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mTOR/AMPK signaling in the brain: Cell metabolism, proteostasis and survival

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Abstract

The mechanistic (or mammalian) target of rapamycin (mTOR) and the adenosine monophosphate-activated protein kinase (AMPK) regulate cell survival and metabolism in response to diverse stimuli such as variations in amino acid content, changes in cellular bioenergetics, oxygen levels, neurotrophic factors and xenobiotics. This Opinion paper aims to discuss the current state of knowledge regarding how mTOR and AMPK regulate the metabolism and survival of brain cells and the close interrelationship between both signaling cascades. It is now clear that both mTOR and AMPK pathways regulate cellular homeostasis at multiple levels. Studies so far demonstrate that dysregulation in these two pathways is associated with neuronal injury, degeneration and neurotoxicity, but the mechanisms involved remain unclear. Most of the work so far has been focused on their antagonistic regulation of autophagy, but recent findings highlight that changes in protein synthesis, metabolism and mitochondrial function are likely to play a role in the regulatory effects of both mTOR and AMPK on neuronal health. Understanding the role and relationship between these two master regulators of cell metabolism is crucial for future therapeutic approaches to counteract alterations in cell metabolism and survival in brain injury and disease.

Graphical abstract

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Keywords

mammalian target of rapamycin; adenosine monophosphate-activated protein kinase; autophagy; mitochondria; glycolysis; cell death; nutrient deprivation; energy failure

1. Introduction

The mechanistic (or mammalian) target of rapamycin (mTOR) and the adenosine monophosphate-activated protein kinase (AMPK) regulate cell growth and metabolism incorporating signals triggered by different stimuli such as variations in the amino acid content, changes in cellular bioenergetics, activation of hormone and growth factor signaling and stress such as oxidative stress, hypoxia or DNA damage. In the brain, AMPK and mTOR signaling are regulated by neurotransmitters and neurotrophin signals. mTOR and AMPK are considered master regulators of cell metabolism. Their activation is directly linked to the regulation of cellular metabolism (mitochondria homeostasis and central carbon metabolism), growth (protein synthesis) and survival (autophagy and cell death pathways). This Opinion paper aims to discuss the current state of knowledge regarding how mTOR and AMPK regulate brain metabolism and survival upon stress and more importantly, the close interrelationship between both signaling molecules (Figure 1 and Supplementary Table 1).

2. mTOR signaling in brief and its role regulating cell metabolism

mTOR is a serine (Ser)/threonine (Thr) protein kinase in the PI3K-related kinase (PIKK) family that forms the catalytic subunit of two distinct protein complexes, known as mTOR Complex 1 (mTORC1) and 2 (mTORC2) (Figure 1). Together with mTOR, the mammalian lethal with sec13 protein 8 (mLST8 or GβL), and the inhibitory DEP domain containing mTOR-interacting protein (DEPTOR) are common to both mTORC1 and mTORC2. Phosphorylation of DEPTOR by mTOR and other kinases promotes its degradation and activation of mTORCs. mLST8 seems to stabilize the kinase activation loop of mTOR but is dispensable for its activity. mTORC1 also includes the regulator-associated protein of the mammalian target of rapamycin (Raptor or RPTOR) and the proline-rich AKT substrate of 40 kDa (PRAS40). Because the interaction between Raptor and mTOR is essential for the

stability of the mTORC1 and the recruitment of substrates, post-translational modifications in Raptor (phosphorylation, cleavage or ubiquitination) regulate mTORC1 activity. PRAS40 inhibits the substrate recruitment sites of mTORC1 and its phosphorylation by AKT and mTOR promotes its dissociation from the complex. On the other hand, the mTORC2 includes the rapamycin-insensitive companion of mTOR (Rictor), the mammalian stress-activated MAP kinase-interacting protein 1 (mSIN1), and the proteins observed with rictor 1 and 2 (PROTOR 1 and 2) [1].

The GTP binding protein Ras homolog enriched in brain (Rheb) is an obligate upstream activator of mTORC1 by growth factors and amino acids (Figure 1). Activation of the phosphoinositide-3 kinase (PI3K)/protein kinase B (PKB/AKT) pathway by growth factor receptors inactivates the tuberous sclerosis complex (TSC), a key negative regulator of mTORC1 (Figure 1). TSC is a heterotrimeric complex comprising TSC1, TSC2, and the Tre-2/BUB2/cdc 1 domain family member TBC1D7. TSC2 acts as a GTPase-activating protein (GAP) to inactivate Rheb (Rheb-GDP). mTORC1 activation requires its localization in the lysosomal surface which is regulated by amino acid and nutrient sensing via Rag GTPases (Figure 1). Induction of protein synthesis by mTORC1 involves the phosphorylation of the ribosomal protein S6 kinase beta-1 (S6K) and the eukaryotic translation initiation factor 4 (eIF4E)-Binding Protein (4E-BP) (Figure 1) [1]. Glucose metabolism has been reported to be regulated by translational regulation of the hypoxia-inducible factor 1- α (HIF1 α) via 4E-BP and mTORC1 [2]. Via 4E-BP, mTORC1 signaling regulates mitochondrial biogenesis as well [3]. mTORC1 also regulates lipid and nucleotide synthesis through the sterol responsive element binding protein (SREBP) transcription factors and the activation of the transcription factor 4 (ATF4), respectively [4,5].

mTORC2 primarily controls proliferation and survival via the activation of members of the AGC family of protein kinases such as PKC that regulate cytoskeletal remodeling and cell migration. AKT phosphorylation by mTORC2 is required for AKT-mediated phosphorylation of specific substrates such as FOXO1/3a. Reciprocally, AKT has been shown to phosphorylate mSIN1 enhancing mTORC2 kinase activity (Figure 1) [1]. mTORC2 has also been demonstrated to regulate glucose and amino acid metabolism [6–9]. Interestingly, a recent report also demonstrates that mTORC2 has the ability to act as a tyrosine kinase [10].

3. AMPK signaling in brief and its role regulating cell metabolism

AMPK is a Ser/Thr kinase that exists as a heterotrimer composed of catalytic α and regulatory β and γ subunits. In the absence of AMP, the autoinhibitory domain of AMPK α maintains the kinase in an inactive conformation. Upon ATP consumption, AMP/ADP directly bind to AMPK γ promoting the phosphorylation of AMPK α . The liver kinase B1 (LKB1) is the primary kinase that phosphorylates AMPK α at Thr172 (Figure 1). LKB1 is found constitutively active as a complex with Ste20-related adaptor (STRAD) and mouse protein 25 (MO25). A second binding event of AMP/ADP to AMPK γ induces a conformational change that protects AMPK α from dephosphorylation. AMPK α phosphorylation has also been reported to be mediated by the Ca²⁺/calmodulin (CaM)-

dependent protein kinase kinase 2 or β (CAMKK2 or β), independent from changes in the AMP/ADP:ATP ratio (Figure 1), or by the transforming growth factor β -activated kinase 1 (TAK-1). Finally, AMP upregulates allosterically the activation of AMPK [11]. A new study shows that AMPK can also be activated by sensing the absence of fructose-1,6-bisphosphate (FBP), via aldolase even if there are not changes in the AMP/ADP:ATP ratio [12].

AMPK activation inhibits anabolic processes, stimulates catabolism, and restores ATP levels. Several conditions that either interfere with ATP synthesis or promote ATP consumption can lead to AMPK activation. At least 60 targets have been identified as substrates of AMPK [11], but we will focus on those involved in the regulation of cell metabolism (Figure 1). AMPK inhibits the *de novo* synthesis of fatty acids and activates lipid catabolism via phosphorylation and inactivation of acetyl-CoA carboxylase (ACC). AMPK also stimulates glucose uptake via the phosphorylation of the TBC domain family members TBC1D1 and TBC1D4, and the thioredoxin-interacting protein (TXNIP) that results in an increased translocation of glucose transporters (GLUT) (Figure 1). Phosphorylation of the bifunctional 6-phosphofructo-2-kinase (PFKFB) by AMPK increases fructose-2,6-bisphosphate (F2,6P2), which activates glycolysis via phosphofructokinase 1 (PFK1) (Figure 1). In contrast, glycogen synthesis and hexosamine biosynthesis are inhibited by the phosphorylation and inhibition of glycogen synthase (GS) (Figure 1) and glutamine-fructose-6-phosphate aminotransferase-1 (GFPT1), respectively [13]. AMPK also promotes mitochondrial biogenesis by phosphorylation of the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α) increasing its transcriptional activity (Figure 1) [14,15], as well as mitochondrial fission and autophagy (mitophagy) [16]. Remarkably, it was recently shown that ROS activate AMPK triggering a PGC-1 α -dependent antioxidant response that limits mitochondrial ROS production [17]. Thus, AMPK is a central regulator of mitochondrial homeostasis.

4. mTOR-AMPK signaling crosstalk

While both mTOR and AMPK seem to regulate different pathways, there are key hubs of crosstalk where both converge to regulate homeostatic processes such as autophagy and cell metabolism (Figure 1 and Supplementary Table 1). AMPK utilizes different targets to effectively suppress mTORC1. AMPK inhibits mTORC1 both directly, through the phosphorylation of Raptor [18], as well as indirectly through the phosphorylation and activation of TSC2 [19]. Reciprocally, mTORC1 signaling has also been proposed to regulate AMPK as S6K has been found to phosphorylate and inhibit AMPK (Figure 1) [20].

Autophagy is a proteostatic quality control mechanism that requires the formation of double membraned autophagosomes that deliver cargo for degradation within the lysosome (Figure 1). The unc-51-like autophagy activating kinase 1 (ULK1 or autophagy related protein1 [Atg1]) drives autophagosome formation and mTORC1 suppresses autophagy by phosphorylating ULK1. In contrast, phosphorylation of ULK1 by AMPK promotes autophagy (Figure 1). Therefore, the relative activity of mTORC1 and AMPK in different cellular contexts largely determines the extent of autophagy induction [21].

Another point of convergence is that of protein synthesis. Within the polypeptide translation elongation cycle, translocation of the ribosome is mediated by the elongation factor eEF2. eEF2 is inhibited by phosphorylation catalyzed by the eEF2 kinase (EEF2K). EEF2K is phosphorylated and inactivated by S6K [22] and mTORC1 [23], while its phosphorylation by AMPK promotes its activation (Figure 1) [24].

The forkhead box O3a protein (FOXO3a) is a transcription factor involved in cell survival whose phosphorylation by AKT is well known to inhibit its activity [25], suggesting a possible feedback loop via mTORC2 [26]. FOXO3a has been reported to inhibit mTORC1 activity via transcriptional control of TSC1 [27]. In contrast, phosphorylation by AMPK activates FOXO3a (Figure 1) [28].

5. mTOR/AMPK signaling in the brain

mTOR signaling is involved in a myriad of processes regulating neurodevelopment (proliferation and differentiation) and brain function (neuronal plasticity). Thus, dysregulation in mTOR signaling has been linked to a number of brain disorders associated with neuronal dysfunction and cell death such as neurodegeneration, epilepsy, autism and neurobehavioral alterations. Previous reviews have focused on the role of mTOR in brain function and development [29,30]. In the brain, energy-sensing neurons in the hypothalamus are involved in the regulation of organismal energy balance via AMPK signaling. AMPK activation in the hypothalamus is modulated by energy-related signals associated with food intake (fasting and feeding), energy expenditure (ATP levels), and body weight (hormones and adipokines) [31]. We will next focus on the role of mTOR and AMPK on the survival and cell death of neuro-glial cells and their link with metabolic stress in brain disorders

Brain metabolism is characterized by a complex interplay between different cell types. Glucose is the primary energy substrate of the brain and it has been proposed to be metabolized through two complementary metabolic pathways in neurons and astrocytes. Neurons seem to predominantly metabolize glucose through the pentose phosphate pathway (PPP) to produce the NADPH necessary for antioxidant defense. On the other hand, astrocytes primarily metabolize glucose through glycolysis to produce lactate, where lactate is shuttled as an energy substrate for oxidative phosphorylation in neurons [32–34]. While this astrocyte-neuron lactate shuttle seems to act at rest, recent studies demonstrate that during energy-demanding conditions neurons have the capacity to upregulate glycolysis [35].

Very little is known regarding the role for both AMPK and mTOR signaling in normal brain metabolism. Deletion of Raptor (mTORC1) or Rictor (mTORC2) in the brain leads to neurodevelopmental alterations [36–39], but whether these effects are related to alterations in cell metabolism is unclear. AMPK α 2 has been reported to be the predominant catalytic subunit in neurons and astrocytes in the brain and spinal cord [40]. In contrast to mTOR, AMPK is not necessary for neuronal development or survival, but its hyperactivation impairs axon growth via inhibition of mTORC1 [41]. Indeed, AMPK antagonizes mTOR activation by neurotrophic factors in neurons [42]. We have observed that mTOR signaling is important for astrocytes' basal glycolytic rate (*unpublished results*). A recent report demonstrates that

in astrocytes and neural stem cells, the G-protein-coupled receptor kinase-interacting protein 1 (GIT1) is a novel mTOR-binding protein within a unique mTOR complex regulated by AKT that lacks both Raptor and Rictor [43]. In glioblastoma cells, mTORC2 upregulates glycolysis via acetylation of FOXO1 and FOXO3a transcription factors that result in an increase in c-Myc levels [9].

6. mTOR/AMPK in neuronal cell death and survival

Because mTOR and AMPK are essential for the regulation of metabolism, their dysregulation can generate negative effects leading to cell death and disease progression. There are different examples where the activation of these two kinases has been found to be protective against pathological processes, but it has also been shown that when dysregulated, their increased activity can be detrimental.

6.1. Brain Ischemia and injury

In ischemic brain injury both mTOR and AMPK have been involved in cell death progression. While this topic has been studied extensively [44,45], there are still contradictory results depending on the experimental conditions used. mTOR protects against neuronal cell death induced by ischemic insults [46,47]. Similarly, mTOR signaling via S6K protects astrocytes from oxygen-glucose deprivation (OGD) and mice from middle artery occlusion (MCAO) [48]. Pharmacological inhibition of AMPK also protects against MCAO and OGD [49], but the opposite is found using a global cerebral ischemia model [50]. AMPK α 2, but not α 1 knockout in mice has been shown to protect against MCAO [51]. Interestingly, a dual role of AMPK in neuronal cell death in neonatal hypoxia has been reported, where inhibition of AMPK prior to OGD increases cell death, while its CAMKK2-dependent activation upon OGD mediates neuronal cell loss [52]. In traumatic brain injury (TBI), pharmacological stimulation of AMPK ameliorates cognitive dysfunction [53].

Accumulation of extracellular excitatory amino acids (glutamate) is a common event associated with neuronal cell death during ischemia and TBI. Neuronal cell death induced by glutamate excitotoxicity has been reported to involve AMPK activation and an increase in the levels of the pro-apoptotic Bim protein [54]. In contrast, AMPK-dependent translocation of GLUT3 and glucose availability have been reported to exert a protective effect against glutamate excitotoxicity [55]. mTOR signaling has also been proposed to contribute to the toxicity of glutamate receptor agonists (N-methyl-D-aspartate [NMDA]) [56]. Finally, mTOR is well known to mediate axon regeneration and myelination after injury [57–59].

6.2. Neurodegeneration

Both mTOR and AMPK signaling modulate the progression of different neurodegenerative disorders, but whether their activation is beneficial or detrimental remains unclear. One of the main mechanisms related to neurodegeneration where mTOR and AMPK converge is autophagy, which can exert protective effects via the degradation of misfolded, damaged or toxic proteins, as well as damaged organelles [60]. Parkinson's (PD), and Huntington's disease (HD), are characterized by the accumulation of intracellular misfolded protein aggregates. Because mTORC1 represses autophagy, its inhibition may represent a plausible

therapeutic approach [61]. Accordingly, rapamycin has been reported to protect neurons by promoting the clearance of protein aggregates of α -synuclein and mutant huntingtin which are found in PD and HD, respectively [62,63]. A decrease in mTOR activity also reduces Alzheimer's disease-like amyloid- β ($A\beta$) deposits *in vivo* via induction of autophagy [64]. Interestingly, while mTOR activation is usually considered to inhibit autophagy, autophagy can be induced by mTOR stimulation as well. Accordingly, activation of mTORC1 signaling in the striatum stimulates autophagy, ameliorates mitochondrial dysfunction and protects against HD [65]. In contrast, hyperactivation of mTORC1 via striatum-specific deletion of TSC1 has been reported to accelerate motor dysfunction and mortality in HD mouse models [66].

Most of the studies regarding mTOR signaling and neurodegeneration have been focused on autophagy. A recent report demonstrates that inhibition of mTOR with rapamycin preserves neuronal ATP levels upon inhibition of mitochondrial function, and this effect was associated with a decrease in energy consumption by protein synthesis [67]. Rapamycin-induced activation of 4E-BP reduces dopaminergic degeneration and mitochondrial dysfunction linked to mutations in the PD-related genes PTEN-induced putative kinase 1 (PINK1) and E3 ubiquitin-protein ligase Parkin [68]. Conversely, the PD-related protein leucine-rich repeat kinase 2 (LRRK2) has been shown to phosphorylate and inactivate 4E-BP [69]. Together these results suggest that alterations in protein translation via the mTORC1-4E-BP signaling pathway might be involved in PD. Contradicting results have been reported regarding the role of AMPK in dopaminergic cell death associated with PD [70–75]. A protective role for AMPK against mitochondrial dysfunction and toxicity induced by Parkin-, LRRK2-mutations, α -synuclein and mitochondrial toxins has been previously reported [70–72]. In contrast, other reports have shown that AMPK mediates dopaminergic cell death induced by 6-hydroxydopamine (6-OHDA) and mitochondrial toxins as well [73,74]. We have demonstrated that AMPK exerts a protective effect against cell death induced by paraquat (PQ), a pesticide recognized as an important PD risk factor, in combination with the PD-related gene, α -synuclein [76]. Importantly, while autophagy protects against PQ toxicity [77], the modulatory effects of AMPK seem to be primarily related to metabolic dysfunction [76].

The intracellular aggregation of abnormally and hyperphosphorylated tau proteins generates neurofibrillary tangles (NFTs), the pathological hallmark of neurodegenerative diseases commonly known as tauopathies. $A\beta$ oligomers activate AMPK via CAMKK2, which mediates tau phosphorylation and neurotoxicity [78,79]. In contrast, short-term exposure to $A\beta$ oligomers transiently decrease AMPK activity and result in a reduction in glucose transport [80]. In HD, activation of AMPK mediates neuronal atrophy downstream of oxidative stress [81]. However, another study suggests that AMPK activation at early stages of HD pathology protects against neuronal cell death [82].

6.3. Environmental neurotoxicity

Exposure to environmental toxicants is a risk factor for neurodegenerative, cognitive and neurodevelopmental disorders. Arsenic, a natural occurring neurotoxicant, impairs neurite outgrowth by inhibition of AMPK signaling [83]. We have observed that AMPK signaling

and autophagy promote apoptotic cell death in cortical astrocytes exposed to inorganic arsenic (*unpublished results*). Cadmium (Cd) neurotoxicity has been shown to be mediated via mTOR signaling [84]. Bisphenol-A (BPA), an endocrine disruptor released from the polycarbonate containers, activates AMPK while it downregulates mTOR signaling, resulting in enhanced autophagy. AMPK signaling and autophagy were reported to exert a protective effect against BPA-induced neurotoxicity in hippocampal neurons [85]. In contrast, the neurotoxicity of tributyltin, a water organotin contaminant, has been linked to the activation of AMPK and excitotoxic glutamate release [84].

7. Conclusions and perspectives

It is now clear that both mTOR and AMPK pathways regulate cellular homeostasis at multiple levels. By continuously sensing the cellular energy and nutrient state mTOR and AMPK have the capacity to facilitate cellular adaptation to stress. In addition, Ca^{2+} , growth factors and oxidative stress have the ability to activate mTOR and AMPK to regulate protein synthesis, autophagy and metabolism. We have aimed to discuss the current state of knowledge regarding how mTOR and AMPK regulate brain metabolism and survival upon stress and the close interrelationship between both signaling pathways. Studies so far have demonstrated that dysregulation in these two pathways is associated with neuronal cell death, but the mechanisms involved remain unclear. Most of the work has been focused on their convergence regulating proteostasis via autophagy, but recent findings highlight that changes in protein synthesis, metabolism and mitochondrial function are likely to play a role in the regulatory effects of mTOR and AMPK on neuronal health. While there is still controversy regarding whether AMPK and mTOR signaling can exert a neuroprotective or neurotoxic effect, some of these controversies might be addressed when considering: 1) the poor specificity of widely used pharmacological approaches to modulate their activity (rapamycin, torin 1, compound C, 5-Aminoimidazole-4- carboxamide ribonucleotide [AICAR] and others); and 2) the time-dependent effect of modulating these signaling pathways. Understanding their roles and the relationship between these two master regulators of cell metabolism is crucial for future therapeutic approaches to counteract alterations in cell metabolism and survival during neuronal cell death and degeneration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- mTOR and AMPK regulate cell survival and metabolism in response to diverse stimuli.
- Studies so far demonstrate that dysregulation in these two pathways is associated with neuronal injury, degeneration and neurotoxicity.
- Recent findings highlight that in addition to autophagy, changes in protein synthesis, metabolism and mitochondrial function play a role in the regulatory effects of mTOR and AMPK on neuronal health.

Figure 1. mTOR/AMPK signaling crosstalk

Signaling by mTOR and AMPK integrates changes in the cellular environment linked to growth factors, nutrient, oxygen and energy availability, excitotoxicity (Ca^{2+}) and stress (oxidative stress). Five major points of convergence include: 1) the transcriptional regulation of genes linked to cell survival/death, proteostasis, redox balance and bioenergetics; 2) metabolism (central carbon and bioenergetics); 3) autophagy; 4) mRNA translation and protein synthesis; and 5) cell survival and growth (AKT). Arrows indicate activation. Stop lines indicate inhibition. Phosphorylation events (P) are color coded according to the kinase involved in phosphorylating the corresponding targeted protein. White background/colored

“P” highlights an inhibitory effect; Colored background/white P highlights an stimulatory (activation) effect. A detailed explanation of the phosphorylation events is included in the Supplementary Table 1. Additional crosstalk might involve indirect pathways not highlighted in this figure.

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