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Review Article

# Pathogenic Role of Autophagy in Rheumatic Diseases

Yun Jung Choi, Wan-Hee Yoo
Division of Rheumatology, Department of Internal Medicine, Chonbuk National University Medical School, Jeonju, Korea

Autophagy is a principle catabolic process mediated by lysosomes in eukaryotic cells. This is an intracellular homeostatic mechanism crucial for degradation in acidic lysosomal compartments of waste components from the cytoplasm. Autophagy research was initially focused on its degradation mechanism, but focus is now shifting to its effects on immunity. It contributes to detection and removal of pathogens as well as regulation of inflammasomes and neutrophil extracellular traps. Moreover, it is pivotal in antigen presentation and immune cell maturation, survival and homeostasis. The importance of autophagic pathways in normal and dysregulated immunity has become increasingly recognized in the past several years. Dysregulation of the autophagic pathway is implicated in the pathogenesis of several rheumatic diseases. In this review, we summarize the immunological function of autophagy in innate and adaptive immunity, and the functions of autophagy in the pathogenesis of rheumatic diseases. **(J Rheum Dis 2016;23:202-211)**

**Key Words.** Autophagy, Immunity, Rheumatic diseases, Systemic lupus erythematosus, Rheumatoid arthritis

## INTRODUCTION

Autophagy (means "eating of self" in greek) was first described by Christian de Duve in the late 1950s. Autophagy is a genetically regulated and ubiquitous catabolic process used by eukaryotic cells. It is a lysosome-mediated pathway of degradation targeting unwanted intra-cytoplasmic contents such as damaged organelles, long lived proteins and invading pathogens [1]. In general, autophagy pathway is essential not only to get rid of unwanted materials but also to get efficient energy and to protect cells from internal and external stressful conditions such as nutrient starvation, oxidative stress, hypoxia and accumulation of protein aggregates [2]. In mammalian cells, three types of autophagy have been documented according to their physiologic function and modality of cytoplasmic cargo transport to lysosome: Macroautophagy (which is focus of this review and herein referred as autophagy), microautophagy and chaperone-mediated autophagy [3]. In macroautophagy, unwanted proteins, organelles, or other materials are engulfed by double membrane vesicle, which is termed as autophagosome. Autophagosome is then delivered to lysosome and the cargo is degraded by lysosomal hydrolase [3]. In microautophagy, cytoplasmic proteins and organelles are processed by inward invagination of the lysosomal membrane. In chaperone-mediated autophagy, target contents are selectively recognized by a cytosolic chaperone that delivers them to the lysosomal-associated membrane protein type 2A and internalization followed by degradation [4,5].

Autophagy is a fundamental process to perform cell homeostasis in almost all cell types at a basal level. Firstly, it was described as a survival mechanism during nutrient starvation, but recent studies have focused on the role of autophagy in infection, inflammation and immunity. The autoimmune diseases arise due to the dysregulation of the immune system caused by diverse factors which have been incompletely understood. Autophagy has emerged as a critical player in immune functions involved in triggering or exacerbating autoimmunity [6]. Here, we focus on the recent advances in innate and adaptive immune control by autophagy, and possible pathogenic roles of au-

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**Corresponding to :** Wan-Hee Yoo, Division of Rheumatology, Department of Internal Medicine, Chonbuk National University Hospital, Chonbuk National University Medical School, 20 Geonji-ro, Deokjin-gu, Jeonju 54907, Korea. E-mail : ywhim@jbnu.ac.kr

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tophagy in several rheumatic diseases.

## MAIN SUBJECTS

### Autophagy pathways

The cascade of autophagy involve 3 morphological steps: initiation (formation of phagophores), phagophore expansion and closure (elongation of phagophore and fusion of the edge of phagophore to form autophagosome—a double membrane vesicle that sequesters the cytoplasmic materials), and maturation (fusion of the autophagosome with lysosome to form an autolysosome where the captured material and inner membrane are degraded) [3,7,8]. It is a complex process of autophagosome formation which is not completely clarified. In mammalian cells, one of the key regulators of autophagy is mammalian target of rapamycin (mTOR), which is the main inhibitory signal that shuts off autophagy. The process of autophagy occurs through inactivation of mTOR complex 1 (mTORC1), which is a conserved nutrient sensing serine/threonine kinase. mTORC1 consists of mTOR, regulatory associated protein of mTOR (raptor), protein-rich AKT substrate 40 kDa (PRAS40), G protein $\beta$ subunit-like protein (G$\beta$L/mLST8), and DEP domain containing mTOR-interacting protein (DEPTOR). Starvation, hypoxia, or rapamycin treatment causes the inactivation of mTORC1, which induces autophagy. Upon autophagy activation, mTORC1 dissociates from the UNC-51-like kinase 1 (ULK1) complex which includes the serine/threonine kinase ULK1/2, autophagy-related protein (ATG) 13, ATG101 and the focal adhesion kinase family interacting protein of 200 kDa (FIP200) to certain domains of endoplasmic reticulum (ER) or closely surrounded structures [9,10]. Subsequently, this process leads to dephosphorylation of ULK1, as enzymatically active state. The activated ULK1 phosphorylates itself, ATG8 and FIP200. The ULK1 complex translocates to ER and activates class III phosphatidylinositol 3-kinase (PI3K) complex, composed of Beclin-1, ATG14, PI3K catalytic subunit type 3 (PIK3C3), PI3K regulatory subunit 4 (PIK3R4) and ultraviolet radiation resistance associated gene protein (UVRAG) [11,12]. Binding of anti-apoptotic B-cell lymphoma (BCL)-2 to Beclin 1 restrains class III PI3K complex from inducing autophagy [13].

Phagophore expansion and closure occur by two ubiquitin-like conjugation systems: ATG12 and light chain (LC) 3 conjunction system. ATG5-ATG12-ATG16L1 complex is a product formed in the first conjugation reaction through the involvement of other ATG proteins (ATG7 and ATG10) [14]. The LC3 is conjugated with phosphatidylethanolamine (PE) to form membrane-bound, lipidated LC3-PE (LC3-II) with the help of ATG3 and ATG7 enzyme [15,16]. Then LC3-II subsequently incorporates the phagophore membrane [17,18]. The ATG5-ATG12-ATG16L1 complex dissociates from outer autophagosomal membrane after its closure, but LC3-II remains at the cytosolic membrane of the autophagosome decoupled with PE. Because LC3-II located in outer surface is deconjugated by ATG4 [19], inner autophagosomal membrane-bound LC3-II can be used as a marker of autophagosome [10]. The autophagosome fuses with lysosome to form autophagolysosome, and sequestered materials are degraded by lysosomal hydrolases (Figure 1) [20]. To access and fuse with lysosome, various cytosolic and lysosomal protein are involved such as small GTPase Rab7A, LAMP1/2, ATG9 [21-23].

## CROSSTALKS BETWEEN AUTOPHAGY AND IMMUNITY

### Autophagy in innate immunity

The dysregulated innate and adaptive immune cells are implicated in triggering of autoimmunity. The roles of autophagy participated in immune system have been extensively studied. Importantly, the activation of adaptive immune system relies on the innate immune cells, and a number of immunological processes which are dependent on autophagy in innate immune system influence the activation of the adaptive immune compartment [24].

Defense mechanism against bacteria and parasites, autophagy machinery plays a critical role in the removal of intracellular foreign bacterial and protozoan pathogens [25]. Because of the eliminative capacity of large cytoplasmic constituents and organelles, autophagy machinery is used to directly remove pathogen such as bacteria or parasite, which is the best characterized process referred to as xenophagy. A number of pathogens have been known to be degraded by xenophagy in vitro, including group A streptococcus, *Mycobacterium tuberculosis*, *Shigella flexneri*, *Listeria monocytogenes* and *Salmonella* species [3,6,26-29]. Autophagy may play a role not only in direct removal of pathogens, but also in the generation of antigenic peptide. Autophagy delivers cytosolic viral nucleic acid to endosomal toll-like receptors in the plasmacytoid dendritic cells, leading to type-I interferon production [30]. Recent studies have shown that autophagy is associated

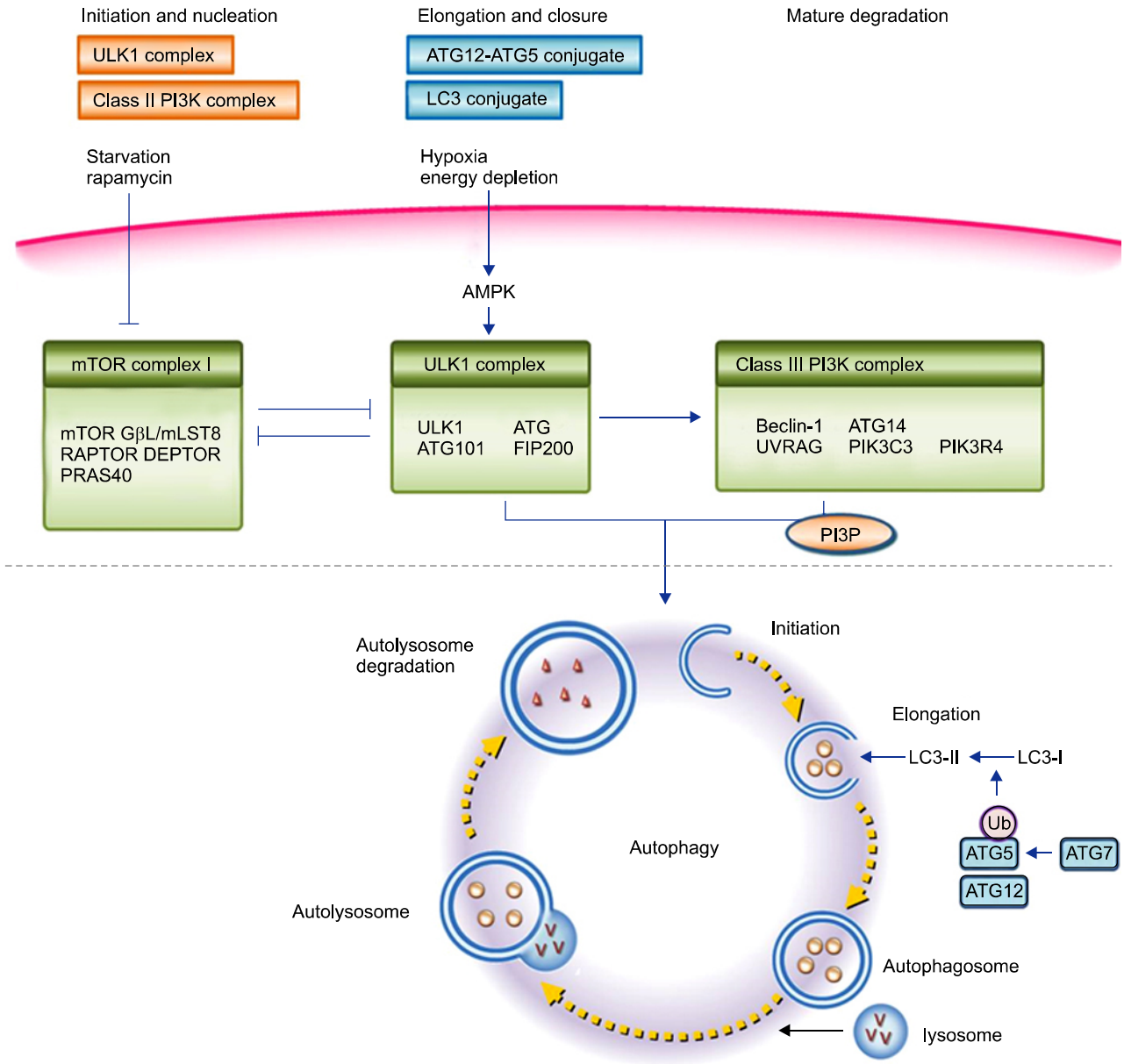


**Figure 1.** Autophagic pathway. The autophagy pathway is induced by inactivation of mTOR complex. Starvation or energy exhaustion inhibits mTOR complex, it enables ULK complex to be dissociated from mTOR complex. The stimulated ULK complex translocates to the ER, and activates class III PI3K complex. The PI3P, which is essential for autophagosomal membrane nucleation, is formed by activated class III PI3K complex. The phagophore expansion and closure mediated through conversion of LC3-I to LC3-II occurred with the help of ATG7-induced, ATG5-ATG12 complex mediated lipidation. After formation of autophagosome, it fuses with lysosome to form autolysosome and sequestered materials are degradaed by lysosomal hydrolase. Adapted from Figure 1 in the article of Levine et al. [20] (Nature 2011;469:323-35). mTOR: mammalian target of rapamycin, ULK: UNC-51-like kinase, ER: endoplasmic reticulum, PI3K: phosphatidylinositol 3-kinase, PI3P: phosphatidylinositol-3-phosphate, LC: light chain, ATG: autophagy-related protein, DEPTOR: DEP domain containing mTOR-interacting protein, FIP200: focal adhesion kinase family interacting protein of 200 kDA, G $\beta$ L/mLST8: G protein $\beta$ subunit-like protein, PRAS40: protein-rich AKT substrate 40 kDA, RAPTOR: regulatory associated protein of mTOR, PIK3C3: PI3K catalytic subunit type 3, PIK3R4: PI3K regulatory subunit 4, UVRAG: UV radiation resistance associated gene protein.

with neutrophil extracellular traps (NETs). NETs are arisen from the activated neutrophil in response to inflammatory stimuli and are composed of DNA, histones and neutrophil antimicrobial granules. They can trap and kill various bacterial, fungal and protozoal pathogens, so it appears to be a form of innate immune response [31].

It is revealed that autophagy is involved with NET cell death (NETosis) by the contribution of intracellular chromatin decondensation, which is essential for NETosis and NET formation [32].

Another important effect of autophagy related to inflammation signalling is inflammasomes. Inflammasomes are cellular multimolecular protein complex consisted of nucleotide oligomerization domain-like receptor cryopyrin proteins, adaptor protein ASC and caspase 1. They are involved in the production of interleukin (IL)-1$\beta$ and IL-18 and activate many pro-inflammatory mediators in cellular infection or other stressful conditions [33,34]. Autophagy is induced by activation of inflammasome through generations of the isolation membrane of the phagosome [35]. However, autophagy limits the activity of inflammasome via engulfment of ubiquitinated inflammasome. It has been demonstrated that knockout of autophagy related-gene (Atg) causes activation of the inflammasome with enhanced IL-1$\beta$ and IL-18 [36]. It represents a negative regulation of autophagy aimed to return to homeostasis during inflammation [26].

### Autophagy in adaptive immunity

Autophagy also participates in adaptive immunity, such as antigen presentation and lymphocyte development [37]. Classically, endogenous antigens bind to major histocompatibility complex (MHC) class I molecule and are presented to CD8+ T cells. The extracellular antigens are processed and loaded to the MHC class II complex and presented to CD4+ T cells. However, crosstalk between these two pathways has been demonstrated. Autophagy has been implicated both in intracellular and extracellular antigen processing in MHC class II presentation to CD4+ T cells [38]. Autophagy strongly contributes to the MHC class II presentation pathway by loading intracellular antigen through the fusion of autophagosome, leading to the activation of CD4+ T lymphocytes. In an analysis of classifying the source proteins of human leukocyte antigen-antigen D related ligands according to their cellular localization, about 20% to 30% of self class II epitopes are derived from cytosolic and nuclear proteins [38]. This self-antigen presented through autophagy is potentially relevant to autoimmune diseases [39]. Atg5$^{-/-}$ dendritic cells showed the defect in the processing and presentation of phagocytosed antigen to MHC II molecules [40]. Besides, autophagy assists with antigen donor cell for cross-presentation on MHC class I molecule to CD8+ T cell [41].

Autophagy is involved in the entire process of T cell repertoire from at the stage of hematopoietic stem cells (HSC) to mature T cells [42]. Autophagy maintains HSC quiescence and self-renewability via degrading mitochondria [43]. In the developmental stage of thymocyte, autophagy regulates antigen presentation by antigen presenting cells (APCs) during positive and negative selection of thymocytes [44,45], and promotes the development of specific T cell subtypes, i.e, regulatory T cell and invariant natural killer T cells [46]. Upon maturation, T cells undergo the reduction of mitochondria and ER by autophagy for the maintenance and survival of themself [47,48]. The autophagy participates in the mature T cell stages, including activation, proliferation and differentiation [42] and finally contributes to the maintenance of memory T cells [49].

Autophagy also plays central role in the development of early B cell progenitors, as well as survival of B lymphocytes. The Beclin 1-deficient Rag1$^{-/-}$ chimeric mice showed the reduced density of lymphoid progenitor populations [50]. It was also demonstrated that Atg plays an important role in the stage of pro-to pre-B cell transition [51] and late B cell activation and plasma cell differentiation [52]. Moreover, autophagy-incompetent differentiating plasma cells showed enhanced immunoglobulin synthesis and antibody secretion in response to increased ER stress signaling [53]. In addition, autophagy contributes to the maintenance of long lived humoral immunity through preservation of the bone marrow plasma cells [53]. Thus, these data indicate that autophagy is essential for the function, survival and homeostasis of plasma cells.

## AUTOPHAGY IN RHEUMATIC DISEASES

### Systemic lupus erythematosus (SLE)

SLE is a systemic autoimmune disorder, characterized by production of autoantibodies, aberrant immune complex infiltration and inflammation on multiple organs [54]. The etiology remains to be elucidated, but some evidences suggest that autophagic defects have a pathogenic role in abnormal immunities in SLE, especially regarding dysregulation of lymphocytes. T cells of SLE in both murine and human models present increased number of autophagosomes [55,56]. Up-regulation of autophagy in T cells, evoked by circulating autoantibodies, could enhance the survival of auto-reactive T cells [55,56]. However, megamitochondria was detected in T lymphocytes of SLE despite of increased number of autophago-

somes due to the defect of mitophagy. The alteration of mitophagy leads to defective clearance of mitochondria and formation of megamitochondria [55]. Another research showed that T lymphocytes from lupus patients were resistant to autophagic induction and presented up-regulation of genes which negatively regulate autophagy [57]. It suggests that autophagy-resistant T lymphocytes could be selected because of chronic exposure to specific antibodies in SLE. Consequently, it leads to mitochondrial clearance defects, aberrant release of apoptosis signal and excessive reactive oxygen species production as shown in SLE [57,58].

The similar results were shown in our experiments previously. The lower level of LC3-green fluorescent protein fusion protein expression and autophagosome were detected in T cells from patients with SLE compared with healthy control at baseline. In addition, we analyzed the effects of thapsigargin-induced ER stress on autophagy and apoptosis. In T lymphocytes from SLE patients, the expression of ER stress sensor molecules decreased and the protein markers for autophagy, including beclin-1 and LC3-II, also decreased in response to thapsigargin-induced ER stress compared with that from healthy individuals. These findings suggest that the attenuated level of ER stress sensors related to a reduced autophagic response when stimulated by ER stress. Furthermore, to find out the role of Beclin-1, one of essential autophagy regulating protein, in a dysregulated state of autophagy and apoptosis in SLE T cells, we used Beclin-1 small interfering RNA (siRNA). The results showed that decreased expression of BCL-2 and BCL-$X_L$ and increased level of Bax and caspase-6 in T cells with Beclin-1 siRNA. That is, the autophagy-deficient T lymphocytes were more prone to thapsigargin-induced apoptosis than those with control. Therefore, our results indicate that autophagy modulates thapsigargin-induced, ER stress-mediated T cell apoptosis through regulating the expression of apoptosis-related protein [59].

The dysregulation of autophagy in B lymphocytes also has been investigated. In human lupus B cells, increased level of autophagic flux was observed, especially in naïve B cells [60]. In addition, inhibition of autophagy resulted in the decrement of B cell survival during culture periods and failure of effective differentiation of B cells into plasma cells. These results suggest that high levels of autophagy is contributed to the survival of autoreactive B cells, and plasmablast formation [60].

Genome-wide association studies have identified nucleotide polymorphisms in autophagy-related genes associated with predisposition to SLE [61]. Specially, single nucleotide polymorphisms in the Atg5 intron 6 (rs2245214) and in the PR domain zinc finger protein 1-Atg5 intergenic region (rs568431) are implicated in the pathogenesis of SLE [61,62]. The detailed mechanisms of altered autophagic activity in SLE are needed to be elucidated, but modulating of this pathway by drugs, such as rapamycin [63], hydroxychloroquine [64] and P140 peptide [65], have a favorable effect on disease progression of SLE patients as well as lupus-prone mouse models, suggesting that modulation of autophagic flux may be an attractive treatment for SLE.

## Rheumatoid arthritis (RA)

RA is the one of the most common chronic inflammatory disease mainly affecting synovial membrane, cartilage and bone. RA synovial fibroblasts (RASFs) are dominant key players in the pathogenesis of RA, linked with synovial inflammation and hyperplasia, progressive destruction of cartilage and bone, consequently progressive disability [66].

Several studies have described the up-regulation of autophagic flux in RASFs. We focused on the resistance of RASFs to apoptosis, which is closely linked to synovial hyperplasia. We examined the response of RASFs and the role of autophagy in the alteration of synovial apoptosis when stimulated by ER stress. The RASFs showed high level of autophagy with increased expression of Beclin-1 and LC3-II conversion compared with osteoarthritis synovial fibroblasts (OASFs). In addition, we evaluated the role of autophagy on cell death against ER stress. In RASFs, transfection of Beclin-1 siRNA decreased autophagy and increased cell death in response to treatment with thapsigargin. Therefore, when RASFs were exposed to ER stress, high level of autophagy is induced and it may contribute to resistance against ER stress-induced cell death [67]. Furthermore, decreased level of miR-30a, which was shown to inhibit Beclin-1 expression, was observed in synovial tissue of RA, and it may contribute to upregulation of autophagy in RASFs [68]. Recently, dual role of autophagy has been investigated in RASFs in response to cellular stress [69]. As mentioned previously, autophagy exhibited cytoprotective effects in proteasome inhibition- induced cell death in RASFs. However, under the condition of severe ER stress, the imbalance between accumulation of p62 and low induction level of autophagy-linked FYVE protein contribute to formation of

p62-positive polyubiquitinated protein aggregates, consequently leads to autophagic cell death. It suggests that autophagy has an antithetical role in cell death regulation of RASFs [69].

In addition, high level of autophagy and autophagy-related protein are activated in osteoclasts as well. The expression of Atg7 and Beclin-1 increased in osteoclasts of RA compared with samples from OA patients [70]. It is also demonstrated that up-regulation of Atg7 and Beclin-1 and conversion of LC3-I into LC3-II in osteoclasts are induced by proinflammatory cytokine, tumor necrosis factor-$\alpha$. Increased autophagy stimulates not only receptor activator of nuclear factor kappa-B ligand (RANKL)-induced osteoclast differentiation, but also osteoclast-mediated bone resorption, whereas genetic or pharmacological suppression of autophagy prevented joint destruction in experimental arthritis [70]. Several autophagy proteins showed the association with the activity of osteoclasts. For example, p62, a specific adaptor protein for autophagy, plays a crucial role in RANKL-induced osteoclastogenesis. The knock down of p62 attenuated the expression of osteoclastogenesis-related genes and formation of tartrate-resistant acid phosphatase-positive multinuclear cells [71]. In addition, it is revealed that autophagy protein, including ATG5, ATG7, ATG4B and LC3, participates in osteoclastic bone resorption. Autophagy protein-deficient osteoclasts exhibit lack of normal ruffled border, impaired lysosomal secretion, consequently limited ability of bone resorption [72]. These findings emphasize that autophagy is up-regulated in osteoclasts and it affects osteoclastogenesis and bone resorption. Thus, inhibition of autophagy could be a potential therapeutic approach for preventing joint destruction.

The association between citrullination and autophagy is not completely elucidated. However, recent studies suggested that autophagy is associated with the generation and presentation of citrullinated peptides in APCs. Furthermore, elevated peptidyl arginine deiminase (PAD) activity was also detected in purified autophagosome [73,74]. The role for autophagy in the generation of citrullinated peptides also reported. After autophagy induction via treatment with tunicamycin, the synoviocyte showed PAD4 activation, consequently resulting in protein cirtrullination. In the same vein, the positive correlation between levels of autophagy and anti-cyclic citrullinated peptide antibody was observed in treatment-naïve early RA patients [75].

## Other rheumatic diseases

In other several rheumatic diseases, the alteration in autophagy has been also reported. In an observational study of systemic sclerosis, the higher autophagy level was detected in punch-biopsied skin of patients with systemic sclerosis compared with skin samples of healthy control [76]. Several feature of systemic sclerosis including presence of antibodies, pruritus and neuropathy was not correlated with autophagy intensity significantly, but shorter duration of systemic sclerosis showed a higher level of intensity staining [76]. In contrast, the opposite results showed the relation between matrix accumulation and low level of autophagic flux, indicating decreased autophagic capacity may trigger the accumulation of extra-cellular matrix protein [77]. Caveolin-1 is a scaffolding/regulatory protein localized in dermal fibroblasts, and it is associated with intracellular turnover of tumor growth factor (TGF)-$\beta$ [78]. The caveolin-1 deficient mice showed scleroderma-like properties of the skin and increased number of autophagic cells in the dermis. These results suggest that dysreulated autophagy is associated with caveolin-1 dysfunction, consequently, increased TGF-$\beta$ signaling and fibrotic changes [79].

In psoriatic arthritis (PsA), impaired immune response of dendritic cells toward intracellular mycobacteria is observed. It is linked to insufficient removal of these bacteria, initiation and perpetuation of chronic inflammation. Because autophagy is responsible for elimination of intracellular pathogen and peptide presentation, the highly expressed ATG16L1 in PsA dendritic cells might be the response against intracellular bacteria, reflecting the disordered immune function of dendritic cells [80].

The autophagic defects in ankylosing spondylitis (AS) also have been investigated. Autophagy regulates IL-1$\beta$ secretion via controlling inflammasome activity. In human and mouse macrophages and dendritic cells, it is demonstrated that treatment with IL-1 increases IL-23 secretion. Thus, the inhibition of autophagy by treatment with 3-methyladenine induces the increased level of both IL-1$\beta$ and IL-23 in dendritic cells [81]. In accordance with these finding, the down-regulation of chaperone-mediated autophagy is observed in the inflamed gut of AS, and it is negatively correlated with IL-23 level. However, elevated ATG16L1 was observed and it showed the relationship with increased level of IL23p19. In addition, ATG5 and ATG12 proteins were also up-regulated, reflecting differentially regulated macroautophagy and chaperone-mediated autophagy in the gut of AS [82].

The summary of autophagic defect in immune cells of rheumatic disease listed in Table 1 [56,57,60,67-70, 75-77,79,80,82-86].

## CONCLUSION

Autophagy was initially viewed as a catabolic recycling pathway, but the potential implications of altered autophagic activity of autoimmune disease are a growing era of concern. As discussed above, through participating in pathogen degradation, inflammasome activation, NETosis, antigen presentation, maturation, survival and homeostasis of immune cells, autophagy is closely associated with innate and adaptive immunity. These supporting evidences have uncovered the possible contribution of autophagic abnormlities in rheumatic diseases, but it is inconclusive and much research needs to be carried out. Thus, we expect that future research may lead the definite understanding of the interplay between autophagy and rheumatic diseases, and it develops new specific therapeutic strategy by modulating autophagy.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

**Table 1.** Autophagic defect of immune cells in the pathogenesis of rheumatic disease

| Disease | Cell or tissue | Model | Dysregulation of autophagy | Ref. |
|---|---|---|---|---|
| SLE | T lymphocyte | Human | Resistant to autophagic induction | 57 |
| | | | Upregulation of genes negatively regulating autophagy | |
| | | Mice | Autophagy increased | 56 |
| | B lymphocyte | Human & mice | No difference | 56 |
| | | | STS-1 increased→JAK-STAT signaling increased→IFN-induced autophagy increased | 83 |
| | | | Autophagy increased in early developmental stage of B cell | 84 |
| | | | Autophagy deficient B cell: failure of differentiation into plasma cell | |
| | | Mice | CD19-Cre-Atg5$^{f/f}$: normal inflammatory response | 60 |
| | Macrophage | Human & mice | Higher expression of Atg | 85 |
| | | | Beclin-1 knockdown: anti-dsDNA antibody, proteinuria, IL-6 and TNF-$\alpha$ decreased | |
| RA | Synovial fibroblast | Human | Autophagy increased and apoptosis decreased: Beclin-1, LC 3 increased and miR-30a decreased | 68 |
| | | | Dual role of autophagy<br>- Cytoprotective in proteasome inhibition-induced apoptosis<br>- Cell death increased under the condition of severe ER stress | 69 |
| | | | Higher level of autophagy induced by ER stress→PAD4 activation →protein citrullination increased | 67 |
| | | | Positive correlation between autophagy and anti-CCP Antibodies in early naïve RA patients | |
| | | Mice | ER stress-induced autophagy increased | 75 |
| | | | Beclin-1 siRNA: autophagy decreased, cell death increased | |
| | Osteoclast | Human & mice | Beclin-1 and Atg 7 increased | 70 |
| | | | Overexpression of Beclin-1: osteoclastogenesis increased | |
| | T lymphocyte | Human | Autophagy decreased | 86 |
| SSc | Skin biopsy specimen | Human | Autophagy increased | 76 |
| | Fibroblast | | Autophagy decreased | 77 |
| | Stromal cell | Mice | Autophagy increased in caveolin-deficient mice | 79 |
| PsA | Dendritic cell | Human | ATG16L1 increased | 80 |
| AS | Ileal biopsy specimen | Human | ATG16L1, ATG5 and ATG12 increased | 82 |
| | | | HSPA8, HSP90AA1 decreased | |

SLE: systemic lupus erythematosus, STS-1: suppressor of T-cell receptor signaling 1, JAK-STAT: Janus kinase–signal transducer and activator of transcription, IFN: interferon, Atg: autophagy-related gene, IL: interleukin, TNF-$\alpha$: tumor necrosis factor-$\alpha$, RA: rheumatoid arthritis, LC: light chain, ER: endoplasmic reticulum, siRNA: small interfering RNA, SSc: systemic sclerosis, PsA: psoriatic arthritis, ATG: autophagy-related protein, AS: ankylosing spondylitis, HSP: heat shock protein.

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