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Review Article

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Roles of mTOR Signaling in Brain Development

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mTOR is a serine/threonine kinase composed of multiple protein components. Intracellular signaling of mTOR complexes is involved in many of physiological functions including cell survival, proliferation and differentiation through the regulation of protein synthesis in multiple cell types. During brain development, mTOR-mediated signaling pathway plays a crucial role in the process of neuronal and glial differentiation and the maintenance of the stemness of neural stem cells. The abnormalities in the activity of mTOR and its downstream signaling molecules in neural stem cells result in severe defects of brain developmental processes causing a significant number of brain disorders, such as pediatric brain tumors, autism, seizure, learning disability and mental retardation. Understanding the implication of mTOR activity in neural stem cells would be able to provide an important clue in the development of future brain developmental disorder therapies.

Key words: mTOR, neurogenesis, gliogenesis, neural stem cell, pediatric brain tumors, brain developmental disorders

INTRODUCTION

Mammalian target of rapamycin (mTOR), complexes, large protein kinases, are composed of multiple protein components. mTOR has been discovered over the late decades showing that its pathways are involved in various human diseases, such as cancer and diabetes, by regulating angiogenesis [1, 2], insulin resistance [3], adipogenesis [4], and immune cell activation [5]. In various cell types, mTOR shows its critical roles in multiple intracellular functions including mitochondrial metabolism, autophagy, cytoskeleton organization, protein synthesis and lipid metabolism (Fig. 1) [4, 6]. Previous works identified two functionally and structurally distinct types of mTOR complexes. Type I mTOR complex (mTORC1) is composed of mTOR, raptor, mLST8, PRAS40 and DEPTOR. mTORC1 has its functions in cell proliferation, growth through the regulation of RNA translation, nutrient metabolism and autophagy (Fig. 1A) [7-10]. mTORC1 signaling pathway is controlled by the signals from receptor tyrosine kinase-RAS in the brain. Type 2 mTOR complex (mTORC2) is composed of rictor, mSIN1, Protor-1, mLST8 and DEPTOR [6, 11]. mTORC2 modulates cell survival and proliferation through the activation of AKT/PKB by direct interaction and the phosphorylation of AKT/PKB on Ser^{473} [12]. However, the upstream signaling molecule which leads to mTORC2 activation is not well identified so far (Fig. 1B). These two types of mTOR complexes were differentially characterized on the basis of rapamycin sensitivity. Rapamycin is the most well-known inhibitor of mTOR with higher efficiency on mTORC1 compared to mTORC2 [6]. Although detailed regulation mechanisms of mTOR activity are not fully understood in the brain, mTOR signaling pathway and its upstream tumor suppressor genes (*NF1, TSC1/2* and *PTEN*) are very closely associated with various brain diseases, including neurodegeneration disorders, brain tumors and neurological disorders in children [13-16]. In this article, we review the insight into the mTOR activity in neural stem cell (NSC) functions thereby illustrating the close relationship between

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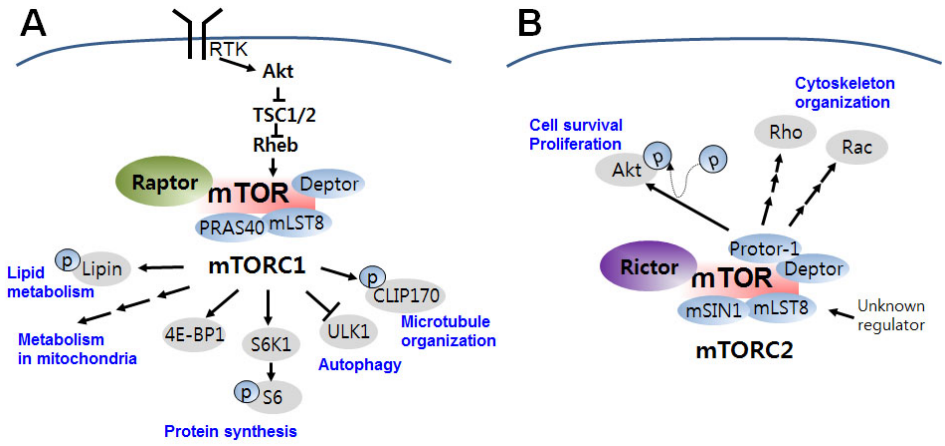

Fig. 1. Involvement of mTOR signaling in multiple cellular functions. Schematic drawing shows the components of mTORC1 (A) and mTORC2 (B) complexes and their downstream signaling targets.

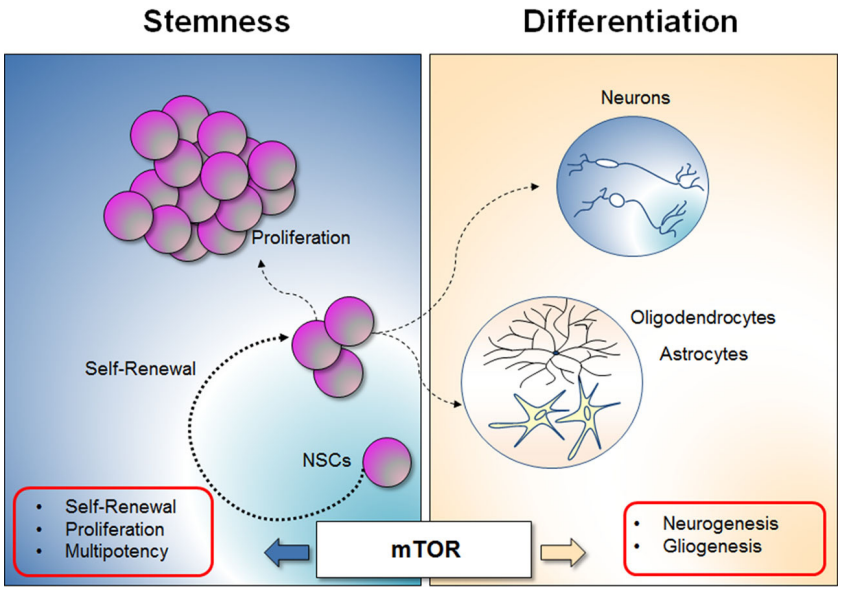

Fig. 2. The functions of mTOR in NSCs. The activity of mTOR complexes is one of the key regulation factors for both the maintenance of NSC stemness and the process of neuronal and glial differentiation.

mTOR and the pathological events which are mainly occurred in brain developmental disorders and pediatric brain tumors.

ASSOCIATION OF mTOR SIGNALING WITH NSC FUNCTIONS

mTOR in stemness

Stem cells have abilities to self-renew, proliferate and differentiate into various lineages of cells (Fig. 2). Maintenance of pluripotency and decision to differentiation in various types of stem cells require very well controlled expression of multiple transcription factors (e.g. *OCT4*, *NANOG* and *SOX2* in embryonic stem cells) involved in stemness [17-20]. Besides of the transcription factor expression, in various stem cell populations, mTOR-mediated intracellular signaling is also considered as one of the key regulators for modulating their stem cell functions (Fig. 2) [21, 22]. In human embryonic stem cells, mTOR mediated protein translation is essential for the regulation of the stem cell functions. During undifferentiated stages, mTORC1/p70S6K activity is maintained at lower levels compared to the level of mTORC2 in embryonic stem cells. Once the cells start their differentiation, mTORC1/p70S6K mediated protein translation is increased [22]. Similarly, the pluripotency of human induced pluripotent stem cells (iPSCs) is controlled by SOX2, a transcription factor which is essential for the maintenance of stem cell functions both in embryonic stem cells and iPSCs, at an early stages of iPSC formation through the transcriptional repression of mTOR [21]. Additionally, DEPTOR, an endogenous inhibitor of mTORC1, functions as a novel stemness factor maintaining the cells at undifferentiated state through the negative regulation of mTOR activity in mouse embryonic stem cells modulating its pluripotency and self-renewal ability [23]. In the brain, mTOR activity in NSCs is implicated in the brain morphogenesis through the modulation of GSK3 and

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STAT3 signaling pathways [24, 25]. Although mTOR activity is controlled at low level in undifferentiated embryonic stem cells, the inhibition of mTOR activity in NSCs also causes serious problems through the reduction of stem cell properties in the brain. Previously, Ka and colleagues demonstrated that mTOR-GSK3 signaling pathway activation is essential for the maintenance of neural progenitor homeostasis showing that the inactivation of mTOR in nestin-positive NSCs results in the smaller size of the brain and abnormalities in NSC self-renewal and proliferation [24]. Additionally, reduced proliferation and multipotency of NSCs are closely related to severe neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease in aged brains. Recent study shows decreased mTOR activity in NSCs of aged brain compared to early stages of brains. Moreover, a recent study shows that the age-associated decrease in neurogenesis is mainly due to reduced proliferation of active NSCs and the stimulation of mTOR by the treatment of ketamine, a known chemical mTOR activator, restores their impairment in proliferation therefore enhancing neurogenesis in the hippocampus of aged mouse brain [26]. These observations strongly suggest that the fine tuning the level of mTOR activation is essential for the maintenance of stemness in various stem cell populations (Fig. 2).

The function of mTOR signaling pathway in neurogenesis

Neuronal differentiation has to be controlled by fine tuning the processes of both spatial and temporal patterning of neurons for normal brain development. The defects in neuronal differentiation result in abnormal neuronal networks in the brain causing serious problems in the functions of cognition, movement and perception. In *Drosophila*, the hyperactivation of insulin receptor/mTOR pathway causes the abnormalities in the timing of photoreceptor differentiation by downregulation of the mTOR downstream transcription factor unk demonstrating that the regulation of mTOR activity and its downstream signaling pathway has a critical role for the differentiation of photoreceptors during eye development [27]. Similarly, mTOR hyperactivation in neural precursor populations also increases the abnormalities in neuronal differentiation in mammalians. Hyperactivation of mTORC1 through the ectopic expression of constitutively active Rheb, an upstream positive regulator of mTORC1, in subventricular neural progenitor cells causes severe problems in neuronal cell migration and brain regional distribution of neuronal subtypes resulting in olfactory bulb heterotopia and circuit abnormalities [28]. Moreover, mTOR signaling pathway is implicated to the process of neuronal differentiation from adult NSCs as well [26, 29]. In aged brains, decreased neurogenesis is very well correlated with cognitive decline. Additionally, Enhancer of zeste homolog2 (Ezh2), a gene silencer which is mainly expressed in actively dividing NSCs involved in cortical neurogenesis, brain morphogenesis and adult neurogenesis, increase the activation of AKT-mTOR through the binding to PTEN promoter region and the suppression of PTEN expression in NSCs. This series of studies demonstrates that deregulation of mTOR activity in NSCs could cause serious neurological problems indicating that the regulation of mTOR activation in a proper level is crucial for the neurogenesis during brain development.

The function of mTOR signaling pathway in gliogenesis

Increasing evidence shows that the functions of glial cells are critical for maintaining homeostasis of neurons with important roles in energy metabolite supply [30] and the clearance of extracellular glutamate [31, 32] and potassium [33], myelination [34], modulation of neuronal activity and synaptic formation of neurons [35] in the brain. Abnormal gliogenesis is implicated with astrocytomas and psychiatric disorders. The effects of abnormalities in the function of astrocytes on rett syndrome are very well illustrated the studies using animal models and *in vitro* disease models with human patient-derived iPSCs [36, 37]. Similarly, oligodendroglial defects are also considered as one of the causing factors of rett syndrome [38]. In the process of astrocyte differentiation, mTORC1 signaling pathway has a crucial function. Deficiency of Raptor, a component of mTORC1, in NSCs results in reduced NSC growth and inhibited astrocyte differentiation through the downregulation of mTOR downstream STAT3 signaling pathway [25]. Additionally, deficiency of RAPTOR, a protein component of mTORC1, in neural progenitor cells reduces gliogenesis [25]. Similar to mTORC1, hyperactivation of rictor containing mTORC2 activation also increases gliogenesis in the brain [13].

THE IMPLICATION OF mTOR ACTIVITY IN BRAIN DEVELOPMENTAL DISORDERS

Brain developmental disorders are impairments of the growth and the development of CNS organs. Brain diseases caused by developmental abnormalities include neurological disorders, such as autism, dyslexia, epilepsy, ADHD and mental retardation. Besides of these neurological disorders, brain tumors (gliomas, ependymomas and medulloblastomas) also have a close relationship with the abnormalities of brain regional NSC/progenitor cell populations during development in children [13, 39, 40]. In general, both developmental disorders and pediatric brain tumors are diagnosed in early developmental stages and childhood [41-44] raising a possibility that the NSC/progenitor

cell populations rather than differentiated brain cells could have an implication in disease phenotypes. Although the causing factors of the diseases are not fully uncovered, there are several known genetic factors which are commonly found in the patients with learning disability, autism, epilepsy and pediatric brain tumors. Interestingly, some of tumor suppressor genes, such as *PTEN, TSC1/2* and *NF1*, in upstream of mTOR are closely associated with developmental disorders and pediatric brain tumors, especially astrogliomas [45].

Pediatric brain tumors

More recently the importance of NSC/progenitor populations has been emphasized in the formation of pediatric brain tumors [39, 46]. In many types of pediatric brain tumors, including medulloblastomas, astrocytomas and ependymomas, histologically identical brain tumors are often composed of distinct subtypes which can be separated by their distinct gene expression patterns reflecting their region specific cellular origin, the embryonic brain region NSC/progenitors [39, 40, 46, 47]. Similarly, our previous study shows that brain region specific activation of mTORC2-AKT in brainstem NSCs but not in cortical NSCs with higher rictor in the brainstem compared to neocortex is associated with the spatial patterning of astrogliomas (higher frequency in the brainstem compared to the neocortex) in neurofibromatosis-1 (NF1) [13]. Moreover, previous study shows that the malignant astrocytomas in adult brain are also arisen from the NSCs in the subventricular zone of the lateral ventricle in genetically engineered mouse model [48]. In this regard, the determination of signaling pathways controlling the cellular functions of NSCs is essential for understanding the process of pediatric and adult brain tumor formation. mTORC1 complex is considered as the prime mediator of receptor tyrosine kinase (RTK) signaling through the growth factors, such as EGF and PDGF, regulating self-renewal, proliferation and differentiation in brain NSCs [25, 28]. Generally, RTK activation leads to downstream activation of mTOR regulators, including RAS, PTEN, AKT, RHEB and TSC1/2. The mutations of PTEN and TSC 1/2 are often detected in adult and pediatric brain tumors [49, 50] (Fig. 3). Although the mutations of AKT and RAS are relatively rare, these signaling molecules can be hyperactivated by the elevation of their positive regulation mechanisms in pediatric brain tumors. In NF1 associated pediatric brain tumors (gliomas), hyperactivation of RAS can be induced by the loss of *NF1* tumor suppressor gene which codes neurofibromin, a negative regulator of RAS [51]. Similarly, the elevation of active Akt level can be induced by the loss of PTEN, a negative upstream regulator of Akt, in high grade gliomas [49]. NSC/progenitors are considered as the cellular origin in pediatric gliomas [46] even though the histology of pediatric gliomas show that tumor contains a significant number of GFAP-positive cells and immune cells as well. The functional

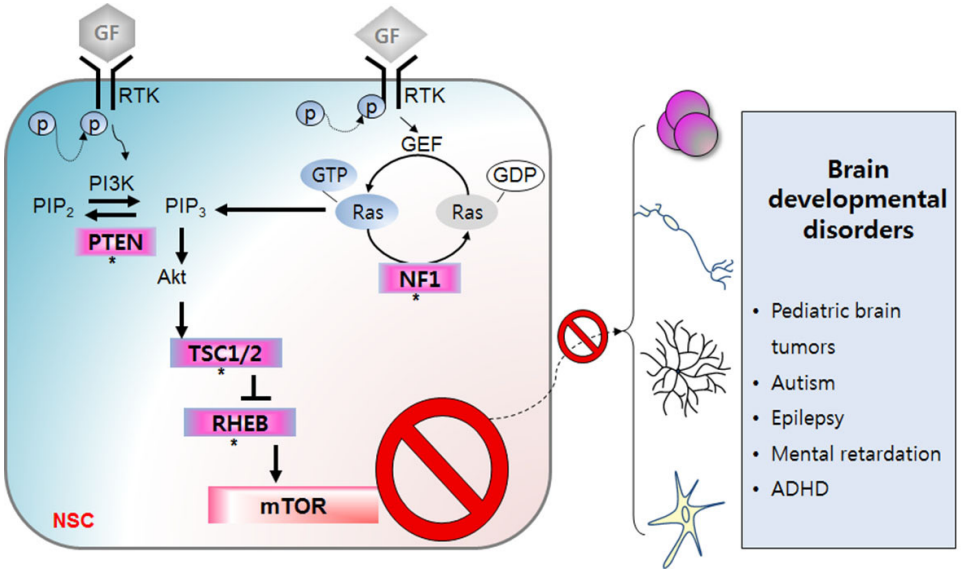

Fig. 3. Clinical implication of mTOR upstream regulators in pediatric brain tumors and various brain developmental disorders. Receptor tyrosine kinase (RTK) signals induced by growth factors (GFs; e.g., EGF and PDGF) lead to the activation of mTOR through the modulation of upstream molecules including RAS, PTEN, AKT, RHEB and TSC1/2 in NSCs. The mTOR signal is involved in multiple NSC functions, such as NSC proliferation and differentiation into neurons and glial cells. The abnormalities in mTOR activity caused by mutations in PTEN, TSC1/2, RHEB and NF1 (neurofibromin) (*) are frequently observed in the patients with pediatric brain tumors (gliomas) and neurological disorders (autism, epilepsy, mental retardation and ADHD).

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defects of mTOR in NSCs are closely implicated to the pediatric gliomagenesis. In NF1 associated pediatric glioma models, loss of *Nf1* affects NSC proliferation and self-renewal in a gene dose-dependent manner *in vitro* [52]. Moreover, *Nf1* inactivation in NSCs at embryonic stages is essential for astroglioma formation in the optic nerve and chiasm of NF1 mouse models *in vivo* [46]. Similar to NF1, the patients with Tuberous sclerosis complex (TSC), an autosomal dominant genetic disorder caused by the mutation of *TSC1*/*2* genes, also have another type of pediatric brain tumor called subependymal giant cell astrocytomas (SGCA), with an abnormal activation of mTOR signaling [50]. NSCs are mainly considered as an important cellular origin of SGCA instead of differentiated glia [53, 54] similar to the case in pediatric gliomas and medulloblastomas [39, 46].

Neurological disorders

Deregulation of tumor suppressors (*PTEN, NF1, TSC1* and *TSC2*) also have an implication to various neurological disorders such as autism spectrum disorder (ASD), mental retardation, epilepsy, learning disability and attention deficit hyperactivity disorder (ADHD) in children (Fig. 3) [14, 16, 45, 55-61]. Neurofibromin coded by *NF1* gene, which has a function as RAS negative regulator, is associated with learning disability and ADHD in children [59-61]. Even though NF1 participates in the signaling pathway of mTOR through RAS inhibition, NF1 associated neuronal defects in hippocampal and cerebellar Purkinje neurons are more dependent on cAMP and/or Ras-MAPK pathways rather than RAS-AKT-mTOR signaling pathways [62, 63]. Mutations in *TSC*1/2 and *PTEN* are closely associated with autism [14, 16, 45]. Clinical reports show that ASD is observed in 20~60% of patients affected by TSC [58, 64]. ASD is more commonly observed in TSC patients with cognitive impairment although approximately 20% of TSC-associated ASD is still observed in individuals with normal intellectual ability [58, 65, 66]. TSC-associated ASD accounts for 1~4% of total cases of ASD [67]. Similar to TSC, the inactivation of PTEN, which negatively regulates PI3K/AKT in upstream of TSC and mTORC1, is also associated with ASD as well [15, 16]. Previous studies show that macrocephaly and epilepsy are also observed in homozygous deletion of TSC1 and PTEN. The inhibition of mTOR by rapamycin treatment at early postnatal stages improves the neurological disease phenotypes (macrocephaly and epilepsy) in TSC mouse models [56, 68, 69]. Moreover, TSC associated intellectual disability is also improved by the treatment of rapamycin in Tsc2+/- mouse models [57]. To understand the causes and the detailed processes of these neurological disorders, previous studies had been mostly focused on the identification of factors causing the malfunction of neurons (especially hippocampal neurons and cerebellar Purkinje cells) instead of other brain cells including progenitors and glial cells in PTEN and TSC associated ASD animal models [16, 55, 70-72]. However, more recent studies are focused on the importance of NSC functions including NSC proliferation, neuronal cell fate decision and brain morphogenesis to better understand the processes of neurological disorders in children [73, 74].

CONCLUSION

Taken together, the studies reviewed here demonstrate that delicate activity balance of mTOR complexes is essential for both the maintenance of NSC stemness and the differentiation into multiple types of brain cells. Although the previous studies reviewed in this article demonstrate that deregulations of mTOR signaling in NSCs are responsible for a number of brain developmental disorders and pediatric brain tumors, it still remains a question whether mTOR signaling is also altered in developmental brain disorders and pediatric brain tumors without the genetic factors listed in this article (TSC, NF1 and *PTEN* mutations). Even though all three genetic factors are involved in the regulation of mTOR pathways, patients with each genetic factors show clearly distinct disease phenotypes from each other. The determination of underlying mechanisms how mTOR signaling can be implicated to different disease phenotypes in the patients with each genetic factors listed above will be the next goal to better understand the relation between mTOR and the diseases in children. So far, the studies to determine the mechanisms of mTOR regulation and its disease phenotypes have been mainly relied on genetically engineered animal models and derived primary cultured cells. More recently, *in vitro* human disease modeling has begun through the formation of patient-derived neurons and glia from iPSCs and organogenesis of the patients with developmental disorders. Using these technical advances, finding the determinants of gene specific disease phenotypes in TSC, NF1 and PTEN disease models would be valuable to envision of effective therapies for brain developmental disorders and brain tumors in children.

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