

REVIEW

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# Autophagy and inflammation

Mengjia Qian, Xiacong Fang and Xiangdong Wang\*

## Abstract

Autophagy is a homeostatic mechanism involved in the disposal of damaged organelles, denatured proteins as well as invaded pathogens through a lysosomal degradation pathway. Recently, increasing evidences have demonstrated its role in both innate and adaptive immunity, and thereby influence the pathogenesis of inflammatory diseases. The detection of autophagy machinery facilitated the measurement of autophagy during physiological and pathophysiological processes. Autophagy plays critical roles in inflammation through influencing the development, homeostasis and survival of inflammatory cells, including macrophages, neutrophils and lymphocytes; effecting the transcription, processing and secretion of a number of cytokines, as well as being regulated by cytokines. Recently, autophagy-dependent mechanisms have been studied in the pathogenesis of several inflammatory diseases, including infectious diseases, Crohn's disease, cystic fibrosis, pulmonary hypertension, chronic obstructive pulmonary diseases and so on. These studies suggested that modulation of autophagy might lead to therapeutic interventions for diseases associated with inflammation. Here we highlight recent advances in investigating the roles of autophagy in inflammation as well as inflammatory diseases.

**Keywords:** Autophagy, Inflammation, Inflammatory diseases

## Introduction

Autophagy is a cellular process for the disposal of damaged organelles, denatured proteins as well as invaded pathogens through a lysosomal degradation pathway [1]. It was demonstrated to be activated during starvation or other stress response, including hypoxia, reactive oxygen species, DNA damage, protein aggregates, damaged organelles or intracellular pathogens. Through autophagy, cells can eliminate damaged or harmful components, thus it allows cells to survive in response to multiple stressors [2]. Autophagy has been implicated in a number of fundamental biological processes, including aging, immunity, development, and differentiation [3].

Besides autophagy, the cellular response to stress involves numerous other pathways, of which, the most common and important is inflammation. Inflammation plays protective or destructive roles in the response to endogenous or exogenous irritation or injury. It can be provoked by physical, chemical and biologic agents, including mechanical trauma, exposure to excessive

amounts of sunlight, x-rays and radioactive materials, corrosive chemicals, extremes of heat and cold, or by infectious agents such as bacteria, viruses, and other pathogenic microorganisms. The pathogenesis of inflammation includes hemodynamic changes, leukocytes exudation, release of chemical mediators and hormonal response [4].

There are increasing evidences suggesting that autophagy plays critical role in the development and pathogenesis of inflammation and immunity response [5]. The autophagy machinery interfaces not only with most cellular stress-response pathways, but also entails direct interaction between autophagy proteins and immune signaling molecules [6]. The relationship between autophagy and inflammation is complex, both inductive and suppressive.

In this review, we summarized recent studies in autophagy and inflammation, and discussed the functions of the autophagy pathway and the autophagy proteins in inflammation and inflammatory diseases.

## Autophagy biology

### Concept understanding

Autophagy is a general term for pathways by which cytoplasmic material, including soluble macromolecules and

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organelles, is delivered to lysosomes for degradation. There are at least three different types of autophagy, including macroautophagy, chaperone-mediated autophagy and microautophagy [2]. Autophagy not only enables the reuse of intracellular constituents and supplies an amino acid pool during periods of starvation and stress response, but also helps to eliminate old/damaged organelles and extracellular organisms, thus provides basic cellular homeostasis. In addition, it was reported to play important roles in multiple pathophysiological processes including development, aging, and degeneration. Aberrant regulation of autophagy may result many diseases such as cancer [7], neurodegenerative diseases [8], and myopathies [9]. Recently, autophagy was found to be involved in immunity [5]. It can act as a direct effector by eliminating invading pathogens, regulating innate pathogen recognition, contributing to antigen presentation via major histocompatibility complex (MHC) class II molecules, and controlling B- and T cell development.

#### Molecular regulation

One breakthrough of the molecular mechanism for autophagy was achieved by identifying the genes in yeast, which are termed as autophagy-related genes (ATG) [10, 11]. These core Atg proteins are composed of four subgroups: (1) The Atg1/unc-51-like kinase (ULK) complex, which regulate the initiation of autophagy; (2) two ubiquitin-like protein [Atg12 and Atg8/microtubule-associated protein light chain 3 (LC3)] conjugation systems, which assist the elongation of the autophagic membrane; (3) the class III phosphatidylinositol 3-kinase (PI3K)/Vps34 complex I, which participate at the early stage of the autophagosome membrane formation; and (4) two transmembrane proteins, Atg9/mAtg9 (and associated proteins involved in its movement such as Atg18/WIP1) and VMP1, which may contribute to the delivery of membrane to the forming autophagosome [12]. The process of autophagy involves two major steps: induction of autophagosome and fusion of autophagosome with lysosome (Fig. 1). The ULK/Atg1 kinase complex, the autophagy-specific PI3-kinase complex, and PI(3)P effectors and their related proteins are important for the nucleation step, whereas the Atg12- and LC3/Atg8-conjugation systems are important for the elongation step.

#### Measurement

Given this strong association between autophagy and different physiological and pathophysiological processes, there is a rapidly growing need among scientists to be able to accurately detect autophagy and to study its function. Details of the autophagy measurement methods have been reviewed elsewhere [13, 14]. For example, the number of autophagosome can be measured through

electron microscopy, which is the most traditional and straightforward method [15]. However, the technique requires considerable specialized expertise since it is not easy to distinguish autolysosomes from endocytic compartments or from other vacuoles/structures once autophagosomes degradation processed. Immuno-gold labeling on ultrathin cryosections is a favorable approach to visualize autophagic structures, while specific antibodies that work properly with aldehyde fixation and the fragility of the autophagic structures are required, as well as the ultrathin cryosections techniques.

To fully understand a given biological process, it is usually critical to perform experiments to modulate the activity of the process. The autophagic activity can be inhibited or activated with agents that regulate autophagosome formation or subsequent degradation steps. However, right now we still lack highly specific autophagy inhibitors and activators. One of the most commonly used inhibitors is PI3-kinase inhibitors, including wortmannin, LY294002, or 3-methyladenine (3-MA). However, all of them are not autophagy specific and can meantime influence other cellular processes [16]. Another consideration for more specific inhibition of the autophagy pathway is to knockout or knockdown of different Atg genes, which has been reported in several studies [17, 18] and it is more specific than pharmacological agents. However even present at very low levels, some Atg proteins still function normally in autophagy, which may affect the experiment results and conclusions [19]. Thus, it is recommended that investigator not only confirm effective knockdown of autophagy protein expression levels with each siRNA, but also confirm effective inhibition of the autophagy pathway using a known autophagy-inducing stimulus such as starvation.

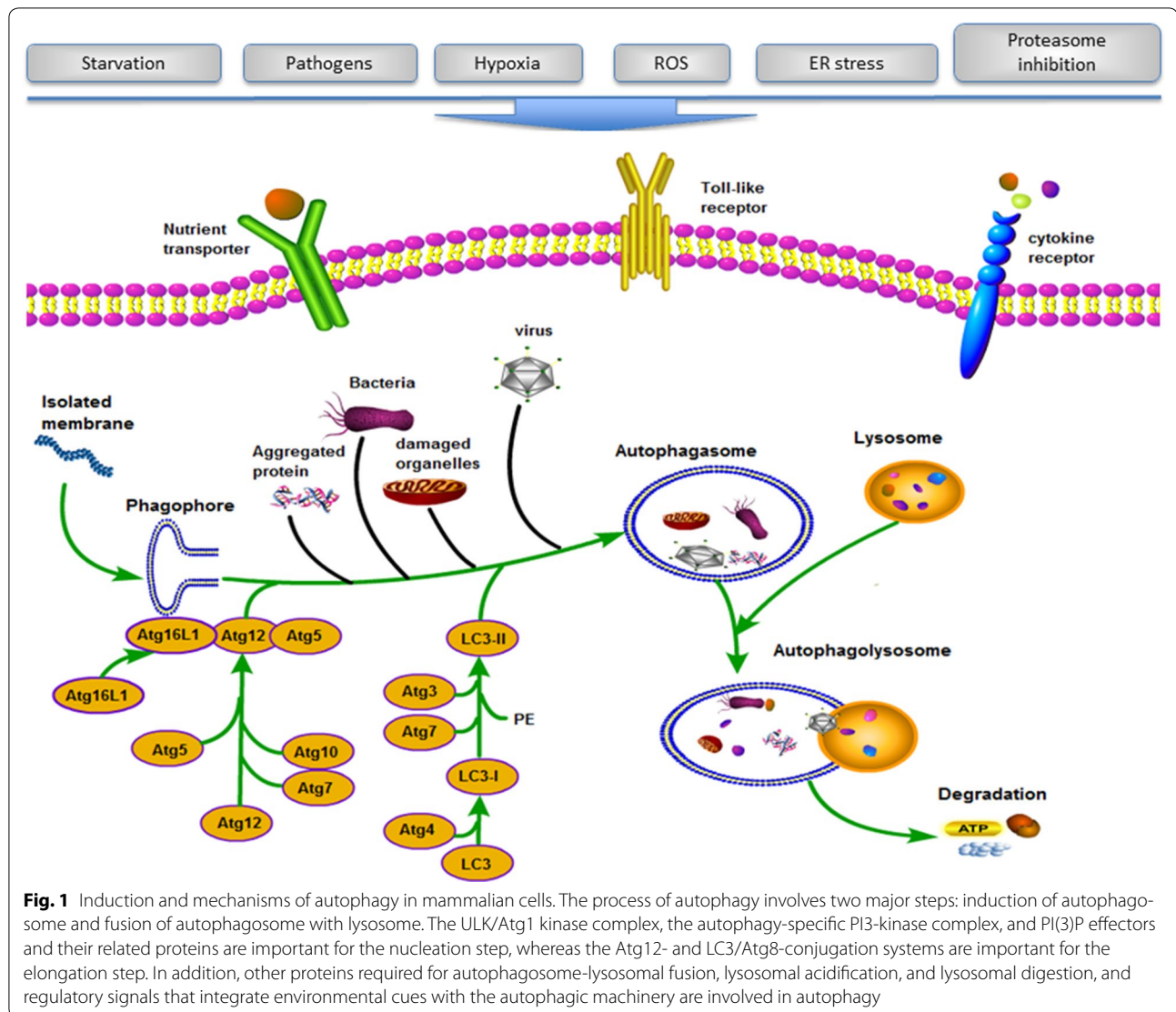
Given these potential limitations for each measurement, it is vital to state that none of these assays can be used alone to monitor or modulate cellular autophagic activity. In order to understand the effects of autophagy in a given biological settings, it is absolutely necessary to carry out multiple assays and compare the results of these investigations as a whole.

#### Autophagy in inflammation

A complex association has been identified between autophagy and inflammation. First, autophagy influences the development, homeostasis and survival of inflammatory cells, including macrophages, neutrophils and lymphocytes, which play critical roles in the development and pathogenesis of inflammation (Fig. 2).

#### Macrophages

Macrophage is essential for the host defense system. As a kind of phagocytes, it is able to uptake and kill pathogens

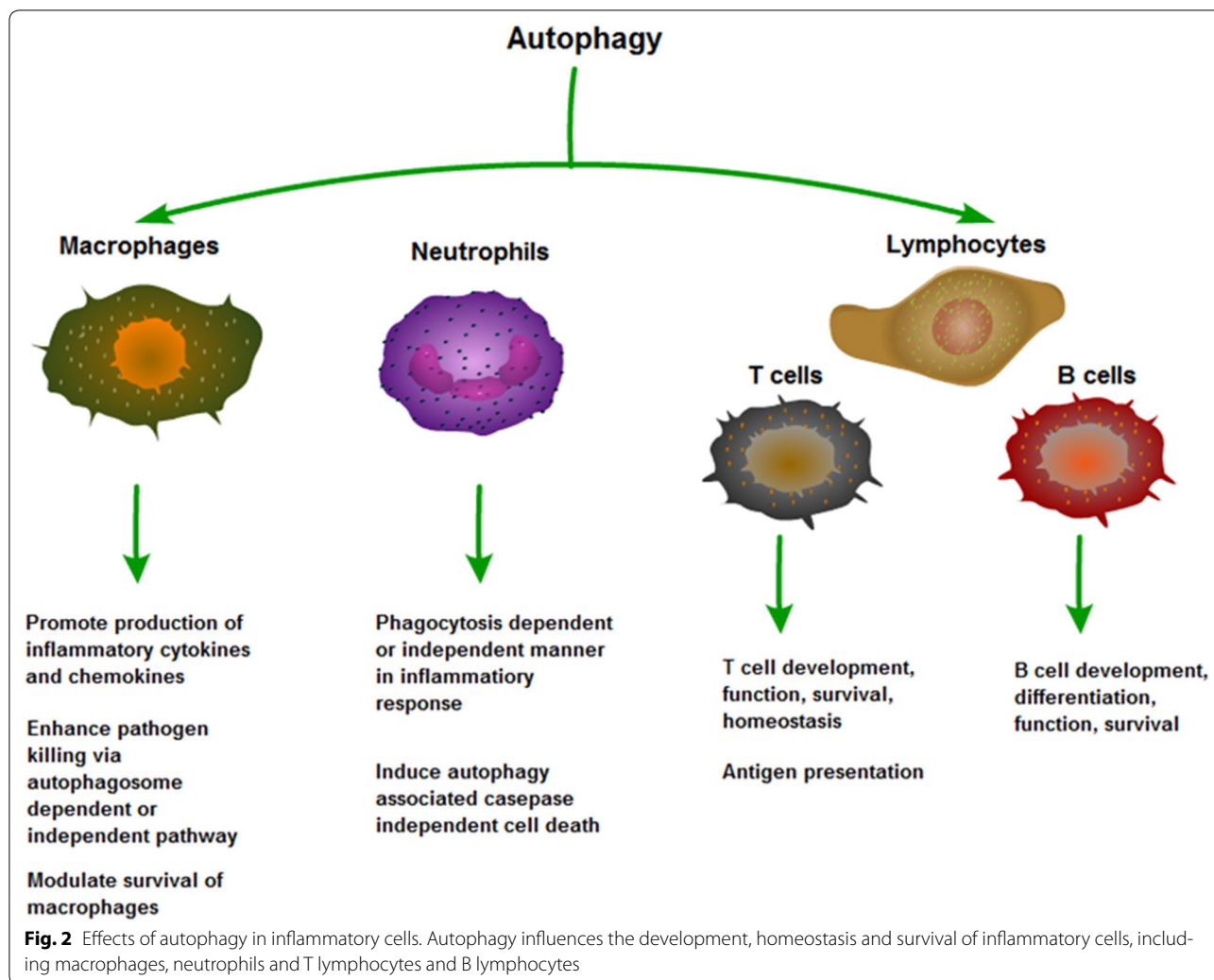


intracellularly as well as producing inflammatory cytokine and chemokines [20]. Studies have shown that macrophages lacking Atg16L1 or Atg7, essential components of the autophagic machinery, appeared enhanced production of interleukin (IL)-1 $\beta$  and IL-18 in response to inflammatory stimulation through toll-like receptor (TLR) 3/4 signal pathway. Besides, the TLR signaling can also enhance phagosome maturation and the fusion of phagosomes and lysosomes depending on the autophagy pathway proteins ATG5 and ATG7, leading to rapid acidification and enhanced killing of the ingested organism in macrophages/monocytes [21, 22]. In mice, knockout of autophagy protein Atg5 in macrophages and neutrophils increases susceptibility to infection with *L. monocytogenes* and the protozoan *T. gondii*. Atg5 was required for interferon (IFN)- $\gamma$ /LPS-induced damage to the *T. gondii* parasitophorous vacuole membrane thus killing

intracellular pathogens via autophagosome-independent process [23]. Recent studies have shown that autophagy contributed to the execution of caspase-independent cell death in activated macrophages. The study detected an increase in poly (ADP-ribose) polymerase activation and reactive oxygen species (ROS) production in lipopolysaccharide + Z-VAD (a pan caspase inhibitor)—treated macrophages, followed by the formation of autophagic bodies and macrophage cell death. The death of activated macrophages could also be beneficial in controlling the level of inflammation [24].

#### Neutrophils

Neutrophils are multifunctional cells, playing a central role in the innate immune system [25]. Inflammatory stimuli attract neutrophils to infected tissues where they engulf and inactivate microorganisms through the



fusion of phagosomes with granules and the formation of phagolysosomes, in which antimicrobial peptides and ROS act synergistically for the clearance of pathogens [26]. In addition, neutrophil activation, degranulation and release of ROS into the extracellular medium, will lead to host tissue injury [27], while neutrophil apoptosis contributes to the resolution of inflammation [28]. There is evidence that autophagy occurs in neutrophils in both phagocytosis-independent and phagocytosis-dependent manner similar to that in macrophages [29]. However, the detailed mechanisms are not completely elucidated. So far, most of the studies focused on the role of autophagy in neutrophil death.

Recent studies have demonstrated that adhesion molecules induced autophagy-associated caspase-independent cell death in neutrophils, characterized by large cytoplasmic vacuolization and organelle fusion [30]. Such vacuolized neutrophils were observed in septic shock, cystic fibrosis, rheumatoid arthritis and several skin

diseases [31], suggesting that induction of autophagy in these cells is a general phenomenon of neutrophilic inflammation response. Besides, neutrophil extracellular traps cell death (also named NETosis), is another type of programmed cell death in neutrophils and involve NADPH oxidase activity. Recent studies have shown that inhibition of autophagy prevented NETosis via preventing intracellular chromatin decondensation, thus resulting in cell death characterized by hallmarks of apoptosis [32].

### Lymphocytes

Apart from innate immunity, autophagy also plays an indispensable role in adaptive immunity, including the development and homeostasis of the immune system and antigen presentation [33]. Several tissue-specific knockout models have been developed during the past few years to study the role of autophagy in T lymphocytes [34]. T cell receptor (TCR) activation is a strong trigger for autophagy in T lymphocytes. Meantime,



autophagy-related genes are required for T cell proliferation upon TCR stimulation. T lymphocytes lacking Atg5, Atg7, Atg3 or Beclin-1 all showed impaired proliferation and enhanced cell death. The deficiency of Atg5 gene leads to the reduction of thymic cellularity and decreased number of peripheral T lymphocytes through enhancing cell death, suggesting the role of autophagic proteins in the regulation of T cell homeostasis [35]. Besides, autophagy also plays an important role in the selection and function of thymocytes. Studies have demonstrated that Atg5-deficient thymic epithelial cells underwent a disrupted process of positive and negative selection; moreover, when these cells transferred, they are apt to induce autoimmune diseases [36]. Via selectively degrading mitochondria [14] and endoplasmic reticulum [37], autophagy helps to maintain intracellular organelle homeostasis. Atg5-deficient T lymphocytes revealed a remarkable enrichment of the content of mitochondria, which was assumed to be the major reservoir of toxic reactive oxygen species [38]. Although it is demonstrated that autophagy is required for T cell survival, excessive autophagy seems to be destructive for T lymphocytes. Besides, autophagy is differentially regulated in each T helper subset. For example, Th2 cells are more resistant to growth factor-withdrawal cell death when autophagy is blocked [39]. Moreover, TCR-induced autophagy is compromised in aged CD4+ T lymphocytes while the mechanisms have been unclear [40].

Besides the indirect effects on the survival and function of T cells through autophagic proteins, autophagy also showed a direct role in antigen presentation to antigen-specific T cells (a process essential for the induction of acquired immunity) [41]. MHC class II molecules are localized on autophagosomes, and the autophagic machinery promotes the presentation of viral and self-antigens by MHC class II molecules to antigen-specific CD4+ T cells [42]. Upon infection by human simplex virus 1, autophagy controls the MHC class I-dependent presentation of viral antigens to CD8+ T cells [43].

Studies of autophagy in B lymphocytes are fewer than that in T lymphocytes. However, present studies on the role of autophagy in B lymphocytes have raised many interest and important questions for further investigation. As in T cells, Atg5 gene is also required in the development and survival of B lymphocytes. However, there is a study shown that Atg5 was only required for the maintenance of B-1a B cells, but not B-1b or B-2 B cells, and affected the number of pre-B but not pro-B cells [44], which suggested that Atg5 genes may play a critical role in the specific stages of B cell differentiation. Analysis of the expression of a Beclin 1-GFP transgene in T and B cells suggests that Beclin 1 may be involved in the development of lymphocytes and provides a critical link

between apoptosis and autophagy. Beclin 1-chimeras had greatly reduced numbers of early B cells in the bone marrow compared with controls, while the peripheral B cell compartment was normal [45]. Recent studies indicated that autophagy was induced specifically by apoptotic B cell antigen receptor signaling [46].

## **Autophagy and production of inflammatory mediators**

### **Regulation of autophagy by cytokines**

Autophagic proteins have important roles in the regulation of inflammatory mediators and will affect cytokine production in macrophages [47]. In fact, it is well established that Th1 cytokines, including IFN- $\gamma$ , TNF- $\alpha$ , IL-1, IL-2, IL-6 and TGF- $\beta$ , have been shown to have the effects of autophagy inducement, while the classical Th2 cytokines, including IL-4, IL-10 and IL-13, have the effects of inhibition [48, 49]. Activation of macrophages with IFN- $\gamma$  leads to the increased maturation of mycobacteria-containing phagosomes and autophagy in an Irgm1/IRGM-dependent manner [50], leading to increased intracellular killing of pathogens. However, IFN- $\gamma$ -induced phagosome maturation can be abrogated by TNF blockers, which suggested that IFN- $\gamma$ -induced phagosome maturation and autophagy might be TNF- $\alpha$  dependent. Interestingly, TNF- $\alpha$  is also demonstrated to play a role in stimulating autophagy in various cell types, while the actions and mechanisms are different between various cell types [51, 52]. For example, TNF- $\alpha$  can up-regulate the expression of the autophagy genes LC3 and Beclin 1 through activation of the Jun kinase signaling pathway as well as the inhibition of Akt activation [53]. TNF- $\alpha$  can also induce autophagy through ERK1/2 pathway [54, 55], while activation of NF- $\kappa$ B can inhibit TNF- $\alpha$ -induced autophagy, which is dependent on the generation of ROS [56]. On the contrary, studies have shown that the Th2 cytokines, like IL-4, IL-13 and IL-10, could inhibit starvation- or inflammatory stimulation-induced autophagy through different pathways. Inhibition of starvation-induced autophagy is dependent on the Akt pathway, while inhibition of IFN- $\gamma$  or rapamycin-induced autophagy is dependent on STAT signaling pathway [57, 58]. In addition, other cytokines, chemokines and growth factors have also been implicated in the regulation of autophagy. TGF- $\beta$  has been shown to induce autophagosome formation and can increase expression of autophagic mRNA, including Atg5, Atg7 [59]. However, the CC chemokine CCL2 (monocyte chemoattractant protein-1) and IL-6 both can stimulate autophagy and up-regulate anti-apoptotic proteins [60]. Moreover, IL-1 has also been demonstrated to stimulate autophagy [61]. However, insulin-like growth factor 1 [62] and fibroblast growth factor

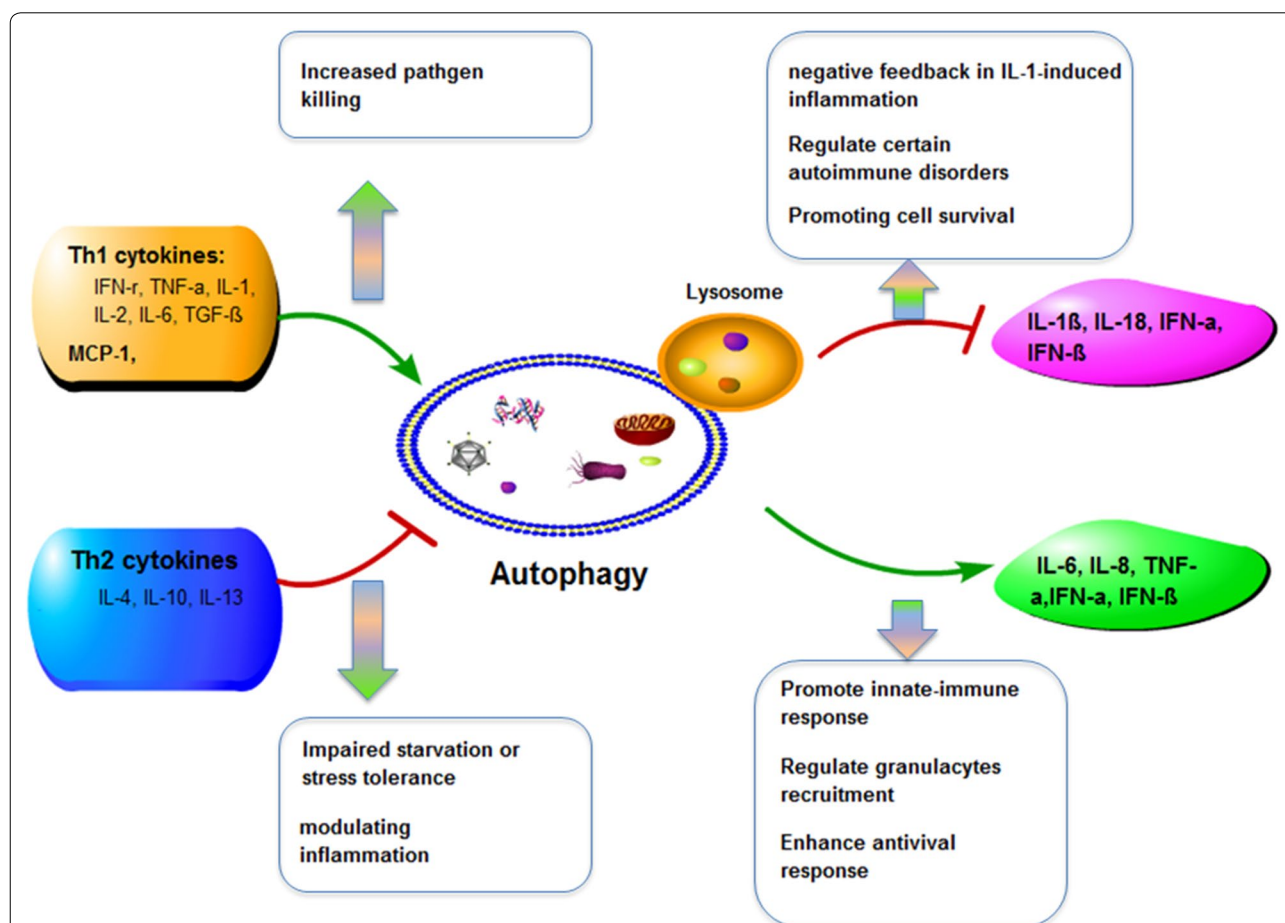
2 [63] both can inhibit autophagy, while the detailed mechanisms still need to be further studied.

**Regulation of cytokines by autophagy**

Autophagy can affect the secretion of cytokines by itself (Fig. 3). Autophagy regulates IL-1 $\beta$  secretion through at least two separate mechanisms. Loss of autophagy in macrophages or dendritic cells, either through knock down of Atg7, Atg16L1 or Beclin 1, or by treatment with the autophagy inhibitor 3-MA, stimulates the processing and secretion of IL-1 $\beta$  in response to TLR agonists [64]. This effect may be dependent on TIR-domain-containing adaptor-inducing IFN- $\beta$  (TRIF) and mitochondrial ROS and/or mitochondrial DNA and at least partially dependent on NLRP3 [65], and also may be independent of TRIF, but dependent on p38 MAPK signaling [66]. Conversely, induction of autophagy with rapamycin inhibits the secretion of IL-1 $\beta$  in murine dendritic cells in response to LPS with ATP or alum.

Given that IL-1 $\alpha$  and IL-1 $\beta$  have both been shown to induce autophagy, this may act as a negative feedback loop to control IL-1-induced inflammation. Similarly, the secretion of IL-18, IL-6 and TNF- $\alpha$  was also regulated by autophagy. Inhibition of autophagy enhanced the production of IL-18, but reduced the production of IL-6, IL-8 and TNF- $\alpha$  [67].

The modulation of autophagy in the secretion of IFN in virally-infected cells is controversial. Atg5 or autophagy deficient plasmacytoid dendritic cells was failed to produce IFN- $\alpha$  in response to infection with vesicular stomatitis virus (VSV) [68]. In contrast, other studies have demonstrated that embryonic fibroblasts from Atg5-/- mice are more resistant to VSV infection and produce higher levels of IFN-a and IFN-b mRNA in response to VSV or stimulation with dsRNA [poly(I:C)], compared with WT controls [69]. In hepatitis C virus infected hepatocytes, Atg7 knockdown induced IFN signal pathway, thus induced cell death [70, 71].



**Fig. 3** The interactions of autophagy and inflammatory cytokines or chemokines. Autophagy can affect the secretion of cytokines by itself, including Th1 cytokines, IFN- $\gamma$ , TNF- $\alpha$ , IL-1, IL-2, IL-6, TGF- $\beta$ , MCP-1 and Th2 cytokines, IL-4, IL-10 and IL-13, as well as other cytokines, IL-1 $\beta$ , IL-18, IFN- $\alpha$ , IFN- $\beta$ , IL-8

### Autophagy in acute and chronic inflammatory disease

Recently, emerging evidences have indicated that the process of autophagy may play an essential role in acute and chronic inflammatory processes, and thereby potentially impact the outcome of disease progression.

#### Crohn's disease

Crohn's disease (CD) is a chronic and sometimes debilitating form of inflammatory bowel disease characterized by inflammation, ulceration, and neutrophil influx in the intestinal epithelia [72]. The underlying cause of CD is unknown; however it is clear that both environmental and genetic factors are required for its development. Recent studies have found links between autophagy related genes such as ATG16L, NOD2 and immunity-related p47 guanosine triphosphatase (IRGM) and the pathogenesis of CD through bioinformatics.

Nod2, a protein of the NLR family, functions as an intracellular bacteria sensor and was required in the induction of autophagy by bacterial peptidoglycan cell wall in intestinal epithelial cells [73]. Three major NOD2 variants are associated with CD; two missense mutations, R702W and G908R, and one frameshift mutation, L1007fsinsC. Human studies suggest that these NOD2 variants result in a loss of function [74]. A T300A variant in the ATG16L gene, which plays a key role in autophagosome formation, has been identified as an associated risk factor for CD [75]. Another genome-wide association study suggested variants in the gene encoding IRGM were associated with CD [76]. Studies revealed variants of these genes may have been associated with the impaired clearance of harmful bacterial species associated with CD, impaired antigen presentation, and also with the higher production of proinflammatory cytokines implicated in the pathogenesis of CD, while further studies are still warranted to examine the contribution of these genes in the pathogenesis and treatment of CD.

#### Infectious disease

Autophagy can exert anti-bacterial and anti-pathogen functions, which have already been demonstrated in several infectious diseases [77]. Take the case of *Mycobacterium tuberculosis* infection, the autophagy pathway and/or autophagy proteins have a crucial role in resistance to bacterial, viral and protozoan infection in metazoan organisms. *Mycobacterium tuberculosis* is an intracellular pathogen persisting within phagosomes through interference with phagolysosome biogenesis [78]; while experimental stimulation of autophagy can overcome the trafficking block imposed by *M. tuberculosis* [79]. Conversely, chemical inhibitors of autophagy will promote infection [80]. Additional studies have implicated the role

of autophagy in defense against other microbial pathogens, such as *Legionella pneumophila* [81], *Dictyostelium discoideum* [82], *Shigella* [83] and so on.

#### Pulmonary hypertension

Pulmonary arterial hypertension (PAH) is a complex disease of varying etiologies which characterized mainly by vasoconstriction, increased pulmonary artery pressure, thickening and fibrosis of the artery [84]. Recent studies have examined the prospective role of autophagic proteins in experimental models of PAH. Exposure to chronic hypoxia in mice resulted in the increased expression of LC3B and its conversion of LC3B-II in the lung. Increased LC3B staining was also observed in small pulmonary vessels of animals subjected to hypoxia. Moreover, hypoxic lungs contained elevated numbers of autophagosomes, as detected by electron microscopy. Importantly, mice genetically deleted for LC3B (LC3B<sup>-/-</sup>) displayed increased indices of pulmonary hypertension, including increased right ventricular systolic pressure, and Fulton's index relative to wild-type mice, after chronic hypoxia [85]. LC3 exerts protective effects in the pathogenesis of PAH through hypoxia-specific inhibitory effects on the parameters involved in proliferative signaling (MAPK3/ERK1–MAPK1/ERK2 activation, VEGF secretion), as well as the inhibitory effects on pulmonary artery endothelial cells proliferation [86, 87].

#### Cystic fibrosis

The pathological features of cystic fibrosis (CF) include aberrant accumulation of hyperviscous mucous in the airways, impaired mucociliary clearance, and increased inflammation partly due to the mutation of cystic fibrosis transmembrane conductance regulator (CFTR) [88]. Recent studies have demonstrated that human airway epithelial cells from CF patients, which bear the mutation in the CFTR gene, have an impaired autophagic response. Defective CFTR-induced upregulation of ROS and tissue transglutaminase drive the crosslinking of Beclin 1, leading to sequestration of PI3-K complex III and accumulation of p62 [89], which regulates aggresomal formation. Both CFTR knockdown and the overexpression of GFP-tagged-CFTRF508del induce Beclin 1 downregulation and defective autophagy in non-CF airway epithelia through the ROS-tissue transglutaminase pathway [90]. These data linked the CFTR defect to autophagy deficiency, leading to the accumulation of protein aggregates and to lung inflammation.

#### Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a chronic airway inflammatory disease characterized by progressive deterioration of lung function [91, 92]. More

and more evidences have demonstrated that macroautophagy plays a significant and complex role in COPD pathogenesis [93, 94]. In lung biopsy specimens from patients with COPD, Western blot detected elevated level of LC3b-II protein when compared with non-COPD control patients. The level of LC3b-II correlated positively with clinical severity as measured by global initiative for COPD score [95]. Further studies confirmed that exposure of lung epithelial cell lines and fibroblasts to cigarette smoke extract induced the accumulation of autophagosomes on electron micrographs and enhanced levels of LC3b-II protein [96]; while genetic depletion of two macroautophagy pathway members, Beclin-1 and LC3b, reduced the rate of cell death in cigarette smoke extract-exposed cells [97]. Besides, studies also found that the macroautophagic flux in macrophages from COPD patients was greatly inhibited, which may contribute to the excessive inflammatory response in airway [98].

#### Other systemic inflammatory diseases

Genome-wide association studies have linked several single nucleotide polymorphisms in Atg5 to systemic lupus erythematosus susceptibility [99]. Systemic lupus erythematosus is a multifactorial, heterogeneous disease characterized by autoimmune responses against self-antigens generated from dying cells. However, further studies are needed to determine the link between autophagy and systemic lupus erythematosus pathogenesis. Studies also suggested that defects in autophagy might contribute to inflammation-associated metabolic diseases such as diabetes and obesity via effecting on endoplasmic reticulum stress and insulin resistance [100].

#### Therapeutic potential and future perspective

The present review summarized the previous studies which discussed the role of autophagic processes in the pathogenesis of inflammation, including elimination of pathogens, regulation of innate or adaptive immune response. Besides, we also referred to the potential therapeutic role of autophagy in some inflammatory diseases. Recently, increasing evidences also identified its role in carcinogenesis [101]. These observations collectively implicate that autophagy is an important modulator of disease pathogenesis. However, although progress has been made in elucidation the role of macroautophagy in inflammation, our understanding of the molecular mechanisms and pathways of autophagy and its relationship with inflammatory of inflammatory disease is still quite primitive.

As with any other core cellular processes, turning basic science knowledge about autophagy into therapies is difficult because of the interdependent nature

of biochemical pathways. However, from a clinical perspective, the contributions of macroautophagy to the pathogenesis of inflammation and inflammatory diseases have potential therapeutic and diagnostic implications. From a therapeutic standpoint, the possibility that macroautophagy may play different physiological roles is depending on the cell type; as well as the fact that its different functions in different inflammatory conditions will lead to the result that when simply providing a chemical stimulator or inhibitor of macroautophagy to patients, they could have unpredictable consequences, such as improving symptoms or getting worse. From a diagnostic standpoint, the fact that macroautophagy marker proteins such as LC3b are increased before the onset of apoptosis suggests that they might prove useful as early biomarkers of some inflammatory disease. Future research will focus on the detailed mechanisms of autophagy pathways in specific diseases, as well as the interaction of autophagy with other pathophysiological processes thus determining whether the autophagic pathway can be manipulated for therapeutic gain in the treatment of inflammatory diseases and/or other diseases including cancer.

#### Abbreviations

MHC: major histocompatibility complex; ATG: autophagy-related genes; ULK: unc-51-like kinase; LC3: microtubule-associated protein light chain 3; PI3 K: phosphatidylinositol 3-kinase; GFP: green fluorescent protein; RFP: red fluorescent protein; TLR: toll-like receptor; IL: interleukin; ROS: reactive oxygen species; TCR: T cell receptor; IFN: interferon; LPS: lipopolysaccharide; VSV: vesicular stomatitis virus; CD: Crohn's disease; PAH: pulmonary arterial hypertension; CF: cystic fibrosis; CFTR: transmembrane conductance regulator; COPD: chronic obstructive pulmonary disease.

#### Authors' contributions

MJQ and XCF was involved in the conception, design and drafting of the manuscript. XDW was involved in the revision and final acceptance of the manuscript. All authors read and approved the final manuscript.

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#### Competing interests

The authors declare that they have no competing interests.

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## References

- Wang C, Wang Y, McNutt MA, Zhu WG (2011) Autophagy process is associated with anti-neoplastic function. *Acta Biochim Biophys Sin* 43:425–432
- Fougeray S, Pallet N (2015) Mechanisms and biological functions of autophagy in diseased and ageing kidneys. *Nat Rev Nephrol* 11:34–45
- Chaabane W, User SD, El-Gazzah M, Jaksik R, Sajjadi E, Rzeszowska-Wolny J et al (2013) Autophagy, apoptosis, mitoptosis and necrosis: interdependence between those pathways and effects on cancer. *Arch Immunol Ther Exp* 61:43–58
- Keta O, Bulat T, Golić I et al (2016) The impact of autophagy on cell death modalities in CRL-5876 lung adenocarcinoma cells after their exposure to  $\gamma$ -rays and/or erlotinib. *Cell Biol Toxicol* 32(2):83–101. doi:10.1007/s10565-016-9319-z
- Zhong Z, Sanchez-Lopez E, Karin M (2016) Autophagy, inflammation, and immunity: a troika governing cancer and its treatment. *Cell* 166:288–298
- Saitoh T, Akira S (2010) Regulation of innate immune responses by autophagy-related proteins. *J Cell Biol* 189:925–935
- Pan H, Chen L, Xu Y, Han W, Lou F, Fei W et al (2016) Autophagy-associated immune responses and cancer immunotherapy. *Oncotarget* 7:21235–21246
- Lee JA, Yue Z, Gao FB (2016) Autophagy in neurodegenerative diseases. *Brain Res* 1649:141–142
- Lai CH, Tsai CC, Kuo WW, Ho TJ, Day CH, Pai PY et al (2016) Multi-strain probiotics inhibit cardiac myopathies and autophagy to prevent heart injury in high-fat diet-fed rats. *Int J Med Sci* 13:277–285
- Tsukada M, Ohsumi Y (1993) Isolation and characterization of autophagy-defective mutants of *Saccharomyces cerevisiae*. *FEBS Lett* 333:169–174
- Thumm M, Egner R, Koch B, Schlumpberger M, Straub M, Veenhuis M et al (1994) Isolation of autophagocytosis mutants of *Saccharomyces cerevisiae*. *FEBS Lett* 349:275–280
- Xie Z, Klionsky DJ (2007) Autophagosome formation: core machinery and adaptations. *Nat Cell Biol* 9:1102–1109
- Demishtein A, Porat Z, Elazar Z, Shvets E (2015) Applications of flow cytometry for measurement of autophagy. *Methods* 75:87–95
- Guimaraes RS, Delorme-Axford E, Klionsky DJ, Reggiori F (2015) Assays for the biochemical and ultrastructural measurement of selective and nonselective types of autophagy in the yeast *Saccharomyces cerevisiae*. *Methods* 75:141–150
- Kovacs AL (2015) The application of traditional transmission electron microscopy for autophagy research in *Caenorhabditis elegans*. *Biophys Rep* 1:99–105
- Liu H, Zhang L, Zhang X, Cui Z (2017) PI3K/AKT/mTOR pathway promotes progesterin resistance in endometrial cancer cells by inhibition of autophagy. *Onco Targets Ther* 10:2865–2871
- Lin CW, Jan MS, Kuo JH (2014) Autophagy-related gene expression analysis of wild-type and atg5 gene knockout mouse embryonic fibroblast cells treated with polyethylenimine. *Mol Pharm* 11:3002–3008
- Dong RQ, Wang ZF, Zhao C, Gu HR, Hu ZW, Xie J et al (2015) Toll-like receptor 4 knockout protects against isoproterenol-induced cardiac fibrosis: the role of autophagy. *J Cardiovasc Pharmacol Ther* 20:84–92
- Hosokawa N, Hara Y, Mizushima N (2007) Generation of cell lines with tetracycline-regulated autophagy and a role for autophagy in controlling cell size. *FEBS Lett* 581:2623–2629
- Satoh T, Akira S (2012) Physiological roles and differentiation mechanism of M2 macrophage. *Nihon Rinsho Jpn J Clin Med* 70(Suppl 8):236–241
- Franco LH, Fleuri AKA, Pellison NAC, Quirino GFS, Horta CV, Carvalho RVH et al (2017) Autophagy downstream of endosomal toll-like receptors signaling in macrophages is a key mechanism for resistance to leishmania major infection. *J Biol Chem*. doi:10.1074/jbc.M117.780981
- Agrawal V, Jaiswal MK, Mallers T, Katara GK, Gilman-Sachs A, Beaman KD et al (2015) Altered autophagic flux enhances inflammatory responses during inflammation-induced preterm labor. *Sci Rep* 5:9410
- Zhao Z, Fux B, Goodwin M, Dunay IR, Strong D, Miller BC et al (2008) Autophagosome-independent essential function for the autophagy protein Atg5 in cellular immunity to intracellular pathogens. *Cell Host Microbe* 4:458–469
- Lai YC, Chuang YC, Chang CP, Yeh TM (2015) Macrophage migration inhibitory factor has a permissive role in concanavalin A-induced cell death of human hepatoma cells through autophagy. *Cell Death Dis* 6:e2008
- Thieblemont N, Wright HL, Edwards SW, Witko-Sarsat V (2016) Human neutrophils in auto-immunity. *Semin Immunol* 28:159–173
- Witter AR, Okunnu BM, Berg RE (2016) The essential role of neutrophils during infection with the intracellular bacterial pathogen *Listeria monocytogenes*. *J Immunol* 197:1557–1565
- Herrmann JM, Meyle J (2000) Neutrophil activation and periodontal tissue injury. *Periodontology* 2015(69):111–127
- El Kebir D, Filep JG (2013) Targeting neutrophil apoptosis for enhancing the resolution of inflammation. *Cells* 2:330–348
- Suzuki E, Maverakis E, Sarin R, Bouchareychas L, Kuchroo VK, Nestle FO et al (2016) T cell-independent mechanisms associated with neutrophil extracellular trap formation and selective autophagy in IL-17A-mediated epidermal hyperplasia. *J Immunol* 197:4403–4412
- Itoh H, Matsuo H, Kitamura N, Yamamoto S, Higuchi T, Takematsu H et al (2015) Enhancement of neutrophil autophagy by an IMiG preparation against multidrug-resistant bacteria as well as drug-sensitive strains. *J Leukoc Biol* 98:107–117
- Mihalache CC, Yousefi S, Conus S, Villiger PM, Schneider EM, Simon HU (2011) Inflammation-associated autophagy-related programmed necrotic death of human neutrophils characterized by organelle fusion events. *J Immunol* 186:6532–6542
- Tang S, Zhang Y, Yin SW, Gao XJ, Shi WW, Wang Y et al (2015) Neutrophil extracellular trap formation is associated with autophagy-related signalling in ANCA-associated vasculitis. *Clin Exp Immunol* 180:408–418
- Zhou J, Zhu Z, Bai C, Sun H, Wang X (2014) Proteomic profiling of lymphocytes in autoimmunity, inflammation and cancer. *J Transl Med* 12:16
- Wang DC, Wang X, Chen C (2016) Effects of anti-human T lymphocyte immune globulins in patients: new or old. *J Cell Mol Med* 20:1796–1799
- Riffelmacher T, Simon AK (2017) Mechanistic roles of autophagy in hematopoietic differentiation. *FEBS J* 284:1008–1020
- Schuster C, Gerold KD, Schober K, Probst L, Boerner K, Kim MJ et al (2015) The autoimmunity-associated gene CLEC16A modulates thymic epithelial cell autophagy and alters T cell selection. *Immunity* 42:942–952
- Stephenson LM, Miller BC, Ng A, Eisenberg J, Zhao Z, Cadwell K et al (2009) Identification of Atg5-dependent transcriptional changes and increases in mitochondrial mass in Atg5-deficient T lymphocytes. *Autophagy* 5:625–635
- Honda S, Arakawa S, Nishida Y, Yamaguchi H, Ishii E, Shimizu S (2014) ULK1-mediated Atg5-independent macroautophagy mediates elimination of mitochondria from embryonic reticulocytes. *Nat Commun* 5:4004
- Kabat AM, Harrison OJ, Riffelmacher T, Moghaddam AE, Pearson CF, Laing A et al (2016) The autophagy gene Atg16l1 differentially regulates Treg and TH2 cells to control intestinal inflammation. *ELife* 5:e12444
- van Loosdregt J, Rossetti M, Spreafico R, Moshref M, Olmer M, Williams GW et al (2016) Increased autophagy in CD4+ T cells of rheumatoid arthritis patients results in T-cell hyperactivation and apoptosis resistance. *Eur J Immunol* 46:2862–2870
- Munz C (2016) Autophagy proteins in antigen processing for presentation on MHC molecules. *Immunol Rev* 272:17–27
- Munz C (2016) Autophagy beyond intracellular MHC class II antigen presentation. *Trends Immunol* 37:755–763
- Chemali M, Radtke K, Desjardins M, English L (2011) Alternative pathways for MHC class I presentation: a new function for autophagy. *Cell Mol Life Sci* 68:1533–1541
- Miller BC, Zhao Z, Stephenson LM, Cadwell K, Pua HH, Lee HK et al (2008) The autophagy gene ATG5 plays an essential role in B lymphocyte development. *Autophagy* 4:309–314
- Arsov I, Adebayo A, Kucerova-Levisohn M, Haye J, MacNeil M, Papanastasiou FN et al (2011) A role for autophagic protein beclin 1 early in lymphocyte development. *J Immunol* 186:2201–2209
- Zhou A, Li S, Khan FA, Zhang S (2016) Autophagy postpones apoptotic cell death in PRRSV infection through Bad-Becn1 interaction. *Virulence* 7:98–109

47. Hosogi S, Kusuzaki K, Inui T, Wang X, Marunaka Y (2014) Cytosolic chloride ion is a key factor in lysosomal acidification and function of autophagy in human gastric cancer cell. *J Cell Mol Med* 18:1124–1133
48. Wu TT, Li WM, Yao YM (2016) Interactions between autophagy and inhibitory cytokines. *Int J Biol Sci* 12:884–897
49. Shi L, Dong N, Fang X, Wang X (2016) Regulatory mechanisms of TGF-beta1-induced fibrogenesis of human alveolar epithelial cells. *J Cell Mol Med* 20:2183–2193
50. Sandri M (2010) Autophagy in health and disease. 3. Involvement of autophagy in muscle atrophy. *Am J Physiol Cell Physiol* 298:C1291–C1297
51. Chen D, Liu J, Lu L, Huang Y, Wang Y, Wang M et al (2016) Emodin attenuates TNF-alpha-induced apoptosis and autophagy in mouse C2C12 myoblasts through the phosphorylation of Akt. *Int Immunopharmacol* 34:107–113
52. Wang XH, Zhu L, Hong X, Wang YT, Wang F, Bao JP et al (2016) Resveratrol attenuated TNF-alpha-induced MMP-3 expression in human nucleus pulposus cells by activating autophagy via AMPK/SIRT1 signaling pathway. *Exp Biol Med* (Maywood) 241:848–853
53. Jia G, Cheng G, Gangahar DM, Agrawal DK (2006) Insulin-like growth factor-1 and TNF-alpha regulate autophagy through c-jun N-terminal kinase and Akt pathways in human atherosclerotic vascular smooth cells. *Immunol Cell Biol* 84:448–454
54. Sivaprasad U, Basu A (2008) Inhibition of ERK attenuates autophagy and potentiates tumour necrosis factor-alpha-induced cell death in MCF-7 cells. *J Cell Mol Med* 12:1265–1271
55. Venkatesan T, Choi YW, Mun SP, Kim YK (2016) Pinus radiata bark extract induces caspase-independent apoptosis-like cell death in MCF-7 human breast cancer cells. *Cell Biol Toxicol* 32:451–464
56. Shen X, Ma L, Dong W, Wu Q, Gao Y, Luo C et al (2016) Autophagy regulates intracerebral hemorrhage induced neural damage via apoptosis and NF-kappaB pathway. *Neurochem Int* 96:100–112
57. Park HJ, Lee SJ, Kim SH, Han J, Bae J, Kim SJ et al (2011) IL-10 inhibits the starvation induced autophagy in macrophages via class I phosphatidylinositol 3-kinase (PI3K) pathway. *Mol Immunol* 48:720–727
58. Ni Cheallaigh C, Keane J, Lavelle EC, Hope JC, Harris J (2011) Autophagy in the immune response to tuberculosis: clinical perspectives. *Clin Exp Immunol* 164:291–300
59. Ding Y, Choi ME (2014) Regulation of autophagy by TGF-beta: emerging role in kidney fibrosis. *Semin Nephrol* 34:62–71
60. Xue H, Yuan G, Guo X, Liu Q, Zhang J, Gao X et al (2016) A novel tumor-promoting mechanism of IL6 and the therapeutic efficacy of tocilizumab: hypoxia-induced IL6 is a potent autophagy initiator in glioblastoma via the p-STAT3-MIR155-3p-CREBRF pathway. *Autophagy* 12:1129–1152
61. Khan NM, Ansari MY, Haqqi TM (2017) Sucrose, but not glucose, blocks IL-1-beta-induced inflammatory response in human chondrocytes by inducing autophagy via AKT/mTOR pathway. *J Cell Biochem* 118:629–639
62. Liu ZQ, Zhao S, Fu WQ (2016) Insulin-like growth factor 1 antagonizes lumbar disc degeneration through enhanced autophagy. *Am J Transl Res* 8:4346–4353
63. Wang X, Qi H, Wang Q, Zhu Y, Jin M, Tan Q et al (2015) FGFR3/fibroblast growth factor receptor 3 inhibits autophagy through decreasing the ATG12-ATG5 conjugate, leading to the delay of cartilage development in achondroplasia. *Autophagy* 11:1998–2013
64. Crisan TO, Plantinga TS, van de Veerdonk FL, Farcas MF, Stoffels M, Kullberg BJ et al (2011) Inflammasome-independent modulation of cytokine response by autophagy in human cells. *PLoS ONE* 6:e18666
65. Alfonso-Loeches S, Urena-Peralta JR, Morillo-Bargues MJ, Oliver-De La Cruz J, Guerri C (2014) Role of mitochondria ROS generation in ethanol-induced NLRP3 inflammasome activation and cell death in astroglial cells. *Front Cell Neurosci* 8:216
66. Wang Q, Ren J (2016) mTOR-independent autophagy inducer trehalose rescues against insulin resistance-induced myocardial contractile anomalies: role of p38 MAPK and Foxo1. *Pharmacol Res* 111:357–373
67. Harris J, Hartman M, Roche C, Zeng SG, O'Shea A, Sharp FA et al (2011) Autophagy controls IL-1beta secretion by targeting pro-IL-1beta for degradation. *J Biol Chem* 286:9587–9597
68. Lee HK, Lund JM, Ramanathan B, Mizushima N, Iwasaki A (2007) Autophagy-dependent viral recognition by plasmacytoid dendritic cells. *Science* 315:1398–1401
69. Jounai N, Takeshita F, Kobiyama K, Sawano A, Miyawaki A, Xin KQ et al (2007) The Atg5 Atg12 conjugate associates with innate antiviral immune responses. *Proc Natl Acad Sci USA* 104:14050–14055
70. Shrivastava S, Raychoudhuri A, Steele R, Ray R, Ray RB (2011) Knock-down of autophagy enhances the innate immune response in hepatitis C virus-infected hepatocytes. *Hepatology* 53:406–414
71. Medvedev R, Hildt E, Ploen D (2017) Look who's talking—the crosstalk between oxidative stress and autophagy supports exosomal-dependent release of HCV particles. *Cell Biol Toxicol* 33(3):211–231
72. Rubin DT, Feld LD, Goepfing SR, Margolese J, Rosh J, Rubin M et al (2017) The Crohn's and colitis foundation of america survey of inflammatory bowel disease patient health care access. *Inflamm Bowel Dis* 23:224–232
73. Kaarniranta K, Tokarz P, Koskela A, Paterno J, Blasiak J (2017) Autophagy regulates death of retinal pigment epithelium cells in age-related macular degeneration. *Cell Biol Toxicol* 33(2):113–128
74. Quaglietta L, te Velde A, Staiano A, Troncone R, Hommes DW (2007) Functional consequences of NOD2/CARD15 mutations in Crohn disease. *J Pediatr Gastroenterol Nutr* 44:529–539
75. Boada-Romero E, Serramito-Gomez I, Sacristan MP, Boone DL, Xavier RJ, Pimentel-Muinos FX (2016) The T300A Crohn's disease risk polymorphism impairs function of the WD40 domain of ATG16L1. *Nat Commun* 7:11821
76. Rufini S, Ciccacci C, Di Fusco D, Ruffa A, Pallone F, Novelli G et al (2015) Autophagy and inflammatory bowel disease: association between variants of the autophagy-related IRGM gene and susceptibility to Crohn's disease. *Dig Liver Dis* 47:744–750
77. Lippai M, Szatmari Z (2017) Autophagy—from molecular mechanisms to clinical relevance. *Cell Biol Toxicol* 33(2):145–168
78. Yu X, Li C, Hong W, Pan W, Xie J (2013) Autophagy during *Mycobacterium tuberculosis* infection and implications for future tuberculosis medications. *Cell Signal* 25:1272–1278
79. Deretic V, Delgado M, Vergne I, Master S, De Haro S, Ponpuak M et al (2009) Autophagy in immunity against *Mycobacterium tuberculosis*: a model system to dissect immunological roles of autophagy. *Curr Top Microbiol Immunol* 335:169–188
80. Honda A, Harrington E, Cornella-Taracido I, Furet P, Knapp MS, Glick M et al (2016) Potent, selective, and orally bioavailable inhibitors of VPS34 provide chemical tools to modulate autophagy in vivo. *ACS Med Chem Lett* 7:72–76
81. Rolando M, Escoll P, Buchrieser C (2016) *Legionella pneumophila* restrains autophagy by modulating the host's sphingolipid metabolism. *Autophagy* 12:1053–1054
82. Lohia R, Jain P, Jain M, Burma PK, Shrivastava A, Saran S (2017) Dictyostelium discoideum Sir2D protein, an ortholog of human 1 SIRT1, modulates cell type specific gene expression and is involved in autophagy. *Int J Dev Biol* 61(1–2):95–104. doi:10.1087/ijdb.160038ss
83. Krokowski S, Lobato-Marquez D, Mostowy S (2016) Mitochondria promote septin assembly into cages that entrap *Shigella* for autophagy. *Autophagy*. doi:10.1080/15548627.2016.1228496
84. Skride A, Sablinskas K, Avidan Y, Rudzitis A, Lejnieks A (2017) Pulmonary arterial hypertension associated with connective tissue disease: insights from latvian PAH registry. *Eur J Intern Med* 40:e13–e14
85. Lee SJ, Smith A, Guo L, Alastalo TP, Li M, Sawada H et al (2011) Autophagic protein LC3B confers resistance against hypoxia-induced pulmonary hypertension. *Am J Respir Crit Care Med* 183:649–658
86. Lahm T, Petrache I (2012) LC3 as a potential therapeutic target in hypoxia-induced pulmonary hypertension. *Autophagy* 8:1146–1147
87. Zhou Y, Zhang S, Dai C, Tang S, Yang X, Li D et al (2016) Quinocetone triggered ER stress-induced autophagy via ATF6/DAPK1-modulated mAtg9a trafficking. *Cell Biol Toxicol* 32:141–152
88. Leung GK, Ying D, Mak CC, Chen XY, Xu W, Yeung KS et al (2017) CFTR founder mutation causes protein trafficking defects in Chinese patients with cystic fibrosis. *Mol Genet Genom Med* 5:40–49
89. Velentzas PD, Velentzas AD, Mpakou VE, Antonelou MH, Margaritis LH, Papassideri IS, Stravopodis DJ (2013) Detrimental effects of proteasome inhibition activity in *Drosophila melanogaster*: implication of ER stress, autophagy, and apoptosis. *Cell Biol Toxicol* 29(1):13–37
90. Luciani A, Villella VR, Esposito S, Brunetti-Pierri N, Medina D, Settembre C et al (2010) Defective CFTR induces aggressive formation and lung inflammation in cystic fibrosis through ROS-mediated autophagy inhibition. *Nat Cell Biol* 12:863–875

91. Wu X, Sun X, Chen C, Bai C, Wang X (2014) Dynamic gene expressions of peripheral blood mononuclear cells in patients with acute exacerbation of chronic obstructive pulmonary disease: a preliminary study. *Crit Care* 18:508
92. Wang X (2016) New biomarkers and therapeutics can be discovered during COPD-lung cancer transition. *Cell Biol Toxicol* 32:359–361
93. Zhang X, Yin H, Li Z, Zhang T, Yang Z (2016) Nano-TiO<sub>2</sub> induces autophagy to protect against cell death through antioxidative mechanism in podocytes. *Cell Biol Toxicol* 32(6):513–527
94. Wu X, Yuan B, Lopez E, Bai C, Wang X (2014) Gene polymorphisms and chronic obstructive pulmonary disease. *J Cell Mol Med* 18:15–26
95. Denardin CC, Martins LA, Parisi MM et al (2017) Autophagy induced by purple pitanga (*Eugenia uniflora* L.) extract triggered a cooperative effect on inducing the hepatic stellate cell death. *Cell Biol Toxicol* 33(2):197–206
96. Chen ZH, Lam HC, Jin Y, Kim HP, Cao J, Lee SJ et al (2010) Autophagy protein microtubule-associated protein 1 light chain-3B (LC3B) activates extrinsic apoptosis during cigarette smoke-induced emphysema. *Proc Natl Acad Sci USA* 107:18880–18885
97. Alarcon-Riquelme ME, Ziegler JT, Molineros J, Howard TD, Moreno-Estrada A, Sanchez-Rodriguez E et al (2016) Genome-wide association study in an amerindian ancestry population reveals novel systemic lupus erythematosus risk loci and the role of European admixture. *Arthritis Rheumatol* 68:932–943
98. Vij N, Chandramani P, Westphal CV, Hole R, Bodas M (2016) Cigarette smoke induced autophagy-impairment accelerates lung aging, COPD-emphysema exacerbations and pathogenesis. *Am J Physiol Cell Physiol*. doi:10.1152/ajpcell.00110.2016
99. You Y, Zhai ZF, Chen FR, Chen W, Hao F (2015) Autoimmune risk loci of IL12RB2, IKZF1, XKR6, TMEM39A and CSK in Chinese patients with systemic lupus erythematosus. *Tissue Antigens* 85:200–203
100. Soussi H, Clement K, Dugail I (2016) Adipose tissue autophagy status in obesity: expression and flux—two faces of the picture. *Autophagy* 12:588–589
101. Carchman EH, Matkowskyj KA, Meske L, Lambert PF (2016) Dysregulation of autophagy contributes to anal carcinogenesis. *PLoS ONE* 11:e0164273

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