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SHEDDING NEW LIGHT ON NEURODEGENERATIVE DISEASES THROUGH THE MAMMALIAN TARGET OF RAPAMYCIN

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Abstract

Neurodegenerative disorders affect a significant portion of the world's population leading to either disability or death for almost 30 million individuals worldwide. One novel therapeutic target that may offer promise for multiple disease entities that involve Alzheimer's disease, Parkinson's disease, epilepsy, trauma, stroke, and tumors of the nervous system is the mammalian target of rapamycin (mTOR). mTOR signaling is dependent upon the mTORC1 and mTORC2 complexes that are composed of mTOR and several regulatory proteins including the tuberous sclerosis complex (TSC1, hamartin/ TSC2, tuberin). Through a number of integrated cell signaling pathways that involve those of mTORC1 and mTORC2 as well as more novel signaling tied to cytokines, Wnt, and forkhead, mTOR can foster stem cellular proliferation, tissue repair and longevity, and synaptic growth by modulating mechanisms that foster both apoptosis and autophagy. Yet, mTOR through its proliferative capacity may sometimes be detrimental to central nervous system recovery and even promote tumorigenesis. Further knowledge of mTOR and the critical pathways governed by this serine/threonine protein kinase can bring new light for neurodegeneration and other related diseases that currently require new and robust treatments.

Keywords

apoptosis; autophagy; mTOR; neurodegeneration; rapamycin; stem cells

1. Introduction

As a serine/threonine protein kinase, mammalian target of rapamycin (mTOR) oversees a number of cellular pathways that involve transcription, cytoskeletal organization, cell maturation, cell proliferation, and survival. The activity of mTOR is modulated through phosphorylation of its specific residues in response to the alteration of nutritional status, growth factors, mitogens, and hormones (Floyd *et al.*, 2007; Good *et al.*, 2008; Recchia *et al.*, 2009) and has been implicated in a variety of diseases (Benjamin *et al.*, 2011; Chong *et*

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Conflicts
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al., 2010b; Hwang and Kim, 2011; Vigneron *et al.*, 2011; Zoncu *et al.*, 2011). mTOR was initially isolated in *Saccharomyces cerevisiae* through the analysis of rapamycin toxicity using rapamycin-resistant TOR mutants in yeast that resulted in the identification of the genes *TOR1* and *TOR2* (Heitman *et al.*, 1991). The gene *TOR* is present as a single gene in higher organisms (Weber and Gutmann, 2012).

The mTOR protein is the catalytic component of two mTOR complexes termed mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2) (Loewith *et al.*, 2002), each of which contains mTOR and several regulatory proteins. mTORC1 and mTORC2 have different sensitivities to rapamycin. Rapamycin (sirolimus) is metabolite that was isolated from the bacterial strain Streptomyces hygroscopicus found in a soil sample from Rapa Nui Island (Easter Island) in the South Pacific (Sehgal *et al.*, 1975; Vezina *et al.*, 1975). The metabolite can specifically inhibit the activity of mTOR was found to have the macrocyclic lactone and identified as macrolide antibiotic, which then was designated as rapamycin in honor of the original point of discovery. mTORC1 is more sensitive and is acutely inhibited by rapamycin treatment, while mTORC2 is relatively resistant to rapamycin and prolonged treatment is required for rapamycin to inhibit mTORC2 (Sarbassov *et al.*, 2006). Rapamycin inhibits mTORC1 by binding to immunophilin FK-506-binding protein 12 (FKBP12) and thereby attaches to mTOR at the C-terminal to prevent mTOR activation (Chen *et al.*, 1995). Rapamycin inhibits mTORC2 *via* disrupting the assembly and the integrity of mTORC2 (Sarbassov *et al.*, 2006).

2. Molecular Domains and Cellular Expression of mTOR

2.1 Molecular Domains of mTOR

mTOR is a 289 kDa, multiple domain-protein that can undergo post-translational changes through phosphorylation and association with multiple proteins. The carboxy-terminal (C-terminal) kinase domain consists of a conserved sequence with homology to the catalytic domain of phosphoinositide 3 –kinase (PI 3-K) (Abraham, 2004) (Table 1). The C-terminal also contains a small regulatory domain for the phosphorylation sites of mTOR that involve serine^{2448} (Reynolds *et al.*, 2002), serine^{2481} (Peterson *et al.*, 2000), threonine^{2446}, serine^{2159}, and threonine^{2164} (Ekim *et al.*, 2011) which function to regulate mTOR activity. Serine^{2448} is an important target for protein kinase B (Akt) and the p70 ribosomal S6 kinase (p70S6K) (Chiang and Abraham, 2005; Reynolds *et al.*, 2002). An autocatalytic site of mTOR phosphorylation that is rapamycin insensitive is serine^{2481} (Soliman *et al.*, 2010). Threonine^{2446} is phosphorylated by AMP activated protein kinase (AMPK) and p70S6K (Holz and Blenis, 2005). Combined phosphorylation at serine^{2159} and threonine^{2164} increases mTOR activity by modulating the mTOR-Raptor and Raptor-PRAS40 interactions and promotes autophosphorylation of serine^{2481} (Ekim *et al.*, 2011). Other domains of the C-terminal are FKBP12 (FK506 binding protein 12)-rapamycin-binding domain (FRB) that is the docking site for FKBP12- rapamycin complex, FAT domain [FKBP associated protein (FRAP), ataxia-telengiectasia (ATM), transactivation/transformation domain-associated protein (TRRAP)], and FATC domain (FRAP, ATM, TRRAP, Carboxy terminal) (Takahashi *et al.*, 2000). The FAT domain is adjacent to the FKBP12-rapamycin binding domain (FRB) and promotes interaction between mTOR and FKBP12 protein when bound to rapamycin (Chen *et al.*, 1995).

The N-terminal of mTOR contains at least a 20 HEAT (Huntingtin, Elongation factor 3, A subunit of protein phosphatase-2A (PP2A), and TOR1) repeat (Table 1). This region provides the site of protein interaction between mTOR and Raptor or the rapamycin-insensitive companion of mTOR (Rictor) and has been associated with multimerization of mTOR (Takahara *et al.*, 2006). Serine^{1261} within the HEAT domain in mTORC1 and mTORC2 can be phosphorylated during insulin signaling through PI 3-K to lead to an

increase in the activity of mTOR. Serine^{1261} phosphorylation also is required for mTOR serine^{2481} autophosphorylation (Acosta-Jaquez *et al.*, 2009).

2.2 Cellular Expression of mTOR

Alterations in the exposure to growth factors, hormones, or mitogens (Carriere *et al.*, 2008; Mounier *et al.*, 2006; Shang *et al.*, 2012) as well as changes in cellular metabolism (Gwinn *et al.*, 2008) can influence the expression and activity of mTOR through its multiple domains. mTOR is ubiquitously expressed in most cells and tissues. mTOR transcript expression has been demonstrated in both differentiated and undifferentiated embryonic stem cells and in the cells of mouse brain, lung, heart, liver, testis, stomach, kidney, spleen, thymus, small intestine, muscle, and skin. The highest expression has been observed in the testis and kidney (Murakami *et al.*, 2004).

In the central nervous system (CNS), mTOR and its signaling components are present in brain endothelial cells (ECs) (Galan-Moya *et al.*, 2011; Land and Tee, 2007), neurons (Cota *et al.*, 2006; Li *et al.*, 2005b), inflammatory microglia (Chong *et al.*, 2007b; Dello Russo *et al.*, 2009; Shang *et al.*, 2011, 2012), and astrocytes (Codeluppi *et al.*, 2009; Pastor *et al.*, 2009). Under normal physiological conditions, cell expression of mTOR and its signaling pathways may be held at low levels of expression, such as in astrocytes and the dorsal root ganglion (Codeluppi *et al.*, 2009; Xu *et al.*, 2010). However, during periods of injury such as ischemia to the spinal cord, mTOR signaling can become highly active (Codeluppi *et al.*, 2009). Exposure to toxic β-amyloid (Aβ) can initially increase and subsequently decrease mTOR signaling that may ultimately determine cell survival. For example, inhibition of mTOR signaling with rapamycin may exacerbate amyloid toxicity (Lafay-Chebassier *et al.*, 2006), amyloid may block mTOR activity that can be protective (Chen *et al.*, 2009b; Lafay-Chebassier *et al.*, 2005), and in several scenarios mTOR activity is required for protection against Aβ toxicity (Lafay-Chebassier *et al.*, 2005; Ma *et al.*, 2010; Shang *et al.*, 2012). In addition, neurodegenerative cell injury during oxidative stress may be influenced by alterations in mTOR expression and activity (Malagelada *et al.*, 2006).

3. Cellular Signaling and Functional Targets of the mTOR Complexes

3.1 mTORC1

The main feature of mTORC1 is that mTOR Complex 1 (mTORC1) uses the rapamycin sensitive scaffolding protein of mTOR, Raptor, to allow mTORC1 to bind to its substrates (Kim *et al.*, 2002). Raptor is a 150 kDa mTOR binding protein, an essential component of the mTORC1, and functions to recruit the mTOR substrates the eukaryotic initiation factor 4E-binding protein 1 (4EBP1) and the serine/threonine kinase ribosomal protein p70S6K to the mTORC1 complex (Hara *et al.*, 2002; Kim *et al.*, 2002). The binding of Raptor to mTOR is necessary for the mTOR-catalyzed phosphorylation of 4EBP1 *in vitro* and raptor strongly enhances mTOR kinase activity toward p70S6K (Hara *et al.*, 2002). Phosphorylation of Raptor regulates the activity of mTORC1. Activation of the Ras- extracellular signal-regulated kinase (ERK) pathway leads to high Raptor phosphorylation on RXRXXpS/T consensus motifs. The ribosomal S6 kinase 1 (RSK1) and RSK2 are required for Raptor phosphorylation, since Raptor mutants lacking RSK-dependent phosphorylation sites markedly reduce mTOR phosphotransferase activity (Carriere *et al.*, 2008). Ras homologue enriched in brain (Rheb) over-expression also increases phosphorylation on Raptor residue serine^{863} as well as on five other identified residues that include serine^{859}, serine^{855}, serine^{877}, serine^{696}, and threonine^{706}. In addition, Raptor leads to mTORC1 activity through serine^{863} phosphorylation, since the site-directed mutation of Raptor on serine^{863} reduces mTORC1 activity (Wang *et al.*, 2009). mTOR, once activated, also controls Raptor activity and phosphorylates Raptor that can be stimulated by insulin and inhibited by rapamycin.

Raptor also can be phosphorylated through protein p90 ribosomal S6 kinase (RSK). RSK can phosphorylate three evolutionarily conserved Raptor serine residues including serin^{719}, serine^{721}, and serine^{722} to activate mTORC1 (Carriere *et al.*, 2008). Yet, mutation of Raptor at RSK-dependent phosphorylation sites dose not affect the interaction between mTOR and its substrates, suggesting that RSK induced Raptor phosphorylation modulates mTORC1 activity without altering the scaffolding function between mTOR and its substrates (Carriere *et al.*, 2008).

Raptor also can regulate mTORC1 activity through other signaling pathways. For example, IκB kinase (IKK) is a downstream target of Akt that regulates the transcriptional activity of nuclear factor-κB (NF-κB). Among three subunits of IKK, IKKα and IKKβ are the catalytic subunits that have serine/threonine kinase activity and IKKγ is a regulatory unit that is essential for IKK function (Maiese *et al.*, 2008c; Maiese *et al.*, 2008e). In resting cells, NF-κB is held captive by proteins of the IκB family and sequestered in the cytoplasm. Tumor necrosis factor-α (TNF-α) or oxidative stress stimulate the activation of the IKK complex, which phosphorylate IκB, ensuring that it is ubiquitinated by the addition of a ubiquitin group, degraded, leading to the release of the bound NF-κB. The liberated NF-κB can then translocate to the nucleus and activate its target genes (Maiese *et al.*, 2005; Teng and Tang, 2010). IKKα can regulate mTOR activity through its association with Raptor. IKKα expression can promote mTORC1 activation that is downstream from Akt (Dan *et al.*, 2007). Of note, IKKβ can physically interact with and phosphorylate TSC1 (hamartin) on serine^{487} and serine^{511}, resulting in the suppression of TSC1 and the subsequent activation of mTOR (Figure 1). The IKKβ-mediated TSC1 phosphorylation impairs the integrity of the tuberous sclerosis complex (TSC1, hamartin/ TSC2, tuberin) complex and activates the mTOR pathway (Lee *et al.*, 2007). Raptor also has been identified as a direct substrate of AMPK. AMPK phosphorylates Raptor at serine^{722} and serine^{792}. The phosphorylation of Raptor results in its dissociation from mTOR and switches the binding of Raptor to the cytoplasmic docking protein 14-3-3, leading to the inhibition of mTORC1 (Gwinn *et al.*, 2008). In addition, Ras small GTPase (Rag) proteins lead to mTORC1 activation through Raptor (Figure 2). Rag proteins are a family of four related guanosine phosphatases (GTPases) that have been linked to the regulation of mTORC1 signaling (Li *et al.*, 2010; Sancak *et al.*, 2010). The expression of a Rag mutant that is constitutively bound to GTP within cells results in the resistance of the mTORC1 pathway to amino acid deprivation. In addition, expression of a GDP-bound Rag mutant prevents amino acid activation of mTORC1 (Sancak *et al.*, 2008). In mammalian cells, RagA or RagB form heterodimers with either RagC or RagD that strongly bind to Raptor. The binding of Rag GTPases to Raptor is necessary and sufficient to mediate amino acid activation of mTORC1 (Sancak *et al.*, 2008).

The remaining components of mTORC1 include the proline rich Akt substrate 40 kDa (PRAS40), mammalian lethal with Sec13 protein 8 (mLST8), and DEP domain-containing mTOR interacting protein (Deptor) (Guertin *et al.*, 2006; Oshiro *et al.*, 2007; Peterson *et al.*, 2009). PRAS40, also termed Akt1s1, contains up to 15% proline residues, a consensus sequence (RXRXXS/T) for protein kinase B (Akt), and a consensus sequence (RXXpS/pT) for protein 14-3-3 binding (Kovacina *et al.*, 2003). PRAS40 inhibits mTORC1 activity by associating with Raptor (Wang *et al.*, 2012a; Wang *et al.*, 2007) and can competitively inhibit the binding of mTORC1 substrates p70S6K and 4EBP1 to Raptor (Sancak *et al.*, 2007; Wang *et al.*, 2007) (Figure 2). Over-expression of PRAS40 can reduce phosphorylation of p70S6K and 4EBP1. Depletion of PRAS40 through RNA interference enhances amino-acid induced phosphorylation of p70S6K and 4EBP1 (Oshiro *et al.*, 2007). In contrast, over-expression of p70S6K or 4EBP1 prevents phosphorylation of PRAS40 and leads to the inability of PRAS40 to bind to Raptor.

PRAS40 activity is regulated by phosphorylation on serine^{183}, serine^{212}, serine^{221}, and threonine^{246} (Oshiro *et al.*, 2007; Wang *et al.*, 2008). Akt phosphorylates threonine^{246} on PRAS40 and results in the dissociation of PRAS40 from mTORC1 (Sancak *et al.*, 2007). This ultimately leads to the binding of phosphorylated PRAS40 to protein 14-3-3 to inhibit PRAS40 and activate mTORC1 (Kovacina *et al.*, 2003; Vander Haar *et al.*, 2007). mTORC1 can phosphorylate PRAS40 at the serine residues. Phosphorylation of PRAS40 on threonine^{246} may be required for mTOR phosphorylation of serine^{183}, since inhibition of threonine^{246} phosphorylation diminishes insulin-induced phosphorylation of PRAS40 on serine^{183} by mTORC1 (Nascimento *et al.*, 2010). mTORC1 phosphorylation of PRAS40 on serine^{221} also leads to PRAS40 dissociation from mTORC1 and the binding to protein 14-3-3 (Nascimento *et al.*, 2010; Wang *et al.*, 2008). Phosphorylation of PRAS40 on serine^{221} and serine^{183}, but not serine^{212} is sensitive to rapamycin (Wang *et al.*, 2008).

Deptor negatively regulates the activity of mTORC1 and binds to the FAT domain of mTOR (Peterson *et al.*, 2009). Growth factors can lead to the activation of RSK1 and S6K1 kinases to phosphorylate Deptor that is subsequently ubiquinated and degraded by SCF (Skp, Cullin, F-box)-βTrCP E3 ligase. This process requires mTOR dependent phosphorylation of Deptor, in conjunction with casein kinase I, to generate a phosphodegron that binds protein βTrCP to control the degradation of Deptor (Duan *et al.*, 2011; Gao *et al.*, 2011). Without βTrCP, Deptor can accumulate and inactivate mTORC1 (Zhao *et al.*, 2011).

mLST8, also termed G protein β-subunit like protein (GβL), is a 36 kDa peripheral membrane protein that contains 7 repeats of tryptophan and aspartate residues (WD-40 repeats) and localizes to endosomal or Golgi membranes (Chen and Kaiser, 2003). mLST8 promotes the stabilization of the Raptor and mTOR association and is a necessary component for rapamycin to disrupt the interaction between Raptor and mTOR (Kim *et al.*, 2003). mLST8 can control insulin signaling through FoxO3 (Guertin *et al.*, 2006).

3.2 mTORC2

mTORC2 is different from mTORC1 since it contains the rapamycin insensitive protein Rictor instead of Raptor. mTORC2 shares several common components with mTORC1, such as mTOR, mLST8, and Deptor. Yet, mTORC2 also associates with mammalian stress-activated protein kinase interacting protein (mSIN1), protein observed with Rictor-1 (Protor-1), and proline rich protein 5 (PRR5) like protein (PRR5L). The primary functions of mTORC2 are to modulate cytoskeleton organization cytoskeleton organization (Jacinto *et al.*, 2004), endothelial cell survival and migration (Dada *et al.*, 2008), and cell cycle progression (Rosner *et al.*, 2009). mTORC2 may regulate the organization of actin cytoskeleton by phosphorylating and activating protein kinase C alpha (PKCα) (Sarbassov *et al.*, 2004) and Akt signaling involving Rho GTPase (Hernandez-Negrete *et al.*, 2007; Jacinto *et al.*, 2004; Sarbassov *et al.*, 2005). Rho signaling pathways through mTORC2 regulate cell-to-cell contact (Gulhati *et al.*, 2011). Expression of the constitutive active forms of the Rho GTPases promote organization of the actin skeleton and prevent the actin defect due to loss of mTORC2. P-Rex1 and P-Rex2 are also targets of mTORC2. P-Rex1 and P-Rex2 are linked to Rac activation and cell migration (Hernandez-Negrete *et al.*, 2007). In addition, serum- and glucocorticoid-induced protein kinase 1 (SGK1) appears to be another mTORC2 substrate. SGK1 is a member of the protein kinase A/protein kinase G/protein kinase C (AGC) family of protein kinases (Maiese *et al.*, 2010) and is activated by growth factors. mTORC2 can control the hydrophobic motif phosphorylation and activity of SGK1 leading to the activation of SGK1 that can control ion transport and cell growth (Garcia-Martinez and Alessi, 2008). mTORC2 also may regulate Rac activation and cell migration through activating Rac guanine exchange factors P-Rex1 (Hernandez-Negrete *et al.*, 2007).

Rictor is relatively insensitive to rapamycin and is essential for the assembly and the activity of mTORC2 to activate Akt (Masri *et al.*, 2007; Sarbassov *et al.*, 2005). The Rictor-mTORC2 complex phosphorylates Akt on serine^{473} and facilitates threonine^{308} phosphorylation by phosphoinositide-dependent kinase 1 (PDK1) (Hresko and Mueckler, 2005; Sarbassov *et al.*, 2005). Acetylation of Rictor also has been demonstrated to promote the activity of mTORC2. In addition to a stability region that is critical for interaction with mSIN1 and mLST8, Rictor also contains a region for acetylation (Glidden *et al.*, 2012). The transcriptional coactivator p300-mediated acetylation of Rictor increases mTORC2 activity toward Akt and inhibition of deacetylases promotes insulin-like growth factor (IGF) induced Akt phosphorylation. In contrast, site-directed mutants within the acetylation region of Rictor prevent IGF induced mTORC2 activation (Glidden *et al.*, 2012). In contrast, phosphorylation of Rictor negatively regulates mTORC2 activity. Serum, insulin and IGF can result in the phosphorylation of Rictor that can be blocked by rapamycin, mTOR knockdown, or expression of integrin-linked kinase (Akcakanat *et al.*, 2007; Boulbes *et al.*, 2010). Phosphorylation of Rictor on threonine^{1135} is dependent upon p70S6K that is downstream of mTORC1 signaling (Dibble *et al.*, 2009; Julien *et al.*, 2010). In relation to mLST8 and Rictor, mLST8 maintains the Rictor-mTORC2 interaction along with the phosphorylation of Akt and PKCα by Rictor (Guertin *et al.*, 2006).

Similar to its effect on mTORC1, Deptor also can negatively regulate the activity of mTORC2 (Peterson *et al.*, 2009). mTORC1 and mTORC2 can inhibit Deptor expression (Benjamin *et al.*, 2011; Chong *et al.*, 2010b; Hwang and Kim, 2011). Deletion of Deptor leads to the activation of mTORC1, mTORC2, and their downstream targets such as p70S6K, Akt, and SGK1. Deptor over-expression suppresses p70S6K, but activates Akt by relieving feedback inhibition from mTORC1 through the PI 3-K signaling pathway. In addition, in some forms of cancer, Deptor expression is necessary for Akt signaling (Peterson *et al.*, 2009).

mSIN1 is necessary for the assembly of mTORC2 and for the ability of mTORC2 to phosphorylate Akt (Frias *et al.*, 2006; Yang *et al.*, 2006). Genetic ablation of *msin1* abolishes Akt serine^{473} residue phosphorylation and disrupts the Rictor-mTOR interaction, suggesting that the mSIN1-Rictor-mTOR complex is necessary for Akt serine^{473} residue phosphorylation that is required for mTORC2 to support cell survival (Jacinto *et al.*, 2006). Rictor and mSIN1 have been shown to stabilize each other to form the structural basis of mTORC2 (Frias *et al.*, 2006). The residue of glycine^{934} in Rictor may play an important role for the interaction between Rictor and mSIN1 and for the maintenance of the mTORC2 integrity, since point mutation of glycine^{934} prevents the binding of Rictor to mSIN1 and the assembly of mTORC2 (Aimbetov *et al.*, 2011). Recently, mTOR has been shown to phosphorylate mSIN1 to prevent its lysosomal degradation, suggesting that mTOR kinase activity is required for mSIN1 stability (Chen and Sarbassov dos, 2011).

Protor-1 and PRR5L also play a role in modulating mTORC2 function. Protor-1 is a Rictor-binding subunit of mTORC2 that does not appear to alter other mTORC2 components to phosphorylate Akt or PKCα (Pearce *et al.*, 2007). Yet, Protor-1 may function to activate SGK1. In experimental models, loss of Protor-1 leads to a reduction in the hydrophobic motif phosphorylation of SGK1 and its substrate N-Myc downregulated gene 1 in the kidney (Pearce *et al.*, 2011). PRR5L interacts with Rictor and also acts downstream of mTORC2. PRR5L binds specifically to mTORC2 via Rictor and/or mSIN1. Yet, PRR5L does not appear to be necessary for the mTOR-Rictor interaction or for mTOR activity toward Akt phosphorylation (Thedieck *et al.*, 2007). PRR5L is pro-apoptotic and its knockdown prevents TNF-α/cycloheximide induced apoptosis (Thedieck *et al.*, 2007). In addition, PRR5L knockdown inhibits platelet-derived growth factor receptor beta induced Akt and

p70S6K phosphorylation and reduces cell proliferation rates, suggesting a role of PRR5L in cell growth and mTORC2 signaling pathways (Woo *et al.*, 2007).

3.3 4EBP1 and p70S6K

Two well-established downstream targets of mTORC1 are 4EBP1 and p70S6K (Figure 2). As previously noted, mTORC1 binds to Raptor to promote the mTOR-catalyzed phosphorylation of 4EBP1 that also increases the kinase activity of mTORC1 toward p70S6K (Hara *et al.*, 2002). Binding of 4EBP1 and p70S6K to Raptor can be prevented during activation of PRAS40. During periods of hypophosphorylation, 4EBP1 can block protein translation by binding to eukaryotic translation initiation factor 4 epsilon (eIF4E) through the eukaryotic translation initiation factor 4 gamma (eIF4G), a protein that transfers mRNA to the ribosome. mTORC1 phosphorylation of 4EBP1 leads to the dissociation of 4EBP1 from eIF4E to allow eIF4G to begin mRNA translation (Bhandari *et al.*, 2001; Gingras *et al.*, 1998). mTORC1 also promotes mRNA biogenesis, translation of ribosomal proteins, and cell growth through the phosphorylation of p70S6K (Fingar *et al.*, 2004; Jastrzebski *et al.*, 2007).

3.4 Tuberous sclerosis complex (TSC1, hamartin/ TSC2, tuberin)

Tuberous sclerosis complex (TSC1, hamartin/ TSC2, tuberin) is closely integrated in the regulation of mTORC1 and mTORC2 (Figure 1). The TSC1/TSC2 complex is a negative regulator of mTORC1 by controlling the activity of Ras homologue enriched in brain (Rheb). Rheb-GTP can directly interact with Raptor and activate mTORC1 complex. Rheb also regulates the binding of 4EBP1 to mTORC1 (Sato *et al.*, 2009). In addition, Rheb can regulate mTOR through FKBP38, a member of FKBP family that is structurally related to FKBP12. FKBP38 is an endogenous inhibitor of mTOR and reduces the activity of mTOR through association with mTORC1. Rheb interacts directly with FKBP38 and prevents its association with mTOR in a guanosine 5'-triphosphate (GTP)-dependent manner (Bai *et al.*, 2007). TSC2 functions as a GTPase-activating protein (GAP) to convert active Rheb-GTP to the inactive GDP-bound form (Rheb-GDP) resulting in the inhibition of mTORC1 (Inoki *et al.*, 2002).

TSC1/TSC2 activity is regulated by phosphorylation with the identification of several sites in TSC1 that include threonine^{417}, threonine^{1047}, and serine^{584} (Astrinidis *et al.*, 2003). However, phosphorylation of TSC2 by Akt, extracellular signal-regulated kinases (ERK), RSK1, AMPK, or glycogen synthase kinase -3β (GSK-3β) may be more important to block TSC1/TSC2 activity (Cai *et al.*, 2006; Inoki *et al.*, 2002; Ma *et al.*, 2005; Nellist *et al.*, 2005). Akt is a central mediator for cell growth and survival (Chong and Maiese, 2007; Faghiri and Bazan, 2010; Fokas *et al.*, 2012; Hou *et al.*, 2010a; Maiese *et al.*, 2009b), cellular metabolism (Chen *et al.*, 2012; Deblon *et al.*, 2012; Hou *et al.*, 2010a; Maiese *et al.*, 2007a; Saha *et al.*, 2010), mitochondrial signaling (Campos-Esparza *et al.*, 2009; Das *et al.*, 2011; Hou *et al.*, 2011; Li *et al.*, 2006a; Wang *et al.*, 2012d; Zeng *et al.*, 2011), and tumorigenesis (Chong *et al.*, 2005a; Chung *et al.*, 2012; Heublein *et al.*, 2010; Janku *et al.*, 2012; Zou *et al.*, 2012). Akt phosphorylates TSC2 on multiple sites resulting in the destabilization of TSC2 and disruption of its interaction with TSC1 (Inoki *et al.*, 2002; Potter *et al.*, 2002). The phosphorylation of TSC2 by Akt on the residues of serine^{939}, serine^{981}, and threonine^{1462} can result in the sequestration of TSC2 by the anchor protein 14-3-3. Once sequestered, TSC2 cannot suppress Rheb and this leads to the activation of Rheb and mTORC1 (Cai *et al.*, 2006). Loss of Akt phosphorylation of TSC2 also inhibits p70S6K activation (Manning *et al.*, 2002). In regards to ERK signaling, Ras-ERK has been associated with the activation of mTORC1. ERK is activated upon Ras induced activation of mitogen activated kinase/ERK kinase (MEK) and the phosphorylation of TSC. ERK-dependent phosphorylation on serine^{664} of TSC2 leads to the dissociation of TSC1-TSC2

and impairment of TSC2 to inhibit mTOR signaling (Ma *et al.*, 2005). ERK activated kinase, p90 RSK1, phosphorylates TSC2 on serine^{1798}, inhibits the function of the TSC1/TSC2 complex, and leads to an increase in activity of mTOR and p70S6K phosphorylation (Roux *et al.*, 2004).

Interestingly, phosphorylation of the TSC1/TSC2 complex may represent one of several mechanisms to control mTORC1. AMPK phosphorylates TSC2 on serine^{1387} (human) or serine^{1345} (rat) to foster GAP activity and turn Rheb-GTP into Rheb-GDP, thus inhibiting the activity of mTORC1 (Inoki *et al.*, 2003). During periods of impaired cellular energy production, AMPK serves as a sensor for cellular energy status and can be activated by increased levels of AMP or the AMP/ATP ratio (Kahn *et al.*, 2005). Low energy activates AMPK and subsequently blocks mTORC1 by phosphorylating TSC2 (Inoki *et al.*, 2003; Sofer *et al.*, 2005). AMPK also can modulate TSC1/2 activity through RTP801 (REDD1/ product of the *Ddit4* gene). During hypoxia, AMPK activity can promote REDD1 expression (Schneider *et al.*, 2008) that can suppress mTORC1 activity by releasing TSC2 from its inhibitory binding to protein 14-3-3 (DeYoung *et al.*, 2008). Disruption of REDD1 blocks the hypoxia-induced inhibition of mTOR (Brugarolas *et al.*, 2004). The tumor suppressor liver kinase B1 (LKB1) also can regulate the activation of AMPK and mTORC1. LKB1 is a serine/threonine kinase and a major kinase that phosphorylates AMPK under the conditions of cellular energy deficiency (Kahn *et al.*, 2005). LKB1 phosphorylates AMPK on the residue of threonine^{172} resulting in AMPK activation followed by mTORC1 inhibition (Shaw *et al.*, 2004). In addition, the tumor suppressor p53 has been demonstrated to activate AMPK under oxidative and genotoxic stress (Budanov and Karin, 2008). Two p53 target genes, *sestrin 1* and *sestrin 2*, have been identified to suppress mTORC1. Over-expression of Sestrin1 and Sestrin 2 activates AMPK, which phosphorylates TSC2 that subsequently inhibits the activity of mTORC1 (Budanov and Karin, 2008).

In contrast to mTORC1, the TSC1/2 complex appears to promote the activity of mTORC2. Loss of a functional TSC1/TSC2 complex can lead to the loss of mTORC2 kinase activity *in vitro* (Huang *et al.*, 2008; Huang *et al.*, 2009a). Studies suggest that the TSC1/2 complex can directly stimulate the *in vitro* kinase activity of mTORC2 through the interaction between the N-terminal region of TSC2 and the C-terminal region of Rictor (Huang *et al.*, 2009a).

4. Stem Cell Proliferation and Differentiation with mTOR

In the nervous system, mTOR signaling provides the necessary guidance for neuronal stem cell development and migration (Table 2). mTOR signaling is necessary for insulin-induced neuronal differentiation in neuronal progenitor cells (Han *et al.*, 2008). In addition, mTOR pathways involving REDD1 can control neuronal migration and cortical patterning (Malagelada *et al.*, 2011). Without mTOR signaling, stem cell development can be halted. Deletion of the C-terminal six amino acids of mTOR, which are essential for kinase activity, leads to a decrease in proliferation of embryonic stem cells (Murakami *et al.*, 2004). Complete ablation of *mTOR* leads to lethality and arrest of embryonic stem cell proliferation (Gangloff *et al.*, 2004). As a downstream target of mTOR, p70S6K is vital for protein translational control and stem cell differentiation. Expression of constitutively active p70S6K or the siRNA-mediated knockdown of both TSC2 and Rictor to increase p70S6K activation results in the differentiation of human embryonic stem cells (Easley *et al.*, 2010). The activity of mTOR is also essential for the long-term undifferentiated growth of human embryonic stem cell, since inhibition of mTOR impairs pluripotency, prevents cell proliferation, and enhances mesoderm and endoderm activities in embryonic stem cells (Zhou *et al.*, 2009). However, the timing and degree of mTOR signaling also can impact neuronal stem cell development. Sustained activation of the mTOR pathway can lead to neuronal stem cell premature differentiation and impaired maturation (Magri *et al.*, 2011).

mTOR signaling also can govern stem cell proliferation in vascular cells and human amniotic fluid stem cells (hAFSCs). hAFSCs may represent a promising research field for tissue regeneration, since hAFSCs usually harbor a lower risk for tumorigenesis, have high proliferation rates, and increased differentiation potential when compared to adult stem cells. The activation of mTOR is essential for hAFSCs to form embryoid bodies, the three-dimensional aggregates that are essential step for the differentiation of pluripotent embryonic stem cells (Valli *et al.*, 2010). In addition, renal tissue formation through hAFSCs is regulated by both mTORC1 and mTORC2 (Siegel *et al.*, 2010). mTOR signaling is also important for the development of the vascular system, since inhibition of mTOR pathways lead to endothelial progenitor cell death that may result from inhibiting growth factor signaling (Miriuka *et al.*, 2006). Growth factors, such as erythropoietin (EPO), can form a vital component for both neuronal and vascular cells and rely upon mTOR pathway signaling. EPO controls neuronal, inflammatory cell, and endothelial cell survival (Brunner *et al.*, 2012; Caprara and Grimm, 2012; Chalhoub *et al.*, 2012; Chong *et al.*, 2002, 2003a; Eipel *et al.*, 2012; Maiese *et al.*, 2008b; Maiese *et al.*, 2008d; Okaji *et al.*, 2012; Shang *et al.*, 2012; Talving *et al.*, 2012). EPO governs mTOR signaling for microglia survival during oxidative stress (Shang *et al.*, 2011) and for osteoblastogenesis and osteoclastogenesis (Kim *et al.*, 2012). Yet, mTOR may be associated with aging, since in hematopoietic stem cells mTOR activity is increased in the hematopoietic stem cells of older mice (Chen *et al.*, 2009a).

In addition to mTOR, pathways that involve PI 3-K and wingless can integrate with mTOR signaling to promote stem cell proliferation and maintain cellular homeostasis. Loss of either PI 3-K or mTOR alone results in reduced proliferation of neural stem cells during growth factor exposure without affecting the capacity to self-renew, illustrating that both PI 3-K and mTOR are dual factors necessary for the maintenance of neural stems (Sato *et al.*, 2010). In consideration of Wnt proteins and the wingless pathway, Wnt signaling oversees a host of cell process that include stem cell proliferation, cell development, cellular survival, and cellular aging (Fernandez-Martos *et al.*, 2011; L'Episcopo *et al.*, 2012; Li *et al.*, 2006c; Maiese *et al.*, 2008f; Maiese *et al.*, 2008h; Shang *et al.*, 2011; Su *et al.*, 2012; Vigneron *et al.*, 2011; Wang *et al.*, 2012c). The Wnt pathway can increase the activity of mTOR through GSK-3β (Li *et al.*, 2005a; Maiese, 2008). GSK-3β phosphorylates TSC2 on serine^{1337} and serine^{1341} in combination with AMPK phosphorylation of TSC2 on serine^{1345}. These post-translation phosphorylations result in the inhibition of mTOR activity (Inoki *et al.*, 2006). As a result, Wnt proteins foster mTOR activation by inhibiting GSK-3β through phosphorylation. In hematopoietic stem cells, a fine balance between Wnt and GSK-3β activation is necessary to control self-renewal and lineage commitment (Huang *et al.*, 2009b).

5. mTOR and Cellular Demise with Oxidant Stress, Apoptosis, and Autophagy

5.1 Oxidant Stress and mTOR

Oxidative stress affects multiple systems of the body and can lead to the induction of both cellular apoptosis and autophagy (Chong *et al.*, 2012a; Maiese *et al.*, 2011b). Diseases associated with aging, cardiac disorders, immune system impairment, gastrointestinal disease, or cellular metabolism may be the result of the release of reactive oxygen species (ROS) that lead to oxidative stress (Ammar *et al.*, 2011; Chong *et al.*, 2005d; Du *et al.*, 2012; Escobar *et al.*, 2012; Rjiba-Touati *et al.*, 2012). In regards to the nervous system, cell injury related to toxin exposure (Wang *et al.*, 2012b; Xie *et al.*, 2012), cerebral ischemia (Chong *et al.*, 2010a; Du *et al.*, 2012; Li *et al.*, 2006b; Simao *et al.*, 2011), inflammation (Kato *et al.*, 2011; Kigerl *et al.*, 2012; L'Episcopo *et al.*, 2012; Shang *et al.*, 2009b, 2010), and Aβ

exposure (Chong *et al.*, 2005c; Lee *et al.*, 2012; Liu *et al.*, 2010b; Shang *et al.*, 2012; Zeng *et al.*, 2011) can be the result of oxidant stress. Oxidative stress in conjunction with mitochondrial dysfunction (Chong *et al.*, 2004b; Escobar *et al.*, 2012; Ghosh *et al.*, 2011; Jayaram *et al.*, 2011; Kang *et al.*, 2003b; Maiese and Chong, 2004) can lead to neurovascular diabetic complications (Jiang *et al.*, 2011; Maiese *et al.*, 2008g, 2011a; Yang *et al.*, 2011; Zengi *et al.*, 2011), cognitive disorders (Chong *et al.*, 2005b; Leuner *et al.*, 2007; Maiese *et al.*, 2009d; Zhang *et al.*, 2011), Alzheimer's disease (AD) (Bajda *et al.*, 2011; Maiese *et al.*, 2009a; Srivastava and Haigis, 2011), Parkinson's disease (PD) (Asaithambi *et al.*, 2011; Chong *et al.*, 2005d; Khan *et al.*, 2010; Park *et al.*, 2011), and epilepsy (Lehtinen *et al.*, 2009; Maiese *et al.*, 2009c; Sales Santos *et al.*, 2009).

ROS can be generated in excessive quantities through agents such as superoxide free radicals, hydrogen peroxide, singlet oxygen, nitric oxide (NO), and peroxynitrite (Chong *et al.*, 2012a; Maiese *et al.*, 2011a). Once generated, ROS alter mitochondrial function, DNA integrity, and the misfolding of proteins leading to cellular injury and the progression of aging mechanisms (Jayaram *et al.*, 2011; Maiese *et al.*, 2010; Yang *et al.*, 2011). Detrimental effects of ROS are usually prevented by endogenous antioxidant systems that include superoxide dismutase, glutathione peroxidase, catalase, and vitamins that include C, D, E, and K (Chong *et al.*, 2005e; Goffus *et al.*, 2010; Herbas *et al.*, 2011; Kuypers and Hoane, 2010; Lappas and Permezel, 2011; Maiese and Chong, 2003; Maiese *et al.*, 2009b; Suzen *et al.*, 2012; Vonder Haar *et al.*, 2011; Wang *et al.*, 2012b; Yuan *et al.*, 2012). During exposure to oxidative stress, mTOR pathways can become depressed and lead to cell injury (Andreucci *et al.*, 2009; Chen *et al.*, 2010; Shang *et al.*, 2011). Oxidative stress that impairs mTOR signaling not only may lead to acute or chronic cell injury (Basile *et al.*, 2012; Chalkias and Xanthos, 2012; Maiese *et al.*, 2009e; Yoo *et al.*, 2012), but also lead to changes in metabolism and cell longevity (Chong *et al.*, 2012b; Maiese *et al.*, 2011a; Maiese *et al.*, 2011b; Wang *et al.*, 2011b). Restoration of mTOR signaling pathways during oxidative stress can preserve cellular function and survival (Chong *et al.*, 2007b; Di Nardo *et al.*, 2009; Shang *et al.*, 2011).

5.2 Apoptosis and mTOR

Apoptosis involves both an early phase consisting of the exposure of membrane phosphatidylserine (PS) residues and a late phase that involves the destruction of genomic DNA (Chong *et al.*, 2005d; Maiese *et al.*, 2008c). The early phase is energy dependent and involves the externalization of PS residues on the surface of cells that can be a signal for inflammatory cells to engulf and dispose of injured cells (Bailey *et al.*, 2010; Maiese *et al.*, 2008c; Schutters and Reutelingsperger, 2010). This process occurs with the expression of the phosphatidylserine receptor (PSR) on microglia during oxidative stress (Hong *et al.*, 2004; Kang *et al.*, 2003a; Li *et al.*, 2006b). Blockade of PSR function in microglia prevents the activation of microglia (Chong *et al.*, 2003b; De Simone *et al.*, 2004; Lin *et al.*, 2000). Membrane PS residue externalization occurs in neuronal, vascular, and inflammatory cells during multiple generators of oxidant stress, such as ischemia (Chong *et al.*, 2004a; Zwaal *et al.*, 2005), Aβ exposure (Chong *et al.*, 2007a; Lee *et al.*, 2002; Shang *et al.*, 2009a), pH disturbance (Czene *et al.*, 1997; Vincent and Maiese, 1999), free radical exposure (Aksu *et al.*, 2011; Balan *et al.*, 2008; Banach *et al.*, 2011; Chong *et al.*, 2003c), and infection (Maiese *et al.*, 2004; Soares *et al.*, 2008). Exposure of membrane PS residues also occurs on platelets and has been associated with clot formation in the vascular system (Popescu *et al.*, 2010). The disposal of “tagged” cells may assist with the repair and regeneration of injured tissues to remove non-functional dying cells, but also at times may lead to the removal of otherwise functional cells if not kept in-check (Koh, 2012; Maiese *et al.*, 2007b). The late phase of apoptosis that involves the cleavage of genomic DNA into fragments usually does not allow for the repair or recovery of cells (Chong *et al.*, 2011a; Kook *et al.*, 2011; Solling, 2011;

Ullah *et al.*, 2012). Several enzymes responsible for DNA degradation include the acidic, cation independent endonuclease (DNase II), cyclophilins, and the 97 kDa magnesium-dependent endonuclease (Chong *et al.*, 2005d; Maiese *et al.*, 2008a). Three separate endonuclease activities have been found in neurons that include a constitutive acidic cation-independent endonuclease, a constitutive calcium/magnesium-dependent endonuclease, and an inducible magnesium dependent endonuclease (Tominaga *et al.*, 1993; Vincent *et al.*, 1999a, b).

In the nervous system, activation of mTOR is usually protective against apoptosis during oxidative stress (Figure 3). Exposure to the oxidant hydrogen peroxide impairs mTOR kinase activity and leads to apoptotic cell death in neuronal cells (Chen *et al.*, 2010). In addition, central nervous system inflammatory cells can succumb to the toxic effects of oxidative stress if deprived of mTOR activation (Chong *et al.*, 2007b; Shang *et al.*, 2012). In contrast, mTOR activation through application of nutrients such as phosphatidic acid can limit oxidative stress and prevent apoptotic cell injury (Taga *et al.*, 2011). Oxidative stress and cell death such as in dopaminergic neurons also can be blocked during application of agents that increase mTOR activity (Choi *et al.*, 2010). Activation of mTOR appears vital for pathways that are known to be cytoprotective. During periods of serum deprivation that prevent mTOR activation, insulin has been shown to be unable to rescue cell survival unless mTOR activity is restored (Wu *et al.*, 2004). Other growth factors that are independent for insulin, such as EPO, have been shown also to be dependent upon mTOR activation (Shang *et al.*, 2011). However, in some instances, inhibition of mTOR activity may provide cytoprotection for post-mitotic neurons that attempt to enter the cell cycle (Maiese *et al.*, 2008e). During neurodegenerative disorders such as AD, post-mitotic neurons that attempt to enter the cell cycle do not replicate, but ultimately succumb to apoptotic cell death (Chong *et al.*, 2006; Lin *et al.*, 2001; Majd *et al.*, 2008; Yu *et al.*, 2012). In studies that examine Aβ oligomer exposure, neurons can be prevented from entering into cell cycle events during the inhibition of mTOR and related pathways of Akt and PI 3-K (Bhaskar *et al.*, 2009).

mTOR depends upon the modulation of p70S6K and 4EBP1 to prevent cell death during apoptosis (Figure 3). Depression of mTOR signaling by siRNA interference inhibits phosphorylation of both p70S6K and 4EBP1 to lead to apoptosis (Hou *et al.*, 2007) (Table 2). Apoptosis in astrocytes is prevented following activation of p70S6K by mTOR that can lead to increased expression of Bcl-2/Bcl-x_L expression to block BAD activity that can result in apoptosis (Pastor *et al.*, 2009). In the absence of mTOR activity, 4EBP1 has increased binding to eIF4E that can lead to the translation of apoptotic promoting proteins and also initiate autophagy (Zhang *et al.*, 2010). Inhibition of apoptosis through mTOR also relies upon Akt activation. Cytoprotection through Akt can occur at several levels to foster cell survival through the maintenance of mitochondrial membrane potential, prevention of cytochrome c release and caspase activation, and regulate inflammatory cell activation (Hou *et al.*, 2010a, b; Su *et al.*, 2011; Zhang *et al.*, 2012; Zhou *et al.*, 2011). mTOR has been shown to require Akt activation to block apoptotic cell death (Hernandez *et al.*, 2011; Magri *et al.*, 2011; Shang *et al.*, 2011, 2012) and require the inactivation of forkhead transcription factors, such as FoxO3a (Chong *et al.*, 2011a; Dormond *et al.*, 2007). Akt also may modulate apoptosis through the inhibition of PRAS40. Activation of PRAS40 can lead to the induction of apoptotic pathways (Thedieck *et al.*, 2007). In the mTOR pathway, phosphorylation of PRAS40 by Akt can inhibit the activity of this substrate and lead to its dissociation from mTORC1 and binding to cytoplasmic 14-3-3 proteins (Nascimento *et al.*, 2010).

5.3 Autophagy and mTOR

Autophagy differs from apoptosis by allowing cells to recycle cytoplasmic components, remove defective organelles, and maintain important cytoskeletal structures during development, cell differentiation, and tissue remodeling (Gumy *et al.*, 2010). Autophagy can be considered under three different categories termed microautophagy, macroautophagy, and chaperone-mediated autophagy (Yamada and Singh, 2012). The process of macroautophagy, usually considered to represent autophagy in general, includes the bulk degradation of cytoplasmic material and the sequestration of the cytoplasmic protein and organelles into autophagosomes. The autophagosomes fuse with lysosomes for degradation and reuse by essential cellular processes (Silva *et al.*, 2011). Microautophagy involves the sequestration of cytoplasmic components by invagination of the lysosomal membrane. The vesicle formed is then transferred to the lumen of the lysosomes for digestion. During chaperone mediated autophagy, the cytoplasmic component is delivered by cytosolic chaperones to the receptors on the lysosomal membranes. Subsequently, the cellular organelle is translocated across lysosomal membranes into the lumen.

Autophagy is maintained at basal levels in most tissues. It can be up-regulated by factors such nutrient depletion (Han *et al.*, 2011), oxidative stress (Deruy *et al.*, 2010), decreased mTOR signaling (Wang *et al.*, 2012e), and growth factor depletion (Bains *et al.*, 2010). In some scenarios, progression of apoptosis may conversely require the inhibition of autophagy (Carayol *et al.*, 2010; Luo and Rubinsztein, 2010; Maiese, 2012), suggesting that autophagy may not be a principal component of cell death in some models of neuronal injury (Wang *et al.*, 2012c). Autophagy also can lead to cell death and be a contributing factor to several disorders. Growth factor deprivation in purkinje neurons (Canu *et al.*, 2005) and sympathetic neurons (Xue *et al.*, 1999) leads to accumulation of autophagic vesicles and cell death. Exposure to glutamate, potassium deprivation, and staurosporine can result in cell death through autophagy (Canu *et al.*, 2005; Kim *et al.*, 2009; Maycotte *et al.*, 2010). Methamphatamine leads to neuronal cell death not only through apoptosis, but also through autophagy by inhibiting the disassociation of the Bcl-2/Beclin 1 complex (Nopparat *et al.*, 2010). Bcl-2/Bcl-x_L is both an antiapoptotic protein and a protein that blocks autophagy through its inhibitory interaction with Beclin 1 (Pattingre *et al.*, 2005) (Table 2). During acute events such as cerebral ischemia, autophagy can lead to injury in cerebral astrocytes (Qin *et al.*, 2010), motor neurons in the spinal cord (Baba *et al.*, 2009), neurons in the cortex (Wang *et al.*, 2011a). However, activation of autophagy may be beneficial as suggested in models of PD (Spencer *et al.*, 2009), AD (Spilman *et al.*, 2010), and prion protein mediated neurotoxicity (Jeong *et al.*, 2012).

Among the thirty-three autophagic related genes (*Atg*) that have been identified in yeast, Atg1, a serine/threonine kinase is a downstream target of TOR. Atg1 has been associated with other autophagic related genes including Atg13 and Atg17 (Kabeya *et al.*, 2005; Kamada *et al.*, 2000; Scott *et al.*, 2007). Atg13 is phosphorylated through an mTORC1 dependent mechanism, resulting in its disassociation with Atg1 and a reduction in Atg1 activity. In contrast, upon starvation and rapamycin application, Atg13 is dephosphorylated, binds to, and activates Atg1, leading to autophagosome formation (Kamada *et al.*, 2000). In mammals, a similar regulation of autophagy by mTOR exists. Two mammalian homologues of Atg1, UNC-51 like kinase 1 (ULK1) and ULK2, have been identified (Kuroyanagi *et al.*, 1998; Yan *et al.*, 1998; Yan *et al.*, 1999). Mammalian Atg13 binds to ULK1, ULK2, and FIP200 (FAK-family interacting protein of 200 kDa) to activate ULKs and facilitate the phosphorylation of FIP200 by ULKs (Hosokawa *et al.*, 2009; Jung *et al.*, 2009). Similar to TOR in yeast, mTOR phosphorylates the mammalian homologue Atg13 and the mammalian Atg1 homologues ULK1 and ULK2 to block autophagy. During inhibition of mTOR, dephosphorylation of ULKs and Atg13 ensues leading to the induction of autophagy (Hosokawa *et al.*, 2009; Jung *et al.*, 2009).

In early studies, activation of mTOR signaling pathways has been demonstrated to block autophagy (Blommaart *et al.*, 1995) (Figure 3). During the early phases of autophagy, mTOR activity can be inhibited (Yu *et al.*, 2010). Re-activation of mTOR appears necessary to continue with the processes of autophagy, but increased mTOR activity can then attenuate autophagy (Yu *et al.*, 2010), suggesting that mTOR may play an important role in maintaining the balance between lysosomal consumption and reconstruction. mTOR activation can prevent neurodegeneration during oxidative stress mediated autophagy in dopamine neurons (Choi *et al.*, 2010). In contrast, loss of mTOR activity can lead to autophagic cell death (Le *et al.*, 2010). However, some chronic disease processes in the nervous or vascular systems may benefit from inhibition of mTOR to allow the progression of autophagy, as suggested in some models of Alzheimer's disease (Spilman *et al.*, 2010) and during normal physiology to prevent cardiomegaly and decreased cardiac contractility (Jaber *et al.*, 2012) (Figure 3). Furthermore, the benefits of exercise may require a brief inaction of mTOR for autophagic pathways to proceed (Ogura *et al.*, 2011). In addition, during nutrient deprivation, mTOR may modulate pathways that promote autophagy (Chong *et al.*, 2011b). For example, death-associated protein 1 (DAP1) has been identified as a novel substrate of mTOR that inhibits autophagy. Knockdown of DAP1 increases autophagic flux (Koren *et al.*, 2010). mTOR phosphorylates DAP1 to inactivate it. Reduction in mTOR activity, such as during starvation, activates DAP1 that functions as an active suppressor of autophagy.

6. mTOR in the Nervous System

6.1 Cognitive Disease

Greater than twenty-four million people suffer from AD, pre-senile dementia, and other disorders of cognitive loss worldwide and at least five million people have AD in the United States (Maiese *et al.*, 2009d; Maiese *et al.*, 2007c). mTOR and its signaling pathways play an important role during memory formation, fear, cognitive loss, and AD (Figure 4). mTOR may be necessary for synaptic plasticity and memory formation in the hippocampus. Loss of mTOR activity can impair late phase long-term potentiation (Tang *et al.*, 2002) and memory consolidation (Slipczuk *et al.*, 2009). Disruption in mTOR signaling also prevents long-term retention of fear memory, suggesting a potential clinical application for mTOR inhibition during post-traumatic stress and anxiety disorders (Blundell *et al.*, 2008; Parsons *et al.*, 2006; Sui *et al.*, 2008).

Although activation of mTOR appears necessary to maintain memory function, it is not entirely clear of the level of mTOR activity that may be required to be beneficial in AD (Chong *et al.*, 2010b; Pei and Hugon, 2008) (Table 2). In some scenarios, mTOR activation has been considered as a contributor to AD progression. Studies have reported increases in the level of phosphorylation of mTOR in conjunction with tau phosphorylation in AD neurons (Griffin *et al.*, 2005; Li *et al.*, 2005b). In brains from AD patients, p70S6K activation has been associated with hyperphosphorylated tau formation and potential neurofibrillary accumulation (An *et al.*, 2003). During mTOR inhibition that is associated with autophagy in murine models of AD, cognition is improved and Aβ levels are reduced (Spilman *et al.*, 2010).

Yet, other studies suggest that some level of activiation of mTOR is necessary to prevent pathology during AD. In AD, Aβ is toxic to cells (Chong *et al.*, 2005c; Echeverria *et al.*, 2011; Kawamoto *et al.*, 2012; Lee *et al.*, 2012; Shang *et al.*, 2012; Silva *et al.*, 2011) through pathways that can involve oxidative stress (Bach *et al.*, 2011; Bajda *et al.*, 2011; Chong *et al.*, 2005b, 2007a). Loss of mTOR activity in peripheral lymphocytes has a positive correlation with the progression of AD in some studies (Paccalin *et al.*, 2006). Exposure to Aβ can inhibit phosphorylation and activation of mTOR and p70S6K in neuroblastoma cells

and in lymphocytes of patients with AD (Lafay-Chebassier *et al.*, 2005). Rapamycin treatment also may exacerbate amyloid toxicity (Lafay-Chebassier *et al.*, 2006). Activation of the mTOR and p70S6K pathways can protect microglia, inflammatory cells responsible for Aβ sequestration, from the toxic effects of Aβ exposure (Shang *et al.*, 2012). Loss of mTOR signaling also has been associated with impairments in long-term potentiation and synaptic plasticity in murine models of AD (Ma *et al.*, 2010). Up-regulation of mTOR signaling improves long-term potentiation in murine models of AD. In addition, genetic deletion of FKBP12 prevents impairment in long-term potentiation by Aβ (Ma *et al.*, 2010). Suppression of mTOR activity also may be associated with neuronal atrophy in AD. This has been attributed to the insufficiency of retinoblastoma tumor suppressor (RB1) inducible Coiled-Coil 1 (RB1CC1). In AD patients, RB1CC1 appears to be necessary for neurite growth and to maintain mTOR signaling, since lack of RB1CC1 expression results in mTOR repression, neuronal apoptosis, and neuronal atrophy (Chano *et al.*, 2007).

6.2 Parkinson's Disease

Similar to AD, mTOR activation may require a fine level of modulation to protect neurons during PD (Figure 4). Loss of mTOR activity may be detrimental during PD. REDD1, an inhibitor of mTORC1 activity (DeYoung *et al.*, 2008), has increased expression in the brains of patients with PD (Malagelada *et al.*, 2006). Loss of mTOR activity during REDD1 expression has been shown in animal models of PD to lead to the death of dopaminergic neurons (Malagelada *et al.*, 2006). Oxidative stress also may be a significant modulator of dopaminergic cell death in neurons that requires mTOR activation for cellular protection (Chong *et al.*, 2010b; Maiese *et al.*, 2011b), since inhibition of mTOR activity can result in autophagic death of dopaminergic neurons during oxidative stress (Choi *et al.*, 2010). In addition, 4EBP1, a downstream target of mTOR, can lead to protein translation when active. Loss of mTOR activity and the chronic activation of 4EBP1 by leucine-rich repeat kinase 2 (LRRK2), a site for dominant mutations PD, is believed to alter protein translation and lead to the loss of dopaminergic neurons (Imai *et al.*, 2008). In contrast, activation of 4EBP1 can suppress pathologic experimental phenotypes of PD including degeneration of dopaminergic neurons in Drosophila (Tain *et al.*, 2009).

Yet, excessive activation of mTOR may lead to disability in PD patients, since some studies have shown that treatment with derivatives a dopamine, such as L-DOPA, lead to dopamine D1 receptor-mediated activation of mTORC1 resulting in dyskinesia (Santini *et al.*, 2009) (Table 2). Other work suggests that mTOR inactivation may preserve dopaminergic neurons. In models of PD, rapamycin offers neuronal protection that is believed to function through the preservation of some signaling pathways of mTOR such as Akt to promote cell survival (Malagelada *et al.*, 2010). Administration of rapamycin to inhibit mTOR signaling in mice treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) as a model for PD had decreased loss of dopaminergic neurons that was believed to be a result of autophagy pathway activation (Liu *et al.*, 2011).

6.3 Huntington's Disease

Inhibition of mTOR activity that fosters autophagy may provide treatment for Huntington's disease (HD) (Figure 4). Blockade of mTOR activity decreases huntingtin accumulation (Floto *et al.*, 2007) and limits polyglutamine expansions in Drosophila and mouse models of HD through autophagy (Ravikumar *et al.*, 2004). Interestingly in neuronal cell models of HD, inhibition of mTORC1 alone does not affect autophagy or huntingtin accumulation, but combined inhibition of mTORC1 and mTORC2 leads to the initiation of autophagy and reductions in huntingtin accumulation, suggesting that multiple components of the mTOR pathway may modulate the pathology observed in HD (Roscic *et al.*, 2011) (Table 2). For example, decreased phosphorylation and activity of p70S6K protects against early decline in

motor performance with beneficial effects on muscle, but mutant huntingtin levels in the brain were not affected (Fox *et al.*, 2010). Neuroprotection in the mTOR pathway may not only require mTORC1 and mTORC2, but also additional proteins such as growth arrest and DNA damage protein 34 (GADD34). Recent work illustrates that GADD34 leads to the dephosphorylation of TSC2 and induction of autophagy in cell models of HD with increased cell survival during GADD34 over-expression (Hyrskyluoto *et al.*, 2012).

6.4 Epilepsy

Increased activity of mTOR may contribute to epileptic discharges and subsequent seizure disorders (Chong *et al.*, 2010b; O'Dell *et al.*, 2012) (Figure 4). In addition, impairments in the regulation of mTOR occur in disorders that have an increased incidence of seizures and autism, such as tuberous sclerosis (TS) (Holmes and Stafstrom, 2007). In animal models, mTORC1 activation has been shown to peak at postnatal week three and yield susceptibility for the induction of seizures (Table 2). Blockade of mTORC1 activity with rapamycin reduces seizure susceptibility and decreases autistic-like behavior. These studies suggest that increased mTOR activity not only leads to seizure onset, but also may impact developmental epileptogenesis and altered social behavior (Talos *et al.*, 2012). Changes in TSC1 and TSC2 that ultimately result in increased activity of mTOR can lead to kindling and epileptic activity irrespective of structural changes that may be associated with TS (Meikle *et al.*, 2008; Waltereit *et al.*, 2006). In animal models of TS, early inhibition of mTOR signaling can prevent astrogliosis, neuronal disorganization, and seizures (Zeng *et al.*, 2008). Inhibition of mTOR pathways also may affect seizure development in other models, such as models of temporal lobe epilepsy. Treatment with rapamycin during kainate-induced epilepsy decreases neuronal cell death, neurogenesis, mossy fiber sprouting, and the development of spontaneous epilepsy (Zeng *et al.*, 2009). Chronic hippocampal infusion of rapamycin also reduces mossy fiber sprouting in a rat pilocarpine model of temporal lobe epilepsy (Buckmaster *et al.*, 2009). In this same model of epilepsy, blockade of mTOR activity can limit aggressive behavior as well as limit seizure activity, indicating that pathways responsible for aggressive behavior and epilepsy may be closely linked through mTOR signaling (Huang *et al.*, 2012).

6.5 Stroke and Trauma

During ischemic injury to the brain, several studies suggest that activation of mTOR signaling pathways may offer neuronal protection (Figure 4). In models of stroke using invertebrates, treatments that increased the expression of Raptor were associated with neuroprotection during hypoxia (Sheng *et al.*, 2012). In middle cerebral artery rat stroke models, agents such as melatonin can reduce stroke size that appears to rely upon mTOR, p70S6K, and Akt activation (Koh, 2008). In addition, inhibition of mTOR activity in primary cerebral microglia (Chong *et al.*, 2007b) and neurons (Chong *et al.*, 2010b) exposed to oxygen-glucose deprivation leads to neuronal cell death through apoptosis. Activation of mTOR is also necessary for the cytokine EPO to prevent microglial cell death during ischemic insults (Shang *et al.*, 2011) (Table 2). However, not all experimental models of stroke support the premise that mTOR activation leads to increased cell survival. Inhibition of PTEN (phosphatase and tensin homolog deleted on chromosome 10) has been demonstrated to lead to increased cerebral infarction that was associated with increased mTOR phosphorylation and activation (Shi *et al.*, 2011). Similar to current work that supports either activation or inhibition of mTOR signaling for cytoprotection during stroke, studies of trauma in the nervous system vary in outcome during mTOR activation (Table 2). Following spinal cord injury, enhanced spinal cord plasticity through exercise may require an increase in mTOR expression and increased p70S6K activity (Liu *et al.*, 2012). In addition, axonal regeneration in the nervous system may require mTOR activation in conjunction with signal transducers and activators of transcription (STAT) pathways (Sun *et*

al., 2011). During loss of PTEN or TSC1, negative regulators of mTOR, axonal regeneration is fostered in adult retinal ganglion cells and in corticospinal neurons after optic nerve injury and spinal cord injury respectively (Liu *et al.*, 2010a; Park *et al.*, 2008). Exogenous ATP administration in a spinal cord injury model can significantly increase Akt/mTOR/p70S6K signaling that is accompanied by improved locomotor function (Hu *et al.*, 2010). In contrast, in some models of closed head injury, rapamycin treatment that inhibits mTOR activity significantly improves functional recovery that is also accompanied by loss of p70S6K activity (Erlich *et al.*, 2007).

6.6 Tumorigenesis

Given the proliferative role pathways of mTOR hold for cellular growth and expansion, multiple studies have focused on the impact of mTOR for tumors throughout the body (Benjamin *et al.*, 2011). Prevention of tumor progression during urothelial carcinoma, (Hansel *et al.*, 2010), neuroendocrine tumors (Pavel *et al.*, 2011), breast and gynecological malignancies (Janku *et al.*, 2012), and solid tumors (Bryce *et al.*, 2011) may result from the inhibition of mTOR activation. In addition, activation of mTORC1 and mTORC2 may contribute to leukemic cell resistance during chronic myelogenous leukemia (Carayol *et al.*, 2010) and colorectal cancer metastases (Gulhati *et al.*, 2011). Downstream pathways of mTOR that include p70S6K and 4EBP1 also may be considered as biomarkers of disease progression (Karlsson *et al.*, 2011).

In regards to the nervous system, hyperactivation of mTOR has been associated with inherited cancer syndromes such as neurofibromatosis type 1 (NF1), tuberous sclerosis (TS), and Lhermitte-Duclos disease (Figure 4). Work is progressing with disorders such as NF1, an autosomal dominant genetic disease characterized by tumor predisposition syndrome with the formation of neurofibromas and astrocytomas. Inhibition of mTOR with rapamycin suppresses the growth of aggressive NF1-associated malignancies in genetically engineered murine models of the disease (Johannessen *et al.*, 2008), suggesting that hyperactivation of mTOR may be responsible for this disorder (Dasgupta *et al.*, 2005). Although multiple cellular pathways may lead to the development of NF1, some studies report the occurance of increased activity of mTORC1 with impairment of mTORC2 activity in human arachnoid and Schwann cells (James *et al.*, 2012). In addition, associated bone pathologies with NF1 also may be tied to increased mTOR activity (Ma *et al.*, 2012).

TS results from heterozygous mutations in the *TSC1* or *TSC2* gene. The disorder is characterized by neuropsychiatric symptoms, including intellectual disability, autism, other behavioral disorders, and epilepsy (Curatolo *et al.*, 2008). In the brain, TSC is associated with cortical tubers consisting of giant cells, dysmorphic neurons, and astrocytes. The *TSC1* and *TSC2* genes encode for proteins to form the TSC1/TSC2 complex. The TSC1/TSC2 complex regulates protein synthesis and cell growth by inhibiting mTORC1 signaling. In both healthy and lesioned skin of TS patients, increased mTOR activity has been reported with the up-regulation of p70S6K (Jozwiak *et al.*, 2009). In animal models of TS that use mTORC1 inhibitors, median survival, behavior, and weight gain are improved (Meikle *et al.*, 2008). Inhibition of mTOR with everolimus (RAD001) also is effective for subependymal giant cell astrocytomas associated with TS. The United States Food and Drug Administration has approved everolimus for the treatment of subependymal giant cell astrocytoma which can lead to reduction in tumor volume and hydrocephalus (Curran, 2012) as well as improvement in patient ambulation and cessation of seizures (Perek-Polnik *et al.*, 2012). Inhibition of mTOR with rapamycin in TS patients also can lead to the reduction of facial angiofibromas (Hofbauer *et al.*, 2008).

Lhermitte-Duclos disease (LDD) involves a rare cerebellar tumor associated with germline mutations in the PTEN gene, a negative regulator of PI-3 K and mTOR pathways.

Hyperactivation of mTOR may lead to posterior fossa tumor growth, since high levels of activated Akt and p70S6K are present in the ganglionic cells forming these tumors (Abel *et al.*, 2005). Additional immunohistochemical analyses of the cerbellar tumors support a role for mTOR in LDD with the observation of activation of the PI 3-K/Akt/mTOR signaling pathways (Takei *et al.*, 2007) (Table 2).

7. Future Perspectives

In the nervous system, mTOR can impact multiple disease entities that include AD, PD, HD, epilepsy, stroke, trauma, and tumors of the nervous system. mTOR signaling can affect the early development of cells through stem cell proliferation and differentiation as well as the end stages of cellular utility that leads to apoptosis and autophagy. Both traditionally known pathways of mTORC1 and mTORC2 that involve p70S6K, 4EBP1, PI 3-K, Akt, AMPK, GSK-3β, REDD1, and the TSC1/TSC2 complex and newly recognized pathways that include wingless, growth factors, and forkhead transcription factors can significantly influence the biological outcome of mTOR signaling. Given the broad array of cellular pathways affected by mTOR, it is conceivable to predict that mTOR may influence not only cellular protection and survival, but also may prevent age related disorders and promote lifespan extension. A number of new studies provide support for this premise by suggesting a role for mTOR with increased longevity (Harrison *et al.*, 2009) and providing tolerance against insulin resistance (Selman *et al.*, 2009).

However, the role of mTOR in several disease entities is not always clear and may lead to variable outcomes. For example, in AD, activation of mTOR may be necessary to prevent neurodegeneration from Aβ exposure (Shang *et al.*, 2012), block neuronal atrophy (Chano *et al.*, 2007), and limit cognitive decline (Ma *et al.*, 2010). Yet, other studies suggest that activation of downstream pathways of mTOR are linked with hyperphosphorylated tau formation and neurofibrillary accumulation (An *et al.*, 2003). Furthermore, mTOR inhibition in some models of AD may improve cognition and limit Aβ levels (Spilman *et al.*, 2010). Other disorders of the nervous system can have similar outcome variability during modulation of mTOR. Loss of mTOR activity in animal models of PD can result in the death of dopaminergic neurons (Malagelada *et al.*, 2006). Yet, additional work suggests that mTOR be a significant factor for disability in PD patients, since treatment with L-DOPA leads to dopamine D1 receptor-mediated activation of mTORC1 resulting in dyskinesia (Santini *et al.*, 2009). As a result, unexpected or adverse consequences may ensue with strategies that modulate mTOR activity. In the most severe of circumstances, unchecked cell growth and tumorigenesis may result.

It is important to recognize that while targeting mTOR in the nervous system, other systems of the body also may be impacted that can be affected by the timing and degree of mTOR signaling. For example, sustained activation of the mTOR pathway can lead to neuronal stem cell premature differentiation and impaired maturation (Magri *et al.*, 2011). In addition, timing of treatments to alter mTOR activity may affect biological and clinical outcome. Early rather than late treatment with rapamycin can reduce plaques, tangles, and loss of cognition in murine models of AD (Majumder *et al.*, 2011). Similar to the nervous system, mTOR activation can protect cardiac tissue during ischemia (Hernandez *et al.*, 2011). Yet, prolonged activation of mTOR may have detrimental consequences to both the cardiac and nervous systems. Chronic activation of mTOR can promote vascular dysfunction. (Popescu *et al.*, 2010) and lead to vasculopathy (Mancini *et al.*, 2003). In addition, during diabetes mellitus, mTOR has been shown with hyperleptinemia to stimulate excessive vascular smooth muscle cell proliferation (Shan *et al.*, 2008). Furthermore, mTOR can have a negative feedback loop and result in glucose intolerance through inhibition of the insulin receptor substrate 1 (Harrington *et al.*, 2004). These scenarios provide an important note of

caution since manipulation of mTOR in one system of the body for therapeutic benefits may unexpectedly lead to unwanted outcomes in other systems of the body. Targeting mTOR in the nervous system offers great excitement for the development of novel therapeutic strategies, especially for disorders that currently lack any effective treatment. Yet, it is vital to elucidate the complexity of mTOR and its signaling pathways to limit the potential for detrimental outcomes and bring forward robust and efficacious treatments for the nervous system.

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Abbreviations

Aβ	beta-amyloid
AD	Alzheimer's disease
AMPK	AMP activated protein kinase
Atg	autophagic related gene
CNS	central nervous system
Deptor	DEP-domain-containing mTOR-interacting protein
4EBP1	eukaryotic initiation factor 4E-binding protein 1
eIF4E	eukaryotic translation initiation factor 4E
EPO	erythropoietin
FIP200	FAK-family interacting protein of 200 kDa
GAP	GTPase-activating protein
HD	Huntington's disease
IKK	I-kappaB kinase
LKB1	tumor suppressor liver kinase B1
mLST8	mammalian lethal with Sec13 protein 8
mSIN1	mammalian stress-activated protein kinase interacting protein
OGD	oxygen glucose deprivation
p70S6K	p70 ribosome S6 kinase
PD	Parkinson's disease
PI 3-K	phosphoinositide 3 kinase
PDK1	phosphoinositide-dependent kinase 1
PRAS40	proline rich Akt substrate 40 kDa
Protor-1	protein observed with rictor-1
PTEN	phosphatase and tensin homolog deleted from chromosome 10
Rac1	Ras-related C3 botulinum toxin substrate 1
Raptor	the regulatory-associated protein of mTOR

REDD1	transcriptional regulation of DNA damage response 1
Rheb	Ras homologue enriched in brain
RhoA	Ras homolog gene family member A
Rictor	rapamycin-insensitive companion of mTOR
SREBP	sterol regulatory element-binding proteins
ROS	reactive oxygen species
TSC	tuberous sclerosis complex
ULK1	UNC-51 like kinase 1
WD-40 repeats	repeats of tryptophan and aspartate residues

References

Abel TW, Baker SJ, Fraser MM, Tihan T, Nelson JS, Yachnis AT, Bouffard JP, Mena H, Burger PC, Eberhart CG. Lhermitte-Duclos disease: a report of 31 cases with immunohistochemical analysis of the PTEN/AKT/mTOR pathway. J Neuropathol Exp Neurol. 2005; 64:341–349. [PubMed: 15835270]

Abraham RT. mTOR as a positive regulator of tumor cell responses to hypoxia. Current topics in microbiology and immunology. 2004; 279:299–319. [PubMed: 14560965]

Acosta-Jaquez HA, Keller JA, Foster KG, Ekim B, Soliman GA, Feener EP, Ballif BA, Fingar DC. Site-specific mTOR phosphorylation promotes mTORC1-mediated signaling and cell growth. Mol Cell Biol. 2009; 29:4308–4324. [PubMed: 19487463]

Aimbetov R, Chen CH, Bulgakova O, Abetov D, Bissenbaev AK, Bersimbaev RI, Sarbassov DD. Integrity of mTORC2 is dependent on the rictor Gly-934 site. Oncogene. 2011

Akcakanat A, Singh G, Hung MC, Meric-Bernstam F. Rapamycin regulates the phosphorylation of rictor. Biochem Biophys Res Commun. 2007; 362:330–333. [PubMed: 17707343]

Aksu U, Demirci C, Ince C. The pathogenesis of acute kidney injury and the toxic triangle of oxygen, reactive oxygen species and nitric oxide. Contrib Nephrol. 2011; 174:119–128. [PubMed: 21921616]

Ammar HI, Saba S, Ammar RI, Elsayed LA, Ghaly WB, Dhingra S. Erythropoietin protects against doxorubicin-induced heart failure. Am J Physiol Heart Circ Physiol. 2011; 301:H2413–2421. [PubMed: 21984540]

An WL, Cowburn RF, Li L, Braak H, Alafuzoff I, Iqbal K, Iqbal IG, Winblad B, Pei JJ. Up-regulation of phosphorylated/activated p70 S6 kinase and its relationship to neurofibrillary pathology in Alzheimer's disease. Am J Pathol. 2003; 163:591–607. [PubMed: 12875979]

Andreucci M, Fuiano G, Presta P, Lucisano G, Leone F, Fuiano L, Bisesti V, Esposito P, Russo D, Memoli B, Faga T, Michael A. Downregulation of cell survival signalling pathways and increased cell damage in hydrogen peroxide-treated human renal proximal tubular cells by alpha-erythropoietin. Cell Prolif. 2009; 42:554–561. [PubMed: 19508320]

Asaithambi A, Kanthasamy A, Saminathan H, Anantharam V, Kanthasamy AG. Protein kinase D1 (PKD1) activation mediates a compensatory protective response during early stages of oxidative stress-induced neuronal degeneration. Molecular neurodegeneration. 2011; 6:43. [PubMed: 21696630]

Astrinidis A, Senapedis W, Coleman TR, Henske EP. Cell cycle-regulated phosphorylation of hamartin, the product of the tuberous sclerosis complex 1 gene, by cyclin-dependent kinase 1/cyclin B. J Biol Chem. 2003; 278:51372–51379. [PubMed: 14551205]

Baba H, Sakurai M, Abe K, Tominaga R. Autophagy-mediated stress response in motor neuron after transient ischemia in rabbits. J Vasc Surg. 2009; 50:381–387. [PubMed: 19631873]

Bach JP, Mengel D, Wahle T, Kautz A, Balzer-Geldsetzer M, Al-Abed Y, Dodel R, Bacher M. The Role of CNI-1493 in the Function of Primary Microglia with Respect to Amyloid-beta. J Alzheimers Dis. 2011; 26:69–80. [PubMed: 21593565]

Bai X, Ma D, Liu A, Shen X, Wang QJ, Liu Y, Jiang Y. Rheb activates mTOR by antagonizing its endogenous inhibitor, FKBP38. Science. 2007; 318:977–980. [PubMed: 17991864]

Bailey TJ, Fossum SL, Fimbel SM, Montgomery JE, Hyde DR. The inhibitor of phagocytosis, O-phospho-L-serine, suppresses Muller glia proliferation and cone cell regeneration in the light-damaged zebrafish retina. Exp Eye Res. 2010; 91:601–612. [PubMed: 20696157]

Bains M, Zaegel V, Mize-Berge J, Heidenreich KA. IGF-I stimulates Rab7-RILP interaction during neuronal autophagy. Neurosci Lett. 2010

Bajda M, Guzior N, Ignasik M, Malawska B. Multi-target-directed ligands in Alzheimer's disease treatment. Curr Med Chem. 2011; 18:4949–4975. [PubMed: 22050745]

Balan V, Miller GS, Kaplun L, Balan K, Chong ZZ, Li F, Kaplun A, VanBerkum MF, Arking R, Freeman DC, Maiese K, Tzivion G. Life span extension and neuronal cell protection by Drosophila nicotinamidase. J Biol Chem. 2008; 283:27810–27819. [PubMed: 18678867]

Banach M, Piskorska B, Czuczwar S, Borowicz K. Nitric Oxide, epileptic seizures, and action of antiepileptic drugs. CNS Neurol Disord Drug Targets. 2011

Basile LA, Ellefson D, Gluzman-Poltorak Z, Junes-Gill K, Mar V, Mendonca S, Miller JD, Tom J, Trinh A, Gallaher TK. HemaMax, a recombinant human interleukin-12, is a potent mitigator of acute radiation injury in mice and non-human primates. PLoS ONE. 2012; 7:e30434. [PubMed: 22383962]

Benjamin D, Colombi M, Moroni C, Hall MN. Rapamycin passes the torch: a new generation of mTOR inhibitors. Nat Rev Drug Discov. 2011; 10:868–880. [PubMed: 22037041]

Bhandari BK, Feliers D, Duraisamy S, Stewart JL, Gingras AC, Abboud HE, Choudhury GG, Sonenberg N, Kasinath BS. Insulin regulation of protein translation repressor 4E-BP1, an eIF4E-binding protein, in renal epithelial cells. Kidney Int. 2001; 59:866–875. [PubMed: 11231341]

Bhaskar K, Miller M, Chludzinski A, Herrup K, Zagorski M, Lamb BT. The PI3K-Akt-mTOR pathway regulates Abeta oligomer induced neuronal cell cycle events. Molecular neurodegeneration. 2009; 4:14. [PubMed: 19291319]

Blommaart EF, Luiken JJ, Blommaart PJ, van Woerkom GM, Meijer AJ. Phosphorylation of ribosomal protein S6 is inhibitory for autophagy in isolated rat hepatocytes. J Biol Chem. 1995; 270:2320–2326. [PubMed: 7836465]

Blundell J, Kouser M, Powell CM. Systemic inhibition of mammalian target of rapamycin inhibits fear memory reconsolidation. Neurobiology of learning and memory. 2008; 90:28–35. [PubMed: 18316213]

Boulbes D, Chen CH, Shaikenov T, Agarwal NK, Peterson TR, Addona TA, Keshishian H, Carr SA, Magnuson MA, Sabatini DM, Sarbassov dos D. Rictor phosphorylation on the Thr-1135 site does not require mammalian target of rapamycin complex 2. Mol Cancer Res. 2010; 8:896–906. [PubMed: 20501647]

Brugarolas J, Lei K, Hurley RL, Manning BD, Reiling JH, Hafen E, Witters LA, Ellisen LW, Kaelin WG Jr. Regulation of mTOR function in response to hypoxia by REDD1 and the TSC1/TSC2 tumor suppressor complex. Genes Dev. 2004; 18:2893–2904. [PubMed: 15545625]

Brunner S, Huber BC, Weinberger T, Vallaster M, Wollenweber T, Gerbitz A, Hacker M, Franz WM. Migration of bone marrow-derived cells and improved perfusion after treatment with erythropoietin in a murine model of myocardial infarction. J Cell Mol Med. 2012; 16:152–159. [PubMed: 21362129]

Bryce AH, Rao R, Sarkaria J, Reid JM, Qi Y, Qin R, James CD, Jenkins RB, Boni J, Erlichman C, Haluska P. Phase I study of temsirolimus in combination with EKB-569 in patients with advanced solid tumors. Invest New Drugs. 2011

Buckmaster PS, Ingram EA, Wen X. Inhibition of the mammalian target of rapamycin signaling pathway suppresses dentate granule cell axon sprouting in a rodent model of temporal lobe epilepsy. J Neurosci. 2009; 29:8259–8269. [PubMed: 19553465]

Budanov AV, Karin M. p53 target genes sestrin1 and sestrin2 connect genotoxic stress and mTOR signaling. Cell. 2008; 134:451–460. [PubMed: 18692468]

Cai SL, Tee AR, Short JD, Bergeron JM, Kim J, Shen J, Guo R, Johnson CL, Kiguchi K, Walker CL. Activity of TSC2 is inhibited by AKT-mediated phosphorylation and membrane partitioning. J Cell Biol. 2006; 173:279–289. [PubMed: 16636147]

Campos-Esparza MR, Sanchez-Gomez MV, Matute C. Molecular mechanisms of neuroprotection by two natural antioxidant polyphenols. Cell Calcium. 2009; 45:358–368. [PubMed: 19201465]

Canu N, Tufi R, Serafino AL, Amadoro G, Ciotti MT, Calissano P. Role of the autophagic-lysosomal system on low potassium-induced apoptosis in cultured cerebellar granule cells. J Neurochem. 2005; 92:1228–1242. [PubMed: 15715672]

Caprara C, Grimm C. From oxygen to erythropoietin: relevance of hypoxia for retinal development, health and disease. Prog Retin Eye Res. 2012; 31:89–119. [PubMed: 22108059]

Carayol N, Vakana E, Sassano A, Kaur S, Goussetis DJ, Glaser H, Druker BJ, Donato NJ, Altman JK, Barr S, Platanias LC. Critical roles for mTORC2- and rapamycin-insensitive mTORC1-complexes in growth and survival of BCR-ABL-expressing leukemic cells. Proc Natl Acad Sci U S A. 2010; 107:12469–12474. [PubMed: 20616057]

Carriere A, Cargnello M, Julien LA, Gao H, Bonneil E, Thibault P, Roux PP. Oncogenic MAPK signaling stimulates mTORC1 activity by promoting RSK-mediated raptor phosphorylation. Curr Biol. 2008; 18:1269–1277. [PubMed: 18722121]

Chalhoub S, Langston CE, Farrelly J. The use of darbepoetin to stimulate erythropoiesis in anemia of chronic kidney disease in cats: 25 cases. J Vet Intern Med. 2012; 26:363–369. [PubMed: 22296687]

Chalkias A, Xanthos T. Post-cardiac arrest brain injury: pathophysiology and treatment. J Neurol Sci. 2012; 315:1–8. [PubMed: 22251931]

Chano T, Okabe H, Hulette CM. RB1CC1 insufficiency causes neuronal atrophy through mTOR signaling alteration and involved in the pathology of Alzheimer's diseases. Brain Res. 2007; 1168:97–105. [PubMed: 17706618]

Chen C, Liu Y, Zheng P. mTOR regulation and therapeutic rejuvenation of aging hematopoietic stem cells. Science signaling. 2009a; 2:ra75. [PubMed: 19934433]

Chen CH, Sarbassov dos D. The mTOR (mammalian target of rapamycin) kinase maintains integrity of mTOR complex 2. J Biol Chem. 2011; 286:40386–40394. [PubMed: 21965657]

Chen EJ, Kaiser CA. LST8 negatively regulates amino acid biosynthesis as a component of the TOR pathway. J Cell Biol. 2003; 161:333–347. [PubMed: 12719473]

Chen J, Zheng XF, Brown EJ, Schreiber SL. Identification of an 11-kDa FKBP12-rapamycin-binding domain within the 289-kDa FKBP12-rapamycin-associated protein and characterization of a critical serine residue. Proc Natl Acad Sci U S A. 1995; 92:4947–4951. [PubMed: 7539137]

Chen JX, Tuo Q, Liao DF, Zeng H. Inhibition of Protein Tyrosine Phosphatase Improves Angiogenesis via Enhancing Ang-1/Tie-2 Signaling in Diabetes. Exp Diabetes Res. 2012; 2012:836759. [PubMed: 22454630]

Chen L, Xu B, Liu L, Luo Y, Yin J, Zhou H, Chen W, Shen T, Han X, Huang S. Hydrogen peroxide inhibits mTOR signaling by activation of AMPKalpha leading to apoptosis of neuronal cells. Lab Invest. 2010; 90:762–773. [PubMed: 20142804]

Chen TJ, Wang DC, Chen SS. Amyloid-beta interrupts the PI3K-Akt-mTOR signaling pathway that could be involved in brain-derived neurotrophic factor-induced Arc expression in rat cortical neurons. J Neurosci Res. 2009b; 87:2297–2307. [PubMed: 19301428]

Chiang GG, Abraham RT. Phosphorylation of mammalian target of rapamycin (mTOR) at Ser-2448 is mediated by p70S6 kinase. J Biol Chem. 2005; 280:25485–25490. [PubMed: 15899889]

Choi KC, Kim SH, Ha JY, Kim ST, Son JH. A novel mTOR activating protein protects dopamine neurons against oxidative stress by repressing autophagy related cell death. J Neurochem. 2010; 112:366–376. [PubMed: 19878437]

Chong ZZ, Hou J, Shang YC, Wang S, Maiese K. EPO Relies upon Novel Signaling of Wnt1 that Requires Akt1, FoxO3a, GSK-3beta, and beta-Catenin to Foster Vascular Integrity During Experimental Diabetes. Curr Neurovasc Res. 2011a; 8:103–120. [PubMed: 21443457]

Chong ZZ, Kang JQ, Maiese K. Erythropoietin is a novel vascular protectant through activation of Akt1 and mitochondrial modulation of cysteine proteases. Circulation. 2002; 106:2973–2979. [PubMed: 12460881]

Chong ZZ, Kang JQ, Maiese K. Erythropoietin fosters both intrinsic and extrinsic neuronal protection through modulation of microglia, Akt1, Bad, and caspase-mediated pathways. Br J Pharmacol. 2003a; 138:1107–1118. [PubMed: 12684267]

Chong ZZ, Kang JQ, Maiese K. AKT1 drives endothelial cell membrane asymmetry and microglial activation through Bcl-xL and caspase 1, 3, and 9. Exp Cell Res. 2004a; 296:196–207. [PubMed: 15149850]

Chong ZZ, Li F, Maiese K. Activating Akt and the brain's resources to drive cellular survival and prevent inflammatory injury. Histol Histopathol. 2005a; 20:299–315. [PubMed: 15578447]

Chong ZZ, Li F, Maiese K. Employing new cellular therapeutic targets for Alzheimer's disease: a change for the better? Curr Neurovasc Res. 2005b; 2:55–72. [PubMed: 16181100]

Chong ZZ, Li F, Maiese K. Erythropoietin requires NF-kappaB and its nuclear translocation to prevent early and late apoptotic neuronal injury during beta-amyloid toxicity. Curr Neurovasc Res. 2005c; 2:387–399. [PubMed: 16375720]

Chong ZZ, Li F, Maiese K. Oxidative stress in the brain: Novel cellular targets that govern survival during neurodegenerative disease. Prog Neurobiol. 2005d; 75:207–246. [PubMed: 15882775]

Chong ZZ, Li F, Maiese K. Attempted Cell Cycle Induction in Post-Mitotic Neurons Occurs in Early and Late Apoptotic Programs Through Rb, E2F1, and Caspase 3. Curr Neurovasc Res. 2006; 3:25–39. [PubMed: 16472123]

Chong ZZ, Li F, Maiese K. Cellular demise and inflammatory microglial activation during beta-amyloid toxicity are governed by Wnt1 and canonical signaling pathways. Cell Signal. 2007a; 19:1150–1162. [PubMed: 17289346]

Chong ZZ, Li F, Maiese K. The pro-survival pathways of mTOR and protein kinase B target glycogen synthase kinase-3beta and nuclear factor-kappaB to foster endogenous microglial cell protection. Int J Mol Med. 2007b; 19:263–272. [PubMed: 17203200]

Chong ZZ, Lin SH, Kang JQ, Maiese K. Erythropoietin prevents early and late neuronal demise through modulation of Akt1 and induction of caspase 1, 3, and 8. J Neurosci Res. 2003b; 71:659–669. [PubMed: 12584724]

Chong ZZ, Lin SH, Kang JQ, Maiese K. The tyrosine phosphatase SHP2 modulates MAP kinase p38 and caspase 1 and 3 to foster neuronal survival. Cell Mol Neurobiol. 2003c; 23:561–578. [PubMed: 14514016]

Chong ZZ, Lin SH, Li F, Maiese K. The sirtuin inhibitor nicotinamide enhances neuronal cell survival during acute anoxic injury through Akt, Bad, PARP, and mitochondrial associated “anti-apoptotic” pathways. Curr Neurovasc Res. 2005e; 2:271–285. [PubMed: 16181120]

Chong ZZ, Lin SH, Maiese K. The NAD+ precursor nicotinamide governs neuronal survival during oxidative stress through protein kinase B coupled to FOXO3a and mitochondrial membrane potential. J Cereb Blood Flow Metab. 2004b; 24:728–743. [PubMed: 15241181]

Chong ZZ, Maiese K. The Src homology 2 domain tyrosine phosphatases SHP-1 and SHP-2: diversified control of cell growth, inflammation, and injury. Histol Histopathol. 2007; 22:1251–1267. [PubMed: 17647198]

Chong ZZ, Shang YC, Hou J, Maiese K. Wnt1 neuroprotection translates into improved neurological function during oxidant stress and cerebral ischemia through AKT1 and mitochondrial apoptotic pathways. Oxid Med Cell Longev. 2010a; 3:153–165. [PubMed: 20716939]

Chong ZZ, Shang YC, Maiese K. Cardiovascular Disease and mTOR Signaling. Trends Cardiovasc Med. 2011b; 21:151–155. [PubMed: 22732551]

Chong ZZ, Shang YC, Wang S, Maiese K. SIRT1: New avenues of discovery for disorders of oxidative stress. Expert opinion on therapeutic targets. 2012a; 16:167–178. [PubMed: 22233091]

Chong ZZ, Shang YC, Zhang L, Wang S, Maiese K. Mammalian target of rapamycin: hitting the bull's-eye for neurological disorders. Oxid Med Cell Longev. 2010b; 3:374–391. [PubMed: 21307646]

Chong ZZ, Wang S, Shang YC, Maiese K. Targeting cardiovascular disease with novel SIRT1 pathways. Future Cardiol. 2012b; 8:89–100. [PubMed: 22185448]

Chung CY, Park YL, Song YA, Myung E, Kim KY, Lee GH, Ki HS, Park KJ, Cho SB, Lee WS, Jung YD, Kim KK, Joo YE. Knockdown of RON Inhibits AP-1 Activity and Induces Apoptosis and

Cell Cycle Arrest Through the Modulation of Akt/FoxO Signaling in Human Colorectal Cancer Cells. Dig Dis Sci. 2012; 57:371–380. [PubMed: 21901254]

Codeluppi S, Svensson CI, Hefferan MP, Valencia F, Silldorff MD, Oshiro M, Marsala M, Pasquale EB. The Rheb-mTOR pathway is upregulated in reactive astrocytes of the injured spinal cord. J Neurosci. 2009; 29:1093–1104. [PubMed: 19176818]

Cota D, Proulx K, Smith KA, Kozma SC, Thomas G, Woods SC, Seeley RJ. Hypothalamic mTOR signaling regulates food intake. Science. 2006; 312:927–930. [PubMed: 16690869]

Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. Lancet. 2008; 372:657–668. [PubMed: 18722871]

Curran MP. Everolimus: in patients with subependymal giant cell astrocytoma associated with tuberous sclerosis complex. Paediatr Drugs. 2012; 14:51–60. [PubMed: 22136276]

Czene S, Tiback M, Harms-Ringdahl M. pH-dependent DNA cleavage in permeabilized human fibroblasts. Biochem J. 1997; 323:337–341. [PubMed: 9163321]

Dada S, Demartines N, Dormond O. mTORC2 regulates PGE2-mediated endothelial cell survival and migration. Biochem Biophys Res Commun. 2008; 372:875–879. [PubMed: 18539142]

Dan HC, Adli M, Baldwin AS. Regulation of mammalian target of rapamycin activity in PTEN-inactive prostate cancer cells by I kappa B kinase alpha. Cancer Res. 2007; 67:6263–6269. [PubMed: 17616684]

Das J, Ghosh J, Manna P, Sil PC. Taurine suppresses doxorubicin-triggered oxidative stress and cardiac apoptosis in rat via up-regulation of PI3-K/Akt and inhibition of p53, p38-JNK. Biochem Pharmacol. 2011; 81:891–909. [PubMed: 21295553]

Dasgupta B, Yi Y, Chen DY, Weber JD, Gutmann DH. Proteomic analysis reveals hyperactivation of the mammalian target of rapamycin pathway in neurofibromatosis 1-associated human and mouse brain tumors. Cancer Res. 2005; 65:2755–2760. [PubMed: 15805275]

De Simone R, Ajmone-Cat MA, Minghetti L. Atypical antiinflammatory activation of microglia induced by apoptotic neurons: possible role of phosphatidylserine-phosphatidylserine receptor interaction. Mol Neurobiol. 2004; 29:197–212. [PubMed: 15126686]

Deblon N, Bourgoin L, Veyrat-Durebex C, Peyrou M, Vinciguerra M, Caillon A, Maeder C, Fournier M, Montet X, Rohner-Jeanrenaud F, Foti M. Chronic mTOR inhibition by rapamycin induces muscle insulin resistance despite weight loss in rats. Br J Pharmacol. 2012; 165:2325–2340. [PubMed: 22014210]

Dello Russo C, Lisi L, Tringali G, Navarra P. Involvement of mTOR kinase in cytokine-dependent microglial activation and cell proliferation. Biochem Pharmacol. 2009; 78:1242–1251. [PubMed: 19576187]

Deruy E, Gosselin K, Vercamer C, Martien S, Bouali F, Slomianny C, Bertout J, Bernard D, Pourtier A, Abbadie C. MnSOD upregulation induces autophagic programmed cell death in senescent keratinocytes. PLoS One. 2010; 5:e12712. [PubMed: 20856861]

DeYoung MP, Horak P, Sofer A, Sgroi D, Ellisen LW. Hypoxia regulates TSC1/2-mTOR signaling and tumor suppression through REDD1-mediated 14-3-3 shuttling. Genes Dev. 2008; 22:239–251. [PubMed: 18198340]

Di Nardo A, Kramvis I, Cho N, Sadowski A, Meikle L, Kwiatkowski DJ, Sahin M. Tuberous sclerosis complex activity is required to control neuronal stress responses in an mTOR-dependent manner. J Neurosci. 2009; 29:5926–5937. [PubMed: 19420259]

Dibble CC, Asara JM, Manning BD. Characterization of Rictor phosphorylation sites reveals direct regulation of mTOR complex 2 by S6K1. Mol Cell Biol. 2009; 29:5657–5670. [PubMed: 19720745]

Dormond O, Madsen JC, Briscoe DM. The effects of mTOR-Akt interactions on anti-apoptotic signaling in vascular endothelial cells. J Biol Chem. 2007; 282:23679–23686. [PubMed: 17553806]

Du Y, Zhang X, Ji H, Liu H, Li S, Li L. Probucol and atorvastatin in combination protect rat brains in MCAO model: upregulating Peroxiredoxin2, Foxo3a and Nrf2 expression. Neurosci Lett. 2012; 509:110–115. [PubMed: 22233727]

Duan S, Skaar JR, Kuchay S, Toschi A, Kanarek N, Ben-Neriah Y, Pagano M. mTOR Generates an Auto-Amplification Loop by Triggering the betaTrCP- and CK1alpha-Dependent Degradation of DEPTOR. Mol Cell. 2011; 44:317–324. [PubMed: 22017877]

Easley CA, Ben-Yehudah A, Redinger CJ, Oliver SL, Varum ST, Eisinger VM, Carlisle DL, Donovan PJ, Schatten GP. mTOR-mediated activation of p70 S6K induces differentiation of pluripotent human embryonic stem cells. Cellular reprogramming. 2010; 12:263–273. [PubMed: 20698768]

Echeverria V, Zeitlin R, Burgess S, Patel S, Barman A, Thakur G, Mamcarz M, Wang L, Sattelle DB, Kirschner DA, Mori T, Leblanc RM, Prabhakar R, Arendash GW. Cotinine Reduces Amyloid-beta Aggregation and Improves Memory in Alzheimer's Disease Mice. J Alzheimers Dis. 2011

Eipel C, Hubschmann U, Abshagen K, Wagner KF, Menger MD, Vollmar B. Erythropoietin as Additive of HTK Preservation Solution in Cold Ischemia/Reperfusion Injury of Steatotic Livers. J Surg Res. 2012; 173:171–179. [PubMed: 21074785]

Ekim B, Magnuson B, Acosta-Jaquez HA, Keller JA, Feener EP, Fingar DC. mTOR Kinase Domain Phosphorylation Promotes mTORC1 Signaling, Cell Growth, and Cell Cycle Progression. Mol Cell Biol. 2011; 31:2787–2801. [PubMed: 21576368]

Erlich S, Alexandrovich A, Shohami E, Pinkas-Kramarski R. Rapamycin is a neuroprotective treatment for traumatic brain injury. Neurobiol Dis. 2007; 26:86–93. [PubMed: 17270455]

Escobar J, Pereda J, Lopez-Rodas G, Sastre J. Redox signaling and histone acetylation in acute pancreatitis. Free Radic Biol Med. 2012; 52:819–837. [PubMed: 22178977]

Faghiri Z, Bazan NG. PI3K/Akt and mTOR/p70S6K pathways mediate neuroprotectin D1-induced retinal pigment epithelial cell survival during oxidative stress-induced apoptosis. Exp Eye Res. 2010; 90:718–725. [PubMed: 20230819]

Fernandez-Martos CM, Gonzalez-Fernandez C, Gonzalez P, Maqueda A, Arenas E, Rodriguez FJ. Differential expression of wnts after spinal cord contusion injury in adult rats. PLoS ONE. 2011; 6:e27000. [PubMed: 22073235]

Fingar DC, Richardson CJ, Tee AR, Cheatham L, Tsou C, Blenis J. mTOR controls cell cycle progression through its cell growth effectors S6K1 and 4E-BP1/eukaryotic translation initiation factor 4E. Mol Cell Biol. 2004; 24:200–216. [PubMed: 14673156]

Floto RA, Sarkar S, Perlstein EO, Kampmann B, Schreiber SL, Rubinsztein DC. Small molecule enhancers of rapamycin-induced TOR inhibition promote autophagy, reduce toxicity in Huntington's disease models and enhance killing of mycobacteria by macrophages. Autophagy. 2007; 3:620–622. [PubMed: 17786022]

Floyd S, Favre C, Lasorsa FM, Leahy M, Trigiante G, Stroebel P, Marx A, Loughran G, O'Callaghan K, Marobbio CM, Slotboom DJ, Kunji ER, Palmieri F, O'Connor R. The insulin-like growth factor-I-mTOR signaling pathway induces the mitochondrial pyrimidine nucleotide carrier to promote cell growth. Mol Biol Cell. 2007; 18:3545–3555. [PubMed: 17596519]

Fokas E, Yoshimura M, Prevo R, Higgins G, Hackl W, Maira SM, Bernhard EJ, McKenna WG, Muschel RJ. NVP-BEZ235 and NVP-BGT226, dual phosphatidylinositol 3-kinase/Mammalian target of rapamycin inhibitors, enhance tumor and endothelial cell radiosensitivity. Radiat Oncol. 2012; 7:48. [PubMed: 22452803]

Fox JH, Connor T, Chopra V, Dorsey K, Kama JA, Bleckmann D, Betschart C, Hoyer D, Frentzel S, Difiglia M, Paganetti P, Hersch SM. The mTOR kinase inhibitor Everolimus decreases S6 kinase phosphorylation but fails to reduce mutant huntingtin levels in brain and is not neuroprotective in the R6/2 mouse model of Huntington's disease. Molecular neurodegeneration. 2010; 5:26. [PubMed: 20569486]

Frias MA, Thoreen CC, Jaffe JD, Schroder W, Sculley T, Carr SA, Sabatini DM. mSin1 is necessary for Akt/PKB phosphorylation, and its isoforms define three distinct mTORC2s. Curr Biol. 2006; 16:1865–1870. [PubMed: 16919458]

Galan-Moya EM, Le Guelte A, Lima Fernandes E, Thirant C, Dwyer J, Bidere N, Couraud PO, Scott MG, Junier MP, Chneiweiss H, Gavard J. Secreted factors from brain endothelial cells maintain glioblastoma stem-like cell expansion through the mTOR pathway. EMBO Rep. 2011; 12:470–476. [PubMed: 21460795]

Gangloff YG, Mueller M, Dann SG, Svoboda P, Sticker M, Spetz JF, Um SH, Brown EJ, Cereghini S, Thomas G, Kozma SC. Disruption of the mouse mTOR gene leads to early postimplantation

lethality and prohibits embryonic stem cell development. Mol Cell Biol. 2004; 24:9508–9516. [PubMed: 15485918]

Gao D, Inuzuka H, Tan MK, Fukushima H, Locasale JW, Liu P, Wan L, Zhai B, Chin YR, Shaik S, Lyssiotis CA, Gygi SP, Toker A, Cantley LC, Asara JM, Harper JW, Wei W. mTOR Drives Its Own Activation via SCF(betaTrCP)-Dependent Degradation of the mTOR Inhibitor DEPTOR. Mol Cell. 2011; 44:290–303. [PubMed: 22017875]

Garcia-Martinez JM, Alessi DR. mTOR complex 2 (mTORC2) controls hydrophobic motif phosphorylation and activation of serum- and glucocorticoid-induced protein kinase 1 (SGK1). Biochem J. 2008; 416:375–385. [PubMed: 18925875]

Ghosh N, Ghosh R, Mandal SC. Antioxidant protection: A promising therapeutic intervention in neurodegenerative disease. Free Radic Res. 2011; 45:888–905. [PubMed: 21615270]

Gingras AC, Kennedy SG, O'Leary MA, Sonenberg N, Hay N. 4E-BP1, a repressor of mRNA translation, is phosphorylated and inactivated by the Akt(PKB) signaling pathway. Genes Dev. 1998; 12:502–513. [PubMed: 9472019]

Glidden EJ, Gray LG, Vemuru S, Li D, Harris TE, Mayo MW. Multiple site acetylation of Rictor stimulates mammalian target of rapamycin complex 2 (mTORC2)-dependent phosphorylation of Akt protein. J Biol Chem. 2012; 287:581–588. [PubMed: 22084251]

Goffus AM, Anderson GD, Hoane M. Sustained delivery of nicotinamide limits cortical injury and improves functional recovery following traumatic brain injury. Oxid Med Cell Longev. 2010; 3:145–152. [PubMed: 20716938]

Good DW, George T, Watts BA 3rd. Nerve growth factor inhibits Na+/H+ exchange and formula absorption through parallel phosphatidylinositol 3-kinase-mTOR and ERK pathways in thick ascending limb. J Biol Chem. 2008; 283:26602–26611. [PubMed: 18660503]

Griffin RJ, Moloney A, Kelliher M, Johnston JA, Ravid R, Dockery P, O'Connor R, O'Neill C. Activation of Akt/PKB, increased phosphorylation of Akt substrates and loss and altered distribution of Akt and PTEN are features of Alzheimer's disease pathology. J Neurochem. 2005; 93:105–117. [PubMed: 15773910]

Guertin DA, Stevens DM, Thoreen CC, Burds AA, Kalaany NY, Moffat J, Brown M, Fitzgerald KJ, Sabatini DM. Ablation in mice of the mTORC components raptor, rictor, or mLST8 reveals that mTORC2 is required for signaling to Akt-FOXO and PKCalpha, but not S6K1. Dev Cell. 2006; 11:859–871. [PubMed: 17141160]

Gulhati P, Bowen KA, Liu J, Stevens PD, Rychahou PG, Chen M, Lee EY, Weiss HL, O'Connor KL, Gao T, Evers BM. mTORC1 and mTORC2 regulate EMT, motility, and metastasis of colorectal cancer via RhoA and Rac1 signaling pathways. Cancer Res. 2011; 71:3246–3256. [PubMed: 21430067]

Gumy LF, Tan CL, Fawcett JW. The role of local protein synthesis and degradation in axon regeneration. Exp Neurol. 2010; 223:28–37. [PubMed: 19520073]

Gwinn DM, Shackelford DB, Egan DF, Mihaylova MM, Mery A, Vasquez DS, Turk BE, Shaw RJ. AMPK phosphorylation of raptor mediates a metabolic checkpoint. Mol Cell. 2008; 30:214–226. [PubMed: 18439900]

Han J, Shi S, Min L, Wu T, Xia W, Ying W. NAD(+) Treatment Induces Delayed Autophagy in Neuro2a Cells Partially by Increasing Oxidative Stress. Neurochem Res. 2011; 36:2270–2277. [PubMed: 21833846]

Han J, Wang B, Xiao Z, Gao Y, Zhao Y, Zhang J, Chen B, Wang X, Dai J. Mammalian target of rapamycin (mTOR) is involved in the neuronal differentiation of neural progenitors induced by insulin. Mol Cell Neurosci. 2008; 39:118–124. [PubMed: 18620060]

Hansel DE, Platt E, Orloff M, Harwalker J, Sethu S, Hicks JL, De Marzo A, Steinle RE, Hsi ED, Theodorescu D, Ching CB, Eng C. Mammalian target of rapamycin (mTOR) regulates cellular proliferation and tumor growth in urothelial carcinoma. Am J Pathol. 2010; 176:3062–3072. [PubMed: 20395440]

Hara K, Maruki Y, Long X, Yoshino K, Oshiro N, Hidayat S, Tokunaga C, Avruch J, Yonezawa K. Raptor, a binding partner of target of rapamycin (TOR), mediates TOR action. Cell. 2002; 110:177–189. [PubMed: 12150926]

Harrington LS, Findlay GM, Gray A, Tolkacheva T, Wigfield S, Rebholz H, Barnett J, Leslie NR, Cheng S, Shepherd PR, Gout I, Downes CP, Lamb RF. The TSC1-2 tumor suppressor controls insulin-PI3K signaling via regulation of IRS proteins. J Cell Biol. 2004; 166:213–223. [PubMed: 15249583]

Harrison DE, Strong R, Sharp ZD, Nelson JF, Astle CM, Flurkey K, Nadon NL, Wilkinson JE, Frenkel K, Carter CS, Pahor M, Javors MA, Fernandez E, Miller RA. Rapamycin fed late in life extends lifespan in genetically heterogeneous mice. Nature. 2009; 460:392–395. [PubMed: 19587680]

Heitman J, Movva NR, Hall MN. Targets for cell cycle arrest by the immunosuppressant rapamycin in yeast. Science. 1991; 253:905–909. [PubMed: 1715094]

Herbas MS, Ueta YY, Ishibashi K, Suzuki H. Expression of erythropoietic cytokines in alpha-tocopherol transfer protein knockout mice with murine malaria infection. Parasitol Res. 2011; 109:1243–1250. [PubMed: 21479575]

Hernandez G, Lal H, Fidalgo M, Guerrero A, Zalvide J, Force T, Pombo CM. A novel cardioprotective p38-MAPK/mTOR pathway. Exp Cell Res. 2011; 317:2938–2949. [PubMed: 22001647]

Hernandez-Negrete I, Carretero-Ortega J, Rosenfeldt H, Hernandez-Garcia R, Calderon-Salinas JV, Reyes-Cruz G, Gutkind JS, Vazquez-Prado J. P-Rex1 links mammalian target of rapamycin signaling to Rac activation and cell migration. J Biol Chem. 2007; 282:23708–23715. [PubMed: 17565979]

Heublein S, Kazi S, Ogmundsdottir MH, Attwood EV, Kala S, Boyd CA, Wilson C, Goberdhan DC. Proton-assisted amino-acid transporters are conserved regulators of proliferation and amino-acid-dependent mTORC1 activation. Oncogene. 2010; 29:4068–4079. [PubMed: 20498635]

Hofbauer GF, Marcollo-Pini A, Corsenca A, Kistler AD, French LE, Wuthrich RP, Serra AL. The mTOR inhibitor rapamycin significantly improves facial angiofibroma lesions in a patient with tuberous sclerosis. The British journal of dermatology. 2008; 159:473–475. [PubMed: 18547304]

Holmes GL, Stafstrom CE. Tuberous sclerosis complex and epilepsy: recent developments and future challenges. Epilepsia. 2007; 48:617–630. [PubMed: 17386056]

Holz MK, Blenis J. Identification of S6 kinase 1 as a novel mammalian target of rapamycin (mTOR)-phosphorylating kinase. J Biol Chem. 2005; 280:26089–26093. [PubMed: 15905173]

Hong JR, Lin GH, Lin CJ, Wang WP, Lee CC, Lin TL, Wu JL. Phosphatidylserine receptor is required for the engulfment of dead apoptotic cells and for normal embryonic development in zebrafish. Development. 2004; 131:5417–5427. [PubMed: 15469976]

Hosokawa N, Sasaki T, Iemura S, Natsume T, Hara T, Mizushima N. Atg101, a novel mammalian autophagy protein interacting with Atg13. Autophagy. 2009; 5:973–979. [PubMed: 19597335]

Hou G, Xue L, Lu Z, Fan T, Tian F, Xue Y. An activated mTOR/p70S6K signaling pathway in esophageal squamous cell carcinoma cell lines and inhibition of the pathway by rapamycin and siRNA against mTOR. Cancer Lett. 2007; 253:236–248. [PubMed: 17360108]

Hou J, Chong ZZ, Shang YC, Maiese K. Early apoptotic vascular signaling is determined by Sirt1 through nuclear shuttling, forkhead trafficking, bad, and mitochondrial caspase activation. Curr Neurovasc Res. 2010a; 7:95–112. [PubMed: 20370652]

Hou J, Chong ZZ, Shang YC, Maiese K. FoxO3a governs early and late apoptotic endothelial programs during elevated glucose through mitochondrial and caspase signaling. Mol Cell Endocrinol. 2010b; 321:194–206. [PubMed: 20211690]

Hou J, Wang S, Shang YC, Chong ZZ, Maiese K. Erythropoietin Employs Cell Longevity Pathways of SIRT1 to Foster Endothelial Vascular Integrity During Oxidant Stress. Curr Neurovasc Res. 2011; 8:220–235. [PubMed: 21722091]

Hresko RC, Mueckler M. mTOR.RICTOR is the Ser473 kinase for Akt/protein kinase B in 3T3-L1 adipocytes. J Biol Chem. 2005; 280:40406–40416. [PubMed: 16221682]

Hu LY, Sun ZG, Wen YM, Cheng GZ, Wang SL, Zhao HB, Zhang XR. ATP-mediated protein kinase B Akt/mammalian target of rapamycin mTOR/p70 ribosomal S6 protein p70S6 kinase signaling pathway activation promotes improvement of locomotor function after spinal cord injury in rats. Neuroscience. 2010; 169:1046–1062. [PubMed: 20678995]

Huang J, Dibble CC, Matsuzaki M, Manning BD. The TSC1-TSC2 complex is required for proper activation of mTOR complex 2. Mol Cell Biol. 2008; 28:4104–4115. [PubMed: 18411301]

Huang J, Wu S, Wu CL, Manning BD. Signaling events downstream of mammalian target of rapamycin complex 2 are attenuated in cells and tumors deficient for the tuberous sclerosis complex tumor suppressors. Cancer Res. 2009a; 69:6107–6114. [PubMed: 19602587]

Huang J, Zhang Y, Bersenev A, O'Brien WT, Tong W, Emerson SG, Klein PS. Pivotal role for glycogen synthase kinase-3 in hematopoietic stem cell homeostasis in mice. J Clin Invest. 2009b; 119:3519–3529. [PubMed: 19959876]

Huang X, McMahon J, Huang Y. Rapamycin attenuates aggressive behavior in a rat model of pilocarpine-induced epilepsy. Neuroscience. 2012

Hwang SK, Kim HH. The functions of mTOR in ischemic diseases. BMB Rep. 2011; 44:506–511. [PubMed: 21871173]

Hyrskyluoto A, Reijonen S, Kivinen J, Lindholm D, Korhonen L. GADD34 mediates cytoprotective autophagy in mutant huntingtin expressing cells via the mTOR pathway. Exp Cell Res. 2012; 318:33–42. [PubMed: 21925170]

Imai Y, Gehrke S, Wang HQ, Takahashi R, Hasegawa K, Oota E, Lu B. Phosphorylation of 4E-BP by LRRK2 affects the maintenance of dopaminergic neurons in Drosophila. Embo J. 2008; 27:2432–2443. [PubMed: 18701920]

Inoki K, Li Y, Zhu T, Wu J, Guan KL. TSC2 is phosphorylated and inhibited by Akt and suppresses mTOR signalling. Nat Cell Biol. 2002; 4:648–657. [PubMed: 12172553]

Inoki K, Ouyang H, Zhu T, Lindvall C, Wang Y, Zhang X, Yang Q, Bennett C, Harada Y, Stankunas K, Wang CY, He X, MacDougald OA, You M, Williams BO, Guan KL. TSC2 integrates Wnt and energy signals via a coordinated phosphorylation by AMPK and GSK3 to regulate cell growth. Cell. 2006; 126:955–968. [PubMed: 16959574]

Inoki K, Zhu T, Guan KL. TSC2 mediates cellular energy response to control cell growth and survival. Cell. 2003; 115:577–590. [PubMed: 14651849]

Jaber N, Dou Z, Chen JS, Catanzaro J, Jiang YP, Ballou LM, Selinger E, Ouyang X, Lin RZ, Zhang J, Zong WX. Class III PI3K Vps34 plays an essential role in autophagy and in heart and liver function. Proc Natl Acad Sci U S A. 2012; 109:2003–2008. [PubMed: 22308354]

Jacinto E, Facchinetti V, Liu D, Soto N, Wei S, Jung SY, Huang Q, Qin J, Su B. SIN1/MIP1 maintains rictor-mTOR complex integrity and regulates Akt phosphorylation and substrate specificity. Cell. 2006; 127:125–137. [PubMed: 16962653]

Jacinto E, Loewith R, Schmidt A, Lin S, Ruegg MA, Hall A, Hall MN. Mammalian TOR complex 2 controls the actin cytoskeleton and is rapamycin insensitive. Nat Cell Biol. 2004; 6:1122–1128. [PubMed: 15467718]

James MF, Stivison E, Beauchamp R, Han S, Li H, Wallace MR, Gusella JF, Stemmer-Rachamimov AO, Ramesh V. Regulation of mTOR Complex 2 Signaling in Neurofibromatosis 2-Deficient Target Cell Types. Mol Cancer Res. 2012

Janku F, Wheler JJ, Westin SN, Moulder SL, Naing A, Tsimberidou AM, Fu S, Falchook GS, Hong DS, Garrido-Laguna I, Luthra R, Lee JJ, Lu KH, Kurzrock R. PI3K/AKT/mTOR inhibitors in patients with breast and gynecologic malignancies harboring PIK3CA mutations. J Clin Oncol. 2012; 30:777–782. [PubMed: 22271473]

Jastrzebski K, Hannan KM, Tchoubrieva EB, Hannan RD, Pearson RB. Coordinate regulation of ribosome biogenesis and function by the ribosomal protein S6 kinase, a key mediator of mTOR function. Growth Factors. 2007; 25:209–226. [PubMed: 18092230]

Jayaram HN, Kusumanchi P, Yalowitz JA. NMNAT Expression and its Relation to NAD Metabolism. Curr Med Chem. 2011; 18:1962–1972. [PubMed: 21517776]

Jeong JK, Moon MH, Bae BC, Lee YJ, Seol JW, Kang HS, Kim JS, Kang SJ, Park SY. Autophagy induced by resveratrol prevents human prion protein-mediated neurotoxicity. Neurosci Res. 2012; 73:99–105. [PubMed: 22465415]

Jiang YL, Ning Y, Ma XL, Liu YY, Wang Y, Zhang Z, Shan CX, Xu YD, Yin LM, Yang YQ. Alteration of the proteome profile of the pancreas in diabetic rats induced by streptozotocin. Int J Mol Med. 2011; 28:153–160. [PubMed: 21567075]

Johannessen CM, Johnson BW, Williams SM, Chan AW, Reczek EE, Lynch RC, Rioth MJ, McClatchey A, Ryeom S, Cichowski K. TORC1 is essential for NF1-associated malignancies. Curr Biol. 2008; 18:56–62. [PubMed: 18164202]

Jozwiak J, Kotulska K, Lojek M, Galus R, Jozwiak S, Polnik D, Wlodarski PK. Fibroblasts from normal skin of a tuberous sclerosis patient show upregulation of mTOR pathway. The American Journal of dermatopathology. 2009; 31:68–70. [PubMed: 19155728]

Julien LA, Carriere A, Moreau J, Roux PP. mTORC1-activated S6K1 phosphorylates Rictor on threonine 1135 and regulates mTORC2 signaling. Mol Cell Biol. 2010; 30:908–921. [PubMed: 19995915]

Jung CH, Jun CB, Ro SH, Kim YM, Otto NM, Cao J, Kundu M, Kim DH. ULK-Atg13-FIP200 complexes mediate mTOR signaling to the autophagy machinery. Mol Biol Cell. 2009; 20:1992–2003. [PubMed: 19225151]

Kabeya Y, Kamada Y, Baba M, Takikawa H, Sasaki M, Ohsumi Y. Atg17 functions in cooperation with Atg1 and Atg13 in yeast autophagy. Mol Biol Cell. 2005; 16:2544–2553. [PubMed: 15743910]

Kahn BB, Alquier T, Carling D, Hardie DG. AMP-activated protein kinase: ancient energy gauge provides clues to modern understanding of metabolism. Cell Metab. 2005; 1:15–25. [PubMed: 16054041]

Kamada Y, Funakoshi T, Shintani T, Nagano K, Ohsumi M, Ohsumi Y. Tor-mediated induction of autophagy via an Apg1 protein kinase complex. J Cell Biol. 2000; 150:1507–1513. [PubMed: 10995454]

Kang JQ, Chong ZZ, Maiese K. Akt1 protects against inflammatory microglial activation through maintenance of membrane asymmetry and modulation of cysteine protease activity. J Neurosci Res. 2003a; 74:37–51. [PubMed: 13130504]

Kang JQ, Chong ZZ, Maiese K. Critical role for Akt1 in the modulation of apoptotic phosphatidylserine exposure and microglial activation. Mol Pharmacol. 2003b; 64:557–569. [PubMed: 12920191]

Karlsson E, Waltersson MA, Bostner J, Perez-Tenorio G, Olsson B, Hallbeck AL, Stal O. High-resolution genomic analysis of the 11q13 amplicon in breast cancers identifies synergy with 8p12 amplification, involving the mTOR targets S6K2 and 4EBP1. Genes Chromosomes Cancer. 2011; 50:775–787. [PubMed: 21748818]

Kato S, Aoyama M, Kakita H, Hida H, Kato I, Ito T, Goto T, Hussein MH, Sawamoto K, Togari H, Asai K. Endogenous erythropoietin from astrocyte protects the oligodendrocyte precursor cell against hypoxic and reoxygenation injury. J Neurosci Res. 2011; 89:1566–1574. [PubMed: 21833990]

Kawamoto EM, Gleichmann M, Yshii LM, Lima Lde S, Mattson MP, Scavone C. Effect of activation of canonical Wnt signaling by the Wnt-3a protein on the susceptibility of PC12 cells to oxidative and apoptotic insults. Braz J Med Biol Res. 2012; 45:58–67. [PubMed: 22124704]

Khan MM, Ahmad A, Ishrat T, Khan MB, Hoda MN, Khuwaja G, Raza SS, Khan A, Javed H, Vaibhav K, Islam F. Resveratrol attenuates 6-hydroxydopamine-induced oxidative damage and dopamine depletion in rat model of Parkinson's disease. Brain Res. 2010; 1328:139–151. [PubMed: 20167206]

Kigerl KA, Ankeny DP, Garg SK, Wei P, Guan Z, Lai W, McTigue DM, Banerjee R, Popovich PG. System x(c)(-) regulates microglia and macrophage glutamate excitotoxicity in vivo. Exp Neurol. 2012; 233:333–341. [PubMed: 22079587]

Kim DH, Sarbassov DD, Ali SM, King JE, Latek RR, Erdjument-Bromage H, Tempst P, Sabatini DM. mTOR interacts with raptor to form a nutrient-sensitive complex that signals to the cell growth machinery. Cell. 2002; 110:163–175. [PubMed: 12150925]

Kim DH, Sarbassov DD, Ali SM, Latek RR, Guntur KV, Erdjument-Bromage H, Tempst P, Sabatini DM. GbetaL, a positive regulator of the rapamycin-sensitive pathway required for the nutrient-sensitive interaction between raptor and mTOR. Mol Cell. 2003; 11:895–904. [PubMed: 12718876]

Kim H, Choi J, Ryu J, Park SG, Cho S, Park BC, Lee do H. Activation of autophagy during glutamate-induced HT22 cell death. Biochem Biophys Res Commun. 2009; 388:339–344. [PubMed: 19665009]

Kim J, Jung Y, Sun H, Joseph J, Mishra A, Shiozawa Y, Wang J, Krebsbach PH, Taichman RS. Erythropoietin mediated bone formation is regulated by mTOR signaling. J Cell Biochem. 2012; 113:220–228. [PubMed: 21898543]

Koh PO. Melatonin prevents ischemic brain injury through activation of the mTOR/p70S6 kinase signaling pathway. Neurosci Lett. 2008; 444:74–78. [PubMed: 18721861]

Koh PO. Nicotinamide attenuates the decrease of astrocytic phosphoprotein PEA-15 in focal cerebral ischemic injury. J Vet Med Sci. 2012; 74:377–380. [PubMed: 22067079]

Kook YH, Ka M, Um M. Neuroprotective cytokines repress PUMA induction in the 1-methyl-4-phenylpyridinium (MPP(+)) model of Parkinson's disease. Biochem Biophys Res Commun. 2011; 411:370–374. [PubMed: 21741364]

Koren I, Reem E, Kimchi A. DAP1, a novel substrate of mTOR, negatively regulates autophagy. Curr Biol. 2010; 20:1093–1098. [PubMed: 20537536]

Kovacina KS, Park GY, Bae SS, Guzzetta AW, Schaefer E, Birnbaum MJ, Roth RA. Identification of a proline-rich Akt substrate as a 14-3-3 binding partner. J Biol Chem. 2003; 278:10189–10194. [PubMed: 12524439]

Kuroyanagi H, Yan J, Seki N, Yamanouchi Y, Suzuki Y, Takano T, Muramatsu M, Shirasawa T. Human ULK1, a novel serine/threonine kinase related to UNC-51 kinase of Caenorhabditis elegans: cDNA cloning, expression, and chromosomal assignment. Genomics. 1998; 51:76–85. [PubMed: 9693035]

Kuypers NJ, Hoane MR. Pyridoxine administration improves behavioral and anatomical outcome after unilateral contusion injury in the rat. J Neurotrauma. 2010; 27:1275–1282. [PubMed: 20486803]

L'Episcopo F, Tirolo C, Testa N, Caniglia S, Morale MC, Deleidi M, Serapide MF, Pluchino S, Marchetti B. Plasticity of Subventricular Zone Neuroprogenitors in MPTP (1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine) Mouse Model of Parkinson's Disease Involves Cross Talk between Inflammatory and Wnt/beta-Catenin Signaling Pathways: Functional Consequences for Neuroprotection and Repair. J Neurosci. 2012; 32:2062–2085. [PubMed: 22323720]

Lafay-Chebassier C, Paccalin M, Page G, Barc-Pain S, Perault-Pochat MC, Gil R, Pradier L, Hugon J. mTOR/p70S6k signalling alteration by Abeta exposure as well as in APP-PS1 transgenic models and in patients with Alzheimer's disease. J Neurochem. 2005; 94:215–225. [PubMed: 15953364]

Lafay-Chebassier C, Perault-Pochat MC, Page G, Rioux Bilan A, Damjanac M, Pain S, Houeto JL, Gil R, Hugon J. The immunosuppressant rapamycin exacerbates neurotoxicity of Abeta peptide. J Neurosci Res. 2006; 84:1323–1334. [PubMed: 16955484]

Land SC, Tee AR. Hypoxia-inducible factor 1alpha is regulated by the mammalian target of rapamycin (mTOR) via an mTOR signaling motif. J Biol Chem. 2007; 282:20534–20543. [PubMed: 17502379]

Lappas M, Permezel M. The anti-inflammatory and antioxidative effects of nicotinamide, a vitamin B(3) derivative, are elicited by FoxO3 in human gestational tissues: implications for preterm birth. The Journal of nutritional biochemistry. 2011; 22:1195–1201. [PubMed: 21414766]

Le XF, Mao W, Lu Z, Carter BZ, Bast RC Jr. Dasatinib induces autophagic cell death in human ovarian cancer. Cancer. 2010

Lee DF, Kuo HP, Chen CT, Hsu JM, Chou CK, Wei Y, Sun HL, Li LY, Ping B, Huang WC, He X, Hung JY, Lai CC, Ding Q, Su JL, Yang JY, Sahin AA, Hortobagyi GN, Tsai FJ, Tsai CH, Hung MC. IKK beta suppression of TSC1 links inflammation and tumor angiogenesis via the mTOR pathway. Cell. 2007; 130:440–455. [PubMed: 17693255]

Lee G, Pollard HB, Arispe N. Annexin 5 and apolipoprotein E2 protect against Alzheimer's amyloid-beta-peptide cytotoxicity by competitive inhibition at a common phosphatidylserine interaction site. Peptides. 2002; 23:1249–1263. [PubMed: 12128082]

Lee ST, Chu K, Park JE, Jung KH, Jeon D, Lim JY, Lee SK, Kim M, Roh JK. Erythropoietin improves memory function with reducing endothelial dysfunction and amyloid-beta burden in Alzheimer's disease models. J Neurochem. 2012; 120:115–124. [PubMed: 22004348]

Lehtinen MK, Tegelberg S, Schipper H, Su H, Zukor H, Manninen O, Kopra O, Joensuu T, Hakala P, Bonni A, Lehesjoki AE. Cystatin B deficiency sensitizes neurons to oxidative stress in progressive myoclonus epilepsy, EPM1. J Neurosci. 2009; 29:5910–5915. [PubMed: 19420257]

Leuner K, Hauptmann S, Abdel-Kader R, Scherping I, Keil U, Strosznajder JB, Eckert A, Muller WE. Mitochondrial dysfunction: the first domino in brain aging and Alzheimer's disease? Antioxid Redox Signal. 2007; 9:1659–1675. [PubMed: 17867931]

Li F, Chong ZZ, Maiese K. Vital elements of the wnt-frizzled signaling pathway in the nervous system. Curr Neurovasc Res. 2005a; 2:331–340. [PubMed: 16181124]

Li F, Chong ZZ, Maiese K. Cell Life Versus Cell Longevity: The Mysteries Surrounding the NAD(+) Precursor Nicotinamide. Curr Med Chem. 2006a; 13:883–895. [PubMed: 16611073]

Li F, Chong ZZ, Maiese K. Microglial integrity is maintained by erythropoietin through integration of Akt and its substrates of glycogen synthase kinase-3beta, beta-catenin, and nuclear factor-kappaB. Curr Neurovasc Res. 2006b; 3:187–201. [PubMed: 16918383]

Li F, Chong ZZ, Maiese K. Winding through the WNT pathway during cellular development and demise. Histol Histopathol. 2006c; 21:103–124. [PubMed: 16267791]

Li L, Kim E, Yuan H, Inoki K, Goraksha-Hicks P, Schiesher RL, Neufeld TP, Guan KL. Regulation of mTORC1 by the Rab and Arf GTPases. J Biol Chem. 2010; 285:19705–19709. [PubMed: 20457610]

Li X, Alafuzoff I, Soininen H, Winblad B, Pei JJ. Levels of mTOR and its downstream targets 4E-BP1, eEF2, and eEF2 kinase in relationships with tau in Alzheimer's disease brain. The FEBS journal. 2005b; 272:4211–4220. [PubMed: 16098202]

Lin SH, Chong ZZ, Maiese K. Cell cycle induction in post-mitotic neurons proceeds in concert with the initial phase of programmed cell death in rat. Neurosci Lett. 2001; 310:173–177. [PubMed: 11585595]

Lin SH, Vincent A, Shaw T, Maynard KI, Maiese K. Prevention of nitric oxide-induced neuronal injury through the modulation of independent pathways of programmed cell death. J Cereb Blood Flow Metab. 2000; 20:1380–1391. [PubMed: 10994860]

Liu G, Detloff MR, Miller KN, Santi L, Houle JD. Exercise modulates microRNAs that affect the PTEN/mTOR pathway in rats after spinal cord injury. Exp Neurol. 2012; 233:447–456. [PubMed: 22123082]

Liu K, Liu C, Shen L, Shi J, Zhang T, Zhou Y, Zhou L, Sun X. Therapeutic effects of rapamycin on MPTP-induced Parkinsonism in mice. Neurochem Int. 2011

Liu K, Lu Y, Lee JK, Samara R, Willenberg R, Sears-Kraxberger I, Tedeschi A, Park KK, Jin D, Cai B, Xu B, Connolly L, Steward O, Zheng B, He Z. PTEN deletion enhances the regenerative ability of adult corticospinal neurons. Nat Neurosci. 2010a; 13:1075–1081. [PubMed: 20694004]

Liu T, Jin H, Sun QR, Xu JH, Hu HT. The neuroprotective effects of tanshinone IIA on beta-amyloid-induced toxicity in rat cortical neurons. Neuropharmacology. 2010b; 59:595–604. [PubMed: 20800073]

Loewith R, Jacinto E, Wullschleger S, Lorberg A, Crespo JL, Bonenfant D, Oppliger W, Jenoe P, Hall MN. Two TOR complexes, only one of which is rapamycin sensitive, have distinct roles in cell growth control. Mol Cell. 2002; 10:457–468. [PubMed: 12408816]

Luo S, Rubinsztein DC. Apoptosis blocks Beclin 1-dependent autophagosome synthesis: an effect rescued by Bcl-xL. Cell Death Differ. 2010; 17:268–277. [PubMed: 19713971]

Ma J, Li M, Hock J, Yu X. Hyperactivation of mTOR critically regulates abnormal osteoclastogenesis in neurofibromatosis Type 1. J Orthop Res. 2012; 30:144–152. [PubMed: 21748792]

Ma L, Chen Z, Erdjument-Bromage H, Tempst P, Pandolfi PP. Phosphorylation and functional inactivation of TSC2 by Erk implications for tuberous sclerosis and cancer pathogenesis. Cell. 2005; 121:179–193. [PubMed: 15851026]

Ma T, Hoeffer CA, Capetillo-Zarate E, Yu F, Wong H, Lin MT, Tampellini D, Klann E, Blitzer RD, Gouras GK. Dysregulation of the mTOR pathway mediates impairment of synaptic plasticity in a mouse model of Alzheimer's disease. PLoS One. 2010; 5

Magri L, Cambiaghi M, Cominelli M, Alfaro-Cervello C, Cursi M, Pala M, Bulfone A, Garcia-Verdugo JM, Leocani L, Minicucci F, Poliani PL, Galli R. Sustained activation of mTOR pathway in embryonic neural stem cells leads to development of tuberous sclerosis complex-associated lesions. Cell Stem Cell. 2011; 9:447–462. [PubMed: 22056141]

Maiese K. Triple play: Promoting neurovascular longevity with nicotinamide, WNT, and erythropoietin in diabetes mellitus. Biomed Pharmacother. 2008; 62:218–232. [PubMed: 18342481]

Maiese K. The Many Facets of Cell Injury: Angiogenesis to Autophagy. Curr Neurovasc Res. 2012; 9:1–2. [PubMed: 22272762]

Maiese K, Chong ZZ. Nicotinamide: necessary nutrient emerges as a novel cytoprotectant for the brain. Trends Pharmacol Sci. 2003; 24:228–232. [PubMed: 12767721]

Maiese K, Chong ZZ. Insights into oxidative stress and potential novel therapeutic targets for Alzheimer disease. Restor Neurol Neurosci. 2004; 22:87–104. [PubMed: 15272144]

Maiese K, Chong ZZ, Hou J, Shang YC. Erythropoietin and oxidative stress. Curr Neurovasc Res. 2008a; 5:125–142. [PubMed: 18473829]

Maiese K, Chong ZZ, Hou J, Shang YC. New strategies for Alzheimer's disease and cognitive impairment. Oxid Med Cell Longev. 2009a; 2:279–289. [PubMed: 20716915]

Maiese K, Chong ZZ, Hou J, Shang YC. The vitamin nicotinamide: translating nutrition into clinical care. Molecules. 2009b; 14:3446–3485. [PubMed: 19783937]

Maiese K, Chong ZZ, Hou J, Shang YC. Oxidative stress: Biomarkers and novel therapeutic pathways. Exp Gerontol. 2010; 45:217–234. [PubMed: 20064603]

Maiese K, Chong ZZ, Li F, Shang YC. Erythropoietin: elucidating new cellular targets that broaden therapeutic strategies. Prog Neurobiol. 2008b; 85:194–213. [PubMed: 18396368]

Maiese K, Chong ZZ, Shang YC. Mechanistic insights into diabetes mellitus and oxidative stress. Curr Med Chem. 2007a; 14:1729–1738. [PubMed: 17627510]

Maiese K, Chong ZZ, Shang YC. “Sly as a FOXO”: New paths with Forkhead signaling in the brain. Curr Neurovasc Res. 2007b; 4:295–302. [PubMed: 18045156]

Maiese K, Chong ZZ, Shang YC. OutFOXOing disease and disability: the therapeutic potential of targeting FoxO proteins. Trends Mol Med. 2008c; 14:219–227. [PubMed: 18403263]

Maiese K, Chong ZZ, Shang YC. Raves and risks for erythropoietin. Cytokine Growth Factor Rev. 2008d; 19:145–155. [PubMed: 18299246]

Maiese K, Chong ZZ, Shang YC, Hou J. Clever cancer strategies with FoxO transcription factors. Cell Cycle. 2008e; 7:3829–3839. [PubMed: 19066462]

Maiese K, Chong ZZ, Shang YC, Hou J. Rogue proliferation versus restorative protection: where do we draw the line for Wnt and forkhead signaling? Expert opinion on therapeutic targets. 2008f; 12:905–916. [PubMed: 18554157]

Maiese K, Chong ZZ, Shang YC, Hou J. Therapeutic promise and principles: Metabotropic glutamate receptors. Oxid Med Cell Longev. 2008g; 1:1–14. [PubMed: 19750024]

Maiese K, Chong ZZ, Shang YC, Hou J. A “FOXO” in sight: targeting Foxo proteins from conception to cancer. Med Res Rev. 2009c; 29:395–418. [PubMed: 18985696]

Maiese K, Chong ZZ, Shang YC, Hou J. Novel Avenues of Drug Discovery and Biomarkers for Diabetes Mellitus. Journal of clinical pharmacology. 2011a; 51:128–152. [PubMed: 20220043]

Maiese K, Chong ZZ, Shang YC, Wang S. Translating cell survival and cell longevity into treatment strategies with SIRT1. Rom J Morphol Embryol. 2011b; 52:1173–1185. [PubMed: 22203920]

Maiese K, Hou J, Chong ZZ, Shang YC. Erythropoietin, forkhead proteins, and oxidative injury: biomarkers and biology. ScientificWorldJournal. 2009d; 9:1072–1104. [PubMed: 19802503]

Maiese K, Hou J, Chong ZZ, Shang YC. A fork in the path: Developing therapeutic inroads with FoxO proteins. Oxid Med Cell Longev. 2009e; 2:119–129. [PubMed: 20592766]

Maiese K, Li F, Chong ZZ. Erythropoietin in the brain: can the promise to protect be fulfilled? Trends Pharmacol Sci. 2004; 25:577–583. [PubMed: 15491780]

Maiese K, Li F, Chong ZZ. New avenues of exploration for erythropoietin. Jama. 2005; 293:90–95. [PubMed: 15632341]

Maiese K, Li F, Chong ZZ, Shang YC. The Wnt signaling pathway: Aging gracefully as a protectionist? Pharmacol Ther. 2008h; 118:58–81. [PubMed: 18313758]

Maiese K, Morhan SD, Chong ZZ. Oxidative stress biology and cell injury during type 1 and type 2 diabetes mellitus. Curr Neurovasc Res. 2007c; 4:63–71. [PubMed: 17311546]

Majd S, Zarifkar A, Rastegar K, Takhshid MA. Different fibrillar Abeta 1-42 concentrations induce adult hippocampal neurons to reenter various phases of the cell cycle. Brain Res. 2008; 1218:224–229. [PubMed: 18533137]

Majumder S, Richardson A, Strong R, Oddo S. Inducing autophagy by rapamycin before, but not after, the formation of plaques and tangles ameliorates cognitive deficits. PLoS ONE. 2011; 6:e25416. [PubMed: 21980451]

Malagelada C, Jin ZH, Jackson-Lewis V, Przedborski S, Greene LA. Rapamycin protects against neuron death in in vitro and in vivo models of Parkinson's disease. J Neurosci. 2010; 30:1166–1175. [PubMed: 20089925]

Malagelada C, Lopez-Toledano MA, Willett RT, Jin ZH, Shelanski ML, Greene LA. RTP801/REDD1 regulates the timing of cortical neurogenesis and neuron migration. J Neurosci. 2011; 31:3186–3196. [PubMed: 21368030]

Malagelada C, Ryu EJ, Biswas SC, Jackson-Lewis V, Greene LA. RTP801 is elevated in Parkinson brain substantia nigral neurons and mediates death in cellular models of Parkinson's disease by a mechanism involving mammalian target of rapamycin inactivation. J Neurosci. 2006; 26:9996–10005. [PubMed: 17005863]

Mancini D, Pinney S, Burkhoff D, LaManca J, Itescu S, Burke E, Edwards N, Oz M, Marks AR. Use of rapamycin slows progression of cardiac transplantation vasculopathy. Circulation. 2003; 108:48–53. [PubMed: 12742978]

Manning BD, Tee AR, Logsdon MN, Blenis J, Cantley LC. Identification of the tuberous sclerosis complex-2 tumor suppressor gene product tuberin as a target of the phosphoinositide 3-kinase/akt pathway. Mol Cell. 2002; 10:151–162. [PubMed: 12150915]

Masri J, Bernath A, Martin J, Jo OD, Vartanian R, Funk A, Gera J. mTORC2 activity is elevated in gliomas and promotes growth and cell motility via overexpression of rictor. Cancer Res. 2007; 67:11712–11720. [PubMed: 18089801]

Maycotte P, Guemez-Gamboa A, Moran J. Apoptosis and autophagy in rat cerebellar granule neuron death: Role of reactive oxygen species. J Neurosci Res. 2010; 88:73–85. [PubMed: 19598251]

Meikle L, Pollizzi K, Egnor A, Kramvis I, Lane H, Sahin M, Kwiatkowski DJ. Response of a neuronal model of tuberous sclerosis to mammalian target of rapamycin (mTOR) inhibitors: effects on mTORC1 and Akt signaling lead to improved survival and function. J Neurosci. 2008; 28:5422–5432. [PubMed: 18495876]

Miriuka SG, Rao V, Peterson M, Tumiati L, Delgado DH, Mohan R, Ramzy D, Stewart D, Ross HJ, Waddell TK. mTOR inhibition induces endothelial progenitor cell death. Am J Transplant. 2006; 6:2069–2079. [PubMed: 16796720]

Mounier C, Dumas V, Posner BI. Regulation of hepatic insulin-like growth factor-binding protein-1 gene expression by insulin: central role for mammalian target of rapamycin independent of forkhead box O proteins. Endocrinology. 2006; 147:2383–2391. [PubMed: 16455781]

Murakami M, Ichisaka T, Maeda M, Oshiro N, Hara K, Edenhofer F, Kiyama H, Yonezawa K, Yamanaka S. mTOR is essential for growth and proliferation in early mouse embryos and embryonic stem cells. Mol Cell Biol. 2004; 24:6710–6718. [PubMed: 15254238]

Nascimento EB, Snel M, Guigas B, van der Zon GC, Kriek J, Maassen JA, Jazet IM, Diamant M, Ouwens DM. Phosphorylation of PRAS40 on Thr246 by PKB/AKT facilitates efficient phosphorylation of Ser183 by mTORC1. Cell Signal. 2010; 22:961–967. [PubMed: 20138985]

Nellist M, Burgers PC, van den Ouweland AM, Halley DJ, Luider TM. Phosphorylation and binding partner analysis of the TSC1-TSC2 complex. Biochem Biophys Res Commun. 2005; 333:818–826. [PubMed: 15963462]

Nopparat C, Porter JE, Ebadi M, Govitrapong P. The mechanism for the neuroprotective effect of melatonin against methamphetamine-induced autophagy. J Pineal Res. 2010

O'Dell CM, Das A, Wallace G. t. Ray SK, Banik NL. Understanding the basic mechanisms underlying seizures in mesial temporal lobe epilepsy and possible therapeutic targets: A review. J Neurosci Res. 2012; 90:913–924. [PubMed: 22315182]

Ogura Y, Iemitsu M, Naito H, Kakigi R, Kakehashi C, Maeda S, Akema T. Single bout of running exercise changes LC3-II expression in rat cardiac muscle. Biochem Biophys Res Commun. 2011; 414:756–760. [PubMed: 22005460]

Okaji Y, Tashiro Y, Gritli I, Nishida C, Sato A, Ueno Y, Del Canto Gonzalez S, Ohki-Koizumi M, Akiyama H, Nakauchi H, Hattori K, Heissig B. Plasminogen deficiency attenuates postnatal erythropoiesis in male C57BL/6 mice through decreased activity of the LH-testosterone axis. Exp Hematol. 2012; 40:143–154. [PubMed: 22056679]

Oshiro N, Takahashi R, Yoshino K, Tanimura K, Nakashima A, Eguchi S, Miyamoto T, Hara K, Takehana K, Avruch J, Kikkawa U, Yonezawa K. The proline-rich Akt substrate of 40 kDa (PRAS40) is a physiological substrate of mammalian target of rapamycin complex 1. J Biol Chem. 2007; 282:20329–20339. [PubMed: 17517883]

Paccalin M, Pain-Barc S, Pluchon C, Paul C, Besson MN, Carret-Rebillat AS, Rioux-Bilan A, Gil R, Hugon J. Activated mTOR and PKR kinases in lymphocytes correlate with memory and cognitive decline in Alzheimer's disease. Dement Geriatr Cogn Disord. 2006; 22:320–326. [PubMed: 16954686]

Park KH, Choi NY, Koh SH, Park HH, Kim YS, Kim MJ, Lee SJ, Yu HJ, Lee KY, Lee YJ, Kim HT. L-DOPA neurotoxicity is prevented by neuroprotective effects of erythropoietin. Neurotoxicology. 2011; 32:879–887. [PubMed: 21683736]

Park KK, Liu K, Hu Y, Smith PD, Wang C, Cai B, Xu B, Connolly L, Kramvis I, Sahin M, He Z. Promoting axon regeneration in the adult CNS by modulation of the PTEN/mTOR pathway. Science. 2008; 322:963–966. [PubMed: 18988856]

Parsons RG, Gafford GM, Helmstetter FJ. Translational control via the mammalian target of rapamycin pathway is critical for the formation and stability of long-term fear memory in amygdala neurons. J Neurosci. 2006; 26:12977–12983. [PubMed: 17167087]

Pastor MD, Garcia-Yebenes I, Fradejas N, Perez-Ortiz JM, Mora-Lee S, Tranque P, Moro MA, Pende M, Calvo S. mTOR/S6 kinase pathway contributes to astrocyte survival during ischemia. J Biol Chem. 2009; 284:22067–22078. [PubMed: 19535330]

Pattingre S, Tassa A, Qu X, Garuti R, Liang XH, Mizushima N, Packer M, Schneider MD, Levine B. Bcl-2 antiapoptotic proteins inhibit Beclin 1-dependent autophagy. Cell. 2005; 122:927–939. [PubMed: 16179260]

Pavel ME, Hainsworth JD, Baudin E, Peeters M, Horsch D, Winkler RE, Klimovsky J, Lebwohl D, Jehl V, Wolin EM, Oberg K, Van Cutsem E, Yao JC. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. Lancet. 2011; 378:2005–2012. [PubMed: 22119496]

Pearce LR, Huang X, Boudeau J, Pawlowski R, Wullschleger S, Deak M, Ibrahim AF, Gourlay R, Magnuson MA, Alessi DR. Identification of Protor as a novel Rictor-binding component of mTOR complex-2. Biochem J. 2007; 405:513–522. [PubMed: 17461779]

Pearce LR, Sommer EM, Sakamoto K, Wullschleger S, Alessi DR. Protor-1 is required for efficient mTORC2-mediated activation of SGK1 in the kidney. Biochem J. 2011; 436:169–179. [PubMed: 21413931]

Pei JJ, Hugon J. mTOR-dependent signalling in Alzheimer's disease. J Cell Mol Med. 2008; 12:2525–2532. [PubMed: 19210753]

Perek-Polnik M, Jozwiak S, Jurkiewicz E, Perek D, Kotulska K. Effective everolimus treatment of inoperable, life-threatening subependymal giant cell astrocytoma and intractable epilepsy in a patient with tuberous sclerosis complex. Eur J Paediatr Neurol. 2012; 16:83–85. [PubMed: 22000822]

Peterson RT, Beal PA, Comb MJ, Schreiber SL. FKBP12-rapamycin-associated protein (FRAP) autophosphorylates at serine 2481 under translationally repressive conditions. J Biol Chem. 2000; 275:7416–7423. [PubMed: 10702316]

Peterson TR, Laplante M, Thoreen CC, Sancak Y, Kang SA, Kuehl WM, Gray NS, Sabatini DM. DEPTOR is an mTOR inhibitor frequently overexpressed in multiple myeloma cells and required for their survival. Cell. 2009; 137:873–886. [PubMed: 19446321]

Popescu NI, Lupu C, Lupu F. Extracellular protein disulfide isomerase regulates coagulation on endothelial cells through modulation of phosphatidylserine exposure. Blood. 2010; 116:993–1001. [PubMed: 20448108]

Potter CJ, Pedraza LG, Xu T. Akt regulates growth by directly phosphorylating Tsc2. Nat Cell Biol. 2002; 4:658–665. [PubMed: 12172554]

Qin AP, Liu CF, Qin YY, Hong LZ, Xu M, Yang L, Liu J, Qin ZH, Zhang HL. Autophagy was activated in injured astrocytes and mildly decreased cell survival following glucose and oxygen deprivation and focal cerebral ischemia. Autophagy. 2010; 6:738–753. [PubMed: 20574158]

Ravikumar B, Vacher C, Berger Z, Davies JE, Luo S, Oroz LG, Scaravilli F, Easton DF, Duden R, O'Kane CJ, Rubinsztein DC. Inhibition of mTOR induces autophagy and reduces toxicity of polyglutamine expansions in fly and mouse models of Huntington disease. Nat Genet. 2004; 36:585–595. [PubMed: 15146184]

Recchia AG, Musti AM, Lanzino M, Panno ML, Turano E, Zumpano R, Belfiore A, Ando S, Maggiolini M. A cross-talk between the androgen receptor and the epidermal growth factor receptor leads to p38MAPK-dependent activation of mTOR and cyclinD1 expression in prostate and lung cancer cells. Int J Biochem Cell Biol. 2009; 41:603–614. [PubMed: 18692155]

Reynolds, T. H. t.; Bodine, SC.; Lawrence, JC, Jr.. Control of Ser2448 phosphorylation in the mammalian target of rapamycin by insulin and skeletal muscle load. J Biol Chem. 2002; 277:17657–17662. [PubMed: 11884412]

Rjiba-Touati K, Ayed-Boussema I, Belarbia A, Achour A, Bacha H. Recombinant human erythropoietin prevents cisplatin-induced genotoxicity in rat liver and heart tissues via an antioxidant process. Drug Chem Toxicol. 2012; 35:134–140. [PubMed: 21834696]

Roscic A, Baldo B, Crochemore C, Marcellin D, Paganetti P. Induction of autophagy with catalytic mTOR inhibitors reduces huntingtin aggregates in a neuronal cell model. J Neurochem. 2011; 119:398–407. [PubMed: 21854390]

Rosner M, Fuchs C, Siegel N, Valli A, Hengstschlager M. Functional interaction of mammalian target of rapamycin complexes in regulating mammalian cell size and cell cycle. Hum Mol Genet. 2009; 18:3298–3310. [PubMed: 19505958]

Roux PP, Ballif BA, Anjum R, Gygi SP, Blenis J. Tumor-promoting phorbol esters and activated Ras inactivate the tuberous sclerosis tumor suppressor complex via p90 ribosomal S6 kinase. Proc Natl Acad Sci U S A. 2004; 101:13489–13494. [PubMed: 15342917]

Saha AK, Xu XJ, Lawson E, Deoliveira R, Brandon AE, Kraegen EW, Ruderman NB. Downregulation of AMPK accompanies leucine- and glucose-induced increases in protein synthesis and insulin resistance in rat skeletal muscle. Diabetes. 2010; 59:2426–2434. [PubMed: 20682696]

Sales Santos I, da Rocha Tomé A, Saldanha G, Ferreira P, Militão G, de Freitas R. Oxidative stress in the hippocampus during experimental seizures can be ameliorated with the antioxidant ascorbic acid. Oxid Med Cell Longev. 2009; 2:23–30.

Sancak Y, Bar-Peled L, Zoncu R, Markhard AL, Nada S, Sabatini DM. Ragulator-Rag complex targets mTORC1 to the lysosomal surface and is necessary for its activation by amino acids. Cell. 2010; 141:290–303. [PubMed: 20381137]

Sancak Y, Peterson TR, Shaul YD, Lindquist RA, Thoreen CC, Bar-Peled L, Sabatini DM. The Rag GTPases bind raptor and mediate amino acid signaling to mTORC1. Science. 2008; 320:1496–1501. [PubMed: 18497260]

Sancak Y, Thoreen CC, Peterson TR, Lindquist RA, Kang SA, Spooner E, Carr SA, Sabatini DM. PRAS40 is an insulin-regulated inhibitor of the mTORC1 protein kinase. Mol Cell. 2007; 25:903–915. [PubMed: 17386266]

Santini E, Heiman M, Greengard P, Valjent E, Fisone G. Inhibition of mTOR signaling in Parkinson's disease prevents L-DOPA-induced dyskinesia. Science signaling. 2009; 2:ra36. [PubMed: 19622833]

Sarbassov DD, Ali SM, Kim DH, Guertin DA, Latek RR, Erdjument-Bromage H, Tempst P, Sabatini DM. Rictor, a novel binding partner of mTOR, defines a rapamycin-insensitive and raptor-independent pathway that regulates the cytoskeleton. Curr Biol. 2004; 14:1296–1302. [PubMed: 15268862]

Sarbassov DD, Ali SM, Sengupta S, Sheen JH, Hsu PP, Bagley AF, Markhard AL, Sabatini DM. Prolonged rapamycin treatment inhibits mTORC2 assembly and Akt/PKB. Mol Cell. 2006; 22:159–168. [PubMed: 16603397]

Sarbassov DD, Guertin DA, Ali SM, Sabatini DM. Phosphorylation and regulation of Akt/PKB by the rictor-mTOR complex. Science. 2005; 307:1098–1101. [PubMed: 15718470]

Sato A, Sunayama J, Matsuda K, Tachibana K, Sakurada K, Tomiyama A, Kayama T, Kitanaka C. Regulation of neural stem/progenitor cell maintenance by PI3K and mTOR. Neurosci Lett. 2010; 470:115–120. [PubMed: 20045038]

Sato T, Nakashima A, Guo L, Tamanoi F. Specific activation of mTORC1 by Rheb G-protein in vitro involves enhanced recruitment of its substrate protein. J Biol Chem. 2009; 284:12783–12791. [PubMed: 19299511]

Schneider A, Younis RH, Gutkind JS. Hypoxia-induced energy stress inhibits the mTOR pathway by activating an AMPK/REDD1 signaling axis in head and neck squamous cell carcinoma. Neoplasia. 2008; 10:1295–1302. [PubMed: 18953439]

Schutters K, Reutelingsperger C. Phosphatidylserine targeting for diagnosis and treatment of human diseases. Apoptosis. 2010; 15:1072–1082. [PubMed: 20440562]

Scott RC, Juhasz G, Neufeld TP. Direct induction of autophagy by Atg1 inhibits cell growth and induces apoptotic cell death. Curr Biol. 2007; 17:1–11. [PubMed: 17208179]

Sehgal SN, Baker H, Vezina C. Rapamycin (AY-22,989), a new antifungal antibiotic. II. Fermentation, isolation and characterization. J Antibiot (Tokyo). 1975; 28:727–732. [PubMed: 1102509]

Selman C, Tullet JM, Wieser D, Irvine E, Lingard SJ, Choudhury AI, Claret M, Al-Qassab H, Carmignac D, Ramadani F, Woods A, Robinson IC, Schuster E, Batterham RL, Kozma SC, Thomas G, Carling D, Okkenhaug K, Thornton JM, Partridge L, Gems D, Withers DJ. Ribosomal protein S6 kinase 1 signaling regulates mammalian life span. Science. 2009; 326:140–144. [PubMed: 19797661]

Shan J, Nguyen TB, Totary-Jain H, Dansky H, Marx SO, Marks AR. Leptin-enhanced neointimal hyperplasia is reduced by mTOR and PI3K inhibitors. Proc Natl Acad Sci U S A. 2008; 105:19006–19011. [PubMed: 19020099]

Shang YC, Chong ZZ, Hou J, Maiese K. The forkhead transcription factor FoxO3a controls microglial inflammatory activation and eventual apoptotic injury through caspase 3. Curr Neurovasc Res. 2009a; 6:20–31. [PubMed: 19355923]

Shang YC, Chong ZZ, Hou J, Maiese K. FoxO3a governs early microglial proliferation and employs mitochondrial depolarization with caspase 3, 8, and 9 cleavage during oxidant induced apoptosis. Curr Neurovasc Res. 2009b; 6:223–238. [PubMed: 19807657]

Shang YC, Chong ZZ, Hou J, Maiese K. Wnt1, FoxO3a, and NF-kappaB oversee microglial integrity and activation during oxidant stress. Cell Signal. 2010; 22:1317–1329. [PubMed: 20462515]

Shang YC, Chong ZZ, Wang S, Maiese K. Erythropoietin and Wnt1 Govern Pathways of mTOR, Apaf-1, and XIAP in Inflammatory Microglia. Curr Neurovasc Res. 2011; 8:270–285. [PubMed: 22023617]

Shang YC, Chong ZZ, Wang S, Maiese K. Prevention of beta-amyloid degeneration of microglia by erythropoietin depends on Wnt1, the PI 3-K/mTOR pathway, Bad, and Bcl-xL. Aging (Albany NY). 2012; 4:187–201. [PubMed: 22388478]

Shaw RJ, Kosmatka M, Bardeesy N, Hurley RL, Witters LA, DePinho RA, Cantley LC. The tumor suppressor LKB1 kinase directly activates AMP-activated kinase and regulates apoptosis in response to energy stress. Proc Natl Acad Sci U S A. 2004; 101:3329–3335. [PubMed: 14985505]

Sheng B, Liu J, Li GH. Metformin preconditioning protects Daphnia pulex from lethal hypoxic insult involving AMPK, HIF and mTOR signaling. Comp Biochem Physiol B Biochem Mol Biol. 2012

Shi GD, OuYang YP, Shi JG, Liu Y, Yuan W, Jia LS. PTEN deletion prevents ischemic brain injury by activating the mTOR signaling pathway. Biochem Biophys Res Commun. 2011; 404:941–945. [PubMed: 21185267]

Siegel N, Rosner M, Unbekandt M, Fuchs C, Slabina N, Dolznig H, Davies JA, Lubec G, Hengstschlager M. Contribution of human amniotic fluid stem cells to renal tissue formation depends on mTOR. Hum Mol Genet. 2010; 19:3320–3331. [PubMed: 20542987]

Silva DF, Esteves AR, Oliveira CR, Cardoso SM. Mitochondria: the common upstream driver of amyloid-beta and tau pathology in Alzheimer's disease. Curr Alzheimer Res. 2011; 8:563–572. [PubMed: 21244356]

Simao F, Matte A, Matte C, Soares FM, Wyse AT, Netto CA, Salbego CG. Resveratrol prevents oxidative stress and inhibition of Na(+)K(+)-ATPase activity induced by transient global cerebral ischemia in rats. The Journal of nutritional biochemistry. 2011

Slipczuk L, Bekinschtein P, Katche C, Cammarota M, Izquierdo I, Medina JH. BDNF activates mTOR to regulate GluR1 expression required for memory formation. PLoS One. 2009; 4:e6007. [PubMed: 19547753]

Soares MM, King SW, Thorpe PE. Targeting inside-out phosphatidylserine as a therapeutic strategy for viral diseases. Nat Med. 2008; 14:1357–1362. [PubMed: 19029986]

Sofer A, Lei K, Johannessen CM, Ellisen LW. Regulation of mTOR and cell growth in response to energy stress by REDD1. Mol Cell Biol. 2005; 25:5834–5845. [PubMed: 15988001]

Soliman GA, Acosta-Jaquez HA, Dunlop EA, Ekim B, Maj NE, Tee AR, Fingar DC. mTOR Ser-2481 autophosphorylation monitors mTORC-specific catalytic activity and clarifies rapamycin mechanism of action. J Biol Chem. 2010; 285:7866–7879. [PubMed: 20022946]

Solling C. Organ-Protective and Immunomodulatory Effects of Erythropoietin - An Update on Recent Clinical Trials. Basic Clin Pharmacol Toxicol. 2011

Spencer B, Potkar R, Trejo M, Rockenstein E, Patrick C, Gindi R, Adame A, Wyss-Coray T, Masliah E. Beclin 1 gene transfer activates autophagy and ameliorates the neurodegenerative pathology in alpha-synuclein models of Parkinson's and Lewy body diseases. J Neurosci. 2009; 29:13578–13588. [PubMed: 19864570]

Spilman P, Podlutskaya N, Hart MJ, Debnath J, Gorostiza O, Bredesen D, Richardson A, Strong R, Galvan V. Inhibition of mTOR by rapamycin abolishes cognitive deficits and reduces amyloid-beta levels in a mouse model of Alzheimer's disease. PLoS One. 2010; 5:e9979. [PubMed: 20376313]

Srivastava S, Haigis MC. Role of sirtuins and calorie restriction in neuroprotection: implications in Alzheimer's and Parkinson's diseases. Curr Pharm Des. 2011; 17:3418–3433. [PubMed: 21902666]

Su J, Zhang A, Shi Z, Ma F, Pu P, Wang T, Zhang J, Kang C, Zhang Q. MicroRNA-200a suppresses the Wnt/beta-catenin signaling pathway by interacting with beta-catenin. Int J Oncol. 2012; 40:1162–1170. [PubMed: 22211245]

Su KH, Shyue SK, Kou YR, Ching LC, Chiang AN, Yu YB, Chen CY, Pan CC, Lee TS. beta Common receptor integrates the erythropoietin signaling in activation of endothelial nitric oxide synthase. J Cell Physiol. 2011; 226:3330–3339. [PubMed: 21321940]

Sui L, Wang J, Li BM. Role of the phosphoinositide 3-kinase-Akt-mammalian target of the rapamycin signaling pathway in long-term potentiation and trace fear conditioning memory in rat medial prefrontal cortex. Learning & memory (Cold Spring Harbor, N.Y. 2008; 15:762–776.

Sun F, Park KK, Belin S, Wang D, Lu T, Chen G, Zhang K, Yeung C, Feng G, Yankner BA, He Z. Sustained axon regeneration induced by co-deletion of PTEN and SOCS3. Nature. 2011; 480:372–375. [PubMed: 22056987]

Suzen S, Cihaner SS, Coban T. Synthesis and comparison of antioxidant properties of indole-based melatonin analogue indole amino Acid derivatives. Chem Biol Drug Des. 2012; 79:76–83. [PubMed: 21883955]

Taga M, Mouton-Liger F, Paquet C, Hugon J. Modulation of oxidative stress and tau phosphorylation by the mTOR activator phosphatidic acid in SH-SY5Y cells. FEBS Lett. 2011; 585:1801–1806. [PubMed: 21510936]

Tain LS, Mortiboys H, Tao RN, Ziviani E, Bandmann O, Whitworth AJ. Rapamycin activation of 4E-BP prevents parkinsonian dopaminergic neuron loss. Nat Neurosci. 2009; 12:1129–1135. [PubMed: 19684592]

Takahara T, Hara K, Yonezawa K, Sorimachi H, Maeda T. Nutrient-dependent multimerization of the mammalian target of rapamycin through the N-terminal HEAT repeat region. J Biol Chem. 2006; 281:28605–28614. [PubMed: 16870609]

Takahashi T, Hara K, Inoue H, Kawa Y, Tokunaga C, Hidayat S, Yoshino K, Kuroda Y, Yonezawa K. Carboxyl-terminal region conserved among phosphoinositide-kinase-related kinases is indispensable for mTOR function in vivo and in vitro. Genes Cells. 2000; 5:765–775. [PubMed: 10971657]

Takei H, Dauser R, Su J, Chintagumpala M, Bhattacharjee MB, Jones J, Adesina AM. Anaplastic ganglioglioma arising from a Lhermitte-Duclos-like lesion. Case report. J Neurosurg. 2007; 107:137–142. [PubMed: 18459885]

Talos DM, Sun H, Zhou X, Fitzgerald EC, Jackson MC, Klein PM, Lan VJ, Joseph A, Jensen FE. The Interaction between Early Life Epilepsy and Autistic-Like Behavioral Consequences: A Role for the Mammalian Target of Rapamycin (mTOR) Pathway. PLoS ONE. 2012; 7:e35885. [PubMed: 22567115]

Talving P, Lustenberger T, Inaba K, Lam L, Mohseni S, Chan L, Demetriades D. Erythropoiesis-stimulating agent administration and survival after severe traumatic brain injury: a prospective study. Arch Surg. 2012; 147:251–255. [PubMed: 22430906]

Tang SJ, Reis G, Kang H, Gingras AC, Sonenberg N, Schuman EM. A rapamycin-sensitive signaling pathway contributes to long-term synaptic plasticity in the hippocampus. Proc Natl Acad Sci U S A. 2002; 99:467–472. [PubMed: 11756682]

Teng FY, Tang BL. NF-kappaB signaling in neurite growth and neuronal survival. Reviews in the neurosciences. 2010; 21:299–313. [PubMed: 21086762]

Thedieck K, Polak P, Kim ML, Molle KD, Cohen A, Jeno P, Arrieumerlou C, Hall MN. PRAS40 and PRR5-like protein are new mTOR interactors that regulate apoptosis. PLoS One. 2007; 2:e1217. [PubMed: 18030348]

Tominaga T, Kure S, Narisawa K, Yoshimoto T. Endonuclease activation following focal ischemic injury in the rat brain. Brain Res. 1993; 608:21–26. [PubMed: 8388311]

Ullah N, Ullah I, Lee HY, Naseer MI, Seok PM, Ahmed J, Kim MO. Protective Function of Nicotinamide Against Ketamine-induced Apoptotic Neurodegeneration in the Infant Rat Brain. J Mol Neurosci. 2012; 47:67–75. [PubMed: 22160932]

Valli A, Rosner M, Fuchs C, Siegel N, Bishop CE, Dolznig H, Madel U, Feichtinger W, Atala A, Hengstschlager M. Embryoid body formation of human amniotic fluid stem cells depends on mTOR. Oncogene. 2010; 29:966–977. [PubMed: 19935716]

Vander Haar E, Lee SI, Bandhakavi S, Griffin TJ, Kim DH. Insulin signalling to mTOR mediated by the Akt/PKB substrate PRAS40. Nat Cell Biol. 2007; 9:316–323. [PubMed: 17277771]

Vezina C, Kudelski A, Sehgal SN. Rapamycin (AY-22,989), a new antifungal antibiotic. I. Taxonomy of the producing streptomycete and isolation of the active principle. J Antibiot (Tokyo). 1975; 28:721–726. [PubMed: 1102508]

Vigneron F, Dos Santos P, Lemoine S, Bonnet M, Tariosse L, Couffinhal T, Duplaa C, Jaspard-Vinassa B. GSK-3beta at the crossroads in the signalling of heart preconditioning: implication of mTOR and Wnt pathways. Cardiovasc Res. 2011; 90:49–56. [PubMed: 21233250]

Vincent AM, Maiese K. Nitric oxide induction of neuronal endonuclease activity in programmed cell death. Exp Cell Res. 1999; 246:290–300. [PubMed: 9925743]

Vincent AM, TenBroeke M, Maiese K. Metabotropic glutamate receptors prevent programmed cell death through the modulation of neuronal endonuclease activity and intracellular pH. Exp Neurol. 1999a; 155:79–94. [PubMed: 9918707]

Vincent AM, TenBroeke M, Maiese K. Neuronal intracellular pH directly mediates nitric oxide-induced programmed cell death. J Neurobiol. 1999b; 40:171–184. [PubMed: 10413448]

Vonder Haar C, Anderson GD, Hoane MR. Continuous nicotinamide administration improves behavioral recovery and reduces lesion size following bilateral frontal controlled cortical impact injury. Behav Brain Res. 2011; 224:311–317. [PubMed: 21704653]

Waltereit R, Welzl H, Dichgans J, Lipp HP, Schmidt WJ, Weller M. Enhanced episodic-like memory and kindling epilepsy in a rat model of tuberous sclerosis. J Neurochem. 2006; 96:407–413. [PubMed: 16300636]

Wang H, Zhang Q, Wen Q, Zheng Y, Philip L, Jiang H, Lin J, Zheng W. Proline-rich Akt substrate of 40kDa (PRAS40): a novel downstream target of PI3k/Akt signaling pathway. Cell Signal. 2012a; 24:17–24. [PubMed: 21906675]

Wang J, Sun P, Bao Y, Dou B, Song D, Li Y. Vitamin E renders protection to PC12 cells against oxidative damage and apoptosis induced by single-walled carbon nanotubes. Toxicol In Vitro. 2012b; 26:32–41. [PubMed: 22020378]

Wang JY, Xia Q, Chu KT, Pan J, Sun LN, Zeng B, Zhu YJ, Wang Q, Wang K, Luo BY. Severe global cerebral ischemia-induced programmed necrosis of hippocampal CA1 neurons in rat is prevented by 3-methyladenine: a widely used inhibitor of autophagy. J Neuropathol Exp Neurol. 2011a; 70:314–322. [PubMed: 21412169]

Wang L, Harris TE, Lawrence JC Jr. Regulation of proline-rich Akt substrate of 40 kDa (PRAS40) function by mammalian target of rapamycin complex 1 (mTORC1)-mediated phosphorylation. J Biol Chem. 2008; 283:15619–15627. [PubMed: 18372248]

Wang L, Harris TE, Roth RA, Lawrence JC Jr. PRAS40 regulates mTORC1 kinase activity by functioning as a direct inhibitor of substrate binding. J Biol Chem. 2007; 282:20036–20044. [PubMed: 17510057]

Wang L, Lawrence JC Jr. Sturgill TW, Harris TE. Mammalian target of rapamycin complex 1 (mTORC1) activity is associated with phosphorylation of raptor by mTOR. J Biol Chem. 2009; 284:14693–14697. [PubMed: 19346248]

Wang RH, Kim HS, Xiao C, Xu X, Gavrilova O, Deng CX. Hepatic Sirt1 deficiency in mice impairs mTorc2/Akt signaling and results in hyperglycemia, oxidative damage, and insulin resistance. J Clin Invest. 2011b; 121:4477–4490. [PubMed: 21965330]

Wang S, Chong ZZ, Shang YC, Maiese K. WISP1 (CCN4) autoregulates its expression and nuclear trafficking of beta-catenin during oxidant stress with limited effects upon neuronal autophagy. Curr Neurovasc Res. 2012c; 9:89–99.

Wang S, Chong ZZ, Shang YC, Maiese K. Wnt1 inducible signaling pathway protein 1 (WISP1) blocks neurodegeneration through phosphoinositide 3 kinase/Akt1 and apoptotic mitochondrial signaling involving Bad, Bax, Bim, and Bcl-xL. Curr Neurovasc Res. 2012d; 9:20–31. [PubMed: 22272766]

Wang Y, Ding L, Wang X, Zhang J, Han W, Feng L, Sun J, Jin H, Wang XJ. Pterostilbene simultaneously induces apoptosis, cell cycle arrest and cyto-protective autophagy in breast cancer cells. Am J Transl Res. 2012e; 4:44–51. [PubMed: 22347521]

Weber JD, Gutmann DH. Deconvoluting mTOR biology. Cell Cycle. 2012; 11:236–248. [PubMed: 22214661]

Woo SY, Kim DH, Jun CB, Kim YM, Haar EV, Lee SI, Hegg JW, Bandhakavi S, Griffin TJ, Kim DH. PRR5, a novel component of mTOR complex 2, regulates platelet-derived growth factor receptor beta expression and signaling. J Biol Chem. 2007; 282:25604–25612. [PubMed: 17599906]

Wu X, Reiter CE, Antonetti DA, Kimball SR, Jefferson LS, Gardner TW. Insulin promotes rat retinal neuronal cell survival in a p70S6K-dependent manner. J Biol Chem. 2004; 279:9167–9175. [PubMed: 14660591]

Xie Q, Hao Y, Tao L, Peng S, Rao C, Chen H, You H, Dong MQ, Yuan Z. Lysine methylation of FOXO3 regulates oxidative stress-induced neuronal cell death. EMBO Rep. 2012; 13:371–377. [PubMed: 22402663]

Xu JT, Zhao X, Yaster M, Tao YX. Expression and distribution of mTOR, p70S6K, 4E-BP1, and their phosphorylated counterparts in rat dorsal root ganglion and spinal cord dorsal horn. Brain Res. 2010; 1336:46–57. [PubMed: 20399760]

Xue L, Fletcher GC, Tolkovsky AM. Autophagy is activated by apoptotic signalling in sympathetic neurons: an alternative mechanism of death execution. Mol Cell Neurosci. 1999; 14:180–198. [PubMed: 10576889]

Yamada E, Singh R. Mapping autophagy on to your metabolic radar. Diabetes. 2012; 61:272–280. [PubMed: 22275084]

Yan J, Kuroyanagi H, Kuroiwa A, Matsuda Y, Tokumitsu H, Tomoda T, Shirasawa T, Muramatsu M. Identification of mouse ULK1, a novel protein kinase structurally related to C. elegans UNC-51. Biochem Biophys Res Commun. 1998; 246:222–227. [PubMed: 9600096]

Yan J, Kuroyanagi H, Tomemori T, Okazaki N, Asato K, Matsuda Y, Suzuki Y, Ohshima Y, Mitani S, Masuho Y, Shirasawa T, Muramatsu M. Mouse ULK2, a novel member of the UNC-51-like protein kinases: unique features of functional domains. Oncogene. 1999; 18:5850–5859. [PubMed: 10557072]

Yang H, Jin X, Kei Lam CW, Yan SK. Oxidative stress and diabetes mellitus. Clin Chem Lab Med. 2011; 49:1773–1782. [PubMed: 21810068]

Yang Q, Inoki K, Ikenoue T, Guan KL. Identification of Sin1 as an essential TORC2 component required for complex formation and kinase activity. Genes Dev. 2006; 20:2820–2832. [PubMed: 17043309]

Yoo KY, Kwon SH, Lee CH, Yan B, Park JH, Ahn JH, Choi JH, Ohk TG, Cho JH, Won MH. FoxO3a changes in pyramidal neurons and expresses in non-pyramidal neurons and astrocytes in the gerbil hippocampal CA1 region after transient cerebral ischemia. Neurochem Res. 2012; 37:588–595. [PubMed: 22076502]

Yu L, McPhee CK, Zheng L, Mardones GA, Rong Y, Peng J, Mi N, Zhao Y, Liu Z, Wan F, Hailey DW, Oorschot V, Klumperman J, Baehrecke EH, Lenardo MJ. Termination of autophagy and reformation of lysosomes regulated by mTOR. Nature. 2010; 465:942–946. [PubMed: 20526321]

Yu Y, Ren QG, Zhang ZH, Zhou K, Yu ZY, Luo X, Wang W. Phospho-Rb mediating cell cycle reentry induces early apoptosis following oxygen-glucose deprivation in rat cortical neurons. Neurochem Res. 2012; 37:503–511. [PubMed: 22037842]

Yuan H, Wan J, Li L, Ge P, Li H, Zhang L. Therapeutic benefits of the group B3 vitamin nicotinamide in mice with lethal endotoxemia and polymicrobial sepsis. Pharmacol Res. 2012; 65:328–337. [PubMed: 22154801]

Zeng KW, Wang XM, Ko H, Kwon HC, Cha JW, Yang HO. Hyperoside protects primary rat cortical neurons from neurotoxicity induced by amyloid beta-protein via the PI3K/Akt/Bad/Bcl(XL)-regulated mitochondrial apoptotic pathway. Eur J Pharmacol. 2011; 672:45–55. [PubMed: 21978835]

Zeng LH, Rensing NR, Wong M. The mammalian target of rapamycin signaling pathway mediates epileptogenesis in a model of temporal lobe epilepsy. J Neurosci. 2009; 29:6964–6972. [PubMed: 19474323]

Zeng LH, Xu L, Gutmann DH, Wong M. Rapamycin prevents epilepsy in a mouse model of tuberous sclerosis complex. Ann Neurol. 2008; 63:444–453. [PubMed: 18389497]

Zengi A, Ercan G, Caglayan O, Tamsel S, Karadeniz M, Simsir I, Harman E, Kahraman C, Orman M, Cetinkalp S, Ozgen G. Increased oxidative DNA damage in lean normoglycemic offspring of type 2 diabetic patients. Exp Clin Endocrinol Diabetes. 2011; 119:467–471. [PubMed: 21472659]

Zhang D, Contu R, Latronico MV, Zhang J, Rizzi R, Catalucci D, Miyamoto S, Huang K, Ceci M, Gu Y, Dalton ND, Peterson KL, Guan KL, Brown JH, Chen J, Sonenberg N, Condorelli G. MTORC1 regulates cardiac function and myocyte survival through 4E-BP1 inhibition in mice. J Clin Invest. 2010; 120:2805–2816. [PubMed: 20644257]

Zhang F, Ding T, Yu L, Zhong Y, Dai H, Yan M. Dexmedetomidine protects against oxygen-glucose deprivation-induced injury through the I2 imidazoline receptor-PI3K/AKT pathway in rat C6 glioma cells. J Pharm Pharmacol. 2012; 64:120–127. [PubMed: 22150679]

Zhang G, Zhao Z, Gao L, Deng J, Wang B, Xu D, Liu B, Qu Y, Yu J, Li J, Gao G. Gypenoside attenuates white matter lesions induced by chronic cerebral hypoperfusion in rats. Pharmacol Biochem Behav. 2011; 99:42–51. [PubMed: 21459105]

Zhao Y, Xiong X, Sun Y. DEPTOR, an mTOR inhibitor, is a physiological substrate of SCF(betaTrCP) E3 ubiquitin ligase and regulates survival and autophagy. Mol Cell. 2011; 44:304–316. [PubMed: 22017876]

Zhou J, Su P, Wang L, Chen J, Zimmermann M, Genbacev O, Afonja O, Horne MC, Tanaka T, Duan E, Fisher SJ, Liao J, Chen J, Wang F. mTOR supports long-term self-renewal and suppresses mesoderm and endoderm activities of human embryonic stem cells. Proc Natl Acad Sci U S A. 2009; 106:7840–7845. [PubMed: 19416884]

Zhou X, Wang L, Wang M, Xu L, Yu L, Fang T, Wu M. Emodin-induced microglial apoptosis is associated with TRB3 induction. Immunopharmacol Immunotoxicol. 2011; 33:594–602. [PubMed: 21275776]

Zoncu R, Efeyan A, Sabatini DM. mTOR: from growth signal integration to cancer, diabetes and ageing. Nat Rev Mol Cell Biol. 2011; 12:21–35. [PubMed: 21157483]

Zou ZQ, Zhang LN, Wang F, Bellenger J, Shen YZ, Zhang XH. The novel dual PI3K/mTOR inhibitor GDC-0941 synergizes with the MEK inhibitor U0126 in non-small cell lung cancer cells. Mol Med Report. 2012; 5:503–508. [PubMed: 22101421]

Zwaal RF, Comfurius P, Bevers EM. Surface exposure of phosphatidylserine in pathological cells. Cell Mol Life Sci. 2005; 62:971–988. [PubMed: 15761668]

Article Highlights and Bullet Points

- mTOR is an integral component of mTORC1 and mTORC2
- mTOR modulates both apoptosis and autophagy during oxidative stress
- mTOR is vital for stem cell maturation, proliferation, and differentiation
- mTOR impacts both cognitive and motor disorders of the nervous system
- mTOR degree of activation can affect cellular survival, demise, and tumorigenesis

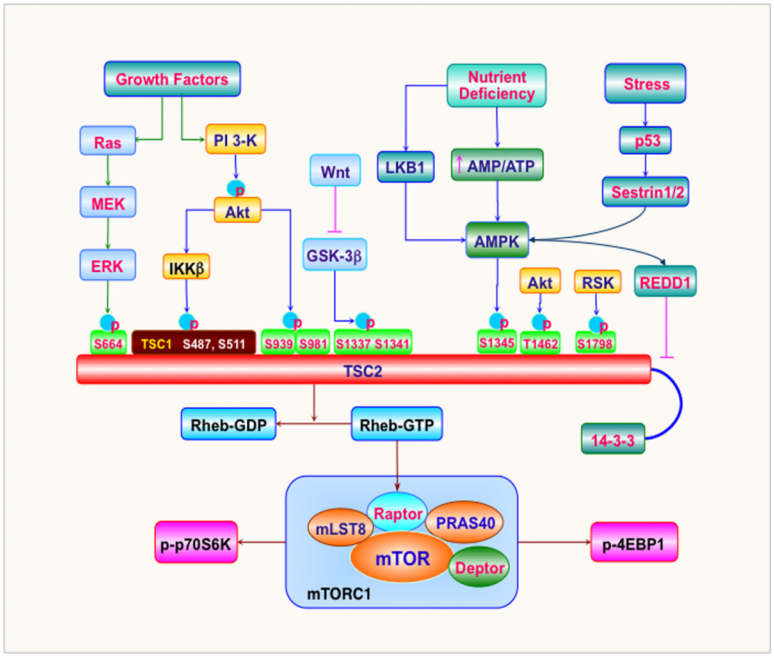

Figure 1. Pathways for TSC1/TSC2 dependent activation of mammalian target of rapamycin complex 1 (mTORC1)

Growth factors or cytokines can stimulate phosphoinositide-3-kinase (PI 3-K) and the activation of Akt. Once activated, Akt can phosphorylate tuberous sclerosis complex-2 (TSC2) on serine^{939} (S939), serine^{981}(S981), and threonine^{1462} (T1462), resulting in the disruption of its interaction with TSC1, the loss of its ability to convert of Ras homologue enriched in brain active form (Rheb-GTP) to the inactive form (Rheb-GDP), and the subsequent activation of mTORC1. Akt also can activate IκB kinase-β (IKKβ) to phosphorylate TSC1 on serine^{487} (S487) and serine^{511} (S511) leading to the inhibition of the TSC1/TSC2 complex and activation of mTORC1. In the pathway involving extracellular signal related kinase (ERK), ERK is activated following Ras activation of mitogen activated kinase/ERK kinase (MEK) and phosphorylates TSC2 on serine^{644} (S664). Nutrient deficiency reduces cellular ATP levels and stimulates AMP activated protein kinase (AMPK) that can phosphorylate TSC2 on serine^{1345} (S1345) promoting its GTPase activating protein activity and turning Rheb-GTP into Rheb-GDP. As a result, mTORC1 activity is inhibited. AMPK also can increase the expression of transcriptional regulation of DNA damage response 1 (REDD1), releasing TSC2 from the binding to protein 14-3-3 and inhibit mTORC1 activity. The tumor suppressor liver kinase B1 (LKB1) can activate AMPK through phosphorylation under conditions of cellular energy deficiency. In addition, the tumor suppressor p53 has been demonstrated to activate AMPK under oxidative and genotoxic stress through its two target genes, *sestrin 1* and *sestrin 2*. The glycoprotein Wnt phosphorylates glycogen synthase-3β (GSK-3β) resulting in the loss of the ability of GSK-3β to phosphorylate TSC2 on serine^{1337} (S1337) and serine^{1341} (S1341). Upon activation, mTORC1 phosphorylates its two major downstream targets p70 ribosome S6 kinase (p70S6K) and eukaryotic initiation factor 4E-binding protein 1 (4EBP1). (p = phosphorylation).

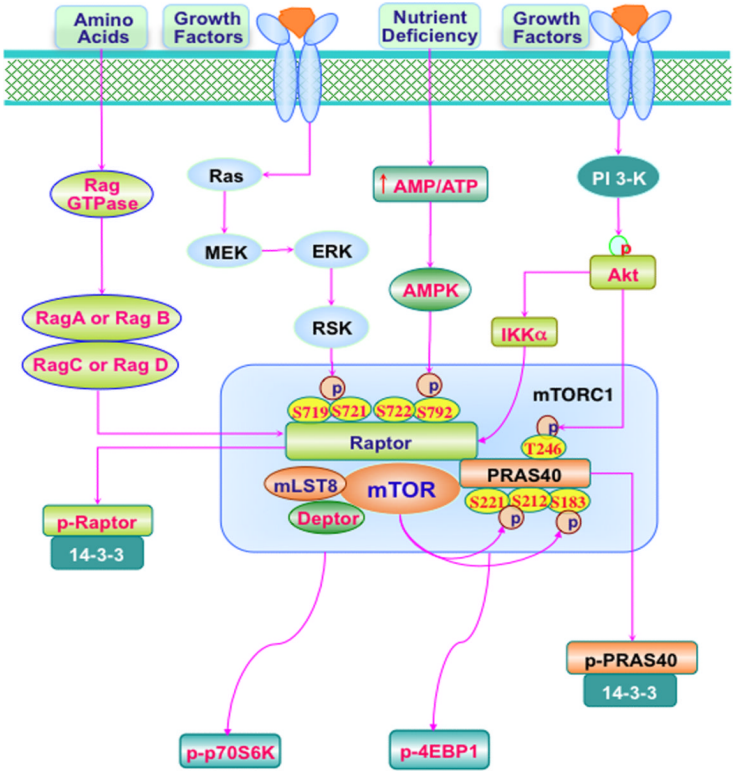

Figure 2. Activation of mammalian target of rapamycin complex 1 (mTORC1) that are independent of TSC1/TSC2

Growth factors activate phosphoinositide 3 kinase (PI 3-K) and Akt. Once active, Akt can directly phosphorylate proline rich Akt substrate 40 kDa (PRAS40) on threonine^{246} (T246), resulting in its dissociation from the regulatory associated protein of mTOR (Raptor) and preventing inhibition of mTORC1. Akt also can also activate IκB kinase-α (IKKα) to increase the activity of mTORC1 through its association with Raptor. In the extracellular signal related kinase (ERK) pathway, ERK is activated following Ras activation of mitogen activated kinase/ERK kinase (MEK). This leads to activation of ribosomal S6 kinase (RSK), which phosphorylates Raptor on the residues of serine^{719}, serine^{721}, and serine^{722} (S719, S721, and S722) resulting in enhanced activation of mTORC1. Nutrient deficiency reduces cellular ATP level and stimulates AMP activated protein kinase (AMPK), which leads to the phosphorylation of Raptor on S722 and serine^{792} (S792) and results in the binding of Raptor to the cytoplasmic docking protein 14-3-3. Amino acids can activate Rag GTPase. In mammalian cells, RagA or RagB forms heterodimers with either RagC or RagD. These heterodimers strongly bind to Raptor, which is necessary to initiate amino acid signaling for mTORC1. Upon activation, mTORC1 phosphorylates its two major downstream targets p70 ribosome S6 kinase (p70S6K) and eukaryotic initiation factor 4E-binding protein 1 (4EBP1). mTOR also can phosphorylate PRAS40 on the serine residues serine^{183}, serine^{212}, and serine^{221} (S183, S212, S221). Phosphorylation of PRAS40 on S221 or T246 promotes its binding to protein 14-3-3. (p = phosphorylation).

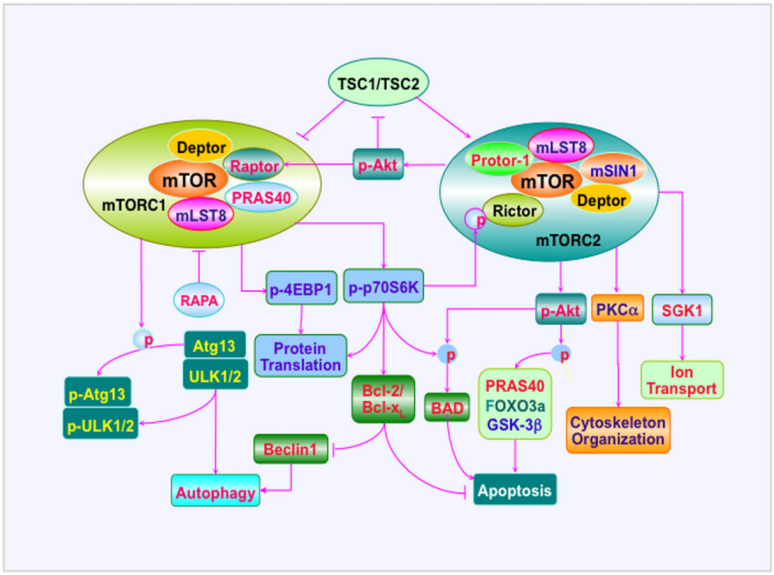

Figure 3. Regulatory pathways of mTORC1 and mTORC2 during apoptosis and autophagy

mTORC1 promotes protein translation through phosphorylating its two major targets, p70 ribosome S6 kinase (p70S6K) and eukaryotic initiation factor 4E-binding protein 1 (4EBP1). The phosphorylaton of p70S6K can then phosphorylate rapamycin insensitive companion of mTOR (Rictor) leading to a series of events that involve the inhibition of mTORC2, the phosphorylation of the pro-apoptotic protein BAD that leads to its inactivation, and increased expression of the anti-apoptotic protein complex Bcl-2/Bcl-x_L to prevent apoptosis. Activation of mTORC2 promotes protein kinase Cα (PKCα) activation to regulate cytoskeleton organization and serum- and glucocorticoid-induced protein kinase 1 (SGK1) control of ion transport. Phosphorylation of Akt leads to activation of mTORC1 through the regulatory-associated protein of mTOR (Raptor). Once activated, Akt can inhibit tuberous sclerosis complex (TSC1/TSC2), which is a negative regulator for mTORC1 but a positive regulator for mTORC2. Akt also phosphorylates and inactivates FoxO3a, glycogen synthase-3β (GSK-3β), BAD, and proline rich Akt1 substrate 40 kDa (PRAS40) contributing to the anti-apoptotic functions of mTOR. To prevent the induction of autophagy, mTORC1 phosphorylates mammalian homologues of autophagic related gene 13 (Atg13) and UNC-51 like kinase 1/2 (ULK1/2). Rapamycin (RAPA) can prevent mTORC1-mediated phosphorylation of Atg13 and ULK1/2 to promote autophagy. Activation of p70S6K also promotes the expression of Bcl-2/Bcl-x_L that inhibits Beclin1 to prevent autophagy. (p = phosphorylation).

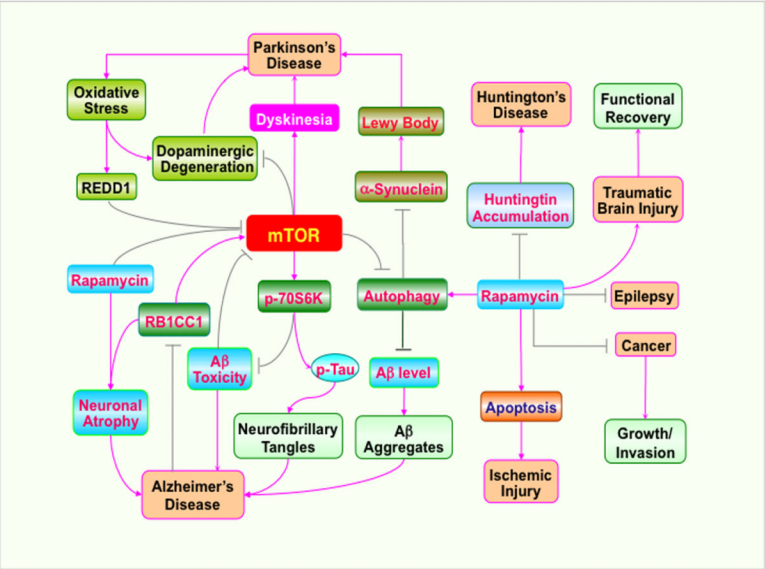

Figure 4. mTOR and disease of the nervous system

mTOR may modulate Alzheimer's disease (AD) through the phosphorylation of p70 ribosome S6 kinase (p70S6K). A number of outcomes may result that include the phosphorylation of tau and neurofibrillary accumulation, reduction in neuronal atrophy and cell injury. Rapamycin can block these processes and autophagy may influence amyloid (Aβ) aggregation. Neuronal atrophy in AD has been attributed to the insufficiency of retinoblastoma tumor suppressor (RB1) inducible Coiled-Coil 1 (RB1CC1), which functions to activate mTOR. Activation of mTOR prevents neurodegeneration of dopaminergic neurons during oxidative stress in Parkinson's disease (PD). The stress response protein REDD1 expressed during PD inhibits the activation of mTOR. In addition, rapamycin application that results in autophagy can accelerate the removal of α-synuclein, a major component of Lewy bodies. Yet, activation of mTOR could aggravate dyskinesia. Inhibition of mTOR activity, such as during rapamycin treatment, also can prevent the progression of Huntington's disease (HD) by autophagic clearance of huntingtin protein, reduce the occurrence of epilepsy, improve functional recovery following traumatic brain injury, increase ischemic neuronal apoptosis, and prevent tumor growth and invasion. (p = phosphorylation).

Table 1

The functional domains of mTOR

	Domain	Function
C-terminal	KD	Serine/threonine kinase activity
	RD	Contains phosphorylation sites for activation, including serine^{2448}, serine^{2481}, serine^{2159}, threonine^{2446}, and threonine^{2164}
	FRB	The docking site for the FKBP12-rapamycin complex
	FAT	Mediates the activity of kinase domain
	FATC	Mediates the activity of kinase domain
N-terminal	HEAT repeats	Provides the site for interaction with Raptor or Rictor; contains the phosphorylation site serine^{1261} that regulates the autophosphorylation on serine^{248} of mTOR

Note: FAT: FKBP associated protein, Ataxia-telengiectasia, Transactivtion/transformation domain-associated protein; FATC: FAT, Carboxy terminal; FRB: FK506 binding protein 12 -rapamycin-binding domain; HEAT: Huntingtin, Elongation factor 3, A subunit of protein phosphatase-2A, and TOR1; KD: kinase domain; RD: regulatory domain.

Table 2

The cellular function mTOR in specific disease entities

Diseases or targets	Biological activity of mTOR activation
Stem cells	Promotes the development, proliferation, and differentiation of stem cells
Apoptosis	Phosphorylates p70S6K, 4EBP1, Akt, and PRAS40 to prevent apoptosis
Autophagy	Phosphorylates the mammalian homologue of Atg13 and ULK1/2 and promotes the association between Bcl-2/Bcl-x_L and Beclin 1 to prevent autophagy.
Alzheimer's disease	Promotes Tau phosphorylation in neurons, reduces autophagic clearance of Aβ, but prevents neuronal atrophy and attenuates Aβ induced neurotoxicity
Parkinson's disease	Protects dopaminergic neurons, but potentiates dyskinesia and attenuates the clearance of α-synuclein protein
Huntington's disease	Impairs autophagic clearance of huntingtin aggregates. Rapamycin prevents the accumulation of huntingtin and its toxicity
Epilepsy	Increases the incidence of epilepsy. Inhibition of mTOR reduces seizures in TS, prevents acquired seizures, and reduces chronic spontaneous seizure activity
Traumatic brain injury	Traumatic brain injury enhances phoshorylated mTOR, p70S6K, and 4EBP1. Activation of the Akt/mTOR/p70S6K pathway improves functional recovery after spinal cord injury Rapamycin reduces microglial activation, protects neurons, and improves functional recovery after closed head injury
Ischemic stroke	Rapamycin increases apoptosis in neurons and microglia during OGD
Cancer	Promotes tumorigenesis, increases metastases, and enhances the resistance of cancer cells to chemotherapy in a broad scope of cancers Promotes tumor growth that is associated with CNS inherited cancer syndromes including tuberous sclerosis, neurofibromatosis type I, and Lhermitte-Duclos disease

Aβ: beta-amyloid; Atg: autophagy related gene; CNS: central nervous system; 4EBP1: eukaryotic initiation factor 4E-binding protein 1; OGD: oxygen glucose deprivation; p70S6K: p70 ribosomal S6 kinase; PRAS40: proline rich Akt substrate 40 kDa; TS: tuberous sclerosis; ULK1/2: UNC-51 like kinase 1/2,