mTOR signalling pathway - A root cause for idiopathic autism?

Harsha Ganesan, Venkatesh Balasubramanian, Mahalaxmi Iyer, Anila Venugopal, Mohana Devi Subramaniam, Ssang-Goo Cho and Balachandar Vellingiri

INTRODUCTION

Autism spectrum disorder (ASD) is a complex neurodevelopmental monogenic disorder with a strong genetic influence. Idiopathic autism could be defined as a type of autism that does not have a specific causative agent. Among signalling cascades, mTOR signalling pathway plays a pivotal role not only in cell cycle, but also in protein synthesis and regulation of brain homeostasis in ASD patients. The present review highlights, underlying mechanism of mTOR and its role in altered signalling cascades as a triggering factor in the onset of idiopathic autism. Further, this review discusses how distorted mTOR signalling pathway stimulates truncated translation in neuronal cells and leads to downregulation of protein synthesis at dendritic spines of the brain. This review concludes by suggesting downstream regulators such as p70S6K, eIF4B, eIF4E of mTOR signalling pathway as promising therapeutic targets for idiopathic autistic individuals. [BMB Reports 2019; 52(7): 424-433]
implicated in higher cognitive functions and behaviour, thus causing autistic phenotypes. Findings of Hutslers and Zhang (16) also prove the hypothesis that disruptions in the mTOR pathway can negatively affect spines and contribute to autism neuropathology in patients. Hence, in this review, we will highlight the importance of mTOR signalling pathway in idiopathic autism. We will also discuss certain mTOR regulators that play a vital role in the disruption of translation initiation and protein synthesis as a triggering factor for the expression of autistic phenotypes. Finally, we suggest that mTOR signalling pathway will be revolutionary in the field of translation research as a promising strategy to discover remedies for idiopathic autism.

COMMON FEATURES OF IDIOPATHIC AUTISM BRAIN

Neurodevelopment comprises of certain crosslinked molecular mechanisms including neurogenesis, corticogenesis, and synaptogenesis. Adult neurogenesis is the development of new neurons in specific regions of the brain such as the hippocampus and olfactory bulb. This process is particularly important for the conversion of Neural Stem Cells (NSCs) and neural precursors into functional neurons (17). Corticogenesis that leads to mammalian neurocortex development is a part of embryonic neurogenesis. It is required for the origin of six layers of the cortex where neuronal migration begins at the ventricular zone and proceeds towards their final position in the brain (18, 19). Synaptogenesis is the concluding step in neural development which comprises of initiation and linkage of pre- and post-synaptic domains in target neurons as well as regulation of synaptic development through mTOR and Wnt signalling pathways. Following synaptogenesis, ratio of excitatory to inhibitory synapses (E/I ratio) is also important for neural circuit assembly and it analysis the synaptic output (20, 21). Alterations in these key regulatory processes has been reported in neurodegenerative and developmental disorders such as ASD, Parkinson’s disease, Alzheimer’s disease, Huntington’s disease, Amyotrophic Lateral Sclerosis and Schizophrenia (17). During corticogenesis, neuronal migration and laminar formation are critical for brain function. Their disruption due to overexpression of certain glycoproteins such as reelin secreted by Cajal-retzius cells and GABAergic interneurons can lead to ASD, bipolar disorder, and schizophrenia (22). Oblak et al. (23) have linked decreased GABA receptor signalling to behavioural abnormalities seen in ASD patients. They confirmed this with autoradiography techniques where densities of GABA receptors were monitored in fusiform gyrus and cingulated cortex regions of the brain involved in corticogenesis. Cortical development, the chief course of action in corticogenesis, requires activation and placement of neuronal progenitor cells at radial and angular axis regions of the cerebral cortex in the brain. One major gene involved in corticogenesis is T-Box Brain 1 (TBR1) gene that is also associated with ASD, in which there is a disrupted localization of TBR1 (24). TBR1 protein can interact with kinase CASK to induce autism (25). Later during synaptogenesis, molecules specific to scaffolding and cell adhesion such as neurexins, neurligin, cadherin, and Shank3 can alter neuronal activity in ASD and idiopathic autism individuals (21). Specifically, interaction of neurexins with neurexins is known to regulate postsynaptic activity of both excitatory and inhibitory synapses (20, 26). Mutations in these molecules have been reported in various cases of autism, leading to inhibition, receptor downregulation, and altered synaptic protein placement at the cingulated cortex and fusiform gyrus (25, 27). The importance of β-catenin, a Wnt signalling molecule, in both corticogenesis and synaptogenesis was reviewed by Williams and Casanova (28). They noted that depleted intelligence level of autistic individuals was related to increased total brain volume (TBV) that was also observed in megalencephaly (28, 29). Megalencephaly is also observed in TSC categorised under syndromic autism. This was proven by the deletion of TSC specific gene through Cre-Lox system knockout in mice, leading to megalencephaly with characteristically enlarged soma and nucleus, decreased to absent astroglial activity, mislamination, ectopic placement of neurons, and mTOR hyperactivity (30). Additionally, syndromic autism has increased E/I ratios in various interrelated systems such as emotional, social and sensory systems of the brain. This imbalance in E/I ratio can lead to hyperexcitation and hypoinhibition at cortical circuits in FXS, a type of ASD (20). E/I imbalance could also disrupt N-methyl-D-aspartic acid receptor (NMDAR) dependent cascade which negatively regulates mTOR pathway (31). Among other factors involved in manifestation of autism etiology, amyloid-β precursor protein (APP) shows elevated levels at synapses, leading to overgrowth of cranial neurons and further alteration of (PI3K/Akt/mTOR) signalling pathways. These alterations are due to PSEN mutations that cause brain tumours and macrocephaly in autism, proving that abnormal cell proliferation could also be associated with mTOR imbalance (32). Furthermore, Osborne (19) has linked hyperactivation of mTOR to PMSE, showing that disruption of corticogenesis is associated with mTOR. Megalencephaly is not only observed in PMSE, but also found in idiopathic autism patient. It is a common feature of idiopathic autism patient where there is an increase of cell growth that could be an outcome of increased protein synthesis due to mTOR hyperactivation (19). Idiopathic autism patients exhibit a loss in socio-emotional and face recognition ability. Such loss is linked to changes in the anterior, posterior cingulated cortex and the fusiform gyrus in the cerebral cortex where GABA receptor binding ability is decreased (23). Alteration in mTOR pathway can lead to heterotrophia and dysplasia where the structure of the cortex is distorted by changing the cortical circuitry (19). Accelerated mTOR activity at late corticogenesis in idiopathic autism individuals can result in misplacement of neurons, leading to alteration of neural identity. These disadvantages could be
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controlled by cap-dependant translation that targets 4E-Binding Proteins (4E-BPs) and prevents ectopic neuron placement and mislamination due to accelerated downstream mTOR signalling (33). Lin et al. (33) have proven that knockdown of 4E-BP can lead to various changes in the neural architecture, including elevated soma size in the neuron, dendritic development, and changes of synaptic potential and spine density. These findings reveal that mTOR signalling pathway alterations could be contributory mediators of idiopathic autism.

SIGNALLING PATHWAYS AS MODULATORS OF SYNDROMIC AND IDIOPATHIC AUTISM

Autism is linked to certain signalling pathways such as Wnt pathway, calcium and calmodulin pathway and PI3K/mTOR signalling pathway. Wnt pathway gives a better understanding of cellular differentiation, polarity, and proliferation in different tissues. Its deregulation leads to various types of cancers and certain cases of ASD as reported by Oron and Elliot (34). Maturation and development of brain are associated with the canonical Wnt pathway. In individuals with ASD, the Wnt signalling pathway is linked to cortical patterning, upregulation of dendritic spine density, and alteration of spine morphology (35). Other than Wnt signalling, calcium concentrations and calmodulin binding capacity can also affect various components of the Central Nervous System (CNS), specifically targeting the pre- and post-synaptic responses of neurons (36). Wen et al. (37) have linked MAPK signalling pathways to 20 other functional pathways and 22 ASD associated genes. They also mentioned the role of calcium and MAPK signalling pathways as interacting hubs for various other interrelated pathways in ASD. Another targeted candidate is nerve growth factor (NGF) induced signalling that leads to significant decrease in 4E-BP1 protein and eukaryotic translation initiation factor 4E (eIF4E) that induces oxidative stress in autistic patients (38). Both 4E-BP1 and eIF4E are major components of the mTOR signalling pathway. Nicolini et al. (9) have reported a deregulation of 4E-BP1 in valproic acid (VPA) exposed mice model for idiopathic autism. Hence, we can correlate NGF signalling pathway and mTOR signalling pathway with oxidative stress related ASD. In this review, we will focus on mTOR pathway which has received wide development, synapse formation and associated functions have been discussed in detail. mTOR signalling pathway is also associated with abnormal developmental features of the brain including Malencephaly (49, 50), hemimegalencephaly (51), pigmentary mosaicism (50), glioblastoma multiforme (52), astrocytoma (52), and focal cortical dysplasia (53). These defects are mainly associated with malfunction of mTOR associated cells either upstream or downstream of the signalling cascade (50, 54). Specifically, in the brain, mTOR is involved in the regulation of synaptogenesis, corticogenesis, and associated functions of neurons. mTOR is also related to a number of neuropsychiatric and neurodevelopmental disorders such as Alzheimer’s disease, ASD, and idiopathic autism (55). Altered mTORC1 activity due to mutations in TSC has been linked to Alzheimer’s disease characterised by accumulation of cellular amyloid-β proteins, decreased soma size, and decreased activities of mTORC1 and mTORC2 (56). Activation and phosphorylation of Akt, a protein kinase, play a major role in the onset of mTOR pathway because Akt targets TSC and

mTOR - THE SIGNALLING HUB

mTOR plays a centralised role in inducing and activating various interlinked pathways. Thus, it acts as a signalling hub and regulates certain physiological features of the cell. Various intracellular and extracellular processes including protein synthesis, RNA biogenesis, autophagy, cell growth, and survival (39) are pictorially presented in Fig. 1. mTOR is also associated with various diseases including various cancers (40, 41) such as prostate cancer (42), kidney cancer (43), and breast cancer (44) due to mutations and misregulations in the mTOR pathway. It is also associated with other diseases including cardiovascular disease (45), renal diseases (46), pulmonary fibrosis (47), and diabetes mellitus (48). Associations of mTOR signalling pathway with normal and abnormal brain, neurite development, synapse formation and associated functions have been discussed in detail. mTOR signalling pathway is also associated with abnormal developmental features of the brain including Malencephaly (49, 50), hemimegalencephaly (51), pigmentary mosaicism (50), glioblastoma multiforme (52), astrocytoma (52), and focal cortical dysplasia (53). These defects are mainly associated with malfunction of mTOR associated cells either upstream or downstream of the signalling cascade (50, 54). Specifically, in the brain, mTOR is involved in the regulation of synaptogenesis, corticogenesis, and associated functions of neurons. mTOR is also related to a number of neuropsychiatric and neurodevelopmental disorders such as Alzheimer’s disease, ASD, and idiopathic autism (55). Altered mTORC1 activity due to mutations in TSC has been linked to Alzheimer’s disease characterised by accumulation of cellular amyloid-β proteins, decreased soma size, and decreased activities of mTORC1 and mTORC2 (56). Activation and phosphorylation of Akt, a protein kinase, play a major role in the onset of mTOR pathway because Akt targets TSC and

Fig. 1. Schematic representation of various molecular inhibitors and stimulators in mTOR signalling pathway. PTEN and Nf1 could inhibit the activation of Akt. Akt when mutated could inhibit the activation of TSC 1 and TSC 2 that are precursors of mTORC1. FMRP inhibition could lead to deactivation of mTORC2. When stimulated, mTORC1 is involved in various cellular processes including microtubule organisation, autophagy, lipid biosynthesis, RNA biosynthesis, and protein synthesis using precursors of CLIP-170, ULK1, Lipin-1, TFE3, and P70S6K, respectively. Stimulation of mTORC2 leads to proper cytoskeletal organisation through RAC, Rho, and PKC. Cell survival is achieved through SGK1.
regulates mTORC1 activity (57). Mutations in TSC1 and TSC2 can lead to alteration in the activity and size of brain, leading to megalencephaly and dysmorphisms of developing neurons, glia, and progenitor cells (58). In contrast to Alzheimer's where altered soma size is the main characteristic feature, hyperactivity of mTOR signalling in ASD leads to megalencephaly, overconnectivity of neurons and increases the spine growth (15).

FUNCTION OF mTOR SIGNALLING PATHWAY IN ASD

Overlaps among cellular phenotypes, genes, and molecular and biochemical pathways have led to the classification of a number of monogenetic syndromes as part of the broader spectrum of ASD as depicted in Fig. 2 (7). Mutations in mTOR signalling including TSC1, TSC2, PTEN, and Phosphoinositide 3-kinases (PI3K) components have also led to expression of these disorders (39) as explained in detail in Table 1. One of the major upstream signalling components that activate mTORC1 is Ras homolog enriched in brain (RHEB) in brain cells. It could be blocked by mutated TSC, leading to tumorous outgrowth in the brain. TSC complex inhibits RHEB and mTORC. When this upstream process is altered, there is hyperactivation of mTORC1. Another regulating molecule is PTEN which is involved in Akt activation and lipid signalling by regulating PI3K levels. Misregulation of PI3K leads to hyperactivity of not just mTORC1, but also Akt pathway (60). Another not well explored aspect of mTOR pathway is the fragile X mental retardation protein (FMRP) that plays a role in activating fragile X syndrome (FXS). It is known that 50% of FXS individuals have ASD and mutation in the Fmr1 gene that codes for FMRP protein which in turn is involved in PI3K regulation (61, 62). Although the contribution of mTOR to this disorder has not been well understood yet, it is known that PI3K subunit has an elevated amount in knockout mouse models of FXS (61, 62). Enlarged murine cerebellum and hippocampus is also a characteristic of Angelman syndrome where there is a deletion in Ube3a gene that causes reduced activation of mTORC2 and hyperactivation of mTORC1 signalling (63). MeCP2 mutation causes Rett syndrome that has decreased protein synthesis and mTORC1 activity (39). These features are due to distorted cell signalling and biochemical pathways, leading to brain enlargement in autism (64). Altered signalling in the brain includes changes in growth factor signalling such as brain derived neurotrophic factor (BDNF), NGF, MAP kinase, ERK signalling systems, protein synthesis, and mTOR pathway (15). Hyper expansion of cortical surface area, etiological heterogeneity, and alteration in corticogenesis are some of prodromal features of an autistic individual. The chief process affected downstream of this signalling cascade is the protein synthesis. S6 protein kinases (S6K) and 4E-BPs are two major substrates that govern mRNA translation. Phosphorylation of ribosomal protein S6 and suppression of methylated cap binding between eIF4E and 4E-BPs can lead to inhibition of translation. Hence, mTORC1 activation is mandatory for protein synthesis (65). Although abnormal mTOR function has been connected to syndromic autism by various studies as mentioned above, its role in idiopathic autism has been scarcely explored.

THE SPARSELY EXPLORED TYPE OF AUTISM: IDIOPATHIC AUTISM

Despite there are increased knowledge about pathways that create havoc in syndromic autism, there are far fewer researches related to the physiology and manifestation of idiopathic autism. VPA (66) induced knockout mouse models and induced Pluripotent Stem Cells (iPSC) (67) are the widely used models to study idiopathic autism. Similar to knockout mice models, BTBR mice can serve a model organism for studying ASD and idiopathic autism. Meyza and Blanchard (68) have highlighted the importance of BTBR T^Itpr3^/+ mouse for studying idiopathic autism as convergence of multiple signalling pathways and exhibition of distinct neuroanatomical features.

mTOR is involved in various neurodevelopmental processes, including neuronal differentiation, axon guidance, cell migration, and neural region patterning. These processes are altered in idiopathic autism. Roles of dendritic spine
Table 1. Effect of various mTOR associated signalling molecules autism spectrum disorders

| mTOR involved molecule (gene/precursor/receptor) | Affected region in brain | Effect of mTOR associated molecule | Model system | Process involved | Disease induced | Analytical methods | Reference |
|-------------------------------------------------|--------------------------|-----------------------------------|--------------|-----------------|----------------|--------------------|-----------|
| PTEN                                           | Hippocampus, Cerebral cortex | Macrocephaly, Neurohypertrophy, Increased length and thickness in dendritic arbors, Variation in response to sensory stimuli, learning and anxiety. | Mouse | AKT/mTOR pathway activation and Gsk3β inactivation | - | Cre mediated recombination in mice, Behavioural testing of mutant mice, Immunohistochemical staining, Cell counting, Golgi staining, Electron microscopy, EEG/EMG recording | 86 |
| PTEN                                           | Hippocampus, Cerebral cortex | Macrocephaly, Neurohypertrophy, Increased seizures, Decreased adaptability to environmental stimuli, Pten's effect on PI3K cascade, Inturn affects the circadian rhythm. | Mouse | Circadian rhythm | - | EEG/EMG recording, Wheel running test, Statistical analysis | 87 |
| Tsc1 Rho | Neural progenitor cells in Sub Ventricular Zone | Heterotropia in RMS and OB, Enlarged microglia, Cell migration disrupted by RhoB with Mash1 cells at the RMS, Neuronal migration speed decreased, Increased mTOR signalling does not affect the action potential | Mouse | Increased mTOR signalling | Tuberous Sclerosis | Electrophoration of plasmid, Migration, morphometric, micronodule assays, Immunostaining, Confocal microscopy | 88 |
| Tsc1 Tsc2 | Hippocampal pyramidal neurons | Increased phosphorylation of S6, Absence of Tsc1 leads to increase in soma size but decrease, decrease in dendritic spines, increased synaptic current | Mouse | Tsc up/down regulation | Tuberous sclerosis | Immunostaining, Two-photon laser scanning microscopy, Electrophysiology | 89 |
| Rictor                                          | Central Nervous System Purkinje cells | mTORC2 affects cell size, Neuronal morphology and function, Only ريψکیا KO mice had synaptic functional changes, mTORC2 plays key role in synaptic homeostasis | Mouse | Rictor deficiency | - | Immunohistochemical analysis, Electrophysiological analysis, Biochemical analysis, RT-PCR, Mouse behaviour analysis | 90 |
| Tsc1 Pen                                         | Hippocampal neurons | Increase in action potential, dendrite length and soma size, Tsc1 loss does not affect the excitatory neurons, unlike pten which increases it, Excitation to inhibition ratio in the neural network is altered | Mouse | Excitatory and inhibitory synaptic transmission | - | Electrophysiological analysis, Immunocytochemistry | 91 |
| Tsc1 Tsc2                                         | Axon | Tsc1/2 plays an important role in axon formation, neural polarity, Tsc2 inhibition leads to mTOR activation, Tsc/mTOR pathway leads to axonal regeneration | Mouse | Polariised activation and inactivation of Tsc pathway | Tuberous sclerosis | Transfection, Lentiviral infection, Immunocytochemistry, Immunohistochemistry | 92 |
formation, function, and neural plasticity at the fusiform gyrus in idiopathic autism have been studied by Nicolini et al. (9). They targeted protein synthesis regulation of mTOR and noted decreased protein expression levels of various isoforms of P13K, p85, Akt, mTOR, p-mTOR, p70S6K, and eIF4B in idiopathic autism. Variance of tropomyosin receptor kinase B (TrKB), a BDNF that monitors the trafficking of postsynaptic density protein-95 (PSD-95) through regulation of P13K/Akt, is also observed in idiopathic autism. TrKB is also expressed at various levels in different regions of the brain (9). TrKB-FL isoforms in neurons are necessary for the activation of TrKB at the glia. Truncation of these molecules leads to alteration of Akt/mTOR pathway which in turn causes adverse effects in dendritic spines and cortical circuits (66-68). Onore et al. (69) have performed similar protein analysis in cells of CNS and immune system. They also compared phosphorylated and total protein levels and found higher total protein levels of IRS1 and RSP6 with higher phosphorylated protein levels of PTEN, TSC2, and mTOR in autistic individuals. De Rosa et al. (70) have analyzed cortical neurogenesis by determining transcriptional changes at two different time points in the developing brain to monitor differentially expressed genes. They reported dysregulations of synaptic activity, calcium signalling, and cell migration in idiopathic autism. Their work showed a gradual decrease of spiking activity in the brain of affected individual (70), further confirming that downregulation of signalling molecules could lead to the onset of idiopathic autism.

mTOR REGULATORS AS POTENTIAL THERAPEUTIC TARGETS

Novel therapeutic target identification and implementation against diseases have become mandatory for various neurodevelopmental conditions, especially ASD and idiopathic autism since the number of individuals affected by them is increasing globally (3). mTOR is involved in the regulation of various intracellular processes as explained in Fig. 1. However, its key role in ASD and idiopathic autism is the maintenance of amino acid pool by regulating protein translation at dendritic spines in the brain (71).

mTOR-S6K is also involved in the regulation of translation by eIF4F, a protein composed of eukaryotic initiation factors elf4E and elf4A (71, 72). Inhibition of cap binding to elf4F by 4EBPs as a major rate altering process could be prevented when mTORC1 phosphorylates 4EBPs which hinders the inhibitory role of this molecule, thereby activating the translation initiation at specific regions of the brain such as dendritic spines (73). Phosphorylation of specific subunits of mTOR involved in translational initiation is necessary to regulate various cellular processes as shown in Fig. 1. These molecules include elf4B which activates elf4A, S6 ribosomal subunit (74), PDCD4 that inhibits elf4A translation by phosphorylation, and various mRNA splicing factors (75). Presence of certain postsynaptic proteins including postsynaptic density protein 95 kDa (PSD-95), NMDA, metabotropic glutamate receptor subtype 5 (mGlu R5) that take part in translational initiation is important for structural organisation of prefrontal cortex of the brain (76). Phosphorylation of these downstream regulators has been studied by Jernigan et al. (76). They found that levels mTOR, p70S6K, elf4B proteins were decreased in major depressive disorder (MDD). They reported a uniform dysregulation of mTOR/p70S6K/elf4B pathway that leads to changes in neuronal architecture, thereby causing encephalopathy, dendritic spine alteration, and cancer in some cases (9, 76, 77). Abnormal spine density has been noted in various forms of ASD and idiopathic autism associated with upregulation or downregulation of mTOR pathway at dendritic spines (68). Roles of p70S6K/elf4B and 4E-BP1/elf4E in dendritic spines are crucial as they are involved in excitatory postsynapses observed in fusiform gyrus of ASD post-mortem brain samples (9). Nicolini et al. (66) have also reported decreased levels of PSD-95 at the fusiform gyrus of idiopathic autism subjects. Furthermore, imbalances of BDNF and TrKB have been widely studied in relation to autism but the change in PSD-95 (postsynaptic marker) protein level could be used as a therapeutic target in treating neural circuitry defects of autism, especially in idiopathic (3, 9, 15, 66). Shott et al. (78) have analysed expression levels of Akt1/p70S6K/elf4B proteins by kinomics using multiplex assay and noted a 6% change in cytoplasmic protein expression level in prion disease. Other postsynaptic proteins associated with autism include neureilin whose levels are increased after translation in 4EBP in 4E-BP2-KO and elf4E over-expressed mice that show significant alteration in E/I ratio. These results further confirm the importance of these downstream regulators of mTOR signalling pathway in circadian regulation and ASD respectively (79, 80). Dennis et al. (81) have studied phosphorylated protein translation in 4E-BP1/2 double knockout (DKO) mice and found higher p70S6K1 protein levels in the liver. They also compared γ-form of 4E-BP1 to other forms (α + β + γ). They further demonstrate that elf4E-elf4-4G complex interaction is critical in cap-dependent mRNA translation. Ribosomal protein kinase p70S6K is another rate altering molecule downstream of mTOR signalling pathway (82, 83). P70S6K has been proposed as a molecular marker for lymphoid cancer (82) and ovarian cancer (84) as it is involved in the regulation of protein synthesis in these particular diseases (81, 83). However, its role as a novel therapeutic target for idiopathic autism has been seldom explored. Effect of p70S6K signalling pathway on murine frontal cortex through protein translation has been studied by treating rats with MK-801 which modulates p70S6K-S6/elf4B pathway in developing rat brain. A significant decrease in phosphorylation of 40S ribosomal subunit 56 by p70S6K has been observed in insular, cingulated, and prefrontal cortex of rat brain (85). This decrease in phosphorylation results in altered protein expression in an idiopathic autism brain as pictorially represented in Fig. 3,
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Fig. 3. Role of mTOR signalling pathway during protein translation. Translation initiation at the brain is regulated by various translation initiation factors including eIF3, eIF4A, eIF4B, eIF4G, and cap binding protein eIF4E. Mechanism of mTOR is regulated by either 4E-BP or P70S6K. 4E-BP binds to eIF4E and inhibits the initiation of translation while S6 kinase from P70S6K binds to the 40S ribosomal subunit and leads to truncated protein synthesis in affected regions. Altered translation leads to development of adverse characteristics in the neuronal phenotype of idiopathic autism individuals.

leading to distorted phenotypic expression. Based on these findings, we propose that interaction between p70S6K/eIF4B and 4E-BP1/eIF4E is a benchmark in autism targeted therapy. It would pave way for future research on idiopathic autism.

CONCLUSION

mTOR plays a critical role in not only the regulation of various cellular functions such as cell growth, cell proliferation, lipid synthesis, and protein synthesis, but also plays a critical role in neurodevelopmental processes such as regulation of neurogenesis, corticogenesis, synaptogenesis, axon guidance, and cellular migration (2). Truncation of signalling molecules of mTOR that govern both upstream and downstream processes in the cascade can lead to developmental disorders such as ASD and idiopathic autism. Subjects with idiopathic autism exhibit drastic decreases in synaptic activity, dendritic spine growth, cellular proliferation, protein synthesis, and spiking activity due to significant downregulation of mTOR signalling molecules in the brain. The major process that could alter the downregulation of mTOR signalling cascade is truncated mRNA translation through binding to protein 4E-BP1 and altering 5' capped mRNA translation initiation by initiation factor eIF4E. eIF4E either up-regulates or decreases p70S6K and eIF4B expression which in turn can modulate mTOR dependent translation (9). As no alteration was reported in 4E-BP1 and eIF4E but a demur in p70S6K signalling was observed in the mTOR pathway, p70S6K could be targeted as a regulator of idiopathic autism. Collectively, we conclude that proper regulation of p70S6K and associated down regulators of mTOR signalling pathway is a critical in the maintenance of brain homeostasis.

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CONFLICTS OF INTEREST

The authors have no conflicting interests.

REFERENCES

1. Al-Zahrani A (2013) Prevalence and clinical characteristics of autism spectrum disorders in school-age children in Taif-KSA. Int J Med Sci Public Health 2, 578-582
2. Gilbert J and Man HY (2017) Fundamental elements in autism: from neurogenesis and neurite growth to synaptic plasticity. Front Cell Neurosci 11, 359
3. Jiang YH, Wang Y, Xiu X, Choy KW, Pursley AN and Cheung SW (2014) Genetic diagnosis of autism spectrum disorders: the opportunity and challenge in the genomics era. Crit Rev Clin Lab Sci 51, 249-262
4. Mattila ML, Kielinen M, Linna SL et al (2011) Autism spectrum disorders according to DSM-IV-TR and comparison with DSM-5 draft criteria: an epidemiological study. J Am Acad Child Adolesc Psychiatry 50, 583-592
5. Harker CM, Stone WL (2014) Comparison of the Diagnostic Criteria for Autism Spectrum Disorder Across DSM-5, DSM-IV-TR, 2 and the Individuals with Disabilities Act (IDEA) 3 Definition of Autism, 1-6
6. King BH, Navot N, Bernier R, Webb SJ (2014) Update on diagnostic classification in autism. Curr Opin Psychiatry 27, 105
7. Howes OD, Rogdaki M, Findon JL et al (2018) Autism spectrum disorder: Consensus guidelines on assessment, treatment and research from the British Association for Psychopharmacology. J Psychopharmacol 32, 3-29
8. Venugopalan A, Chandran M, Eruppakott N, Kizhakkilach S, Breezeville SC and Vellingiri B (2018) Monogenic diseases in India. Mutat Res 776, 23-31
9. Nicolini C, Ahn Y, Michalski B, Rho JM and Fahnestock M (2015) Decreased mTOR signalling pathway in human idiopathic autism and in rats exposed to valproic acid. Acta Neuropathol Commun 3, 3
10. Sandin S, Lichtenstein P, Kuja-Halkola R, Larsson H, Hultman CM and Reichenberg A (2014) The familial risk of autism. JAMA 311, 1770-1777
11. Berko ER, Suzuki M, Beren F et al (2014) Mosaic epigenetic dysregulation of ectodermal cells in autism spectrum disorder. PLoS Genet 10, e1004402
12. St-Hilaire S, Ezike VO, Stryhn H and Thomas MA (2012) An ecological study on childhood autism. Int J of Health Geog 11, 44
13. Tordjman S, Davlantis KS, Georgieff N et al (2015) Autism as a disorder of biological and behavioral rhythms: toward new therapeutic perspectives. Front Pediatr 3, 1
14. Volk HE, Lurmann F, Penfold B, Hertz-Picciotto I and McConnell R (2013) Traffic-related air pollution, particulate matter, and autism. JAMA Psychiatry 70, 71-77
15. Subramanian M, Timmerman CK, Schwartz JL, Pham DL and Meffert MK (2015) Characterizing autism spectrum disorders by key biochemical pathways. Front Neurosci 9, 313
16. Hutslers JJ, Zhang H (2010) Increased dendritic spine densities on cortical projection neurons in autism spectrum disorders. Brain Res 1309, 83-94
17. Horgusluoglu E, Nudelman K, Nho K, and Saykin AJ (2017) Adult neurogenesis and neurodegenerative diseases: A systems biology perspective. Am J Med Genet B Neuropsychiatr Genet 174, 93-112
18. Betizeau M and Dehay C (2016) From stem cells to synapse development: mechanisms of neuronal subtype transitions. Front Neurosci 9, 435-443
19. Osborne LR (2010) Caveat mTOR: aberrant signaling disrupts corticogenesis. J Clin Invest 120, 1392-1395
20. Gatto CL and Broadie K (2010) Genetic controls balancing excitatory and inhibitory synaptogenesis in neurodevelopmental disorder models. Front Synaptic Neurosci 2, 4
21. Zatkova M, Bakos J, Hodovy J and Ostatnikova D (2016) Synapse alterations in autism: Review of animal model findings. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 160, 201-210
22. Ishii K, Kubo KI and Nakajima K (2016) Reelin and neurexin/nerve growth factor receptors defects in autism spectrum disorders. Front Neurosci 10, 274
23. Oblak AL, Gibbs TT and Blatt GJ (2010) Decreased GABAB receptors in the cingulate cortex and fusiform gyrus in autism. J Neurochem 114, 1414-1423
24. Notwell JH, Heavner WE, Darbandi SF et al (2016) TBR1 deregulation of the EGFR/PI3K/PTEN/Akt/mTORC1 pathway in breast cancer: possibilities for therapeutic intervention. Oncotarget 5, 4603
25. Samidurai A, Kukreja RC and Das A (2018) Emerging Role of mTOR Signalling-Related miRNAs in Cardiovascular Diseases. Oxid Med Cell Longev 2018, 23
26. Lahiri DK, Sokol DK, Erickson C, Ray B, Ho CY and Maloney B (2013) Autism as early neurodevelopmental disorder: evidence for an sAPPα-mediated anabolic pathway. Front Cell Neuro 7, 94
27. Williams E and Casanova M (2011) Above genetics: a splice site-specific ligand for β-neurexins. Cell 81, 828-839
28. Fu Y and Li X (2014) Synaptic proteins and integration in the cerebral cortex. Front Neurosci 9, 828
29. Wisniewska MB (2013) Physiological role of β-catenin/TCF signaling in neurons of the adult brain. Neurochem Res 38, 1144-1155
30. Feliciano DM, Su T, Lopez J, Platel JC and Bordey A (2011) Single-cell Tsc1 knockout during corticogenesis generates tuber-like lesions and reduces seizure threshold in mice. J Clin Invest 121, 1596-1607
31. Won H, Mah W and Kim E (2013) Autism spectrum disorder causes, mechanisms, and treatments: focus on neuronal synapses. Front Molecu Neurosci 6, 19
32. Davis NM, Sokolosky M, Stadelman K et al (2014) Impaired induction of long-term potentiation-like plasticity in patients with high-functioning autism and Asperger syndrome. Dev Med Child Neurol 55, 83-89
33. Wen Y, Alshikho MJ and Herbert MR (2016) Pathway network analyses for autism reveal multisystem involvement, major overlaps with other diseases and convergence upon MAPK and calcium signaling. PLoS One 11, e0153329
34. Jung NH, Janzanki WG, Delvendahl I et al (2013) N-acetyl-cysteine abolishes hydrogen peroxide-induced modification of eukaryotic initiation factor 4F activity via distinct signalling pathways. Cell Signal 24, 21-31
35. Lawrence J and Nho R (2018) The role of the mammalian mTOR signalling pathway in idiopathic autism. Oxid Med Cell Longev 2018, 471
target of rapamycin (mTOR) in pulmonary fibrosis. Inter J Mol Sci 19, 778

48. Chau GC, Im DU, Kang TM et al (2017) mTOR controls ChREBP transcriptional activity and pancreatic β cell survival under diabetic stress. J Cell Biol 216, 2091-2105

49. Striano P, Zara F (2012) Genetics: mutations in mTOR pathway linked to megalencephaly syndromes. Nat Rev Neuro 8 (10), 54

50. Mirzaa GM, Campbell CD, Solovieff N et al (2016) Association of mTOR mutations with developmental brain disorders, including megalencephaly, focal cortical dysplasia, and pigmentary mosaicism. JAMA Neurol 73, 836-845

51. Lee JH, Huynh M, Silhavy J et al (2012) De novo somatic mutations in components of the PI3K-AKT3-mTOR pathway cause hemimegalencephaly. Nat Genet 44, 941

52. Panner A, James CD, Berger MS, Pieper RO (2005) mTOR controls FLIPS translation and TRAIL sensitivity in glioblastoma multiforme cells. Mol Cell Biol 25, 8809-8823

53. Lim JS, Kim W, Kang HC et al (2015) Brain somatic mutations in mTOR cause focal cortical dysplasia type II leading to intractable epilepsy. Nat Med 21 (4), 395

54. Ryskalin L, Lazzeri G, Flaibani M et al (2017) mTOR-dependent cell proliferation in the brain. Biomed Res Int 2017, 14

55. Dan Mattioli M and Monteggia LM (2013) mTOR complexes in neurodevelopmental and neuropsychiatric disorders. Nat Neurosci 16, 1537-1543

56. Takei N and Nawa H (2014) mTOR signaling and its roles in normal and abnormal brain development. Front Mol Neuro 7, 28

57. Cao R, Robinson B, Xu H (2013) Translational control of mTOR signaling in neuropsychiatric disorders: therapeutic implications. Neuropsychopharmacol Biol Psychiatry 35, 1774-1779

58. Xiao Z, Casey KA, Jameson SC, Curtsinger JM and Baldwin AS (2014) Akt-dependent activation of mTORC1 Involves phosphorylation of mTOR by raptor. J Bio Chem 288, 25227-25240

59. Jernigan CS, Goswami DB, Austin MC et al (2011) The role of adaptive behavior in autism spectrum disorders: Implications for functional outcome. J Autism Dev Disord 41, 1007-1018

60. Onore C, Yang H, Van de Water J and Ashwood P (2017) Dynamic Akt/mTOR signaling in protein translation regulation: implications in cancer genesis and therapeutic interventions. Mol Biol Int 2014, 14

61. Zhao XF and Gartenhaus RB (2009) Phospho-p70S6K and 4E-BP1 as therapeutic targets for diffuse large B-cell lymphoma. Cancer Res 69, 7492-7497

62. Sossé L, Xie J, Proud CG and Smales CM (2016) mTORC1 signalling and elf4E/4E-BP1 translation initiation factor stochiometry influence recombiant protein productivity from GS-CHOK1 cells. Biochem 1473, 4651-4664

63. Showkat M, Beigh MA and Andrabii I (2014) mTOR signaling in protein translation regulation: implications in cancer genesis and therapeutic interventions. Mol Biol Int 2014, 14

64. Dowling RJ, Topisirovic I, Alain T et al (2010) mTORC1-mediated cell proliferation, but not cell growth, controlled by the 4E-BPs. Science 328, 1172-1176

65. Jossé L, Xie J, Proud CG and Mames CM (2016) mTORC1 Signalling and elf4E/4E-BP1 Translation initiation factor stoichiometry influence recombinant protein productivity from GS-CHOK1 cells. Biochem 1473, 4651-4664

66. De Rosa BA, El Hokayer J, Artimovich E et al (2018) Convergent Pathways in Idiopathic Autism Revealed by Time Course Transcriptional Analysis of Patient-Derived Neurons. Sci Rep 8, 8423

67. Dowling RJ, Topisirovic I, Alain T et al (2010) mTORC1-mediated cell proliferation, but not cell growth, controlled by the 4E-BPs. Science 328, 1172-1176

68. Meyza KZ and Blanchard DC (2017) The BTBR mouse model of idiopathic autism-Current view on mechanisms. Neurosci Biobehav Rev 76, 99-110

69. Onore C, Yang H, Van de Water J and Ashwood P (2017) Dynamic Akt/mTOR signaling in protein translation regulation: implications in cancer genesis and therapeutic interventions. Mol Biol Int 2014, 14

70. Jossé L, Xie J, Proud CG and Smales CM (2016) mTORC1 Signalling and elf4E/4E-BP1 Translation initiation factor stochiometry influence recombiant protein productivity from GS-CHOK1 cells. Biochem 1473, 4651-4664

71. Xia Z, Casey KA, Jameson SC, Curtisinger JM and Mescher MF (2009) Programming for CD8 T cell memory development requires IL-12 or type I IFN. J Immunol 182, 2786-2794

72. Jossé L, Xie J, Proud CG and Smales CM (2016) mTORC1 Signalling and elf4E/4E-BP1 Translation initiation factor stochiometry influence recombiant protein productivity from GS-CHOK1 cells. Biochem 1473, 4651-4664

73. Shott RH, Appanaah C, Grenier C, Tremblay G, Roucou X and Schang LM (2014) Development of kinomic analyses to identify dysregulated signaling pathways in cells expressing cytoplasmic Pp. Virol J 11, 175

74. Showkat M, Beigh MA and Andrabii I (2014) mTOR signaling in protein translation regulation: implications in cancer genesis and therapeutic interventions. Mol Biol Int 2014, 14

75. Meyza KZ and Blanchard DC (2017) The BTBR mouse model of idiopathic autism-Current view on mechanisms. Neurosci Biobehav Rev 76, 99-110

76. Shott RH, Appanaah C, Grenier C, Tremblay G, Roucou X and Schang LM (2014) Development of kinomic analyses to identify dysregulated signaling pathways in cells expressing cytoplasmic Pp. Virol J 11, 175

77. Jossé L, Xie J, Proud CG and Smales CM (2016) mTORC1 Signalling and elf4E/4E-BP1 Translation initiation factor stochiometry influence recombiant protein productivity from GS-CHOK1 cells. Biochem 1473, 4651-4664

78. Shott RH, Appanaah C, Grenier C, Tremblay G, Roucou X and Schang LM (2014) Development of kinomic analyses to identify dysregulated signaling pathways in cells expressing cytoplasmic Pp. Virol J 11, 175

79. Cao R, Robinson B, Xu H (2013) Translational control of entrainment and synchrony of the suprachiasmatic circadian clock by mTOR/4E-BP1 signaling. Neuron 79, 712-724

80. Gkogkas CG, Khoutsorsky A, Ran I et al (2013) Autism-related deficits via dysregulated elf4E-dependent translational control. Nature 493, 371

81. Dennis MD, Kimball SR and Jefferson LS (2013) Mechanistic target of rapamycin complex 1 (mTORC1)-mediated phosphorylation is governed by competition between substrates for interaction with raptor. J Bio Chem 288, 10-19

82. Zhao XF and Gartenhaus RB (2009) Phospho-p70S6K and cdc2/cdk1 as therapeutic targets for diffuse large B-cell...
lymphoma. Expert Opin Ther Targets 13, 1085-1093
83. Bahrami BF, Ataie-Kachoie P, Pourgholami MH, and Morris DL (2014) p70 Ribosomal protein S6 kinase (Rps6kb1): an update. J Clin Pathol 12, 1019-1025
84. Bahrami F, Pourgholami MH, Mekkawy AH, Rufener L and Morris DL (2014) Monepantel induces autophagy in human ovarian cancer cells through disruption of the mTOR/p70S6K signalling pathway. Am J Can Res 4, 558-571
85. Biever A, Valjent E and Puighermanal E (2015) Ribosomal protein S6 phosphorylation in the nervous system: from regulation to function. Front Mol Neuro 8, 75
86. Kwon CH, Luikart BW, Powell CM et al (2006) Pten regulates neuronal arborization and social interaction in mice. Neuron 50, 377-388
87. Ogawa S, Kwon CH, Zhou J, Koovakkattu D, Parada LF and Sinton CM (2007) A seizure-prone phenotype is associated with altered free-running rhythm in Pten mutant mice. Brain Res 1168, 112-123
88. Lafourcade CA, Lin TV, Feliciano DM, Zhang L, Hsieh LS and Bordey A (2013) Rheb activation in subventricular zone progenitors leads to heterotopia, ectopic neuronal differentiation, and rapamycin-sensitive olfactory microdendrites and dendrite hypertrophy of newborn neurons. J Neurosci 33, 2419-2431
89. Tavazoie SF, Alvarez VA, Ridenour DA, Kossiakoff DA and Sabatini DL (2005) Regulation of neuronal morphology and function by the tumor suppressors Tsc1 and Tsc2. Nat Neurosci 8, 1727
90. Thomanetz V, Angliker N, Cloëtta D et al (2013) Ablation of the mTORC2 component rictor in brain or Purkinje cells affects size and neuron morphology. J Cell Biol 201, 293-308
91. Weston MC, Chen H and Swann JW (2014) Loss of mTOR repressors Tsc1 or Pten has divergent effects on excitatory and inhibitory synaptic transmission in single hippocampal neuron cultures. Front Mol Neurosci 7, 1
92. Choi YJ, Di Nardo A, Kramvis I et al (2008) Tubercous sclerosis complex proteins control axon formation. Genes Dev 22, 2485-2495