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REVIEW ARTICLE

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# Research progress of statins on immune regulation of multiple sclerosis and experimental allergic encephalomyelitis

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### Abstract

**Objective:** The aim of this study is to summarize studies on statins used to treat multiple sclerosis (MS) and experimental allergic encephalomyelitis (EAE) and its underlying mechanisms.

**Methods:** We searched some representing databases. Some studies were included if the effects of statins were tested on MS and EAE. The methodological quality was evaluated by the Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies checklist.

**Results:** Studies have confirmed that statins have immunomodulatory, neuroprotective and anti-inflammatory effects, and can be used in combination with immunomodulators of different mechanisms to treat MS and EAE. Statins have been shown to improve the following symptoms MS, reduce the number of attacks and the number of lesions, through immunomodulatory, neuroprotective and anti-inflammatory effects, and has a good safety profile.

**Conclusions:** In short, statins represent an attractive new measure for treating MS. Some studies indicate that in addition to immunomodulatory effects, statins may have neuroprotective and neuro-repairing effects. The combination of statins with other immunosuppressive drugs has also produced encouraging results. This can be broadly prospects prospected to treat MS and EAE. It is hoped that in the near future, a combination of statins with less adverse reactions and high efficacy combined with other immunomodulators will bring exact results to patients with MS.

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## Introduction

Animal models, such as the Experimental Autoimmune Encephalomyelitis (EAE), have been extensively used to investigate the potential therapeutics for MS. While the sensitization to autoantigens naturally happens due to an unknown mechanism, the EAE model needs an external immunization. EAE is an organ-specific cell-mediated, auto-immune demyelinating disease of the CNS in which macrophages and T lymphocytes mediate the injury to myelin sheath. Multiple Sclerosis (MS) is a more common type of inflammatory demyelinating autoimmune disease of the central nervous system (CNS). It occurs in young and middle-aged people and has a chronic course. Seizures, clinical manifestations have the characteristics of multiple times and lesions,<sup>1</sup> and often have sequelae of severe neurological deficits, which is one of the most important causes of nontraumatic disability in young people in European and American countries.<sup>2,3</sup> At present, the etiology of MS has not been fully elucidated and the pathogenesis is more complicated. As we all know, MS has both humoral immune participation and cellular immunity. Among them, the infiltration of central nervous system toxic T lymphocytes and destruction of the blood-brain barrier are important mechanisms that cause the pathogenesis of MS.<sup>4</sup> Pathological changes in MS include demyelination, glial cell proliferation, axonal injury, and neuronal necrosis.<sup>5</sup>

In recent years, many studies have found that inflammation and immune response, as an important mechanism, are directly involved in the development of many diseases of the nervous system, such as stroke, epilepsy, Parkinson's disease, and Alzheimer's disease.<sup>6</sup> The pathogenesis of MS. Therefore, the treatment of MS involves immunomodulation and immunosuppression. At present, commonly used drugs include glucocorticoids, interferon (IFN), and mitoxantrone, but these drugs can only partially alleviate the condition of MS and have obvious toxic and side effects. Statins act by inhibiting HMG-CoA reductase within the mevalonate pathway. It is well-described that TCR stimulation induces expression of HMG-CoA reductase, generating metabolites affect T cell function at a range of different levels, including immunological synapse formation, migration, proliferation, and cytotoxic effector responses. In recent years, the results of statins in the treatment of autoimmune diseases have received widespread attention. This article summarizes the immunomodulatory mechanisms and effects of statins.

## Animal experiments and clinical observations

Experimental autoimmune encephalomyelitis (EAE) is a classic animal model for studying MS. The efficacy of statins for MS comes mainly from the study of its animal model EAE. It has been proved that statins can prevent the occurrence of EAE or improve the condition of EAE and delay the occurrence of dysfunction, and the effect is longer-lasting. Statin intervention can transform EAE from a pro-inflammatory response to an anti-inflammatory state.<sup>7,9</sup> Oral atorvastatin has been reported to prevent and reverse chronic relapse EAE.<sup>7</sup> The dose of atorvastatin in these studies: 0.1, 1.0, or 10 mg/kg of body weight per day

can significantly inhibit the development of EAE disease. Nath et al.<sup>10</sup> found that the treatment of SJL/J mice with lovastatin can reduce the duration of EAE and reduce the clinical symptoms, and thought that it was related to the inhibition of T-bet, NF- $\kappa$ B and STAT4 signaling pathways. In addition, lovastatin induces the conversion of TH1 to TH2, accompanied by the production of APC-dependent and APC-independent anti-inflammatory cytokines IL-10. Interestingly, only a few animals had mild EAE symptoms when treatment was discontinued, revealing the long-lasting therapeutic effect of this drug.<sup>7</sup>

Currently, preliminary studies have found that statins are beneficial for MS. After treatment with lovastatin and simvastatin, laboratory studies have found that many immunological parameters in patients with MS are transformed in the direction of returning to a normal immune state, and these responses are dose-dependent. Its effect is very similar to the response after interferon beta treatment. The combination of the two can increase the efficacy. From its anti-inflammatory mechanism research, it was found that statins mainly work in the early stages of MS and cannot effectively improve the existing disability of patients. Therefore, it is currently used as an adjuvant drug for MS treatment and further research is ongoing. Vollmer et al.<sup>11</sup> conducted a clinical study of simvastatin in the treatment of MSII. A total of 28 patients with relapsing-remitting MS (RRMS) received simvastatin 80 mg daily for 6 months. At the 4th, 5th, and 6th months of treatment, a series of MRI scans were performed and it was found that the number of new radon enhancement lesions was reduced by an average of 44% ( $P < 0.0001$ ) and the lesion volume was reduced by an average of 41% ( $P = 0.0018$ ). No serious adverse events or significant clinical changes occurred in this short-term study. This experiment is uncontrolled and its results should be interpreted with caution. But it is clear that treatment with high doses of simvastatin is safe and effective in some patients with RRMS. It is currently believed that the mechanism of action of statins may not be beneficial for the later stage of neurodegeneration, but rather more effective for the early stage of inflammation. To further evaluate the prospects for the use of statins in MS, placebo-controlled phase II and III studies and studies of the effects of combined use with other approved MS therapies are needed. These studies should be able to determine the role of statins in combination with approved drugs for MS or alone in the treatment of MS.<sup>12</sup>

## Statins and their pharmacological effects

Statins are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors. By inhibiting HMG-CoA reductase, they prevent the production of L- mevalonate (MA) and reduce blood. The purpose of cholesterol concentration is a clinically effective lipid-lowering drug. At the same time, such drugs can also interfere with the production of isoprenoid intermediates in the mevalonate pathway, which are the membrane lipid attachments of various intracellular signaling molecules such as GTP-binding proteins Ras, Rac, and Rho. It plays a very important role in maintaining various cell functions, such as morphology, proliferation, secretion, and differentiation. Therefore, statins

can prevent isoprenylation of RhoA, Ras, etc., regulate the balance of Th1/Th2, and have immunomodulatory and anti-inflammatory effects.<sup>13-15</sup> In addition, statins can directly affect the activity of certain cell surface molecules such as LFA-1, CD40, CD80, and CD86 in the body.

## Effects on the immune system

### *Effect on Th1 and Th2 T cells*

It is well known that CD4 + T cells play a leading role in the occurrence and development of autoimmune diseases. Th1 and Th2 are the two major subtypes of CD4 + T cells. Th1 can promote inflammation, and Th2 can inhibit inflammation. Th1/Th2 imbalance is currently considered to be one of the main reasons for the formation of autoimmune diseases. The balance between cytokines can determine tolerance and sensitivity in autoimmunity.<sup>16</sup> With the activation of the initial immunogenic polypeptide, the initial T cells can differentiate and become two helper T lymphocytes, and these two helper T cells have two main memories of different phenotypes, Th1 and Th2 cells.<sup>17</sup> Th1 cells can characteristically produce cytokines such as IL-2 and IFN- $\gamma$ , induce the activation of macrophages, and regulate the infection of intracellular antigens. Th2 cells can secrete cytokines such as IL-4, IL-5, and IL-13, help B cells to produce some antibodies, and play an essential role in eradicating worm and parasite infections.<sup>18</sup>

Youssef et al.<sup>7</sup> first discovered that statins can inhibit Th1 expression and promote Th 2 expression. This is a landmark and significant discovery that provides sufficient and reliable experimental evidence for statins to treat MS. They found that atorvastatin interfered with EAE induced by different antigens and was administered at different times. As a result, they found that the disease was alleviated to varying degrees, so they considered that statins had a beneficial effect on both the acute and remission stages of EAE. More importantly, they found that the Th2 cells in mice treated with statins were transferred to recipient mice, and the recipient mice induced EAE, and found that the transferred Th2 cells protected the recipient mice. effect. This fully illustrates that statins help restore the function of Th2 cells. Dunn et al.<sup>19</sup> also found that atorvastatin can significantly improve the condition of EAE by inhibiting the proliferation of Th1 and regulating the expression of Th2 in the body, and plays a significant role in immune regulation.

Some scholars have studied the effects of lovastatin on Th1/Th2 from the perspective of cell differentiation.<sup>10</sup> T-bet is a transcription factor of Th1 cells, which determines whether it secretes IFN- $\gamma$ . NF- $\kappa$ B is a nuclear transcription factor and also determines the translation of many pro-inflammatory cytokines. GATA3 is a transcription factor of Th2 cells, which determines whether it secretes IL-4. STAT4 and STAT6 in nuclear transcription factors determine Th0 cells to differentiate into Th1 and Th2, respectively. Now studies on EAE have shown that statins can inhibit T0 cells from differentiating into Th1 cells by inhibiting T-bet, NF- $\kappa$ B, and STAT4, thereby reducing inflammatory cytokines such as IL-2, IL-12, IFN - $\gamma$ , TNF- $\alpha$ ); can also promote the differentiation of Th0 cells to Th 2 cells by promoting the expression of GATA3 and STAT6 (secretes IL-4, IL-5,

IL-10 and transforming growth factor-B)<sup>8</sup>). In summary, the multiple immunomodulatory effects of statins can inhibit CNS damage, delay onset, and improve the severity of EAE disease.<sup>10</sup>

### *Effect of thallium on Th17 and Treg cells*

Under different microenvironments of cells and cytokines, the initial CD4 + T cells can be activated and polarized into different helper T cell subsets (Th). In addition to Th1 and Th2, there are Th17 and Treg cells.<sup>20</sup> In contrast, Treg cells prevent autoantigen-responsive effector immune cells, such as playing an important inhibitory role in the autoimmune response produced by Th1 and Th17. The absence of Treg cells can cause autoimmune diseases. Studies have confirmed the absence of Treg cells in MS patients and EAE mice.<sup>21</sup> In addition, Tregs are key to controlling autoimmune and tissue damage in vivo, and are also important antagonists of Th17. These two antagonistic cells are regulated by TGF- $\beta$  or TGF- $\beta$  in cooperation with IL-6, respectively.<sup>22</sup> Recently found that Th17 also plays a very important role in the occurrence and development of MS and EAE. According to recent research reports: Th17 can enhance the severity of EAE; anti-IL-17 can be used to inhibit the development of disease. Therapeutic methods show that IL-17 is a key inflammatory factor in the process of autoimmune diseases such as EAE.<sup>23,24</sup> Simvastatin can induce cytokines IFN- $\gamma$ , IL-4 and IL-27, and inhibit the production of cytokines such as IL-23 and IL-6 in monocytes, and can down-regulate the transcription factor RORC of Th17 T cells. Expression, which in turn inhibits the transcription and secretion of IL-17 in CD4 + T cells. A recent study showed that NO is involved in suppressing the expression of FOXP3 in autoimmune diseases, and statins, as inhibitors of inducible nitric oxide synthase (iNOS), can relieve this inhibition of FOXP3 expression.<sup>25</sup> Therefore, statins help increase the Treg/Th17 ratio.<sup>8</sup>

### *Reduce MHC-II molecules and costimulatory signals required for T cell activation*

In addition to specific CNS autoantigens, CD4 + T cell activation requires (for) MHC-II molecules and co-stimulatory signals, etc.<sup>26</sup> Studies have shown that statins inhibit the expression of IFN- $\gamma$ -induced MHC-II molecules in different non-professional APCs. Atorvastatin can almost completely prevent CIITA promoter-directed IFN- $\gamma$ -induced CIITA transcription.<sup>7</sup> Atorvastatin can inhibit the expression of MHC-II molecules induced by IFN- $\gamma$  in microglia, and this effect can be reversed by L-mevalonic acid. In addition to the T cell receptor (TCR) binding to the antigen that binds to the MHC-II molecular antigen-binding groove, CD4 + T cell activation requires a second signal, a co-stimulatory signal. Once activated, T cells express CD40 ligand (CD40L) on their own cell surface, which binds to costimulatory molecules on the surface of APCs. The cross-linking of CD40 and CD40L led to the expression of co-stimulatory molecules B7-1 (CD80) and B7-2 (CD86) of APCs, which bind and activate CD28 of T cells. Recently reported that atorvastatin can inhibit the expression of several co-stimulatory

**Table 1** Summary of key relapsing-remitting MS (RRMS) treatments approved.

Drug	Trial size Duration	Efficacy	Safety
Simvastatin 28	6 months	It was found that the number of new radon average of 44% (P<0.0001) and the lesion volume was reduced by an average of 41% (P=0.0018). <sup>11</sup>	No serious adverse events or significant clinical changes occurred.
Lovastatin 7	12 months	Lovastatin can reduce the number of radon-enhancing lesion, but not the patient's EDSS scord. <sup>38</sup>	No adverse with therapy were observed.
Simvastatin 85	12 months	The total number of attacks in the simvastatin group was significantly lower than the therapy placebo group. <sup>39</sup>	The combination was safe and well tolerated, and no serious adverse effect was noted.
Atorvastatin 80 or and IFN-B	9 months	MRI analysis indicates that atorvastatin is used alone or the combination of IFN-B is very beneficial for reducing the occurrence of radon-enhancing lesions. <sup>46</sup>	The treatment was safe and tolerated.
Atorvastatin 45 or and IFN-B	24 months	The contrast-enhanced lesions in the combination group were significantly reduced (P=0.007). <sup>47</sup>	The results show the combination therapy was safe and well tolerated.

molecules induced by IFN- $\gamma$ , including CD40, CD80 (B7-1), CD86 (B7-2) on APCs. In addition, statins can also reduce the expression of HLA-DR on the surface of B (CD19 +) cells, which is required for the process of antigen presentation to T cells.<sup>27</sup>

### **Reduce T cells from entering the CNS**

The blood-brain barrier is a biological barrier between plasma and cerebrospinal fluid formed by intracranial vascular endothelial cells and glial cells. It can effectively restrict the flow of cells or substances between plasma and cerebrospinal fluid, especially to prevent harmful substances and cells from entering the nerve center and maintain the stability of the central nervous system plays an important role. The destruction of the blood-brain barrier leads to the increased permeability of the blood-brain barrier and the easy infiltration of toxic T lymphocytes into the center, which is one of the important links in the pathogenesis of MS.<sup>28,29</sup> If the intracranial vascular endothelial cytoskeleton structure is intact, it will reduce the apoptosis of endothelial cells and stabilize the blood-brain barrier.<sup>30</sup> If inflammatory T cells enter the central nerve through the blood-brain barrier, it can cause an autoimmune response, recruit more effector cells, expand the inflammatory response, promote the release of inflammatory mediators such as lymphotoxin or tumor necrosis factor, and cause extensive myelin sheaths. Nervous system damage such as loss.<sup>31</sup>

It has been reported that, independent of its effect on inhibiting HMG-CoA reductase, lovastatin binds LFA-1 and can directly inhibit LFA-1-ICAM-1-mediated cell adhesion.<sup>32</sup> Statins can significantly inhibit the expression of ICAM-1 in activated T cells cultured in vitro, but have no effect on LFA-1 and VLA-4. Once T cells in the body cross the endothelial barrier, they still need to disrupt other physiological barriers, namely the vascular basement membrane and the extracellular matrix in the CNS to reach the brain and spinal cord. Proteolytic enzymes, called MMPs,

are considered to be one of the physiological mediators of T cells through biological membranes.<sup>33</sup> MMPs can also degrade myelin basic protein (MBP) into peptide fragments that cause encephalitis. MBP is one of the CNS autoantigens in MS. Statins have been shown to reduce the secretion of white blood cell MMP-9. Lovastatin and simvastatin can reduce MCP-1 production in peripheral blood by monocytes and human endothelial cells in a dose-dependent manner. In studying the anti-inflammatory effects of statins in the treatment of atherosclerosis, it was also found that lovastatin and pravastatin can inhibit the production of MCP-1, which has a chemotactic effect on monocytes.

### **Effect on cytokine signal inhibitors**

More than 10 cytokine signaling pathways have been discovered, and the JAK/STAT system involves a wide range of cytokines. To date, a total of 7 members of the STAT family have been identified, namely STAT1-4, STAT5a, STAT5b and STAT6, and STAT5a and STAT5b. STAT3 not only plays an important role in Th17 differentiation, but also participates in the regulation of Treg differentiation.<sup>34</sup> The suppressor of cytokine signaling (SOCS) system is a common molecular regulatory mechanism for cells to external stimuli. The binding of cytokines to the corresponding receptors can lead to the activation of signal transduction pathways, transmitting the signals of cytokines from the cell membrane to the cytoplasm, and finally to the nucleus, thereby causing the expression of the target gene. The SOCS system discovered in 1997 explains exactly the negative regulation mechanism of the JAK/STAT signal system. SOCS consists of at least 8 components, namely SOCS1-7 and CIS. For example, SOCS-1 can inhibit cell signaling to LIF, OM, IFN- $\gamma$ , TPO, growth hormone, and IL-6, suggesting that the SOCS system is a common molecular regulatory mechanism for cells to external stimuli. Some studies have found that inflammatory factors can promote the inhibition of the activation of inflammatory cytokine signaling (SOCS), thereby inhibiting the signaling pathway (STAT) pathway of over-activating

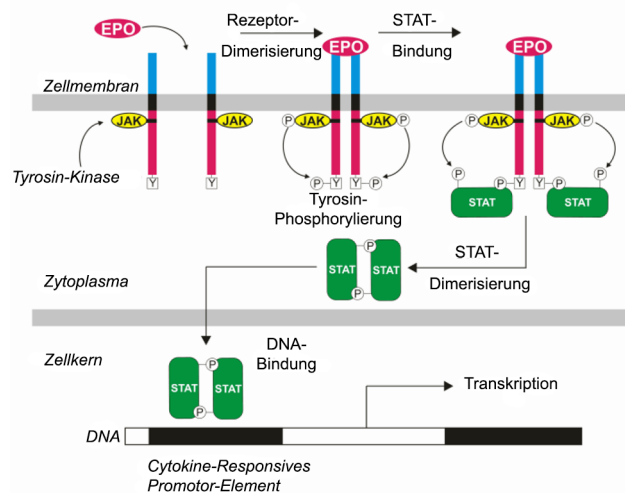
protein-restricted transcriptional activation.<sup>35</sup> Studies have shown that treatment with simvastatin increases the expression of SOCS7 and SOCS3 in PBMCs and monocytes in RRMS patients and healthy subjects. Individual SOCS proteins can regulate the transcription of multiple cytokines, the expression of MHC class II molecules and co-stimulatory molecules, and are attractive treatments for inflammatory diseases.<sup>35</sup> The SOCS3 protein that has penetrated into cells has been successfully used to treat inflammatory liver disease in animal models. In animal models of rheumatoid arthritis, intra-articular injection of recombinant SOCS3 can reduce joint inflammation. Therefore, statin-induced SOCS3 expression may be an effective treatment for MS. Li et al.<sup>36</sup> reported that SOCS3-transduced dendritic cells expressed decreased levels of MHC class II molecules and CD86, reducing the production of IL-12 and IL-23. Zhang et al.<sup>37</sup> showed that simvastatin can enhance the expression of SOCS, reduce the expression of IL-6, IL-17, IL-23, and INF- $\gamma$ , and (and) directly inhibit IL-17. The transcription factor retinoic acid-associated orphan nuclear receptor C, which collectively reduces the expression of cytokines in Th17 cells, has revealed that statins act as an immunosuppressant by inhibiting Th17 cells. (Figures 1-3).

### Clinical study of statins in the treatment of multiple sclerosis

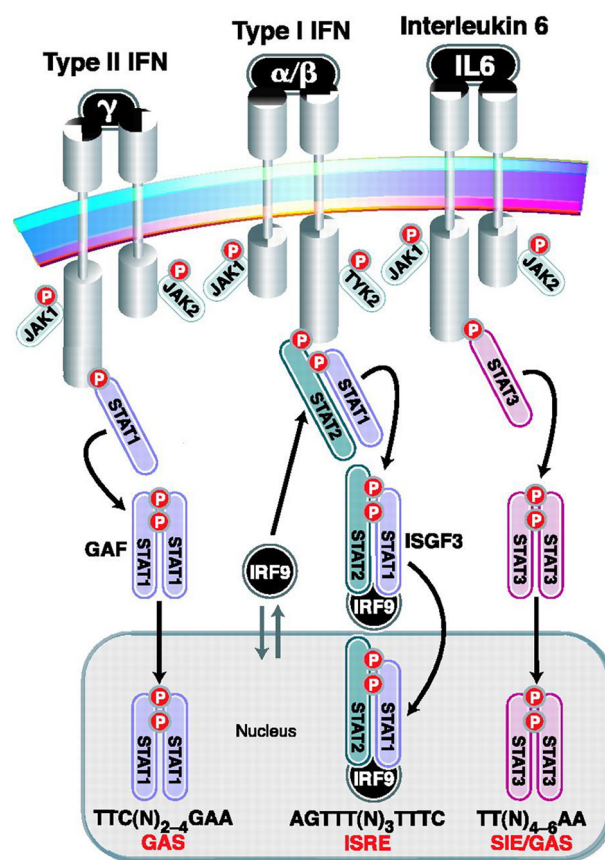
In recent years, the immunomodulatory and neuroprotective effects of statins have been recognized. But clinical trials of statins in inflammatory diseases are just beginning.

#### Studies on statin monotherapy

Sena et al.<sup>38</sup> clinically observed that 7 patients with RRMS were treated with lovastatin for more than 12 months, and found that lovastatin can reduce the number of radon-enhancing lesions, but not the patient's EDSS score. Later,



**Figure 1** In the JAK/STAT pathway, STAT proteins contain SH and other domains that can bind to specific phosphorylated tyrosine-containing peptides.

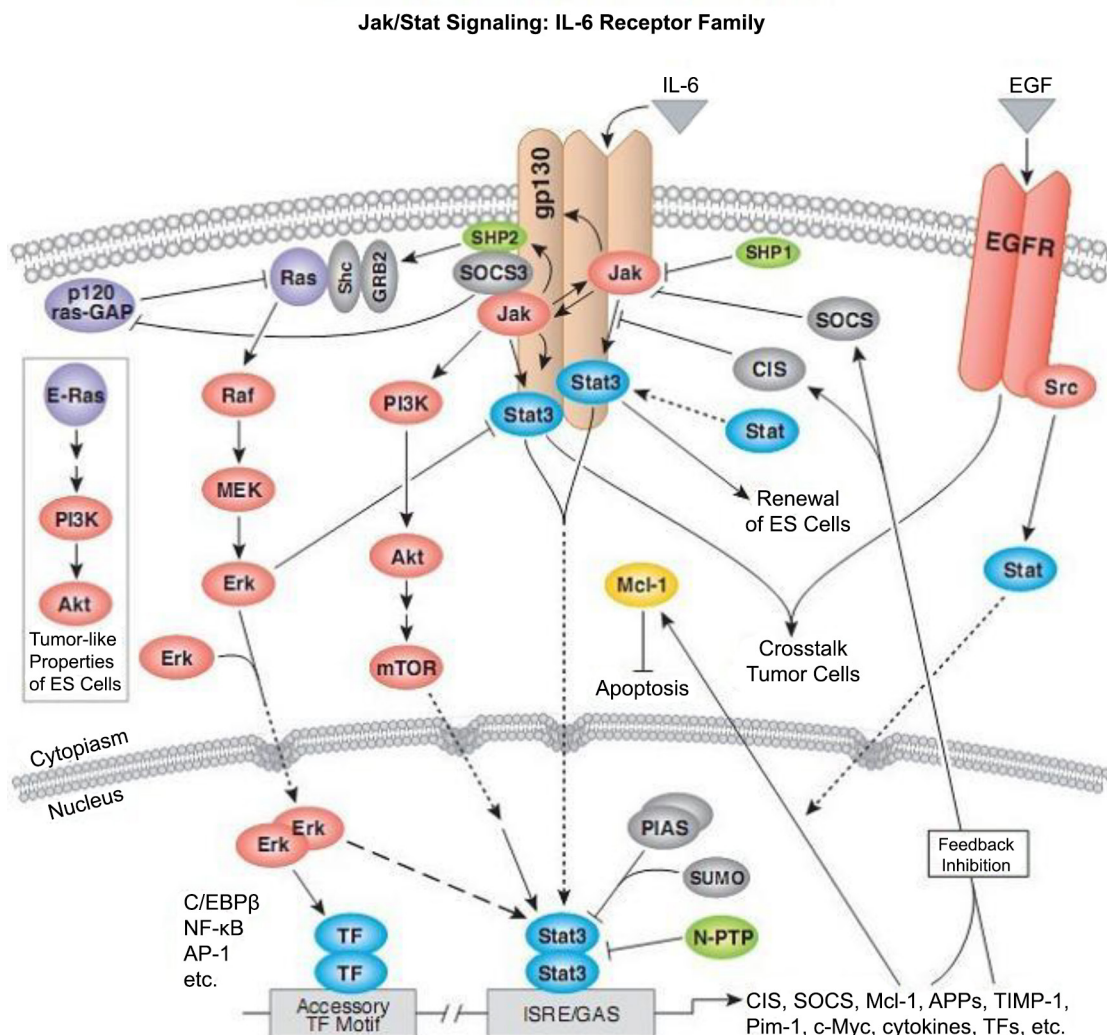


**Figure 2** When STAT is phosphorylated, it aggregates into an activated transcriptional activator in the form of homologous or heterodimer, which enters the nucleus and binds to a specific site of the target gene promoter sequence to promote its transcription.

Togha et al.<sup>39</sup> reported that simvastatin 40 mg/d, a total of 85 RRMS patients, continued treatment for 12 months, the total number of attacks in the simvastatin group was significantly lower than the placebo group. Further research shows that simvastatin increases the production of SOCS3 and SOCS7, can negatively regulate the STAT/JAK signal transduction pathway, inhibits the expression of IL-23 gene signal in monocytes, and reduces IL-6 and IL-23. And induce the production of IFN- $\gamma$ , IL-4 and IL-27, these factors can jointly inhibit the secretion of IL-17 from CD4 + cells in MS patients and healthy subjects.<sup>40</sup> The results of this study characterize the anti-inflammatory mechanisms of statins (new) and can selectively target the regulation of cytokine transcription and the occurrence of human autoimmune responses. This also makes statins promising as one of the promising measures for treating MS. We are also encouraged by the results of statins in the treatment of other autoimmune diseases.<sup>41-45</sup>

#### He studied statin in combination with other drugs

In vitro studies have shown that statins may work synergistically with other immunomodulatory drugs, including interferon.<sup>27</sup> As a result, some scholars have begun clinical



**Figure 3** One of the pathway proteins involved in cell surface to nucleus: JAK/STAT signaling (IL-6 Receptor Family).

studies of statins and other immunomodulatory drugs in the treatment of MS. In 2008, Paul et al.<sup>46</sup> reported promising results. In this open phase II trial, atorvastatin 80 mg/d was used alone or in combination with IFN- $\beta$  to treat RRMS. After 9 months of treatment, the results show that the vast majority of patients are safe and tolerable of high-dose atorvastatin 80 mg, whether or not combined with IFN- $\beta$ ; MRI analysis indicates that atorvastatin is used alone or The combination of IFN- $\beta$  is very beneficial for reducing the occurrence of radon-enhancing lesions. The authors point out that this study provides a reliable basis for the II/III trial of atorvastatin in combination with approved immunomodulatory treatment regimens for RRMS. In 2010, Lanzillo et al.<sup>47</sup> reported that 45 patients who had failed to treat with IFN- $\beta$ 1a44 $\mu$ g (three times a week) for 12 months, and RRMS patients were randomly assigned to the combination treatment group (INF + Atorvastatin 20mg/d, n = 21) and single INF group (n = 24). After 24 months of treatment, compared with the baseline value, the contrast-enhanced lesions in the combination group were significantly reduced ( $P = 0.007$ ), and the recurrence rate was also significantly reduced in the following 2 years ( $P < 0.001$ ), while the EDSS score was slightly higher in the INF group In the combined treatment group

( $P = 0.053$ ). The authors point out that low-dose atorvastatin, as an additional treatment, may be beneficial in patients who are not responding to high-dose INF- $\beta$ 1a.

## Conclusions

In short, statins represent an attractive new measure for treating MS. Animal model studies indicate that in addition to immunomodulatory effects, statins may have neuroprotective and neuro-repairing effects. The combination of statins with other immunosuppressive drugs has also produced encouraging results.<sup>48</sup> It is hoped that in the near future, a combination of statins with less adverse reactions and high efficacy combined with other immunomodulators will bring exact results to patients with MS.

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## Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

## Competing interests

The authors state that there are no conflicts of interest to disclose.

## Contribution of authors

Dongsheng Xu and, Manxia Wang designed the study, completed the experiment and supervised the data collection, Dongsheng Xu analyzed the data, interpreted the data, Manxia Wang prepare the manuscript for publication and reviewed the draft of the manuscript. All authors have read and approved the manuscript.

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