

Frontier of Epilepsy Research - mTOR signaling pathway

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Abbreviations: 4E-BP, eukaryotic initiation factor 4 (eIF4) binding proteins; ACEA, arachidonyl-2-chloroethylamide; AD, Alzheimer's disease; AED, anti-epileptic drug; AICAR, 5-amino-4-imidazole-carboxamide ribose; AKT, acutely transforming retrovirus AKT8 in rodent T cell lymphoma; AMPK, AMP-activated protein kinase; AR, androgen receptor; ASD, autism spectrum disorder; ASK, apoptosis signal-regulating kinase; BID, BH3-interacting domain death agonist; BIM, Bcl-2-interacting mediator of cell death; BRG1, brahma-related gene 1; CaMKK β , calcium/calmodulin-dependent protein kinase β ; Cdc42, cell division cycle 42; Cdk, cyclin-dependent kinase; CLIP-170, CAP-GLY domain containing linker protein 1; CR, cannabinoid receptor; DAG, diacylglycerol; DAPK, death-associated protein kinase; DDIT4, DNA-damage-inducible transcript 4; DEPTOR, DEP-domain containing mTOR-interacting protein; DISC1, disrupted-in-schizophrenia 1; EGF, epidermal growth factor; eIF4, eukaryotic initiation factor 4; ER, estrogen receptor; FADD, Fas-associated protein with death domain; FGF, fibroblast growth factor; FKBP12, FK506 binding protein 12; FMRP, fragile X mental retardation protein; FIP200, focal adhesion kinase interacting protein of 200 kD; FOXO, forkhead box O; GAP, GTPase-activating protein; GEF, guanine nucleotide exchange factor; GSK, glycogen synthase kinase; HCMV, human cytomegalovirus; HSP70, heat shock protein 70; HSV, Herpes simplex virus; hVPS34, human vacuolar protein sorting 34; IGF, insulin-like growth factor; IKK β , Inhibitor of NF- κ B kinase β ; IP₃, inositol triphosphate; IRS-1, insulin receptor substrate-1; LTD, long-term depression; LTP, long-term potentiation; mATG13, mammalian autophagy related protein 13; mGluR, metabotropic glutamate receptor; mLST8, mammalian lethal with Sec13 protein 8; Mnk1, MAPK-interacting kinase 1; mSIN-1, mammalian stress-activated protein kinase interacting protein; mTOR, mammalian target of rapamycin, NDRG1, N-myc downstream regulated gene 1; PA, phosphatidic acid; PAP, phosphatidate phosphatase; PDCD4, programmed cell death 4; PDK1, 3-phosphoinositide-dependent protein kinase-1; PGC1 α , PPAR γ coactivator-1 α ; PHLPP1/2, PH domain leucine-rich repeat protein phosphatase; PI3K, phosphoinositide 3-kinase; PIM-1, provirus integration site for Moloney murine leukemia virus; PIP₂, phosphatidylinositol 4, 5 bisphosphate; PIP₃, phosphatidylinositol 3, 4, 5 trisphosphate; PMSE, polyhydramnios, megalencephaly and

symptomatic epilepsy; PP2A, protein phosphatase 2A; PRAS40, proline-rich AKT substrate of 40 kDa; P-REX1, PIP3-dependent Rac exchanger 1; Protor-1, protein observed with RICTOR-1; PTEN, phosphatase and tensin homolog; Rag, Ras-related GTPase; RAPTOR, regulatory-associated protein of mTOR; REDD1, regulated in development and DNA damage responses 1; Rheb, Ras homolog enriched in brain; RICTOR, rapamycin-insensitive companion of mTOR; RSK, RPS6K1 ribosomal protein S6 kinase; S6K, p70 ribosomal protein S6 kinase; SCOP, suprachiasmatic nucleus circadian oscillatory protein; SE, status epilepticus; SF2/ASF, splicing factor, arginine/serine-rich factor; SGK1, serum- and glucocorticoid-induced kinase 1; SHIP-2, SH2-domain containing inositol 5-phosphatase 2; SKAR, S6K1 Aly/REF-like target; SREBP, sterol responsive element binding protein; STAT3, signal transducers and activators of transcription 3; STRAD α , STE20-related adaptor protein α ; TBI, traumatic brain injury; TCTP, translationally controlled tumor protein; TNFR, tumor necrosis factor receptor; TRADD, TNFR-associated protein with death domain; TSC, tuberous sclerosis complex; ULK1, unc-51-like kinase 1

Abstract

Studies of epilepsy have mainly focused on the membrane proteins that control neuronal excitability. Recently, attention has been shifting to intracellular proteins and their interactions, signaling cascades and feedback regulation as they relate to epilepsy. The mTOR (mammalian target of rapamycin) signal transduction pathway, especially, has been suggested to play an important role in this regard. These pathways are involved in major physiological processes as well as in numerous pathological conditions. Here, involvement of the mTOR pathway in epilepsy will be reviewed by presenting; an overview of the pathway, a brief description of key signaling molecules, a summary of independent reports and possible implications of abnormalities of those molecules in epilepsy, a discussion of the lack of experimental data, and questions raised for the understanding its epileptogenic mechanism.

Keywords: epilepsy; mTOR; rapamycin

Introduction

In 'On the sacred disease', the first book on epilepsy, Hippocrates correctly described epilepsy as a brain disorder. However, for hundreds of years, epilepsy patients have been considered possessed or contagious, and persons with epilepsy have been

stigmatized, prohibited, or even segregated from their communities. Even today, epilepsy still remains a mysterious disease. It is one of the most common neurological problems in the world, and approximately 1% of the general population has epileptic episodes at some point in their lives (WHO, 2005). It has the genetic, environmental, and epigenetic components, and these factors are differentially interwoven in individual patients with various types of epilepsy (Berkovic *et al.*, 2006).

Since the first report of an $\alpha 4$ neuronal nicotinic receptor subunit mutation in humans was linked to epilepsy, the list of epileptic mutations in both voltage- and ligand-gated ion channels has continued to grow (Steinlein *et al.*, 1995; Helbig *et al.*, 2008). Thus, the knowledge of molecular mechanism of seizures caused by those mutations has been deepened over last decade (Reid *et al.*, 2009). However, genetic defects are only a partial, if not minor, cause of epilepsy. The effectiveness of anti-epileptic drugs (AEDs) against ion channels is limited for the treatment and management of 'acquired' epileptic conditions (Beck, 2007). Epileptic seizures result from abnormal synchronous firing of neuronal population (Scharfman, 2007). Since epilepsy show multiple events; cell death, cell survival and ectopic neurogenesis, aberrant axonal sprouting, and synaptic reorganization, the existence of the core signaling pathway involved in these processes should have been expected. However, we have not been able to have the luxury of intracellular signaling mechanism for epilepsy like other neurological diseases until recently (Swiech *et al.*, 2008). Here, I will summarize and frame individual reports of epilepsy-related molecules into the mTOR pathway and try to set the common ground that can be served for the continuing discussion. This may be helpful for researchers especially in the epilepsy field who are not familiar with the intracellular signaling pathway.

Known involvement of the mTOR pathway in epilepsy

The mTOR pathway has been studied extensively over the last decade and has been involved both in various normal physiological processes (metabolism, cell growth, proliferation, differentiation, longevity, apoptosis, and autophagy) and several disease conditions (tumorigenesis, type 2 diabetes, inflammation, and neurodegenerative diseases) (Figure 1).

Recently, the mTOR pathway has been examined in animal models of medial temporal lobe epilepsy (Buckmaster *et al.*, 2009; Zeng *et al.*, 2009; Huang *et al.*, 2010). In these studies, kainate or pilo-

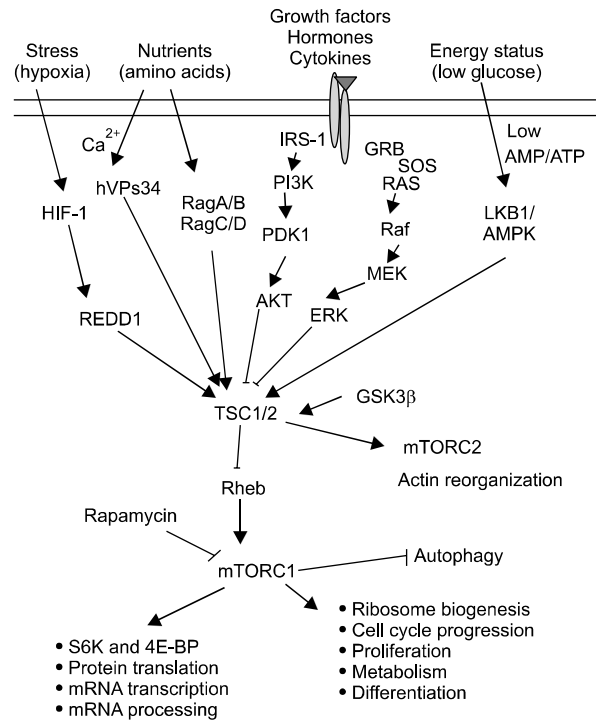


Figure 1. Overview of mTOR signaling pathway. Activation and inhibition of signaling molecules by phosphorylation are shown in red and blue respectively.

carpine was injected into rats to induce *status epilepticus* (SE) and the animals went on to develop spontaneous seizures. It has been shown that S6, a ribosomal protein involved in translation initiation, and a downstream molecule in the mTOR signaling pathway, became phosphorylated (activated). Treatment of rapamycin, an mTOR kinase inhibitor, given either as a pretreatment or given after SE, reduced both mossy fiber sprouting, an abnormal change in the dentate gyrus and hilus, and seizure frequency (Davenport *et al.*, 1990).

Some diseases caused by genetic mutations in the molecules on the mTOR pathway show epileptic seizures (Figure 2). For example, Tuberous sclerosis complex (TSC), a multi-organ disorder, is mainly caused by mutations in TSC1 and/or TSC2. Its tuber formation is highly associated with mental retardation, autism and epilepsy (Curatolo *et al.*, 2008). TSC2, a tumor suppressor forming a complex with TSC1, has been known as a key regulator of the mTOR kinase, and its functional failure results in uncontrolled mTORC1 activity (Inoki *et al.*, 2005). Treatment with rapamycin reduced the seizure frequency in TSC patients and mouse models of TSC (Meikle *et al.*, 2008; Zeng *et al.*, 2008; Muncy *et al.*, 2009).

Similarly, PTEN (phosphatase and tensin homo-

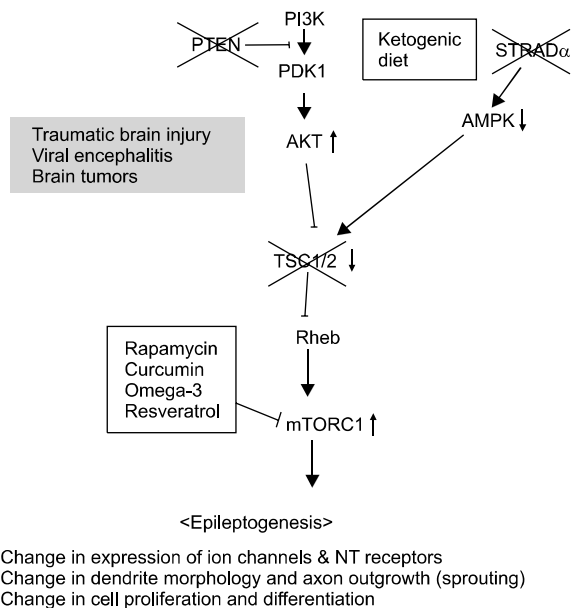


Figure 2. Genetic mutations of signaling molecules implicated in mTOR pathway (red Xs). Red arrows (up- or downward) indicate the changes in activity of particular molecules in epileptic conditions. Causatives for acquired epilepsy are described in gray. Therapeutic intervening possibilities are shown in boxes. NT - neurotransmitter receptor.

log) is a molecule found mutated in autosomal dominant hamartoma and epilepsy-associated glioblastoma, and the conditional knockout mice showed cortical dysplasia, ataxia, and seizures (Backman *et al.*, 2001). PTEN is a negative regulator of phosphoinositide 3-kinase (PI3K) which is located at upstream of mTOR (Cully *et al.*, 2006). Treatment with rapamycin inhibits seizures in this animal model (Ljungberg *et al.*, 2009; Zhou *et al.*, 2009a).

Lafora disease is an autosomal recessive epilepsy which is caused by defective laforin or malin proteins (Ganesh *et al.*, 2006) (Figure 3G). This neurodegenerative disease has lafora bodies, which are polyglucosans masses, are found in neurons, myocytes, and hepatocytes. Polyglucosans, insoluble and abnormally formed glycogen molecules, are produced by failure to regulate glycogen synthase (GS) activity. Laforin (encoded by EPM2A gene) dephosphorylates GSK3 β , thus controlling GS. Malin (encoded by EPM2B gene) is an E3 ubiquitin ligase which binds GS and laforin, regulating their degradation (Gentry *et al.*, 2005; Lohi *et al.*, 2005). GSK3 β is phosphorylated by AKT and S6K1, and it phosphorylates TSC1, TSC2, and REDD1 which all are on the mTOR pathway (Zhang *et al.*, 2006; Inoki *et al.*, 2006; Allard *et al.*, 2008; Katiyar *et al.*, 2009).

PMSE (Polyhydramnios, megalencephaly and symptomatic epilepsy) has been recently found

having gene deletion in STRAD α (Puffenberger *et al.*, 2007) (Figures 2 and 3F). STRAD α forms a complex with LKB1 and MO25 α , and this complex regulates AMPK which controls mTORC1 and TSC2, an upstream regulator of mTORC1 (Hardie, 2005).

The mTOR pathway overview

The mTOR is a master regulator which integrates multiple upstream signals: both extracellular (e.g., growth factors) and intracellular (e.g., energy status) to regulate gene expression, translational rates and metabolic processes (Hay and Sonenberg, 2004) (Figure 1). When the ligand such as insulin-like growth factor (IGF) binds to its receptor (e.g., IGF receptor) on the plasma membrane, the activated signal (phosphorylation) transduces to PI3K either directly or indirectly via mediator proteins such as Insulin receptor substrate-1 (IRS-1). PI3K makes phosphatidylinositol 3, 4, 5 trisphosphate (PIP₃) from phosphatidylinositol 4, 5 bisphosphate (PIP₂), PIP₃ activates PDK1, and PDK1 phosphorylates and activates AKT/PKB at Thr308. PI3K reaction can be reversed by PTEN and/or SHIP-2, and PI3K can be activated by Ras or PI3K enhancer (PIKE). Activated AKT inhibits TSC2 by phosphorylation, subsequently disinhibits Rheb to activate mTORC1. AKT can be fully activated by phosphorylation at Ser473 by mTORC2, inhibiting mTORC2-regulating molecules such as FOXO and BAD. PHLPP reverses mTORC2-mediated phosphorylation of AKT. TSC2 forms a complex with TSC1 inhibiting Rheb by keeping it GDP bound form (Rheb-GDP), and Rheb-GTP activates mTORC1. Signaling through mTORC1 promotes protein synthesis via phosphorylation which causes the inactivation of translation repressor 4E-BPs and the activation of S6 Kinases and ribosomal protein S6. TSC2/TSC1 complex integrates another inhibitory signal from growth factor-related signaling pathway of Ras/MAPK including ERK/RSK, and activating signals of energy status through LKB1/AMPK, stress or oxygen level via HIF-1/REDD1, and Wnt signaling through GSK3. Signals of amino acid availability are transduced to mTORC1 directly via RagA/B and RagC/D, hVps34 or MAP4K3. AKT, AMPK, and RSK can regulate mTORC1 activity either directly or via TSC2/TSC1 complex.

Feedback regulation is important in the mTOR pathway. TSC1/2-mediated activation of mTORC2 phosphorylates and activates AKT. S6K phosphorylates IRS-1, mTORC1, and GSK3 which is inhibited by AKT and activates TSC2. Cross-talk between signaling pathways is also important;

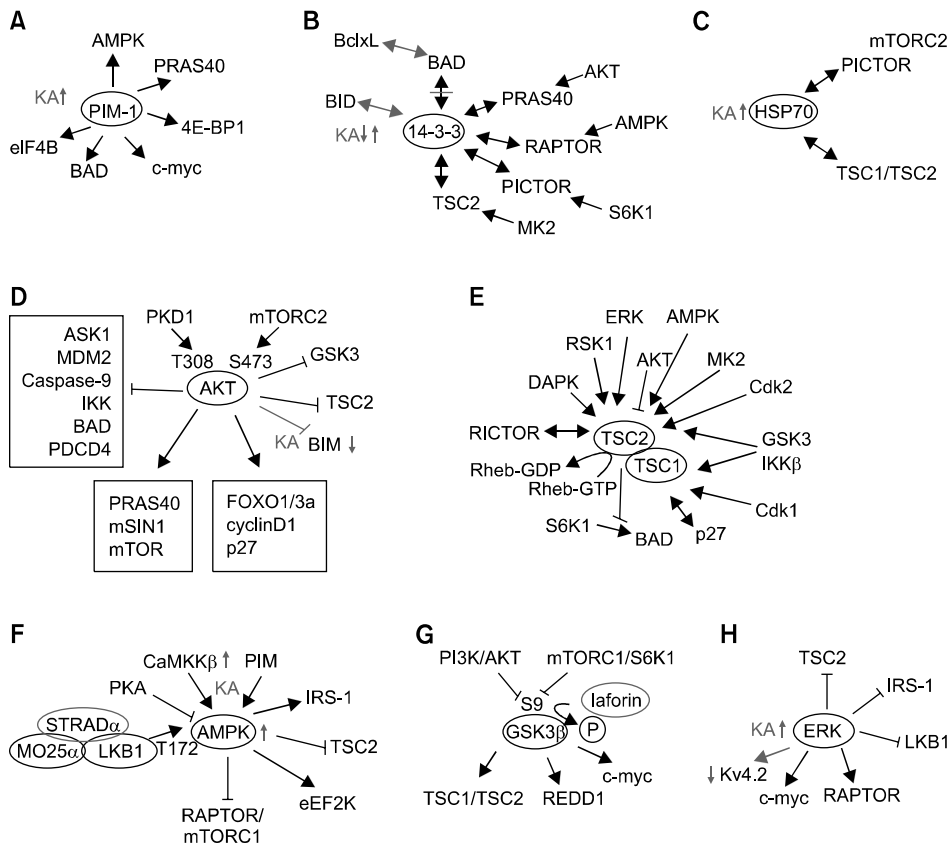


Figure 3. Signaling molecules implicated in epilepsy (see the text for the detail). Arrows indicate the phosphorylation events. Up- and downward arrows indicate the changes in the expression level or activity of particular molecules. Double arrows indicate the protein-protein interaction. Some interactions were induced by phosphorylation. (A) PIM-1 is increased in kainate model. (B) 14-3-3 interacts with BID and dissociates from BAD in kainate model. (C) HSP70 level is increased in kainate model. (D) AKT decreased BIM expression in epilepsy model. AKT is activated by PDK1 phosphorylation at T308 and mTORC2 phosphorylation at S473. AKT modulates molecules involved in apoptosis and cell cycle as well as other molecules in the mTOR pathway. (E) Various protein-protein interactions with TSC1 and TSC2. When mutated, TSC1/2 lose control of Rheb activity. (F) AMPK and CaMKKβ are increased in kainate model, causing TSC2 inhibition. STRADα in an epileptic condition was indicated in red. AMPK is phosphorylated at T172 by STRADα-MO25α-LKB1 complex. (G) GSK3β is inhibited by phosphorylation at S9. In lafora disease, GSK3β can not be regulated due to the mutation in laforin, a phosphatase. (H) Activation of ERK decrease the surface expression of Kv4.2 channels in kainate model. KA - kainic acid, T-Threonine, S-Serine.

mTORC1 activation induces phosphorylation of ERK1/2 at Thr202, inhibiting its activity via PP2A (Harwood *et al.*, 2008). Ras activates PI3K as well as MAPK pathway, ERK inhibits TSC2 either directly or indirectly via RSK, and it also regulates eIF4B via RSK or MNK1/2.

Components of mTORC1 and mTORC2

mTORC1 and mTORC2 are two different protein complexes that mTOR partners with, executing different but related functions. Substrate specificity of mTOR is therefore determined by the core proteins with which mTOR forms a complex and

they are also regulated in distinct ways.

mTORC1 comprises five different components: 3 common proteins that it shares with mTORC2 (mTOR, mLST8, and DEPTOR), and 2 mTORC1-specific proteins (RAPTOR and PRAS40). mTORC1 plays a major role in controlling cell growth in response to amino acids, energy status, stress, oxygen levels, hormones, growth factors and cytokines by regulating several cellular processes, including translation, transcription, ribosome biogenesis, nutrients transport and autophagy (Reiling and Sabatini, 2006; Wullschleger *et al.*, 2006; Dunlop and Tee, 2009; Mizushima, 2010). mTORC1 is known to be rapamycin-sensitive via its FKBP12 interaction (Sabers *et al.*, 1995). Identified down-

stream targets of mTORC1 for regulating these processes at the translational level are S6K1, 4E-BP1, eEF2K, eIF3F, and eIF4G (Browne and Proud, 2004; Hay and Sonenberg, 2004; Harris *et al.*, 2006; Csibi *et al.*, 2010). At the transcriptional level, SREBP1, Lipin-1, c-Myc and STAT3 interact with mTORC1 to control expression of their specific target genes (Yokogami *et al.*, 2000; Huffman *et al.*, 2002; Porstmann *et al.*, 2008; Zhang *et al.*, 2008). mTORC1 phosphorylates CLIP-170 to reorganize microtubule, and ULK1 (ATG1)/ATG13 to inhibit autophagy (Choi *et al.*, 2002; Jung *et al.*, 2009). PP2A, PIM-1, and 14-3-3 interact closely with mTORC1 (Harwood *et al.*, 2008; Gwinn *et al.*, 2008; Zhang *et al.*, 2009).

mTORC2 has six components: 3 common proteins that it shares with mTORC1 (mTOR, mLST8, and DEPTOR) and 3 mTORC2-specific proteins (RICTOR, mSIN1, and Protor-1). The upstream regulators of mTORC2 are less clearly defined- it is TSC1/2-dependent, possibly via direct TSC2-RICTOR interaction (Huang *et al.*, 2008, 2009a). mTORC2 is generally known as rapamycin-insensitive, and it seems to be regulated only by growth factors (Yang *et al.*, 2006a). However, prolonged treatment of rapamycin (> 12 h) blocks mTORC2 assembly (Sarbasov *et al.*, 2006). AKT/PKB, PKC α , and SGK1 are known downstream targets of mTORC2 (Jacinto *et al.*, 2004; Sarbasov *et al.*, 2005; García-Martínez and Alessi, 2008). By releasing the inhibitory action of TSC via AKT, mTORC2 controls the upstream of mTORC1 activity (Inoki *et al.*, 2002; Sancak *et al.*, 2008). Through AKT activation, mTORC2 controls the expression of transcription factors such as FOXO, and an apoptosis regulator, BAD (Datta *et al.*, 1997; Guertin *et al.*, 2006). mTORC2 also reorganizes actin cytoskeleton through Rho-associated kinase (ROCK1) and PKC α (Jacinto *et al.*, 2004; Sarbasov *et al.*, 2004; Shu and Houghton, 2009). P-REX1, HSP70, and 14-3-3 interact closely with mTORC2 (Hernández-Negrete *et al.*, 2007; Martin *et al.*, 2008; Dibble *et al.*, 2009).

Individual molecules of the mTOR complexes and closely interacting molecules

Here, a brief description will be given of the individual molecules in the mTOR pathway, their phosphorylation patterns and protein-protein interactions, phenotypes of null mice, drugs modulating their activities, and epilepsy-related findings.

mTOR

The mTOR is a Ser/Thr protein kinase of phosphatidy-

linositide-kinase-related family (Keith and Schreiber, 1995). It was first identified in *Saccharomyces cerevisiae*, and it is highly conserved among eukaryotes (Jacinto and Hall, 2003; Wullschleger *et al.*, 2006). It is also called FRAP (FKBP-rapamycin associated protein), RAPT (Rapamycin target), RAFT (rapamycin and FKBP12 target) or SEP (sirolimus effector protein). Expression of mTOR is ubiquitous, high expression of mRNA is found in brain, kidney, placenta and skeletal muscle (Kim *et al.*, 2002). Multiple subcellular localization of mTOR has been reported in endoplasmic reticulum, Golgi apparatus, mitochondria, cytoplasm, and nucleus, implicating its multi-functionality (Kim and Chen, 2000; Desai *et al.*, 2002; Liu and Zheng, 2007). Ubiquitination of mTOR by FBXW7 leads to the proteosomal degradation (Mao *et al.*, 2008). Knockout mice (*mTOR*^{-/-}) die at E5.5 and these embryos show the inability to establish embryonic stem cells (Gangloff *et al.*, 2004; Murakami *et al.*, 2004). Heterozygous mTOR (*mTOR*^{+/-}) knockout mice did not develop any noticeable abnormality and were fertile (Gangloff *et al.*, 2004; Murakami *et al.*, 2004). mTOR participates in signaling pathways associated with human diseases including tuberous sclerosis complex, lymphangioleiomyomatosis, Cowden disease, Peutz-Jeghers syndrome, neurofibromatosis, familial cardiac hypertrophy, and cancers characterized by hyperactivation of PI3K/AKT (Guertin and Sabatini, 2005; Shaw and Cantley, 2006). There are three phosphorylation sites (Thr2446, Ser2448, and Ser2481) on mTOR: Thr2446 has been shown to be phosphorylated by AMPK and S6K1 (Cheng *et al.*, 2004; Holz and Blenis, 2005), Thr2448 by AKT and S6K1 (Sekulić *et al.*, 2000; Holz and Blenis, 2005), and Ser2481 has been reported to be autophosphorylated by mTOR itself (Peterson *et al.*, 2000). There is a report that Ser2448 is predominantly phosphorylated with mTORC1, whereas Ser2481 with mTORC2 (Copp *et al.*, 2009).

mLST8

mLST8 (mammalian lethal with Sec13 protein 8) is a positive regulator of mTORC1 and mTORC2 (Kim *et al.*, 2003; Guertin *et al.*, 2006). It is also known as G β L, a protein homologous to β subunits of heterotrimeric G proteins (Kim *et al.*, 2003). It has seven WD40 repeats for protein-protein interaction, and it binds near the catalytic domain of mTOR required for the full kinase activity (Kim *et al.*, 2003). mLST8 null mice have defective vascular development and die at E10.5 (Guertin *et al.*, 2006; Shiota *et al.*, 2006).

DEPTOR

DEPTOR (DEP-domain containing mTOR-interacting protein) is a negative regulator of mTOR complexes, and it binds to mTOR via its PDZ domain (Peterson *et al.*, 2009). When DEPTOR is activated by mTORC1 phosphorylation, the mTORC1-DEPTOR interaction became weak. RNAi-mediated knockdown of DEPTOR shows that increased cell size, reduced vulnerability for apoptosis. DEPTOR appears to inhibit mTORC1 more strongly than mTORC2.

RAPTOR

RAPTOR (regulatory-associated protein of mTOR) is a positive regulator of mTORC1, and recruits mTOR substrates (Kim *et al.*, 2002). It has a distinctive amino-terminal region followed by three HEAT motif and seven WD40 repeats (Kim *et al.*, 2002). RAPTOR binds to 4E-BP1 and S6K1 using carboxy-terminal TOR signaling (TOS) motifs, and TOS motifs were also identified in PRAS40, PLD2 and eIF3F (Schalm and Blenis, 2002). RAPTOR is phosphorylated at Ser792 by AMPK, inducing 14-3-3 binding to AMPK-ULK1-mTORC1 complex to inhibit mTORC1 activity (Gwinn *et al.*, 2008; Lee *et al.*, 2010). It is also phosphorylated by ERK1/2 at Ser8, Ser696, and Ser863 and by RSK at Ser719, Ser721 and Ser722, activating mTORC1 activity (Carrière *et al.*, 2008a, 2011). RAPTOR null mice die early in development - between E6.5 and E8.5 (Gangloff *et al.*, 2004; Murakami *et al.*, 2004; Guertin *et al.*, 2006).

PRAS40

PRAS40 (Proline-rich AKT substrate of 40 kDa; also known as AKT1 substrate 1 (AKTS1)) is phosphorylated at Thr246 by AKT and this promotes its binding with 14-3-3, relieving from mTORC1, thus disinhibits mTORC1 (Vander Haar *et al.*, 2007). PIM-1 kinase also phosphorylates PRAS40 at Thr246 (Zhang *et al.*, 2009). PRAS40 has a TOS motif and is phosphorylated at Ser183, Ser212 and Ser221 by mTORC1 (Oshiro *et al.*, 2007; Wang *et al.*, 2008). Ser221 and Thr246 are involved in its binding to 14-3-3 (Wang *et al.*, 2008).

RICTOR

RICTOR (Rapamycin-insensitive companion of mTOR) is a key component of mTORC2 (Sarbasov, *et al.*, 2004). RICTOR null embryos exhibit growth arrest and die at E11.5 and cells deficient of RICTOR showed low proliferation rate and metabolic activity (Shiota *et al.*, 2006). By RNAi-mediated knockdown, RICTOR (thus mTORC2) has been shown

to regulate organization of actin cytoskeleton and phosphorylate/activate AKT (Jacinto *et al.*, 2004; Sarbasov *et al.*, 2004, 2005). RICTOR directly interacts with TSC2, stimulating mTORC2 activity (Huang *et al.*, 2009a). Among 21 identified phosphorylation sites of RICTOR, Thr1135 is phosphorylated by SGK1, AKT, or S6K1 via mTORC1, and this phosphorylation is acutely sensitive to rapamycin (Dibble *et al.*, 2009). This phosphorylation dissociates RICTOR/Cullin1 complex, an E3 ubiquitin ligase and stimulates binding of RICTOR to 14-3-3 proteins without affecting mTORC2 kinase activity (Dibble *et al.*, 2009; Gao *et al.*, 2010).

mSIN-1

mSIN-1 (mammalian stress-activated protein kinase interacting protein; also known as MIP1 (MEKK2 interacting protein 1)) is necessary for mTORC2 assembly and for phosphorylation at Ser473 of AKT (Frias *et al.*, 2006). Among five alternative splicing variants (mSin1.1 - mSin1.5), three can assemble into mTORC2 to make distinct mTORC2s (mSin1.1, 1.2, and 1.5). Only two of them (mSin1.1 and mSin1.2) are insulin-responsive (Frias *et al.*, 2006). *mSin1*^{-/-} mice are embryonic lethal but *mSin1*^{+/-} appears to develop normally (Jacinto *et al.*, 2006). Knockdown of mSin1 results in decrease of RICTOR phosphorylation and protein levels, and disruption of the RICTOR-mTOR interaction (Yang *et al.*, 2006b). This knockdown also decreases the phosphorylation of AKT substrates and makes cells more sensitive to apoptosis.

PROTOR-1

PROTOR-1 (Protein observed with RICTOR-1, also called PRR5 (Proline-rich protein 5)) was identified to bind to RICTOR, and silencing of its gene inhibits AKT and S6K1 phosphorylation (Pearce *et al.*, 2007; Woo *et al.*, 2007). It has ubiquitous expression including in the brain (Shan *et al.*, 2003). PRR5-like protein (PRR5L, Q6MZQ0) is likely to be PROTOR-2 which also binds to mTORC2 (Pearce *et al.*, 2007; Thedieck *et al.*, 2007).

FKBP12

FKBP12 (FK506 binding protein 12) is an immunophilin which inhibits mTORC1 by forming a complex with rapamycin (Vignot *et al.*, 2005). FKBP12 also has peptidyl-prolyl isomerase activities and regulates intracellular calcium release, cellular trafficking and gene expression by interacting with ryanodine receptors, IP₃ receptors, and TGFβ

receptors (Harrar *et al.*, 2001). FKBP38 is an endogenous inhibitor of mTORC1 and it is closely related to FKBP12 (Bai *et al.*, 2007). FKBP38 is removed from mTOR when Rheb binds to it, thus activating mTORC1 and this Rheb-FKBP38 interaction is regulated by mitogens and amino acid availability. Its brain expression is very low, therefore, FKBP12 has been considered as the major repressor of mTORC1 activity (Bai *et al.*, 2007). FKBP12 null mice showed severe congenital heart symptoms, and brain-specific deletion of FKBP12 shows the enhancement of long-term potentiation (LTP) in the hippocampus and memory (Shou *et al.*, 1998; Hoeffler *et al.*, 2008).

PIM-1

PIM-1 (provirus integration site for Moloney murine leukemia virus) is a Ser/Thr kinase which localizes to the nucleus and dendrites of activated neurons (Konietzko *et al.*, 1999) (Figure 3A). It phosphorylates PRAS40 on Thr246, and this modification releases PRAS40 from mTORC1, activating mTORC1 kinase (Zhang *et al.*, 2009). It activates AMPK by phosphorylating it at Thr172, thus inhibiting mTORC1 activity (Beharry *et al.*, 2011). It stabilizes c-Myc, an mTORC1 substrate by phosphorylation on Thr62 and Ser329 (Zhang *et al.*, 2008). It also phosphorylates 4E-BP1 on Thr37 and Thr46 and eIF4B on Ser406, enhancing protein synthesis (Chen *et al.*, 2005; Peng *et al.*, 2007). It phosphorylates and inactivates BAD on Ser112 *in vitro*, improving the cell survival (Aho *et al.*, 2004). Kainate injection induces PIM-1 expression in dentate gyrus in rats (Feldman *et al.*, 1998). PIM-1 expression is induced by and required for LTP (Konietzko *et al.*, 1999). Pim null mice develop normally, and are fertile without any significant abnormality in the brain (Laird *et al.*, 1993). Compound 24 and 4a were developed to inhibit PIM-1 (Grey *et al.*, 2009; Xia *et al.*, 2009).

Phosphatidic acid

Phosphatidic acid (PA) is made by phospholipase D (PLD), diacylglycerol kinase, and lysophosphatidic acid acyltransferase and it transduces mitogenic signals to mTORC1 (Foster, 2009). PA specifically binds to the FKBP12 binding domain of mTOR and it also binds to and activates S6K1 (Fang *et al.*, 2001; Lehman *et al.*, 2007).

14-3-3

14-3-3 proteins are involved in extraordinarily broad cellular process in all eukaryotes, and they function as a dimer by binding to phosphorylated target pro-

teins at the specific site, causing a conformational change (Mackintosh, 2004) (Figure 3B). Among the many proteins that interact with 14-3-3, several are on the mTOR pathway: 1) PRAS40 binds to 14-3-3 when phosphorylated at Ser221 and Thr246 by AKT (Wang *et al.*, 2008). 2) RAPTOR binds to 14-3-3 when phosphorylated at Ser722 and Ser792 by AMPK (Gwinn *et al.*, 2008). 3) RICTOR binds to 14-3-3 when phosphorylated at Thr1135 by S6K1 (Dibble *et al.*, 2009). 4) TSC2 is phosphorylated at Ser1210 by MK2, enhancing binding to 14-3-3 (Li *et al.*, 2003). 5) REDD1 competes with TSC2 on binding to 14-3-3 under stressed condition (DeYoung *et al.*, 2008). In kainate injected rats, a pro-apoptotic molecule, BAD is dephosphorylated to disrupt binding to 14-3-3, and BAD dimerized with anti-apoptotic molecule BCL-XL (Meller *et al.*, 2003). During seizure-induced neuronal death, another pro-apoptotic molecule, BID (BH3-interacting domain death agonist) is cleaved, increasing its binding to 14-3-3, although level of 14-3-3 was decreased (Shinoda *et al.*, 2003). 14-3-3 ϵ and 14-3-3 ζ levels were increased in human temporal lobe epilepsy specimen (chronic period) than control, however, 14-3-3 ϵ and 14-3-3 ζ level were decreased in acute kainate injected rats (Schindler *et al.*, 2006). 14-3-3 ϵ and 14-3-3 σ null mice appear normal (Steinacker *et al.*, 2005; Su *et al.*, 2011).

P-REX1

P-REX1 (PIP3-dependent Rac exchanger 1) is a guanine nucleotide exchange factor for Rac and it connects G-protein coupled receptors through G $\beta\gamma$ and PI3K to Rac activation (Barber *et al.*, 2007). Through its DEP domains, it interacts with mTORC2, serves as an effector of mTOR to Rac activation and cell migration (Hernández-Negrete *et al.*, 2007). It is also implicated in migration of cortical neurons and neurite differentiation (Yoshizawa *et al.*, 2005; Waters *et al.*, 2008). P-REX1 null mice are healthy except for mild neutrophilia (Welch *et al.*, 2005).

HSP70

HSP70 (heat shock protein 70) has been shown to interact with RICTOR for the formation and activity of mTORC2 in addition to the interaction with TSC1 and TSC2 (Martin *et al.*, 2008; Inoue *et al.*, 2009) (Figure 3C). HSP70-1/HSP70-3 double knockout mice are more susceptible to ischemia-induced damages (Kim *et al.*, 2006). In kainate-induced epileptic rat, gene expression of HSP72, a mammalian homolog, is enhanced (Gass *et al.*, 1995). Overexpression of HSP72 helps the survival

of dentate granule cells from cell death induced by kainate (Yenari *et al.*, 1998). It remains to be seen how epileptic insult induces this stress protein to interact with TSC1/2 and/or mTOR complexes for the neuroprotective effect.

Upstream signaling molecules

IRS-1

IRS-1 (Insulin receptor substrate-1) transduces activation signals via tyrosine phosphorylation from Insulin- or IGF receptors to PI3K (Ogawa *et al.*, 1998). Phosphorylation of IRS-1 promotes its proteasomal degradation (Gual *et al.*, 2005). Phosphorylation patterns at multiple sites are complicated in the pathological conditions such as tumorigenesis and diabetes (Gibson *et al.*, 2007). IRS-1 is phosphorylated at Ser 270 and Ser1101 by S6K1, at Ser794 by AMPK, and at Ser636, Ser639, Ser662 and Ser639 by mTORC1 (Tzatsos and Kandror, 2006; Tzatsos and Tschlis, 2007; Tremblay *et al.*, 2007; Zhang *et al.*, 2008). ERK also phosphorylates IRS-1 at Ser612 (Andreozzi *et al.*, 2004). IRS-1 null mice showed half-size compared to controls and impaired glucose tolerance, and female IRS-1 null mice lived longer than controls (Araki *et al.*, 1994; Selman *et al.*, 2008).

PI3K

PI3K (phosphoinositide 3-kinase, Class I) phosphorylates PIP₂ to produce PIP₃. It consists of a catalytic (p110 α , p110 β , p110 γ , or p110 δ) and a regulatory subunit (p85 or p101 for p110 γ) (Zhao and Vogt, 2008). Insulin, IGF, and epidermal growth factor (EGF) use p110 α /p85 to make PIP₃, further activate mTOR signaling cascade (Knight *et al.*, 2006). PI3K negatively controls FOXO-mediated neuronal excitability, and PI3K activation increases axon size and synapse number in mTOR/S6K-dependent manner (Howlett *et al.*, 2008). Several PI3K-specific inhibitors including LY294002 are available (Kong and Yamori, 2008). Specific inhibitors against both mTORC1 and PI3K are extensively being developed to circumvent the drug resistance (Brachmann *et al.*, 2009). Phenotypes of knockout mice of PI3K isoforms are described in detail elsewhere (Vanhaesebroeck *et al.*, 2005). In epilepsy-associated gangliogliomas, PI3K and other mTOR pathway signaling molecules have been shown to be activated in patients' specimen (Boer *et al.*, 2010).

PTEN

PTEN (phosphatase and tensin homolog) is a lipid phosphatase found mutated in autosomal dominant hamartoma, and it converts PIP₃ to PIP₂, and further to phosphatidylinositol 5-monophosphate (Cully *et al.*, 2006) (Figure 2). PTEN is transported to the plasma membrane via myosin V by its phosphorylation at Ser380, Thr 382 and Thr 383 by GSK3 β (van Diepen *et al.*, 2009). PTEN suppresses transcription of rRNAs and tRNAs by disrupting the binding of transcription factors either to their promoters or other proteins (Zhang *et al.*, 2005a; Woiwode *et al.*, 2008). PTEN has been shown to be involved in NMDA receptor-dependent long-term depression (LTD) (Jurado *et al.*, 2010). Formation of a new growth cone after axotomy and axon regeneration after injury in retinal ganglion cells is modulated by PTEN/mTOR signaling pathway (Verma *et al.*, 2005; Park *et al.*, 2008). PTEN null mice are embryonic lethal and heterozygous null mice have multiple tumors (Di Cristofano *et al.*, 1998; Suzuki *et al.*, 1998). Potassium bisperoxo (1, 10-phenanthroline) oxovanadate inhibits PTEN (Lai *et al.*, 2009).

SHIP-2

SHIP-2 (SH2-domain containing inositol 5-phosphatase 2) is a negative regulator of the insulin signaling pathway and it hydrolyses PIP₃ to PIP₂, inhibiting PDK1 and AKT activation (Vinciguerra and Foti, 2006). SHIP-2 null mice show the high resistance to the weight gain on high-fat diet (Sleeman *et al.*, 2005).

PIKEs

PIKEs (PI3K enhancers) are a family of GTPase that interacts with and stimulates PI3K and AKT, especially in the brain (Ahn and Ye, 2005). PIKE-S localizes in the nucleus, PIKE-L shows multiple localizations, and PIKE-A directly activates AKT. PIKE-L binds to Homer, connecting mGluR to PI3K (Rong *et al.*, 2003). PIKE-A is important for insulin to modulate AMPK phosphorylation, PIKE null mice are resistant to diabetes (Chan *et al.*, 2010).

PDK1

PDK1 (3-phosphoinositide-dependent protein kinase-1) has been characterized as an essential link between PI3K and AKT by phosphorylating and activating AKT at Thr308 (Wick *et al.*, 2000). Interestingly, PDK1 has been shown to shuttle between cytoplasm and nucleus (Kikani *et al.*, 2005). PDK1 also phosphorylates RSK at Ser227,

SGK at Thr256 and S6K at Thr252 (Alessi *et al.*, 1998; Frödin *et al.*, 2000; Biondi *et al.*, 2001). It phosphorylates and stabilizes several PKC isoforms (Balendran *et al.*, 2000). PDK1 null embryos die at E9.5, hypomorphic mice are half-size compared to controls (Lawlor *et al.*, 2002). PDK1 deficient brain showed microcephaly and increased phosphorylation of AKT at Ser473 in glia, not in neurons (Chalhoub *et al.*, 2009). 3-Hydroxyanthranilic acid specifically inhibits PDK1 (Hayashi *et al.*, 2007).

AKT/PKB

AKT/PKB (acutely transforming retrovirus AKT8 in rodent T cell lymphoma/Protein Kinase B) is a Ser/Thr kinase which is a key intracellular mediator of diverse cellular processes, and is activated in a PI3K-dependent manner (Manning and Cantley, 2007) (Figure 3D). AKT phosphorylates TSC2 and suppresses GTPase-activating protein (GAP) activity, thus activating mTORC1 (Inoki *et al.*, 2002). Full activation of AKT requires the phosphorylation at Thr308 by PDK1 and at Ser473 (and Thr450) by mTORC2, a long-sought PDK2 (Sarbasov *et al.*, 2005; Shiota *et al.*, 2006; Facchinetti *et al.*, 2008). When fully activated, AKT acts both as an upstream activator of mTORC1 and as a downstream substrate of mTORC2 (Sarbasov *et al.*, 2006). Phosphorylation at Ser 473 is necessary for FOXO1/3a phosphorylation, but not other AKT targets including TSC2 and GSK3 *in vivo* (Jacinto *et al.*, 2006). In addition to PRAS40, mSIN1 and mTOR (Sekulić *et al.*, 2000; Frias *et al.*, 2006; Vander Haar *et al.*, 2007), protein substrates of AKT are grouped in two: 1) cell cycle regulation - FOXO1/3a, cyclin D1, and p27 (Liang and Slingerland, 2003), and 2) apoptosis - ASK1, MDM2, caspase-9, IKK, BAD, and PDCD4 (Cardone *et al.*, 1998; Lawlor and Alessi, 2001; Franke *et al.*, 2003; Palamarchuk *et al.*, 2005; Zhang *et al.*, 2005b; Dan *et al.*, 2008). AKT is implicated in suppressing apoptosis, and kainate-injury induces phosphorylation of mTOR and AKT (Zhang *et al.*, 2005b; Shacka *et al.*, 2007). AKT activation may be neuroprotective against kainate-induced epilepsy by inhibiting BIM (Bcl-2-interacting mediator of cell death) expression (Shinoda *et al.*, 2004). AKT1 null mice showed the impairment in adult neurogenesis and LTP in the hippocampus (Balu *et al.*, 2010). AKT2 null mice develop insulin resistance and other abnormality in glucose metabolism (Cho *et al.*, 2001). AKT3 null mice have smaller brains and the phosphorylation level of S6 is reduced via mTOR/S6K (Easton *et al.*, 2005). Interestingly, *Akt3*^{Nmf350}, dominant mutant mice have enlarged

brain, increased phosphorylation of S6, ectopic neurogenesis in the hippocampus and low seizure threshold (Tokuda *et al.*, 2011). AKT1/AKT2 double knockout mice show impaired development of skin, muscle, bone and adipogenesis (Peng *et al.*, 2003). A-443654, perifosine, and triciribine are selective AKT inhibitors with distinctive mechanisms (Han *et al.*, 2007; Dieterle *et al.*, 2009; Gill and Dennis, 2009).

PHLPP1/2

PHLPP1/2 (PH domain leucine-rich repeat protein phosphatase) dephosphorylates AKT at Ser473, the site is important in mTORC2-mediated AKT signaling to promote apoptosis and suppressing cancerous growth (Gao *et al.*, 2005; Brognard *et al.*, 2007). In addition to regulating the common inhibitory effect of AKT on TSC2 and GSK3 β , PHLPP1 interacts with AKT2 and AKT3, and PHLPP2 interacts with AKT1 and AKT3, differentially regulating HDM2 and p27 (Brognard *et al.*, 2007). PHLPP1/2 dephosphorylates PKC α at Ser657, promoting their degradation (Gao *et al.*, 2008). One of two PHLPP1 isoforms PHLPP1 β , also called SCOP (suprachiasmatic nucleus circadian oscillatory protein), was found that its expression oscillates, increasing during the subjective night (Shimizu *et al.*, 1999). SCOP negatively regulates K-Ras and CREB-mediated transcription, affecting long-term memory in the hippocampus (Shimizu *et al.*, 2007).

TSC1 (hamartin) and TSC2 (tuberin)

TSC1 (hamartin) and TSC2 (tuberin) are well studied tumor suppressors due to the fact that their autosomal dominant mutations cause Tuberous Sclerosis Complex (Jansen *et al.*, 2008). Over 70% of patients who suffer from TSC exhibit epileptic symptoms (Thiele, 2004) (Figure 3E). The disease-causing genes (TSC1 and TSC2) are identified (Consortium E.C.T.S. 1993; van Slegtenhorst and de Hoogt, 1997). The inhibitory function of TSC1/TSC2 obligate heterodimer acts through TSC2's GAP activity which turns Rheb from GTP-bound active state to GDP-bound inactive state (Zhang *et al.*, 2003). TSC2 regulates cell cycle by binding to p27, a cyclin-dependent kinase (cdk) inhibitor and this interaction prevents p27 degradation (Rosner and Hengstschlager, 2004). TSC2 inhibits phosphorylation on Ser126 of BAD by S6K, which induces apoptosis (Freiling *et al.*, 2006). The growing list of more than fifty TSC1/TSC2-interacting proteins is described in detail elsewhere (Rosner *et al.*, 2008). TSC1 is phosphorylated at

Thr310, Ser332, Thr417, Ser584, and Thr1047 by CDK1, at Thr357 and Thr390 by GSK3, and at Ser487 and Ser511 by IKK β (Astrinidis *et al.*, 2003; Mak *et al.*, 2005; Lee *et al.*, 2007). TSC2 is phosphorylated at Ser939, Ser981 and Thr1462 by AKT, at Thr1227 and Ser1345 by AMPK, at Ser664 by ERK, at Ser1210 by MK2, at Ser1337 and Ser1341 by GSK3, and at Ser939, Ser1462 and Ser1798 by RSK1 (Inoki *et al.*, 2003; Li *et al.*, 2003; Tee *et al.*, 2003; Roux *et al.*, 2004; Ma *et al.*, 2005; Cai *et al.*, 2006; Inoki *et al.*, 2006; Carrière *et al.*, 2008b). Serum-activated death-associated protein kinase (DAPK) phosphorylates TSC2 *in vitro* (Stevens *et al.*, 2009). TSC2 physically interact with RICTOR, activating mTORC2 activity (Huang *et al.*, 2009a). TSC null mice (TSC1^{-/-} and TSC2^{-/-}) die around at E11 (Kobayashi *et al.*, 1999, 2001) and heterozygotes (TSC1^{+/-} and TSC2^{+/-}) have no seizure episode (Onda *et al.*, 1999; Kobayashi *et al.*, 2001). Interestingly, mice with cell-type specific deletion of TSC genes develop epilepsy: astrocyte-specific TSC1 knockout (TSC1^{GFAPI}) mice start developing the seizures at 4 week-old, and neuron-specific TSC1 knockout (TSC1^{syn1}) mice also show seizure episodes (Uhlman *et al.*, 2002; Meikle *et al.*, 2007). Astrocyte-specific TSC2^{hGFAPI} knockout mice showed enlarged cells, megalencephaly and astrocytosis, and start dying after 3 weeks old (Way *et al.*, 2009). Disturbed balance between excitatory and inhibitory synaptic transmission might be linked to seizure incidents in tissues from patients as well as genetically manipulated mouse models (Uhlmann *et al.*, 2002; Meikle *et al.*, 2007; Wang *et al.*, 2007). A rat model carrying a spontaneous TSC2 mutation (Eker rat, TSC2^{+/-}) showed improved performance in episodic-like memory test, and impaired LTP and LTD in the hippocampus (Von der Brélie *et al.*, 2006; Waltereit *et al.*, 2006).

Rheb

Rheb (Ras homolog enriched in brain) is a Ras family small GTPase, an immediate-early gene product, and a direct activator of mTORC1 (Yamagata *et al.*, 1994; Bai *et al.*, 2007). When TSC1/TSC2 inactivated, GTP-bound Rheb activates mTORC1 (Inoki *et al.*, 2003; Zhang *et al.*, 2003). TCTP (Translationally controlled tumor protein) serves as GEF (guanine nucleotide exchange factor) for Rheb that leads to GTP-bound Rheb accumulation (Dong *et al.*, 2009). FKBP38 or BNIP3 binds to Rheb and inhibits mTORC1 (Bai *et al.*, 2007; Li *et al.*, 2007). Rheb also physically associates with NMDA receptor subunit NR3A (Sucher *et al.*, 2010). Recently, a glycolytic enzyme,

glyceraldehyde-3-phosphate dehydrogenase (GAPDH) has been shown to interact with Rheb and inhibits mTORC1 activity when glucose level is low (Lee *et al.*, 2009b). Glyceraldehyde-3-phosphate, an intermediate metabolite of glycolysis, binds to GAPDH, weakening the GAPDH-Rheb interaction, thus activating Rheb/mTORC1 signaling. A cAMP-specific phosphodiesterase, PED4D, interacts with Rheb negatively to control mTORC1 activity (Kim *et al.*, 2010). In this manner, the mTOR pathway may respond to change in the glucose and cAMP levels. Rheb also block aggresome formation by disrupting dynein-mediated transport of misfolded proteins (Zhou *et al.*, 2009b). Although TSC deficient cells do not show aggresome formation but undergo autophagic process, it will be interesting to see how Rheb behave in affected cells on epilepsy-related diseases such as the aggresome forming Lafora disease and microtubule-involved Type 1 lissencephaly (Fricott *et al.*, 2003; Mittal *et al.*, 2007).

AMPK

AMPK (AMP-activated protein kinase) is a Ser/Thr kinase and composed of a catalytic subunit (α 1 or α 2), a regulatory subunit (β 1 or β 2), and an AMP-binding regulatory subunit (γ 1, γ 2, or γ 3). AMPK is activated both by the direct AMP binding and its phosphorylation at Thr172 by LKB1 (Hardie, 2005) (Figure 3F). AMPK α 1 is phosphorylated at Ser173 by PKA, impeding LKB1-mediated AMPK activation (Djouder *et al.*, 2010). AMPK phosphorylates IRS-1 at Ser794 to promote apoptosis when cells encounter energy depletion via LKB1 or oxidative stress via CaMKK β (calcium/calmodulin-dependent protein kinase kinase β) (Tzatsos and Tschlis, 2007). AMPK can be phosphorylated at Thr172 by CaMKK β and PIM kinases (Hawley *et al.*, 2005; Woods *et al.*, 2005; Beharry *et al.*, 2011). AMPK activation transmits this energy demand signal to inhibit TSC2 and RAPTOR by phosphorylating at Thr1227 and Ser1345, and at Ser722 and Ser792, respectively (Inoki *et al.*, 2003; Gwinn *et al.*, 2008). AMPK also phosphorylates mTOR at Thr2446 and eEF2K at Ser398 (Browne *et al.*, 2004; Cheng *et al.*, 2004). AMPK activation induces 14-3-3 binding to AMPK-ULK1-mTORC1 complex via Ser792 phosphorylation of RAPTOR (Lee *et al.*, 2010). AMPK activation downregulates the gene expression and the activity of SREBP-1c in mTOR-dependent manner (Zhou *et al.*, 2001). AMPK modulates LTP based on the energy status (Potter *et al.*, 2010). Activation of AMPK and CaMKK β in the mouse hippocampus has been shown 2 h after kainate injection (Lee *et*

et al., 2009a). AMPK binds and phosphorylates GABA_B receptors, enhancing synaptic inhibition especially in ischemic injury condition (Kuramoto *et al.*, 2007). AMPK γ 1 null mice are viable, and AMPK α 2 null mice showed impaired insulin secretion (Viollet *et al.*, 2003; Jørgensen *et al.*, 2004). AMPK γ 3 null mice have reduced effect of hypoxia-induced glucose transport in the skeletal muscle (Deshmukh *et al.*, 2009). AICAR (5-amino-4-imidazole-carboxamide ribose) is an AMP mimetic and AMPK agonist (Pruznak *et al.*, 2008; Kwon *et al.*, 2010). Dinitrophenol and 2-deoxy-D-glucose also activates AMPK (Pelletier *et al.*, 2005; Potter *et al.*, 2010). Metformin, a drug commonly used to treat type II diabetes, activates AMPK with less defined mechanism of its action (Leverve *et al.*, 2003; Rotella *et al.*, 2006). Compound-C and ATP mimetic ara-A inhibit AMPK (Potter *et al.*, 2010).

LKB1

LKB1 (also known as STK11 or AMPK Kinase) is a master Ser/Thr kinase and a tumor suppressor that controls at least 13 AMPK subfamily kinases (Lizcano *et al.*, 2004; Hezel and Bardeesy, 2008). Under falling energy status (starvation or low glucose level) or stress conditions (such as hypoxia or ischemia) that facilitates ATP consumption or inhibits ATP production, AMP/ATP ratio rises, then this high ratio activates LKB1 (Hardie *et al.*, 2005). LKB1 forms a heterotetramer with STRAD α and a scaffolding protein, MO25 α , and it activates AMPK by phosphorylation at Thr172 (Hawley *et al.*, 2003). This LKB1-AMPK activation facilitates glucose uptake and cellular catabolism to have more ATP available and inhibits the cellular biosynthetic processes to save ATP (Hardie, 2004). LKB1 is phosphorylated at Ser431 by ERK1/2, PKA, and RSK (Sapkota *et al.*, 2001). BDNF- or cAMP-induced axonal differentiation is mediated by LKB1-STRAD α interaction, and it is induced LKB1's phosphorylation at Ser431, a PKA site (Shelly *et al.*, 2007). LKB1 also associates with BRG1 (brahma-related gene 1), another tumor suppressor on the same chromosome 19 (Marignani *et al.*, 2001). Germline mutation on LKB1 causes the Peutz-Jeghers syndrome, a hamartomatous syndrome similar to PTEN and TSC mutations (Hemminki *et al.*, 1998). LKB1 null embryos are lethal and heterozygous knockout mice developed intestinal polyps identical to the human specimens (Bardeesy *et al.*, 2002).

STRAD α

STRAD α (STE20-related adaptor protein α) is a

pseudo kinase that binds to either MO25 α or ATP to stabilize the interaction with LKB1, and it localizes LKB1 to the cytoplasm (Boudeau *et al.*, 2003; Zehiraj *et al.*, 2009) (Figure 3F). This complex regulates AMPK which then control TSC2 and mTOR (Hardie, 2005). Mutation in STRAD α was recently found to cause PMSE, an epileptic disease (Puffenberger *et al.*, 2007).

Rag

Rag (Ras-related GTPase) is required for mTORC1 activation by nutrients level, is independent from PI3K/AKT/TSC/Rheb axis (Shaw, 2008). RagA and RagB are closely related to each other, and it is the same with RagC and RagD (Sekiguchi *et al.*, 2001). RagA or RagB forms a stable heterodimer with RagC or RagD, and these heterodimers interact with RAPTOR directly in an amino-acid dependent fashion (Kim *et al.*, 2008a; Sancak *et al.*, 2008). Only when RagA/B is bound to GTP and RagC/D is bound to GDP, these heterodimers increases its affinity to RAPTOR. Rag-bound mTORC1 then relocalizes to Rab9-containing perinucleolar membrane structure where Rheb resides, thus activates mTORC1 activity (Sancak *et al.*, 2008). However, Rag proteins do not sense the amino acid itself, and Vam6/Vps39 is suggested to be a GEF for RagA or Rag B (Price *et al.*, 2000; Binda *et al.*, 2009). How Vam6/Vps39 activity is controlled in response to the level of amino acids remains to be examined.

hVPS34

hVPS34 (human vacuolar protein sorting 34) is class III PI3K which senses the availability of amino acids (Nobukuni *et al.*, 2005). It forms a complex with Vps15, recruiting either MTM1 or Rab5/7 for the endocytic sorting, or Beclin-1 and UVRAG (UV irradiation resistance-associated gene) for autophagy during nutrient deprivation (Backer, 2008). When a branched amino acid such as leucine increases intracellular concentration of calcium, calcium/calmodulin complex binds to hVps34, activating mTORC1/S6K1 (Gulati *et al.*, 2008). MAP4K3 has been also identified as a kinase that senses and mediates amino acids signals to TOR in *Drosophila* (Findlay *et al.*, 2007). It remains to be seen how MAP4K3 and hVPS34 are differentially sense and transduce amino acid signals in mammalian brains.

REDD1

REDD1 (regulated in development and DNA damage

responses 1, also called DDIT4 (DNA-damage-inducible transcript 4) or RTP801) is a negative regulator of the mTOR signaling by modulating TSC2 activity (Brugarolas *et al.*, 2004). REDD1 is activated in stress condition (e.g., hypoxia) and competes with TSC2 on binding to 14-3-3, thus inhibiting mTORC1 activity (DeYoung *et al.*, 2008). Expression of REDD1 is ubiquitous and regulated by stress proteins, p53 and HIF1 (Ellisen *et al.*, 2002; Jin *et al.*, 2007). The mTORC1 signaling is rapidly modulated due to the fast degradation of REDD1 (Kimball *et al.*, 2008). When REDD1 is phosphorylated by GSK3 β , β -TRCP recruits ubiquitin ligase complex DDB1-CUL4A-ROC1 to REDD1 for its degradation and mTORC1 activity restoration (Katiyar *et al.*, 2009). REDD1 null mice are viable (Sofer *et al.*, 2005).

GSK3 β

GSK3 β (glycogen synthase kinase 3 β) is a ubiquitous multifunctional Ser/Thr kinase which is involved in cell division, proliferation, differentiation and adhesion in addition to regulating glycogen synthase activity (Jope and Johnson, 2004) (Figure 3G). Phosphorylation of Tyr216 is essential for its basal activity, in contrast, phosphorylation at Ser9 inactivates it (Liang and Chuang, 2007). Both PI3K/AKT and mTORC1/S6K1 activation phosphorylates GSK3 β at Ser9, thus stimulating glycogen synthesis (Cross *et al.*, 1995; Zhang *et al.*, 2006; van Diepen *et al.*, 2009). Among many substrates of GSK3 β PTEN, TSC1, TSC2, and REDD1 are on the mTOR pathway (Mak *et al.*, 2005; Inoki *et al.*, 2006; Katiyar *et al.*, 2009; van Diepen *et al.*, 2009). It also phosphorylates to stabilize c-Myc (Lutterbach and Hann, 1994). GSK3 β has been shown to be involved NMDA-dependent LTP and LTD in the hippocampus (Peineau *et al.*, 2008). Epilepsy-related lafora disease is caused by defective mutation in laforin which dephosphorylates GSK3 at Ser9, thus inhibits glycogen synthase (Lohi *et al.*, 2005). GSK3 β null embryos die at E14, and heterozygotes were healthy and fertile (Hoeflich *et al.*, 2000). 6-bromindirubin-3'-oxime has been used as a specific inhibitor of GSK3 (Sato *et al.*, 2004).

DISC1

DISC1 (Disrupted-in-schizophrenia 1) is a susceptibility gene for schizophrenia and other mental disorders, and it is involved in neurogenesis (Brandon *et al.*, 2009). It regulates adult neurogenesis by modulating the mTOR pathway via a protein KIAA1212 (Kim *et al.*, 2009). It also regulates glutamatergic dendritic spines via Karlin-7 and

Rac1 interaction (Hayashi-Takagi *et al.*, 2010). DISC1 expression has been shown to be decreased in dentate granule cell layer in kindling model of epilepsy, and downregulation of DISC1 leads to the abnormal neuronal morphology, hyperexcitability, and impaired adult neurogenesis (Duan *et al.*, 2007; Fournier *et al.*, 2010). Conditional knock-in mice with the forebrain-restricted expression of mutant DISC1 associated with schizophrenia show that spontaneous hyperactivity and impaired spatial memory (Pletnikov *et al.*, 2008).

ERK1/2

ERK1/2 (ERK1 = p44 mitogen-activated protein kinase (MAPK); ERK2 = p42 MAPK1) are Ser/Thr kinases of Ras/MAPK signaling pathway particularly involved in neuronal and synaptic plasticity (Roux and Blenis, 2004; Thomas and Huganir, 2004) (Figure 3H). ERK activation increases dendritic protein synthesis at CA1 pyramidal neurons when high frequency stimulation given via PI3K/PDK1/AKT/mTOR pathway (Tsokas *et al.*, 2007). ERK phosphorylates and inhibits TSC2 at Ser 664 and LKB1 at Ser431, possibly by RSK activation, and IRS-1 at Ser612 (Sapkota *et al.*, 2001; Andreozzi *et al.*, 2004; Ma *et al.*, 2005). ERK1/2 also phosphorylate RAPTOR at Ser8, Ser696, and Ser863 and c-myc at Ser63 (Seth *et al.*, 1992; Carrière *et al.*, 2011). Increased activation of ERK has been reported in pilocarpine- or kainate- induced SE and during chronic seizures (Kim *et al.*, 1994; Garrido *et al.*, 1998; Houser *et al.*, 2008). Constitutive ERK activation has been shown to induce spontaneous seizures in mice (Nateri *et al.*, 2007). In traumatic brain injury model ERK has been shown to be activated in hippocampal mossy fiber, possibly mediating mossy fiber reorganization (Hu *et al.*, 2004). Phosphorylation of Kv4.2 by activated ERK decreases the surface expression of the channel and dendritic A current in SE (Lugo *et al.*, 2008). Erk1 null mice showed that ERK1 may be involved in regulating neuronal excitability in hippocampal CA1 area under certain stimulation patterns (Selcher *et al.*, 2003). Erk2 conditional knockout mice have impaired proliferation of neuronal progenitors, fewer neurons and more astrocytes, and deficits in associative learning (Samuels *et al.*, 2008). FR180204 is a specific inhibitor against ERK (Ohuri *et al.*, 2005).

RSK1

RSK1 (RPS6K1 ribosomal protein S6 kinase, 90kDa, polypeptide 1) is a Ser/Thr kinase downstream of Ras/Raf/MEK/ERK signaling pathway

that regulates diverse cellular processes such as cell growth, motility, survival and proliferation (Anjum and Blenis, 2008). Four isoforms are ubiquitously expressed and they are localized both in the cytoplasm and nucleus. RSK is phosphorylated at Thr573 by ERK1/2 and at Ser227 by PDK1 (Smith *et al.*, 1999; Frödin *et al.*, 2000). It phosphorylates LKB1 at Ser431, RAPTOR at Ser719, Ser721 and Ser722, and TSC2 at Ser939, Ser1462 and Ser1798, regulating mTORC1 activity (Sapkota *et al.*, 2001; Roux *et al.*, 2004; Carrière *et al.*, 2008a). RSK also phosphorylates ribosomal protein S6 at Ser235/236, eEF2K (elongation factor 2 kinase) at Ser366 and eIF4B at Ser422 (Wang *et al.*, 2001; Shahbazian *et al.*, 2006; Roux *et al.*, 2007). Rsk2 null mice show mild impairment of learning and long-term memory deficits, mimicking Coffin-Lowry syndrome associated with RSK2 mutations (Poirier *et al.*, 2007). SL0101, Fmk, and BI-D1870 are specific inhibitors against RSK (Anjum and Blenis, 2008).

PP2A

PP2A (Protein Phosphatase 2A) is a major Ser/Thr phosphatase in mammalian cells that regulates the phosphorylation status of proteins involved in various cellular processes (Westermarck and Hahn, 2008). It is composed of a catalytic subunit (PP2A_C), a regulatory subunit (PP2A_A), and one of many associate proteins (PP2A_B), generating more than 70 combinations. The mTORC1 activation induces phosphorylation of ERK1/2 at Thr202, inhibiting its activity via PP2A (Harwood *et al.*, 2008). This is a cross-talk-between Ras/MAPK and mTOR signaling pathways. PP2A directly dephosphorylates and activates 4E-BP1 at Thr45 and Ser64, thus inhibiting protein synthesis (Guan *et al.*, 2007). It also dephosphorylates c-Myc at Ser62, promoting its ubiquitination-mediated proteosomal degradation (Arnold and Sears, 2006). A pro-apoptotic molecule, BAD is dephosphorylated at Ser112 by PP2A (Hui *et al.*, 2005). Activation of group I mGluR signaling through PP2A to dephosphorylate the fragile X mental retardation protein (FMRP), facilitating protein synthesis, however, the later signals through mTOR inhibit PP2A activity (Narayanan *et al.*, 2007). PP2A α knockout mice is embryonic lethal (Götz and Schild, 2003). Okadaic acid and calyculin A inhibit PP2A (Garcia *et al.*, 2002).

PLC

PLC (Phospholipase C) hydrolyzes phosphatidyl-

inositol-4, 5-bisphosphate (PIP₂) to produce inositol triphosphate (IP₃) and diacylglycerol (DAG) which activate downstream signaling cascade including IP₃ receptors and PKC, respectively (Rhee, 2001). Among many isoforms, PLC β 3 has been shown to be upregulated by IGF-1 via PI3K and S6K, and PLC γ 1-mediated activation of mTOR/S6K pathway (Schnabel *et al.*, 2000; Markova *et al.*, 2010). PLC β 1 null mice showed epilepsy, and age-dependent hippocampal mossy fiber sprouting (Kim *et al.*, 1997; Böhm *et al.*, 2002). PLC β 1 is coupled to muscarinic receptors, and activation of muscarinic receptors induces mTOR-dependent phosphorylation of ribosomal protein S6 (Popova and Rasenick, 2000; Slack and Blusztajn, 2008). Pilocarpine elicits SE through muscarinic receptors and mGluR5/PLC β 1 (el-Etri *et al.*, 1993; Liu *et al.*, 2008b).

PLD

PLD (Phospholipase D) hydrolyzes phosphatidylcholine to generate phosphatidic acid, which can activate the mTOR pathway (Fang *et al.*, 2001; Klein, 2005). PLD1 is activated by Rheb and Cdc42-S6K1 interaction (Fang *et al.*, 2003; Sun *et al.*, 2008). PLD2 has a TOS-like motif and forms a complex with mTOR/RAPTOR (Ha *et al.*, 2006). Elevated PLD activity suppressed binding of PP2A with S6K and 4E-BP1 (Hui *et al.*, 2005). PLD level is increased in reactive astrocytes in kainate model, and interestingly, PLD1 and PLD2 showed differential patterns of gene expression in the hippocampus (Kim *et al.*, 2004). They may be differently involved in epilepsy.

CDC42

CDC42 (cell division cycle 42) is a Rho family GTPase that regulates cytoskeleton organization, and membrane trafficking (Sinha and Yang, 2008). It binds to activate S6K, and it also activates PLD, producing PA which activates mTOR (Chou and Blenis, 1996; Fang *et al.*, 2003). The expression of CDC42 in the hippocampus is increased in kainate model, and its downstream target N-WASP, important in regulating actin cytoskeleton, is also increased in the postmortem brains of human epilepsy patients (Carlier *et al.*, 1999; Xiao *et al.*, 2008; Sharma *et al.*, 2009). Cdc42 null mice are embryonic lethal and CDC42 is essential for PIP₂-induced actin reorganization (Chen *et al.*, 2000). Secramine B inhibits CDC42 (Pelish *et al.*, 2006).

Downstream signaling molecules

S6K1/2

S6K1/2 (p70 ribosomal protein S6 kinase 1/2) is a positive regulator of protein translation initiation and one of mTORC1 substrates (Burnett *et al.*, 1998; Park *et al.*, 2002). Ribosomal protein S6, a well-known target of S6K1/2, is a component of the small ribosomal subunit, although the functional significance of phosphorylation of S6 remains to be elucidated in more detail (Ruvinsky *et al.*, 2005). Thr389 of S6K1 is phosphorylated by mTORC1, and Thr229 by PDK1 (Kim *et al.*, 2002; Saitoh *et al.*, 2002). Thr421 and Ser424 are phosphorylated by ERK and Ser411 by CDC2-cyclinB or CDC5-p35 kinase (Papst *et al.*, 1998; Page *et al.*, 2006; Hou *et al.*, 2007). PA binds to activate S6K1 *in vitro* (Lehman *et al.*, 2007). S6K1 phosphorylates mTOR on Thr2446 and Thr2448, SKAR on Ser383 and Ser385, eIF4B at Ser422, and eEF2K at Ser366 (Wang *et al.*, 2001; Richardson *et al.*, 2004; Holz and Blenis, 2005; Shahbazian *et al.*, 2006). S6K phosphorylates CBP80, a subunit of nuclear RNA cap-binding complex to activate CDC42-mediated pre-mRNA splicing process, and UBF, a transcription factor, to regulate ribosomal gene transcription (Wilson *et al.*, 2000; Hannan *et al.*, 2003). It phosphorylates PDCD4, an eIF4A inhibitor, at Ser67 and subsequently recruits β TRCP, an E3 ubiquitin ligase, to be ubiquitinated and degraded (Dorrello *et al.*, 2006). S6K phosphorylates BAD, a pro-apoptotic molecule, at Ser136, and CREM, a cAMP responsible activator at Ser117, a PKA site (de Groot *et al.*, 1994; Harada *et al.*, 2001). The negative feedback inhibition of PI3K via IRS-1 phosphorylation by S6K1 is very significant in the mTOR pathway (Tremblay *et al.*, 2007; Zhang *et al.*, 2008). Activated S6K1 by mTORC1 activation phosphorylates IRS-1 at multiple sites (Rui *et al.*, 2001). S6K1 null mice showed upregulation of AMPK and similar pattern of gene expression with the effect of caloric restriction on life-span (Aguilar *et al.*, 2007; Selman *et al.*, 2009). S6K2 null mice are slightly larger than wild-type controls in contrast to significantly smaller S6K1 null mice (Pende *et al.*, 2004). mGluR-dependent LTD is normal in S6K1 null mice, but it is enhanced in S6K2 null and S6K1/2 double knockout mice (Antion *et al.*, 2008). Ro31-6045 specifically inhibits S6K (Marmy-Conus *et al.*, 2002).

4E-BPs

4E-BPs (eukaryotic initiation factor 4 (eIF4) binding proteins, also known as PHAS-I) are negative regulators of protein translation initiation and one

of mTORC1 substrates (Burnett *et al.*, 1998). 4E-BP1 binds to eIF-4E (a 7-methyl-guanosine mRNA cap-binding protein) to inhibit the formation of eIF-4F via blocking eIF-4E's binding to eIF-4G, a translational scaffolding protein (Ma and Blenis, 2009). Among four phosphorylation sites of 4E-BP1 (Thr36, Thr45, Ser64, and Thr69), Thr36 and Thr45 are preferred by mTORC1 activation (Burnett *et al.*, 1998; Mothe-Staney, 2000). This phosphorylation causes 4E-BP1 to dissociate from eIF4E, which cascades binding eIF4G, eIF3, and eIF4A to initiate translation (Ma and Blenis, 2009). 4E-BP1 can be also phosphorylated by PIM-2, PKC δ , and c-Abl (Kumar *et al.*, 2000; Fox *et al.*, 2003). There are three 4E-BP isoforms, and 4E-BP2 is the major one in the brain whereas expression of 4E-BP1 is low, and that of 4E-BP3 is absent in the brain (Tsukiyama-Kohara *et al.*, 2001). 4E-BP2 null mice showed impaired spatial learning and memory, and altered behavior on several other tests (Banko *et al.*, 2005, 2007).

STAT3

STAT3 (Signal Transducers and Activators of Transcription 3) transduces activation signals from the receptor binding of IL-6, IL-10 and other cytokines families to regulate the expression of genes involved in many different cellular processes (Levy and Lee, 2002). STAT3 is phosphorylated at Ser727 by mTORC1 (Yokogami *et al.*, 2000). Serine phosphorylation of STAT3 regulates mitochondrial energy production by interacting with GRIM-19 and possibly gene transcription (Reich, 2009). STAT3 is also phosphorylated at Tyr705 by Janus kinases (Reich, 2009). In kainate-injected rats, STAT3 is activated in reactive astrocytes in the hippocampus (Choi *et al.*, 2003). Homozygous Stat3 null embryos die at E7 (Takeda *et al.*, 1997).

C-Myc

The c-Myc is a transcription factor that controls the expression of genes involved in cell cycle progression, proliferation, and differentiation where its activity is highly context-dependent (Wierstra and Alves, 2008). The c-Myc inhibits anti-apoptotic molecules, Bcl2 and Bcl-XL and it activates pro-apoptotic molecules, Bak, Bax, Bad and Bim (Hoffman and Liebermann, 2008). The c-Myc represses TSC2 expression and it also controls expression of IRS-1, TSC1, G β L, and S6 (Ravitz *et al.*, 2007). The c-Myc is stabilized by phosphorylation at Thr58 by GSK3 and at Ser63 by ERK, and it is destabilized by dephosphorylation at Ser62 by PP2A (Seth *et al.*, 1992; Lutterbach and Hann,

1994; Arnold and Sears, 2006). The c-Myc is also phosphorylated at Thr62 and Ser329 by PIM-1 (Zhang *et al.*, 2008). c-myc null embryos die at E10.5 and heterozygous c-myc female mice have reduced fertility (Davis *et al.*, 1993).

CLIP-170

CLIP-170 (CAP-GLY domain containing linker protein 1) is phosphorylated by mTOR and its phosphorylation positively regulates its microtubule-binding properties (Choi *et al.*, 2002). Downregulation of CLIP-170 rescued the abnormal microtubule arrangement in *Tsc2*^{-/-} cells (Jiang and Yeung, 2006).

ULK1/mATG13/FIP200

ULK1/mATG13/FIP200 (unc-51-like kinase 1 = ATG1/ mammalian autophagy related protein 13/focal adhesion kinase interacting protein of 200 KD) complex is essential for autophagy initiation (Mizushima, 2010). ULK1 and mATG13 bind to RAPTOR and they are phosphorylated by mTORC1, inhibiting autophagy process under nutrient-rich condition (Ganley *et al.*, 2009; Hosokawa *et al.*, 2009; Jung *et al.*, 2009). ULK1 has a kinase activity and phosphorylates mATG13 and FIP200 (Ganley *et al.*, 2009; Jung *et al.*, 2009). In *C. elegans*, Unc51 has been shown to be involved in axonal elongation (Tomoda *et al.*, 2004).

SGK1

SGK1 (Serum- and glucocorticoid-induced kinase 1) regulates diverse effects of extracellular agonist by phosphorylating regulatory proteins that control cellular process such as ion transport and growth (Lang *et al.*, 2006). Changes in cell volume such as dehydration increased SGK1 expression in the hippocampal CA3 neurons, and SGK1 increased Kv1.3 activity (Wärntges *et al.*, 2002). Ser422 of SGK1 is phosphorylated by mTORC2, and Thr256 by PDK1 (Biondi *et al.*, 2001; García-Martínez and Alessi, 2008). SGK1 phosphorylates NDRG1 (N-myc downstream regulated gene 1) at Thr346, Thr356, and Thr366 and FOXO3a at Thr32 and Ser315 (Brunet *et al.* 2001; Murray *et al.*, 2004). SGK1 null mice showed impaired renal function and increased expression of FOXO3a (Wulff *et al.*, 2002; Nasir *et al.*, 2009).

PKCs

PKCs (Protein kinase Cs) are Ser/Thr protein kinases widely expressed in mammalian cells

(Parekh *et al.*, 2000). Among several isoforms, PKC α , PKC δ , PKC ϵ , PKC η and PKC ζ are shown to interact with the mTOR pathway (Parekh *et al.*, 1999; Aeder *et al.*, 2004; Guan *et al.*, 2007; Leseux *et al.*, 2008). PKC α is phosphorylated at Ser638 and Ser657 by mTORC2 (Ikenoue *et al.*, 2008). PKC α interacts with mTOR directly that EGFR activation signal can be transduced to activate protein translation (Kumar *et al.*, 2000; Fan *et al.*, 2009). It also hypophosphorylates 4E-BP1 by increasing PP2A activity, which results in the inhibition of protein translation in PI3K/AKT/mTOR-independent manner (Guan *et al.*, 2007). PKC ϵ is required for ET-1-stimulated phosphorylation of S6K1 at Thr389, Thr421 and Ser424, and mTOR at Ser 2448 (Moschella *et al.*, 2007). PKC δ are required for ET-1- and insulin-stimulated phosphorylation of mTOR at Ser2448 and S6K1 at Thr389 (Moschella *et al.*, 2007). PKC ζ phosphorylates PKC δ , and this process is rapamycin sensitive, and it also activates mTOR via MAPK activation (Ziegler *et al.*, 1999; Leseux *et al.*, 2008). Downregulation of PKC δ is regulated by PKC ϵ and mTORC2 (Basu *et al.*, 2009). Phosphorylation of PKC δ at Ser662 and PKC ϵ at Ser729 is rapamycin-sensitive (Parekh *et al.*, 1999). PKC η phosphorylates and activates AKT and mTORC1 in glioblastoma (Aeder *et al.*, 2004). Several inhibitors against PKC isoforms are available (Mackay and Twelves, 2007).

FOXO proteins

FOXO proteins (Forkhead box O) are transcription factors that regulate diverse processes (Nakae *et al.*, 2008). FOXO1, FOXO3a, and FOXO4 are phosphorylated and inhibited at Thr32 and Ser253 by AKT and FOXO3a at Thr32 and Ser315 by SGK1 (Brunet *et al.*, 2001; Allard *et al.*, 2008). Phosphorylation at Thr32 and Ser316 of FOXO1 recruits 14-3-3 for the nuclear export (Brunet *et al.*, 2002). Phosphorylation of FOXOs by ERK induces ubiquitination-mediated proteosomal degradation with MDM2 interaction (Fu *et al.*, 2009). FOXO1 interacts with and regulates negatively TSC2 through mTOR/S6K signaling pathway (Cao *et al.*, 2006). Other FOXO-binding proteins are described in detail elsewhere (van der Vos and Coffey, 2008). Under nutrients/insulin limited condition, FOXOs inhibits AKT by inhibiting TRB3 and they also turns on gene expression of insulin receptor, insulin receptor substrate 2 (IRS-2), and 4E-BP1 (Puig *et al.*, 2003; Ide *et al.*, 2004; Naïmi *et al.*, 2007). FOXO1 null mice are embryonic lethal, however, FOXO3a and FOXO4 knockout mice are viable (Castrillon *et al.*, 2003).

mTOR on transcription

Although most of the study of mTOR regulation is focused on translational regulation and post-translational modification (phosphorylation), the mTOR pathway also interacts with nuclear receptors, transcription factors, and splicing factors at the transcriptional level. In addition, mTOR regulates the pre-rRNA processing, expression of ribosomal proteins, the synthesis of 5S rRNA and transcription at large by all three classes of RNA polymerases (Mayer and Grummt, 2006). Some of these molecules interacting with the mTOR pathway are implicated in epilepsy. Transcriptional activation of rRNA genes by RNA polymerase I depends on IGF, PI3K, mTOR and S6K by increased binding of SL1, an essential RNA polymerase I transcription factor, to corresponding promoters (James and Zomerdijk, 2004). PTEN suppresses RNA polymerase I-mediated transcription by disrupting SL1 binding to its promoter (Zhang *et al.*, 2005a). It also suppresses RNA polymerase III-mediated transcription of tRNAs and 5S rRNAs by disrupting TFIIIB binding with TATA-binding protein and BRF1 (Woiwode *et al.*, 2008). PTEN-induced decrease in serine phosphorylation and consequent destabilization of BRF1 may be mediated by AKT (Benjamin *et al.*, 2006).

Estrogen receptor α

Estrogen receptor α (ER α) are nuclear receptors for estrogen (E). E-ER binding changes its conformation, allowing transport to nucleus. This complex binds either to the estrogen response element or to other proteins so that it regulates gene expression as homo- or hetero-dimers (Matthews and Gustafsson, 2003). This is a classical estrogen's genomic effect which has a delayed onset (several minutes to hours) and long-lasting effect. Estrogen's proliferative effect is mediated by ERs, therefore, antagonists against ERs are used for breast cancer treatment. One prognostic biomarker of resistance to anti-estrogen therapy is phosphorylation at Ser167 of ER α , and it is mediated by mTOR/S6K and MAPK/RSK (Yamnik and Holz, 2010). ER α s are expressed in cytoplasm and nucleus of neurons and glia (Mhyre and Dorsa, 2006). Their expression in CA1 and CA3 pyramidal neurons is decreased in kainate-induced acute seizure. In contrast, it appears in the gliotic reactive astrocytes in CA1 (Sakuma *et al.*, 2009). In female animals, estrogen is neuroprotective against SE-induced neuronal damage in the hippocampus (Reibel *et al.*, 2000). However, estrogen's effect on male animals is controversial. Estradiol increases

seizure susceptibility but decreases seizure severity by facilitating neuropeptide Y release from inhibitory presynaptic boutons during kainate-induced seizures (Ledoux *et al.*, 2009).

Androgen receptors

Androgen receptors (ARs) are ligand-dependent transcription factors which regulate gene expression by its binding to androgen-responsive promoter elements (Mellinghoff *et al.*, 2004). Protein levels of ARs are rapamycin-sensitive (Cinar *et al.*, 2005). Testosterone is known as neuroprotective, and its metabolites, androgens (As) such as dihydrotestosterone can potentiate GABA_A receptors directly, exerting neuroprotective function (Reddy, 2003). Although there is no direct evidence that ARs are involved in epilepsy, there are some indirect reports worth pursuing the possibility. In man with temporal lobe epilepsy major metabolites of testosterone (e.g., 5 α -androstan-3 α -ol-17-one; 5 α 3 α -A) level is reduced, and A-ARs binding activates ERK1/RSK signaling pathway and neuroprotection (Nguyen *et al.*, 2005). When phenytoin, an AED, is given to animals, testosterone level is decreased, testosterone metabolizing enzymes cytochrome P450 are upregulated. Testosterone metabolites such as 17 β -oestradiol are increased, and AR expression is increased in CA1 pyramidal neurons (Meyer *et al.*, 2006). In an epilepsy mouse model, 5 α 3 α -A showed anticonvulsant properties (Kaminski *et al.*, 2005).

SREBP1

SREBP1 (Sterol responsive element binding protein 1; SREBF1) are transcription factors which recognize the sterol responsive element containing promoters that regulate gene expression of lipid and cholesterol biosynthesis (Laplante and Sabatini, 2009; Porstmann *et al.*, 2009). Mammals have three SREBPs: SREBP1a, SREBP1c, and SREBP2. SREBP1c is activated by insulin and involved in fatty acid synthesis (Foufelle and Ferre, 2002). SREBP2 is activated in response to cellular sterol status, and it controls cholesterol and fatty acid biosynthesis (Schmidt *et al.*, 2006). DNA microarray data showed that stearoyl-CoA desaturase 1, a SREBP1a target gene, is upregulated in human cortical specimen of temporal lobe epilepsy (Arion *et al.*, 2006). In kainate model, protein and mRNA levels of SREBP2 are reduced in pyramidal neurons of hippocampal CA1 and CA3 area (Kim and Ong, 2009). mTORC1 activates SREBP1 to upregulate lipid biosynthesis likely by phosphorylation (Porstmann *et al.*, 2008). GSK3 β phosphorylates

SREBP1 at Ser434, Ser430 and Thr426 sequentially and this phosphorylation cascade recruits a tumor suppressor FBW7 which ubiquitinates mTOR to be degraded proteosomally (Mao *et al.*, 2008; Bengoechea-Alonso and Ericsson, 2009). SREBP-1c is negatively regulated by AMPK directly (Zhou *et al.*, 2001).

Lipin-1

Lipin-1 plays a role in lipid biosynthesis by acting as a phosphatidate phosphatase (PAP) in the microsome and cytoplasm as well as an inducible transcriptional coactivator with PPAR γ coactivator-1 α (PGC1 α) and PPAR α in the nucleus (Reue and Zhang, 2008). Lipin-1 is shuttled from cytoplasm to nucleus by sumoylation and Lipin-1 α is the dominant form in the neurons (Liu and Gerace, 2009). Lipin's PAP activity makes DAG from phosphatidate. Ser106 is the major phosphorylation site by insulin stimulation (Harris *et al.*, 2007). Rapamycin reduces the phosphorylation of lipin-1 by mTORC1 (Huffman *et al.*, 2002). Kainate injection increases the amount of DAG in the brain, which could be an enzymatic product of lipin-1 (Cole-Edwards and Bazan, 2005). The reverse reaction enzyme, DAG kinase ϵ regulates seizure-susceptibility, and DAG kinase ϵ null mice show reduced LTP in perforant path-dentate granule cell synapses (Rodriguez de Turco *et al.*, 2001).

SF2/ASF

SF2/ASF (Splicing Factor, Arginine/Serine-rich Factor) is involved in alternative splicing, non-sense-mediated mRNA decay, mRNA export, and translation (Long and Caceres, 2009). It activates mTORC1 and regulates translation initiation by enhancing phosphorylation of 4E-BP1 (Karni *et al.*, 2008; Michlewski *et al.*, 2008). SF2/ASF null embryos die early during development (Xu *et al.*, 2005).

SKAR

SKAR (S6K1 Aly/REF-like target) is a nuclear protein that links pre-mRNA splicing to the enhanced translation efficiency of spliced mRNA mediated by mTOR/S6K1. It is a specific substrate of S6K1 and is phosphorylated at Ser383 and Ser385 (Richardson *et al.*, 2004; Ma *et al.*, 2008a).

Traumatic brain injury, medial temporal lobe epilepsy and mTOR pathway

Traumatic brain injury (TBI) is one of the main

causes of medial temporal lobe epilepsy (Lowenstein, 2009). Recently, in fluid-percussion brain injury model, 4E-BP1, S6K, and S6 were phosphorylated by activated mTOR, and eIF4E was phosphorylated by Mnk1 (MAPK-interacting kinase 1) in parietal cortex and hippocampus (Chen *et al.*, 2007). TBI was also shown to induce autophagy by increased expression of LC3-II (microtubule-associated protein light chain 3) and widely redistributed the autophagy-related gene products, ATG12-ATG5 conjugates (Liu *et al.*, 2008a). Rapamycin injection 4 hours after TBI reduced phosphorylation of S6K and reduced activation of microglia/macrophages (Erlich *et al.*, 2007). It remains to be seen that TBI-initiated epilepsy has activated signaling molecules of mTOR pathway.

Viral infection in epilepsy and mTOR pathway

One of the causes of acquired epilepsy and a major cause of febrile seizure could be viral infection of central nervous system and its complications such as high fever and consequential neuronal damages (Eeg-Olofsson, 2003; Getts *et al.*, 2008). Viral encephalitis increases risk of developing seizures and epilepsy even after treatment of infection completed, and its epileptogenic mechanism - both acute and chronic - remains to be solved (Misra *et al.*, 2008). For example, human herpesvirus 6 (HHV6) infection has been associated with febrile seizure and mesial temporal lobe epilepsy (Fotheringham *et al.*, 2007). Its viral antigen is localized to GFAP-positive glia in the hippocampus (Laina *et al.*, 2010). Influenza A virus infection can also cause febrile seizure (Chiu *et al.*, 2001).

Recently, several viral proteins have been shown to interact with the mTOR pathways (Buchkovick *et al.*, 2008). A) Herpes simplex virus type 1 (HSV-1) infection is the most frequently associated with epilepsy (Gannicliffe *et al.*, 1985; Hsieh *et al.*, 2007; Misra *et al.*, 2008). HSV-1 infection reduces depolarizing membrane potential, thus making neurons hyperexcitable (Chen *et al.*, 2004). HSV-1 protein ICP0 directly activates phosphorylation of 4E-BP1, inducing protein synthesis (Walsh and Mohr, 2004). HSV-2 has ICP10 protein which activates PI3K/AKT/mTOR pathway (Smith, 2005). B) Adenovirus infection has been associated with febrile seizure (Chung and Wong, 2007). An adenoviral protein E4-ORF1 directly binds to activate PI3K, and E4-ORF4 does PP2A, inhibiting dephosphorylation of mTORC1 (O'Shea *et al.*, 2005). C) Human immunodeficiency virus (HIV)-

positive patients show HIV-associated encephalitis and seizure/epilepsy in some cases (Nardacci *et al.*, 2005; Kellinghaus *et al.*, 2008). In this condition, overexpression and activation of mTOR, and HIV gp120 interaction with mTOR has been reported. This mTOR activation phosphorylates p53 at Ser15, and upregulates and translocates Bax into mitochondria (Castedo *et al.*, 2001; Nardacci *et al.*, 2005). D) Epilepsy has been also reported in congenital cytomegalovirus infection cases (Dunin-Wasowicz *et al.*, 2007; Suzuki *et al.*, 2008). Two immediate-early proteins (72KDa IE1 and 86KDa IE2) of human cytomegalovirus (HCMV) can activate AKT by phosphorylating at Thr308 and Ser473 (Yu and Alwine, 2002). HCMV infection also modulates AMPK activity, thus affecting protein synthesis (Kudchodkar *et al.*, 2007). Under this condition, mTORC2 becomes rapamycin-sensitive and is able to phosphorylate 4E-BP1 and S6K, thus altering mTOR substrate specificities (Kudchodkar *et al.*, 2004, 2006). Another HCMV protein pUL38 inhibits host cells' apoptosis by interacting with TSC1/TSC2 (Moorman *et al.*, 2008). E) Enterovirus infection has been reported in febrile seizure patients and enterovirus-induced autophagy decreases phosphorylated mTOR and phosphorylated S6Ks (Hosoya *et al.*, 1997; Huang *et al.*, 2009b). It is yet to be shown whether, when viral infection is likely the cause of epilepsy, abnormal activation of the signaling molecules of mTOR pathway occurs.

Brain tumors, mTOR pathway and epilepsy

Large number of the patients with dysembryoblastic neuroepithelial tumors, ganglioglioma, low-grade astrocytoma, meningioma, or glioblastoma multiforme has epileptic seizures (van Breemen *et al.*, 2007). Although the molecular mechanism of comorbidity of brain tumors and epilepsy remains to be elucidated, there is enough evidence that abnormal activities of the mTOR pathway prevail in several types of brain tumors. A) Gangliogliomas have been shown that the mTOR pathway (from PDK1 to S6) is activated in patients' specimen (Boer *et al.*, 2010). Reelin has been involved in ganglioglioma as well as granule cell dispersion in temporal lobe epilepsy and cortical dysplasia (Haas *et al.*, 2002; Kam, 2004; Crino, 2009). Reelin binds to VLDL Receptor/ApoER2, and its activation signal is transduced to Dab1 and PI3K/AKT/mTOR (Hiesberger *et al.*, 1999; Kam *et al.*, 2004; Jossin and Goffinet, 2007). Decrease of Reelin expression in subsets of interneurons in the dentate gyrus was reported in human specimen

and kainate- and pilocarpine-induced epilepsy models, and Dab1 expression is increased in hilar-ectopic neuroblasts (Heinrich *et al.*, 2006; Gong *et al.*, 2007). Increased methylation in the promoter of reelin was also shown in human temporal lobe epilepsy (Kobow *et al.*, 2009). It will be interesting to see whether interneuron-specific knockout of reelin show the seizure behavior. B) In meningioma, expression of fibroblast growth factor (FGF) and one of its receptors, FGFR-3 are significant (Takahashi, *et al.*, 1990; Johnson *et al.*, 2010). FGFR3 activation transduces signal through PI3K-AKT-mTORC1-STAT3 route as well as AKT-RAF1-MEK1-MAPK (Johnson *et al.*, 2009; 2010). In addition, most sporadic meningiomas have somatic mutations of NF2/Merlin, a negative regulator of mTORC1 (James *et al.*, 2009). NF2/Merlin is a membrane cytoskeleton anchor, and its inactivating mutation causes constitutively activation of mTORC1 signaling, resulting in neurofibromatosis 2 and epilepsy-associated meningioma (Scoles, 2008; López-Lago *et al.*, 2009). Interacting with CD44, a hyaluronan receptor on the plasma membrane, Merlin negatively regulates the mTOR pathway via PIKE/PI3K/AKT (Morrison *et al.*, 2001; James *et al.*, 2009). AKT directly phosphorylates Merlin at Thr230 and Ser315, increasing its binding to CD44 (Tang *et al.*, 2007; Okada *et al.*, 2009). The expression of CD44 is increased in the dentate gyrus 3 days after pilocarpine-induced SE, lasting up to 4 weeks (Borges *et al.*, 2004). It remains to be seen how Merlin's activity is changed in epilepsy. NF2 null mice die around at E7, and heterozygous NF2 knockout mice show highly invasive and metastatic tumors (McClatchey *et al.*, 1997, 1998). C) Glioblastoma multiforme, the most aggressive primary brain cancer, is PI3K-AKT dependent (Knobbe and Reifenberger, 2003). Although rapamycin doesn't work well with patients of this type, it is yet to be studied that it is effective in other brain tumors related to mTOR pathway (Galanis *et al.*, 2005; Albert *et al.*, 2009).

Brain inflammation in epilepsy and mTOR pathway

Reactive gliosis is apparent in the epileptogenic tissues, and The level of inflammatory cytokines such as IL- β , TNF- α , and IL-6 in the area of seizure generation is increased both in clinical specimen and animal models of epilepsy (Vezzani and Granata, 2005; Binder and Steinhäuser, 2006). Although direct evidence of cytokine-mediated mTOR activation in epilepsy is still lacking, the mTOR pathway has been shown to be involved in

cytokine-dependent microglial activation (Dello Russo *et al.*, 2009). Activation of the mTOR pathway inhibits the pro-inflammatory cytokines such as TNF- α , and IL-6, and it promotes the release of anti-inflammatory cytokine (IL-10) via NF κ B and STAT3 (Weichhart *et al.*, 2008). The mTORC1 activation regulates the activity of NF κ B which is associated with IKK (Dan *et al.*, 2008). IKK β (Inhibitor of NF- κ B Kinase β) phosphorylates and inactivates TSC1, thus activating the mTOR pathway (Lee *et al.*, 2007). The expression of NF- κ B is increased in human specimen of temporal lobe epilepsy and kainate model (Lerner-Natoli *et al.*, 2000; Crespel *et al.*, 2002). PA, an essential regulator of inflammatory response, activates the mTOR pathway (Lim *et al.*, 2003; Foster, 2009).

Cell death in Epilepsy and mTOR pathway

Epileptogenic insults cause cell deaths which have been classically categorized as apoptosis, necrosis, and autophagy (Edinger and Thompson, 2004; Henshall and Murphy, 2008). However, they are inter-connected and regulated by each other, and their boundaries become overlapped such as in programmed necrosis or necroptosis (Repici *et al.*, 2007; Eisenberg-Lerner *et al.*, 2009; Christofferson and Yuan, 2010). mTOR pathway has been shown to be involved in apoptosis and autophagy. In kainate-induced epilepsy model, both apoptotic and necrotic cell deaths were observed (van Lookeren *et al.*, 1995; Humphrey *et al.*, 2002).

Apoptosis

Apoptosis (also called 'programmed cell death') is the cell's intrinsic suicide process. Apoptosis shows nuclear condensation and fragmentation, and chromosomal DNA cleavage, and it has apoptotic bodies without inflammation. It requires caspase activation either by death-related receptor activation or pro-apoptotic molecules released from mitochondria (Levine *et al.*, 2008). In the sera of children and adolescents with idiopathic epilepsy, a pro-apoptotic molecule, Fas and an anti-apoptotic molecule, Bcl-2 were elevated (El-Hodhod *et al.*, 2006). In temporal lobe epilepsy patients, the levels of tumor necrosis factor receptor 1 (TNFR1), TNFR-associated protein with death domain (TRADD), Fas-associated protein with death domain (FADD), cleaved caspase8, and apoptosis signal-regulating kinase 1 (ASK1) are higher than controls (Yamamoto *et al.*, 2006). ASK1 is activated by rapamycin treatment via reducing PP5 activity and

it interacts with FIP200, an autophagic molecules regulated by mTOR (Huang *et al.*, 2004; Gan *et al.*, 2006). TNF α is increased after kainate injection in rodents and its expression has been shown to be regulated by mTORC2 in melanoma B16 cells (de Bock *et al.*, 1996; Wang *et al.*, 2007). TSC2 inhibits the phosphorylation of a pro-apoptotic molecule, BAD on Ser136, and this phosphorylation facilitates BAD/BCL-2 and BAD/BCL-X_L interactions which lead to apoptosis (Freilinger *et al.*, 2006). S6K and PIM-1 also phosphorylates BAD (Harada *et al.*, 2001; Aho *et al.*, 2004). PDCD4 (Programmed cell death 4) is phosphorylated on Ser67 and Ser457 by both AKT and S6K1 for nuclear translocation and/or proteosomal degradation (Palamarchuk *et al.*, 2005; Dorrello *et al.*, 2006).

Necrosis

Necrosis is generally conceived as passive form of cell death, resulting from ATP depletion, toxic insults, or physical damage. It is characterized by cytoplasmic vacuolation, breakdown of the plasma membrane, and inflammation surrounding the dying cells. In a kainate model of epilepsy, cytoplasmic shrinkage and nuclear condensation consistent with necrosis are far more significant than apoptosis in the entorhinal cortex (Puig and Ferrer, 2002). In a pilocarpine model, necrotic cell deaths were prominent in hippocampus and other brain regions (Fujikawa *et al.*, 2002). Pilocarpine-induced SE in P14 rat shows activation of caspase-3 and necroptosis (Niquet *et al.*, 2007). RIP3 is a necroptosis-specific marker which forms a complex with RIP1, triggering production of reactive oxygen species (Cho *et al.*, 2009). It remains to be seen how RIP1 and RIP3 interact with each other in epilepsy, and whether a specific inhibitor, necrostatin-1 prevents epilepsy-induced cell death (Dgeterev *et al.*, 2005).

Autophagy

Autophagy is a catabolic process that cells use autophagosomal/lysosomal machineries to degrade own cytoplasmic components (Ravikumar *et al.*, 2009). It is triggered by starvation (ATP exhaust), oxidative stress, and glutamate. The mTOR is a negative regulator of autophagy, and rapamycin can induce autophagy (Rubinsztein *et al.*, 2007). The mTOR interacts with ULK1-mATG13-FIP200 complex, one of autophagic pathways (Jung *et al.*, 2009). By mTOR-mediated phosphorylation of ULK1 and mATG13, ULK's kinase activity regulates mATG13, FIP200 and ULK itself. FIP200 null mice are embryonic lethal (Gan *et al.*, 2006). Kainate

treatment induces phosphorylation and activation of mTOR and AKT (Shacka *et al.*, 2007). The amount of LC3-II, a specific marker of autophagosomes, is increased by kainate or pilocarpine injection (Shacka *et al.*, 2007; Cao *et al.*, 2009). Therefore, it remains to be seen if mTOR-mediated autophagy is induced via ULK1-mATG13-FIP200 in kainate or pilocarpine-induced epileptic models or patients' specimen.

Ectopic neurogenesis and mTOR pathway

Severity of spontaneous seizures is associated with the increased number of ectopic adult neurogenesis of granule cells in the hilus as well as the normal adult neurogenesis in the dentate gyrus (Parent, 2007). DISC1 regulates adult neurogenesis in mTOR-dependent manner and it inhibits AKT activity via DISC1-KIAA1212 binding (Porteous, 2008; Kim *et al.*, 2009). DISC1 has been also shown to have decreased level in kindling model (Fournier *et al.*, 2010). The mTOR is activated both in insulin-activated neuronal differentiation of neural progenitor cells and in EGF/FGF2-mediated maintenance of neural stem cells (Han *et al.*, 2008; Sato *et al.*, 2010). It will be exciting to see how the mTOR pathway contributes to neurogenesis after epileptic insults in detail.

Synaptic plasticity and mTOR pathway

The mTOR pathway has been shown to be involved in both (short-term) activity-dependent local protein synthesis and (long-term) synaptic plasticity (Hoeffler and Klann, 2010). Induction and maintenance of NMDA receptor-mediated LTP in hippocampal CA1 neurons has been shown to be rapamycin-sensitive (Vickers *et al.*, 2005). Brief glutamate stimulation in primary cultured neurons activates PI3K/AKT, ERK1/2, and mTOR/S6K in NMDAR- and CaMKII-dependent manner, although sustained stimulation inhibits ERK, AKT and S6K (Lenz and Avruch, 2005). AMPA receptors-mediated synaptic transmission is not mTOR-dependent, but mGluR- or BDNF-mediated neosynthesis of AMPA receptor subunit (GluR1 and GluR2) is (Mameli *et al.*, 2007; Slipczuk *et al.*, 2009). Metabotropic glutamate receptor (mGluR)-mediated synaptic plasticity via the mTOR pathway has been relatively well studied (Mameli *et al.*, 2007; Hou and Klann, 2004). Homer 1a couples mGluR1 to PI3K/mTOR pathway via PIKE interaction in mGluR-dependent synaptic plasticity (Rong *et al.*, 2003). Homer 1b/c couples mGluR5 to activate S6K via ERK signaling

cascade independent of the mTOR pathway (Mao *et al.*, 2005). Pilocarpine-induced SE decreased protein levels of mGluR5 and Homer, losing mGluR-dependent LTD (Kirschstein *et al.*, 2007). Homer1a mRNA expression is drastically increased in acute phase of kindling- and pilocarpine-models (Potschka *et al.*, 2002; Avedissian *et al.*, 2007). Forskolin, an adenylate cyclase activator, activates PKA and subsequently ERK, and/or activates BDNF/TrkB signaling, thus enhancing mTOR-dependent mRNA translation in hippocampal slice culture (Gobert *et al.*, 2008). ERK activation increases dendritic protein synthesis at CA1 pyramidal neurons via PI3K/PDK1/AKT/mTOR pathway when high frequency stimulation given (Tsokas *et al.*, 2007). D1/D5 dopamine receptor-mediated memory consolidation in auditory cortex has been shown to be rapamycin-sensitive (Tischmeyer *et al.*, 2003; Schicknick *et al.*, 2008). Protein Kinase M ζ , an autonomous brain-specific atypical PKC isoforms which is important in LTP maintenance in hippocampus, must be phosphorylated by PDK1 (Kelly *et al.*, 2007).

Endocannabinoid receptors, epilepsy and mTOR pathway

Endocannabinoid CB1 receptors are localized at glutamatergic terminal in the hippocampus and its activation controls neuronal excitability by the increase of GABA release (Monory *et al.*, 2006). Cannabinoids display anticonvulsive properties and specific CB1 receptor agonists such as marijuana extract Δ^9 -THCV (tetrahydrocannabinol) or ACEA (arachidonyl-2-chloroethylamide) are being developed as AEDs (Wallace *et al.*, 2003; Ma *et al.*, 2008b; Kozan *et al.*, 2009). Hippocampal long-term memory is transiently modulated by CB1 receptor activation via mTOR/p70S6K signaling pathway (Puighermanal *et al.* 2009). In this report, this modulation was mediated by CB1Rs expressed on GABAergic interneurons - presumably basket cells - through a NMDA receptor-mediated mechanism. Short-term pilocarpine-injected rats showed increased levels of CB1 receptors and 2-arachidonylglycerol, an endogenous CB1 ligand, in the hippocampus (Wallace *et al.*, 2003). However, long-term effect of SE showed the decreases in CB1 receptors in the pyramidal cell layer neurophil and the inner molecular layer of dentate gyrus, and increases in CA1-3 *stratum oriens* and *stratum radiatum* (Falenski *et al.*, 2007). In febrile seizure model, it has been shown that an increase in number of presynaptic CB1 receptors and long-term increase in CB1 receptor-mediated retrograde signaling at

GABAergic synapses (Chen *et al.*, 2003). In epileptic patients, hippocampus has reduced expression of CB1 receptors (Ludanyi *et al.*, 2008). Thus, CB1 receptor agonists likely become less effective as AEDs. Therefore, modulating downstream signaling molecule of mTOR pathway seems to be the better approach for the anti-epileptic treatment.

Astrocytes in epilepsy and mTOR pathway

Astrogliosis is a common phenomenon caused by epileptogenic insults such as head trauma, infection, excitotoxic injury (McGraw *et al.*, 2001; Ortinski *et al.*, 2010). Astrogliosis shows a decrease in glutamate and potassium uptake which can aggravate seizure activity (Tian *et al.*, 2005; Binder and Steinhäuser, 2006; Seifert *et al.*, 2010). Astrocyte-specific deletion of TSC2 mice showed astrogliosis and reduced uptake of potassium and glutamate by astrocyte, and the seizures (Uhlmann *et al.*, 2002; Wong *et al.*, 2003). STAT3 has been shown to be activated in reactive astrocytes in the hippocampus in kainate model (Choi *et al.*, 2003). The mTOR pathway is activated in reactive astrocytes in spinal cord injury (Codeluppi *et al.*, 2009). The levels of ER α in CA1 astrocytes and PLD were increased in KA model (Kim *et al.*, 2004; Sakuma *et al.*, 2009). ERK/MAPK is activated in mechanical trauma-induced astrogliosis and human reactive astrocytes (Mandell and VandenBerg, 1999; Mandell *et al.*, 2001). It remains to be seen whether mTOR pathway is activated specifically in astrocytes when epileptogenic insults given.

mTOR inhibitors as new anti-epileptic drugs

More than thirty FDA-approved AEDs are available, and more are in the process of development and approval to treat the epileptic patients, however at least a third of patients respond poorly or become refractory to the current AEDs, particularly people with TSC (Shorvon, 1996; Curatolo *et al.*, 2006; Bialer and White, 2010). Although mTOR inhibitors have not been tested for non-TSC patients with epilepsy, those may have the broader therapeutic effects in treating various types of epilepsy. Therefore, a new class of AEDs should be considered to be developed against the intracellular signaling molecules in the mTOR pathway (Wong, 2010).

Rapamycin (also known as sirolimus) is first developed as antifungal agent but widely used now as immunosuppressant and anticancer agents (Law, 2005). It was originally discovered from

Streptomyces hygroscopicus in a soil sample collected from Easter Island (Vézina *et al.*, 1975). It has structural resemblance with a macrolide antibiotic FK506 (Chang *et al.*, 1991). It does not directly inhibit the mTOR kinase activity *per se* but it binds to FKBP12 and disrupts mTOR-RAPTOR interaction (Vignot *et al.*, 2005). By this disruption, rapamycin fails to phosphorylate S6K1 and 4E-BP1, thus inhibits protein translation. Rapamycin itself does not seem to have any immediate effect on electrophysiological (voltage-gated sodium and potassium currents) properties of neurons *in vitro* (Rüegg *et al.*, 2007). However, rapamycin has been shown to modulate the protein level of some voltage-gated potassium channels (Raab-Graham *et al.*, 2006; Tyan *et al.*, 2010).

It is noteworthy that rapamycin inhibits axonal sprouting in pilocarpine model only when it was continuously infused, and this abnormal sprouting reoccurs when its administration was terminated (Buckmaster *et al.*, 2009). It might be related to the fact that animals become refractory to the drug or drug's effect subsidizes, and also that prolonged rapamycin treatment inhibits mTORC2 assembly and AKT/PKB (Sarbasov *et al.*, 2006). Therefore, we may need to develop the better strategy of drug administration and/or the new drug candidates against other targets on the mTOR pathway.

There are three types of drug have been developing against mTOR complexes:

Rapalogue

Due to the poor water solubility, high toxicity, and resistance development with rapamycin, rapamycin analogs are being developed to overcome these problems: for example, CCI-779 (Temsirolimus), RAD001 (Everolimus), and AP23573 (deforolimus and MK-8669) (Plas and Thomas, 2009). For the preclinical trial of rapalogues against tumor regression of TSC patients, rapamycin was given to the mice model of TSC to examine the tumor regression (Lee *et al.*, 2009c). Although side effects are tolerable, responses are incomplete, and tumor regrowth is common when rapamycin is stopped. In a small clinical trial, RAD001 reduced seizure frequency in TSC patients with an intractable epilepsy (Krueger *et al.*, 2010).

PI3K/mTOR dual inhibitors

Both PI3K and mTOR belongs to the broad phosphatidylinositol kinase family (Kong and Yamori, 2008). Specific inhibitors against mTORC1 and PI3K are extensively under development to circumvent the drug resistance and to treat inherited

hematoma syndromes which show the hyperactivity of both protein kinases (Krymskaya and Goncharova, 2009; Liu *et al.*, 2009). NVP-BEZ235, PI-103, BGT226, XL765, and SF1126 are PI3K/mTOR dual inhibitors (Knight *et al.*, 2006; Brachmann *et al.*, 2009).

Inhibitors against catalytic site of mTOR

These inhibitors are designed to block the catalytic active site of mTOR. Therefore, they could block both mTORC1 and mTORC2 (Feldman *et al.*, 2009; Thoreen *et al.*, 2009). Torin1 is a highly potent and selective ATP-competitive mTOR inhibitor that directly inhibits both complexes (Thoreen *et al.*, 2009). In acute leukemia model, PP242 delays the disease onset but has less effect on the normal lymphocytes' function than rapamycin (Janes *et al.*, 2010). PP30, AZD8055 and OSI-027 are other inhibitors of this kind (Maira *et al.*, 2008; Yap *et al.*, 2008; Brachmann *et al.*, 2009).

Ketogenic diet, anti-epileptic food supplements, and mTOR pathway

Ketogenic diet, a high fat and low carbohydrate diet, has been used especially for children since 1920s, and it has been often effective reducing seizure frequency, but its mechanism of action is poorly understood (Vamecq *et al.*, 2005; Keene, 2006). Although recent small pilot study with TSC patients on tumor growth didn't show any effect of ketogenic diet, ketogenic diet has been shown to attenuate kainate-induced cell death in the hippocampus through AMPK, which activates the mTOR pathway (Jeon *et al.*, 2009; Chu-Shore and Thiele, 2010) (Figure 2). Insulin level has been shown to be reduced on ketogenic diet (Thio *et al.*, 2006). In kainate model, ketogenic diet reduces mossy fiber sprouting and shows fewer and briefer seizures (Muller-Schwarze *et al.*, 1999).

Curcumin, a polyphenol natural product from the plant *Curcuma longa*, is in early clinical trial as a potential anti-cancer agent against various types of cancer (Strimpakos and Sharma, 2008). It inhibits cancerous proliferation by disrupting mTOR-RAPTOR complex (Beevers *et al.*, 2009) (Figure 2). It will be very interesting if curcumin inhibits seizure by inhibiting mTOR kinases (Kang *et al.*, 2006; Marcu *et al.*, 2006). It also induces neurogenesis in the hippocampus which is also hampered in medial temporal lobe epilepsy (Hattiangady *et al.*, 2004; Kim *et al.*, 2008b).

Omega-3, a long-chain polyunsaturated fatty acids found in fish oil, has been shown to reduce seizure

frequency in patients, and reduce neuronal excitability and promotes neuroprotection in animal models (Schlanger *et al.*, 2002; DeGiorgio *et al.*, 2008; Scorza *et al.*, 2008). Recently, omega-3 has been shown to regulate protein metabolism via the mTOR pathway in bovine muscle (Gingras *et al.*, 2007). It will be interesting to see whether omega-3 supplementation will modulate the mTOR pathway in the brain to have the anti-epileptic activity.

Resveratrol (*trans*-3',4',5'-trihydroxystibene) is natural polyphenolic substance present in grapes and red wine or isolated from the root of several plants such as *Polygonum cuspidatum*. It has antioxidant, anti-inflammatory, and anti-cancer properties (Frémont, 2000; Kimura and Okuda, 2001). It suppressed kainate- and NMDA-receptor-mediated synaptic transmission in CA1 pyramidal neurons and inhibited the K channels (Gao and Hu, 2005; Gao *et al.*, 2006). Thus, it can inhibit abnormal kainate-evoked currents at the mossy fiber synapses in epilepsy (Epsztein *et al.*, 2005). As predicted, it has been shown to decrease the seizure frequency, inhibited epileptiform discharges, protected neuronal cell death in the hippocampus, and depressed mossy fiber sprouting in the kainate model (Wu *et al.*, 2009). Resveratrol inhibits mTORC1 activity by promoting mTOR/DEPTOR and by activating LKB1/AMPK or SIRT1-TSC1/2 and inhibiting PI3K (Dasgupta and Milbrandt, 2007; Frojdo *et al.*, 2007; Ghosh *et al.*, 2010; Liu *et al.*, 2010). It will be interesting to see how resveratrol specifically modulates the downstream signaling molecules of mTOR pathway to have the anti-epileptic activity.

Epilepsy-comorbid diseases and mTOR pathway

Among several neurological and neuropsychiatric diseases that are comorbid with epilepsy, autism spectrum disorder and Alzheimer's disease are associated to the abnormal activity of the mTOR pathway.

Autism spectrum disorders

Autism spectrum disorders (ASD) covers heterogeneous population which show the three typical characteristics; poor social interaction, delayed language development, and stereotypical repetitive behavior (Geschwind, 2009). About 0.6 % of general population is affected in ASD, up to 40% of ASD individuals show epileptic symptoms (Canitano, 2007). Although genes susceptible to ASD remain largely unknown, some genes (such as TSC1/

TSC2 or PTEN when mutated) primarily responsible for ASD are on the mTOR pathway (Bill and Geschwind, 2009). Therefore, it is likely that this common pathway is, at least in part, involved in this developmental disorder. Interestingly, another ASD-related gene product, fragile X mental retardation protein (FMRP) negatively regulates mTOR/S6K1-dependent protein synthesis in neurons as an RNA binding protein, and it inhibits PIKE, then PI3K and mTOR activities (Narayanan *et al.*, 2008; Sharma *et al.*, 2010). It remains to be seen whether modulators of the mTOR pathway improve ASD individuals with epilepsy.

Alzheimer's disease

Alzheimer's disease (AD) has been reported with higher incidence of epileptic seizures than general population (Amatniek *et al.*, 2006). In mouse model overexpressing mutant form of human amyloid precursor protein, high level of amyloid- β peptide, axonal sprouting of dentate granule cells, epileptiform activities in the hippocampus, and behavioral seizures were observed (Palop *et al.*, 2007). In AD patients' specimen and animal models, mTOR, S6K, 4E-BP1 and eEF2K were shown to be activated, and hyperphosphorylation of tau, a pathological biomarker found in neurofibrillary tangles, is mediated by S6K and GSK3 (An *et al.*, 2003; Li *et al.*, 2005; Meske *et al.*, 2008; Pei and Hugon, 2008). It remains to be seen whether mTOR-related therapeutic approach on Alzheimer's disease will reduce the seizure frequency of this subpopulation.

Challenges

One may become convinced of the involvement of the mTOR pathway in epilepsy from this review, however, there are enormous amount of evidences that need to be accumulated. To have a clear insight of intracellular signaling mechanism in epilepsy, the signaling molecules need to be examined to see whether they are activated or suppressed in the relevant types of cells in affected brain region, not just changes in the level of certain proteins described previously. It will be very exciting to figure out distinct patterns of protein-protein interactions in particular cell types at critical points during epileptogenesis. Different types of epilepsy may have different patterns of signaling footprint, and other conditions that people with epilepsy have may show unique signatures. It may

also be different at different time points during the brain development or after the incident of epileptogenic insults. In addition, the number of proteins interacts with individual molecules in the mTOR pathway is still growing, and their specific interaction(s) may exclude or recruit other proteins to transduce the unique signals. There are mammalian homologs of components of mTOR complex yet to be identified, such as AVO2 and BIT61, two components of yeast TORC2 complex as well as Tco89, Bit61, Toc1, Tel2, Tti1 and Cka1 in mTOR pathway. Furthermore, we can not simply ignore the possibility of involvement of certain genes in the epilepsy based on the expression pattern in normal condition. It is because epileptogenic mechanism could initiate the expression of certain genes, unique post-translational modifications, or new pattern of protein-protein interaction. It will be fascinating to see if (and how) the mTOR pathways are connected to ion channels that are epileptogenic, and also whether other non-ion channel proteins that are genetically linked to epilepsy (e.g. LGI1, ME2, EFHC1 and BRD2) are implicated in the mTOR pathway (Lucarini *et al.*, 2007).

Summary

It should be noted that the full scope of signaling events in epilepsy is unknown. Neuronal insult-driven epileptogenic process leading toward chronic spontaneous seizures have multiple aspects including cell death, cell survival and proliferation to recovery, abnormal neuronal differentiation, consequent changes in neuronal network activity. Therefore, there are numerous possibilities of distinct signaling mechanisms could be involved. In this review, I tried to link epileptic causatives to the abnormal activities of signaling molecules in the mTOR pathway. I also briefly summarized the most of individual signaling molecules of the mTOR pathway. It will be exciting to watch (or study) how extensively the mTOR pathways are involved in all different types of epilepsy in years to come.

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