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Moments in autophagy and disease: past and present

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Abstract

Over the past several decades, research on autophagy, a highly conserved lysosomal degradation pathway, has been advanced by studies in different model organisms, especially in the field of its molecular mechanism and regulation. The malfunction of autophagy is linked to various diseases, among which cancer and neurodegenerative diseases are the major focus. In this review, we cover some other important diseases, including cardiovascular diseases, infectious and inflammatory diseases, and metabolic disorders, as well as rare diseases, with a hope of providing a more complete understanding of the spectrum of autophagy's role in human health.

Keywords

Autophagy; cardiovascular diseases; COVID-19; metabolic disorders; rare diseases

Overview of Autophagy

For the past several decades, our understanding about the basic mechanism of autophagy, a pathway targeting cytoplasmic materials for lysosomal degradation and recycling, has expanded tremendously (Klionsky et al., 2021; Noda and Inagaki, 2015; Yang and Klionsky, 2010). Under normal nutrient conditions, autophagy occurs continuously at a low, basal level to inhibit the accumulation of damaged cytoplasmic components, but this process can be massively upregulated when cells face stress conditions such as nutrient deprivation (Mizushima, 2007; Wen and Klionsky, 2016). Three types of autophagy, including macroautophagy, microautophagy and chaperone-mediated autophagy (CMA), have been characterized based on different types of cargo and various modes of cargo delivery to lysosomes (Parzych and Klionsky, 2014). Microautophagy involves invagination or protrusion of endosomes or lysosomes, in which portions of cytoplasm in close proximity to the endosome and lysosome are sequestered and degraded, and the detailed mechanism is still under investigation (Schuck, 2020). CMA relies on chaperones to recognize individual

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KFERQ motif-containing cargo proteins, and then translocates the unfolded proteins across the lysosomal membrane (Kaushik and Cuervo, 2012).

Macroautophagy (hereafter autophagy) is the major regulated form of autophagy in response to intracellular or extracellular stimulus or stress. The basic mechanism of autophagy has been well-characterized, including sequestration of cytoplasmic cargo into double-membrane phagophores that mature into autophagosomes, followed by delivery to lysosomes, subsequent degradation of the cargo and final efflux of the breakdown products back into the cytosol (Feng et al., 2014; Galluzzi et al., 2017). As stated in many previous publications, one of the key features in autophagy is the formation of the double-membrane autophagosome, which can fuse with an endosome or directly with a lysosome for subsequent degradation of the cargo (Mizushima and Komatsu, 2011; Yang and Klionsky, 2009). Autophagy can be either non-selective to degrade random parts of the cytoplasm, or selective to degrade specific cargos such as mitochondria (mitophagy), peroxisomes (pexophagy), endoplasmic reticulum (reticulophagy), lipid droplets (lipophagy), glycogen (glyophagy), and intracellular microbes (xenophagy) (Gatica et al., 2018). More than 40 evolutionarily conserved autophagy-related (*ATG*) genes have been identified in fungi, and approximately 20 of these are regarded as core genes—that is, those required for autophagosome formation—in this lysosomal degradation pathway (Dikic and Elazar, 2018; Levine and Kroemer, 2019). However, the core ATG proteins are not sufficient for degradative autophagy, and some key factors have been identified in recent years, such as the HOPS complex, the RAB GTPase RAB7, and SNARE proteins (Wen and Klionsky, 2020).

Autophagy plays a fundamental role in many aspects of cell physiology, including protein quality control, prevention of genomic damage, and adaptions to intracellular or extracellular stimuli, as well as maintaining homeostasis (Wirawan et al., 2012; Yin et al., 2016). Given the importance of autophagy in these different aspects of cellular function, the magnitude of autophagy must be tightly regulated to ensure appropriate levels. During the past decades, our understanding of autophagy has also expanded from characterizing the basic mechanism to a knowledge of the complicated regulation of this process. Regulation covers various aspects, including the physiological or pathological stresses that influence autophagy, and the way that core autophagy proteins are regulated, as well as the interconnection between autophagy and other cellular stress response pathways (He and Klionsky, 2009; Ravikumar et al., 2010). Posttranslational modifications of ATG proteins, such as phosphorylation, ubiquitination, glycosylation and acetylation, as well as transcriptional and epigenetic control mechanisms also contribute to autophagic regulation (Xie et al., 2015). For example, MTOR (mechanistic target of rapamycin kinase) is a primary inhibitor of autophagy, whereas AMP-activated protein kinase (AMPK) is a major energy sensor and a positive regulator of autophagy (Corona Velazquez and Jackson, 2018).

Using mice as the model system, researchers have found that failure of autophagy can promote cellular degeneration, age-related changes, tumor formation and pernicious infection (Kuma et al., 2017). During the past several years, further human genetic studies have shown the involvement of autophagy, or autophagic dysfunction, in many diseases (Jiang and Mizushima, 2014; Levine and Kroemer, 2019). In this review, we briefly discuss the relation between cancer and neurodegenerative diseases, which have been the major

focus of many published reviews (Frake et al., 2015; Levine and Kroemer, 2008; Mizushima et al., 2008; White, 2015; Yang and Klionsky, 2020). More importantly, our review summarizes some cutting-edge research on the relation between autophagy (including non-selective and selective autophagy as well as CMA) and many other diseases, with a hope of providing an appreciation of a wider landscape of autophagy-related diseases as well as an addition to the understanding of autophagy in human health.

Autophagy and Cardiovascular Diseases

As a pivotal housekeeping mechanism to maintain energy balance and cell metabolism, autophagy has been hypothesized and subsequently confirmed to play a critical role in the pathogenesis of cardiovascular diseases, including heart failure, hypertrophic cardiomyopathy, dilated cardiomyopathy, cardiac aging, and diabetic cardiomyopathy (Wu et al., 2021). In this section, we briefly review the genetic association of human *ATG* genes and cardiovascular diseases. We then summarize animal studies seeking to define the distinct roles of autophagy in disease models and highlight the involvement of mitophagy and CMA in cardiovascular diseases.

1. Mutations of *ATG* genes in Cardiovascular Diseases

Early in 2000, a study published in *Nature* showed for the first time that human cardiomyopathy is primarily caused by mutations of the lysosome membrane protein LAMP2 that is closely correlated with autophagy (Nishino et al., 2000). In addition, the accumulation of autophagosomes has been observed in LAMP2-deficient mice (Tanaka et al., 2000). In recent years, the mutated protein products of a subset of core *ATG* genes have been identified to have a close link with cardiovascular diseases. For example, in 2018, it was reported that many variants in the *ATG7* gene promoter in acute myocardial infarction alter the transcriptional level of *ATG7* and consequently lead to dysfunctional autophagy (Zhang et al., 2018a). In 2019, another study investigating the roles of 21 *ATG* genes in cardiovascular diseases elegantly elucidated that single-nucleotide polymorphisms in *ATG4C*, *ATG4D*, *ATG7*, *MAP1LC3A* and *ATG3* are associated with the pathologies and related traits of cardiovascular diseases (Portilla-Fernandez et al., 2019). In addition, differential DNA methylation analysis showed that CpGs located in *ULK1*, *ATG4B* and *ATG4D* are correlated with several cardiometabolic traits (Portilla-Fernandez et al., 2019). Altogether, globally identified genetic alterations in the genes closely correlated with autophagy implicate this process as a promising target for the therapeutic intervention in cardiovascular diseases.

2. Distinct Roles of Autophagy in Animal Cardiovascular Disease Models

Given the fact that autophagy promotes adaptation to stress and supports cellular viability, it is plausible to regard autophagy as a process that confers cardio-protection. In this regard, the first set of papers linking autophagy to cardiac diseases was published in the 1970s (Sybers et al., 1976; Wildenthal and Mueller, 1974). However, with the recent intense interest in examining the exact roles of autophagy in cardiovascular diseases, the process has been revealed as having distinct roles (i.e., protective versus detrimental) in the heart under different cardiac conditions.

On the one hand, there is a series of important studies using animal models revealing that inactivation of autophagy in the heart is associated with cardiac pathologies, including genetic cardiomyopathy, chronic cardiac remodeling and heart failure (Valentim et al., 2006). For example, in a mouse model, temporal deficiency of cardiac-specific ATG5 results in the development of cardiac dysfunction and left ventricular dilatation after pressure overload (Nakai et al., 2007). Crossing BECN1 (beclin 1, autophagy related)-deficient mice with mice having DES (desmin)-related cardiomyopathy results in dramatically hastened heart failure progression, accelerated ventricular dysfunction, and early mortality (Tannous et al., 2008). Consistent with these findings, a BECN1 overexpression mouse model conversely showed that increased autophagy improves cardiac function (Sun et al., 2018; Zhu et al., 2007). In addition, autophagy is activated to promote myocardial survival during ischemia through an AMPK-dependent mechanism (Matsui et al., 2007). All these observations suggest a protective role of elevated autophagy in cardiac diseases.

On the other hand, there are also some contrary studies showing that reduced autophagy may protect the heart from injuries. It is noteworthy that a study generating heterozygous disruption of *Becn1* in mice showed that compared with wild-type mice, BECN1-deficient mice that display diminished cardiomyocyte autophagy have blunted pathological remodeling and reduced cardiac damage upon reperfusion (Matsui et al., 2007). In these studies, mice that overexpress BECN1 display accentuated pathological remodeling (Sun et al., 2018; Zhu et al., 2007). Diabetes is often accompanied by cardiac dysfunction, and frequently causes diabetic cardiomyopathy and heart failure. Another study focusing on the pathogenesis of diabetic cardiomyopathy showed that autophagy activity is diminished in the type 1 diabetic heart, but further depletion of BECN1 and ATG16L1 in mice substantially attenuates diabetes-induced cardiac damage (Xu et al., 2013a).

To date, the mechanism of how the beneficial or detrimental nature of autophagy in the context of cardiovascular diseases is determined remains an enigma. It has been suggested that distinguishing the roles of autophagy during ischemia and reperfusion is important. Initially, autophagy may serve to maintain energy production during acute ischemia, but subsequently switches to removing dysfunctional organelles during chronic ischemia or reperfusion. To provide a thorough understanding of the roles of autophagy under various cardiac conditions, we summarize animal studies seeking to define the distinct roles of autophagy in disease models (Table 1).

3. Mitophagy and CMA in Cardiovascular Diseases

In a recent publication we discussed the fundamental concepts of CMA and mitophagy, and their roles in neurodegenerative diseases (Yang and Klionsky, 2020). Interestingly, it has been largely accepted that the pathogenesis of cardiovascular diseases is also closely linked to CMA and mitophagy.

As discussed in the last section, mutations in *LAMP2*, encoding the protein family to which the CMA receptor LAMP2A belongs, have been identified as being associated with human cardiomyopathy (e.g., Danon disease) (Nishino et al., 2000). A study in 2017 showed that the levels of CMA markers, including LAMP2A and HSPA8/HSC70 decline in cardiac muscle during aging (Zhou et al., 2017). These studies suggest the importance of unraveling

the contribution of CMA in cardiac pathogenesis, and the role of CMA in cardiomyocytes is becoming a research hotspot (Kaludercic et al., 2020).

The role of mitophagy in cardiovascular diseases has been demonstrated in several mouse models. It is well known that loss-of-function mutations in *Prkn/Parkin* result in neurodegenerative diseases such as Parkinson disease. *prkn*$^{-/-}$ mice also have more severe cardiac injury and reduced survival following myocardial infarction compared with wild-type mice (Kubli et al., 2013). Furthermore, overexpression of PRKN in cardiac myocytes attenuates hypoxia-mediated cell death (Kubli et al., 2013). Haploinsufficiency of DNM1L/Drp1 abolishes mitophagy and exacerbates heart failure induced by transverse aortic constriction in mice (Shirakabe et al., 2016). In a diabetic mouse model, inhibition of ATG16L1 restores mitophagy in an ATG16L1-independent manner through PINK1 and PRKN upregulation, suggesting that mitophagy may function as an adaptive mechanism to attenuate diabetic cardiac injury (Xu et al., 2013b).

4. Autophagy as a Target for Therapeutic Intervention in Cardiovascular Diseases

In the previous sections, we have discussed the fact that autophagy can play distinct roles at different stages and in different conditions concerning cardiovascular diseases. From this perspective, many drugs that are related to or have an impact on autophagy are used in the treatment of cardiovascular diseases. For example, trehalose, which exhibits an ability to protect cells from multiple stresses via autophagy activation, efficiently improves cardiac remodeling following myocardial infarction (Sciarretta et al., 2018). In addition, mitophagy modulation is another promising therapy, which is confirmed in several mouse models. Aspirin heightens cardioprotective mitophagy through inhibition of EP300 acetyltransferase in mice and worms (Pietrocola et al., 2018). Injection of Tat-Beclin1 also partially rescues mitophagy dysfunction and heart failure induced by overload in cardiac hypertrophy transverse aortic constriction mice (Shirakabe et al., 2016). Collectively, these studies rationally suggest that autophagy/mitophagy activation is a promising strategy for treating cardiovascular diseases under certain circumstances.

Autophagy in Infectious and Inflammatory Disorders

In recent years, accumulating evidence has suggested that both the pathogen degradation and housekeeping function of autophagy are essential for the outcome of infection and immunological balance. Autophagy, with its ability to clear inflammasomes and cytokines, plays an important role in regulating inflammation. Through genetic association studies, it has been found that defective autophagy confers susceptibility to a number of autoimmune and inflammatory disorders, particularly inflammatory bowel disease (IBD) and infectious diseases. In this section, we address the progress in understanding the dual roles of autophagy in infectious diseases, and particularly we focus on coronavirus disease 2019 (COVID-19), to provide novel insights in the defense against pathogen infection. We also highlight the prominent roles of autophagy-related proteins in inflammatory bowel diseases. By emphasizing these two diseases, we try to demonstrate how two dual decisive functions of autophagy (i.e., maintaining cellular homeostasis and activating defense mechanisms), work in concert in inflammatory disorders. Due to space constraints, we mention other

inflammatory disorders (except IBD and infectious diseases) and the associated core *ATG* genes with genetic mutations in Table 2.

1. Autophagy and Infectious Diseases

Autophagy has a crucial role in the defense against microorganisms that are responsible for many infectious diseases that pose severe threats to human lives. Similar to its role in cancers, autophagy also acts as a double-edged sword in pathogen infection. In the following section, we briefly introduce the mechanism of how autophagy both controls and promotes pathogen infections. We overview studies investigating the roles of autophagy in various infectious diseases (Table 3), using COVID-19 as an example to describe in detail the contribution of *ATG* genes in the pathogenesis and treatment of life-threatening infectious diseases.

1.1 Dual Roles of Autophagy in Microbial Infections—

After pathogenic infection, autophagy is activated by the innate immune system to clear out the invading pathogens. Specifically, xenophagy, a type of selective autophagy that recognizes and delivers intracellular microorganism to lysosomes for degradation, is frequently involved in the process. There are many ways for microbes to induce xenophagy, including cell-to-cell signaling, immune surveillance, cellular stress induction, microbiol protein stimuli, etc. (Steele et al., 2015). For example, pattern recognition receptors such as Toll-like receptors recognize pathogen-associated molecular patterns and then induce xenophagy by the modulation of BECN1/Beclin1 activity through alteration of the BECN1-BCL2 interaction (Delgado et al., 2008; Shi and Kehrl, 2008). Similar to other types of selective autophagy (e.g., mitophagy), xenophagy targets its intracellular cargos (i.e., pathogens) towards lysosomes for autophagic degradation via ubiquitination (Yin et al., 2020).

Importantly, instead of being eliminated by autophagy, some pathogens have evolved the ability to exploit autophagy-generated structures, metabolites, and energy as their own resources for replication. For example, the optimal intracellular bacterial growth of *Francisella tularensis* takes advantage of ATG5-independent autophagy in order to harvest nutrients for bacterial replication (Nishida et al., 2009; Steele et al., 2013). In addition, *Brucella abortus* and *Mycobacterium marinum* exploit ATG5-independent autophagy to facilitate cell-to-cell spread (Collins et al., 2009; Starr et al., 2012). It is not fully understood how pathogens preferentially induce ATG5-independent autophagy and avoid xenophagy during infections. Taking advantage of host autophagy is also common in viral infection. Lipophagy, another selective type of autophagy that targets intracellular lipid droplets (i.e., triglycerides, cholesterol), is subverted during viral infection for two primary reasons: lipid droplets can provide a platform for virion assembly, and upregulated lipophagy is able to provide the high level of ATP needed for viral replication (Choi et al., 2018). ATG machinery can be hijacked by several picornaviruses, including coxsackievirus, poliovirus, and rhinovirus, to support efficient viral replication (Klein and Jackson, 2011). A limited number of animal studies have investigated the dominant mechanism for how the ATG machinery is exploited by highly pathogenic viruses and bacteria to support their invasion. Currently, the most convincing evidence that autophagy is critical to support viral replication is a study published in 2012, which showed that in pancreatic acinar cells of ATG5-deficient

mice, *coxsackievirus B3* (CVB3) fails to optimally infect pancreatic cells and therefore cannot induce pancreatic pathology (Alirezaei et al., 2012).

1.2 Autophagy and SARS-CoV-2 in COVID-19—The COVID-19 pandemic has had a dramatic impact on healthcare and socioeconomic systems all over the world. Autophagy, due to its roles in the defense against viruses and bacteria, has attracted the attention of scientists interested in developing treatments for this disease and became an emerging target for COVID-19 therapeutics.

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is a type of positive-sense single-stranded RNA virus and belongs to the coronavirus (CoV) family (Mijaljica and Klionsky, 2020). Though substantial effort has been made recently to unravel the complex relationship between autophagy and COVID-19 pathogenesis, a complete understanding of autophagy and SARS-CoV-2 remains elusive because of a lack of practical animal studies in the limited time since the disease outbreak. Therefore, we summarize studies on autophagy and SARS-CoV-2-related pathogens, such as coronavirus mouse hepatitis virus (MHV) from the CoV family. We highlight how investigations at the cellular level are delineating the pathogenesis of CoV, hopefully to provide insights and perspectives on implications of autophagy in COVID-19 pathogenesis and treatments.

The controversy of whether the CoVs preferentially trigger autophagy for self-usage has been a topic of debate for nearly two decades. Early in 2004, viral replication of MHV was found to be affected in *atg5*$^{-/-}$ embryonic stem cell lines (Prentice et al., 2004). Intriguingly, a subsequent study in 2007 described an opposite finding in either *atg5*$^{-/-}$ bone marrow-derived macrophages (BMDMs) or primary low-passage *atg5*$^{-/-}$ mouse embryonic fibroblasts, suggesting that ATG5 is not required for CoV replication (Zhao et al., 2007). Moreover, a nonlipidated form of LC3/Atg8 (a key autophagy marker) is extensively detected on the CoV-induced double-membrane vesicles, which are the targeted sites for CoV replication and transcription (Reggiori et al., 2010). It is noteworthy that LC3 lipidation is not observed, and ATG7 is not required to form these LC3-positive double-membrane vesicles, suggesting an unknown role of LC3, probably independent of autophagy. To date, our understanding of whether autophagy is at least partially involved in CoV replication is far from complete. The exact mechanism behind the interplay between autophagic machinery and CoV replication could be highly informative from the perspective of COVID-19 treatment.

In addition to the utilization of autophagy for replication, researchers are also interested in determining if CoVs block autophagy in the late stage of viral infection to eliminate the cellular surveillance function of autophagy to fight against invading pathogens. A very recent study showed that SARS-CoV-2 blocks autophagy by inhibiting autophagosome/amphisome-lysosome fusion via the STX17-SNAP29-VAMP8 SNARE complex (Miao et al., 2021), suggesting a potential therapeutic target for COVID-19 treatment.

Since the outbreak of COVID-19, several studies have been conducted to elucidate the possibility of targeting autophagy in terms of therapeutic aspects. In vitro studies show

that SARS-CoV-2 inactivates MTOR complex 1 (MTORC1) but also AMPK, resulting in diminished autophagy activity. Exogenous administration of drugs including spermidine, MK-2206, and niclosamide to pharmacologically modulate autophagy results in the inhibition of SARS-CoV-2 propagation by >85% (Gassen et al., 2020). In addition, PIK3C3/VPS34 inhibitors, which block autophagy, potently inhibit SARS-CoV-2 replication (Silvas et al., 2020).

As well-known lysosomal inhibitors, chloroquine (CQ) and its derivatives such as hyxdroxychloroquine had gained high expectations from a pharmacological perspective to block autophagy safely and effectively in the treatment of COVID-19. A study in early 2020 showed that CQ has a strong ability to block the viral infection of SARS-COV-2 in Vero E6 cells in vivo (Wang et al., 2020). Later in June 2020, a meta-analysis based on unpublished and published reports available on the internet at that time illustrated that CQ derivatives are effective to improve clinical and virological outcomes as well as to reduce mortality in patients with COVID-19 (Million et al., 2020). However, there are also some clinical studies showing that post-exposure prophylaxis treatment with hyxdroxychloroquine does not present obvious differences compared with the placebo (Boulware et al., 2020; Delorme-Axford and Klionsky, 2020; Group, 2020). The controversy in the potential of CQ and its derivatives to treat COVID-19 is largely dependent on realistic limitations such as the heterogeneous sample population, different dosing, early stoppage of trials and lack of considering confounders (Elavarasi et al., 2020). Therefore, systematic clinical trial analysis is required to further illustrate the efficacy of CQ and its derivatives in COVID-19 treatment.

2. Autophagy and IBD

IBD, including ulcerative colitis and Crohn disease, describes the disorders of chronic and relapsing inflammation of the digestive system, due to an imbalance in the co-existence of host and gut microbiota. The pathophysiology of both diseases is associated with changes of the intestinal microbiota, which may orchestrate chronic inflammation in genetically susceptible hosts. In fact, the two diseases share some common genetic mutations in autophagy pathways.

A non-biased genome-wide study in 2007 identified a strong susceptibility variant for Crohn disease in ATG16L1 (T300A) (Hampe et al., 2007). Since then, a substantial number of subsequent studies focusing on the role of autophagy in mediating host-microbe interactions in the gut has emerged, mostly focusing on the contribution of the aforementioned ATG16L1 loss-of-function mutant. For example, numerous studies showed that mice and human cells expressing the ATG16L1^{T300A} variant are defective in xenophagy, antigen presentation, and inflammatory cytokine production; and furthermore the impaired autophagy is due to CASP3 (caspase 3)-mediated cleavage and degradation of the ATG16L1 variant (Cadwell et al., 2010; Gao et al., 2017; Lassen et al., 2014; Saitoh et al., 2008). It has also been demonstrated that multiple roles of ATG16L1 are involved in the pathogenesis of Crohn disease. For example, ATG16L1 is essential for SQSTM1/p62 ubiquitination via neddylation of CUL3, as well as suppressing IL1B/IL-1β signaling (J. Lee et al., 2012). The recruitment of ATG16L1 to the plasma membrane via NOD1 and NOD2 is required to sequester invading pathogens within autophagosomes (Lee et al., 2012; Travassos et al.,

2010). Collectively, these observations reveal the critical roles of autophagy in cellular stress regulation and microbial pathogen sensing in intestinal inflammation-associated diseases. Macrophages expressing the murine ATG16L1^{T316A} mutant, which is equivalent to the human ATG16L1^{T300A} mutant, display few defects in LC3-associated phagocytosis (LAP) (Martinez et al., 2015), suggesting that the genetic association between the ATG16L1^{T300A} variant and Crohn disease affect xenophagy rather than LAP.

After the discovery of the ATG16L1^{T300A} mutant, many other ATG machinery components were subsequently linked to Crohn disease. A tagging single-nucleotide polymorphism in *ULK1* was reported to demonstrate a genetic association with Crohn disease (Henckaerts et al., 2011); however, the exact role of ULK1 in Crohn disease is not clear at present. Another study focused on granulomas, an aggregation of macrophages that is suggested to correlate with impaired processing of bacterial components in Crohn disease patients, found that variants in *ATG4A*, *ATG2A*, *ATG4D* and *FNBP1L* are associated with granuloma formation (Brinar et al., 2012). A genome-wide association study to identify IBD susceptibility genes revealed that some risk variants associated with IBD are in the DNA regulatory elements of *ATG9A* (Meddens et al., 2016; van Beek et al., 2018). It is widely appreciated that OPTN (optineurin) is a receptor for some types of selective autophagy, such as mitophagy. In addition to being a selective receptor, OPTN is required for facilitating the recruitment of the ATG12–ATG5-ATG16L1 complex to the forming phagophore for membrane expansion (Bansal et al., 2018). In one study, a subgroup of Crohn disease patients, which comprised 10% of the study cohort, expressed reduced OPTN in macrophages (Smith et al., 2015). Another example showing the essential role of selective autophagy in intestinal homeostasis is the discovery of associations between *CALCOCO2/NDP52* mutations and Crohn disease (Till et al., 2013).

Clearly, many ATG proteins appear to play a nonnegligible role in the development of Crohn disease. However, given the fact that some ATG proteins appear to have autophagy-independent functions, it requires further in-depth study as to whether the ATG variants leads to defective xenophagy, or other pathways, such as LAP (Galluzzi and Green, 2019).

Autophagy and Metabolic Disorders

The most important and evolutionarily conserved role of autophagy is to maintain metabolic homeostasis, primarily by regenerating and releasing amino acids, lipids, and other metabolic precursors (Galluzzi et al., 2014). Conversely, the metabolic status can control the nature and extent of autophagic induction. Potentially, autophagy could be a critical part in the MTORC1- or AMPK-hub against various metabolic diseases, such as obesity, diabetes, and non-alcoholic fatty liver disease (NAFLD). The complex interplay between genetic and environmental factors is responsible for these metabolic disorders, among which excess caloric intake and unbalanced energy expenditure are the major contributors that have been well-documented to inhibit autophagy activities (Zhang et al., 2018b). However, both increased and decreased levels of autophagy have been observed in these disorders, while most mouse genetic studies have shown that the block of autophagy could facilitate the transition from obesity to diabetes, as well as enhancing the risk of atherosclerosis and NAFLD (Levine and Kroemer, 2019; Ueno and Komatsu, 2017). Therefore, the precise

mechanism of autophagy in these metabolic disorders is complicated, and we need further investigation on the controversial research results to fill in the knowledge gap. In this section, we highlight some findings of autophagy related to metabolic disorders, with both genetic variance studies from human patients and mouse studies.

The prevalence of obesity has been increasing during the past decade worldwide, which poses a severe threat to human health, and the altered expression of autophagy has been reported in obesity (Pi-Sunyer, 2009). One hallmark of obesity is the accumulation of dysfunctional adipose tissues, and early reports have observed upregulated autophagy activity in adipose tissues from obese patients (Jansen et al., 2012; Kovsan et al., 2011). Over 30 genes related to autophagic response were found to be upregulated in adipocytes when challenged with TNF/TNFα (tumor necrosis factor) (Ju et al., 2019). Additionally, mouse models offer us more insights into the role of autophagy in obesity. Dating back to 2008, two different groups of researchers knocked out *Atg7* in beta cells in mice, which results in degeneration of islets, impaired glucose tolerance, and decreased serum insulin level (Ebato et al., 2008; Jung et al., 2008). Some evidence from 2009 showed that mice feeding on a high-fat diet (HFD) have suppressed hepatic autophagy activities (Liu et al., 2009). Using the HFD model of obesity, researchers have further shown that autophagy can be induced by acute exercise or by replenishing ADIPOQ/adiponectin, a type of adipocytokine in skeletal muscles (He et al., 2012; Liu et al., 2015). With both genetic and dietary mouse models, a 2010 study reported a downregulation of autophagy resulting from the low ATG7 expression level in the liver. The further suppression of ATG7 can result in defective insulin signaling and elevated ER stress (Yang et al., 2010). In contrast, adipose-specific deletion of *Atg7* might lead to differentiation of adipose tissue and increased insulin sensitivity (Zhang et al., 2009). Interestingly, mice with a knockout of *Atg4* experience an excessive increase in body weight in response to different obesity-associated metabolic challenges (Fernandez et al., 2017). Upon HFD, mice with a knockout of *Atg12* in POMC (proopiomelanocortin)-alpha-expressing neurons also exhibit accelerated weight gain, adiposity, and glucose intolerance (Malhotra et al., 2015).

As stated above, obesity could increase the risk of developing diabetes, one of the most common chronic metabolic diseases. An emerging body of evidence supports a role of autophagy in the pathophysiology of type I and type II diabetes mellitus (T2D). The suppression of autophagy in β-cells could promote hyperglycemia and lead to progression from obesity to diabetes (Quan et al., 2012). Heterozygous $Atg7^{+/-}$ mice can develop diabetes when crossed with *ob/ob* mice, showing aggravated insulin resistance and increased lipid content that is a result of autophagy insufficiency (Lim et al., 2014). The researchers have also observed impaired autophagic flux in islets of mice with obesity-induced diabetes, and intermittent fasting can help restore autophagy and improve glucose tolerance (Liu et al., 2017). A groundbreaking study from 2014 has shown that CLEC16A can control β-cell function and prevent type 1 diabetes mellitus by controlling autophagy, and further studies have shown more diabetes susceptibility factors including PDX1, RNF41/NRDP1 and USP8 are involved in the process (Pearson et al., 2018; Soleimanpour et al., 2015; Soleimanpour et al., 2014). Autophagy can defend pancreatic β-cells against toxicity induced by accumulated IAPP (islet amyloid polypeptide), which is responsible for T2D (Rivera et al., 2014). This result was further demonstrated by recent research, showing that autophagy can facilitate

the clearance of amyloidogenic oligomer (Kim et al., 2021). In T2D patients' adipose tissue samples, the abnormal autophagy activity is observed in accordance with accumulation of autophagosomes and increased levels of *LC3* and *ATG5* gene expression (Kosacka et al., 2015). The relation between mitophagy and T2D has also revealed that the increased level of reactive oxygen species in T2DM patients' adipocytes can lead to excessive mitophagy (He et al., 2021).

Studies have also provided insights into the role of autophagy in NAFLD, which is a liver disease that is gradually becoming a global health problem. The human gene *IRGM* is required for assembly and activation of the autophagy machinery, whose genetic variants are associated with the increased risk of NAFLD (Lin et al., 2016). Moreover, patients with NAFLD exhibit elevated hepatic levels of RUBCN/rubicon which is an inhibitor of class III phosphatidylinositol 3-kinase activity. The hepatocyte-specific knockout of *Rubcn* protects mice against HFD-induced impaired autophagy and steatosis (Tanaka et al., 2016). The correlation between autophagy and atherosclerosis has also been observed. With the specific deletion of *Atg5* in macrophages, mice are more prone to developing atherosclerotic plaques (Liao et al., 2012a; Razani et al., 2012). Similarly, macrophage-specific *Atg7* knockout could lead mice to be more prone to the onset and development of atherosclerotic plaques with the infiltration of lipid-engorged spumous cells (Soussi et al., 2016).

Autophagy and Rare Diseases

The importance of autophagy in human health has been further underscored by its emerging role in rare diseases. A rare disease is defined differently depending on geographical region; for example, this is a condition that affects fewer than 200,000 or 2,000 people in the United States and the European Union, respectively (Rubinstein et al., 2020). While individual diseases are rare, the total population that is suffering from rare diseases is large. There is an estimation of over 7,000 rare diseases existing, and exact causes of many of them are still unknown. Fortunately, accumulating studies have revealed the relation between autophagy and rare disease, and some are listed in Table 2. Here we discuss exciting achievements in this area, which can help open new directions for future treatment.

1. Autophagy and Neuro-Related Rare Diseases

The role of autophagy in neurodegenerative diseases, including Alzheimer, Huntington, and Parkinson diseases, has been studied extensively for the past several years, and the progress has been well-documented in many reviews (Fujikake et al., 2018; Menzies et al., 2015; Nixon, 2013). Not surprisingly, autophagy plays a role in many rare diseases that are related to neurodevelopment and neurodegeneration.

Vici syndrome is a severe neurodevelopmental disorder that is inherited in an autosomal recessive manner (Byrne et al., 2016). Groundbreaking research in 2013 has revealed that recessive mutations in *EPG5* can cause Vici syndrome and defects in autophagy (Cullup et al., 2013). It was further shown that defective autophagy is a result of autophagosome-lysosome failure because *EPG5* encodes a RAB7 effector (Hori et al., 2017). Interestingly, the importance of RAB7 has further been underscored by another rare inherited peripheral neuropathy, Charcot-Marie-Tooth type 2B disease (Colecchia et al., 2018). This autosomal

dominant disease is caused by five different mutations in the *RAB7* gene, and autophagy is blocked in patient skin fibroblasts carrying the *RAB7* mutation (Colecchia et al., 2018).

As a severe form of progressive myoclonus epilepsy inherited in an autosomal-recessive manner, Lafora disease is largely caused by mutations in two genes: *EPM2A* (EPM2A glucan phosphatase, Laforin), and *NHLRC1/EPM2B/Malin* (NHL repeat containing E3 ubiquitin protein ligase) (Duran et al., 2014). The impairment of autophagy was found in both EPM2A- and NHLRC1/EPM2B-deficient mice, and in fibroblasts derived from Lafora disease patients (Aguado et al., 2010; Puri et al., 2012).

Hereditary spastic paraplegia is a heterogeneous group of genetic neurodegenerative disorders, and three forms (SPG11, SGP15 and SPG49) have been reported to have severely reduced autophagy activity (Oz-Levi et al., 2012; Salinas et al., 2008; Vantaggiato et al., 2013; Varga et al., 2015). Spinocerebellar ataxia is a rare and specific type of ataxia that is inherited in an autosomal dominant manner: SNX14 mutation-related spinocerebellar ataxia shows impaired lysosome-autophagosome function, whereas the pharmacological induction of autophagy can help degrade mutant ATXN3 (ataxin 3) levels and reduce toxicity in mice with spinocerebellar ataxia type 3 (Akizu et al., 2015; Menzies et al., 2010). Besides, the dysregulation of autophagy was reported in cell culture and a mouse model of spinal muscular atrophy, an early-onset, autosomal recessive neuromuscular disease (Custer and Androphy, 2014; Lefebvre et al., 1995). The loss of functional survival of motor neuron protein due to the *SMN1* gene mutation is the major cause of the disease (Burghes and Beattie, 2009). A further study shows that SMN1 can interact with SQSTM1; reducing SQSTM1 levels or inhibition of autophagy can markedly increase the SMN1 level, thus expanding lifespan in the SMN mouse model (Rodriguez-Muela et al., 2018).

Autophagy also plays a role in some X-linked rare neuro-specific diseases. Defective autophagy is associated with the *MECP2* (methyl-CpG binding protein 2) gene, in which sporadic mutation can lead to Rett syndrome, an X-linked dominant neuro-developmental disorder (Sbardella et al., 2017). This progressive condition primarily affects girls. The altered splicing of *ATP6AP2* results in the deficiency of the corresponding protein, causing X-linked parkinsonism with spasticity/XPDS and impaired autophagy and lysosome clearance (Korvatska et al., 2013). Neurodegeneration with iron accumulation-5/NBIA5, also referred to as static encephalopathy of childhood with neurodegeneration in adulthood/ SENDA, is another X-linked dominant neurodegenerative disorder (Jiang and Mizushima, 2014). Mutation in the autophagy gene *WDR45/WIPI4* is the cause of static encephalopathy of childhood with neurodegeneration in adulthood and can lead to lower autophagic activity and aberrant early autophagic structures (Haack et al., 2012; Saitsu et al., 2013).

Although amyotrophic lateral sclerosis (ALS) is the most common type of motor neuron disease, it is still regarded as a rare progressive neurodegenerative disorder that may lead to irreversible muscular paralysis (Brown and Al-Chalabi, 2017). Autophagy can play a distinct role during the development of ALS: autophagic function is involved in maintaining neuromuscular innervation at the early stage of the disease, whereas it will promote disease progression in a non-cell-autonomous manner once the disease has initiated in motor neurons (Rudnick et al., 2017). Approximately 90 to 95 percent of ALS cases are sporadic,

whereas the remaining familial ALS cases are inherited in an autosomal-dominant pattern. The most common genetic cause of ALS has been identified as a hexanucleotide repeat expansion in *C9orf72*, which leads to reduced gene expression. The C9orf72 protein can regulate autophagy by interacting with SMCR8, WDR41, RAB1A and the ULK1 complex (Renton et al., 2011; Sullivan et al., 2016; Webster et al., 2016). In addition, many other factors involved mostly in selective autophagy, including SQSTM1, OPTN, TBK1 (TANK binding kinase 1) and UBQLN2 (ubiquilin 2), are associated with ALS (Cirulli et al., 2015; Nguyen et al., 2019). It is important to point out that these studies on ALS also show a similar result to frontotemporal dementia (FTD), which is exemplified by shrinking of the frontal and temporal anterior lobes of the brain (Pang and Hu, 2020). For example, C9orf72-FTD is inherited in an autosomal dominant manner, and SQSTM1 and TBK1 are also implicated in this disease. Furthermore, a loss-of-function mutation in *GRN* (granulin) leads to FTD, and deficits in xenophagy have been found in mice lacking GRN (Chang et al., 2017).

2. Autophagy and Cancer-Related Rare Diseases

As noted above, autophagy may act as a double-edged sword in the context of cancer. As a previous review summarized, the role of autophagy in tumorigenesis is complex, depending on the context (Wen and Klionsky, 2020). During the tumor-forming stage, autophagy may function to prevent tumorigenesis, acting to maintain cellular and genomic integrity. However, once the tumor is formed, autophagy may lead to the opposite outcome, facilitating tumor progression and proliferation (Rybstein et al., 2018; White, 2012). With extensive ongoing research, autophagy is also becoming a hot therapeutic target for tumor treatment development. The topic of autophagy and its role in the most common types of cancer has been covered extensively (Amaravadi et al., 2019; Folkerts et al., 2019; Levy et al., 2017; Xia et al., 2021). Accordingly, here we focus on some examples of less prevalent forms of this disease.

Comparatively, some types of cancers occur at a much lower rate among the population, and the role of autophagy in these cases is also controversial. Mesothelioma is a rare cancer developing in the thin layer of tissue that surrounds the lungs, chest wall, or abdomen (Ohnishi et al., 2020). A study has shown that inhibiting the early step of autophagy with a ULK1/2 inhibitor can enhance chemosensitivity in mesothelioma (Follo et al., 2018). However, the same group later reported that autophagy can help release immunogenic signals to facilitate immunogenic cell death following chemotherapy in this tumor (Follo et al., 2019). In addition, a recent study showed that asbestos might induce the release of HMGB1 (high mobility group box 1) to initiate autophagy, and the inhibition of autophagy can increase cell death in mesothelioma (Xue et al., 2020). Another rare cancer example is seen with gallbladder cancer, which has an extremely poor prognosis. Recent trials have shown that inhibiting autophagy can help with treatment for gallbladder cancer, whereas activation of autophagy will induce chemoresistance (Cai et al., 2019; Cai et al., 2020).

The role of autophagy is crucial in some rare diseases that are highly related to tumorigenesis. For example, tuberous sclerosis, a rare, multi-system genetic disease, can cause benign tumors to grow in the brain and other vital organs (De Waele et al., 2015). The

disease is caused by mutations in *TSC1* or *TSC2* that are well-studied tumor suppressors that can negatively regulate MTORC1 (Huang and Manning, 2008). The tumorigenesis in tuberous sclerosis has also been demonstrated to rely on autophagy (Huang and Manning, 2008; Parkhitko et al., 2011). Primarily affecting males, Wiskott-Aldrich syndrome (WAS) is a disease in which the patient displays immunological deficiency and reduced ability to form blood clots. Children with WAS have a high probability to develop cancers such as lymphoma (Lee et al., 2017b). Deficiency of the WAS protein causes insufficient autophagosome formation and further results in deficient xenophagy (Lee et al., 2017b).

3. Autophagy and Other Rare Diseases

Another important group of rare diseases is the lysosomal storage diseases (LSDs), which are a group of inherited metabolic disorders characterized by enzyme deficiencies; the role of autophagy has also been recognized in many of them (Lieberman et al., 2012). One of the most extensively studied LSDs is Niemann-Pick type C disease, which is characterized by accumulation of lipids in various tissues (Meske et al., 2014). The disease is caused by mutations in the *NPC1* or *NPC2* gene, which are inherited in an autosomal recessive manner. The NPC1 protein is a late-endosomal protein, whereas NPC2 is a ubiquitous soluble glycoprotein (Li et al., 2016; Vanier and Millat, 2004). The accumulation of autophagosomes and lysosomes have been observed in this disease, and the resulting defects of autophagy are regarded as a major cause of the disease phenotype (Liao et al., 2007; Maetzel et al., 2014; Meske et al., 2014). A failure in the STX17 (syntaxin 17)-VAMP8 SNARE machinery, and reduced levels of VEGF (vascular endothelial growth factor) are responsible for the impaired autophagy activity (Lee et al., 2014; Sarkar et al., 2013).

The loss of GBA/glucocerebrosidase activity in Gaucher disease leads to accumulation of glucocerebroside and widespread pathology (Hruska et al., 2008; Mistry et al., 2017). A mutation in GBA1 may be the cause of the block in autophagy; concomitant downregulation of TFEB and the associated impairment in autophagosome maturation is seen in neurons differentiated from patient-specific induced pluripotent stem cells (Awad et al., 2015). The disease mouse model shows accumulation of secondary autophagy substrates including SQSTM1, dysfunctional mitochondria and ubiquitinated protein aggregates, accompanied by impaired autophagic influx (Farfel-Becker et al., 2014; Osellame et al., 2013; Sun et al., 2010; Xu et al., 2014).

Danon disease is a rare X-linked dominant disorder characterized by weakening of the heart muscle (cardiomyopathy) and of the muscles used for movement (skeletal muscle myopathy), and we have discussed its relationship with *LAMP2* in a previous section. The accumulation of SQSTM1 and LC3-II-positive autophagic vesicles are found from patients' muscle biopsies (Nascimbeni et al., 2017). Moreover, impaired mitophagy was identified by using both patient cells and *Lamp2*-deficient mice (Hashem et al., 2017). The name of the disease X-linked myopathy with excessive autophagy/XMEA already reveals its relationship with autophagy. This recessive inherited disease is caused by a mutation in the *VMA21* gene, which encodes a protein modulating the assembly of the vacuolar-type proton-translocating ATPase that is required for lysosomal acidification (Dowling et al., 2015). The mutation leads to decreased activity of lysosomal hydrolases, suggesting a

block of autophagic flux (Ramachandran et al., 2013). Along these lines, the lysosomal dysfunction in cystinosis, marked by an inability to transport cystine out of lysosomes that requires proper lysosomal acidification, can lead to defective mitophagy (Festa et al., 2018).

Other rare diseases that influence different parts of human bodies are also associated with autophagy. Snyder-Robinson syndrome, inherited in an X-linked recessive manner, is characterized by many abnormalities during development (Schwartz et al., 1993). The loss-of-function mutation in SMS (spermine synthase) is the major cause of the disease, and the deficiency of SMS can impair autophagy activity (Li et al., 2017). Primary microcephaly is a disorder of brain development in which the head circumference and brain volume are reduced (Jayaraman et al., 2018). Linkage analysis and whole-exome sequencing have revealed that a dominant mutation in *WDFY3/ALFY*, which encodes a scaffold protein in autophagy, causes this disease (Kadir et al., 2016).

Zellweger syndrome spectrum (ZSS), inherited in an autosomal recessive pattern, is highly related to peroxisome biogenesis disorders. More than ten human PEX proteins have been identified as acting in different stages of peroxisome biogenesis (Fujiki et al., 2014). Mutation of *PEX13* was found in ZSS, and a specific mutation might lead to defective regulation of mitophagy, therefore causing ZSS (Lee et al., 2017a; Liu et al., 1999).

Finally, Fanconi anemia is a serious blood disorder marked by inherited bone marrow failure syndromes, and affected individuals display an increased risk of developing cancers (Sumpter et al., 2016). This disease is usually inherited in an autosomal recessive manner, but X-linked inheritance has also been reported (Meetei et al., 2004). Interestingly, many Fanconi anemia pathway genes are required for virophagy and mitophagy and can also modulate inflammatory pathways (Sumpter et al., 2016).

Conclusion and Future Directions

The relation between autophagy and human health has been a major focus during the past several years, and we are excited to witness many groundbreaking studies linking dysfunctional autophagy with different human diseases. In this review, we have summarized the exciting research findings concerning various pathophysiologies including cardiovascular diseases, infectious and inflammatory diseases, metabolic diseases, and rare diseases. With the appearance of COVID-19, the importance and potential of autophagy is further underscored. More studies about the role of autophagy in rare diseases can also promote the development of orphan drugs, which is a good addition to the health improvement of underserved patients. Besides, the emerging role of selective autophagy and CMA in human diseases is worth noting, because the specificity of these diseases can help better shape drug design and treatment development.

Although many preclinical and clinical trials for diseases such as cancer show that autophagy can be a promising therapeutic target, we should be aware that the complexity of autophagy might create substantial problems with regard to disease treatment. For example, the role of autophagy is tissue-specific in metabolic disorders, suggesting that the global pharmacological modulation of autophagy may lead to worsened conditions. Considering

the double-edged sword role of autophagy in many diseases, whether it is ultimately better to induce or to inhibit autophagy is still a prominent question. In addition, the measurement of autophagy activity is not consistent in many studies, leaving some results controversial and unreliable. It is critical to have more solid answers to these questions to move forward. We still have a long way to go in treating diseases by specifically targeting autophagy, but we are optimistic that an increasing numbers of studies are establishing the bridge between autophagy and human health.

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Abbreviations:

ALS	amyotrophic lateral sclerosis
AMPK	AMP-activated protein kinase
ATG	autophagy-related
CMA	chaperone-mediated autophagy
CoV	coronavirus
COVID-19	coronavirus disease 2019
CQ	chloroquine
FTD	frontotemporal dementia
HFD	high-fat diet
IBD	inflammatory bowel disease
LAP	LC3-associated phagocytosis
LSD	lysosomal storage disease
MHV	mouse hepatitis virus
MTOR	mechanistic target of rapamycin kinase
NAFLD	non-alcoholic fatty liver disease
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
T2D	type II diabetes mellitus
WAS	Wiskott-Aldrich syndrome
ZSS	Zellweger syndrome spectrum

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Table 1.

Mouse models implicating autophagy involvement in cardiovascular diseases

Disease model	Genetic Intervention in mice	Results	Ref
Aging	*Atg5* transgene (Tg) overexpression	Reduced age-related cardiac fibrosis, increased lifespan extension	(Pyo et al., 2013)
	BECN1^{F121A} knockin	Reduced age-associated cardiac alterations, increased lifespan	(Fernández et al., 2018)
	Prkn Tg overexpression	Reduced age-associated cardiac abnormalities	(Hoshino et al., 2013)
Atherosclerosis	*atg5* $^{-/-}$	Accelerated atherosclerosis	(Liao et al., 2012b)
Cardiomyopathy	*Atg5* $^{+/-}$	Exacerbated cardiac hypertrophy	(Zhao et al., 2014)
	Atg7 Tg overexpression	Reduced cardiac hypertrophy, limited intracellular protein aggregation, and increased mouse survival	(Bhuiyan et al., 2013)
	Becn1 $^{+/-}$	Accelerated heart failure	(Tannous et al., 2008)
	Becnl Tg overexpression	Exacerbated pathogenic remodeling	(Zhu et al., 2007)
Myocardial infarction	*Becn1* $^{+/-}$	Reduced cardiac damage at reperfusion	(Matsui et al., 2007)
	prkn $^{-/-}$ *prkn* $^{-/-}$	Exacerbated cardiac injury and reduced survival Increased infarct size, hypertrophy	(Kubli et al., 2013)
	atg5 $^{-/-}$	Increased sensitivity, exacerbated hypertrophy	(Nakai et al., 2007)
I/R injury	*Becn1* $^{+/-}$	Cardioprotective during reperfusion	(Matsui et al., 2007)
Pressure overload	*atg5* $^{-/-}$	Increased sensitivity, exacerbated hypertrophy	(Nakai et al., 2007)
	Becn1$^{+/-}$ *Becn1* Tg overexpression	Reduced pathological cardiac remodeling Exacerbated pathological cardiac remodeling	(Zhu et al., 2007)
Sepsis	*Becn1* $^{+/-}$	Cardioprotective during reperfusion	(Sun et al., 2018)

Table 2.

Inflammatory diseases associated with abnormal core ATG machinery (except IBD) and correlated genes

Inflammatory diseases	Genes	Ref
Behçet disease	*ATG5*	(Zheng et al., 2015)
Celiac disease	*ATG7, BECN1*	(Comincini et al., 2017)
Chronic obstructive pulmonary disease	*PRKN, PINK1*	(Ito et al., 2015)
Cystic fibrosis	*BECN1*	(Luciani et al., 2010)
Pulmonary hypertension	*LC3B*	(Lee et al., 2011)
Rheumatoid arthritis	*ATG5, ATG7, BECN1*	(Lin et al., 2013; LU et al., 2011)
Systemic lupus erythematosus	*ATG5, ATG7, MAP1LC3B, PRDM1*	(Qi et al., 2018; Zhou et al., 2011)
Systemic sclerosis	*ATG5*	(Mayes et al., 2014)
Vogt-Koyanagi-Harada syndrome	*ATG10*	(Zheng et al., 2015)

Table 3.

Pathogens and ATG machinery targets in infectious diseases

Infectious diseases	Target	Models	Ref
Bacterial infection			
Gastroenteritis *(Salmonella enterica* serovar Typhimurium infection)	*ULK1, ATG16L1*	Mouse model and cell culture	(Liu et al., 2019; Tan et al., 2018; Xu et al., 2019)
Tuberculosis *(Mycobacterium tuberculosis* infection)	*ATG5, SQSTM1, CALCOCO2*	Mouse model and cell culture	(Castillo et al., 2012)
Group A *Streptococcus*	*ATG5*	Cell culture	(Nakagawa et al., 2004)
Legionella pneumophila	*LC3*	Cell culture	(Choy et al., 2012)
Listeria monocytogenes	*SQSTM1, LC3*	Mouse model and cell culture	(Yoshikawa et al., 2009)
Shigella flexneri	*ATG5*	Mouse model and cell culture	(Ogawa et al., 2005)
Fungal infection			
Cryptococcus neoformans and *Candida albicans*	*ATG5*	Mouse model	(Nicola et al., 2012)
Viral infection			
Coxsackievirus B3	*ATG5, SQSTM1*	Mouse model and cell culture	(Alirezaei et al., 2012) (Shi et al., 2013)
Hepatitis C virus (HCV)	*BECN1, ATG7*	Cell culture	(Shrivastava et al., 2011)
Herpes simplex virus type 1 (HSV-1)	*BECN1*	Mouse model and cell culture	(Leib et al., 2009)
Human immunodeficiency virus (HIV)	*BECN1*	Cell culture	(Kyei et al., 2009)
Influenza	*ATG5*	Mouse model and cell culture	(Schlie et al., 2015)
Murine γ-herpesvirus 68 (MHV-68)	*BECN1*	Mouse model and cell culture	(Xiaofei et al., 2009)
Poliovirus	*LC3*	Cell culture	(Taylor and Kirkegaard, 2007)