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Mini review article

THE MAMMALIAN/MECHANISTIC TARGET OF RAPAMYCIN COMPLEX 2 AND ITS ROLE IN NERVOUS SYSTEM

KOMPLEKS 2 METE RAPAMICINA U SISARA I NJEGOVA ULOGA U NERVNOM SISTEMU

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Abstract

The protein kinase known as the mammalian/mechanistic target of rapamycin (mTOR) is present in numerous cells and plays a vital role in regulating cellular growth, metabolism, and survival through two complexes, mTORC1 and mTORC2. Even though the role of mTORC1 in development and metabolism has been extensively studied, the regulatory signals of mTORC2 and diversity of its function in the cell still need to be fully understood. The body of research shows that mTORC2 plays an important role in regulating cellular metabolism, and its dysregulation is associated to many diseases such as cancer, diabetes, and neurodegenerative disorders. Studies have reported altered mTORC2 signaling in several neurodegenerative and neurodevelopmental disorders. Furthermore, genetic studies have revealed the crucial role of mTORC2 in maintaining physiological structure and function in neurons, as well as oligodendrocytes myelination. This protein complex is responsible for various processes related to the structural organization and movement of neurons, interneuronal communication, and their adaptive ability. These processes include organizing the actin cytoskeleton, control of ion channels' function and neurotransmitter receptors, and regulating signal transduction. This review aims to provide an overview of the current understanding of mTORC2, including its components and known functions, in regulating various cellular processes, with special accent on its role in the nervous system.

Keywords:
mTORC2,
nervous system,
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Sažetak

Protein kinaza poznata kao mehanistička meta rapamicina u sisara (mTOR) prisutna je u mnogim ćelijama i kroz dva kompleksa, mTORC1 i mTORC2, ima veoma bitnu ulogu u regulisanju ćelijskog rasta, metabolizma i preživljavanja. Iako je uloga mTORC1 u razvoju i metabolizmu opsežno proučavana, regulatorni signali mTORC2 i raznolikost njegovih funkcija u ćeliji još uvek su u fazi istraživanja. Dosadašnja istraživanja su pokazala da mTORC2 igra važnu ulogu u regulisanju ćelijskog metabolizma, a poremećaj njegove regulacije je povezan sa mnogim bolestima kao što su tumori, dijabetes i neurodegenerativni poremećaji. Primećeno je da mTORC2 signalizacija može biti izmenjena u nekoliko neurodegenerativnih i neurorazvojnih poremećaja. Štaviše, genetske studije su otkrile ključnu ulogu mTORC2 u održavanju fiziološke strukture i funkcije neurona, kao i u mijelinizaciji oligodendrocita. Ovaj proteinski kompleks je odgovoran za različite procese koji uključuju strukturnu organizaciju i kretanje neurona, interneuronsku komunikaciju i njihovu sposobnost prilagođavanja. Ovi procesi podrazumevaju organizaciju aktinskog citoskeleta, kontrolu funkcije jonskih kanala i receptora za neurotransmitere, kao i regulaciju sprovođenja signala. Ovaj rad ima za cilj da pruži pregled postojećih znanja o mTORC2, uključujući informacije o komponentama ovog kompleksa, kao i njegove poznate funkcije u regulisanju različitih ćelijskih procesa, sa posebnim naglaskom na njegovu ulogu u nervnom sistemu.

Ključne reči:
mTORC2,
nervni sistem,
bolesti nervnog sistema

Introduction

Neurological disorders are a major challenge and represent significant global health problem (1). With the rise in life expectancy globally, significant increase in the prevalence of non-communicable diseases can be expected, particularly diabetes mellitus and neurodegenerative disorders (2). Pathological features, which are typical for different neurodegenerative diseases and include accumulation of misfolded proteins, oxidative stress, and impaired protein clearance mechanisms, lead to neuronal dysfunction and cell death and present significant obstacles to effective therapy (3).

The role of signalling mechanisms in proteostasis disruption, oxidative stress, and mitochondrial dysfunction has been studied, revealing numerous complex interactions that underlie the pathophysiology of various diseases. Among these mechanisms, the Mammalian Target of Rapamycin (mTOR) pathway stands out due to its central role in cellular growth, metabolism, and survival (4, 5). Disruption of this signalling pathway has been observed in various neurological diseases, including neurodegenerative diseases, autism spectrum disorders, and epilepsy (6).

This review aims to summarize available knowledge regarding mTORC2 and its roles and mechanisms in nervous system functioning and diseases.

Relevant studies were researched using the MEDLINE database (PubMed) and a set of specific keywords such as mTORC2 AND nervous system diseases, mTORC2 AND neurodegeneration, mTORC2 AND neurodegenerative diseases, and mTORC2 AND metabolism.

Mammalian/mechanistic target of rapamycin complexes

The mammalian/mechanistic target of rapamycin (mTOR) is a multimeric serine/threonine protein kinase belonging to the family of protein kinases related to phosphatidyl-inositol-3-kinases (PI3K). It is important in regulation of different processes in the cell, such as transcription, protein synthesis, cytoskeleton organization, metabolism, cell proliferation and survival (7).

In mammals, mTOR forms two signaling complexes, known as mTOR complex 1 and 2 (mTORC1 and mTORC2). Some of the subunits (mTOR, DEP Domain-Containing mTOR-Interacting Protein (DEPTOR), and Mammalian Lethal with SEC13 Protein 8 (mLST8)) are common for both complexes, whereas Raptor and PRAS40 are present in mTORC1, while Stress-Activated Protein Kinase-Interacting Protein 1 (Sin1), Rapamycin-Insensitive Companion of mTOR (Rictor), and Protein Observed with Rictor (Protor) are mTORC2-specific **(figure 1)**. These complexes have unique substrates and functions, and they differ in sensitivity to rapamycin. Despite common structural components and the fact that both complexes can be stimulated by growth factors, their regulatory mechanisms include different pathways and stimuli (8). mTORC1 serves as a central hub for sensing nutrients (including glucose and amino acids), energy sources like oxygen and ATP, growth factors, and specific neurotransmitters. Within this hub, it integrates information regarding nutrient availability and the cellular environment, orchestrating crucial functions such as protein synthesis, energy and lipid metabolism, autophagy, and lysosome formation. In contrast, mTORC2 doesn't respond to nutrient levels but is highly responsive to growth factors, regulating critical cellular activities like cell survival, proliferation, and the preservation of cell morphology (7, 8).

While mTORC1 has been extensively studied, and the roles and regulation of this complex are known, a significant knowledge gap remains concerning mTORC2 regulation and functions, particularly in the nervous system (9).

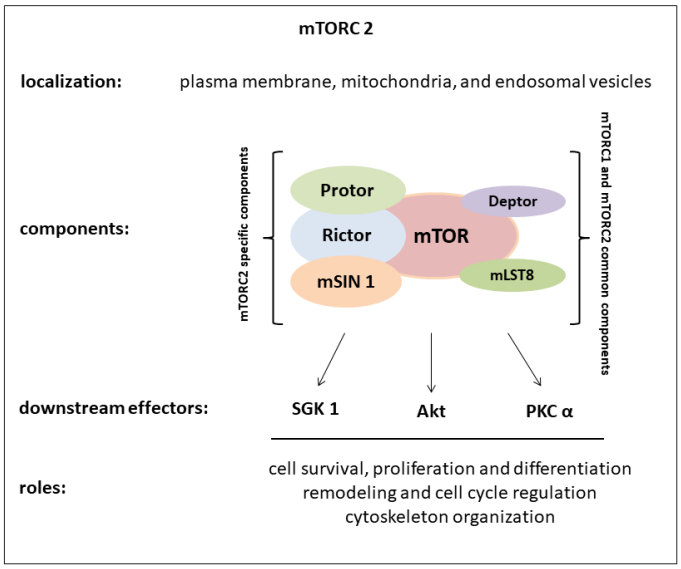

Figure 1. The components of mTOR complex 2 and its roles: mTORC2 consists of Mammalian/mechanistic target of rapamycin (mTOR), Rapamycin-Insensitive Companion of mTOR (Rictor), Stress-Activated Protein Kinase-Interacting Protein 1 (Sin1), Protein Observed with Rictor (Protor), Mammalian Lethal with SEC13 Protein 8 (mLST8), and DEP Domain-Containing mTOR-Interacting Protein (DEPTOR); mTORC2 is important for cell survival, as well as cytoskeleton organization and remodeling and cell cycle regulation

Mechanistic target of rapamycin complex 2

Recent studies have shown that mTORC2 can be found in various parts of the cell, such as the cytoplasm, nucleus, plasma membrane, mitochondria, lysosomes, Golgi apparatus, endoplasmic reticulum, and ribosomes. The recent discovery of the LocaTOR2 reporter has enabled the detection of mTORC2 kinase activity at different cellular locations, revealing its prominent activity at the plasma membrane, mitochondria, and a subset of endosomal vesicles. This mitochondrial activity aligns with observed connections between mTORC2 and mitochondria. Furthermore, mTORC2's localization to mitochondrial-associated membranes (MAM) and ribosomes suggests a potential link between its activity at mitochondria and its presence at these cellular junctions, where it activates its downstream kinase Akt and controls survival, metabolism and integrity (10, 11).

Mechanisms of mTORC2 activation and its relations with other crucial cellular pathways are not elucidated yet. Previous studies showed that important mechanism regulating mTORC2 activity depends on growth factors, mediated via the PI3 kinase signaling pathway (10). Alternatively, recent studies using the LocaTOR2 reporter suggest that mTORC2 constitutively resides at the plasma membrane and is not necessarily influenced by growth factors or PI3K. Additionally, Akt-mediated mSIN1 Thr86 phosphorylation and the subsequent increase in mTORC2 activity have been suggested as another layer of mTORC2 activation by growth factors, highlighting the complexity of mTORC2 regulation. Further research is needed to clarify the precise mechanisms governing mTORC2 activation and its localization within the cell (12). Furthermore, recent studies revealed the potential involvement of small GTPases in mTORC2 activation, with GTPases like Ras-GTP, Rab35, Rac1, and Rit playing various roles either indirectly, through PI3K, or directly by binding to mTORC2 components, offering new insights into the regulatory mechanisms of mTORC2 activity (13). Current studies also indicate that kinases which regulate mTORC1 activity, such as AMPK and Erk, can regulate mTORC2 activity, either directly or by acting on TSC1/2, an integrator of various growth conditions (14, 15).

It is also known that mTORC2 has several downstream substrates, such as Akt, PKCα, and SGK, which are part of the AGC protein kinase family (16). These downstream kinases regulate cellular growth, survival, cell cycle, metabolic processes, migration, and other cellular functions (10). It is shown that mTORC2 interacts with PDK1 and, in that manner, activates kinases from the AGC family. Akt is the best-characterized substrate of mTORC2 and central effector in the PI3K signaling pathway, and its phosphorylation on Serine 473 is a good indicator of mTORC2 activity (17).

However, the complex relationship between mTORC2 and Akt kinase is still poorly understood. Namely, mTORC2 activity is not necessary for the basal activation of Akt, but active mTORC2 is required for the full activity of Akt and phosphorylation of some of its substrates (10).

Relationship between mTORC1 and mTORC2

Both complexes mTORC1 and mTORC2 interact in a complex regulatory network, with mTORC2 being an upstream regulator of mTORC1 in certain cellular contexts (17). mTORC1 over-activation can lead to inhibition of mTORC2 via S6K-mediated phosphorylation of Rictor (18). Unlike the well-defined mechanisms of mTORC1 activation (such as mTORC2/Akt-mediated phosphorylation of TSC2 or PRAS40), the upstream signals for the regulation of mTORC2 activity are still under investigation. Furthermore, mTORC1/S6K-mediated phosphorylation of Insulin Receptor Substrate 1 (IRS-1) and Growth Factor Receptor-Bound Protein 10 (Grb10) represents a negative feedback mechanism to reverse mTORC2 activation initiated by insulin/IGF-1. Both IRS-1 and Grb10 function by inhibiting insulin/IGF-1 signaling and thereby affecting mTORC1 and mTORC2. Thus, whether mTORC1 can directly regulate mTORC2/Akt is still a matter of debate (19). Although it has long been considered that mTORC2 is insensitive to rapamycin, recent studies showed that long-term high-dose treatments can inhibit this complex by preventing the binding of mTORC2 components, Rictor and Sin1 (20).

The components of mTORC2 and their roles

Previous studies have highlighted the role of Sin1 in regulating mTORC2 activity, with alternatively spliced

Sin1 isoforms governing distinct mTORC2 cellular pools, two of which (mTORC2 containing mSin1.1- or mSin1.2-) respond to insulin, positioning Sin1 as a mediator between growth factor signalling and mTORC2 activity. The Sin1 phospholipid-binding pleckstrin homology (PH) domain facilitates its interaction with mTORC2 and membranes (21). It plays a crucial role in modulating mTORC2 activity, since its phosphorylation at Thr86 or Thr398 by S6K or Akt, respectively, leads to Sin1 dissociation from mTORC2, resulting in mTORC2 inhibition. The clinical significance of Sin1 phosphorylation is underscored by the R81T mutation in Sin1, which reduces Sin1 Thr86 phosphorylation and Ser473 phosphorylation of Akt in response to PI3K activation, ultimately bypassing the negative regulation of mTORC2 activity mediated by Sin1 phosphorylation and impacting cell growth control (19). Moreover, the interaction between PtdIns(3,4,5)P3, a product of PI3K at the plasma membrane, and Sin1-PH can either positively or negatively influence mTORC2 activity, depending on PtdIns(3, 4, 5)P3 levels. Upon PI3K activation, the binding of Sin1-PH to PtdIns(3, 4, 5)P3 not only alleviates mTOR kinase inhibition, but also promotes mTORC2 translocation to the plasma membrane and subsequent phosphorylation of its physiological substrates (21). Silencing of Sin1 disrupts Akt-Ser473 phosphorylation, impairs Rictor-mTOR interaction, and selectively influences specific Akt substrates, like FoxO1/3a, while leaving other Akt targets, such as TSC2 and GSK3, as well as mTORC1 effectors, like S6K and 4E-BP1, unaffected, indicating the complexity of Sin1 role in mTORC2 regulation (22).

Rapamycin-insensitive companion of mTOR (Rictor) is a component required for mTORC2 assembly and stability (10). Rictor is necessary for mTORC2 signaling in various tissues, and thus is involved in cell growth and metabolism. Knockdown of Rictor leads to defects of insulin signaling, and thus to disturbances in glucose and lipid metabolism in pancreatic cells, myocytes, hepatocytes and adipocytes (23). It is also involved in the turnover of monoamines (dopamine) in brain regions involved in cognition and reward. Rictor phosphorylates downstream kinases, Akt, SGK1, and PKC at their hydrophobic regions (23). Rictor is a very important regulator of embryonic development, and its inhibition can lead to embryonic death (24). Its silencing in neuronal tissue could lead to behavioral disorders such as hyperactivity, reduced anxiety, and damage of the sensorimotor system (25, 26). These findings suggest that Rictor/mTORC2 may play an important role in the neuronal damage that occurs in psychiatric and neurodegenerative diseases.

Mammalian Lethal with SEC13 Protein 8 (mLST8) is required for mTOR-Rictor interaction, while both Rictor and mLST8 are required for Akt and PKCα phosphorylation, but not for S6K1. Also, mLST8 and Rictor are necessary for insulin effects via FOXO3, but not via TSC2 and GSK3β, thus suggesting that mTORC2 is a necessary component of the Akt-FOXO and PKCα signaling pathways (27). Although mLST8 is a common component of both mTORC1 and mTORC2, it is shown that its silencing does not affect mTORC1, while inhibiting binding of mTOR to Rictor and Sin1 at the same time. In some cancer model systems, mLST8 mutation has been shown to inhibit Akt473 and thus lead to a decrease in tumor cell proliferation (28).

Mammalian/Mechanistic Target of Rapamycin Complex 2 in the nervous system

Even though mTORC2 is an important regulator of cellular function, there are only a few studies regarding its role in the nervous system. The role and function of mTORC2 in neurodevelopmental disorders is the most investigated. Still, there are some investigations of energy metabolism, synaptic plasticity and the role of this complex in other nervous system diseases. Here, available studies were reviewed concerning its role in different areas of the nervous system.

It is known that mTORC2 has an important role in the nervous system functioning. This complex is involved in the processes necessary for neuronal morphology and migration, synaptic transmission and plasticity, such as actin cytoskeletal organization, regulation of ion channels and neurotransmitter receptors. Also, mTORC2 plays a role in signal transmission in the nervous system, for instance, for oligodendrocytes myelination process (29-33).

The role of mTORC2 in the energy metabolism of the CNS has yet to be fully elucidated, but it has been revealed that disrupting Rictor activity in neurons causes an increase in fat content, impaired glucose regulation and increased resistance to leptin. Knockdown of Rictor from POMC neurons in mice results in obesity, excessive eating, elevated fasting blood sugar levels, and severe glucose intolerance in mice (34). These findings highlight mTORC2's role in the brain's management of energy. Further investigations should explore how mTORC2 signaling influences food intake and overall energy regulation in the body.

Besides, it has been shown that mTORC2 has an important role in glutamate synaptic transmission. This complex regulates presynaptic function in mouse primary hippocampal neurons, mainly by affecting the calcium sensitivity of synaptic vesicle release. Its inactivation changes presynaptic parameters, emphasizing its importance in synaptic transmission and overall neuronal function (35). Also, previous studies revealed that midbrain dopaminergic neurons in mice are sensitive to mTOR signalling, probably because of their high metabolic demands and specific physiology. However, Kossilo et al. reported that Rictor KO mice showed minimal changes in DA synthesis-related proteins and no significant change in overall DA tissue content (36).

A study examining the role of mTOR complexes in developing dendrites of primary rat hippocampal neurons revealed that both mTOR complexes are essential for adequate dendrite morphology in the hippocampus under normal conditions and for dendritic growth dependent on mTOR. It also showed that Akt, a downstream target

of mTORC2, is crucial for dendritic arbour morphology, suggesting the essential role of mTORC2 in this process (37). Also, dysregulation of mTOR signalling pathways (mTORpathies), especially mTORC1, has been observed in some neurodevelopmental and neuropsychiatric disorders (38).

Cullen et al. showed that mTORpathies, such as loss-of-function (LOF) in the PTEN gene, also caused an increase in mTORC2 activity in mice. Although mTORC2 inactivation in PTEN inhibition-induced damage partially prevented morphological and electrophysiological changes in the dentate gyrus, it failed to prevent seizures, indicating that increased excitability and synaptic dysfunction following PTEN loss are crucial to seizure onset (39).

In a mouse model, it was shown that deletion of Rictor in developing CNS leads to microcephaly, a smaller brain size, but at the expense of a reduction in the neuronal size, and not their number. Although there was a reduction in the level of Akt phosphorylation (downstream mTORC2 target), this effect was not observed in downstream Akt targets such as S6K and 4E-BP, indicating that mTORC2 affects neuronal size independently of mTORC1 (30).

Additionally, mTORC2 plays an important role in both Alzheimer's disease and Krabbe disease, influencing the pathogenesis of these disorders (40, 41). Lee et al. showed on the AD patients' brain samples that Alzheimer's disease could be associated with impairment of mTORC1 and mTORC2. The activity of both complexes was reduced in both human brain samples and AD mammalian models, while mTORC1 had reduced activity in a neuronal cell model of AD. In neuronal cell cultures, intracellular amyloid did not affect mTORC2 activity. These results suggest that preservation of mTORC2 or inhibition of mTORC1 may be potential therapeutic targets for AD (40). Krabbe's disease is associated with the accumulation of glycosphingolipids that damage cell membranes. In this disease model, it has been shown that the inactivation of the IGF-1-PI3K-Akt-mTORC2 signalling pathway is important for maintaining the neuronal function and survival. Psychosine, a glycosphingolipid that accumulates in this disease, inhibits this signalling pathway by interfering with the coupling of IGF-1 receptor phosphorylation and Akt activation, and prevents the PI3K and mTORC2 recruitment to lipid rafts (41).

Conclusion

It has been shown that mTORC2 may have an important role in the pathogenesis of neurodevelopmental disorders and diseases of the nervous system (Alzheimer's dementia, Krabbe's disease etc.). This complex is important in the neuronal metabolism of lipids and glucose; it affects the neuronal size and dendritic arbour morphology. Also, it is involved in the processes necessary for neuronal migration, synaptic transmission and plasticity, such as actin cytoskeletal organization, regulation of ion channels and neurotransmitter receptors. Additionally, mTORC2 plays a role in signal transmission in the nervous system. Due to its importance in the functioning of the nervous system, further studies are needed to unravel the exact role of mTORC2 in nervous system disorders and its potential for therapeutic modulation.

Abbreviations

AD – Alzheimer's Disease
DEPTOR – DEP Domain-Containing mTOR-Interacting Protein
GSK3 – Glycogen Synthase Kinase 3
Grb10 – Growth Factor Receptor-Bound Protein 10
IGF-1 – Insulin-Like Growth Factor 1
IRS-1 – Insulin Receptor Substrate 1
LOF – Loss of Function
MAM – Mitochondria-Associated Membranes
mLST8 – Mammalian Lethal with SEC13 Protein 8
mTORC – Mammalian/Mechanistic Target of Rapamycin Complex
PDK1 – Phosphoinositide-Dependent Protein Kinase-1
PI3K – Phosphatidyl-Inositol-3-Kinase
PKCα – Protein Kinase C Alpha
POMC – Pro-Opiomelanocortin
PRAS40 – Proline-Rich Akt Substrate of 40 kDa
PTEN – Phosphatase and Tensin Homolog
Protor – Protein Observed with Rictor
Rictor – Rapamycin-Insensitive Companion of mTOR
SGK – Serum and Glucocorticoid-Regulated Kinase
Sin1 – Stress-Activated Protein Kinase-Interacting Protein 1
TSC2 – Tuberous Sclerosis Complex 2

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