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Mammalian Target of Rapamycin Regulates Oligodendrocyte Differentiation, during Developmental Myelination and Remyelination

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ABSTRACT

Myelination refers to the formation of the myelin sheath around axons to guarantee rapid action potential conduction and provide trophic support to axons. It is a highly orchestrated process, which occurs in a regulated and stepwise manner. During development, oligodendrocytes progenitor cells (OPCs) proliferate and migrate to the different areas of the central nervous system (CNS). These cells then differentiate to mature oligodendrocytes, which extend their process toward axons and wrap around them. Many studies have examined the intracellular signaling pathways underlying the myelination process. PI3K/Akt pathway is one of the critical regulators of the oligodendrocyte maturation and CNS myelination. The mammalian target of rapamycin (mTOR) is the main downstream target of the PI3K/Akt pathway and its role in oligodendrocyte differentiation and developmental myelination has been previously identified. Here we summarized the current knowledge of the mTOR signaling pathway during developmental myelination and possible applications in remyelination. Details of the intracellular signaling mechanisms that regulate myelination might provide insight into pharmacological approaches to manipulate this process to enhance therapeutic approaches toward remyelination in demyelinating disorders.

Keywords: Myelination, mTOR pathway, Actin polymerization, Myelin wrapping, Remyelination.

INTRODUCTION

Myelin is an insulating layer that surrounds axons of the central nervous system (CNS), which allows rapid conduction of the electrical impulse, and provides metabolic support to axons (1). Developmental myelination is an exceedingly coordinated process, which happens in a stepwise manner. This process consists of oligodendrocyte progenitor cells (OPCs) proliferation and migration to the desired distinction. This process is followed by OPCs differentiation into mature oligodendrocytes, extending their process toward axons, interacting with axons they wish to wrap, and then compacting (2).

The fundamental importance of myelin is highlighted in disorders with the pathological loss of myelin such as multiple sclerosis (MS). The pathological hallmark of MS is focal demyelinated lesions, which fail to remyelinate completely (3). Remyelination is a spontaneous process in which progenitor cells migrate to the site of demyelination, differentiate into mature cells, and then wrap around demyelinated axons. Many steps occurring during developmental myelination are believed to be recapitulated during myelin repair (4).

Identifying the details of the signaling mechanisms that regulate the oligodendrocyte development and CNS myelination provides insight for developing new therapies for disease in which failure of OPCs differentiation within a demyelinated lesion diminish myelin repair. Many studies have examined the intracellular signaling pathways underlying the myelination process. Some evidence has identified the PI3K/Akt pathway as the critical regulator of oligodendrocyte maturation and CNS myelination (5-7). The mammalian target of rapamycin (mTOR) is the main downstream target of PI3K/Akt pathway and its role in oligodendrocyte differentiation and developmental myelination has been well-established (8-10).

Here we aim to discuss the current knowledge of mTOR signaling pathway during myelination. Given that myelin development mechanisms might also function during remyelination, understanding pathways/molecules involved in oligodendrocytes derived myelination may have important implications for understanding remyelination in the adult nervous system.

The role of mTOR pathway in OPCs differentiation

mTOR signaling pathway has a vital role in many CNS physiological functions. mTOR activity regulates cell metabolism, growth, proliferation, and survival by regulating gene transcription and protein synthesis (11, 12). The role of the mTOR signaling pathway in the developmental myelination of zebrafish is well established. Pharmacological inhibition of mTOR reduces OPC morphological complexity in zebrafish embryos (13). Owning to similarities between oligodendrocytes structure and function of zebrafish and mammals, they are known as a valuable model to study vertebrate myelination *in vivo* (14). The downstream signaling of mTOR seems to be complex. A recent study revealed that mTOR promotes early oligodendrocyte differentiation by suppressing the bone morphogenetic protein pathway (BMP) in OPC (15). Furthermore, inhibition of mTOR pathway in OPCs leads to impairment in the initiation and extension of myelination and reduced morphological complexity and the number of mature oligodendrocytes (16). In contrast, increasing the activity of Akt/mTOR pathway by genetically deleting its inhibitor leads to increased myelin production (5, 17). Furthermore, depletion of mTOR in patients with neonatal white matter dysplasia (NWMD) leads to a decrease in OPCs proliferation and differentiation during embryonic and early postnatal stages (18).

One downstream effect of mTOR pathway is regulating oligodendrocyte cytoskeletal organization and major myelin protein expression (Figure 1) (9). During differentiation, OPCs undergo extensive morphological changes. Several new processes are formed in which dynamics of the actin cytoskeleton are required

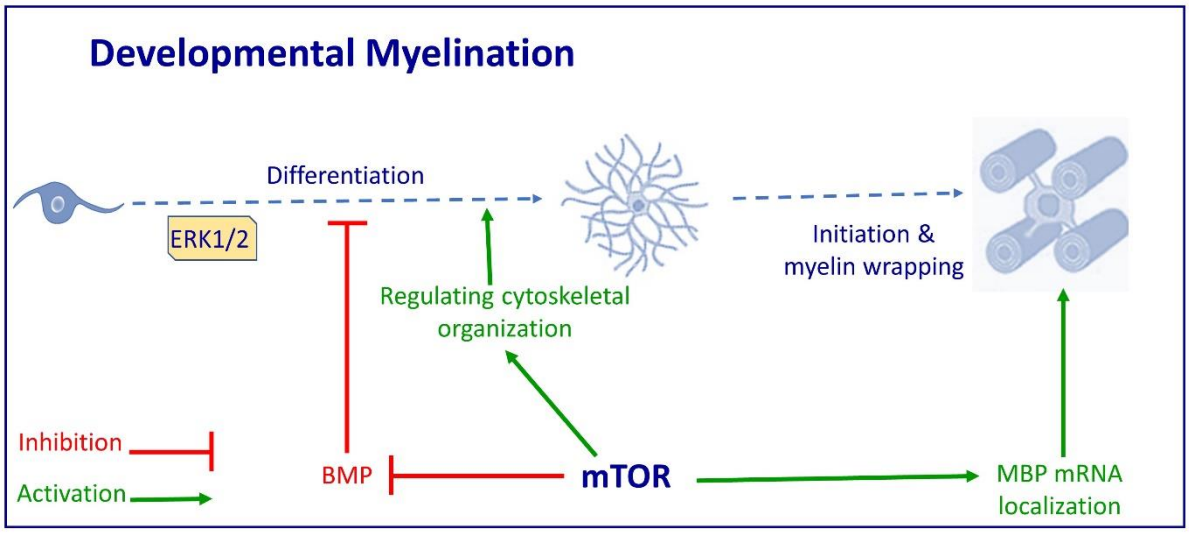

Figure 1. Schematic illustration of mTOR role during developmental myelination. mTOR pathway regulates oligodendrocytes differentiation by suppressing BMP and regulating oligodendrocytes cytoskeleton proteins. mTOR also has a role in myelination initiation and wrapping through regulating MBP localization.

for this process. The polymerizing force of F-actin is found to push out the leading edge of the growing process whereas actin filament depolymerization promotes myelin wrapping (19, 20). It has been shown that actin-regulating proteins including profilin, ARPC2/3 complex and cofilin, are involved in OPCs morphological differentiation (21). Little evidence on mTOR downstream cytoskeletal targets is available, but given its role in regulating cytoskeletal dynamics during morphological changes of oligodendrocytes, Musah et al. showed that mTOR regulates cytoskeletal proteins involved in actin assembly and disassembly. Inhibition of mTOR by rapamycin reduced the level of profilin2 and increased the active form of cofilin that are respectively involved in the assembly and disassembly of cytoskeletal actin in differentiating OPCs *in vitro* (13). The ArpC3 is previously found to be an important subunit of the ARP2/3 complex that is necessary for actin nucleation and branching (22). Moreover, the impairment in process extension and initiation of myelination is identified in ArpC3 knockout mice (20). Furthermore, the expression of ArpC3 which is involved in actin nucleation and branching, decreased following mTOR inhibition, which leads to a decrease in morphological complexity (13). Taken together, mTOR signaling pathway seems to regulate actin polymerization/depolymerization proteins and promotes cellular branching complexity.

Further investigation using mTOR cKO mice confirmed the fundamental importance of mTOR on myelination. mTOR signaling was previously found to have a distinct effect on myelination in different regions of the CNS. For instance, mTOR deletion leads to hypomyelination of spinal cord and cerebellum, while does not affect brain and optic nerve (16, 23, 24). Moreover, the effect of mTOR signaling on myelination of dorsal and ventral regions of the spinal cord is different. mTOR knockout leads to decrease in the number of profilin2^{+} and ArpC3^{+} mature oligodendrocytes in the ventral white matter (VWM) of the spinal cord but not in the dorsal white matter (DWM) (13), which provides evidence for the distinct and less severe effect of the mTOR signaling pathway on differentiation in DWM region. Therefore, further investigations are required to determine whether actin dynamics is regulated by regionally heterogeneous mechanisms in the VWM and DWM. Furthermore, the compensatory signaling pathways and other regulating proteins and promoting factors remain to be investigated.

The recovery from the differentiation deficit is also reported in mTOR cKO mice (13), which suggests that this signaling pathway has more complex interactions with other signaling pathways. Some studies provide evidence for the coordinated role of ERK and mTOR signaling during OPCs differentiation and suggest that Erk1/2 and mTOR signaling sequentially regulate distinct stages of OPC differentiation. Therefore, these two pathways are likely to compensate for each other (9, 25). Furthermore, junction mediating and regulatory protein, Jmy, is an actin polymerization regulator because of its intrinsic activity of nucleating actin monomers (26). Therefore, it may likely be that other cytoskeletal regulators compensate morphological differentiation deficit. Furthermore, mTOR KO led to a delay in the initiation of myelination that could be due to either impairment in differentiation or direct effect of mTOR on the initiation of myelination (13).

The role of mTOR pathway in myelin wrapping

Once myelination is initiated, F-actin disassembly is important in the switch from myelination initiation to myelin wrapping (27). Myelin basic protein (MBP) is one of the major myelin proteins involved in these processes. Some evidence suggests that MBP competes with actin depolymerization factor, cofilin/gelsolin, for binding to phosphatidyl inositol 4, 5 bisphosphate (PIP2) in the membrane of oligodendrocyte. This competition leads to releasing of actin disassembly factors followed by depolymerization of F-actin and myelin wrapping (20). Recently, it is shown that MBP mRNA and protein expression are impaired in mTOR cKO mice. Moreover, the *in vitro* results indicated that there is an accumulation of MBP in the cell body and proximal process suggesting a deficit in proper MBP mRNA localization into the extended process. Furthermore, the expression of kinesin family member 1B (kif1B), the protein

involved in MBP transport to the process (28), decreased in mature oligodendrocytes (13). Depletion of mTOR in oligodendrocytes leads to the expression of forkhead box O3 (FoxO3), which finally repress the expression of MBP (18).

mTOR pathway in remyelination

It is believed that common signaling pathways are involved in both developmental myelination and remyelination (29). Considering the prominent role of mTOR pathway in initial myelination, various studies have investigated this pathway in endogenous remyelination following induction of demyelination conditions (30). The cuprizone-induced demyelination model is widely used for myelin repair studies (31, 32). Ursolic acid which is able to sustain the activity of induced mTORC1 (33), enhances myelin repair following cuprizone demyelination, even after long term (12 weeks) cuprizone administration in mice (31). Feeding animals with cuprizone for 6 weeks leads to demyelination, which is followed by efficient remyelination, whereas 12 weeks of cuprizone feeding leads to extensive demyelination with insufficient remyelination, mostly due to exhaustion of OPCs (34, 35). This may imply for the possibility of mTOR pathway targeting to recue exhausted OPCs in progressive phase of MS. Since in the mid-term cuprizone feeding, remyelination occurs in a short time after cuprizone cessation, only acceleration of remyelination could be evaluated in this model (36). In recent years, an mTOR inhibitor, rapamycin, was used in combination with cuprizone to induce more complete demyelination. Using rapamycin during cuprizone feeding provides approximately complete demyelination at week 6 which is followed by a longer demyelination course, making it suitable to evaluate the mechanisms initiating remyelination (37).

The role of mTOR pathway in other myelination processes

Intermediate molecules in mTOR signaling and the role of this pathway in other myelination processes such as OPC migration is not well understood. Even though there is evidence that mTOR function is not essential for OPC migration (38), the activity of Arp2/3 complex, which is one of the downstream goals of mTOR pathway, has already been identified in OPC migration (39). Since the first stage of remyelination requires the recruitment of OPCs, investigating the pathways/molecules involved in the migration of OPCs during CNS development is of great importance to improve remyelination in pathological condition.

CONCLUSION AND FUTURE PERSPECTIVE

mTOR has a regulatory role in both initiation of myelination and axonal wrapping through regulating actin binding proteins and MBP localization, respectively. Given that developmental myelination, mechanisms might also function during remyelination, understanding pathways/molecules involved in oligodendrocytes-derived myelination may have important implications for understanding remyelination in the adult nervous system. Details of the intracellular signaling mechanisms that regulate myelination might provide insight into pharmacological approaches to manipulate this process to enhance therapeutic approaches toward remyelination in demyelinating disorders. However, the challenge now is to extend this knowledge to reveal the molecular mechanisms required for OPCs differentiation and axonal myelination at the proper developmental time. Such insight will be necessary for designing novel therapeutic approaches to enhance remyelination in pathological conditions such as multiple sclerosis.

DECLARATIONS

The authors declare no conflict of interest.

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