

Mammalian Target of Rapamycin (mTOR): An Emerging Drug Target for Neurological Disorders

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Abstract

mTOR signalling pathways entailed in the pathophysiology of various neurological disorders such as schizophrenia, cognition deficient, epilepsy, depression etc. mTOR controls cell growth and involve in the metabolism, cellular energy, nutrients including cell growth. Growing evidences highlight that alteration of mTOR signaling can affect various pathways such as cellular energy production, glucose metabolism, cell growth and mitochondrial functions etc. Deregulation of mTOR contributes significantly in the development of neurological and neurodegenerative disorders. Targeting brain mTOR pathway may therefore have been proposed as an emerging drug target for several neurological problems. However, challenges are still exist for a successful drug development targeting mTOR. The present review is an attempt to discuss the regulation of mTOR signalling and its emerging role in various neurological disorders.

Keywords: mTOR; Schizophrenia; Memory; Epilepsy; Depression

Introduction

mTOR (Mammalian target of rapamycin) is a serine/threonine kinase molecular complex with a 289-kDa molecular weight which acts through the PI3K-related kinase (PIKK) family. It was identified as a mechanistic target of rapamycin drug (lipophilic macrolide compound synthesized by *Streptomyces hygroscopicus* bacterium) on the bases of this referred to as mTOR [1]. It has been studied that reduced mTOR signalling can lead to neurological disorders, whereas hyperactivation of mTOR cascade can lead to abnormal growth of neurons and glia that further can cause malfunctioning of the brain [2]. Catalytic subunit of mTOR communicates with various proteins and forms two functionally complexes known as mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2). These mTOR complexes composed of a catalytic subunit (small protein known as mLSt8), which is a core protein for mTORC1 and mTORC2 along with these two more components like Tti1/Tel2 regulatory

proteins that make a scaffold for the selection of substrates and the negative regulator Deptor, which prevent the binding of substrate. There are some growth factors or environmental stimulus, which potentiate the activation of mTOR via PI3K/PTEN/Akt pathway [3]. Moreover, growth factors and insulin binding to tyrosine kinase receptors (RTKs) and activate the lipid kinase PI3K, which phosphorylates the phosphatidylinositol-4,5-phosphate (PIP2) for the synthesis of phosphatidylinositol-3,4,5-phosphate (PIP3), which further contributes to activate the PDK1 (3-phosphoinositide-dependent protein kinase 1) and Akt is subsequently activated via phosphorylation resulting in inhibition of TSC2 that acts as a downstream regulator of mTORC2 (mammalian target of rapamycin complex 2) through inhibition of Rheb which is an activator of mTORC2. Activated Akt involve in the phosphorylation of various molecules including GSK-3 which is responsible for glucose metabolism, neuronal differentiation and development, synaptic plasticity, intracellular trafficking,

apoptosis and regulation of gene transcription [4]. Most of the pathways that stimulate mTORC1 collectively inhibit the TSC1-TSC2 (hamartin-tuberin) complex, a heterodimer which act as a potent endogenous mTOR inhibitor, whereas amino acids activate mTORC1 independently from TSC complex. Specifically, mTORC1 activation is occurred by blocking TSC complex through its phosphorylation on specific sites via various kinases like canonical Akt, ribosomal S6 kinases (RSK), or even IKKB (I κ B kinase β) [5]. Upon activation it contributes in synthesis, ribosome and lipid biogenesis. AMPK (AMP-dependent kinase) is another mechanism entailed in the regulation of mTOR signalling. It is activated by a high AMP/ATP ratio which acts as a key sensor for the energy status in the cell upstream of mTOR. Initially, it phosphorylates and stimulates TSC2 function to inhibit mTOR activity additionally it can directly block mTORC1 by phosphorylating raptor. Hence, lack of energy states where the AMP/ATP ratio is high as a result of increased AMPK activity and suppression of mTOR based growth pathways (Figure 1) [6,7].

Role of mTOR in Neurological Disorders

Schizophrenia

Reelin is a glycoprotein secreted by cajal retzius cells to control cortical layering and by hippocampal GABAergic and cerebellar glutaminergic granular cells in the adult brain to maintain neural networks. There is significant downregulation of reelin expression in psychosis by inducing recruitment of Akt and PI3K via phosphorylation of disrupted-in-schizophrenia 1 (DISC1) that regulate cell arrangement during the development of the brain. Since, mTOR signalling cascade has not directly involved in the development of cortical, but it has trophic effects on hippocampal dendrite growth and branching by regulating expression of reelin [8]. Moreover, BDNF induced activation of the mTOR signalling pathway and involved in the cognitive process [9]. Therefore, any disruption in the signalling of mTOR pathway either depressed or overactive has a significant pathological role in psychosis or schizophrenia. The disrupted in schizophrenia 1 (DISC1) gene codes for a scaffolding protein which interacts with the various cellular proteins to alter their functional activities at several stages of neurodevelopment. Further, mTOR signalling is negatively regulated by DISC1, where DISC1 knockdown mice possess abnormal morphology and excitability of neuronal networks, deficits in aspects of cognition, depressive along with anxiety-like behaviors of schizophrenia [10].

Learning and memory

mTOR involved in the neural functioning of CNS like learning and memory that achieved by long-term synaptic plasticity (long term potentiation). A study on Aplysia and crayfish and rat

hippocampal slices demonstrate that treatment to rapamycin blocked long-term synaptic plasticity and interfere with normal learning and memory functions. Genetic ablation of mTOR inhibitors FKBP12 and S6K1 not completely mimic the action of rapamycin [11]. mTORC1 also cause long term depression similar to activation of metabotropic glutamatergic receptor causing long term depression (LTD) by increasing the level of MAP kinase and PI3- kinase-mTOR signalling and protein synthesis synapse, consistent blocking mTOR signalling block the mGlu-R dependent LTD [12]. mTORC2 control the actin cytoskeleton in non-neuronal cell and play important role in regulating the neuronal process rapamycin treatment reverse the behavioral phenotype of TSC1/2(Tuberous Sclerosis Complex (TSC)) mutant mice suggest that both mTORC1and mTORC2 to regulate the synaptic physiology and behavior [13].

Epilepsy

As the mTOR signalling regulates protein synthesis, synaptic plasticity decreases the pathological abnormality occurs in epilepsy it can be hypothesized that mTOR also involved in the mechanism of epileptogenesis in TSC patients. Inhibitors of mTOR signalling have antiepileptogenic property that provides satisfactory treatment of epilepsy. Treatment of rapamycin prevents the development of epilepsy and other pathological and molecular changes that likely promote epileptogenesis. In TSC models of epilepsy, seizure return within a week of rapamycin therapy cessation which suggest that beneficial effect of rapamycin on seizure not persist if rapamycin is stopped and the intermittent rapamycin treatment can treat epileptogenesis [14].

Depression

Several studies reported a decrease in the activation phosphorylated mTOR in animal model of depression-like in chronic unpredictable stress (CUS) model of depression in mice and rat shows a reduced level of phosphorylated mTOR and its downstream signalling components such as Phosphor-P70S6K in prefrontal cortex hippocampus and amygdala. Acute administration of ketamine increasing the brain-derived neurotrophic factor and phosphorylated mTOR in hippocampus of rat and shows antidepressants property in force swim test (FST). Some other modulators like ascorbic acid, creatin, zinc, erythropoietin, scopolamine also shows antidepressant property by increasing the amount of phosphorylated mTOR in the brain [15,16].

Others Neurological Problems

Role of mTOR signaling has been well reported in other neurological problems particularly neurodegenerative diseases [17]. Varous neurodegenerative disease such as Parkinson,

huntington, autism, Alzheimer disease are occurred to accumulation of misfolded protein leading to lose of memory, tremor and motor incorordinatoon.

Conclusion

mTOR is a serine/ threonine kinase has mTOR has an emerging role in brain disorders. It is found in two functionally complexes, which regulates various functions like protein synthesis, lipid metabolism, energy metabolism, autophagy, mitochondria etc. Moreover, it's signalling also controls regulate synaptic plasticity, neuronal development, memory formation, and cognition. Hence, it is seen that mTOR has an emerging role in brain disorders. Preclinical as well as clinical investigation suggested that mTORC1 inhibitors have therapeutic role in psychosis, cognitive impairment and epilepsy, while activation of mTORC1 can be helpful in depression, axonal growth and regeneration.

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Conflict of Interest

The authors declare no conflict of interest.

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