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Review

Contribution of autophagy to antiviral immunity

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ABSTRACT

Although identified in the 1960's, interest in autophagy has significantly increased in the past decade with notable research efforts oriented at understanding as to how this multi-protein complex operates and is regulated. Autophagy is commonly defined as a "self-eating" process evolved by eukaryotic cells to recycle senescent organelles and expired proteins, which is significantly increased during cellular stress responses. In addition, autophagy can also play important roles during human diseases, such as cancer, neurodegenerative and autoimmune disorders. Furthermore, novel findings suggest that autophagy contributes to the host defense against microbial infections. In this article, we review the role of macroautophagy in antiviral immune responses and discuss molecular mechanisms evolved by viral pathogens to evade this process. A role for autophagy as an effector mechanism used both, by innate and adaptive immunity is also discussed.
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1. Introduction

Autophagy is a major cellular pathway involved in the degradation of decaying organelles and expired proteins inside eukaryotic cells [1,2]. To date, three major autophagy pathways have been described: macroautophagy, microautophagy and chaperone-mediated autophagy [3]. In this review we will focus on macroautophagy and refer to it as autophagy hereafter. Although autophagy was initially described as a process carried out for the maintenance of cellular homeostasis [1,2], accumulating studies have also provided data that associate alterations in autophagy components with important diseases, such as neurodegenerative disorders, cancer, chronic autoimmune-inflammatory syndromes and infectious diseases [4,5]. Because a role for autophagy in pathogen control has also been suggested by various studies, important research efforts are currently being invested on better characterizing the contribution of this process to antiviral immunity. Indeed, autophagy has been proposed to work as an intrinsic cell immune defense mechanism against viral infections by targeting intracellular pathogens,

such as viruses, for degradation [6]. Paradoxically, certain viruses and other pathogens seem to rely on autophagy elements to replicate and persist inside the host. Thus, viruses have evolved molecular strategies to exploit and modulate the function of autophagy components to use them for their benefit [7–11]. Some of these findings are discussed below in this article.

2. The autophagy pathway

Autophagy is a process that requires the concerted assembly of multiple proteins into molecular complexes that carry out sequential steps with defined functions [2]. The identification of autophagy components was significantly advanced due to the use of yeast genetic screening assays. Indeed, multiple autophagy-related proteins (Atgs) have been identified using the yeast genetic screening assay with further mammalian counterparts being defined in other systems [12]. The major common physiological activator of autophagy is starvation and growth factor deprivation [2]. However, immune-inflammation signals can also lead to an increase in autophagy [13], as well as the expression of several proteins involved in this process (Fig. 1). mTOR, the mammalian target of rapamycin, has been shown to be involved in the negative modulation of autophagy [14]. It is thought that mTOR keeps both, Unc51-like kinase 1 (ULK1) and Atg13 in a hyperphosphorylated

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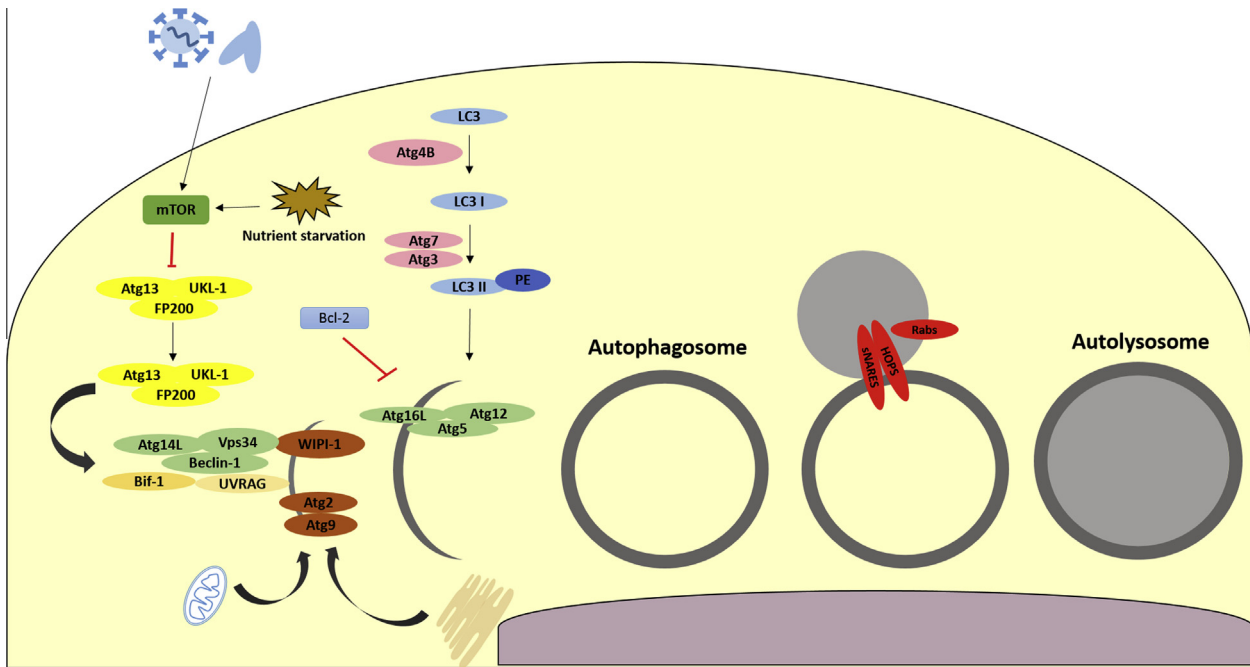E-mail address: akalergis@bio.puc.cl (A.M. Kalergis).

Fig. 1. The autophagy pathway. In response to stimuli that promote autophagy, such as nutrient starvation or pathogen infection, mammalian target of rapamycin (mTOR) dephosphorylates Unc51-like kinase 1 (ULK-1) and autophagy related protein 13 (Atg13), leading to the dissociation of mTOR from the ULK-1-Atg13-FAK family-interacting protein of 200kD (FIP200) complex that together with the vacuolar protein sorting 34 (Vps34)-Atg14L-Beclin-1 complex favor nucleation of the membrane that will become the autophagosome. Afterwards, autophagosome elongation and completion follows with the help of WD repeat domain phosphoinositide-interacting protein 1 (WIPI-1)-Atg2, Atg9, Vps34 and the ubiquitin-like conjugations of Atg12-Atg5-ATG16L and Atg4B-Atg3-Atg7 complexes. Further, light chain 3 (LC3) precursor is cleaved by Atg4B to produce the cytosolic form (LC3 I) and thereafter convert to membrane bound (LC3 II) – phosphatidylethanolamine (PE) conjugated through the activity of Atg7 and Atg3. The Atg12-Atg5-ATG16L complex determines the sites for LC3 lipidation. Once the autophagosome is formed, it is fused with the lysosome to become autolysosome through recruitment of the soluble N-ethylmaleimide-sensitive factor attachment (NSF) protein receptor (SNARE) proteins and its interaction with the homotypic fusion and vacuole protein sorting (HOPS) and vesicle trafficking by GTPases. At the end, the components are trapped inside the autophagolysosome and degraded.

state within the ULK1-Atg13-FAK family-interacting protein of 200 kD (FIP200) complex [15]. Stimuli that promote autophagy, such as nutrient starvation and pathogen infections, initiate mTOR-mediated desphosphorylation of ULK-1 and Atg13, leading to the dissociation of mTOR from the FIP200 complex [15]. Avibirnavirus and human cytomegalovirus (hCMV) have been described to induce autophagy in a mTOR-dependent manner [16,17]. MTOR dephosphorylation activates autophagy, initiating the nucleation of a cellular membrane (lipid bilayer) that will ultimately become the autophagosome. This enveloping membrane has been named as the "isolation membrane" or "phagophore" [18]. Importantly, it has been proposed that the endoplasmic reticulum, the Golgi apparatus and mitochondria may be the suppliers of lipid bilayers that form the phagophore [19–21]. To promote the formation of this membrane, the class III phosphoinositide-3-kinase (PIK3) complex, which is composed of vacuolar protein sorting 34 (Vps34), Atg14 and Beclin-1, is recruited to the phagophore [18]. Indeed, Beclin-1 is a scaffolding protein for the regulation of the PIK3 pathway [22]. Alternatively, the UV irradiation resistance-associated gene (UVRAG) may induce this PI3K complex [23] and promotes Atg9 trafficking [24]. Although Atg9 has been shown to be essential for starvation-induced autophagy [25], the specific function of this transmembrane protein remains somewhat unknown. During the first steps of phagophore generation, Vps34 is recognized by the beta-transducin repeat domain (WD) phosphoinositide-interacting protein 1 (WIPI-1), which cooperates with Atg2 and Atg9 to form of this structure [26]. These events trigger a downstream Atg conjugation system, which regulates autophagosome elongation [18].

Subsequently, autophagosome formation is catalyzed by two ubiquitin-like conjugation systems: the Atg12-Atg5-ATG16L and

Atg4B-Atg3-Atg7 complexes [27,28]. As part of this process, light chain 3 (LC3) precursor is cleaved by Atg4B to produce a cytosolic form (LC3 I) and later converted into a membrane-bound form (LC3 II), which is conjugated with phosphatidylethanolamine (PE) through the activity of Atg7 and Atg3 [29–31]. The Atg12-Atg5-ATG16L complex in turn acts as an E3-like enzyme and determine particular sites for LC3 lipidation [32]. Gamma-aminobutyric acid receptor-associated protein (GABARAP) and Golgi-associated ATPase enhancer of 16kDa (GATE-16) are homologs of LC3 and are involved in the late stages of autophagosome maturation [33]. P62 (also known as the sequestosome, SQSTM1) and the curvature-driving protein (Bif-1) are ubiquitination-binding proteins that contribute also to this maturation process [34]. Bif-1 also interacts with Beclin-1 through UVRAG as a positive regulator, aiding to autophagosome formation [35]. Importantly, conversion from LC3-I to LC3-II has been extensively used as a marker of autophagy [36–40]. Concomitantly, because p62 accumulates when autophagy is inhibited, this protein has also been used as an autophagic flux marker [41]. Once the autophagosome is formed, it fuse with the lysosome to form the autolysosome through the recruitment of the soluble N-ethylmaleimide-sensitive factor attachment (NSF) protein receptor (SNARE), protein syntaxin 17 (Stx17) and interact with the homotypic fusion and vacuole protein sorting (HOPS) complex [42,43]. HOPS is a class-C Vps complex which is composed by Vps11, Vps16, Vps18, Vps33, Vps39 and Vps41. The vesicle trafficking process that occurs during this fusion is regulated by GTPases such as Ras superfamily of monomeric G protein (Rab) 7, Rab8b and Rab24 [44]. At the end of the process, specific components, such as decaying organelles and expired proteins are trapped inside the autophagolysosome and degraded [1].

3. Autophagy and antiviral innate immunity

3.1. Virus recognition

Toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) and Retinoic acid-inducible gene (RIG-1)-I-like receptors (RLRs) are the pattern recognition receptors (PRR) involved in detecting pathogen components, such as single- and double-stranded viral RNAs [45,46]. Several TLRs are known to activate innate responses after virus infection, including TLR2, TLR3, TLR4, TLR7 and TLR8 [45,46]. TLR2 and TLR4 are expressed on the cell surface whereas TLR3, TLR7 and TLR8 are localized within cytoplasmatic compartments, such as endosomes [47–49]. TLR activation within endosomes requires endocytosis of pathogen associated molecular patterns (PAMPs), such as viral RNA molecules, damage associated molecular patterns (DAMPs), apoptotic cells or the induction of autophagy [50,51]. Several viruses can evade immediate recognition by TLRs after entering cells through endosome-associated compartments, thereby delaying the onset of an immune response [50]. TLR signaling results in the activation of nuclear factor kappa B (NF-κB), interferon regulatory transcription factor (IRF)-3 and IRF-7 and the assembly of inflammasome to activate caspase-1 and further process pro-interleukin (IL)-1β and IL-18 into their active forms [52]. Upon viral RNA detection, cytosolic PRRs, for instance Nod domain 2 (Nod2), RNA helicases such as melanoma differentiation-association gene-5 (MDA5), and RIG-I are activated [53]. RIG-I interacts with the adaptor interferon (IFN)-β promoter stimulator (IPS-1; also known as MAVS, VISA or CARDIF) on the mitochondrial membrane, and consequently activates the transcription factors IRF-3 and NF-κB, leading to the production of IFN-β and other cytokines (Fig. 2). IPS-1 has been shown to contribute to the type-I IFN-mediated mechanisms of antiviral host defense [50]. This notion is supported by the observation that IPS-1-knockout mice show an increased recruitment of inflammatory neutrophils, monocytes and dendritic cells (DCs) in the lungs after human respiratory syncytial virus (hRSV) infection [50], evidencing the importance of this adaptor in antiviral responses for the clearance of hRSV. The papain-like protease 2 (PLP2) protein from coronaviruses promotes Beclin-1 association with STING [10]. Another protein that has been shown to regulate autophagy and the antiviral defense is Tripartite motif protein family (TRIM) [54], which blocks IRF-3/7 via serine/threonine protein kinase (TBK1) and NF-κB [55]. In addition, TRIMs associate with autophagy factors. Indeed, TRIM5 was found to recognize and target human immunodeficiency virus 1 (HIV-1) for destruction [56].

3.2. Innate immunity components and autophagy-related proteins

Molecular components related to autophagy have been frequently described to contribute to the replication of certain viruses [57–59]. Indeed, RIG-1 has been described to be modulated by Atgs activated by viruses, such as vesicular stomatitis virus (VSV) [57]. For instance, embryonic fibroblasts from Atg5-deficient mouse were shown to be resistant to VSV replication, suggesting that autophagy components can contribute to viral replication in host cells. The constitutive overexpression of a mutant of RIG-1 induced the activation of NF-κB and IFN-β, which was suppressed by the co-expression of the Atg5-Atg12 complex [57]. This suppression seemed to be dependent on infection with VSV and was reported to induce a conformational change in RIG-1 [57]. Nucleotide-binding domain and leucine-rich-repeats containing proteins
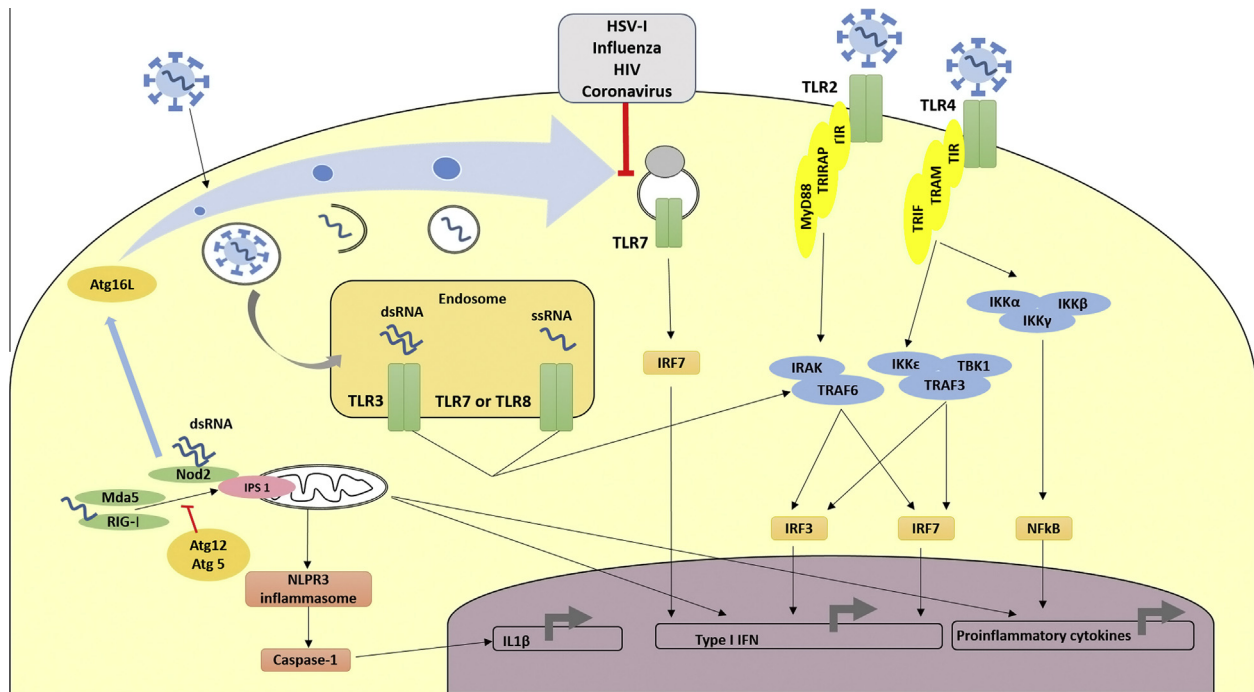

Fig. 2. Autophagy and antiviral innate immunity. Viruses may enter cells by endocytosis resulting in the delivery of viral RNA in the endosome. Once in the endosome, dsRNA can be recognized by Toll-like receptor 3 (TLR3) and ssRNA by TLR7 or TLR8, triggering interleukin 1 (IL-1) receptor associated kinase (IRAK) and tumor necrosis factor (TNF) receptor associated receptor 6 (TRAF6) followed by Type I interferon (IFN) production. Cytosolic RNA can also trigger autophagosome formation followed by fusion with lysosomes. Herpes simplex virus 1 (HSV-1), influenza virus, human immunodeficiency virus and viruses from *Coronaviridae* have been shown to inhibit autophagy by directly blocking Beclin-1. The phagosome-lysosome fusion induces activation of interferon regulatory factor 7 (IRF7) via TLR7. Autophagy can be triggered by the cytosolic presence of retinoic acid-inducible gene-1 (RIG-I), nucleotide-binding oligomerization domain (NOD) or melanoma differentiation-association gene 5 (MDA5). RIG-I interacts with the adaptor IFNP promoter stimulator (IPS-1) on the mitochondrial membrane triggering activation of IRF3/7 and nuclear factor kappa B (NF-κB). This interaction can be blocked by Atg12-Atg5 complex. The mitochondrial cascade triggers induction of NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome, which triggers caspase-1-mediated IL-1β production. IRF3 and IRF7 are transcription factors of type-I IFN and NF-κB of proinflammatory cytokines.

(NLRX1), as well as the mitochondrial Tu translation elongation factor (TUFM) in turn have been shown to modulate autophagy via RIG-1 signaling and activation of IFN-I, as well as the association with the Atg5-Atg12 complex and ATG16L [60]. The induction of autophagy by NLRX1 was specifically shown in VSV-infected peritoneal macrophages from *nlrxl* knockout mice [60]. Similarly, it was shown that IFN-β-induced phagosomes were directed to lysosomes for degradation in hepatitis B virus (HPV) infection in a non-structural serine protease 3(NS3)/4A transgenic mouse model [61].

Inhibition of Nod-dependent response by ATG16L has also been described in mouse embryonic fibroblasts and epithelial cells [62]. Nod1, Nod2 have been shown to colocalize with ATG16L and Nod2 to trigger autophagy by recruiting ATG16L at the site of pathogen entry [63]. TLR4 recognition via tumor necrosis factor (TNF) receptor-associated factor (TRAF) also induces the K63-linked ubiquitination of Beclin-1, triggering autophagy as well as blocking the inhibitor of autophagy anti-apoptotic B-cell lymphoma 2 (Bcl-2) [64]. Thus, the Atg5-Atg12 complex, ATG16L and Beclin-1 all autophagy-related proteins that have been reported to interact with components of the innate immune system.

3.3. Autophagy and inflammatory cytokines

Viruses have evolved several molecular strategies to evade antiviral host responses, such as modulation of inflammatory cytokines. Recently, it was shown that a lack of Atg5 in dendritic cells (DCs) infected with herpes simplex virus (HSV), resulted in reduced IFN-β production [65]. Autophagy has also been shown to be important for the production of cytokines produced from innate immune cells. Indeed, blockade of autophagy by the 3-methyladenine (3-MA) inhibitor in DCs infected with hRSV has been shown to prevent the expression of interferons, chemokines and cytokines, such as IFN-β, TNF-α, C-C motif ligands 5 (CCL5), IL-6, and IL-12p35, but not IL-1b [66]. Furthermore, knock-out of Beclin-1 resulted in increased lung pathology in hRSV-infected mice [67].

An association between autophagy and lung inflammation with other viruses, different than hRSV has also been described. Consistent with this notion, autophagy has been shown to be involved in avian influenza A virus (IAV)-induced lung inflammation [68]. Influenza A virus subtype H5N1 infection induces IL-1β, TNF-α, IL-6, IL-8, and CCL2, CCL5 and C-X-C motif ligand 2 (CXCL2) chemokines. Treatment with the autophagy inhibitor 3-MA or either Atg5 or Beclin-1 siRNA, significantly reduced the production of cytokines and chemokines as well as the nuclear translocation of NF-κB in human lung epithelial cells [68]. Interestingly, the administration of the autophagy inhibitor 3-MA to H5N1-infected mice resulted in an attenuation of lung inflammation, as well as the activation of NF-κB and p38 mitogen-activated protein kinases (MAPK) [68].

4. Autophagy and antiviral adaptive immunity

4.1. Autophagy in antigen presentation

In addition to playing a role during innate immune responses to virus infections, autophagy also contributes to the regulation of adaptive immune responses against these and other pathogens. For instance, autophagy contributes to antigen presentation to T cells by antigen presenting cells and is required for an effective initiation of the adaptive immune response [11,67,69]. Indeed, presentation of pathogen-derived peptides on major histocompatibility complex (MHC) class II molecules to CD4+ T cells has been reported to be facilitated by autophagy [70] (Fig. 3). Antigen acquired by phagocytosis will be degraded into peptides by the

autophagosome and eventually loaded onto MHC molecules [71]. The peptide-MHC (pMHC) complexes generated are then transported to the cell surface and presented to CD4+ T cells. In contrast to antigen presentation on MHC-II molecules, antigen presentation on MHC-I molecules can be mediated by two pathways in which only one involves autophagy. During conventional MHC-I antigen presentation, endogenous protein antigens are degraded into peptidic fragments by the proteasome and then transported into the endoplasmic reticulum, where they are translocated to the lumen through the transporter associated with antigen processing (TAP) [71]. Once in the endoplasmic reticulum, peptides are loaded onto MHC-I molecules and then transported to the surface for presentation to CD8+ T cells [71]. It has been suggested that the alternative pathway for antigen presentation on MHC-I molecules, called cross-presentation, may require autophagy components [72–74]. Cross-presentation consists on the presentation of exogenous antigens on MHC I molecules to CD8+ T cells [71]. This pathway has been reported practically in every type of immune response, such as tumor immunity [74], autoimmunity [75] and microbial infections, such as in macrophage infection by HSV-1 [72], as well as DCs stimulated with the yellow fever vaccine [73]. Furthermore, it has been shown that viral proteins undergo vacuolar processing in autophagosomes, which is followed by proteasome degradation and peptide loading on MHC-I molecules in the endoplasmic reticulum [72]. However, the molecular mechanisms involved in vacuolar processing of viral proteins remains unknown.

4.2. Evasion of autophagy mediated antigen presentation by viral pathogens

Because of the importance of antigen presentation on MHC molecules for virus clearance by the host immune response, pathogens have evolved molecular mechanisms to evade this process. Along these lines, it has been shown that human hepatitis virus C (HVC) reduces cathepsin S through IRF-1 and upstream stimulatory factor (UPS-1), thereby altering the degradation of the invariant chain and consequently antigen presentation [76]. Similarly, LC3-deficient DCs show a significant impairment in their capacity to present HIV-1-derived antigens to CD4+ T cells [69]. Epstein-Barr virus nuclear antigen 1 (EBNA-1) has been shown to inhibit autophagy, thereby decreasing recognition by EBNA-1-specific CD4+ T cell clones [77]. An association between autophagy and adaptive immunity is suggested by observation that Atg5-deficient DCs fail at presenting antigens on MHC class II molecules, as well as at priming and promoting the proliferation of T cells in vivo after HSV infection [65]. However, abrogation of Atg5 in DCs had no effect on antigen cross-presentation on MHC class I molecules, suggesting that Atg5 is not essential for this pathway [65]. Interestingly, phagosomes coated with LC3 protein maintain antigens for prolonged periods of time, favoring antigen presentation on MHC class II molecules [78]. Recently, a Beclin-1+/− mouse showed that loss of autophagy function could lead to decreased MHC-II expression after hRSV infection and failure to produce IFN-γ and IL-17, thereby impairing both DC maturation, as well as the onset of an effective antiviral adaptive immune response against this virus [67]. Furthermore, the expression of granzyme B in CD8+ T cells has been shown to be decreased in Beclin-1+/− mice [67].

4.3. Therapeutic strategies to improve antigen presentation

Due to the fact that weak CD4+ T cell-mediated responses have been observed in more than one HIV vaccine clinical trial [79,80], Jin and coworkers [81] designed a recombinant simian immunodeficiency virus expressing Gag fused to LC3b. Such a construction caused that Gag localizes to the autophagosome and lysosomes,
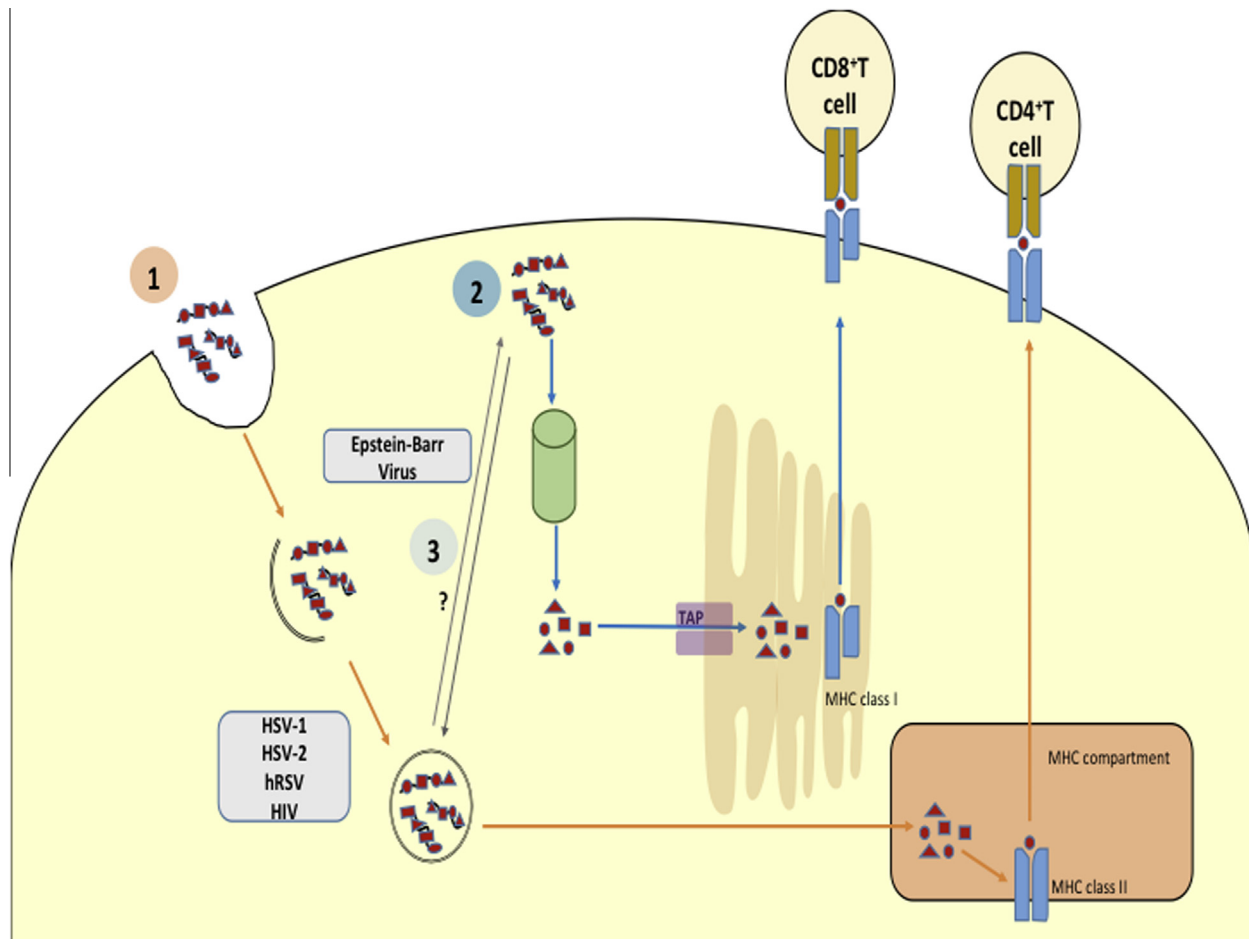
Fig. 3. Autophagy and antiviral adaptive immunity. (1) Major histocompatibility complex (MHC) II antigen presentation. Antigen is captured by phagocytosis, degraded by the autophagosome and then loaded onto MHC molecules in the late endosomal MHC compartment and eventually peptide-MHC complexes trafficked to be presented to CD4^{+} T cells. (2) Conventional MHC I antigen presentation. Endogenous antigen is degraded into peptides fragments in proteosomes, transported to the endoplasmic reticulum via antigen processing (TAP), loaded into MHC class I molecule and then transported to the surface to be presented to CD8^{+} T cells. (3) Antigen cross presentation on MHC-I. Autophagy is suggested to be involved in exogenous antigen processing but its mechanism is unknown. In cells infected with respiratory syncytial virus (RSV), herpes simplex virus (HSV)-1, HSV-2 and human immunodeficiency virus, autophagy have been shown to be important for antigen presentation on MHC class II molecules. Vacuolar viral proteins processing has been reported for Epstein-Barr virus nuclear antigen 1 (EBNA1) and HSV-1.

which promotes presentation in MHC-II molecules. This strategy was shown to significantly improve the immunogenicity of HIV antigens and the induction of an adaptive immune responses upon infection [81]. Along these lines, other novel strategies have been undertaken to enhance antigen presentation and immune response induction. For instance, a peptide derived from HSV that induces autophagosomal degradation of antigens was implemented to protect from tumor challenge [82]. Such a peptide could be attached to antigenic viral proteins for vaccine design, as a manner to enhance immunogenicity. However, as noted above not all autophagy proteins are essential for antigen presentation, as Atg7-deficient thymocytes and DCs showed no alterations in any antigen presentation pathway for exogenous or endogenous antigens [83]. Taken together, these studies provide an important link between antigen presentation of virus-derived proteins and the autophagosome function in antigen presenting cells. Ultimately, modulating autophagy during infection could improve the overall immune response to pathogens.

5. Autophagy exploitation by viruses to evade host immunity

Autophagy is critical for limiting infection by pathogens [84,85]. However, some microorganisms, such as coronavirus, HIV and cytomegalovirus have developed mechanisms to evade this microbicide system [13,86,87]. Numerous evasion mechanisms evolved by these microbes have been associated with the inhibition of autophagosome-lysosome fusion, escape from phagocytic vacuoles in the cytoplasm and resistance to lysosome degradation components. Indeed for antiviral responses, an important role for autophagy has been shown in several virus infections (Table 1).

5.1. Autophagosome-lysosome fusion modulation by viruses

HSV-1, influenza virus, HIV, HCV and coronavirus are all able to induce autophagy. However, at the same time these viruses have been shown to inhibit the last step of autophagosome-lysosome fusion, which promotes viral replication and reduces cell apoptosis or death [7–11]. HSV-1 induces autophagy in such a way that it antagonizes autophagosome maturation by the interaction of HSV γ34.5 protein with Beclin-1 [7]. It has been suggested that an inefficient fusion between autophagosomes and lysosomes in HSV-infected cells is induced by oxidative stress and has been associated with neurodegeneration [88]. In addition, γ34.5 has been shown to be important for HSV virulence in the brain of adult and neonatal animals and dependent on type-I IFN only in adults [89]. HCV has also been reported to induce autophagy and endoplasmic reticulum stress, leading to an accumulation of autophagosomes that require the activation of the unfolded protein response

Table 1
Interactions of various viruses with the autophagy pathway.

Virus	Interactions viruses with autophagy machinery	Viral proteins involved	Autophagy related proteins	References
Herpes Simplex Virus 1 (HSV-1)	HSV-1 triggers autophagy but inhibit autophagosome-lysosome fusion, autophagosomes are accumulated	γ34.5 protein	Beclin-1, Atg5	[7,65]
Influenza virus	Influenza induces autophagy but inhibit autophagosome-lysosome fusion, autophagosomes are accumulated	Matrix protein 2 (MP2)	LC3, Atg5	[8,39]
Human immunodeficiency virus (HIV)	HIV triggers autophagy but inhibit autophagosome-lysosome fusion, autophagosomes are accumulated in CD4+ T cells while HIV interferes in autophagosome-mediated degradation	Nef protein	Beclin-1	[9,101,102]
Coronaviridae family	Viruses from Coronaviridae family trigger autophagy but inhibit autophagosome-lysosome fusion, autophagosomes are accumulated. Autophagy is critical for virus replication	Membrane-associated papain-like protease PLP2 (PLP2-TM)	Beclin-1, LC3	[10,103]
Vesicular stomatitis virus (VSV)	Autophagy in plasmacytoid dendritic cells are required for VSV recognition and autophagy is required for virus replication	Unknown	Atg5	[65]
Sindbis virus	Sindbis virus induces autophagy and overexpression autophagy proteins protects from infection	Capside protein	p62, Atg7, Atg5	[58,59]
Human respiratory syncytial virus (hRSV)	Beclin −/+ mice show higher levels Th2, lower IFN and IL17, decrease expression granzyme B in CD8+ T cells and increased viral replication	Unknown	Beclin-1	[50,67]
Human hepatitis virus C (HVC)	HVC induces autophagy and ER stress, and autophagosomes are accumulated. HVC core and NS5A proteins reduce expression cathepsin S which is involved in the degradation of the autophagy cargo	HVC core and NS5A	UPR	[11,76,90,91]
Human hepatitis virus B (HVB)	HVB triggers autophagy favoring replication of DNA HVB, the production of viral envelopment and release of naked capsides	Unknown	Unknown	[115–117]
Cytomegalovirus	Cytomegalovirus induces autophagy in early stages but inhibits it in late stages	TRS protein	Beclin-1	[36–38]
Varizella-zoster (VZV)	VZV triggers complete autophagy which facilitate VZV glycoproteins biosynthesis and processing	Unknown	Unknown	[92]
Measles (MeV)	MeV increases autophagy flux	Unknown	LC3	[93]
Adenovirus	Adenovirus is more efficiently replicated in cells with induced autophagy	Unknown	Unknown	[97]
Simian immunodeficiency virus type I (SIV)	SIV inhibits neuronal autophagy	Unknown	Unknown	[109]

(UPR) [90,91]. Interestingly, serum from HCV-infected patients has been reported to block autophagy in differentiating monocytes suggesting the participation of soluble components in sera with this particular capacity [11]. In contrast, varicella-zoster virus (VZV) promotes a complete autophagy process, which has been evidenced by the degradation of some of its long-lived proteins [92]. Autophagy in this latter case seems to be used by the virus to facilitate VZV glycoprotein biosynthesis and processing [92]. Similar to VZV, measles virus (MeV) increases autophagy but prevents the degradation of viral proteins [93]. Interestingly, MeV-induced autophagy is required for the replication of the virus. In addition, enteroviruses, such as coxsackievirus and rotavirus have also been reported to interact with autophagy elements to evade immunity by increasing respectively protein- and calcium-activated signaling in infected cells [94–96]. Another example of virus exploitation of the autophagy machinery is provided by adenoviruses [97]. These pathogens replicate more efficiently in the airways when epithelial cells undergo nutrient deprivation-induced autophagy [97]. The mechanisms used by other viruses that induce autophagy, such as dengue and parvovirus B19 remain to be undetermined [98,99].

5.2. Viral proteins interacting with autophagy-related proteins

An extended two-hybrid array, with 35 associated autophagy proteins and 80 different viral proteins from 5 different families of RNA viruses (Paramyxoviridae, Flaviviridae, Orthomyxoviridae, Togaviridae and Retroviridae), showed that these viruses targeted several autophagy proteins [100]. Among these proteins, immunity-associated GTPase family M (IRGM) was a common target for all the viruses studied [100]. Importantly, autophagosome accumulation due to the inhibition of autophagosome-lysosome fusion in MeV, HCV and HIV was shown to be IRGM-dependent by confocal microscopy [100]. In addition, it is likely that IRGM can modulate initial autophagy steps because this molecule

targeted Atg5, Atg10 and LC3, all components of the initial phase of autophagy [100].

Viral γ34.5 protein from HSV-1 [7], Nef protein from HIV [9,101,102], non-structural protein 3 from coronavirus [10] and matrix protein 2 (M2) protein from influenza viruses [8] have been shown to interact with Beclin-1, thereby modulating the function of autophagy. PLP2 from coronaviruses induces an incomplete autophagy process by interacting with LC3 and Beclin-1 [10]. In addition, the deletion of Beclin-1 has been shown to activate IFN-β promoter and increase viral replication in infected coronavirus cells [10]. Alternatively, non-structural protein 6 (Nsp6) from viruses belonging to the Coronaviridae family induces LC3-positive vesicles.

5.3. Autophagy in different cell types infected with viruses

On the other hand, the mouse hepatitis coronavirus (hCMV), induces autophagy in murine embryonic stem cells, which is critical for the replication of the virus [103]. In contrast, Atg5 was not required for mHPV replication in both primary bone marrow macrophages and primary low-passage mouse embryonic fibroblasts [104]. Therefore, it is likely that this virus may be interacting differently with the autophagy components depending on the cell type encountered. Similar to mHPV, infectious bronchitis virus induces the formation of autophagosomes when inhibited through the silencing of Atg5 [105]. However, this phenomenon did not alter the replication of the virus, which suggests that this protein is not essential for autophagosome induction by this virus [105].

It has been shown that autophagy can be inhibited in epithelial cells during influenza infection [8]. Autophagosome fusion with acidified proteolytic lysosomes in influenza-infected human epithelial cell lines is significantly inhibited [8], thereby influenza may exploit autophagy as a mechanism to avoid degradation by lysosomes. The M2 influenza protein, which plays important roles in several steps of influenza virus infection, which works as a

proton channel and has been shown to be key for the modulation of autophagy in infected cells [8,39]. While M2-transfected cells showed autophagosome accumulation, calls transfected with other influenza A virus proteins did not show alterations of the autophagy pathways [39]. In addition, M2 has been shown to interact with LC3 and promotes its LC3 redistribution to the plasma membrane [39]. Along these lines, different compounds with anti-influenza activity have been shown to either block or modulate autophagy, by altering host-virus protein interactions [40,106]. Indeed, the replication of influenza within the autophagosome may be reduced by blocking the induction of autophagy. Baicalin, a flavonoid compound with antiviral properties, shows inhibitory activity over autophagy by inhibiting mTOR signaling and Atg5-Atg12 during influenza infection [106]. Interestingly, the same group showed that simvastatins can also promote the accumulation of LC3-II levels that could favor autophagosome building up [40].

HIV has also received significant attention because of its capacity to modulate autophagy in a cell type-dependent manner [80]. HIV modulates autophagy in adipocytes, CD4$^+$ T cells, macrophages and DCs, by different mechanisms depending on the cell type [69,107,108]. HIV has been shown to trigger autophagy in CD4$^+$ T cells, leading to higher LC3-II, Atg5 and Beclin-1 [9,108]. In contrast, HIV-1 infection in DCs leads to the loss of LC3-II accumulation, which interferes with autophagosome-mediated degradation of the virus [69].

Autophagy in neurons is also of particular interest. Overexpression of Beclin-1 in neurons from neonatal mice showed protection against a lethal Sindbis virus infection [58]. Atg5 and Atg7 have also been shown to trigger autophagy in Sindbis virus-infected neurons and to prevent virus-induced cell death in vivo and in vitro when performing studies using knockout techniques [59]. Interestingly, Atg5 disruption in neurons did not vary viral titers in the central nervous system, suggesting that Atg5 does not play an essential role in the clearance of Sindbis virus, at least in these cells [59]. On the other hand, simian immunodeficiency virus type I-infected microglia inhibits neuronal autophagy, thereby decreasing neuron survival [109]. An association between autophagy and apoptosis and cell death derives from the interaction of Beclin-1 with the major anti-apoptotic B-cell lymphoma (Bcl) family protein [110]. These observations suggest that autophagy has been shown to be critical for blocking cell death in virus-infected neurons. Because autophagy can be considered as a process opposite to cell death or apoptosis in cells, the promotion of this process may provide an advantageous environment for viruses to replicate and spread onto neighboring cells.

A role for autophagy components in immune cells, such as invariant natural killer T (NKT) cells has also been evidenced. Indeed, deletion of Atg7 has been reported to impair NKT cell development in a T cell-intrinsic manner [83]. These findings suggest that autophagy may play a role in the development and function of these cells during antiviral responses. Similar to DCs, different populations of NKT cells have been shown to contribute to the immune response against HSV-1 [111], HSV-2 [112], encephalomyocarditis virus [113] and hRSV [114]. Thus, it is likely that autophagy could modulate the function of NKT cells during anti-viral immune responses against viral infections. Based on reports that support a role for autophagy during the replication and life cycle of certain viruses, the use of specific autophagy-inducing agents has been proposed as a strategy for treating or preventing several infectious diseases [102].

5.4. Autophagy and virus components needed for replication

A role for autophagy in viral infection with HPV has also acquired particular attention. HPV induces autophagy and exploits the components of this cellular process for genome replication and viral envelope formation. However, the mechanisms involved in the interactions between autophagy components and virus determinants remains controversial [115,116]. For instance, HPV utilizes some of the host's autophagy machinery molecules to release its naked viral capsids, requiring for example Rab33B, a GTPase that participates in autophagosome formation via the Atg5-Atg12-ATG16L complex [117]. Nevertheless, the suppression of conventional autophagy processes using chemical inhibitors, such as 3-MA did not produce any effect on capsid release, indicating that the virus does not require an intact autophagosome to release capsids [117].

6. Concluding remarks

Autophagy components, which include autophagy-related proteins and adaptors have been demonstrated to interact with numerous components belonging to innate and adaptive immune responses. However, whether autophagy is positive or negative for viral infection and pathology remains to be elucidated. Indeed, in the context of an infection, autophagy may act as a double edge sword. While autophagy may help to eliminate pathogens, it can also could work as a reservoir for pathogen growth and escape from apoptosis or cell death. However, consistent with an important role for autophagy during viral infections, viruses have evolved different mechanisms to counteract this cellular process. Because of its involvement during viral infections, autophagy is actively being explored as a cellular target for the development of vaccines and therapies for preventing virus spread or dissemination [81,82,118]. Undoubtedly, further research is required to understand the interactions occurring between components of autophagy and the immune system. This knowledge will contribute explaining as to how viruses counteract this defensive host system for their own benefit and open new possibilities to improve antiviral therapeutics and vaccines.

Acknowledgments

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