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Review

A review of autophagy mechanism of statins in the potential therapy of Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is a neurodegeneration csharacterized by amyloid-β (Aβ) deposition and abnormally phosphorylated Tau protein aggregation. Autophagy, as an important cellular metabolic activity, is closely related to the production, secretion and clearance of Aβ peptide and Tau phosphorylation level. Therefore, autophagy may become a potential target for AD treatment. A large number of molecules are involved in the mammalian target of rapamycin (mTOR)-dependent or mTOR-independent pathway of autophagy. More and more evidences show that statins can intervene autophagy by regulating the activity or expression level of autophagy-related proteins and genes. On the one hand, statins can induce autophagy through Sirtuin1 (SIRT1), P21, nuclear P53 and adenylate activated protein kinase (AMPK). On the other hand, statins inhibit the mevalonate metabolism pathway, thereby interfering with the prenylation of small GTPases, leading to autophagy dysfunction. Statins can also reduce the levels of LAMP2 and dynein, destroying autophagy. In this review, we focused on the role of autophagy in AD and the autophagy mechanism of statins in the potential treatment of AD.

Keywords: Alzheimer's disease; Amyloid-β; Tau protein; Autophagy; Autophagy flux; Statin; Mevalonate pathway

1. Introduction

Alzheimer's disease (AD) is a progressive and irreversible degenerative disease of the nervous system. Its main clinical features are cognitive decline, mental and behavioral symptoms, and decreased ability of daily living. The pathological manifestations are mainly senile plaques formed by the accumulation of amyloid-β (Aβ) and neurofibrillary tangles (NFTs) formed by abnormal phosphorylation of Tau protein. Statins are a class of classic drugs that regulate blood lipids. In recent years, they have been reported to have obvious therapeutic effects on delaying the progression of AD [1,2]. Particularly, experiments have proved that simvastatin can reduce the production of Aβ [2], and lovastatin can inhibit Tau protein hyperphosphorylation [3]. This neuroprotective effect of statins may be achieved by regulating autophagy [4], but at the same time, it has also been suggested that the toxic effect of statins is related to its inhibition of autophagy flux [5]. This article aims to discuss and summarize the mechanisms by which statins regulate autophagy pathways in AD brain.

2. Classical autophagy signaling pathway

Autophagy is the process of cell self-digestion. It swallows its own cytoplasmic contents and wraps it to form vesicles, then fuse with lysosomes to form autolysosomes, which play a degrading role. At first, autophagy is considered to be a large-scale and non-selective degradation system, but in recent years, it has been gradually discovered that autophagy can selectively degrade senescent organelles, error proteins and other substrates, thereby maintaining the homeostasis of the cell environment. According to the different ways in which cell components are transported to the lysosome, autophagy can be divided into the following types: (1) Microautophagy-the membrane of the lysosomes directly wraps long-lived proteins and so on, and is degraded in the lysosomes; (2) Macroautophagy-the membrane derived from endoplasmic reticulum surrounds the substance to be degraded to form autophagosomes, which then fuse with the lysosomes and degrade its contents; (3) Chaperone-mediated autophagy-intracytoplasmic proteins are transported to lysosomal cavities after binding to molecular chaperones, and then digested by lysosomal enzymes [6]. This article focuses on macroautophagy, hereinafter referred to as autophagy.

The formation of autophagy includes several stages. The first is the formation and expansion of isolation membrane, also known as phagophore. Secondly, phagophore encapsulates cytoplasmic contents to form autophagosomes. Then the autophagosomes and lysosomes fuse to form autolysosomes, producing degradation [7].

The classical autophagy signaling pathways include mammalian target of rapamycin (mTOR)-dependent and mTOR-independent (Fig. 1). mTOR is the most concerned autophagy regulatory molecule, including mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). mTOR activity is affected by many factors, such as hypoxia, cytokines, energy level, insulin, etc. [8]. Intracellular phosphatidylinositol kinase/protein kinase B (PI3K/Akt) is a positive regulatory molecule upstream of mTOR. The activation of PI3K is realized by stimulating receptor tyro-

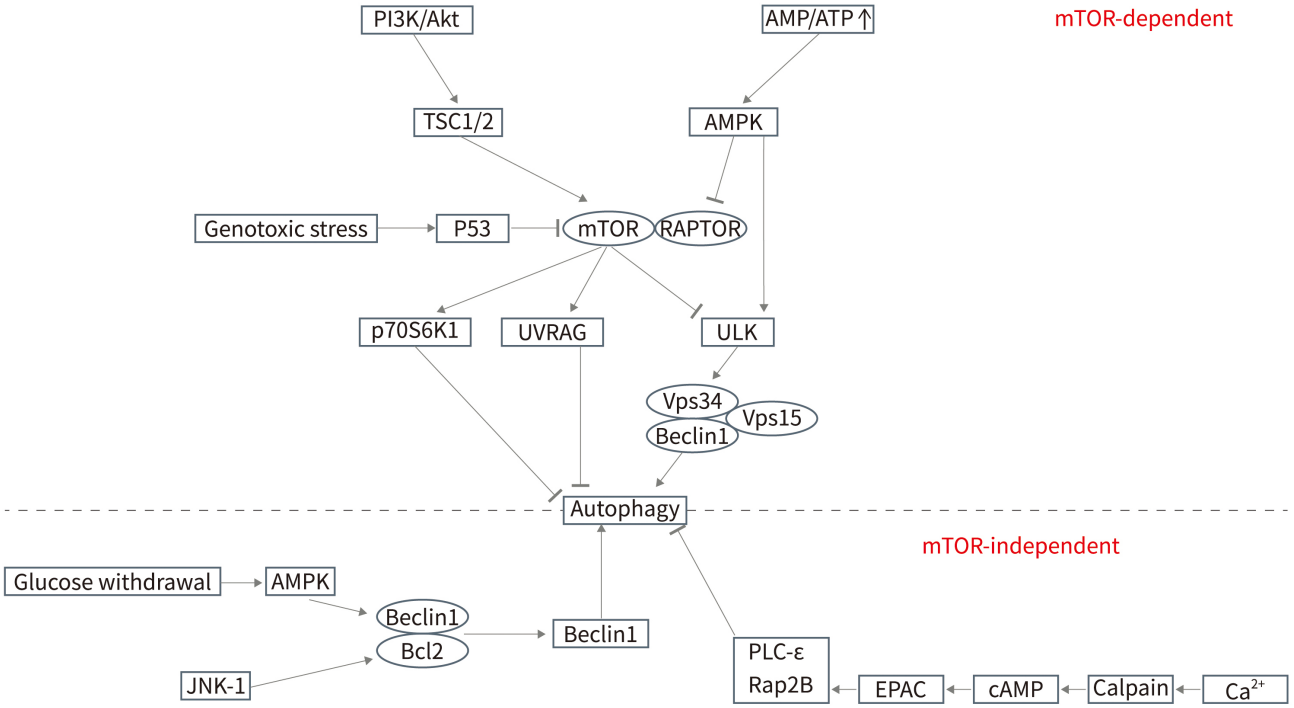

Fig. 1. Classical autophagy signaling pathway. Classical autophagy regulation pathways include mTOR-dependent and mTOR-independent. mTOR is a key molecule in autophagy signal, which inhibits autophagy by phosphorylating downstream p70S6K1, UVRAG and ULK. PI3K/Akt upstream of mTOR can activate mTOR by preventing the formation of TSC1/2 complex. Changes in energy status can activate AMPK, and activated AMPK phosphorylates RAPTOR to inactivate mTOR. Moreover, AMPK and JNK-1 are able to promote the dissociation of Beclin1 and Bcl2-2 by phosphorylation, thus promoting the formation of autophagy complex. Finally, Ca^{2+} and cAMP activate PLC-ε and Rap2B via the EPAC pathway, and ultimately inhibit autophagy.

sine kinase, and the second messenger phosphatidylinositol triphosphate (PIP3) is produced in this process. PIP3 transfers downstream Akt from cytoplasm to cell membrane and phosphorylates Akt at its serine/threonine sites (Ser473 and Thr308). Activated Akt phosphorylates tuberous sclerosis complex 2 (TSC2) at Ser939 and Thr1462, hinders the formation of TSC1/2 complex and then prevents its negative effect on Ras homolog enriched in brain (Rheb) (a member of the small GTPase superfamily), thus enhancing the activation of mTOR. Activated mTOR further phosphorylates its downstream protein p70S6K1 to inhibit autophagy [9,10]. Adenylate activated protein kinase (AMPK) is another important molecule upstream of mTOR and is a trigger signal for autophagy. AMPK is sensitive to changes in the energy state of cells. An increase in the ratio of adenosine monophosphate/adenosine triphosphate (AMP/ATP) can phosphorylate AMPK at Thr172. Activated AMPK can inhibit mTOR activity by phosphorylating regulatory-associated protein of mTOR (RAPTOR) in mTORC1 [11]. Besides this, AMPK directly phosphorylates unc-51-like kinase (ULK) at Ser467, Ser555, Thr574 and Ser637 [12,13]. Unc-51-like kinase (ULK) is the only core protein with serine/threonine kinase activity in the autophagy signaling pathway. Active ULK activates vacuole sorting protein 34 (Vps34) in the downstream complexes of autophagy, and phosphorylates PI to produce PIP3, which is essential for the recruitment of autophagy-related genes (Atg) protein to autophagic vesicles [14,15]. When cell nutrition is sufficient, mTOR can combine with Ser757 of ULK1 to disturb the interaction between ULK1 and AMPK, which leads to the inactivation of ULK1 and finally turns off autophagy signal [14]. Activated mTOR also binds to and phosphorylates anti-ultraviolet radiation related genes (UVRAG), promotes the connection between UVRAG and RUN domain Beclin-1- interacting and cysteine-rich containing protein (RUBICON), and inhibits the maturation of autophagy [16]. Finally, under genotoxic stress, p53 enhances autophagy by up-regulating the negative regulator of mTOR [17].

Apart from the classic mTOR-dependent pathways, Ca^{2+}, calpain, c-Jun N-terminal kinase (JNK), Beclin-1 and other molecules can also regulate autophagy in mTOR-independent pathways. When autophagy does not occur, Beclin-1 binds to apoptosis inhibitory protein Bcl-2 through its Bcl-2 homology domain (BH3). The initiation of autophagy is accompanied by the formation of the Vps34-Vps15-Beclin1 complex, and then Atg14 is added to the complex to catalyze the production of PIP3, which has a significant role in autophagy nucleation and elongation. In the glucose withdrawal state, AMPK is activated, leading

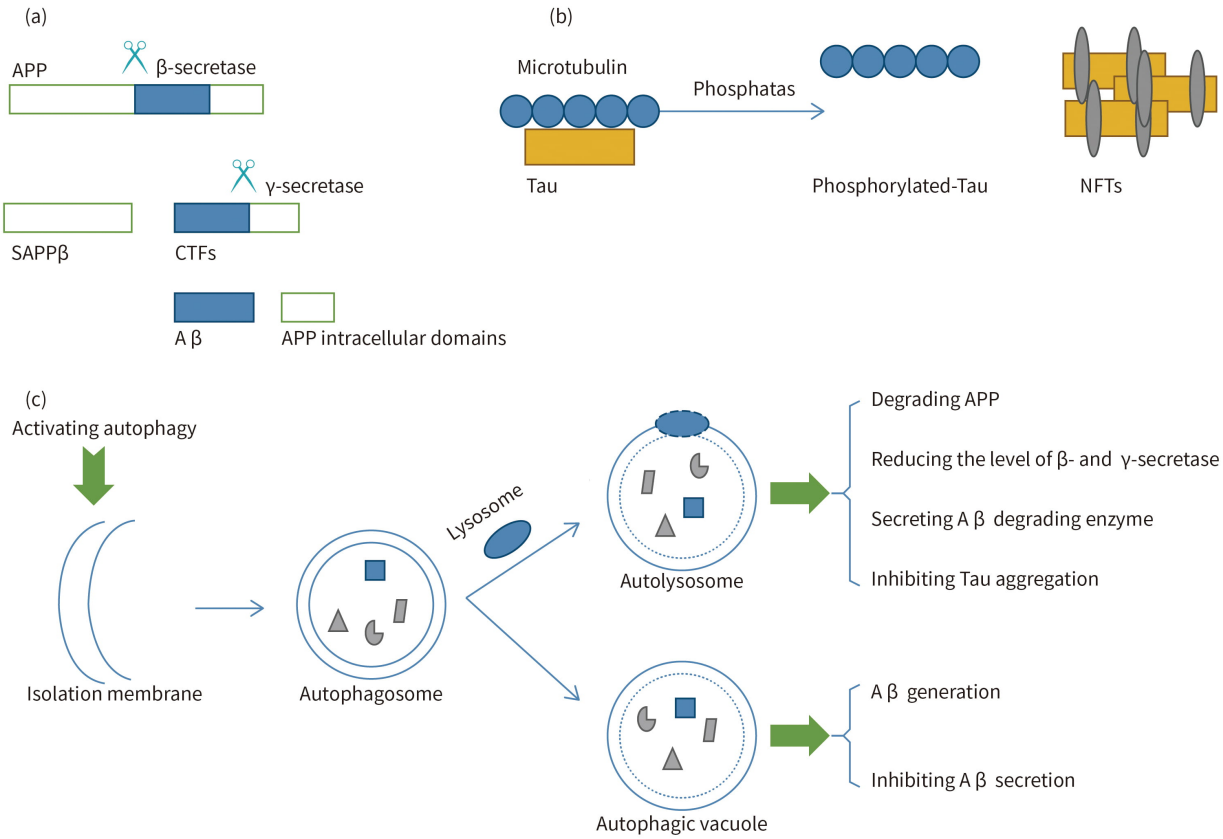

Fig. 2. Autophagy in AD Brain. (a) Aβ is derived from the metabolism of APP. APP is continuously cleaved by β- and γ- secretases and finally produces Aβ and APP intracellular domains. (b) The combination of normal Tau protein and tubulin promotes microtubule formation and maintains microtubule stability. When Tau is hyperphosphorylated, it loses its affinity for microtubules and aggregates itself to form NFTs. (c) Autophagy is an important degradation pathway in cells and participates in the metabolism of Aβ and Tau proteins. Autophagy can reduce Aβ production by degrading APP and reducing secretase levels, and can secrete Aβ degrading enzymes. Autophagy inhibits the accumulation of hyperphosphorylated Tau. However, autophagy defect may be the site of Aβ production.

to the phosphorylation of Beclin1 at Thr388, which promotes the dissociation of Beclin1 and Bcl to form the forementioned autophagy complex [18]. On the other hand, the Thr69, Ser70, and Ser87 sites of Bcl-2 can be phosphorylated by JNK-1, thereby dissociating from Beclin-1 to stimulate autophagy [19]. Calpain is activated by intracellular Ca^{2+}, resulting in an increase in adenylate cyclase activity and cyclic adenosine monophosphate (cAMP) content. High levels of cAMP activate phospholipase C-ε (PLC-ε) and Rap2B through the EPAC pathway, which is accompanied by the production of inositol triphosphate and subsequent inhibition of autophagy [20,21]. Besides, high intracellular Ca^{2+} level will also obstruct the recruitment of Rab7 to late endosomes, and further block the maturation process of autophagosomes and lysosomes fusion [22].

3. Autophagy in Alzheimer's disease brain

Previous reports have suggested that autophagy and autophagy disorders are related to a variety of neurodegenerative diseases, including AD, Parkinson's disease (PD), Huntington's disease (HD), etc. [23]. Since abnormal protein aggregation can lead to synaptic dysfunction and neuronal degeneration, clearing abnormal protein aggregation is an important target for the treatment of such diseases. Autophagy is the key way to clear the allosteric protein in neurons. Therefore, it is crucial to protein homeostasis and neuronal health.

Regarding the etiology and pathogenesis of AD, it has always been the focus in the field of neurology. At present, what has been generally recognized is the deposition of the toxic protein Aβ and the hyperphosphorylation of Tau protein. Aβ is the main component of senile plaques in the cerebral cortex, which can cause a series of pathological changes such as Tau hyperphosphorylation, insulin resistance, oxidative stress, synaptic loss, etc., leading to neuronal damage in AD [24]. The combination of normal Tau protein and tubulin promotes the formation of microtubules and maintains microtubule stability. When Tau is hyperphosphorylated, it loses its affinity to microtubules, destroys the microtubule system, affects axon transport and neuronal function, and then aggregates itself to form NFTs [25] (Fig. 2b).

As an important cellular metabolic activity, autophagy participates in the metabolism of Aβ and Tau protein (Fig. 2c). First, autophagy directly interferes with the production of Aβ. Aβ originates from the metabolism of amyloid-β protein precursor (AβPP) (Fig. 2a). AβPP is a type I transmembrane protein widely expressed in the central nervous system with a membrane receptor-like structure, which is thought to be closely linked with the occurrence and development of AD. It is cleaved by β-secretase to produce soluble AβPP β fragment and C-terminal fragment linked to the membrane. The latter continues to be cleaved by γ-secretase to produce Aβ and AβPP intracellular domains [26]. Autophagy can accelerate the degradation of AβPP, as well as the cleavage products including Aβ, thereby directly and indirectly reducing the accumulation of Aβ [27]. In the transgenic AD mouse model, activation of autophagy was also found to reduce the level of β -secretase [28]. Relatively, the experiment of Cai *et al*. [29] showed that inhibition of autophagy enhanced the activity of γ -secretase. This once again shows that autophagy activity is negatively correlated with Aβ production. However, new research evidence indicates that under pathological conditions, autophagy can also be the place where Aβ is produced. The failure of fusion with lysosomes to form autolysosomes leads to the accumulation of autophagosome-like structures, and autophagic vacuole accumulation may constitute a unique site for the production and/or accumulation of pathogenic Aβ [30]. There are obvious autophagy disorders in AD animal models and AD patients. In AD mouse hippocampal neurons, abnormal accumulation of immature autophagic vacuoles in axons has been observed before synapses and neurons are lost [31]. Nixon *et al*. [32] discovered immature autophagic vacuoles accumulated in the AD brain through immunogold labeling and electron microscopic. AβPP and active γ -secretase exist in autophagic vacuoles, suggesting that Aβ can be produced in immature autophagic vacuoles [33,34].

Secondly, autophagy increases the clearance of Aβ by secreting Aβ degrading enzymes. Insulin degrading enzyme (IDE) is an enzyme with substrate specificity that degrades both intracellular and extracellular Aβ [35]. IDE lacks a secretory signal sequence, and the study by Son *et al*. [36] found that in astrocytes, the secretion of IDE depends on the autophagy pathway.

At last, autophagy also plays a role in the secretion of Aβ. Atg is an important regulatory protein in the autophagy process and participates in all stages of autophagy. A recent study found that in Atg knockout mice, the secretion of Aβ was significantly inhibited, which resulted in the deposition of intracellular Aβ [37].

At the same time, the relationship between autophagy and Tau protein has also received attention. Normal autophagy plays an important role in the clearance of tau (Fig. 2c). Rapamycin is a specific mTOR inhibitor. When rapamycin is used to inhibit mTOR to activate autophagy, Tau phosphorylation level, Tau entanglement and the ability of insoluble Tau generation are all reduced [38]. Similarly, the mTOR-independent autophagy enhancer trehalose can also inhibit Tau protein aggregation [39]. Chen's team conducted a study on the effect of metformin on hyperphosphorylated Tau levels in mice with diabetic encephalopathy, and found that metformin enhanced autophagy activity, thereby improving tau pathology and cognitive impairment [40]. In addition, like Aβ peptide, tau secretion also depends on neuron autophagy. Kang *et al*. [41] confirmed that the secretion of both normal and hyperphosphorylated Tau is increased by autophagy activation, while beclin1 (an important protein involved in autophagy) knockout or autophagy inhibitors will down-regulate this secretion process.

4. Statins and autophagy

Statins, namely 3-hydroxy -3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are currently the most effective lipid-lowering drugs. In recent years, studies have found that statins also have various non-lipid lowering effects, including anti-senile dementia. Early use of statins significantly ameliorates the progression of mild to moderate AD patients [1]. Shakour *et al*. [42] showed the direct interaction between statins and Aβ through a computer study of molecular docking, which provided the basis for the neuroprotective effect of statins on AD. The mechanism of statins is to block the metabolic pathway of mevalonate in cells by competitively inhibiting HMG-CoA reductase, an endogenous cholesterol synthesis rate limiting enzyme, so as to reduce the intracellular cholesterol synthesis (Fig. 3). When the cholesterol content is too high, in order to maintain the balance, the excess cholesterol will be converted into oxidized sterol, while oxidized sterol will promote the production of Aβ and damage the neuronal function [43]. Several lipoproteins involved in cholesterol metabolism are also associated with amyloid deposition and AD pathogenesis. For example, apolipoprotein E is known to be a strong risk factor for AD [44]. Therefore, it can be inferred that statins can play a protective role on AD in a cholesterol-dependent manner.

In the meantime, we pay more attention to the direct regulation of statins on autophagy pathway (Fig. 4). A considerable number of reports have proved that statins can improve AD by inducing autophagy. However, it has also suggested that although autophagy initiation is boosted due to the suppression of mevalonate pathway by statins, the basic autophagy flux is also lessened due to the blocking of autophagy maturation [45].

4.1 Statins induce autophagy

Some experimental evidence confirms that the pleiotropic effect of statins is in connection with its ability to induce autophagy: Atorvastatin can reduce the levels of tumor necrosis factor (TNF)-α, interleukin (IL)-1β and

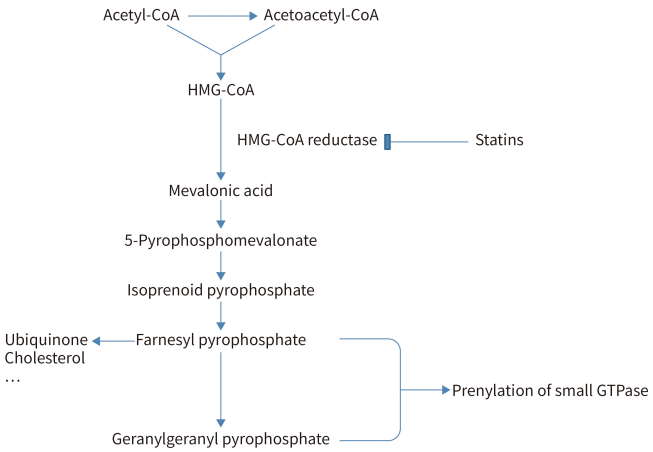

Fig. 3. A diagram of the mevalonate pathway. Mevalonate pathway uses acetyl CoA as raw materials to synthesize cholesterol, ubiquinone, isoprenoid and other compounds. Statins block this metabolic process by inhibiting HMG-CoA reductase. Reduction of isoprenoid synthesis interferes with post-translational modification of small GTPases.

nucleotide-binding oligomerization domain-like receptor family, pyrin domain-containing-3 (NLRP3) inflammasomes by enhancing autophagy [46]; Pravastatin's ability to delay cartilage degradation is related to improving autophagy impairment [47]; The beneficial effect of rosuvastatin on cerebral ischemia/reperfusion injury may be due to the up-regulation of autophagy [48]. Still, the more attractive topic is the potential molecular mechanism, which is also what we will discuss next.

In the mixed model of type 2 diabetes and AD, rosiglitazone, the peroxisome proliferator-activated receptor (PPARγ) activator, significantly increased IDE level, reduced Aβ accumulation and improved cognitive impairment [49]. In sporadic cerebral amyloid angiopathy mice treated with memantine, an increase in IDE expression was also found to reduce Aβ deposition [50]. These results indicate that IDE can regulate Aβ and have an important influence on the occurrence and progression of AD. Simvastatin can induce astrocytes to secrete IDE, and this effect is regulated based on autophagy pathway. Liver kinase B1 (LKB1) is the upstream signal of AMPK, and simvastatin can induce its phosphorylation at Ser428, thereby activating the AMPK/mTOR pathway, and then autophagy occurs, IDE is secreted. The above process improves AD progression [36,51]. Another relevant evidence is that the administration of simvastatin before hypoxic-ischemic brain damage blocked the depletion of Sirtuin1 (SIRT1), enhanced the autophagy reaction and exerted a neuroprotective effect [52]. SIRT1 is a histone deacetylase that depends on nicotinamide adenine dinucleotide (NAD+). It has a deacetylation effect on a variety of proteins participated in autophagy formation, which can increase autophagy and alleviate AD pathology [53,54]. The microtubule-associated light chain protein 3 (LC3) (a kind of autophagy marker protein) in the nucleus is deacetylated by SIRT1 and redistributed to cytoplasm, and then binds to the autophagosome membrane [55]. Forkhead transcription factor (FOXO1) deacetylated by SIRT1 enhances the transcription of Rab7, which is involved with the recruitment of endosomes and the maturation process of autophagosomes [56]. Furthermore, SIRT1 can also deacetylate transcription factor EB (TFEB) to regulate autophagy. TFEB is the main regulator of lysosomal biogenesis and can affect autophagy/lysosomal function [57,58]. Consistently, a decrease in SIRT1 expression level in SH-SY5Y cells exposed to Aβ1-42 was detected, while co-treatment with atorvastatin restored it to the control level, accompanied by an increase in LC3 expression [59].

In addition to the above, there are several reports that statins affect autophagy from multiple pathways. First of all, as an HMG-CoA reductase inhibitor, cerivastatin interferes with mevalonate metabolic pathway and synthesis of the geranylgeranyl pyrophosphate (GGPP), and low level GGPP can activate AMPK, leading to autophagy [60]. Secondly, the induction of autophagy by fluvastatin depends on P53. The effect of P53 on autophagy is associated with its localization in the cell. Nuclear P53 protein acts as a transcription factor to activate a series of autophagy-promoting genes, while cytoplasmic P53 inhibits autophagy. Fluvastatin increased the level of nuclear P53 protein to activate AMPK-mTOR-dependent autophagy [61]. In addition, lovastatin can induce the expression of P21 mRNA and protein by inhibiting histone deacetylase (HDAC) activity. Akt phosphorylates P21 at Thr145 and localizes it in the cytoplasm. Subsequently, endoplasmic reticulum stress and autophagy are induced [62,63]. To sum up, we can draw the hypothesis that statins can improve AD through cholesterol-dependent pathway and autophagy pathway, which is expected to provide a new inspiration for the treatment of AD.

4.2 Statins block autophagosome maturation

Nowadays, most researches on autophagy activity are carried out by measuring the level of autophagy marker. As an intermediate product in autophagy, the increase of autophagy markers may indicate that autophagy is induced, or it may be the result of inhibition of certain steps downstream of autophagy, which has brought great controversy to the regulation effect of statins on autophagy.

Mevalonate pathway is a metabolic pathway that uses acetyl coenzyme A as raw material to synthesize cholesterol, ubiquinone, isoprenoid and other compounds, among which isoprenoid is related to the post-translational modification of various proteins. Therefore, this pathway is crucial to the function and localization of Rho and Rab small GTPases (Fig. 3) [64]. Statins act on the early steps of mevalonate pathway, which not only reduces cholesterol level, but also affects the biosynthesis of isoprenoid, thus leading to the reduction of the prenylation level of

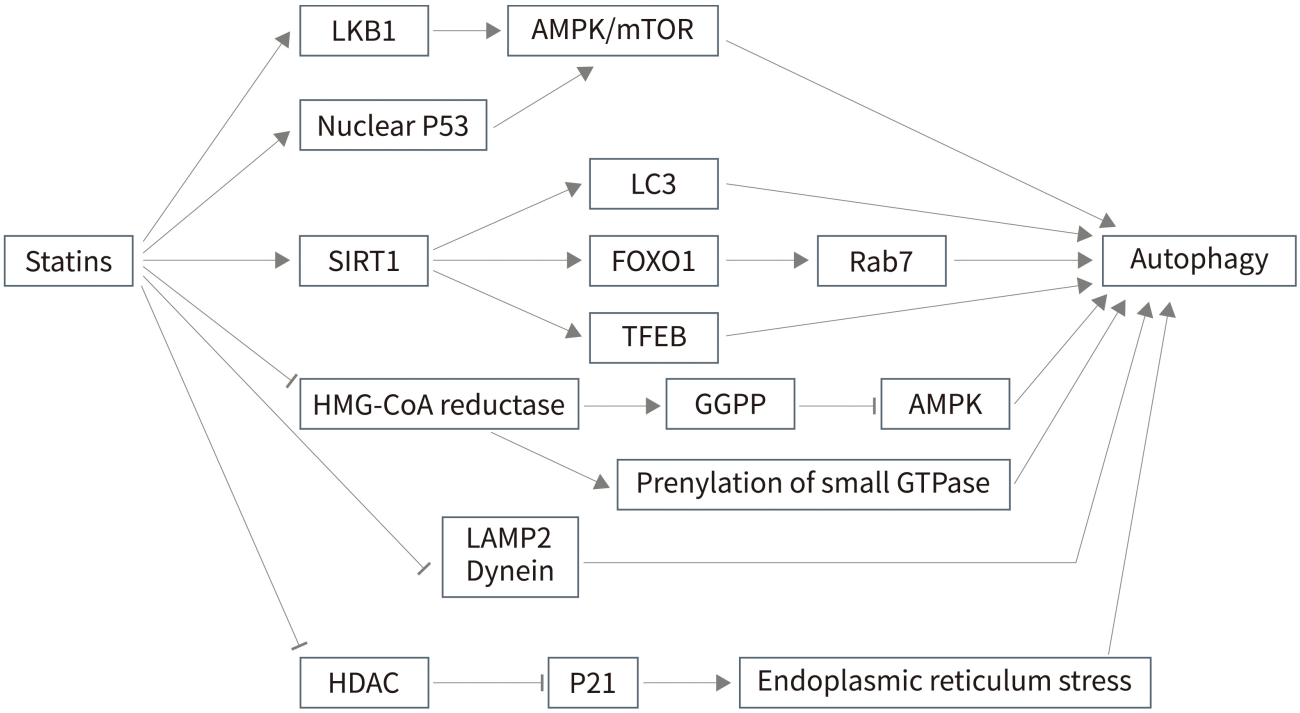

Fig. 4. Direct regulation of autophagy by statins. Statins have a two-way regulatory effect on autophagy. Statins can induce autophagy through SIRT1, P21, nuclear P53 and LKB1-AMPK/mTOR. At the same time, statins inhibit HMG-CoA reductase, leading to a decrease in GGPP synthesis. Low levels of GGPP can activate AMPK and promote autophagy. On the other hand, GGPP is related to the post-translational modification of small GTPases, and its reduced synthesis interferes with the prenylation of small GTPases, which in turn leads to autophagy dysfunction. Statins can also inhibit the levels of LAMP2 and dynein, destroying autophagy.

Rab11, a small GTP enzyme required in autophagy maturation process, and the final result is to reduce autophagy flux [65,66]. Consistently, simvastatin can also increase the level of Rho A without prenylation, which in turn activates Akt, causing autophagy block [67]. In an experiment conducted by Zhu *et al.* [68], lovastatin inhibited the levels of lysosomal-associated membrane protein 2 (LAMP2) and dynein. While LAMP2 and dynein, as important mediators in the fusion process of autophagosomes and lysosomes, the reduction of their levels helped to block autophagy, i.e., inhibited autophagy flux [68–70]. Qian *et al.* [71] observed similar results. Immunofluorescence staining of rat insulinoma cells treated with rosuvastatin for 24 hours showed that the staining amounts of LC3 and LAMP2 were significantly reduced. In addition, Qi *et al.* [72] research on amyotrophic lateral sclerosis (ALS), simvastatin can also interfere with autophagy flux by blocking GGPP synthesis.

5. Statins, autophagy and neurodegenerative diseases

Neurodegenerative diseases are a large group of diseases that cause dysfunction and death. Due to the complex etiology and pathogenesis, the treatment has always been a difficult problem. More and more evidences show that autophagy plays a role in neurodegenerative diseases [73]. We have discussed the role of autophagy in AD and the direct regulation of statins on autophagy pathway. The influence of statins on AD may also come from controlling inflammation and restoring autophagy destroyed by inflammation. Studies have shown that neuroinflammation also has correlation with AD pathology [74]. Moderate inflammation plays a protective role in the body. Astrocytes and microglia, as the main cell types of central nervous system inflammation, have the ability to swallow toxic products, release cytotoxic factors, and filter the extracellular environment [75]. Particularly, microglia can bind to soluble Aβ oligomers through cell surface receptors including CD36, CD14, Toll-like receptors (TLR2, TLR4, TLR6, and TLR9). These receptors are subsequently activated to promote the secretion of cytokines to initiate an inflammatory response. Activated microglia transport extracellular Aβ to the lysosomal pathway to be eliminated [76]. However, persistent inflammatory stimulation is associated with neurodegeneration. There is evidence that reactive glial cells are closely related to amyloid plaques and NFTs in AD brain [77]. Inflammatory cytokines secreted by microglia and astrocytes can increase the expression level of secreted enzymes, thereby promoting the transformation of APP into toxic Aβ [78–80]. Moreover, reactive astrocytes can directly express β-secretase and increase the production and accumulation of Aβ [81]. On the other hand, although the exact mechanism is still unclear, experiments

Table 1. The modulatory effects of statins on autophagy.

Year	Author	Stain	Effect on autophagy	Nervous system disease
2015	Son *et al*. [36]	Simvastatin	Activating autophagy by LKB1-AMPK-mTOR signaling pathway	Alzheimer's disease
2018	Liu *et al.* [48]	Rosuvastatin	Upregulating autophagy by increasing LC3 and Beclin1 levels	Cerebral ischemia/reperfusion injury
2020	Carloni *et al*. [52]	Simvastatin	Enhancing autophay by blocking the depletion of Sirtuin 1	Hypoxic-ischemic brain damage
2020	Celik *et al*. [59]	Atorvastatin	Promoting autophay by increasing the expression of Sirtuin 1	Alzheimer's disease
2012	Araki *et al*. [60]	Cerivastatin	Promoting autophay by AMPK-mTOR signaling pathway	-
2017	Yang *et al*. [61]	Fluvastatin	Promoting autophagy by increasing the expression of nuclear P53	-
2008	Lin *et al*. [62,63]	Lovastatin	Activating autophagy by inducing P21 expression and endoplasmic reticulum stress	-
2014	van der Burgh *et al*. [67]	Simvastatin	Reducing autophagy flux by disturbing prenylation of small GTPases	Neurodegeneration
2019	Zhu *et al*. [68–70]	Lovastatin	Reducing autophagy flux by inhibiting the level of LAMP2 and dynein	-
2019	Qian *et al.* [71]	Rosuvastatin	Reducing autophagy flux by inhibiting the level of LAMP2 and LC3	-
2019	Qi *et al*. [72]	Simvastatin	Reducing autophagy flux by blocking GGPP synthesis	Amyotrophic lateral sclerosis
2017	Qi *et al*. [90]	Rosuvastatin	Enhancing autophay by inhibiting mTOR and increasing Beclin1	Parkinson's disease
2018	Kang *et al*. [85]; McFarland *et al*. [93]	All	Repairing autophagy by inhibiting neuroinflammation	Neuroinflammation and neurodegeneration
2018	Zhang *et al*. [96]	Atorvastatin	Decreasing autophagy activity	Cerebral ischemia injury

LKB1, liver kinase B1; AMPK, adenylate activated protein kinas; mTOR, mammalian target of rapamycin; LC3, microtubule-associated light chain protein 3; SIRT1, Sirtuin 1; LAMP2, lysosomal-associated membrane protein 2; GGPP, geranylgeranyl pyrophosphate.

have confirmed that activation of microglia and release of pro-inflammatory factors will damage autophagy flux, which may be in connection with the decrease of LAMP2 expression [82]. The anti-inflammatory effects of statins are considered to be one of the possible mechanisms for their neuroprotective effects. In multiple neuroinflammation models, it has been confirmed that statins can reduce the activation of microglia and the release of various inflammatory factors [83–85].

We also pay attention to the relationship between statins, autophagy and other neurological diseases. PD is another most common neurodegenerative disease. Autopsy of PD patients provided evidence for the involvement of autophagy in the pathogenesis of PD. Abnormal autophagy structures were observed in substantia nigra neurons of PD patients [86]. The level of autophagy-related protein LAMP2 in peripheral blood of sporadic PD patients was also lower than that of healthy subjects [87]. In fact, autophagy has a bidirectional relationship with PD. PD-related genes are related to the regulation of various autophagy pathways, and their mutations can impair the autophagy initiation and autophagy fiux. In turn, autophagy defect makes the transcription and translation of genes and downstream signaling pathways or enzyme activities unregulated. Besides, blockade of autophagy increases the accumulation of pathological α-synuclein in the PD brain [88]. Previously, a large meta-analysis that included both case-control studies and cohort studies confirmed that the use of statins is associated with a reduction in the risk of PD [89]. However, there was no explanation for the possible mechanism. Kang's team used rotenone-induced SH-SY5Y cells to construct an *in vitro* model of PD, and observed rotenone enhanced mTOR expression, inhibited Beclin-1 and α-synuclein expression, and reduced cell viability by immunoblotting. Rosuvastatin treatment restored these changes, demonstrating that rosuvastatin exerted a neuroprotective role by enhancing autophagy [90]. A similar phenomenon also exists in HD. HD is resulted of protein misfolding caused by huntington gene mutation. Mutant huntington protein disrupts the transport of autophagosomes and the recognition of substrates [91]. Schultz *et al*. [92] conducted a clinical study to match carriers of aura HD mutations using statins with carriers who did not use statins. The follow-up results showed that statin use was related to the delayed onset age of HD. A study comparing the neuroprotective effects of various statins showed that all statins (atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin) decreased the formation of autophagic vacuoles in the *in vitro* models of lipopolysaccharide-induced effects in ALS [93]. Although the results of meta-analysis exhibited no significant correlation between statins and the incidence and progression of ALS [94,95]. In the ALS model, simvastatin administration led to the accumulation of autophagic vacuoles and the decrease of cell viability. Further investigation showed that this is due to the inhibition of GGPP synthesis and damage to autophagic flux

[72]. Zhang *et al*. [96] also found that the protective effect of atorvastatin on cerebral ischemia injury is related to reducing autophagy activity and relieving endoplasmic reticulum stress. Summing up, statins have fully demonstrated their potential in regulating autophagy, and this feature is of great significance in neurodegenerative diseases (Table 1, Ref. [36,48,52,59–63,67–72,85,90,93,96]). AD is one of the common neurodegenerative diseases. Although it still lacks more direct researches on the involvement of statins in the pathology of AD via autophagy pathway, we were able to speculate that statins regulating autophagy may become a target for AD therapy.

6. Summary

AD is one of the most important neurodegenerative diseases, which seriously affects people's life quality and adds to the social burden. Although the etiology of AD is still unclear, many factors, including environment, genes, poisoning, metabolic abnormalities, etc., are considered as risk factors for disease. With the deepening of research, the important role of autophagy in AD is gradually being realized. Autophagy not only participates in the production, secretion and clearance of Aβ peptide, but also affects the level of Tau phosphorylation. Therefore, therapy based on autophagy regulation provides a new direction for the treatment of AD. Existing researches have pointed out that statins can not only play a neuroprotective role by lowering cholesterol level, but also degrade Aβ peptide and reduce Tau protein phosphorylation level by inducing autophagy, thereby reducing AD risk, which may become a potential hope. However, there is still a lot of controversy on this point. Statins can regulate autophagy in two directions. Which one is the dominant position and what are the important influencing factors? These issues are still waiting for further discussion. In the future research, we need to pay more attention to the key molecules of autophagy and the fine regulation mechanism of statins in order to provide more valuable reference for the treatment of AD.

Author contributions

All authors contributed to the manuscript. XCZ had the idea for the article. Material preparation and analysis were performed by LL, WZD and TM. The first draft of the manuscript was written by LL and XCZ critically revised the work. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

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