Review

# Roles of autophagy in rheumatoid arthritis

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**ABSTRACT**

*Autophagy, a vital mechanism restricted in tissues, exerts its cytoprotective role through the degradation mechanism of damaged or aging organelles, harmful protein aggregates and intracellular pathogens, followed by energy furnishment. However, dysfunctional autophagy is associated with the development of autoimmune diseases such as rheumatoid arthritis (RA). In pathological conditions, autophagy may be involved in the maturation, survival and proliferation of various immune and non-immune cells and plays a key role in the pathogenesis of RA. Furthermore, autophagy appears to be involved in the citrullination of T lymphocytes and the presentation of citrullinated peptides, which are presented to T lymphocytes via the major histocompatibility complex, causing immune responses and chronic inflammation, as well as bone and cartilage destruction associated with apoptosis resistance of RA fibroblast-like synoviocyte (RA-FLS) and osteoclastogenesis. In this review, we have summarised the roles of autophagy in the pathogenesis of RA including citrullination, immune tolerance break, osteoclastogenesis, RA FLS cell dysplasia, apoptosis resistance, together with the therapeutic potentials of autophagy regulators.*

## Introduction

Autophagy is a housekeeping and pro-survival degradation pathway of specific cytoplasmic material, contributing to turning over basal organelles and removing or eliminating cytosolic components (1, 2). Under normal conditions, it maintains homeostasis and has a cytoprotective effect via inhibiting the accumulation of protein aggregates (3, 4). Thus, it is not surprising that the dysfunction of autophagy could be responsible for rheumatoid arthritis (RA) (5).

RA is a chronic destructive autoimmune-mediated arthritis that ultimately leads to bone and articular cartilage damage, thereby decreasing quality of life and even causing disability. It is a chronic inflammation and autoimmune disorder initiated by several antigen-presenting cells (APCs) processing and presenting autoantigens to T cells (6). Persistent inflammation in the joints is responsible for the secretion of pro-inflammatory cytokines and characteristic autoantibodies against citrullinated proteins, leading to synoviocytes hyperplasia, osteoclast activation, and joint destruction (7). Emerging evidences have revealed the roles of autophagy mechanism in RA pathology and estimated that there could be various anomalies in autophagy and its related factors in the context of RA (8, 9). A number of pharmacological or genetic autophagy modulation methods have been recognised as potentially potent therapeutic strategies for the treatment of RA (10, 11). However, further research is required to clarify the exact role of autophagy in the pathogenesis of RA. In this review, we have focused on the latest studies that have given rise to a better understanding of the role of autophagy in the pathogenesis of RA and potential clinical applications.

## Autophagy

### *Mechanism of autophagy*

Macro-autophagy (or autophagy) is an energy-producing and catabolic mechanism through which redundant organelles or cytoplasmic molecules are sequestered in double-membrane autophagosomes that are delivered towards and fuse with lysosomes for bulk degradation and recycling of the autophagic cargo (5, 12). After autophagy induction, the biogenesis is mediated by the appearance and formation of the isolation membrane inside the cytoplasm, followed via its expansion, extension and subsequent fusion with

lysosome to form auto-lysosome. Then, the autophagosomes are derived with phagophore structure, which originates from the endoplasmic reticulum, golgi complex, and plasma membrane (13). After nucleation, membrane elongation and closure, autophagosome becomes mature and then fuses with lysosome to form an autolysosome which consists of lysosomal hydrolase and is responsible for the hydrolysis of substances within the autolysosome (14). The degradation products such as amino acids and lipids are released to the cytoplasm and reused to enhance cell survival during nutrient deprivation (15).

*Autophagy in immunity*

Autophagy plays a crucial role in initiating and supporting several processes in both innate and adaptive immunity (16). In innate immunity, ATG (autophagy-associated genes) proteins control inflammasome activation and limit the production of various cytokines responsible for the pathology of multiple chronic inflammatory diseases (17). In adaptive immunity, autophagy modulates autoantibody production and regulates the development of lymphocytes. Anti-citrullinated protein autoantibody (ACPA) is a highly specific biomarker for RA diagnosis and is correlated with disease severity, with autophagy participating in the ACPA formation process through citrullination and antigen presentation (18-20). Besides, autophagy also has an impact on adaptive and innate immune tolerance. In normal immunological tolerance conditions, autophagy occurs in almost all of the innate and adaptive immune cells, contributing to the induction of central tolerance and peripheral tolerance at multiple levels in the immune system through autophagy flux directly or immune signalling pathways via autophagy-related proteins in an autophagy-independent manner (21).

## RA pathogenesis overview

Rheumatoid arthritis (RA), a chronic autoimmune disease, is marked with inflammation in joints, bone, and synovial and progressive bone loss, which also invades and attacks other organs such as the heart (22). Dysfunction of RA fibroblast-like synoviocytes (RA-FLS) and related immune cells is responsible for the process of initiating an auto-immune and chronic response leading to articular structure destruction and intimal lining hyperplasia (23). RA-FLS are tissue-specific cells capable of producing cytokines and local inflammatory enzymes that play a key role in the pathogenesis of RA. Another important factor affecting the development of RA is osteoclast differentiation. Accumulation of osteoclast precursors and mature osteoclasts at sites of inflammation leads to joint erosion and systemic osteoporosis (24). Moreover, auto-antibodies, as well as pro-inflammatory cytokines, also participate in bone destruction (25, 26). Interestingly, previous studies have elucidated that autophagy is involved in the regulation of the above pathogenesis progression (5, 27).

## Roles of autophagy and its regulators in RA

*Autophagy and fibroblast-like synoviocytes*

RA is a common autoimmune disease characterised by persistent synovial hyperplasia, pannus formation and progressive cartilage destruction (28). Moreover, considered as an important local immune microenvironment regulator, RA-FLS also degrade the extracellular matrix, and exhibit several tumour cell-like characteristics, secrete cytokines and inflammatory factors to recruit and stimulate neutrophils, macrophages, and lymphocytes secreting inflammatory mediators to the synovial fluid, thus they are considered one of the main cell types of proliferative synoviocytes and pannus in RA, leading to invasion and destruction of cartilage and bone erosion (29-31). Compared with normal fibroblast-like synoviocytes, RA-FLS usually exhibit induced activation of autophagy and resistance to apoptosis which is regulated via various signalling pathways (32, 33), including tumour necrosis factor alpha (TNF-α), interleukin-36 (IL-36) and IL-38, IL-17, Hippo, optineurin, transcription factor EB (TFEB), reactive oxygen species (ROS) and Toll-like receptor 4 (TLR4), hypoxia-inducible factor-1α (HIF-1α), Notch-1 and Notch-3, CXCR4 and SERPINA1, miR-218-5p, miR-449a and high-mobility group box protein 1 (HMGB1), and long non-coding RNAs (lncRNAs) signalling pathway (Fig. 1).

Several cytokines are involved in the pathogenesis of RA. Treated with TNF-α, FLS show upregulated Beclin1 and LC3II protein levels and decreased p62 protein level, exhibiting an increased level of autophagy followed by a lower apoptosis level. However, while TNF-α and specific blockers of the nuclear factor-kappa B (NF-κB) pathway act synergistically on FLS, these changes are completely reversed, suggesting that the NF-κB signalling pathway may also be involved in the regulation of RA-FLS autophagy induced by TNF-α (34, 35). IL-36 and IL-38, belonging to the IL-1 cytokine family, are both elevated in RA patients (36-38). IL-36 accelerates the activation of autophagy and inhibits autophagy-restrained proliferation, migration, and invasion in synovial cells, leading to symptom relief, while IL-38 impedes autophagy and promotes proliferation, migration, and invasion. Moreover, IL-38 signalling also promotes the production of several autophagy-regulating inflammatory cytokines such as IL2, IL-6, IL-13, and IL-17 (39). IL-17 has positive effects on autophagy and tumour-like proliferation in RA-FLS and these effects could be suppressed by the inhibition of autophagy or signal transducer and activator of transcription-3 (STAT3), with the inhibition of autophagy and STAT3 suppressing the proliferation and autophagy activation of FLS in lL-17-treated FLS, respectively (27, 40).

Hippo signalling regulates cell proliferation and survival. Both YAP (yes-associated protein) and TAZ (transcriptional coactivator with PDZ-binding motif), the downstream effectors of the Hippo signalling pathway, are regulated in RA-FLS and the knockdown of YAP or TAZ enhances autophagy and inhibits the migration and invasion of RA-FLS which can be partially reversed by autophagy inhibitors (41). Optineurin, considered as an autophagy

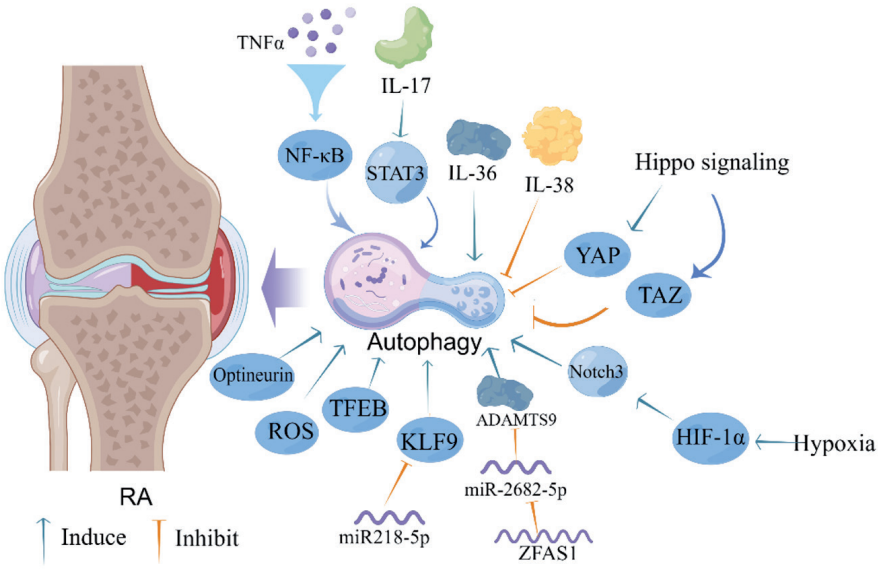


**Fig. 1.** The major mechanisms involved in the autophagy regulation in RA-FLS.
YAP: yes-associated protein; TAZ: transcriptional coactivator with PDZ-binding motif; KLF: Krüppel-like factor; ADAMTS9: a disintegrin-like and metalloproteinase domain with thrombospondintype 1 motifs; ZFAS1: ZNFX1 antisense RNA1.

adaptor/receptor and extensively involved in multiple steps of autophagy, is up-regulated in RA-FLS induced by proinflammatory cytokines to have a protective effect on RA with decreased receptor activator of NF-κB (RANKL) (42, 43). TFEB regulates autophagy to participate in the progress of RA, with the silence of TFEB in the RA-FLS exhibiting decreased expressions of LC3B (33). ROS/TLR4-coupled activation may participate in the pathogenesis of RA in FLS by the induction of autophagy, with increased intracellular ROS inducing oxidative stress and inhibiting apoptosis by inducing autophagy (44).

The hypoxia microenvironment leads to a significantly up-regulated HIF-1α level in RA tissue, accompanied by increased IL-6 and autophagy levels in RA-FLS. Meanwhile, RA-FLS exhibits an immune activation function medicated by IL-6, which could be reversed by autophagy inhibitors (30). Moreover, Chen *et al*. reported that HIF-1α also directly regulates the expression of Notch-1 intracellular domain (N1ICD) and N3ICD under hypoxic conditions, leading to induced RA-FLS invasion and angiogenesis, which could be reversed by HIF-1α siRNA, Notch-1 siRNA and Notch-3 siRNA. Moreover, Notch-1 and Notch-3 has different effects under hypoxic conditions. Notch-1 is considered to regulate synovial fibroblasts migration and epithelial-mesenchymal transition under hypoxic conditions, whereas Notch-3 plays a role in regulating the processes of anti-apoptosis and autophagy (45). Huang *et al*. constructed an Autophagy-Related Index (ARI) based on *CXCR4* and *SERPINA1*, the major autophagy-related genes of differentially expressed genes between RA and OA (osteoarthritis). Correlated with autophagy and immune infiltration, ARI demonstrates a high level of accuracy in identifying OA and RA based on differential autophagy levels of the two diseases (46).

Non-coding RNAs are involved in important post-transcriptional gene regulation, affecting the activation of autophagy in RA-FLS and playing considerable roles in the pathogenesis as well. Chen *et al*. discovered that markedly upregulated miR218-5p and downregulated KLF9 protein, the target of miR218-5p and a member of the Krüppel-like factor (KLF) family, in RA-FLS compared with healthy synovial fibroblasts, leads to induced proliferation and oxidative stress, and inhibits autophagy and apoptosis, with induced JAK2/STAT3 pathway involvement. Thus, the knockdown of miR218-5p may serve as a potential therapy strategy of RA (47). Cai *et al*. reported that miR-449a downregulated in RA synovial tissue and inhibited RA-FLS proliferation, migration, and IL-6 production, partly via inhibiting the expression of HMGB1, which promoted cell proliferation, migration, invasion, and autophagy in RA-FLSs (48). Moreover, miR-2682-5p were downregulated in RA-FLS and related with elevated cell proliferation, autophagy, inflammatory response, and reduced cell apoptosis, regulated by its target lncRNAs, ZNFX1 antisense RNA1 (ZFAS1) and a disintegrin-like and metalloproteinase domain with thrombospondintype 1 motifs (ADAMTS9), which were both upregulated in RA-FLS and modulated inflammatory response via ZFAS1/miR-2682-5p/ADAMTS9 axis (49). miR-27a was also inactivated by ZFAS1 and then improved the migration and invasion in RA-FLS (50). Moreover, Shang *et al*. reported the different expressed lncRNAs before and after autophagy in RA-FLSs involved in cytokine secretion regulation, including IL-6, TGF-β, TNF-α and IL-17, differentiation of osteoclasts and immune cells, such as Th17, Th1, Th2 cells, and several signalling pathways, such as autophagy pathway, MAPK, and FoxO, with ENST0000584721.1 upregulated and ENST0000615939.1 down-regulated after autophagy, respectively (29).

Furthermore, unlike the normal FLS cells, the RA-FLS cells could use compensatory mechanism with the proteasome and autophagy pathways to degrade malfunctional or atypical proteins, so as to suppress apoptosis and increase cell survival (20). Therefore, reduction of autophagy and increase in apoptosis may serve as a potential and novel therapy strategy to reach a favourable clinical outcome in RA patients, such as methotrexate (MTX) and Theaflavin 3,3′-digallate (TF3)(51, 52). Further detailed investigations are required to explore the exact roles of autophagy in apoptosis resistant and potential therapy strategy of RA.

### *Autophagy in osteoclasts*

In addition to inflammation, osteoclast-mediated cartilage and bone destruc-

tion is a principal feature in RA (53). Osteoclasts play a role in bone resorbing and are recognised as the major cells responsible for bone destruction in RA. They are derived from haematopoietic stem cells and experience proliferation and differentiation, which requires the urnover of organelles and intracellular protein, and are then converted to multinucleated bone-resorbing osteoclasts (53-55). The increased autophagy flux in osteoclasts leads to promoted osteoclast differentiation, with the defects of autophagy-related proteins seeming to reduce bone and joint destruction (5). Many studies have shown that autophagy regulates the differentiation process of osteoclasts from monocyte lineage. Suppression of the AMPK (adenosine monophosphate-activated protein kinase)-MTOR (mechanistic target of rapamycin kinase)-ULK1 (unc-51 like autophagy activating kinase 1) signalling axis decreases autophagy in glucose-mediated osteoclast differentiation, and overexpression of KLF2 (Kruppel-like factor 2 [lung]) decreased CSF1/MCSF (colony stimulating factor 1 [macrophage]) - and TNFSF11/RANKL (tumour necrosis factor (ligand) superfamily, member 11)-induced autophagy and osteoclastogenesis (53, 56). Additionally, the number of osteoclast cells and the level of bone destruction is also decreased after autophagy inhibition in experimental arthritis mouse models (57). These evidences suggest that autophagy could be one of the major factors affecting osteoclastogenesis and bone erosion in RA.

Osteoclasts predominantly mediate bone erosion in RA, with the formation and activity of osteoclasts increasing as a result of increased production of pro-inflammatory cytokines, such as TNF and RANKL, which activate NF-κB (58). It has been reported that the autophagy system is involved in obtaining osteoclasts from the synovial tissues of patients with active rheumatoid arthritis RA and the autophagy level in the synovial tissues is correlated with disease severity (20, 32). On the contrary, the inhibition of autophagic–lysosomal system blocked the differentiation process from mouse macrophages to osteoclast and reduced bone destruction and the number of osteoclasts in RA mouse model (59). Thus, it can be concluded that autophagy and autophagy-related factors influence human skeletal homeostasis via regulation of the function of osteoclasts. The essential autophagy proteins, such as Atg5 (autophagy-related 5), Atg7, Atg4B (autophagy-related 4B cysteine peptidase) and LC3, are vital for the generation of the osteoclasts ruffled border, and the secretory function of osteoclasts and bone resorption *in vitro* and *in vivo*. On the contrary, osteoclasts with autophagy- related protein deficiency generally show poor bone resorption ability and impaired actin ring construction, and the absence of normal ruffled borders, which reflects failed secretory lysosome/plasma membrane fusion (60). Based on the findings of the above studies, autophagy- and autophagy-related factors may influence osteoclastogenesis and the function of osteoclasts. Therefore, autophagy could play roles in the destruction of bone and cartilage of RA patients via its effects on osteoclasts in a direct or indirect manner.

*Autophagy and RA immunopathogenesis*

Besides the pathogenesis discussed above, autophagy is also involved in the mediation of the inflammation processes via secretion and release of inflammatory cytokines and immunity function, including removal of self-tolerance and production of anti-citrullinated protein autoantibody in RA (58). Dysregulation of autophagy can be a major reason for the immunological tolerance break and anti-citrullinated protein autoantibody production, leading to the progression of autoimmune diseases such as RA. Several animal models of autophagy deficiency have been generated by eliminating related genes such as Atg5 and Atg16L, and several studies have shown that autophagy deficiency leads to severe autoimmune diseases, suggesting that autophagy dysregulation plays an important role in autoimmune diseases (61, 62).

Among circulating immune cells, especially the $CD4^+$ T and $CD8^+$ T cells, elevated LC3-II expression levels and decreased p62 expression levels indicate a higher level of autophagic flux (63). A number of studies focusing on RA have shown that numerous types of immune cells including $CD4^+$ T cells, macrophages, and B cells are responsible for the pathogenesis of RA (64, 65). Through the interaction of the T cell receptor with costimulatory molecules and various cytokines, naive $CD4^+$ T cells can be polarised to functionally distinct Th cells, such as Th1, Th2, Th17, follicular Th (Tfh), and regulatory T (Treg) cells. Although most $CD4^+$ T cell subsets can potentially contribute to RA pathogenesis, RA was naturally interpreted as a Th1/Th2-associated disorder and gradually recognised as a Th17-driven disease recently, with Th17 cell numbers and synovial IL-17 expression found to be increased in RA (66, 67). Th17 acts as a major source of pro-inflammatory IL-17 and Th17-related cytokines can trigger synovial fibroblasts and macrophages, which further produce some inflammatory factors and gather in the inflammatory site to heighten synovial inflammation and induce osteoclastogenesis, thus resulting in cartilage tissue destruction and bone erosion (68). B lymphocytes mediate the pathogenesis of RA through a variety of mechanisms, including serving as APCs, serving as a source and/or uptake of cytokines and chemokines, interacting with effector cells, and serving as a source of autoreactive antibodies (69). Moreover, T and B lymphocytes are responsible for the production of RANKL, which stimulates the progenitor cells to produce mature osteoclasts upon binding of RANKL by monocytes and macrophages.

As discussed above, autophagy plays a crucial role in RA immunopathogenesis via initiating and supporting several processes in both innate and adaptive immunity, including the production of ACCP and immune tolerance break. The inhibition of autophagy can be used for preventing immunopathogenesis processes in patients with RA (70). In conclusion, autophagy may sustain aberrant immune responses in RA.

*Autophagy and apoptosis resistance*

Cell proliferation and anti-apoptosis are considered as the features of the

**Table I.** Drugs and treatment measures functions and their mechanisms of action in rheumatoid arthritis (RA).

| Drug or treatment measure | Associated mechanisms |
|---|---|
| **Autophagy inducer** | |
| Metformin | Induce AMPK to inhibit STAT3 and mTORC1 |
| Jinwu Jiangu Capsule | Inhibiting the PI3K/Akt/mTOR pathway |
| Shikonin | Activating the production of reactive oxygen species (ROS) and inhibiting intracellular ATP levels, glycolysis-related proteins, and the PI3K-AKT-mTOR signalling pathway |
| Resveratrol | Induced the noncanonical autophagy pathway and restricted the cross-talk with inflammation |
| Curcumin | Restricted NF-κB signalling pathway to suppress IL-1β-induced chondrocyte apoptosis |
| Melittin | Promoted autophagy and apoptosis, and inhibited IL-1β secretion |
| TIPTP | Interacted with Rubicon to exert anti-inflammatory effects |
| Oridonin | Inhibited autophagy and proliferation, and induced apoptosis in RA-FLSs, which could be significantly reinforced by Chloroquine |
| All-trans-retinoic acid | Regulated inflammatory cytokines, inhibited NF-κB signal transduction, and promoted apoptosis and angiogenesis |
| Arsenic trioxide | Decreased p62, inflammation and catabolism protein |
| Celastrol | Calcium-dependent/-binding proteins in $Ca^{2+}$ signalling |
| Tomorou | ULK-1(unc-51 like autophagy activating kinase 1) independent autophagy pathway |
| **Autophagy inhibitor** | |
| Hydroxychloroquine and Chloroquine | Increases lysosomal pH, inhibits the process of osteoclastogenesis via inhibiting osteoclast differentiation of precursor osteoclasts into matured and antigen presentation to the T cells |
| 3-methyladenine | Phosphoinositide 3-kinase (PI3K) inhibitors |
| Electroacupuncture | Inhibit autophagy and proliferation in synoviocytes |
| Estradiol | Suppress acid-sensing ion channel 1a (ASIC1a) expression through G-protein coupled estradiol receptor 1 (GPER1) |
| Quercetin | Inhibited the formation of neutrophil extracellular traps and neutrophil activities |
| Daphnetin | Downregulated the PI3K/AKT/mTOR signaling pathway and inhibited autophagy to induces apoptosis |
| Tripterygium | Activate AKT signalling pathway to inhibit cell mobility and maintain redox balance |
| Anti-TNF drugs | Caused a significant reduction of autophagy and an increased apoptotic activation in peripheral blood mononuclear cells |
| Berberine | Inhibit of IL-21/IL-21R dependent autophagy and regulate the Th17/Treg imbalance in RA |

RA synovium (71). Autophagy promotes cell survival during stress conditions, whereas apoptosis is a process of programmed cell death (72). Several studies have reported finding elevated levels of autophagy in synovial fibroblasts and $CD4^+$ T cells from RA patients, suggesting that autophagy may play a protective role against apoptosis (73). Moreover, indirect apoptosis and apoptotic markers were reduced in the synovium of RA patients, and RA-FLS cells appeared to be resistant to apoptosis, suggesting that autophagy is involved in the progression of RA and promotes inflammatory survival and self-reactivity (51). Compared with OA FLSs, RA FLS showed increased autophagosome formation and dysfunction of mitochondrial respiration, and inhibition of autophagy could restore autophagic IL-17 resistance to apoptosis, suggesting that mitochondrial dysfunction in RA FLS was associated with cell survival (27). Besides, the homeostasis of RA FLS can be restored via inducing apoptosis and/or inhibiting autophagy, which can be a potential therapeutic strategy for RA (51, 74). Therefore, the homeostasis and dysplasia of RA pathogenesis related cells, especially RA-FLS, could be modulated by autophagy.

## The clinical application of autophagy in RA therapy

Based on the vital role autophagy plays in the regulation and homeostasis of various kinds of RA pathogenesis related cells, including adaptive and innate immune cells, osteoclasts, and FLS, thus pharmacologic manipulation of autophagy could be considered as a potential and new therapeutic strategy in RA. A variety of inducers and inhibitors of autophagy have been identified and tested in RA, based on a variety of different mechanisms (Table I).

### *Autophagy inducer*

Metformin, the agent usually used for type 2 diabetes, exerts anti-inflammatory effects by improving impaired autophagy and regulating apoptosis (75, 76). Morover, metformin also inhibits the proliferation and migration of RA FLS, downregulates the production of inflammatory cytokines of RA-FLS, inhibits osteoclast differentiation, and regulates the Th17-Treg cell imbalance via inducing AMPK to inhibit STAT3 and mTORC1 (76). Jinwu Jiangu Capsule, a medicinal formula from the Chinese Miao nationality, induced autophagy by inhibiting the PI3K/Akt/mTOR pathway in RA, with increased levels of key autophagy proteins, including Atg1, Atg5 and Atg14, and decreased the level of PI3k, Akt, and mTOR protein in synovial cells (28). Shikonin obviously reduced apoptosis-related protein levels and swelling in rat arthritic tissues, and inflammatory factors in peripheral blood with inducing apoptosis and autophagy in RA-FLSs via activating the production of reactive oxygen species (ROS) and inhibiting intracellular ATP levels, gly-

colysis-related proteins, and the PI3K-AKT-mTOR signalling pathway (77). Resveratrol induced the non-canonical autophagy pathway and restricted the cross-talk with inflammation, contributing to inhibit synovial hyperplasia in an antigen-induced arthritis model (78). Curcumin may induce autophagy and restrict the NF-κB signalling pathway to suppress IL-1β-induced chondrocyte apoptosis, exhibiting protective effects on degeneration in articular cartilage diseases (79). Melittin, the major medicinal component of honeybee venom, promotes autophagy and apoptosis, inhibits IL-1β secretion and then impairs viability in RA-FLS, preventing damage to the joints during accidental local stimulation (80). Rubicon is a negative regulator of autophagy and increases with age leading to the decline in autophagy, which could connect with TIPTP (2-(tetrahydroindazolyl) phenoxy-N-(thiadiazolyl)propanamide 2) to exert anti-inflammatory effects in RA(81). Oridonin inhibits autophagy and proliferation, and induces apoptosis in RA-FLS, which could be significantly reinforced by Chloroquine (74). All-trans-retinoic acid regulates inflammatory cytokines, inhibits NF-κB signal transduction and potentially promotes autophagy, apoptosis and angiogenesis, contributing to alleviate synovial inflammation in patients with RA (82). Low-dose arsenic trioxide synergised with Vitamin D enhances autophagic flux through significantly decreasing p62, inflammation and catabolism protein to alleviate RA symptoms (83). Celastrol induces autophagic cell death in RA synovial fibroblasts/RA-FLS and ameliorates arthritis in adjuvant-induced arthritis rats via calcium-dependent/-binding proteins in $Ca^{2+}$ signalling (84). Tomorou exerted its anti-inflammatory effects and attenuated progression of RA with upregulated microtubule-associated proteins light chain 3b (LC3b) and downregulated UNC51-like kinase 1 (ULK-1), suggesting a shift in ULK-1 independent autophagy pathway in collagen-induced arthritis mice model (85).

*Autophagy inhibitor*

As well autophagy inducers, autophagy inhibitors have also been shown to exercise protective effects on RA. Hydroxychloroquine and Chloroquine, an autophagy inhibitor which increases the lysosomal pH, has been demonstrated to have anti-inflammatory effects and be effective in RA, particularly when used in combination with other immunosuppressive drugs (86, 87). Phosphoinositide 3-kinase (PI3K) inhibitors, including 3-methyladenine (3-MA) and wortmannin, are commonly used autophagy inhibitors (88). Since the activation of PI3K is critical for the proliferation of lymphocytes, the decrease in activated lymphocytes can also be attributed to the role of 3-MA in autoimmune diseases. Electroacupuncture alleviated symptoms and synoviocyte injury of RA rats partly via inhibiting autophagy and proliferation in synoviocytes, with regulating the expression of ULK1, LC3, and Beclin1 (89). Estradiol treatment alleviated cartilage damage of rats with adjuvant arthritis against acidosis-mediated damage and autophagy by suppressing acid-sensing ion channel 1a (ASIC1a) expression through G-protein coupled estradiol receptor 1 (GPER1) with decreased autophagy level in chondrocytes (90, 91). Quercetin suppressed autophagy and promoted the apoptosis in neutrophils to inhibited the formation of neutrophil extracellular traps and neutrophil activities, contributing to ameliorate inflammation in RA mice (25). Daphnetin inhibited the proliferation of FLS in rats with collagen-induced arthritis by down-regulating the PI3K/AKT/mTOR signalling pathway and inhibited autophagy in order to induce apoptosis (92). Triptolide, the main active ingredient in Tripterygium glycosides, suppressed autophagy through activating the AKT signalling pathway to inhibit cell mobility and maintain redox balance in human synoviocyte MH7A cells (93). Therapy with anti-TNF drugs caused a significant reduction of autophagy and an increased apoptotic activation in peripheral blood mononuclear cells (51). Berberine might attenuate adjuvant-induced arthritic-FLS proliferation through inhibiting IL-21/IL-21R dependent autophagy and regulate the Th17/Treg imbalance in RA (94).

*Autophagy and therapeutic effect*

Autophagy level has also been associated with the therapeutic effect of several drugs in RA. Cai *et al*. reported that high autophagy score was found in non-responders compared with that in responders to infliximab (IFX) treatment for RA, in which Derlin-1 (DERL1) may participate in the regulation of autophagy (95).

## Conclusions

RA is a chronic autoimmune disease associated with an autoimmune response involving inappropriate activation of multiple immune cells. As mentioned above, autophagy dysfunction is an important pathophysiological process that may be involved in immune pathogenesis and associated with the innate and acquired immune systems. Autophagy had been shown to directly increase immune and non-immune cell survival, citrullinated peptides, citrullinated peptide presentation, and formation of immune and non-immune cells, such as osteoclasts, RA-FLS, DCs, B cells, and T cells. Hyperactivation of autophagy leads to apoptotic resistance, proliferation, and production of inflammatory mediators detrimental to RA, which is associated with hyperactive and dysplasia of RA-FLS and osteoclasts, leading to further destruction of joints and cartilage.

Several existing autophagy regulators, for example, CQ and HCQ, have a broad mechanism of action except for autophagy, which may cause unpredictable side effects (88). Due to the various mechanisms involved in dysregulated autophagy in RA, such as interleukin, hypoxia microenvironment, transcription factor, miRNA, and lncRNA, it is valuable to explore novel therapeutic approaches regulating autophagy based on these targets for the management and treatment of RA and which may improve clinical outcomes.

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