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NEUROSCIENCE FOREFRONT REVIEW

MOLECULAR NEUROBIOLOGY OF mTOR

KATARZYNA SWITON,[a] KATARZYNA KOTULSKA,[b] ALEKSANDRA JANUSZ-KAMINSKA,[a] JUSTYNA ZMORZYNSKA[a] AND JACEK JAWORSKI[a]*

[a] *International Institute of Molecular and Cell Biology, 4 Ks. Trojdena Street, Warsaw 02-109, Poland*

[b] *Department of Neurology and Epileptology, Children's Memorial Health Institute, Aleja Dzieci Polskich 20, Warsaw 04-730, Poland*

Abstract—Mammalian/mechanistic target of rapamycin (mTOR) is a serine-threonine kinase that controls several important aspects of mammalian cell function. mTOR activity is modulated by various intra- and extracellular factors; in turn, mTOR changes rates of translation, transcription, protein degradation, cell signaling, metabolism, and cytoskeleton dynamics. mTOR has been repeatedly shown to participate in neuronal development and the proper functioning of mature neurons. Changes in mTOR activity are often observed in nervous system diseases, including genetic diseases (e.g., tuberous sclerosis complex, Pten-related syndromes, neurofibromatosis, and Fragile X syndrome), epilepsy, brain tumors, and neurodegenerative disorders (Alzheimer's disease, Parkinson's disease, and Huntington's disease). Neuroscientists only recently began deciphering the molecular processes that are downstream of mTOR that participate in proper function of the nervous system. As a result, we are gaining knowledge about the ways in which aberrant changes in mTOR activity lead to various nervous system diseases. In this review, we provide a comprehensive view of mTOR in the nervous system, with a special focus on the neuronal functions of mTOR (e.g., control of translation, transcription, and autophagy) that likely underlie the contribution of mTOR to nervous system diseases. © 2016 Published by Elsevier Ltd on behalf of IBRO.

Key words: mTOR, neuronal development, neuronal plasticity, CNS disease, rapamycin.

Contents

INTRODUCTION

Mammalian/mechanistic target of rapamycin (mTOR) is a serine-threonine kinase that controls several important aspects of mammalian cell function (Malik et al., 2013b). Its activity is modulated by various intra- and extracellular factors, and the task of mTOR is to check whether intracellular resources and the health of the cell are sufficient to respond to extracellular stimuli. In the early

*Corresponding author. Address: International Institute of Molecular and Cell Biology, 4 Ks. Trojdena Street, Warsaw 02-109, Poland.
E-mail address: jaworski@iimcb.gov.pl (J. Jaworski).

Abbreviations: 4E-BPs, 4E-binding proteins; Atg13, autophagy-related protein 13; BDNF, brain-derived neurotrophic factor; CGG, trinucleotide; EGF, epidermal growth factor; FXS, Fragile X syndrome; Hif1α, hypoxia-inducible factor 1-α; LTD, long-term depression; LTP, long-term potentiation; MAMs, mitochondrion-associated membranes; mTOR, mammalian/mechanistic target of rapamycin; NSC, neural stem cell; p70S6K1, p70 ribosomal S6 protein kinase 1; PKC, protein kinase C; Rheb, Ras homolog enriched in brain protein; SVZ, subventricular zone; Tsc, Tuberous Sclerosis Complex; ULK1, unc-51-like kinase 1.

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2000s, when neuroscientists' interest in mTOR began, very few mTOR targets were known and confirmed in mammals. The most studied targets at the time were p70 ribosomal S6 protein kinase 1 (p70S6K1) and eukaryotic initiation factor 4E-binding proteins (4E-BPs). The major focus was on the initiation of translation by mTOR (Burnett et al., 1998). A widely accepted notion was that mTOR allows an increase in the rate of translation in response to extracellular stimuli. Long-term synaptic plasticity, learning, and memory rely on *de novo* protein synthesis. Therefore, mTOR took center stage in molecular studies of neuronal plasticity. Consequently, mTOR was shown to be critical for such forms of neuronal plasticity as long-term potentiation (LTP) and long-term depression (LTD) and learning and memory (Jaworski and Sheng, 2006; Swiech et al., 2008). Soon afterward, mTOR was proven to be critical for neuronal survival, differentiation, and morphogenesis. The list of its known neuronal functions is expanding every year. Changes in mTOR activity began to be correlated with such neurological symptoms as epilepsy, mental retardation, autism, and brain tumors (Swiech et al., 2008; Garelick and Kennedy, 2011; Lipton and Sahin, 2014; Bockaert and Marin, 2015).

The list of physiological states and neuropathologies that are linked to mTOR grew very fast, but a comprehensive understanding of mTOR regulation and its cellular effectors in neurons was lagging. With the advent of transcriptomics, proteomics, and new imaging technologies, our understanding of the importance of mTOR and its cellular functions greatly expanded. Changes in mTOR activity are now known to result in increases in translation, transcription, autophagy, cell signaling, and metabolism and modifications in cytoskeleton dynamics (Malik et al., 2013b). This review focuses on (*i*) new developments in downstream mTOR processes that are relevant to neuronal function, (*ii*) newly identified neuronal functions of mTOR complexes 1 and 2 (mTORC1 and mTORC2), and (*iii*) diseases that are associated with mTOR dysregulation and their underlying molecular mechanisms.

mTOR AND ITS SIGNALING NETWORK

mTOR complexes

mTOR is a large multidomain protein that exists in two distinct multiprotein complexes: mTORC1 and mTORC2 (Hay and Sonenberg, 2004; Bhaskar and Hay, 2007; Malik et al., 2013b; Fig. 1). Proteins that are present in both complexes include mTOR protein itself, mammalian lethal with SEC13 protein 8 (mLST8), DEP domain-containing mTOR-interacting protein (Deptor), Tel two-interacting protein 1 (Tti1), and telomere maintenance 2 (Tel2; Sarbassov et al., 2004; Peterson et al., 2009; Kaizuka et al., 2010). Specific to mTORC1 is regulatory-associated protein of mTOR (Raptor) and proline-rich AKT1 substrate 40 kDa (PRAS40; Kim et al., 2002; Sancak et al., 2007; Vander Haar et al., 2007). mTORC2 contains rapamycin-insensitive companion of mTOR (Rictor), mammalian stress-activated protein kinase-interacting protein 1 (mSin1), and protein observed with Rictor (Protor; Sarbassov et al., 2004; Frias et al., 2006; Pearce et al., 2007). FK506-binding protein (FKPB12) is a nonobligate mTOR-interacting protein that inhibits mTORC1 activity by blocking the catalytic domain of mTOR in the presence of the drug rapamycin (Brown et al., 1994; Jacinto et al., 2004; Sarbassov et al., 2006). mTORC2 was initially considered insensitive to rapamycin, but prolonged treatment with rapamycin also inhibited this complex, perhaps by sequestering mTOR kinase, which cannot form the mTORC2 complex (Sarbassov et al., 2006). In recent years, new insights into the exact structure of the mTORC1 complex have been gained, thanks to advances in cryo-electron microscopy. mTORC1 is an obligate dimer, and its dimerization is necessary for its activity and the phosphorylation of downstream targets (Yip et al., 2010; Aylett et al., 2016). The dimerization of mTORC1 complexes is regulated by newly characterized WAC protein and the TTT (Tel2, TTI1, TT12)–Reptin/Pontin complex (Kim et al., 2013; David-Morrison et al., 2016).

Regulation of mTORCs

Canonical pathways of mTORC1 activation by extracellular signals. The activation of both mTOR complexes requires the integration of specific signals, allowing the proper orchestration of multiple cellular events, and it

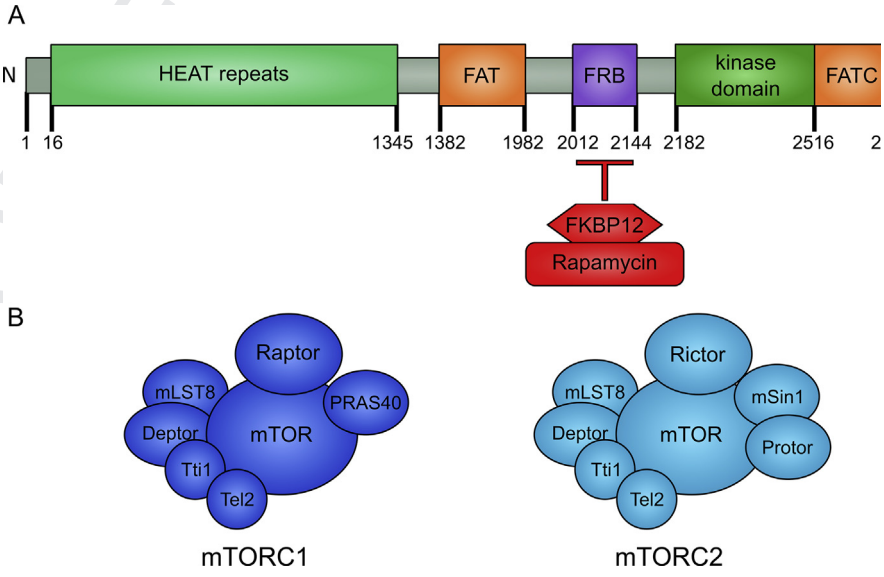

Fig. 1. mTOR and its protein complexes. (A) Protein domain composition of mTOR. HEAT – huntingtin, elongation factor 3, regulatory subunit A of PP2A, TOR1 domain, FAT – FRAP, ATM, TTRAP domain, FRB – FKBP12-rapamycin-binding domain, FATC – C-terminal domain, FKBP12 – FK506-binding protein of 12 kDa. (B) Protein composition of mTOR complexes. mTOR forms two protein complexes mTORC1 and mTORC2, which have different protein composition and non-overlapping sets of cellular substrates. See text for more details