Rapamycin reduces degeneration of neurons by inhibiting Akt/mTOR/p70S6K pathway and restoring autophagy in EAE mice

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Abstract: Objective: Neurodegeneration is an important pathological feature of multiple sclerosis, which is an autoimmune disease of the central nervous system. Autophagy plays an important role in maintaining neuronal homeostasis. In the present study, we investigated the role of autophagy in neurodegeneration. Methods: We used a myelin oligodendrocyte glycoprotein experimental autoimmune encephalomyelitis (MOG-EAE) mouse model. We also used double immunofluorescence staining, western blot analysis and Nissl staining in this study. Results: At the disease peak, LC3 was mainly localized in the neurons of the vertebrae with lumbar enlargement, less localized in the oligodendrocytes, and least localized in the astrocytes. Compared with control mice of matched age, colocalization of LC3 and NeuN was much more common in the EAE mice. Furthermore, the p-Akt level in the spinal cords of the EAE mice was reduced. Sequential changes in p-p70S6K expression were basically similar to those in p-Akt expression. Moreover, rapamycin treatment caused a considerable increase in LC3-II and Beclin-1 expression in the spinal cords of the EAE mice, whereas there was a reduction in phosphorylated Akt and p70S6K. Furthermore, treatment with rapamycin greatly reduced the neurological scores. Compared with the blank control group, the number of Nissl- and NeuN-stained neurons decreased in the positive control and rapamycin treatment groups. There were more NeuN-stained neurons in the rapamycin treatment group than in the positive control group. Conclusions: Our results indicate that rapamycin alleviates neurodegeneration by inhibiting the Akt/mTOR/p70S6K signaling pathway, which restores the autophagic activities of spinal neurons in a mouse model of EAE.

Keywords: Rapamycin, degeneration, neurons, Akt/mTOR/p70S6K pathway, autophagy

Introduction

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) [1]. Neurodegeneration is an important pathological feature of MS, and leads to the progressive loss of neurons, altered activity of the protein hydrolysis system, and deposition of protein aggregates. Neurons are post-mitotic cells and cannot dilute toxins and folded proteins, which are prone to aggregation by cell division [2]. Therefore, autophagy is necessary to control protein quality, remove protein aggregates, and maintain neuronal homeostasis (in cell bodies, dendrites, and axons) [3]. Autophagic dysfunction can cause incessant accumulation of proteins and toxins, and hinder axonal transport (occupying intracellular space), resulting in transcriptional dysregulation (inactivation of transcription factors). This ultimately leads to neurodegeneration.

Autophagy plays a pivotal role in the physiology and pathology of neurons. Under normal physiological conditions, autophagy is activated in neurons [4], and is involved in the regulation of neurons and axonal LC3 vesicles (LC3 is an abbreviation for microtubule-associated protein 1 light chain 3 alpha). LC3-II is closely associated with autophagosomes number, suppression of LC3-II expression reflects the impaired autophagy [5]. Li and colleagues found that...
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the autophagy markers LC3-II were decreased in EAE mice [6]. Another study also showed that endogenous LC3 is a marker for autophagy [7]. Improper or defective autophagy accelerates the death of neurons [8]. Neuron death, which includes autophagic cell death, apoptosis, and cytoplasmic death, is one of the most important features of neurodegeneration [9]. The pathological mechanism of neurodegeneration in MS requires further clarification, and there is currently no effective treatment for the disorder. However, in recent years, drug-related autophagy has been considered as a potential treatment option for neurodegeneration [10]. Research into the relationship between autophagic changes in MS and neurodegeneration will contribute to the understanding of this disease and to the development of new drugs.

The mTOR pathway is the most important signaling pathway that regulates autophagy. mTOR is a serine/threonine kinase and belongs to the phosphoinositide 3-kinase (PI3K) family [11]. The mTOR pathway plays an important role in the regulation of the cell cycle, and in cell growth and proliferation. It can regulate autophagy by directly or indirectly integrating intracellular anoxia and ATP signals, thereby helping the cells to cope with internal and external changes [12]. In eukaryotic cells, mTOR inhibits the acetylation of ULK1, a core component related to autophagic activation; it therefore negatively regulates autophagy [13]. Like amino acid deficiency, rapamycin and related compounds are capable of inducing autophagy [14]. Inducing autophagy can promote the dissipation of protein aggregates from neurons, thereby delaying the progression of neurodegenerative diseases. In neurodegenerative models, rapamycin or its analogues can relieve the clinical symptoms by inhibiting mTOR and inducing autophagy. Promoting autophagy can help cells dissipate pathogenic and toxic proteins in Huntington’s disease [15]. A growing body of evidence suggests that inducing autophagy is a potential new treatment for neurodegenerative diseases. In vivo and in vitro experiments have demonstrated that rapamycin can alleviate MS [16, 17]. Such experiments have mainly focused on the anti-inflammatory and immunosuppressive effects of rapamycin. However, the potential neuroprotective effect of rapamycin is rarely reported.

In the present study, we investigated the regulatory mechanism of autophagy using a myelin oligodendrocyte glycoprotein experimental autoimmune encephalomyelitis (MOG-EAE) mouse model, and explored possible connections between autophagy and neurodegeneration in MS. We investigated the effect of rapamycin-an autophagy inducer-on neuronal injury, and postulated a working mechanism for its action. Our research will help clarify the pathogenesis of neuronal degeneration in MS and provide experimental data for devising a treatment strategy based on the regulation of autophagy.

Materials and methods

Animals

C57BL/6 female mice aged 6-8 weeks and weighing 18-20 g were purchased from Beijing Vital River Laboratory Animal Technology Co., Ltd. (SCXK 2006-0009). The mice were acclimatized at 24 ± 2°C in a 12 h/12 h light/dark cycle. They were given ad libitum access to food and clean water. The animal experiments were approved by the Institutional Animal Care and Use Committee at Hebei Medical University, and by a local ethics committee.

Construction and assessment of EAE models

MOG 35-55 antigen was diluted with normal saline to 5 mg/mL and added to an equal volume of complete Freund’s adjuvant (CFA). Mycobacterium tuberculosis H37Ra was added to obtain a final concentration of 4 mg/mL, and the mixture was emulsified thoroughly. The mice were then injected subcutaneously with the emulsion at four points on the two sides of the spine at a dose of 0.1 mL per mouse. At 0 h and 48 h post-injection, 0.5 mL of PTX was injected peritoneally (500 ng/mouse). An assessment of nerve function was performed according to a five-point score on the day of immunization. The scoring criteria were as follows: 0 points, asymptomatic; 1 point, loss of tail tension; 2 points, hindlimb weakness; 3 points, forelimb and hindlimb paralysis; and 4 points, approaching death or already dead. If the severity of the symptoms was intermediate between two adjacent levels, the score was considered to be the lower severity level plus 0.5 points.
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**Grouping and treatment**

To observe the sequential changes in autophagy of the spine in the EAE mice, the C57BL/6 mice were equally and randomly divided into two groups: a blank control group and an EAE model group. Then, at specific times after immunization, each group was subdivided into three subgroups: before onset (13 days), peak of disease (20 days), and late-stage onset (30 days).

To observe the effect of rapamycin on the neurons, the C57BL/6 mice were equally and randomly divided into three groups: a blank control group, an EAE-vehicle group, and an EAE-rapamycin group. The low-dose rapamycin treatment group received a peritoneal injection of rapamycin (1 mg/kg; Sigma, California, USA) once per day, commencing on the day of immunization. For the EAE-vehicle group, an equal volume of sterile water was injected peritoneally once per day commencing on the day of immunization. The mice were sacrificed at the peak of the disease.

**Double immunofluorescence staining and laser confocal microscopy**

The mice were anesthetized by peritoneal injection of 10% chloral hydrate (350 mg/kg). Cardiac perfusion of 4% paraformaldehyde was performed for approximately 30 min. The lumbar spinal cord was harvested and soaked in 4% paraformaldehyde for several days. Specimens were sliced using a Leica CM1850 system to a thickness of 30 µm. The slices were washed three times in 0.01 M phosphate-buffered saline (PBS) for 10 min each time. They were permeabilized with 0.3% Triton X-100 for approximately 20 min, then sealed with 10% equine serum for 1 h. The slices were then incubated on a 96-well plate containing anti-LC3 primary antibody (1:800; Sigma), anti-NeuN primary antibody (1:2000, Abcam), and anti-GFAP primary antibody (1:2000, Abcam) while shaking at 4°C overnight. The next day, the slices were washed three times with 0.01 M PBS, and incubated with fluorescent-label- ed secondary antibodies in a 96-well plate for 1 h. Subsequently, the slices were washed three times with 0.01 M PBS, soaked in distilled water for several seconds, and placed on a clean glass slide. After air drying in the dark, one drop of quencher was added to seal the slices. The slices were then examined under an Olympus FV1000 confocal microscope.

**Total protein extraction from the lumbar spinal cord**

At 13, 20, and 30 days after immunization, five mice were randomly selected from each group and anesthetized with chloral hydrate. The mice were sacrificed by removing their eyeballs, and decapitated. All these procedures were performed on ice. Vertebrae with lumbar enlargement were harvested, preserved in liquid nitrogen, and placed in a fridge at -80°C. A sample of the lumbar spinal cord (10 mg) was placed in an Eppendorf (EP) tube. After adding 0.6 mL of lysis buffer, the tissues were cut into pieces and ultrasonically treated. The homogenate (0.5 mL) was transferred to a 1.5 mL EP tube and 1 mL of extraction solvent was added. The tube was left to stand at 4°C for 10 min, with occasional shaking. Later, the tube was centrifuged at 10000 g and 4°C for 10 min. The mixture was separated into two phases, between which there was a thick protein film. The upper phase and the majority of the lower phase were carefully removed while retaining the flocculent protein film between the two phases. The tube was left to stand without a cap to dry the precipitate at room temperature. Subsequently, 200 µL of a protein-dissolving buffer (2% sodium dodecyl sulfate (SDS)) was added and the tube was placed in a water bath at 95°C for 10 min. The tube was left at room temperature for 20 min to dissolve the precipitate, and the insoluble substances were removed by centrifugation. The product was preserved at -70°C in a fridge.

**Western blotting analysis**

Protein concentration was quantified using the bicinchoninic acid assay (BCA) method. An appropriate amount of protein was loaded for electrophoresis by running through a stacking gel at 80 V and a separating gel at 100 V. Electrophoresis was stopped when all the marker bands were observed. The proteins were electronically transferred onto a polyvinyliden difluoride (PVDF) membrane at a constant pressure of 100 V for 120 min. The membrane was sealed with TBST (a mixture of Tris-buffered saline and Tween 20) containing 5% defatted milk at room temperature for 1 h. The membrane was then incubated with primary anti-
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bodies (anti-p-AKT, anti-ATK, anti-p-p70S6K, anti-p70S6K, and GAPDH antibody, purchased from Cell Signaling Technology and diluted with sealing buffer) at 4°C overnight. Next, the membrane was incubated with the corresponding secondary antibodies diluted with sealing buffer at room temperature for 2 h. An enhanced chemiluminescence (ECL) detection reagent was added, and the membrane was exposed to X-rays, developed, and fixed.

Nissl staining

At 17-21 days post-immunization, five mice were randomly selected from each group and anesthetized with chloral hydrate. After perfusion using 4% paraformaldehyde, the lumbar spinal cords were harvested, embedded in paraffin, and cut into 5-μm serial sections. Nissl staining and terminal deoxynucleotidyl transferase (TdT) dUTP nick-end labeling (TUNEL) staining were performed. The sections were dewaxed, hydrated, stained with cresyl fast violet, and dehydrated in 95% alcohol. The sections were rendered transparent in xylene and sealed with neutral balsam. The number of motor neurons that satisfied the following criteria was estimated: (1) neurons located within the line connecting the anterior horn of the spinal cord and the terminal of the ventral central canal; (2) neurons that were at least 20 μm thick; (3) neurons with different nucleoli.

Statistical analysis

Statistical analysis was performed using SPSS 13.0 software. Indicator data are expressed as mean ± standard deviation (Mean ± SD). Neurologic scores were analyzed using the Mann-Whitney U test. Other measurements were

Figure 1. Effects of rapamycin on clinical signs and neuronal injury. A. Clinical scores for the experimental autoimmune encephalomyelitis (EAE)-rapamycin and EAE-vehicle mice. C57BL/6J mice were administered vehicle or rapamycin (1 mg/kg) for 30 days after the induction of EAE. The clinical score values are presented as the mean ± SD (n = 15). B. Nissl staining revealed neuronal loss in lumbar spinal cord cross sections of the control, EAE-vehicle, and EAE-rapamycin mice. C. Quantitation of motor neurons by Nissl staining (n = 5, *p < 0.05, **p < 0.01).
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compared between two groups using Student’s t-test. Multiple group statistical comparisons were performed using an ANOVA. p-value < 0.05 was taken to indicate a significant difference.

Results

Rapamycin improved the clinical symptoms of the EAE mice

A growing body of evidence suggests that inducing autophagy is a potential new treatment for neurodegenerative diseases. Numerous in vivo and in vitro studies have proved that rapamycin can alleviate MS [17]. In the present study, the effect of rapamycin on neuronal loss was observed in a MOG 35-55-induced EAE mouse model. Symptoms were observed in all mice in the EAE-vehicle group, which presented appetite loss, body weight reduction, reduced mobility, and reduced smoothness of hair commencing 10 days after immunization. Later, symptoms of neurologic deficiency appeared, including tail drooping and limb weakness. The symptoms were observed in 90% of the mice in the rapamycin treatment group. Compared with the EAE-vehicle group, rapamycin delayed the onset of symptoms, but not to a significant extent (12.75 ± 2.36 days vs 11.25 ± 1.71 days, p > 0.05). However, rapamycin greatly reduced the neurologic scores at the peak of the disease, the average being 1.9 ± 0.652 vs 2.8 ± 0.758 (p < 0.01) (Figure 1A). Rapamycin also alleviated the symptoms of neurologic deficiency in the late stage of the disease. These data show that rapamycin improved the clinical symptoms of the EAE mice.

Rapamycin mitigated neuronal loss in the spinal cord

The potential effectiveness of rapamycin for delaying or inhibiting neuronal death was assessed by estimating the neuronal survival rate at the peak of the disease. Compared with the control group, the number of Nissl-stained neurons in the vertebrae with lumbar enlargement decreased in the EAE-vehicle group (39.33 ± 3.055 vs 58.33 ± 3.512, p < 0.01) and the rapamycin treatment group (46.333 ± 2.517 vs 58.33 ± 3.512, p < 0.01). This implies neuronal death in the acute stage in addition to inflammatory demyelination. Compared with the EAE-vehicle group, the rapamycin treatment group exhibited an increase in the number of Nissl-stained neurons (46.333 ± 2.517 vs 39.333 ± 3.055, p < 0.05) (Figure 1B, 1C), indicating the neuroprotective effect of rapamycin.

Figure 2. Rapamycin alleviated neuronal injury in experimental autoimmune encephalomyelitis (EAE) mice. A. NeuN immunostaining-labeled alpha motor neurons in the spinal cords of the control, EAE-vehicle, and EAE-rapamycin mice at 20 days post-immunization. B. Quantitation of alpha motor neurons using NeuN staining (n = 5, *p < 0.05, **p < 0.01, ***p < 0.001).
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Rapamycin increased the number of alpha motor neurons in the spinal cord

Nissl staining revealed a reduction in motor neurons, especially in the magnocellular body, in the EAE-vehicle group, compared with the rapamycin treatment group. Large transverse sections of vertebrae with lumbar enlargement were prepared to quantify the motor neurons. The DNA-binding protein NeuN can be used to label alpha motor neurons but not gamma motor neurons [18]. Therefore, specific immunofluorescent labeling of alpha motor neurons was performed using anti-NeuN antibody, and the number of NeuN-positive neurons was determined. Compared with the blank control group, the numbers of NeuN-positive neurons in the EAE-vehicle group (16.33 ± 4.09 vs 25 ± 1.9, p < 0.01) and rapamycin treatment group (21 ± 1.87 vs 25 ± 1.9, p < 0.00) decreased, in accordance with the Nissl staining result.

Compared with the EAE-vehicle group, the rapamycin treatment group had more number of NeuN-positive neurons (21 ± 1.87 vs 16.33 ± 4.09 p < 0.05) (Figure 2A, 2B). These results indicate that rapamycin can alleviate the symptoms of neurologic deficiency in the acute stage of EAE, reducing neuronal loss in the spinal cord and delaying neurodegeneration.

Decreased accumulation of autophagosomes in the spinal neurons of EAE mice

Autophagy plays an important role in the physiological and pathological processes of neurons. Under normal physiological conditions, autophagy is activated in neurons, and is involved in the regulation of neurons and axonal LC3 vesicles [4]. Improper or defective autophagy accelerates the death of neurons [19, 20]. To investigate the effect of EAE on autophagosomes in spinal neurons, we examined the
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Immunofluorescent colocalization of LC3 (an autophagosome marker) and NeuN (a neuronal nuclear antigen marker) in astrocytes (glial fibrillary acidic protein, GFAP) and mature oligodendrocytes (anti-adenomatous polyposis coli, APC). The type of autophagic cells that are specific to the spinal cords of EAE mice was identified. The results revealed that the LC3 (fluorescent green) in the vertebrae with lumbar enlargement was mainly localized in the neurons, less commonly localized in the oligodendrocytes, and least localized in the astrocytes (Figure 3A). Compared with control mice of matched age, the immunofluorescent colocalization of LC3 and NeuN showed a decrease in the accumulation of autophagosomes in the spinal cords of EAE mice (Figure 3B). These results indicate that accumulation of autophagosomes was increased in the spinal neurons of EAE mice.

Rapamycin inhibited the Akt/mTOR/p70S6K signaling pathway in the spinal cord of EAE mice

To determine whether rapamycin effectively inhibited the mTOR signaling pathway in the EAE model, we detected the expression levels of Akt and p70S6K proteins at 20th day. The results revealed that the levels of phosphorylated Akt (0.489 ± 0.075 vs 0.922 ± 0.196, p < 0.05) (Figure 4A, 4B) and p70S6K (0.695 ± 0.015 vs 0.412 ± 0.054, p < 0.05) were significantly reduced (Figure 4A, 4C). These results indicate that rapamycin inhibited the Akt/mTOR/p70S6K signaling pathway in the spinal cord of the EAE mice.

Rapamycin restored autophagy in the spinal cords of the EAE mice

To determine whether inhibiting the mTOR signaling pathway activates autophagy, we assessed the changes in autophagy after treatment with the mTOR inhibitor rapamycin. The results revealed that rapamycin caused a significant decrease in the expression levels of LC3-II (0.377 ± 0.051 vs 0.705 ± 0.185, p < 0.05) (Figure 4A, 4D) and increase in Beclin-1 (0.387 ± 0.065 vs 0.712 ± 0.102, p < 0.05) compared with vehicle control group in the spinal neurons (Figure 4A, 4E). These data suggest that rapamycin restores autophagy in the spinal cords of EAE mice.

Discussion

Rapamycin is a targeted inhibitor in mammals and is the most commonly used inducer of autophagy. It can be used to provide neuroprotection in the treatment of several neurodegenerative diseases including Huntington’s disease [23], Parkinson’s disease [24], and Alzheimer’s disease [25]. In the present study, we
discovered that autophagosomes accumulated in the spinal neurons of the EAE mice, indicating that defective autophagy is one of the pathogenic mechanisms of neurodegenerative diseases in such mice. Furthermore, the Akt/mTOR/p70S6K pathway mediated autophagy in the EAE mice, and rapamycin restored autophagy in the spinal neurons. Moreover, rapamycin effectively relieved the symptoms of neurologic deficiency during the acute stage of EAE, thereby alleviating neuronal damage. These findings suggest the neuroprotective effect of rapamycin when used as a drug for the treatment of MS.

Autophagy plays a housekeeping role in neurons. Normal neurons can survive for decades, and autophagy is the only mechanism for removing aging and defective organelles in neurons. In the healthy brain, the number of autophagosomes and the expression level of MAP1LC3-II remain low [26]. A recent study revealed that autophagy is continuously activated in neurons [27]. When clearing by autophagy does not work, or when there is a defect in autophagy, autophagosomes accumulate rapidly, which indicates changes in baseline autophagy [28]. We observed the colocalization of LC3 and NeuN in the main nerve cells by immunofluorescent double labeling. The majority of LC3, the marker of autophagosomes, was localized in the neurons, less commonly localized in the oligodendrocytes, and least localized in the astrocytes. We speculated that defective autophagy in the neurons is involved in the pathogenesis of neurodegeneration in MS. Controlling autophagy in the neurons may offer new hope for the treatment of MS.

The autophagy-related signaling pathway is highly complex and elaborate. The mTOR signaling pathway is the most important pathway that negatively regulates autophagy in eukaryotes [13]. The PI3K/Akt/mTOR signaling pathway can regulate cell division and autophagy, and promote transcription and signal translation through phosphorylation. In response to nutrient deprivation, autophagy is regulated by activating AMP kinase and downregulating mTOR, or through secondary TSC1/2 and other regulatory proteins. Other autophagy signaling pathways include the Ras/Raf/ERK pathway, the CaMKII pathway [29], and the mTOR-independent PI pathway [30]. Moreover, autophagy can be directly induced by intracellular inclusions [31]. However, extracellular signal-regulated kinase (ERK) and p38 mitogen-activated protein kinase (MAPK) signaling pathways do not regulate autophagy in all cells. There is still disagreement about whether these signaling pathways promote or suppress autophagy [32, 33]. In the present study, we explored the regulatory mechanism of autophagy in MS in an EAE mouse model. We discovered that the phosphorylation level of Akt in the spinal neurons increased. More importantly, the phosphorylation level of ribosomal S6 kinase (S6K), the downstream effector of the Akt and mTOR pathways, also increased dramatically. In the PI3K/Akt/mTOR pathway, growth factors bind to receptors, thereby activating the mutant insulin receptor substrate 1 (IRS1) [34]. This leads to the activation of PI3K, and hence the activation of an important downstream effector Akt (PKB). The activated Akt can directly activate mTOR. Akt activation further affects the TSC1/TSC2 heterodimer (TSC is an abbreviation for tuberous sclerosis complex), which causes deactivation of the TSC1/TSC2 complex and activation of mTOR [35]. mTOR starts or stops mRNA translation by regulating the phosphorylation of two substrates: EIF4E-binding protein 1 (4E-BP1) and S6K1 [36]; it also alters the status of the Atg13-Agt1 complex by activating or deactivating Atg13, which interferes with the formation of autophagosomes [37].

Our results also showed that at the peak stage of MOG-induced EAE, there was excessive activation of Akt and p70S6K, the upstream and downstream kinases of the mTOR pathway, respectively. It has been reported that excessive activation of the Akt/mTOR/p70S6K pathway is an important factor in autophagic damage [38]. Persistent activation of mTORC1 causes direct phosphorylation of ULK1, suppresses the initiation of autophagy, and leads to LC3-I reconstruction. Moreover, it inhibits autophagy, translocation, and the activation of transcription factor EB (TFEB), the key regulator of lysosomal activity [39], thereby reducing the synthesis of lysosomal hydrolase and impairing lysosomal degradation. As a result, the degradation of autophagic substrates and LC3-II ceases. We further investigated the regulatory effect of rapamycin on autophagy and its
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mechanism of action. The results showed that the expression levels of the autophagy markers LC3-II and Beclin-1 increased considerably in the spinal neurons of the EAE mice treated with rapamycin. This indicated the restoration of autophagic activity by rapamycin, which also effectively inhibited the activity of Akt and p70S6K. We believe that the rapamycin-induced autophagy was at least partially the result of the inhibition of the PI3K/Akt/mTOR signaling pathway. Furthermore, rapamycin relieved the clinical symptoms and reduced neuronal loss in the EAE mice, thereby proving the neuroprotective effect of rapamycin.

To conclude, Rapamycin effectively relieved the symptoms of neurologic deficiency and reduced spinal neuronal damage in the acute stage of EAE in the mice. Therefore, rapamycin can offer neuroprotective effects and a new option for the treatment of MS. Rapamycin reduces the degeneration of neurons by inhibiting the Akt/mTOR/p70S6K pathway and restoring autophagy in EAE mice.

Disclosure of conflict of interest

None.

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References

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