significant decrease of Kiss1 expression at the hypothalamus, with dramatic suppression of Kiss1 mRNA levels at the arcuate nucleus.[109]

Neuroregeneration. Axon regeneration has been involved synthesis of raw material and axonal compartment by the neuronal soma and therefore translational control of protein synthesis plays an important role in the process of axon regeneration.[112-115] As a major translational regulator, mTOR may acquire the ability to regulate neuronal regeneration. The ability of sensory and retinal axon to regenerate in vivo correlates with the capability of forming a new growth cone after axotomy in vitro and axonal protein synthesis and degradation are necessary for growth cone regeneration.[116] Interestingly, inhibition of mTOR, p38 mitogen-activated protein kinase (MAPK) and caspase 3 represses growth cone formation, suggesting that mTOR, p38MAPK and caspase 3 associated protein synthesis and degradation initiates growth cone formation after axotomy.[116]

The PTEN/mTOR signaling has been recently implicated in neuronal regeneration. Phosphatase and tensin homolog (PTEN) appears to be a critical regulator of PI 3-K signaling. PTEN can dephosphorylate tyrosine-, serine- and threonine phosphorylated peptides and negatively regulates PI 3-K pathways by specifically dephosphorylating PIP_2 and PIP_3 at the D3 position.[117] As a result, a reduction in the membrane phospholipid pool that is necessary for the recruitment of Akt can ensue during PTEN activation.[117-119] The activation of mTOR is the downstream of PI 3-K/Akt activation in response to growth factors as mentioned in proceeding sections and therefore PTEN is also a negative regulator of mTOR. Deletion of PTEN in adult retinal ganglion cells (RGCs) and in corticospinal neurons promotes robust axon regeneration after optic nerve injury and spinal cord injury respectively.[120] In wild-type adult mice, the regeneration failure may be contributable to the suppression of mTOR activity and new protein synthesis in axotomized RGCs, since reactivating this pathway by conditional knockout of TSC1, which negatively regulate the mTOR pathway, leads to axon regeneration.[115] In cortical neurons, mTOR activity is downregulated during development and further diminishes after axotomy,[120] suggesting downregulation of mTOR contributes to the lost of the ability of axon to regenerate in the CNS after injury.

Yet, neurotrophins induced mTOR signaling pathway may interfere the axon regeneration through the modulation of astrocyte response to the CNS injury. The CNS damage activates astrocytes and the reactive astrocytes upregulate the expression of intermediate filament proteins that inhibit axonal growth. Over time, reactive astrocytes deposit extracellular matrix molecules and form a glial scar. The glial scar, in one aspect, plays an important role in the repair process,[121] but the glial scar also represents a physical barrier that interferes the regeneration of damaged axon.[122-126] Therefore, limiting astrocytic responses represents a potential therapeutic strategy to improve functional recovery after CNS injury. The epidermal growth factor (EGF) receptor is upregulated in astrocytes after injury and EGF promotes the transformation of astrocytes into reactive forms may through an mTOR associated pathway.[121] The inhibition of EGF receptor enhances axon regeneration in the injured optic nerve and promotes recovery after spinal cord injury. In cultures of

adult spinal cord astrocytes, EGF activates the mTOR pathway through Akt-mediated phosphorylation of the GAP. Further study indicates that Rheb is required for EGF-dependent mTOR activation in spinal cord astrocytes. Moreover, elevated levels of activated EGF receptor and mTOR signaling in reactive astrocytes in vivo in an ischemic model of spinal cord injury was observed and EGF-dependent chemoattraction of astrocytes was inhibited by rapamycin, suggesting that inhibition of mTOR signaling could limit astrocytic responses in the damaged nervous system and may be beneficial to axon regeneration.[121] As a result, the regulation of mTOR activating level is very important for neuroregeneration in the CNS.

As a result, comparing to the CNS, the axons in the peripheral nerve system (PNS) seems to have a more robust ability to regenerate after injury since they have fewer barrier that influences the axon regeneration, however, the recovery after injury of the peripheral neurons is still limited. Activation of mTOR has been reported in dorsal root ganglial neurons (DRGs) following injury and inhibition of mTOR by rapamycin blocks the axon regeneration, suggesting that mTOR activation enhances axonal growth capacity.[127] Moreover, genetic upregulation of mTOR activity by deletion of TSC2 in DRGs is sufficient to enhance axonal growth capacity in vitro and in vivo. The regeneration promoting effect of mTOR activity may associate with synthesis of growth associated protein-43 (GAP-43), a crucial component of axonal outgrowth.[127]

Neurodegenerative diseases. Alzheimer disease (AD) is a progressive neurodegenerative disorder with cognitive dysfunction and loss of memory. The National Institute on Aging estimates that almost five million people have AD in the United States. Furthermore, more than twenty-four million people suffer from AD, pre-senile dementia, and other disorders of cognitive loss worldwide. AD is characterized by two pathologic hallmarks that consist of extracellular plaques of amyloid-β (Aβ) peptide aggregates and intracellular neurofibrillary tangles composed of hyperphosphorylated microtubular protein tau.[40,128,129] The β-amyloid deposition that constitutes the plaques is composed of a 39–42 amino acid peptide, which is the proteolytic product of the amyloid precursor protein (APP).[130-132] In AD,[133] Aβ is toxic to cells,[134-138] can lead to oxidative stress,[40,139,140] and result in cell death.[141-144]

Oxidative stress occurs through the generation of reactive oxygen species (ROS) that consist of oxygen free radicals and other chemical entities.[145-147] Oxygen free radicals can be generated in elevated quantities during the reduction of oxygen and lead to cell injury. ROS can involve superoxide free radicals, hydrogen peroxide, singlet oxygen, nitric oxide (NO) and peroxynitrite.[40,132,139,148] Oxidative stress may be tempered by different vitamins, such as vitamin D_3,[149] and the amide form of niacin or vitamin B_3, nicotinamide.[150-156] Oxidative stress leads to the destruction of multiple cell types through apoptotic pathways[157-159] and also through autophagy.[160] Apoptotic induced oxidative stress in conjunction with processes of mitochondrial dysfunction[161-164] can contribute to a variety of disease states such as diabetes,[165-168] ischemia, cognitive loss, AD,[40,139,140] Parkinson disease,[139,169] sepsis,[170,171] Huntington disease,[139,172] acute[173-175] traumatic and chronic injuries,[40,139,176-178] and immune dysfunction.[179-181] Oxidative stress can lead to apoptosis in neurons, endothelial cells (ECs), cardiomyocytes[148,182-186] and smooth muscle cells that involve separate as well as overlapping pathways.[176,187-191]

Dysfunction of mTORC1 has been associated with both of the pathogenic mechanisms of AD (**Table 2**). The activation of p70S6K, downstream of mTORC1, has been identified as a contributor to hyperphosphorylated tau accumulation in neurons with neurofibrillary tangles.[192] Significant increase in the level of phosphorylated mTOR (serine 2448 and serine 2481) and tau (serine 214) has been detected in AD neurons.[193,194] Alteration of mTOR level in lymphocyte of AD patients correlates with memory and cognitive decline.[195] The level of activated p70S6K is significantly reduced in lymphocytes of AD patients, and is statistically correlated with Mini Mental Status Examination scores.[196] These findings demonstrate that alteration of mTOR/p70S6K signaling could contribute to the pathogenesis of AD.

Yet, the major pathogenic agent of AD, Aβ seems to downregulate the mTORC1 signaling pathway and inhibition of mTOR by rapamycin enhances Aβ induced cell death, suggesting that mTOR provides cell protection against Aβ toxicity.[196] Aβ also produces a rapid and persistent downregulation of mTOR/p70S6K phosphorylation in murine neuroblastoma cells associated with caspase 3 activation in the cortex of double APP/PS1 transgenic mice compared with control mice.[196] The mTOR signaling is inhibited in hippocampal slice of wildtype mice upon exposure to Aβ and the downregulation of mTOR signaling has also been observed in both cultured neurons and hippocampal slice from AD transgenic mice.[197] The dysregulation of mTOR induced by Aβ correlates with the impairment of synaptic plasticity, which is rescued by pharmacological or genetic upregulation of mTOR signaling.[197] However, recently, inhibition of mTOR by rapamycin was shown to reduce the level of Aβ and improve the cognitive function in a mouse model of AD.[198] To review the above information, controversial results concerning the relation between mTOR signaling and the progression of AD exist and thereby further study is necessary to confirm the definite function of mTOR signaling in AD.

In addition, the mTOR signaling may also associate with neuronal atrophy in AD involving insufficiency of retinoblastoma tumor suppressor (RB1) inducible Coiled-Coil 1 (RB1CC1). RB1CC1 expresses in many tissues, including skeletal muscles, heart, kidneys and neurons, and plays an important role in cell size control.[199,200] The abundance of RB1CC1 has been found to maintain the level of RB1 and mTOR contributing to the non-proliferating enlarged cell phenotype in neuromuscular tissues.[199] RB1CC1 introduction into Neuro-2a neuroblastoma cells enhances neurite growth. In contrast, RNAi-mediated knockdown of *RB1CC1* or rapamycin treatment causes neurite atrophy and apoptosis in the differentiated Neuro-2a cells.[201] In the brains of AD patients, the balance between TSC1 and RB1CC1 seems to be required for cells to maintain mTOR signaling activation, since lack of RB1CC1 expression, which is less than TSC1, causes mTOR signaling repression and neuronal atrophy.[201] These findings suggest that RB1CC1 insufficiency may result in mTOR signaling repression through unbalanced

Table 2. Implications of mammalian target of rapamycin (mTOR) signaling in neurological diseases

Neurological diseases	Potential implication of mTOR signaling	References
Alzheimer disease (AD)	p-mTOR and p-4EBP1increased in AD neurons, correlating with increased hyperphosphorylated tau p-p70S6K increased in lymphocytes correlating with cognitive impairment	Griffin, et al. 2005; Li, et al. 2005; Lafay-Chebassier, et al. 2005
Parkinson disease	mTORC1 activation potentiates dyskinesia mTOR activation prevents oxidative stress induced dopaminergic neuronal death	Santini, et al. 2009; Choi, et al. 2010
Huntington disease	Inhibition of mTOR induces autophagy, increases the clearance of mutant huntingtin aggregate, and prevents huntingtin fragment toxicity	Floto, et al. 2007; Ravikumar, et al. 2003
Tuberous sclerosis (TS)	Inhibition of mTOR increases median survival in a mouse model of TS Inhibition of mTOR improves facial angiofibroma lesion in TS patients Inhibition of PI 3-K-mTOR suppresses kidney tumor in a mouse TS model	Meikle, et al. 2008; Hofbauer, et al. 2008; Pollizzi, et al. 2009
Neurofibromatosis type I (NF1)	*Nf1* mutant increases the activity of mTOR, inhibition of which suppresses NF1 associated tumorigenesis	Dasgupta, et al. 2005; Hegedus, et al. 2008; Johannessen, et al. 2008
Fragile X syndrome	FMR1 knockout in mice increases mTOR activity and p70S6K activation; p70S6K can phosphorylate FMRP	Sharma, et al. 2010; Narayanan, et al. 2008
Traumatic brain injury (TBI)	mTOR, p70S6K and 4EBP1 phosphorylation level increases in brains after TBI in rats Rapamycin improves functional recovery after closed head injury in mice Activation of Akt/mTOR/p70S6K improves locomotor function recovery after spinal cord injury	Chen, et al. 2007; Erlich, et al. 2007; Hu, et al. 2010
Epilepsy	Inhibition of mTOR reduces seizure in TS mouse model, prevents acquired seizure, and reduces chronic spontaneous seizure activity	Meikle, et al. 2008; Zeng, et al. 2008; Zeng, et al. 2009; Huang, et al. 2010
Ischemic stroke	Rapamycin potentiates OGD induced injury in microglia and neurons Deletion of p70S6K enhance OGD induced apoptosis in astrocytes	Chong, et al. 2007; Figure 2 Pastor, et al. 2009

4EBP1, eukaryotic initiation factor 4E-binding protein 1; FMRP, fragile X syndrome mental retardation protein; OGD, oxygen glucose deprivation; p70S6K, p70 ribosomal S6 kinase; PI 3-K, phosphoinositide 3-kinase; p-4EBP, phosphorylated 4EBP; p-p70S6K, phosphorylated p70S6K.

TSC1 abundance leading to neuronal atrophy, which may be linked to the pathogenesis of AD.

Parkinson disease (PD) is a movement disorder characterized by resting tremor, rigidity and bradykinesia. The pathophysiological basis of the symptoms rests upon the degeneration of dopaminergic neurons in the substantia nigra (SN). In some scenarios, it has been hypothesized that dopamine may even be a culprit in precipitating disease progression.[139,163,202]

The activity of mTOR has been associated with PD through a stress response protein RTP801. The stress response gene *RTP801* can be induced by DNA damage and oxidative stress[203,204] which has been linked to the pathogenesis of PD. RTP801 is highly induced in several cellular models of PD such as treatment with 6-hydroxydopamine (6-OHDA), MPP^+ and rotenone.[205] Moreover, RTP801 is also induced in an animal model of PD and is elevated in dopaminergic neurons of PD patients. Short hairpin RNA (shRNA) knocking out RTP801 is protective against 6-OHDA application in cellular model of PD. These findings suggest that RTP801 as a potential contributor to neuronal degeneration in PD. Interestingly, RTP801 is a negative regulator of mTOR, working downstream of Akt and upstream of TSC2 to inhibit mTOR activity.[203] RTP801 and 6-OHDA trigger neuronal death by suppressing activation of mTOR. The logic sequence is that PD-associated stresses induce RTP801, suppress mTOR signaling and induce neuronal degeneration and death.[206] Yet, the activation of mTOR may potentiate dyskinesia during treatment. In a mouse model of PD, administration of l-DOPA results in the activation of the mTORC1 in a dopamine receptor dependent manner, which is occurred selectively in the GABAergic neurons that project directly from the striatum to the output structures of the basal ganglia. The l-DOPA-mediated activation of mTORC1 persists in mice that have developed dyskinesia and the mTORC1 inhibitor rapamycin prevents the development of dyskinesia without affecting the therapeutic efficacy of l-DOPA.[207]

Oxidative stress has been closely associated with dopaminergic neurodegeneration[208,209] and a neuroprotective protein Oxi-alpha has been shown to be downregulated in dopamine neurons during oxidative stress.[210] Oxi-alpha protects dopaminergic neurons against autophagic cell death induced by oxidative stress, in contrast, Oxi-alpha knockdown increases the vulnerability of neurons to oxidative insult. Moreover, the downregulation of Oxi-alpha by knockdown suppresses the activation of mTOR signaling exhibiting a decrease in the level of the mTOR kinase activity and phosphorylation of p70S6K and 4EBP1. These results indicate that dysfunction of mTORC1 signaling is involved in the pathogenesis of PD, suggesting that targeting mTORC1 signaling pathway may be a promising strategy for the treatment of PD (**Table 2**).

Huntington disease (HD) is an autosomal dominant neurodegenerative disease characterized by impairment of involuntary movement and cognitive impairment. Selective loss of neurons in the basal ganglia and cerebral cortex is one of the anatomical hallmarks of this disease. Genetically, HD is caused by CAG trinucleotide repeat expansion mutations that are translated into abnormally long polyglutamine tracts.[211,212] The HD gene encodes a protein called huntingtin and the disease is associated

with expansions of more than 37 consecutive glutamines that are found close to its N-terminus.

The mTOR signaling may impact on the polyglutamine toxicity by autophagy (**Table 2**). Autophagy is the process by which cells recycle cytoplasmic components and dispose of defective organelles. The process includes a bulk degradation of cytoplasmic material during nutrient deficiency or other conditions and subsequent sequestration of the cytoplasm including protein and organelles into autophagsomes that fuse with or are imported into lysosomes for degradation and reused by essential cellular process.[213] Autophagy can occurs at basal levels in most tissues and can also be induced by the variety of environmental conditions such as nutrient depletion and injury. In addition to turnover of cellular components, autophagy has been implicated in development, differentiation and tissue remodeling in various organisms. Autophagy has also been linked to a growing number of diseases, such as cancer, infectious diseases and neurodegenerative diseases.[214-219] Autophagy can serve a double-edged sword that is protective or detrimental to cells.

In the CNS, autophagy may function as a major mechanism underlying the degradation and clearance of aggregate-prone, intracytosolic proteins causing neurodegenerative disorders, such as HD. As a result, enhancing autophagy is a potential therapeutic strategy for clearing these disease-causing proteins.[220] The key role of mTOR signaling in the regulation of autophagy had been established long time ago[221] and confirmed by extensive investigations.[222] In HD, mTOR is sequestered in polyglutamine aggregates in cell models, transgenic mice and human brains, impairing its kinase activity and inducing autophagy. The specific inhibitor of mTOR rapamycin can enhance the autophagic clearance of proteins with long polyglutamines and a polyalanine-expanded protein and reduces their toxicity.[223] Rapamycin also attenuates huntingtin accumulation and cell death in cell models of HD and protects against neurodegeneration in a fly model of HD.[223,224] In addition to rapamycin, some small molecular enhancers of rapamycin induce autophagy with both mTOR dependent and independent mechanisms in mammalian cells and enhance the clearance of a mutant huntingtin fragment in a HD cellular model and also protects against a mutant huntingtin fragment toxicity in Drosophila.[225] The rapamycin analog CCI-779 improves behavioral performance and decreases aggregate formation in a mouse model of HD.[224] In this regard, inhibitors of mTOR may be regarded as potential therapeutic agents in aggregate diseases including HD.

Glucose/glucose-6-phosphate has been identified as a novel stimulus for autophagy via mTOR and Akt and this leads to enhanced clearance of the toxic huntingtin exon 1 fragment.[226,227] Raised intracellular glucose level in HD cell models increases clearance of mutant huntingtin correlating with increased autophagy and reduced phosphorylation of mTOR, p70S6K1 and Akt. Thus, raised intracellular glucose and the consequence of glucose 6-phosphate level reduce mutant huntingtin toxicity through autophagy by using a mechanism that is associated with modulation of mTOR signaling.[226]

Genetic diseases. Tuberous sclerosis (TS) is a multi-organ disorder including the brain caused by heterozygous mutations in the *TSC1* or *TSC2* gene and is often associated with neuropsychiatric symptoms, including intellectual disability, specific neuropsychological deficits, autism, other behavioral disorders and epilepsy.[228] In the brain, tuberous sclerosis complex (TSC) is associated with cortical tubers consisting of giant cells, dysmorphic neurons and astrocytes. The *TSC1* and *TSC2* genes encoded proteins form TSC1/TSC2 complex which functions to regulate protein synthesis and cell growth by inhibiting mTORC1 mediated signaling pathway.[229] In addition, skin lesion is one of the characteristic features in TS. In cultured fibroblasts from healthy skin of a TS patient, the upregulation of p70S6 ribosomal protein was found, suggesting enhancing activity of mTORC1 in TS.[230]

Given the role of mTORC1 signaling downstream of TSC1/TSC2 complex, it is not surprised to find that application of rapamycin and RAD001 [40-O-(2-hydroxyethyl)-rapamycin] improves the median survival from 33 d to more than 100 d and also improves the behavior, phenotype and weight gain with reduced levels of phospho-p70S6K, a downstream target of mTORC1, in a mouse neuronal model of TS[229] (**Table 2**). Rapamycin treatment can significantly improves facial angiofibroma lesion in TS patients, which affects 70–80% of patients with TS, typically on the face.[231] Both mTORC1 blockade alone by RAD001 and combined PI 3-K-mTOR blockade by pan class I PI 3-K/mTOR catalytic small molecule inhibitor NVP-BEZ235 leads to suppression of kidney tumor development in a mouse TS model.[232]

The elevation of both endoplasmic reticulum and oxidative stress has been observed in *TSC2* deficient rat hippocampal neurons and brain lysates from a *TSC1* deficient mouse. Neurons lacking functional *TSC1/TSC2* have increased vulnerability to endoplasmic reticulum stress induced cell death, suggesting that oxidative stress may contribute to the neuronal dysfunction in TS.[233] More importantly, the mTOR inhibitor rapamycin prevents oxidative stress in TSC1/TSC2 dysfunctional neurons. As a result of above studies, targeting mTORC1 signaling pathway may represent a therapeutic strategy against TS.

Neurofibromatosis type 1 (NF1) is a common autosomal dominant tumor predisposition syndrome characterized by formation of neurofibromas and astrocytoma (glioma). The *Nf1* gene encodes neurofibromin, an inhibitor of RAS signaling and a mutation of *NF1* gene disrupt neurofibromin synthesis resulting in the activation of RAS followed by upregulation of PI 3-K and mTOR activity. The *Nf1*-deficient astrocytes exhibit high levels of mTOR activity revealed by high level of p70S6K phosphorylation, which is inhibited by blocking K-RAS or PI 3-K activation in both *Nf1* mutant mouse optic nerve gliomas and in human NF1-associated pilocytic astrocytoma tumors.[234] Moreover, inhibition of mTOR signaling in $Nf1^{-/-}$ astrocytes abrogates their growth advantage in culture, restoring normal proliferative rate.[234] In genetically engineered mouse models of low-grade glioma, pharmacologic inhibition of mTOR reduces tumor cell proliferation and tumor volume in a dose dependent manner.[235] mTORC1 activity has been found to be essential for NF1 associated tumorigenesis.[236] The mTOR inhibitor rapamycin potently suppresses the growth of aggressive NF1-associated malignancies in a genetically engineered murine model of NF1 through suppressing the mTOR target cyclin D1.[236] These results suggest that

mTORC1 associated signaling pathway may represent a logical therapeutic target for brain tumors in NF1 (**Table 2**).

Fragile X syndrome is the most common form of inherited mental retardation caused by transcriptional silencing of *FMR1* gene encoding the fragile X mental retardation protein (FMRP). FMRP is an RNA binding protein preventing the translation in neurons through binding to mRNA.[237] Posttranslational modification of FMRP has also been associated with modulation of protein synthesis. Non-phosphorylated FMRP associates with actively translating polyribosomes, whereas phosphorylated FMRP (primarily at serine 499) is found in potentially stalled ribosomes.[238] The cognitive deficit and group I metabotrophic glutamate receptor (mGluR) dependent LTS exaggeration has been found in the most commonly used *RMR1* knockout mouse model of fragile X syndrome.[239] FMRP is dephosphorylated immediately following stimulation of group I mGluR by protein phosphatase 2A (PP2A), however, longer stimulation of group I mGluR rephosphorylate FMRP in a PP2A and mTOR dependent manner. Further study has identified the downstream target of mTORC1, p70S6K, as a major FMRP kinase in the mouse hippocampus, which can phosphorylate FMRP and mediate the mGluR induced FMRP phosphorylation.[240] More importantly, the dysfunction of mTORC1 signaling has been found in fragile X syndrome. The *FMR1* knockout mouse exhibits increased mTOR phosphorylation and signaling, including an increased association of Raptor with mTOR, a elevation in mTOR kinase activity, and an increase in the level of phosphorylation of mTOR downstream targets p70S6K and 4EBP and formation of eukaryotic initiation factor complex 4F (eIF4F) (**Table 2**).

Traumatic brain injury. In response to traumatic brain injury (TBI), neurons initiate neuroplastic processes through the activation of intracellular signaling pathways; activation of mTOR signaling may represent one of these mechanisms. In a fluid-percussion brain injury model, rats received moderate injury on the right side of parietal cortex, the mTOR, p70S6K and 4EBP1 phosphorylation levels were significantly increased in the ipsilateral parietal cortex and hippocampus from 30 min to 24 h after TBI, whereas total protein levels were unchanged. In accordance with these results, eIF4E, a key rate-limiting mRNA translation factor, was also phosphorylated by mitogen-activated protein kinase-interacting kinase 1 (Mnk1) 15 min after TBI. These results suggest that changes in mRNA translation associated with activation of mTOR signaling pathway may be one mechanism that neurons use to respond to TBI and may contribute to the neuroplasticity during trauma in the brain.[241] But, the exact effects of mTOR signaling activation remain elusive. Yet, in a closed head injury model in mice, rapamycin injection 4 h following the onset of injury significantly improves functional recovery as manifested by changes in the Neurological Severity Score accompanied by decreased level of p70S6K phosphorylation, microglia/macrophages activation and increased number of surviving neurons at the site of injury.[242] Interestingly, with ATP administration in a spinal cord injury model, a significant increase in activated Akt/mTOR/p70S6K signaling pathway was accompanied by improved locomotor function after injury, which is inhibited by rapamycin treatment, indicating that the induction of Akt/mTOR/p70S6K activation by ATP produces a beneficial effect on motor function recovery after spinal cord injury[243] (**Table 2**).

Epilepsy. Epilepsy is a common chronic neurological disorder. Epilepsy is characterized by recurrent seizures that are unpredictable and sometimes progressively severe. Epilepsy is also associated with significant mortality and morbidity. The mTOR signaling pathway has been implicated in epilepsy in TS. One of common neurological manifestations of TS is epilepsy that occurs in over 80% of TS patients.[244] Mutations of TSC1 and TSC2 that act upstream of the mTOR leads to a high incidence of epilepsy.[245] Rapamycin treatment that inhibits the mTOR pathway attenuates structural abnormalities and reduces seizures in TS mouse models,[229,246] suggesting that the aberrant mTOR activation interferes with normal brain development and leads to epilepsy. The mTOR signaling activation has also been linked to acquired epilepsy and pharmacological inhibition of the mTOR pathway, either before or immediately following neurological insults, can prevent pathological changes in animal brains and the development of spontaneous recurrent seizure in an acquired epilepsy model.[247] Furthermore, chronic hippocampal infusion of the mTOR inhibitor rapamycin reduces mossy fiber sprouting in a rat pilocarpine model of temporal lobe epilepsy.[248] The mTOR is hyperactivated in rat brains with chronic spontaneous seizures and inhibition of the mTOR pathway by rapamycin markedly reduces chronic spontaneous seizure activity, along with inhibition of mossy fiber sprouting.[249] Therefore, mTOR activated signaling pathway could represent a potential therapeutic target for epilepsy (**Table 2**).

Ischemic stroke. Ischemic stroke is a leading cause of serious, long-term disability in the developed countries, but the effective approach for management in patients is limited. To restore the blood flow of the brain by using t-PA is the only approved treatment for ischemic stroke in the United States, yet it may thereby induce reperfusion-induced injury to neurons. As a result, to find novel approaches to increase the resistance of neurons to reperfusion-induced injury is still tough task for patients with ischemic stroke. With further work and insight into novel therapeutic mechanisms against ischemic brain injury may bring more practical approaches for the management of ischemic stroke.

Apoptosis has been closely associated with neuronal loss in ischemic brain injury and consists of both the early exposure of membrane phosphatidylserine (PS) residues and the late destruction of genomic DNA.[128,250] Externalization of membrane PS residues is an early event during cell apoptosis,[251,252] can become a signal for the phagocytosis of cells that is controlled by caspase 1 and caspase 3,[38,159,253] and control cell proliferation.[37,179-181,189,254] The loss of membrane phospholipid asymmetry leads to the exposure of membrane PS residues on the cell surface and assists microglia to target cells for phagocytosis.[37,156,189,255,256] This process occurs with the expression of the phosphatidylserine receptor (PSR) on microglia during oxidative stress.[202,257] It has been shown that blockade of PSR function in microglia prevents the activation of microglia.[37,258] Externalization of membrane PS residues occurs in neurons, vascular cells and inflammatory microglia during reduced oxygen exposure,[159,259,260] β-amyloid (Aβ) exposure,[135,179] nitric oxide exposure,[261-265] and during the administration of

agents that induce the production of reactive oxygen species, such as 6-hydroxydopamine.[266] Membrane PS externalization on platelets also has been associated with clot formation in the vascular system.[267]

The cleavage of genomic DNA into fragments[259,268,269] usually occurs after membrane PS exposure[187] and is considered to be a later event during apoptotic injury.[189,269-271] Several enzymes responsible for DNA degradation include the acidic, cation independent endonuclease (DNase II), cyclophilins and the 97 kDa magnesium-dependent endonuclease.[139,272] Three separate endonuclease activities also have been found in neurons that include a constitutive acidic cation-independent endonuclease, a constitutive calcium/magnesium-dependent endonuclease and an inducible magnesium dependent endonuclease.[273,274]

Although ischemic neurons often die from necrosis, a large amount of neurons may succumb to apoptosis and subsequently result in the loss of neurons if there is no salvaging measure. The development of neuronal apoptosis has been demonstrated following either focal or global cerebral ischemia.[275-277] Inhibition of caspases reduces neuronal injury in both transient focal and global cerebral ischemia. In in vitro experiments, anoxia and oxygen-glucose deprivation (OGD) that mimic the in vivo ischemic injury also result in neuronal apoptosis in primary cultured neurons.[258,275,278] As a result, apoptotic cell death has been considered as a major cause of neuronal loss during ischemic injury. Consequently, research into the signaling pathways that mediate neuronal apoptosis as well as checkpoint of apoptotic signaling pathways may find new neuroprotective approach for ischemic stroke.

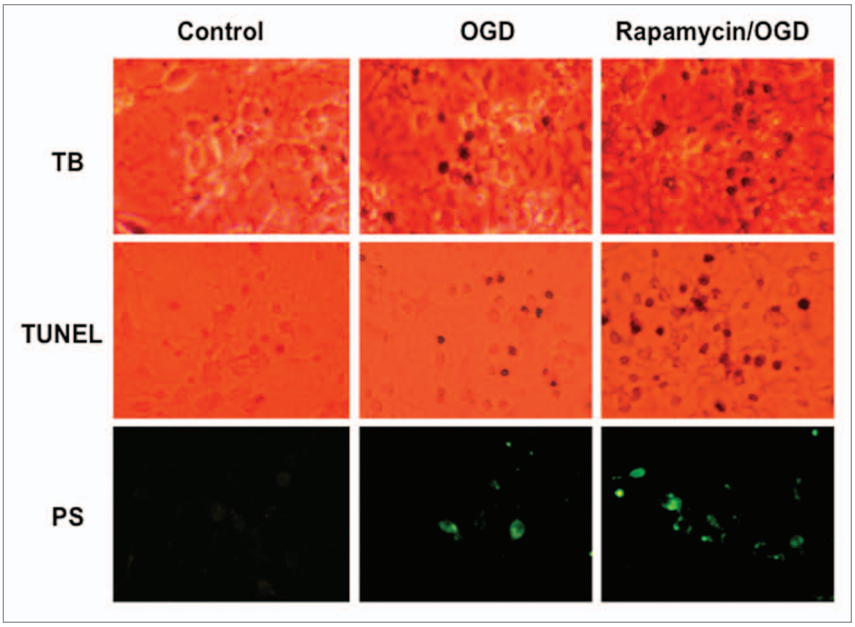

Figure 2. Inhibition of mTOR increases oxygen-glucose deprivation (OGD) induced neuronal injury. The mTOR specific inhibitor rapamycin (20 nM) was given to the cultures of hippocampal neurons of rats 1 hour prior to a 3 hour period of OGD, cell survival, apoptotic DNA fragmentation and membrane phosphatidylserine (PS) exposure were determined by Trypan blue exclusion, TUNEL and Annexin V-conjugated to phycoerythrin (PE) labeling method respectively 24 hours following OGD. OGD in neuronal cultures was performed by replacing media with glucose-free HBSS containing 116 mM NaCl, 5.4 mM KCl, 0.8 mM $MgSO_4$, 1 mM NaH_2PO_4, 0.9 mM $CaCl_2$ and 10 mg/L phenol red (pH 7.4) and cultures were maintained in an anoxic environment (95% N_2 and 5% CO_2) at 37°C for 3 hours. Representative pictures were illustrated. Following OGD exposure, neurons were observed to undergo cell injury and apoptosis manifested by increased permeability to Trypan blue dye (TB), chromatin condensation and nuclear fragmentation (TUNEL) and Annexin V labeling (PS). Administration of rapamycin (20 nM) 1 hour prior to OGD potentiated neuronal injury with further increased Trypan blue staining, DNA fragmentation and PS exposure.

Activation of mTOR prevents apoptosis and promotes cell survival in many cell systems, showing that specific inhibition of mTOR induces apoptosis in a variety of cancer cells,[279-293] endothelial progenitor cells,[294] and endothelial cells.[295] Since inhibition of mTOR increases the vulnerability of tumor cells to apoptosis,[72,296-300] inhibitors of mTOR have been extensively tested as a chemotherapeutic agents for cancers.[301-305] In neurons, oxidative stress (H_2O_2) induces apoptosis in PC12 cells and primary murine neurons by inhibiting mTOR mediated phosphorylation of p70S6K and 4EBP1.[306] Serum deprivation induces apoptosis in differentiated R28 rat retinal neuronal cells and induction of mTOR/p70S6K activation is necessary for insulin to protect retinal neurons against apoptotic cell death induced by serum deprivation since the cytoprotective effects of insulin can be prevented by mTOR inhibitor rapamycin or by a dominant-negative mutant of p70S6K.[307] However, increased mTOR signaling activation level seems to sensitize neurons to cadmium induced apoptosis and rapamycin and mTOR siRNA markedly downregulates the activation of mTOR targets and prevents cadmium induced neuronal apoptosis.[308] In addition, we used injury model of OGD in microglia and applied rapamycin to inhibit mTOR signaling prior to OGD. The results indicate that OGD induces a significant injury in microglia revealed by Trypan blue staining, DNA fragmentation and PS externalization. Pharmacological inhibition of mTOR by rapamycin further increases OGD-induced cell injury in microglia,[188] suggesting that mTOR activation may protect cells against ischemic injury in the CNS.

The anti-apoptotic effect of mTOR has been associated with the modulation of 4EBP1 and p70S6K. Inhibition of mTOR signaling increases binding of 4EBP1 to eukaryotic initiation factor 4E (eIF4E) leading to translation of mRNA for pro-apoptotic proteins.[309-311] Abrogation of mTOR by siRNA interference inhibits phosphorylation of its down stream targets p70S6K and 4EBP1 and induces apoptosis.[309] OGD-induced apoptosis in astrocytes is enhanced by the combined deletion of p70S6K1 and p70S6K2 genes, as well as by treatment with rapamycin. Further study indicate that astrocytes lacking p70S6K1 and p70S6K2 succumb to apoptosis may due to a defect both in BAD phosphorylation and in the expression of the Bcl-2 and Bcl-x_L,[312] suggesting that activation of mTOR downstream target p70S6K

prevents apoptosis may through promoting anti-apoptotic proteins Bcl-2/Bcl-x_L expression and inactivating pro-apoptotic protein BAD.

Based on the evidence of the link between mTOR and cell survival, we have investigated the role of mTOR during ischemic brain injury. Our results demonstrate that loss of mTOR activity by its inhibitor rapamycin decreases neuronal survival and increases apoptotic injury in neurons during OGD, an in vitro ischemic model in primary neurons (**Fig. 2**). In an animal model of focal cerebral ischemia in rats, rapamycin can not only inhibit the activation of mTOR, but also increase the brain infarct size as well as reduce the neurological deficit scores in rats (unpublished data), suggesting that mTOR activation may protect ischemic brain injury and improve functional recovery. Accordingly, some protective agents have been found to protect against ischemic brain injury through activation of mTOR signaling pathway.[313,314]

Future Directions

Growth factors, amino acids, cellular energy and oxygen supply critically regulate the activation of mTOR signaling cascade. To oversee the cap-dependent protein translation upon activation, mTOR phosphorylates its two major downstream targets, p70S6K and 4EBP1 to promote cell growth, cell proliferation and cell survival. The implication of mTOR signaling pathway in both physiological and pathological process has been extensively investigated with enthusiasm. In addition to its critical role in tumorigenesis, the pathophysiological role of mTOR in the CNS has come to light in recent years. Given the findings that mTOR signaling pathway is involved in the pathogenesis of a variety of neurological diseases, even though the precise underlying mechanisms of mTOR signaling pathway in these diseases are far from clear, targeting mTOR signaling may be a promising strategy against the CNS diseases. Specifically, modulation of cell signaling towards mTOR may initiate neuroprotection and hopefully find a novel therapies for neurodegenerative disorders.

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