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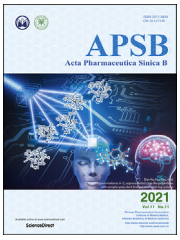

REVIEW

Pharmacological insights into autophagy modulation in autoimmune diseases

Ming-Yue Wu[a], Er-Jin Wang[a], Du Feng[b], Min Li[c], Richard D. Ye[d], Jia-Hong Lu[a,*]

[a]*State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Macau 9999078, China*
[b]*Key Laboratory of Protein Modification and Degradation, State Key Laboratory of Respiratory Disease, College of Basic Medical Science, Guangzhou Medical University, Guangzhou 510000, China*
[c]*School of Pharmaceutical Sciences, National and Local United Engineering Lab of Druggability and New Drugs Evaluation, Guangdong Provincial Key Laboratory of New Drug Design and Evaluation, Sun Yat-sen University, Guangzhou 510000, China*
[d]*Kobilka Institute of Innovative Drug Discovery, School of Life and Health Sciences, the Chinese University of Hong Kong, Shenzhen 518000, China*

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Autophagy inducer;
Autophagy inhibitor

Abstract As a cellular bulk degradation and survival mechanism, autophagy is implicated in diverse biological processes. Genome-wide association studies have revealed the link between autophagy gene polymorphisms and susceptibility of autoimmune diseases including systemic lupus erythematosus (SLE) and inflammatory bowel disease (IBD), indicating that autophagy dysregulation may be involved in the development of autoimmune diseases. A series of autophagy modulators have displayed protective effects on autoimmune disease models, highlighting the emerging role of autophagy modulators in treating autoimmune diseases. This review explores the roles of autophagy in the autoimmune diseases, with emphasis on four major autoimmune diseases [SLE, rheumatoid arthritis (RA), IBD, and experimental autoimmune encephalomyelitis (EAE)]. More importantly, the therapeutic potentials of small molecular autophagy modulators (including autophagy inducers and inhibitors) on autoimmune diseases are comprehensively analyzed.

*Corresponding author.
E-mail address: jiahonglu@um.edu.mo (Jia-Hong Lu).

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1. Introduction

Autophagy is a vital, conserved, and life-sustaining mechanism by which cytoplasmic cargo is delivered to lysosomes for degradation and by which cellular homeostasis is maintained[1]. There are at least three types of autophagy (macroautophagy, microautophagy, and chaperone-mediated autophagy), but macroautophagy (hereafter referred to as autophagy) is the major autophagic degradation form governing organelle quality control and cellular homeostasis in eukaryotic cells. In the process of autophagy, cytosolic components, including toxic protein aggregates and superfluous or damaged organelles, are sequestered into isolated double membrane and delivered to lysosomes for degradation[2]. Dysfunction of autophagy is involved in various kinds of diseases, including cancer, neurodegenerative diseases, infectious diseases, and metabolic diseases[3].

Emerging evidence in recent years has revealed that autophagy intrinsically regulates the immune system function[4]. For example, autophagy regulates polarization of macrophages[5,6], regulates and be regulated by a wide range of inflammatory cytokines[7], controls T cell function[8], and modulates antigen presentation[9]. In the innate immune system, autophagy not only protects cells against invading microbial pathogens[10], but also regulates stress-induce immune cell dysfunction, such as regulation of oxidative stress-induced T cell dysfunction[11], modulation of anoxic stress-induced tumor infiltrating lymphocytes activation[12], regulation of endoplasmic reticulum (ER) stress-induced Ig production[12,13], and modulation of LPS-triggered inflammatory responses[14]. Autophagy-related genes have been implicated in tissue-destructive inflammation and in the pathogenesis of several autoimmune and inflammatory disorders, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), inflammatory bowel disease (IBD), pancreatitis, and cancer[15–18]. Interestingly, SLE, RA, and IBD all belong to autoimmune diseases, indicating that autophagy may play critical role in autoimmune regulation. In fact, a number of autophagy activators and inhibitors have been applied for modulation of autoimmune diseases, making pharmacological autophagy modulation a potentially potent therapeutic strategy for treating these diseases[19].

However, there remain many unanswered questions. For example, whether autophagy regulates autoimmune response through a universal regulatory mechanism? Whether autophagy functions differently in different autoimmune diseases? Whether autophagy modulation is a promising approach for autoimmune diseases treatment? These questions are discussed in this review.

2. Molecular mechanism of autophagy

Autophagy proceeds in five main steps: (1) autophagy initiation, (2) phagophore formation, (3) phagophore expansion, (4) fusion with lysosome, and (5) degradation by lysosome (Fig. 1). Firstly, the complex including Unc-51 like autophagy activating kinase 1 (ULK1), FAK family kinase-interacting protein of 200 kDa (FIP200), autophagy-related protein 13 (ATG13), and autophagy-related protein 101 (ATG101), is the major player to regulate the autophagy initiation[20]. ULK1 kinase can be activated by AMP-activated protein kinase (AMPK) under glucose starvation condition[21] and by inhibition of mammalian target of rapamycin complex 1 (mTOR1) under amino acid deficiency condition to induce autophagy[22]. After autophagy induction, ATG9-containing vesicles are recruited by the ULK1 complex to the autophagosome to facilitate membrane delivery[23]. Subsequently, the class III phosphatidylinositol 3-kinase (PI3KC3) complex [vacuolar protein sorting 34 (VPS34), vacuolar protein sorting 15 (VPS15), Beclin-1 (BECN1), autophagy-related protein 14 (ATG14), and nuclear receptor binding factor 2 (NRBF2)] is activated to generate phosphatidylinositol 3-phosphate [PI(3)P] on the phagophore. The PI(3)P effectors, such as FYVE-containing protein 1 (DFCP1) and WD-repeat protein that interact with PtdIns (WIPI) proteins, are recruited to phagophore to induce autophagosome formation[24]. Then, two ubiquitin-like systems, the ATG12−ATG5−autophagy-related 16 like 1 (ATG16L1) complex and the microtubule-associated protein light chain 3 (LC3) complex, are recruited to drive autophagosome membrane elongation and vesicle expansion[25]. Besides autophagosome membrane elongation, LC3-II is also involved in autophagosome closure. Finally, the autophagosomes fuses with the lysosome *via* soluble *N*-ethylmaleimide-sensitive-factor attachment protein receptor (SNARE) for degradation[26].

3. Overview of autoimmune diseases

Autoimmunity is defined as immune responses that attack an organism's own cells or tissues[27,28]. In the development of autoimmune diseases, genetic predisposition or environmental stimulus break immune tolerance, resulting in autoantibodies and self-reactive lymphocytes formation which ultimately cause tissue damage[28]. Autoimmunity-derived disease is one of the major health problems in the world, and autoimmunity has been viewed as an ever endless world[29]. There are nearly 100 distinct autoimmune diseases based on different syndromes; typical examples

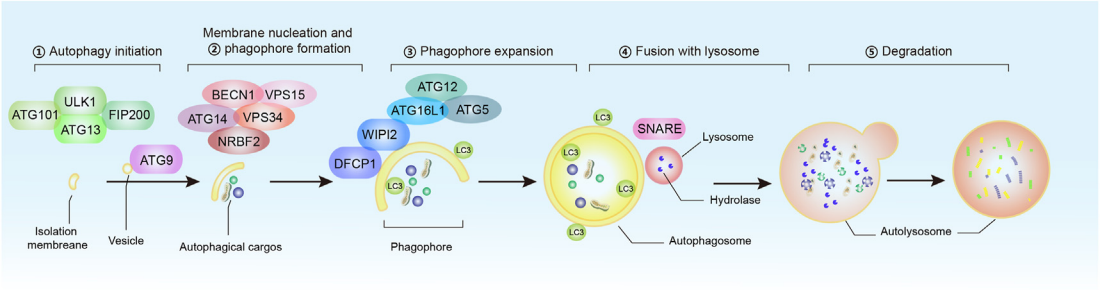

Figure 1 Process of autophagy. Autophagy is initiated and proceeds by diverse autophagy-related proteins to deliver different cargos to lysosomes for degradation.

of autoimmune diseases include multiple sclerosis (MS), type 1 diabetes (T1D), RA, and SLE.

Multiple genes have been reported to be associated with autoimmune diseases. Monogenic mutations of *AIRE, TNFRSF6, FOXP3*, and *CD25* have been found to induce autoimmune diseases. These genes are mostly associated with lymphocyte development or the functional regulation of lymphocytes, impairing T cell selection in the thymus and periphery tolerance[30−33]. In fact, most autoimmune diseases involve multiple genetic factors. The major histocompatibility complex (MHC) is the strongest gene complex associated with human autoimmunity[34,35]. For example, genetic variants *HLA-II-DQ2* and *HLA-II-DQ8* have been found in T1D and coeliac disease (CeD), *HLA-II-DR3*, *HLA-II-DR2*, and *HLA-II-DR8* have been found in SLE, while *HLA-II-DR4* and *HLA-III-TNF* have been identified in RA[35]. Other genes such as protein tyrosine phosphatase non-receptor type 22 (*PTPN22*), *IRF5-TNPO3*, and *BACH2* have all been found to be associated with autoimmunity[28]. Environmental influence is a risk factor for the induction of autoimmune diseases. Nutrition, microbiota, invading pathogens, pharmacological agents, hormones, ultraviolet light, silica solvents, heavy metals, vaccines, and collagens implants are all potential stimuli that can elicit autoimmune responses[28,36,37]. For example, Epstein−Barr virus (EBV) has been identified as a cofactor in numerous autoimmune diseases, such as SLE, RA, and MS[38,39]. Excess intake of dietary iodine increases the incidence of autoimmune thyroid diseases (AITD)[40], and smoking is a well-recognized risk factor for RA and SLE[41,42].

As the precise etiology of autoimmune diseases is poorly understood, treatment is a challenge for clinicians. Currently, the basic therapeutic approach is to block the inflammatory pathway, such as by administration of agents to inhibit tumor necrosis factor (TNF-α), interleukin 6 (IL-6), or IL-12[43−45]. Other immunotherapies, such as stem cell therapies, have been introduced[42]. However, none of these methods can cure the autoimmune diseases, and not all have been proven effective in humans. Modifying host immune system and identification of novel means of effective modulation are crucial for improving therapy of autoimmune diseases.

4. Autophagy in autoimmune diseases

Evidence from genome-wide association studies (GWAS) study and autophagy-defective animal models reveals autophagy dysregulation is associated with a number of autoimmune diseases, such as SLE, Crohn's disease (CD), RA, MS, and T1D[19]. Clarifying the roles of autophagy in these different autoimmune diseases can consolidate our understanding and perhaps suggest promising pathway for future research (Fig. 2).

4.1. SLE

SLE is an autoimmune disease characterized by production of large amounts of antibodies that act against self-antigens, especially double-stranded DNA (dsDNA), phospholipids, and small nuclear RNA-binding proteins. Various organs, such as joints, skin, kidneys, blood cells, brain, heart, and lungs can be affected[46−48]. Polymorphisms of several autophagy-related genes have been associated with SLE. Five SLE-related single-nucleotide polymorphisms (SNPs) have been found near to or in the *ATG5* gene *locus*[49,50]. In 2010, phosphatidylinositol 3-kinase catalytic subunit type 3 (*PIK3C3*) promoter variant (rs3813065 C) was reported to be strongly associated with the presence of SLE in African−American patients[51]. In the following years, several autophagic proteins, including BECN1, ATG5, and ATG7 were observed to be required in LC3-associated phagocytosis (LAP) to facilitate apoptotic cell clearance which inhibits the development of autoimmunity[52]. Precise analysis revealed that deficiency of LAP-related proteins, including BECN1, ATG7, ATG3, ATG5, ATG12, ATG16L1, and Run domain BECN1-interacting and cysteine-rich domain-containing protein (RUBICON), accelerated the development of SLE-like disease condition in mice. However, mice lacking ULK1 and FIP200 that are not required for LAP in myeloid cells, did not show SLE-like disease[18]. Therefore, whether LAP is a critical factor to connect autophagy and SLE remains a topic worth intensive studying. In the clinical study, LAP levels were found to be elevated in blood and liver monocytes from patients with fibrosis and cirrhosis, two conditions often accompanying autoimmune diseases, because SLE-induced chronic liver damage may eventually develop into liver cirrhosis. It appears possible that LAP activation might protect against chronic inflammation-induced liver damage[53].

Mitophagy, a selective form of autophagy to degrade damaged mitochondria, is also an essential factor in SLE pathogenesis. Mitochondrial homeostasis is fundamental to maintaining immune system balance. In the innate immune system, diverse damage-associated molecular patterns (DAMPs), such as phospholipid cardiolipin, *N*-formyl peptides, ATP, and mitochondrial DNA (mtDNA) which released from damaged mitochondria, were threaten to activate the immune response[54] and induce autoimmune diseases[55,56]. In addition, mitochondrial reactive oxygen species (ROS) is able to drive spontaneous neutrophil extracellular traps (NETs) formation, which is implicated in the SLE pathogenesis[57]. Mitophagy serves as a protective mechanism to keep mitochondria homeostasis and is proposed to be involved in autoimmune diseases, such as SLE. In fact, mitophagy levels were found to be suppressed in T cells in SLE patients[58]. In addition, in mitophagy-deficient mice lacking PTEN-induced kinase 1 (*PINK1*) or Parkin RBR E3 ubiquitin protein ligase (*PRKN*) after exhaustive exercise, released mtDNA was able to activate the stimulator of interferon genes protein (STING)-mediated DNA sensing pathway, resulting in higher levels of type I interferon (IFN), a potential enhancer of autoimmunity, compared to wild-type mice[59]. Interestingly, deletion of immune-related GTPase family M protein (IRGM), a protein linking autoimmunity to autophagy, displayed defective mitophagy flux and resulted in overproduced DAMPs. These DAMPs stimulated DNA/RNA sensing-signaling to activate IFN expression and its responses[60]. Thus, promoting mitophagy emerges as a possible way to inhibit autoimmune diseases, although the mechanism remains unclear[61]. Collectively, LAP and mitophagy are two vital cellular processes to limit auto-antigen production.

Innate inflammatory pathways that are regulated by autophagy may aggravate SLE. Retinoic acid-inducible gene 1 (RIG-1)-mitochondrial antiviral signaling protein (MAVS) RNA-sensing and cyclic GMP-AMP (cGAS)−STING DNA-sensing pathways are two innate immune responses to defend against pathogenic viral genomes or endogenous damaged DNA[62]. In the activated state, sensors stimulate multiple signaling cascades for production of type I IFNs and proinflammatory cytokines to eliminate threats. Notably, excessive activation of cGAS−STING pathway is implicated in auto-inflammatory and autoimmune diseases, such as Aicardi−Goutiéres syndrome and SLE[63−65]. Accumulating evidence suggested that RIG-1 or the STING sensing pathway-induced

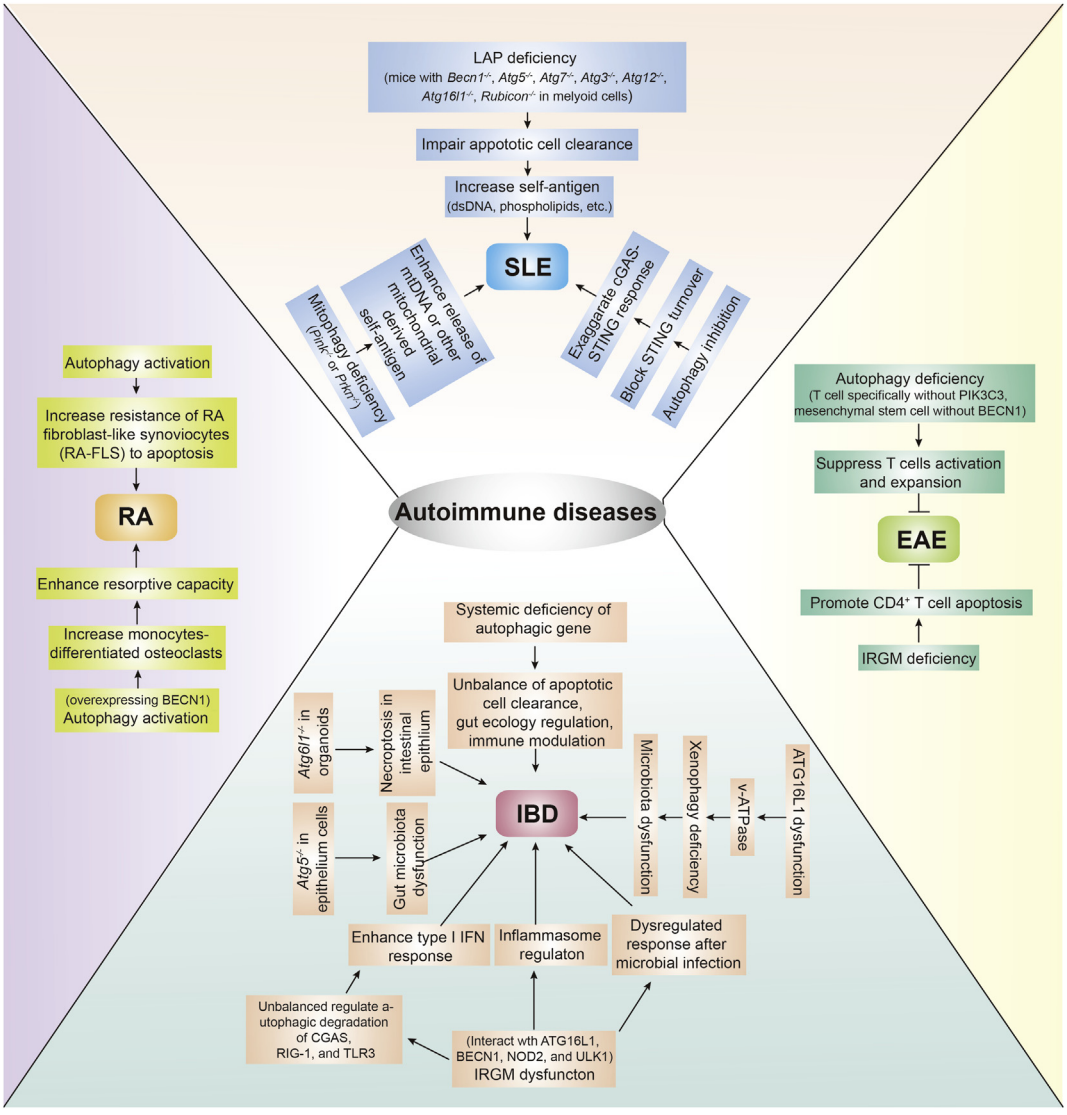

Figure 2 Autophagy regulation in autoimmune diseases. Autophagy displays differently in different autoimmune diseases. In SLE or IBD, autophagy enhancement contributes to ameliorating syndrome *via* reducing self-antigens production, cell-specific function regulation, and inflammatory pathway regulation. However, autophagy activation can aggravate RA disease syndrome by inhibiting RA-FLS apoptosis and increasing osteoclast differentiation. Inhibition of autophagy attenuates EAE by prohibiting T cell proliferation and activation.

sustained IFN response is detrimental to autoimmune diseases therapy[66,67]. Interestingly, autophagy is able to regulate STING turnover *via* phosphorylating p62 by TANK-binding kinase 1 (TBK1) and attenuate cGAS−STING signaling[68]. Evidence indicates that STING can be degraded *via* autophagy pathway. Considering STING is closely associated with ER[69], and it's a primordial function of cGAS−STING pathway to induce autophagy in a manner independent of TBK1 or IFN induction[70], It is highly possible that autophagy regulates autoimmune response through the STING pathway by promoting STING turnover.

4.2. *IBD*

IBD is a complicated idiopathic inflammatory disease that can be triggered by genetic or environmental stimuli. It is classified into CD and ulcerative colitis (UC) based on the region of the gastrointestinal (GI) tract that is inflamed. UC is confined to the inflammation occurring at the mucosal surface, while CD involves transmural inflammation from mouth to anus[71]. It is widely accepted that the pathogenesis of IBD results from the loss of immune tolerance to intestinal antigens due to genetic or environmental factors. Several studies also defined IBD as autoinflammatory syndrome of the gastrointestinal tract considering the limited observations of self-antigens[72].

Since genetic polymorphisms in ATG16L1 have been identified as a strong risk for developing CD[73], roles of autophagy in the development of IBD have been extensive studied. Different autophagy-related genes such as *ULK1*[74], *ATG4B*[73], *PIK3C3*[75], and *NRBF2*[76], have been revealed to be implicated in IBD. Studies have determined that autophagy is essential for intestinal homeostasis maintenance, gut ecology regulation, immune modulation, and anti-microbial protection[77]. However, the questions of what are the critical factors associating autophagy and IBD have not been answered.

It should be noted that in zebrafish, *pik3c3* mutants showed IBD-like features with high inflammatory response, and cell

junctions in intestinal epithelial cells were disrupted[75]. However, gut microorganisms seem unnecessary for these IBD-like features[75], indicating that gut microbiome dysfunction may not be a critical pathogenic element. In our recent study, NRBF2, as a component of the PI3KC3 complex, has been revealed to be involved in the IBD regulation *via* modulating apoptotic cell clearance[76], initiating a discussion as to whether apoptotic cell-derived factors are vital targets for IBD therapy and whether PI3KC3-regulated apoptotic cell clearance is one of the critically affected factors involved in autoimmune diseases.

Autophagy-related inflammatory signaling regulation is another vital process implicated in IBD. Myeloid deficiency in *ULK1*, a LAP-unnecessary autophagic gene, is not necessary in SLE[18], but is involved in IBD[78]. These results suggest that ULK1 perhaps regulates a LAP-independent immune response, which contributes to the IBD pathogenesis. Interestingly, IRGM was able to interact and stabilize autophagic proteins, such as ATG16L1, BECN1, nucleotide-binding oligomerization domain-containing protein 2 (NOD2), and ULK1, to govern the autophagy-dependent microbial infection defense and regulate inflammatory response, Interestingly, all the genes that encode the above mentioned proteins were identified in IBD genetic polymorphism study[73,75,78]. These findings suggested that autophagy can be involved in IBD *via* the IRGM-associated inflammatory pathway. IRGM is closely associated with auto-inflammatory or autoimmune diseases. IRGM deficiency has been found to be involved in ankylosing spondylitis[79], AITD[80], CD[81], experimental autoimmune encephalomyelitis (EAE)[82], and hepatic steatosis[83]. Genetically *Irgm* knocked-out mice show hallmarks of Sjogren's syndrome, a kind of autoimmune diseases[84]. Although the core mechanism by which IRGM acts in innate immune systems remains undetermined, IRGM has been involved in distinct inflammatory responses. For instance, IRGM is involved in the autophagic degradation of inflammasomes[85]. Recently, a study has found that IRGM may mediate autoimmune diseases *via* regulating autophagic degradation of cGAS, RIG-1, and toll-like receptor 3 (TLR3), resulting in the regulation of type I IFN response[60]. This is the beginning of uncovering the precise mechanism by which IRGM modulates the autoimmune system and autophagy.

Xenophagy and autophagy-regulated epithelium cell function are two factors assumed to be involved in IBD pathogenesis. Autophagy induced by invading pathogens is termed xenophagy[86]. As microbiota dysfunction is a critical part of the pathogenesis of IBD, xenophagy is regarded as an essential connection between autophagy and IBD. Studies have found that ATG16L1 is linked with V-ATPase and critically mediates xenophagy[87], and ULK1 kinase also directly phosphorylates ATG16L1 to drive xenophagy[88]. Therefore, xenophagy is a potential mechanism to regulate IBD pathogenesis. However, there is still very limited evidence that directly supports the roles of xenophagy in IBD. Intestinal epithelium function is another hotspot in recent studies of IBD pathogenesis. Epithelium not only acts as a physical barrier to pathogens, but also communicates with other immune cells for immune regulation[86]. Previous studies have found that *Atg5* deficiency in epithelium cells alters the composition of the gut microbiota. Transcriptome analysis has showed that two IBD-associated factors, nuclear receptor ROR-gamma (RORC) and T-box transcription factor 21 (TBX21), were upregulated in mice with impaired autophagy in intestinal epithelial cells[89]. In addition, *pik3c3* mutation in zebrafish displayed disrupted cell-junctions in intestinal epithelial cells[75], *Atg4b*$^{-/-}$ mice presented abnormal Paneth cells[90] and intestinal organoids lacking ATG16L1 elevated necroptosis in intestinal epithelium[77]. The current evidence revealed that defects of xenophagy or autophagy in epithelial cells may contribute to the pathogenesis of IBD.

4.3. RA

RA is a chronic autoimmune disease characterized by synovial inflammation and bone loss. Dysfunction of immune cells and RA fibroblast-like synoviocytes (RA-FLS) have been identified as players in RA[91]. CD4$^+$ T cells, B cells, macrophages, and RA-FLS infiltrate the synovium, resulting in destroyed articular structure and hyperplasia of the intimal lining[91].

In the pathogenesis of RA, RA-FLS is a key player since it is a tissue-specific cell and is capable of producing local inflammatory cytokines and enzymes. Inhibition of aggressive RA-FLS formation or induction of RA-FLS apoptosis is one of the therapeutic approaches for treating RA. Interestingly, previous studies have elucidated that autophagy is able to regulate RA-FLS survival. Autophagy activation enhanced the resistance of RA-FLS to apoptosis *via* releasing ER stress and attenuating mitochondria dysfunction[92,93].

Another vital factor affecting development of RA is the differentiation of osteoclasts. Accumulation of osteoclast precursors and mature osteoclasts at inflammatory sites contributes to articular erosion and systemic osteoporosis[94]. In the previous study, autophagy is also able to mediate osteoclast-mediated bone destruction in RA. Autophagy activation by overexpressing BECN1 increased monocyte-differentiated osteoclasts and enhanced resorptive capacity. In contrast, genetic and pharmacologic inhibition of autophagy reduced bone resorption and protected mice from TNF-α-induced bone erosion, proteoglycan loss and chondrocyte death[17].

Unlike beneficial roles of autophagy in immune cell regulation in LAP and IBD, autophagy regulation in RA seems to be controversial. Autophagy activation drives RA development, which elicits discussions about the roles of autophagy in different cell types and auto-immune diseases.

4.4. EAE

EAE is a widely used mouse model for multiple sclerosis study. EAE is typically triggered by activated T cells migration into the central nervous system (CNS), and displays robust inflammatory response after immunization of susceptible mice with myelin-associated proteins[95]. Although multiple innate immune cell types are involved during EAE, autophagy has been mostly studied in T cell differentiation and surviving in the EAE models. *Atg5*-deficient T lymphocytes dramatically increased dead CD8$^+$ T cells in periphery. In addition, CD4$^+$ and CD8$^+$ T cells failed to undergo efficient proliferation while T cell receptor (TCR) activation after knocking out *Atg5*[96]. These results suggested that autophagy is necessary in the adaptive immune response. One successful therapeutic strategy for EAE is silencing over-activated T cells by either inducing T cell apoptosis or blocking T cell activation, indicating autophagy inhibition is beneficial for EAE.

One study has revealed that *Pik3c3* deficiency contributes to EAE resistance in a mouse model[97]. The study established *Pik3c3*-deficient T cells, and found that these cells failed to differentiate into T helper 1 cells, and the mice without *Pik3c3* in T cells cannot mount autoreactive T cell response in experimental autoimmune EAE. Further, they found that mice with *Pik3c3*-deficient T cells exhibited impaired metabolism and lower levels

of active mitochondria. Researchers have also found *Becn1*-deficiency and pharmacological inhibition of autophagy in mesenchymal stem cells (MSC) suppressed $CD4^+$ T cells activation and expansion in EAE[98]. Moreover, deficiency of *Irgm* was reported to suppress EAE by promoting apoptosis of activated $CD4^+$ T cells[82]. These results indicate that inhibiting autophagy is beneficial for therapy of EAE, whose pathogenesis is guided by T cell dysfunction. There is less evidence confirming whether over-reacted autophagy can exaggerate EAE in these studies; however, autophagy inducers, such as rapamycin and spermidine, have been proven to inhibit EAE development[99,100].

Taken together, in the innate immune system, autophagy may exert a general inhibitory effect of immune response to ensure the accurate control of immune responses, at least partially by regulating inflammasome and DNA sensing pathway *via* degrading the functional proteins. Thus, the autoimmune diseases with over-activated inflammatory response can possibly be regulated by autophagy induction. However, autophagy as a cytoprotective mechanism enhances cellular resistance to cell death, by which to prohibit the death of over reacted lymphocytes or RA-FLS in EAE and RA, may result in enhanced autoimmune responses. Moreover, autophagy functions quite differently in various cell types and results in distinct influences in autoimmune diseases. For examples, mitophagy, xenophagy, and LAP are selective autophagic ways to degrade potential antigens that may induce autoimmune response in IBD and SLE. While mitophagy and xenophagy are present in all the cell types, LAP is limited to phagocytes. Therefore, precise understanding of autoimmune disease pathogenesis is important for utilization of autophagy regulator in therapeutic strategy. Tissue- or cell-specific autophagy function may be a pivotal topic for discussion in the future work for autoimmune study.

5. Therapeutic potential of autophagy regulators in autoimmune diseases

Although novel therapeutic strategies such as the use of anti-TNF-α and cytokines inhibitors are being developed, application of immunosuppressors to suppress the systemic immune system is still the most common approach for autoimmune diseases treatment[101]. However, the adverse effects of immunosuppressors limit their long-time administration. There is an urgent need for safe drugs that can be used long-term. Exploring novel therapeutic strategies is an important avenue for developing these drugs. Autophagy dysregulation, as a common biological event in the development of autoimmune diseases, has triggered interests in testing small molecule autophagy regulators in the treatment of autoimmune diseases. A wide spectrum of small molecule autophagy regulators have been identified and tested in various disease models. Several autophagy inducers and inhibitors have already been applied for autoimmune disease therapies in multiple models (Fig. 3 and Table 1[2,100,102–135]). Autophagy inducers, such as rapamycin, spermidine, and vitamin D, and autophagy inhibitors, such as chloroquine, have been used for the regulation of diverse autoimmune diseases. In addition, certain drugs used for autoimmune therapy have also been found to be associated with autophagy. For example, the anti-inflammatory drug, glucocorticoids, has been found to initiate autophagy[136].

5.1. *Autophagy inducers*

Among the positive autophagy regulators used for autoimmune modulation, two categories are noteworthy. One is mTOR pathway inhibitors; the other one is histone deacetylase inhibitors.

mTOR is a master regulator of cell growth and proliferation[137]. Genetic or pharmacologic inhibition of mTOR has been demonstrated for autophagy induction[138,139]. Inhibition of mTORC1 can directly activate ULK1 activity to induce autophagy[140], and mTORC2 inhibition indirectly allows forkhead box O3a (FOXO3A) nuclear translocation to accelerate autophagic vesicles formation[141]. The mTOR pathway also plays regulatory roles in the immune system, especially in mTOR-modulated T cell development and differentiation[142]. Therefore, mTOR is a critical regulator both in autophagy and the immune system. In fact, rapamycin and its analog, as notable mTORC1 pathway inhibitors, are accepted as promising immunosuppressants because of their anti-proliferative effects on immune cells and their ability to induce Treg differentiation[143–146]. In fact, these drugs have been utilized in different autoimmune diseases, such as allergic encephalomyelitis, adjuvant arthritis, and the humoral (IgE) immune response. Extensively, rapamycin administration blocks T cell activation in SLE patients and show obvious therapeutic efficacy[147–149]. Rapamycin-mediated mTORC1 pathway inhibition regulates lineage specification in the T cell compartment, which has been regarded as target for autoimmune diseases treatment[150,151]. As autophagy and immune system regulation can be regulated in parallel by mTOR, whether the rapamycin-induced immunosuppression effects are, to some extent, dependent on autophagy is still unclear. Assessing therapeutic effects of rapamycin on autoimmune disease models in autophagy deficiency condition may help to answer the question.

Histone deacetylase inhibitors (HDACIs) are repeatedly reported to activate autophagy in different cellular and animal models[152–154]. At present, the molecular mechanism underlying HDACIs-induced autophagy is unclear, but several studies suggested it is potentially associated with the mTORC1 pathway and FOXO-dependent pathway[152,155,156]. In addition, many HDACIs have been observed to modulate the autoimmune response and been applied in treating different autoimmune diseases. Trichostatin A (TSA) was suggested to ameliorate EAE and suppress collagen antibody-induced arthritis in animal models[122,123]. Valproic acid treatment attenuated inflammation in experimental autoimmune neuritis (EAN) and EAE[126,127]. Vorinostat treatment ameliorated EAE[124]. These studies explain that the HDACIs were able to upregulate Treg cells, suppress dendritic functions and diminish lymphoproliferation. However, since molecular functions of histone modification are complicated, it's difficult to dissect how HDACIs regulate autoimmune diseases. Whether autophagy functions as a strong mediator in the connections between HDACIs and autoimmune diseases can be examined in advanced studies.

Other autophagy inducers, such as spermidine and vitamin D, have also been implicated in the regulations of autoimmune diseases. Spermidine is a kind of polyamines that exists in all mammalian cells. Administration of spermidine has been demonstrated to extend the lifespan in diverse animals and cells *via* inducing autophagy[157]. In aging yeast, spermidine administration triggered deacetylation of histone H3, resulting in autophagy induction[157,158]. In recent years, people have found that spermidine can affect autoimmune diseases[100,159,160]. Spermidine administration alleviated severity of EAE *via* inducing inhibitory macrophages[100,160]. Most recently, a novel study found that spermidine can also elicit metabolic fitness of dendritic cells (DC) and mediate the autoimmune response[159]. Vitamin D (VD) is a precursor of a multifunctional hormone, the major types of which are

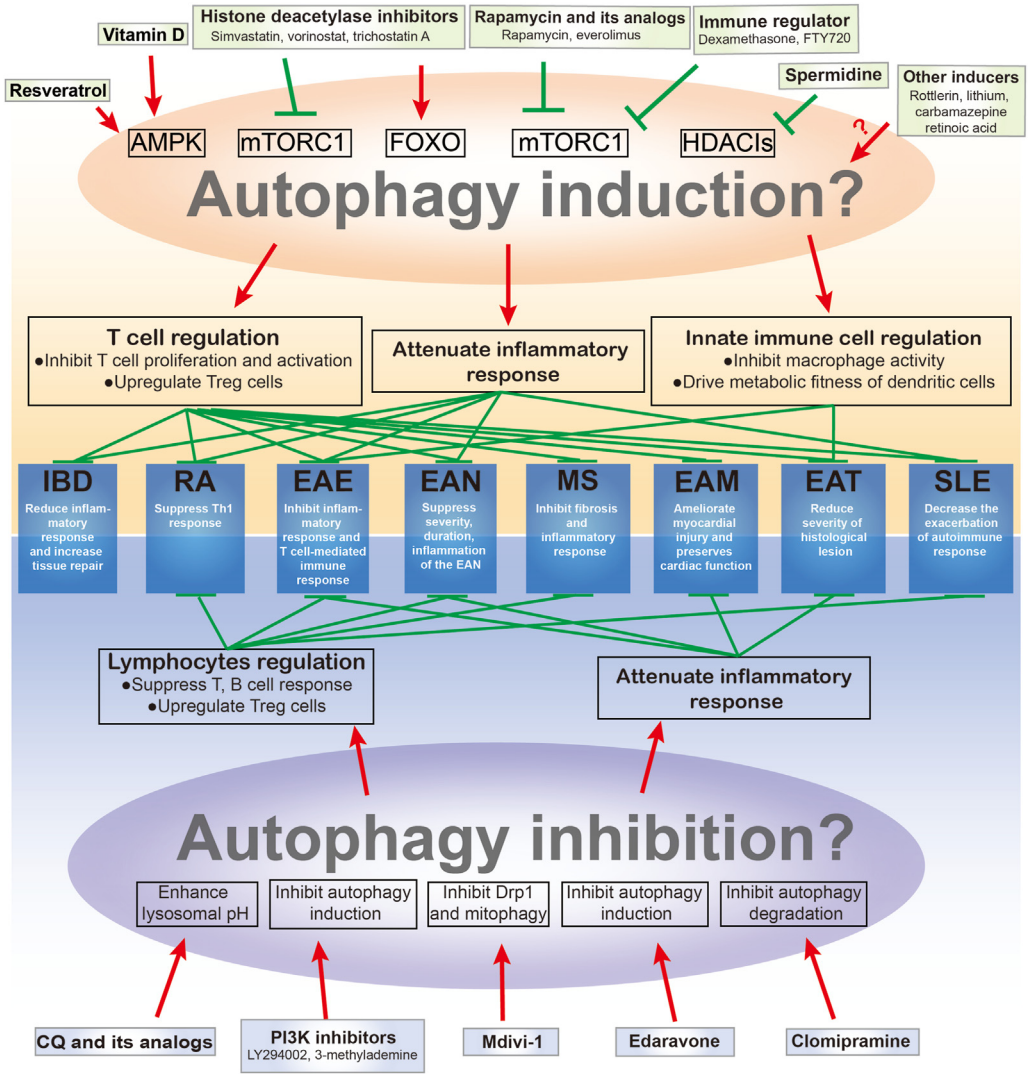

Figure 3 Potential autophagic regulators of autoimmune diseases. Typical autophagy regulators that have been utilized to treat autoimmune diseases in diverse animal models are shown.

ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3)[161]. Once VD diffuses into cells, it binds with VD receptor (VDR) to dimerize with the retinoid X receptor and regulate multiple gene expressions[162]. Low VD status and VDR polymorphism have been regarded as environmental risk factors in autoimmune diseases[163]. A deficiency of VD has been found in multiple sclerosis, SLE, RA, thyroiditis, and autoimmune gastritis[164–167]. However, it's still not clear whether the low level of VD in patients with autoimmune diseases is the cause or the consequence. Some animal experiments found that VD administration reduced the incidence and severity of EAE symptoms, suggesting that VD or VDR potentially play protective roles in autoimmune diseases[168,169]. Interestingly, accumulating evidence demonstrates that VD treatment can trigger autophagy in different cell types including cancer cells and monocytes *via* CAMKK-β- and AMPK-dependent cascades[170–172]. Another study uncovered that VD improved autophagy in M2 macrophages[172]. It would be interesting to check whether VD enhances LAP, and in this way, regulates autoimmune diseases. Spermidine and VD are important molecules which display multiple biological functions in different cell types. Whether autophagy regulation is an important mediator for their activity in anti-autoimmune diseases should be further investigated.

5.2. *Autophagy inhibitors*

Not only autophagy inducers, but also autophagy inhibitors have been revealed to exert protective effects on different autoimmune diseases. Blocking autophagy disturbs lymphocyte proliferation or activation, resulting in reduced autoimmune response in several autoimmune disease models.

Chloroquine (CQ), an anti-malarial drug and autophagy inhibitor that works by increasing lysosomal pH, has been proven to have anti-inflammatory effects and to act on RA, especially when used with other immunosuppressive drugs[173]. Numerous studies have revealed that CQ played diverse roles in antigen presentation, inflammatory pathway and Treg cell proliferation[129,174]. However, CQ is a strong lysosome activity inhibitor which also has autophagy-independent functions. To what extent the autophagy inhibition is involved in the anti-inflammatory effects of CQ need further investigated.

Table 1 Pharmacological studies of autophagy regulators on autoimmune diseases therapy.

Compound	Effect on autophagy	Animal model	Dose	Administration	Effect	Ref.
Rapamycin	Activator	Myelin oligodendrocyte glycoprotein (MOG)-induced EAE	1 mg/kg/day	ip or oral gavage for 15 days, and followed 3 days once for another 45 or 80 days	Inhibit EAE	102
		Murine autoimmune lymphoproliferative syndrome (ALPS)	5 mg/kg/day	Oral gavage for 5 days a week	Attenuate ALPS	103
		Experimental autoimmune myositis (EAM)	1 or 3 mg/kg/day	Oral gavage for about 10 days	Relieve symptoms of EAM	104
		Experimental autoimmune myocarditis	2 mg/kg/day	Oral gavage for about 17 days	Ameliorate myocardial injury and preserves cardiac function	105
		Experimental autoimmune uveoretinitis (EAU)	0.1 mg/kg/day	Intravenous infusion by a mini osmotic pump for about 14 days	Reduce number of cells in the immunization sites, lower lymphocyte proliferative response	106
Resveratrol	Activator	EAM	50 mg/kg/day	Intraperitoneal injection for 2 weeks	Ameliorate myocardial injury and preserves cardiac function	107
		EAE and Theiler's murine encephalomyelitis virus-induced demyelinating disease (TMEV-IDD)	0.04% in the chow (approximately 20 mg/kg/day)	Resveratrol containing food for about 2 months	Exacerbate demyelination and inflammation	108
		MOG-induced EAE	10, 25, and 50 mg/kg/day	ip injection for 20 days	Ameliorate the clinical severity of MS	109
Retinoic acid	Activator	Lupus nephritis in NZB/WF_1 mice	0.5 mg each time	ip injection three times per week for 5−7 months	Alleviate autoimmune renal disorder and prolongs survivals	110
		EAE	75 mg/kg/day	Oral gavage from Days 6−11	Suppressive activity on T cell-mediated immune response	111
		EAU	0.2 mg/mouse/day	ip injection every other day for 21 days	Ameliorate severity of EAU and reduces the Th1/Th17 responses	112
Carbamazepine	Activator	EAE	N/A	Carbamazepine-supplemented chow for 28 days	Improve the clinical course of the disease	113
Everolimus/ RAD001	Activator	Immunization with hIPRBPp161−180-induced autoimmune uveoretinitis	5 mg/kg/day	Oral gavage daily for 21 days	Reduce the histopathological uveitis score	114
		P0 peptide 180−199-induced autoimmune neuritis	1 mg/kg/day	Oral gavage daily for 16 consecutive days post-immunization	Protect mice from the symptoms of EAN	115
Lithium	Activator	EAE	0.2% lithium carbonate in pelleted food	Lithium-containing food and two injections of LiCl on the 1st and 2nd days	Markedly suppress the clinical symptoms of EAE	116
FTY720	Activator	Experimental autoimmune neuritis (EAN)	1 mg/kg FTY720 in 1 mL PBS	ip injection once daily for 30 days	Greatly reduce the severity and duration of EAN	117
		Experimental autoimmune myasthenia gravis (EAMG)	1 mg/kg	Oral administration (three days a week) for 5 weeks	Suppress the production of both anti-torpedo californica AChR antibody and anti-mouse AChR antibody	2
Spermidine	Activator	EAE	30 mmol/L in drinking water	Administration by drinking water for about one month	Alleviate the severities of EAE, particularly of optic neuritis	100

(*continued on next page*)

Table 1 (*continued*)

Compound	Effect on autophagy	Animal model	Dose	Administration	Effect	Ref.
Vitamin D	Activator	EAE	0.1 μg	Every other day for 15 days	The association of MOG with VD was able to control EAE development	118
		Experimental autoimmune thyroiditis (EAT)	0.1 or 0.2 μg/kg/day	ip injection for 21 days	Administration alone did not affect the incidence of thyroiditis and reduced by up to 26% the severity of histological lesion	119
Dexamethasone	Activator	MRL-lpr female mice that developed an aggressive autoimmune nephritis	0.4 mg/kg per day	Administrated by drinking water	Nephritis was ameliorated without alteration of TNF-α and ICAM-1 gene transcription	120
Rottlerin	Activator	Silica-exacerbated systemic autoimmune disease in New Zealand mixed mice	10 μg/instillation once a week	Instillation for 14 weeks	Decrease the exacerbation of autoimmunity by silica exposure	121
Trichostatin A	Activator	Collagen-induced rheumatoid arthritis (CIA)	2 mg/kg/day	ip for 7 days	Suppress Th1 response and exert protective effects on CIA	122
		EAE	7.5 mg/kg/dose/day	ip for 40 days	Histone deacetylase (HDAC) inhibition by trichostatin A ameliorate EAE	123
Vorinostat	Activator	EAE	100 mg/kg/day	Oral gavage for 1 month	Suppress DCs and DCs-mediated Th1 and Th17 cell functions in EAE	124
Simvastatin	Activator	*Fasl*$^{gld/gld}$ *apoE*$^{-/-}$ mice that lack functional Fas ligand and apolipoprotein E and exhibit accelerated atherosclerosis and aggravated lupus-like features	0.125 mg/kg/day	ip for 12 weeks	Atherosclerosis degree and inflammatory response were reduced.	125
Valproic acid	Activator	EAE	250 or 500 mg/kg/day	Oral gavage daily from Days 7 −18 or from Days 9−19	Suppress systemic and local inflammation to improve EAE	126
		EAN	300 mg/kg/day	Days 10−21	Effectively suppress inflammation in EAN	127
Niclosamide	Activator or Inhibitor	HOCl-induced systemic sclerosis	10 mg/kg every other day	ip injection for 6 weeks	Reverse fibrosis and inhibit immune response	128
Chloroquine	Inhibitor	EAE	3, 5, and 10 mg/kg/day	ip injection for 5 days	Suppress inflammation and increase Treg cells	129
LY294002	Inhibitor	EAM	40 μmol/L, 10 μL volume per day	ip injection for about 1 week	Inhibit cardiac injury	130
Mdivi-1	Inhibitor	EAE	25 mg/kg/day	ip injection for 27 days	Modulate the balance between Th1/Th17 and regulatory T cells	131
Edaravone	Inhibitor	EAM	1−10 mg/kg/day	ip for 3 weeks	Protect against acute EAM by scavenging hydroxyl free radicals	132
		EAE	6 mg/kg/day	From Days 5−19	iNOS was reduced	133
3-Methylademine (3-MA)	Inhibitor	EAE	24 mg/kg/day	ip on Days 5, 10, 15, and 20	Attenuate IL-17-induced aggravated EAE	134
Clomipramine	Inhibitor	EAN	20 mg/kg/day	ip for 28 days	Suppress clinical signs of EAN	135

Phosphoinositide 3-kinase (PI3K) inhibitors, such as 3-methyladenine (3-MA), wortmannin, and LY294002, are widely used autophagy inhibitors based on their inhibitory effects on autophagy induction. Both 3-MA and LY294002 have been utilized in different autoimmune animal models, in which, the autoimmune diseases syndrome was ameliorated. 3-MA administration ameliorated the neurologic severity of EAN[175] and inhibited IL-17-induced aggravated myocarditis severity[134]. LY294002 significantly alleviated experimental autoimmune myositis (EAM) injury in mice[130]. As PI3K activation is essential for lymphocyte proliferation, the reduction of activated lymphocytes may also be attributed to the effects of 3-MA or LY294002 on autoimmune diseases.

Many other autophagy inhibitors with unsettled understanding in autophagy are used in autoimmune diseases. Mitochondrial division inhibitor 1 (Mdivi-1) is a selective dynamic-related protein 1 (Drp1) inhibitor. It has been found to act as a mitophagy inhibitor[176]. In 2019, Li et al.[131] reported that Mdivi-1 reduced EAE severity. Th1 and Th17 cells were reduced, and regulatory T cells were promoted after Mdivi-1 administration. Edaravone is an oxygen-free radical scavenger and showed effects of inhibiting autophagy after oxygen-glucose deprivation or recovery injury[177]. Accumulating evidence from different animal models shows that edaravone is a promising compound to be utilized for autoimmune therapy. Edaravone significantly ameliorated EAE[133], acute autoimmune myocarditis[132], experimental autoimmune thyroiditis[178], and fibrosis in skin models of systemic sclerosis[179]. Clomipramine is an anti-depressant, which also inhibits autophagic degradation[180,181]. In 1998, clomipramine was found to suppress clinical signs of EAN and inhibit adaptive immune responses[135]. In addition, clomipramine has been systematically screened out for progressive sclerosis treatment as it has displayed the ability to inhibit T cell proliferation and B lymphocytes activity[182]. Again, though these compounds displayed both anti-autoimmune effects and autophagy inhibition activity, more work still need to confirm that autophagy inhibition plays a clear role in their pharmacological effects on autoimmune diseases.

6. Conclusions and discussion

Autoimmune disease is a category covering a wide range of diseases, all associated with an abnormally activated self-immunoresponse, and involving diverse immune cells. In innate immune disorders, dysfunction of autophagy has been repeatedly reported. For example, phagocytosis deficiency, xenophagy, or mitophagy dysfunction limits the clearance of apoptotic cells, pathogens, and damaged mitochondria, inducing over-productions of self-antigens. In addition, over-active innate immune responses (dysregulated DNA and RNA sense pathways) and dysregulated proliferation or activation in lymphocytes can also aggravate self-immune responses. In this complicated autoimmune scenario, autophagy seems to play quite complicated roles in regulating different autoimmune diseases.

A large number of studies have found that autophagy or autophagy-related proteins have protective roles in autoimmune diseases. Many autophagy-related proteins have been found to regulate LAP and enhance apoptotic cell clearance. As such, LAP becomes a link to connect autophagy and autoimmune diseases, especially SLE. Innate immune signaling, including inflammasome and DNA or RNA sensing pathways, are essential targets to be regulated by autophagy. The autoimmune diseases-related gene IRGM has recently been found to regulate autophagic degradation of cGAS, RIG-1, and TLR3, and by this way to limit IFN production. However, it is not known whether IRGM is a key mediator connecting autophagy function and immune responses; research into this question and into the exact regulating mechanism involved is ongoing. Mitophagy, as a selective form of autophagy, is another key event to be considered in autoimmune diseases. Many DAMPs can be released from damaged mitochondria, and mitophagy is an essential way to inhibit the immune response by removing damage mitochondria, but the specific modulation mechanism is still largely unknown. Knowing more about the mitophagy and identifying specific modulation factors would help to establish the link between mitophagy modulation and autoimmune diseases therapy.

However, we found that autophagy was not always beneficial in all autoimmune conditions. For example, it was reported that, in mice, inhibition of autophagy promotes resistance of mice to EAE, inhibits T cell differentiation, and reduces T cell responses. In RA model, apoptosis of over-activated RA-FLS is restricted. Therefore, autophagy appears to play different roles in different autoimmune diseases, possibly depending on cell type. We also noticed that unlike SLE[18] and IBD[75], EAE and RA symptoms do not spontaneously appeared in autophagy-deficient conditions, suggesting a fact that EAE and RA may be less sensitive to autophagy inhibition, compared with SLE and IBD.

Pharmacological regulators of autophagy have been used for autoimmune disease therapy. It triggers concerns because autophagy regulators have displayed different roles in pharmacological studies. Both autophagy activators and inhibitors can be beneficial in some autoimmune disease models. Although more and more autophagy regulators have been identified, most of them do not specifically target autophagy. For example, rapamycin, spermidine, VD, and CQ are all compounds that regulate autophagy and autoimmune diseases, but there is limited evidence showing that the effects on autoimmune diseases are based on autophagy regulation; other cellular pathways could be involved. Lack of specific autophagy regulators makes it difficult to evaluate the effects of autophagy regulation in treating autoimmune diseases. Though rapamycin, 3-MA, and CQ are largely used as autophagy inducers or inhibitors in research articles, autophagy is not the solely affected pathway. Identification of highly specific autophagy regulators would be of great importance for future therapeutic application.

The complex pathogenesis of autoimmune diseases has been depicted as a mosaic of genetic predisposition, hormonal effects, and environmental factors. Autophagy appears to play various roles in different autoimmune diseases *via* distinct regulation pathway. Taken together, knowing more about autophagy regulation in the autoimmune system and identifying specific pharmacological autophagy regulators or pathways of regulation are vital for applying autophagy regulators in autoimmune diseases therapy.

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Author contributions

Jia-Hong Lu initiated this review and designed the fame. Ming-Yue Wu wrote the manuscript. Er-Jin Wang, Du Feng, Min Li, and Richard Ye helped revise the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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