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

Monu Yadav1,2, Anil Kumar1*, Naresh Kumar4 and Mini Dahiya3
1University Institute of Pharmaceutical Sciences, UGC Centre of Advanced Studies (UGC-CAS), Panjab University, Chandigarh, India
2Science and Engineering Research Board, Department of Science and Technology, Government of India, India
3Department of Pharmaceutical Sciences, Chaudhary Bansi Lal University, Bhiwani, Haryana, India
*Corresponding Author: Anil Kumar, Professor; Dean of Faculty of Pharmaceutical Science, University Institute of Pharmaceutical Sciences, UGC Centre of Advanced Studies (UGC-CAS), Panjab University, Chandigarh, India.

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Abstract

mTOR signalling pathways entailed in the pathophysiology of various neurodegenerative disorders such as Alzheimer’s disease, Huntington’s, Parkinson’s disease, schizophrenia etc. mTOR controls cell growth and also involve in the metabolism in cellular energy, nutrients and growth factors. Growing evidences highlight that alteration in mTOR signaling can affect various pathways such as energy production, glucose metabolism, cell growth and mitochondrial function. Deregulation of mTOR contributes in the development of several neurodegenerative disorders. Targeting mTOR in brain may propose new area for drug development; still more studies are needed to understand mTOR signaling which direct of various signals involved in the pathogenesis of neurodegenerative disorders. This review discussed the regulation of mTOR signaling in brain.

Keywords: mTOR; Kinase; Neurological Disorders

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 as mTOR [1]. It has been studied that reduced mTOR signaling can lead to neurodegenerative disorder; whereas hyperactivation of mTOR cascade can lead to abnormal growth of neurons and glia that further can cause malfunctioning of 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 Dep- tor; 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 act as downstream regulator of mTORC2 (mammalian target
of rapamycin complex 2) through inhibition of Rheb which is 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 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 (IκB 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 m-TOR signaling. It is activated by 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 in increased AMPK activity and suppression of mTOR based growth pathways [6]. Various studies have been reported that dysregulated mTOR signaling contributes in the neuropathology of psychosis [7]. 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 disabled-1 gene that regulate cell arrangement during the development of brain. Since, mTOR signaling cascade has not directly involved in 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 signaling pathway and involved in the cognitive process [9]. Therefore, any disruption in the signaling 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 signaling 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 psychiatric disorders [10].

Conclusion

mTOR is a serine/threonine kinase has mTOR has 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, its signaling also controls regulate synaptic plasticity, neuronal development, memory formation, and cognition. Hence it is clearly seen that mTOR has emerging role in brain disorders. Preclinical as well as clinical investigation suggested that mTORC1 inhibitors have therapeutic role in cognitive impairment, brain tumors 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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