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Review Article

Herpesviral Interaction with Autophagy

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Autophagy constitutes a major catabolic hub for the quality control of intracellular entities of eukaryotic cells, and is emerging as an essential part of the host antiviral defense mechanism. However, in turn, viruses have evolved elegant strategies to co-opt various stages of the cellular autophagy pathway to establish virulence *in vivo*. This is particularly the case in the ubiquitous and persistent herpesvirus infection. In this review, I will focus on recent findings regarding the crosstalk between the herpes virus family and the autophagy pathway, with a look at the molecular mechanisms they use to disturb cells' autophagy regulation and eventually result in persistence and pathogenesis.

Key Words: Autophagy, Virus, Innate immunity, Infection

I. Introduction

Initially discovered as a cellular response to adapt to nutrient deficiency, macroautophagy (hereafter referred to as autophagy) has since been recognized as a fundamentally important homeostatic process that is also involved in innate and adaptive immunity against diverse pathogens (1~5). As obligate intracellular parasites, viruses have evolved strategies that either deploy or subvert key stages of the autophagy pathway to guarantee their invasion, survival and propagation (1, 5, 6). Significantly, representatives of all three herpesvirus subfamilies, alpha (α), beta (β), and gamma (γ), encode proteins or induce cellular signaling pathways to manipulate autophagy (1, 3). It is also now being appreciated that viral autophagy-modulator proteins have great potential for use in probing the molecular mechanisms of autophagy as well as its communications with other cellular pathways upon infection. Thus, delineating viral interaction with the host autophagy machinery helps to advance our understanding of fundamental cell biological mechanisms and uncover new targets for antiviral therapies. In this review, we focus on recent findings about the multifaceted roles of autophagy in herpesviral infections and on immune modulation mechanisms of herpesviruses that target this pathway.

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II. Autophagy at a Glance

Evolution has transformed a once primitive autophagic route that was dedicated to starvation response into a sophisticated signal transduction and membrane-remodeling network (7, 8). Over 30 distinct autophagy-related (Atg) genes have been identified so far in yeast, and more numbers of Atg genes or genes with Atg functions are probably expressed in mammals (8). While constitutively active at low levels to maintain a relatively stable intracellular milieu, autophagy is rapidly upregulated under conditions of cellular stress, viral infection being included (5). The basic tenet of autophagy is outlined as a lysosome-directed transportation

and degradation of intracellular cargoes (in contrast to extracellular cargoes in the endocytic route) through a double membrane-bound vesicle, the autophagosome (7, 8). Formed within the cell, the autophagosome, a biological hallmark of autophagy, serves to sequester and seal off extraneous components such as bulk cytoplasm, protein aggregates, defective organelles, invading pathogens and their products, from the rest of the inside of the cell. The autophagosome is then progressively acidified by sequential fusion with the endosome and the lysosomal compartment to form the autolysosome, exposing its inner membrane together with the encapsulated contents for lysosome digestion, and having the resultant macromolecules recycled (Fig. 1) (7, 8). Thus, in concern of protein degradation, autophagy constitutes a second scavenging system to maintain a healthy proteome; in concern of cargo selection and trafficking, autophagy is considered as an additional membrane-remodeling event that converges with endocytic trafficking on its journey to the lysosome. Notwithstanding extensive studies on the molecular details of autophagy, much remains unknown regarding how the rate of autophagic degradation is controlled and how the specific cargo is selected in response to various forms of cellular stress.

Autophagy can be largely divided into several sequential steps; autophagy induction, autophagosome nucleation, elongation, maturation, and lysosomal degradation that require specific Atg genes (Fig. 1) (9). Simply stated, autophagy induction is often tightly controlled by the 'nutrient sensor', the mammalian target of rapamycin (mTOR), which senses and integrates signals from numerous sources including growth factors, amino acids, hypoxia, and energy levels (10, 11). Under nutrient-rich conditions, mTOR is active and represses autophagy by precluding the formation of the ULK1/2-Atg13-FIP200 signaling complex, which is required for the initiation of autophagy (9, 10). On inactivation of mTOR by upstream signaling, the de-repression and assembly of the ULK complex triggers the autophagy cascade (Fig. 1). It is noteworthy that not all autophagy signals are transduced through mTOR; for instance, protein kinase R (PKR)-mediated phophorylation of eukaryotic initiation factor 2alpha (eIF2α) provokes herpes simplex virus type 1 (HSV-1)-induced autophagy (12). Other molecules such as inositol 1,4,5-triphosphate receptor (IP_3R), calcium, c-Jun-N-terminal kinase 1 (JNK1), and p53 have all been implicated in autophagy induction in different physiological and pathological settings likely by different mechanisms (9, 13). Following induction, divergent signals are resolved in space, to the membrane nucleation sites (also called phagophore) rich in phophatidylinositol-3-phosphate (PtdIns(3)P), which surprisingly, but not unexpectedly, can be generated from multiple membrane sources including endoplasmic reticulum (ER), Golgi apparatus, nuclear, endosome, mitochondrial membrane, and plasma membrane (14~18). Notably, production of PtdIns(3)P and vesicle nucleation is mainly governed by the Beclin1-associated phosphatidylinositol 3-kinase class III (PI3KC3) complex. Beclin1, by itself, does not have any enzymatic activity but acts as a platform to recruit other cofactors including Atg14, UV radiation resistance-associated gene (UVRAG), Bif-1 (also called endophilin B1), and Ambra-1, which activates the PI3KC3 complex, or factors that counteract Beclin1-mediated autophagy such as Bcl-2, NAF-1, and Rubicon (Fig. 1) (9, 11, 19). The importance of Beclin1, as one might expect from its scaffolding property, is reflected by its serving a frequent target of herpesviruses as discussed below (20~22). The elongation or expansion of autophagosome membrane for cargo sequestration involves two evolutionarily conserved ubiquitin-like conjugation systems: LC3 (mammalian Atg8)-phosphatidylethanolamine (PE) conjugation and Atg12-Atg5 conjugation (8). After proteolytic cleavage by the Atg4 cysteine protease, LC3 is conjugated to the membrane lipid PE after sequential processing by E1-like enzyme Atg7 and E2-like enzyme Atg3. Concomitantly, Atg12 is conjugated to Atg5 in a similar manner except that Atg10, instead of Atg3 is used as the E2 enzyme (Fig. 1) (8, 9). Notably, recent study revealed an Atg5/Atg7-independent autophagy pathway that is not associated with LC3 lipidation but specifically involves membranes derived from Golgi or late endosomes (23), further highlighting the diversity and complexity of autophagic trafficking processes that have evolved to match the dynamic demands in different environments. Auto-

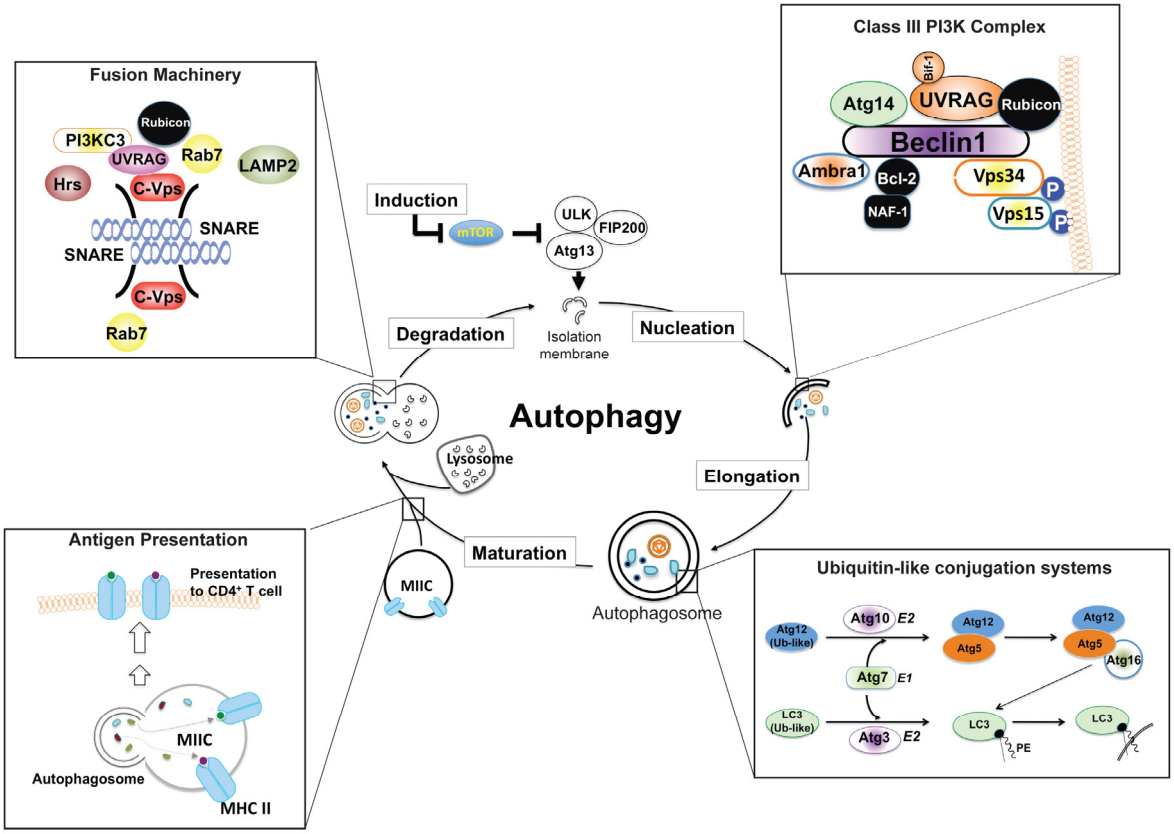

Figure 1. Overview of the autophagy pathway. Autophagy proceeds through a series of steps including autophagy signal induction, vesicle nucleation, membrane elongation, completion of the autophagosome, autophagosome maturation by fusion with endosomes and lysosomes, followed by degradation of autophagic cargoes, and recycling of the resulting molecules. The induction of autophagy by various stimuli signals through the 'nutrient sensor' mTOR. Under nutrient-rich conditions, mTOR binds and hyper-phosphorylates the ULK1/2 complex comprised of ULK1/2, Atg13, and FIP200 to repress autophagy. Inactivation of mTOR leads to the ULK1/2 complex hypo-phosphorylated, which allows the isolation membrane to expand. Vesicle nucleation is confined to the phosphatidylinositol-3-phosphate (PtdIns(3)P)-containing vesicles and is driven by the PI3KC3 complex, which consists of three major components, including Vps34, Vps15, and Beclin1. The activity of this lipid kinase complex is regulated by various positive and negative (*black*) regulators that associate with Beclin1. Two ubiquitin-like conjugation systems are involved in autophagosomal membrane expansion and completion: one is LC3-phosphatidylethanolamine (PE) conjugation and the other is Atg12-Atg5-Atg16 conjugation. The last steps of autophagy involve the docking and fusion of completed autophagosomes with endosomes and lysosomes sequentially, which signifies the maturation stage of autophagy regulated by various endosome/lysosome-related factors and inhibitory regulators (*black*). Finally, the inner membrane of the autophagosome and its sequestered materials are degraded by the lysosomal enzymes with the end products of proteolysis recycled. In antigen-presenting cells, autophagosome can also fuse with MHC class II loading compartments (MIICs), a subset of multivesicular bodies (MVBs), whereby autophagic cargoes including viral antigens can be delivered for MHC class II presentation.

phagosome maturation and lysosome degradation serves not only as a pivotal checkpoint for the overall autophagy flux *per se* but also as the convergence point of endocytic signaling and trafficking, whereby soluble NSF attachment protein receptor (SNARE) proteins like Vam7, tethering factors like the class C vacuolar protein sorting (Vps) complex, Rab family members such as Rab7, Rubicon-containing PI3KC3 complex, and lysosome membrane proteins all seem involved to different extent (Fig. 1) (2, 24~28). Recent studies further provided intriguing evidence that autophagic digestion facilitates the processing of intra- and extra-cellular antigens for both MHC class I and II presentation, hence significantly expanding the role of catabolic autophagy in adaptive immunity (29~31).

III. Autophagy Restricting Herpesviral Infection

Herpesviruses are highly successful pathogens as they

establish long-term latency in neurons or lymphoid cells from which they can reactivate, sometimes frequently, to cause recurrent disease and virus spreading, without being cleared off by the host immune system (32~35). As autophagy is key to clearing the intracellular environment, the interplay between the herpes pathogen and its host cell reflects a constant battle for control.

Xenophagy eating herpes

One striking aspect of autophagy in anti-microbial infection is achieved by its selective capture of foreign microbial invaders into autophagosome for degradation, a process that has been termed as xenophagy (36), to discriminate it from the degradation of self-constituents. The first and insofar as the only direct evidence for xenophagic degradation of virions was provided by studies with the neurotropic α-herpesvirus, herpes simplex virus type 1 (HSV-1) (37). Upon HSV-1 infection, activation of the host-defense molecule, the double-stranded RNA-dependent PKR, stimulates autophagy induction through the translation initiation factor eIF2α phosphorylation (12, 38). As a countermeasure, the HSV-1-encoded neurovirulence factor ICP34.5 (39) is expressed to recruit a host phosphatase, PP1α, which dephosphorylates eIF2α and thus reverses PKR effects in both autophagy and host cell translational shutoff (37, 38). Accordingly, mutant HSV-1 deficient in ICP34.5 caused higher levels of autophagic response in permissive cells compared to wild-type virus, and more ICP34.5-null virions were found to gain entry into autophagosome-like compartments, leading to the consumption that xenophagic degradation of virions helps control HSV-1 infection (22, 37). However, it remains unclear whether the autophagosome-resembling structures induced by HSV-1 are contributed by the autophagy machinery. Further, if xenophagy indeed mediates HSV-1 virions degradation, as shown in bacterial clearance (40), one would expect that elimination of the autophagic pathway in cells would rescue the infectivity of ICP34.5-null HSV-1, at least to certain extent. Surprisingly, the replication of this ICP34.5-null virus remained unchanged in autophagy-deficient cells, casting some doubts on the significance of xenophagy in *de novo* HSV-1 infection *in vitro* (41). It is noteworthy, however, that the mutant HSV-1 unable to counteract autophagy is severely neuroattenuated with regards to lethal encephalitis in mice (22, 42), highlighting a divergent requirement of xenophagy *in vitro* and *in vivo*, and/or an alternative mechanism other than xenophagic degradation might be involved in the immune control by autophagy.

Autophagy presenting herpesviral antigens

In addition to functioning as a degradation process by itself, autophagic delivery of cytoplasmic contents including various antigens (viral, tumor, or self antigen) to the endosome/lysosome system provides a detour pathway for the MHC class II presentation of intracellular antigens and thereof aids adaptive immune activation (9, 43). A well documented example is provided by Epstein-Barr virus (EBV) nuclear antigen 1 (EBNA1), the only viral protein that is expressed by EBV latently infected B cells and is found in all EBV-associated malignancies (44). It has been shown that autophagy inhibition accumulated EBNA1 in autophagosomes and concomitantly attenuated the presentation of EBNA1 to the MHC class II-restricted EBNA1-specific $CD4^+$ T cell clones, suggesting that endogenous herpesviral antigens degraded by autophagy can be delivered to the MHC class II pathway (45). Question remains, however, concerning that EBNA1 is a native nuclear protein, whereas autophagy is mainly a cytoplasmic event. How would EBNA1 get enough access to the autophagy-MHC II pathway? A further study revealed that when the nuclear localization of EBNA1 is artificially disabled, efficient presentation of $CD4^+$ T cell epitopes from cytoplasmic EBNA1 was observed (46). In other words, by sheltering the latent antigen EBNA1 in the nucleus, EBV successfully evades frequent autophagic access to the MHC II pathway, while simultaneously escaping proteasomal processing for the MHC class I antigen presentation, maximizing immune evasion (47). The influence of autophagy-mediated MHC II antigen presentation is further demonstrated in the study of HSV-1 pathogenesis, whereby the mutant HSV-1 no longer counteracting autophagy stimulated a significantly

stronger HSV-1-specific $CD4^+$ T cell response *in vivo*, resulting in rapid removal of virus from all tissues compared to wild-type HSV-1 infection (48). Thus, autophagy can strengthen $CD4^+$ T cell immunity by assisting herpesviral antigen presentation on MHC class II molecules.

Could autophagy also facilitate $CD8^+$ T cell immunity as well in herpesviral infection? Indeed, it has been found that mice infected with the neuroattenuated HSV-1 mutant lacking the autophagy inhibitor ICP34.5 also showed enhanced proliferation of $CD8^+$ T cells compared to mice infected with wild-type virus (49). More recent study of murine macrophage infected with HSV-1 provided a mechanistic view of autophagy assisting the processing and loading of viral gB antigen onto MHC class I molecules (16). In this case, unlike conventional autophagy, a novel form of autophagosome, originated from a coiling process of both inner and outer nuclear membranes and thus exhibiting a unique four-layered structure, was shown to be able to wrap HSV-1 antigens or even capsids during the late stages of infection (16, 50). Intriguingly, both conventional and this nuclear-membrane-derived autophagy appear competent for efficient 'cross-presentation' of endogenous herpesviral antigens on MHC I molecules, which leads to the activation of $CD8^+$ T cell (16, 50). Hence, by communicating with ER, autophagy is able to deliver the vacuolar processed herpesvirus antigen to the MHC class I pathway, and by connecting to the endocytic route, autophagy leads to enhanced MHC II presentation of viral antigens (3, 31). Given the broad involvement of autophagy in antigen presentation, it is an ideal target for herpesviruses to interfere with the presentation of viral peptides to T lymphocytes, and an ideal target for the host to boost adaptive immunity against herpesviral infections.

IV. Herpesvirus Reshaping Cellular Autophagy

Although autophagy has the demonstrated ability to control herpesvirus infection, herpesviruses seem to be able to adapt to the pervasiveness and strength of cellular autophagy and persist efficiently until waning host immunity leads to viral reactivation from latency and the onset of disease (32, 51). One possibility is that herpesviruses have developed strategies to sabotage autophagy recognition, degradation, and/or antigen presentation. Below are brief discussions of these potential evasion strategies that have been documented in the literature for the herpesvirus family (Fig. 2).

Neurotropic α-herpes simplex virus

As aforementioned, α-herpesvirus HSV-1 encodes the neurovirulence factor, ICP34.5, which is essential for fatal encephalitis both in mice and in humans (39, 52). It has long been known that ICP34.5 effectively reverses the PKR-mediated host protein shutoff by the dephosphorylation of eIF2α through its interaction with PP1α, thereby enhancing viral replication and virulence (38, 53). However, mutant HSV-1 strains that retain PP1α interaction of ICP34.5 and thereof the ability to reverse translational shutoff were still avirulent *in vivo*, suggesting that host cell shutoff is not the sole action of ICP34.5, and that other targets are also involved in ICP34.5-mediated neurovirulence (54, 55). Recent study from Orvedahl *et al*. (21, 22) provides a good illustration. It was found that ICP34.5 directly targets Beclin1 and blocks the induction of autophagy in a manner independently of its interaction with PP1α (21, 22). Interestingly, the attenuated neurovirulence of the ICP34.5 mutant virus incapable of antagonizing Beclin1 is fully rescued in mice genetically lacking PKR, suggesting that HSV-1-induced PKR activation lies upstream of Beclin1-mediated autophagy *in vivo* (21, 22). Considering that autophagy is an eIF2α- and PKR-dependent pathway, the functional dedication of ICP34.5 in autophagy regulation is then reflected in two aspects: counteracting phospho-eIF2α-mediated autophagy activation by recruiting PP1α and blocking PKR-induced autophagy response by binding Beclin1 (22, 40, 56). Indeed, ICP34.5 is not the only autophagy modulator of HSV-1. Another HSV-1 protein, US11, was previously shown to bind PKR and block its phosphorylation of eIF2α, likely working in concert with ICP34.5 to control autophagy (57, 58). Further, glycoprotein B (gB) of HSV-1 appears to bind to ER stress sensor, PERK, and preclude PERK-mediated eIF2α-phosphorylation and

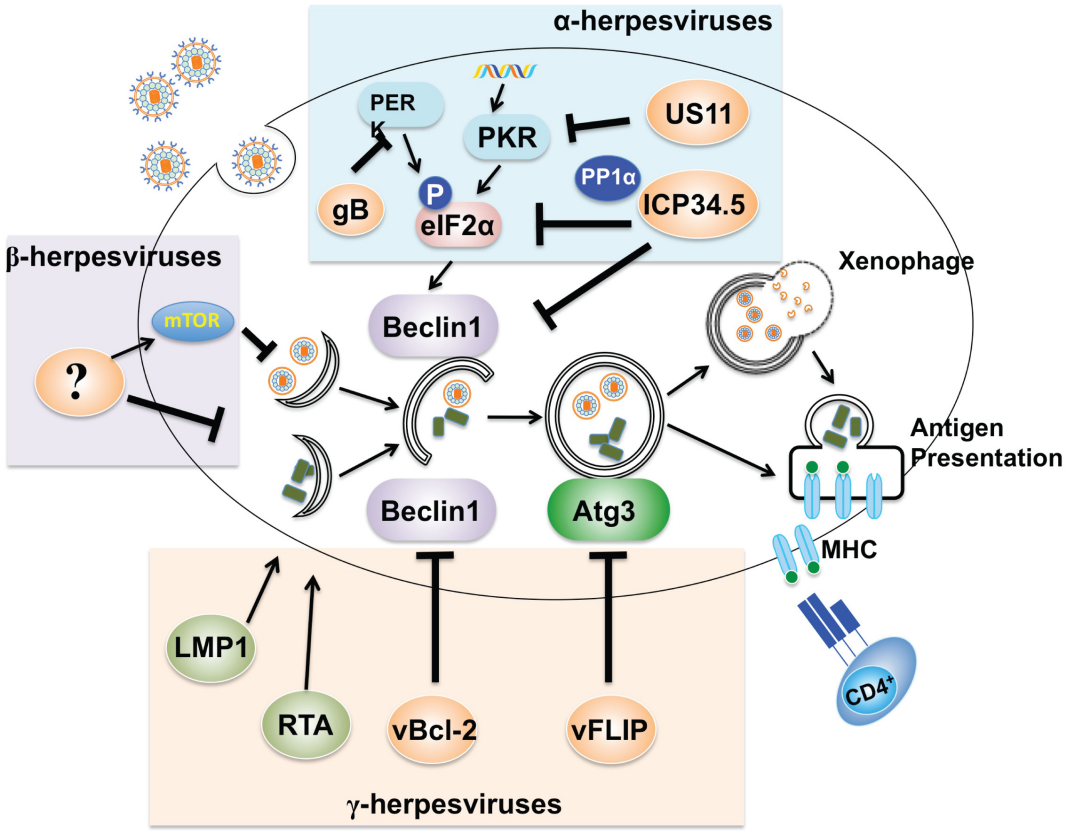

Figure 2. Herpesviral interaction with the autophagy machinery. Autophagy can sanitize intracellular environment by directly capturing virions or viral components and delivering them for lysosomal degradation. It can also facilitate the antigen presentation of viral peptides to the MHC I/II pathway for adaptive immune response. The colored boxes present potential mechanisms that are used by herpesviruses to subvert or hijack cellular autophagy for their survival, propagation, and pathogenesis. The neurotropic α-herpesvirus HSV-1 proteins, ICP34.5, US11 and gB, have been shown to block the PKR-eIF2α-mediated autophagy activation or directly target Beclin1 for autophagy subversion (ICP34.5). The β-herpesvirus, HCMV, appears to blunt autophagy through both the mTOR-dependent or -independent pathways. γ-herpesviruses encode vBcl-2 and vFLIP to inhibit Beclin1-mediated autophagosome formation and Atg3-mediated autophagosome elongation, respectively, whereas the LMP1 protein of EBV and the RTA protein of KSHV were found to trigger autophagy either for the optimal survival of infected cells or for the acute replication and spreading of the virus. Thus, autophagy modulation is a common strategy employed by herpesviruses.

autophagy induction (59). Despite the different strategies used by ICP34.5, US11, and gB to antagonize host response, a common theme of these proteins is to ensure sufficient viral protein synthesis without triggering ER stress response which leads to apoptosis and autophagy which leads to virion degradation and viral antigen presentation, as discussed above. More insights into the molecular mechanisms of these autophagy inhibitors encoded by HSV-1 could help to understand how these events act synergistically during infection and how they contribute to viral lytic/latent lifecycle balance and neurovirulence.

β-herpesvirus

Analogous to α-herpesvirus, human cytomegalovirus (HCMV), which belongs to the β-herpesvirus family, is also associated with severe neurological conditions (e.g. CMV encephalitis) particularly in neonates and immunosuppressed adults (60). However, very little is known about the interaction between HCMV and autophagy. Recent study by Chaumorcel *et al.* (61) indicated that HCMV infection in primary human fibroblasts robustly inhibited the activation of cellular autophagy by a mechanism likely involving the stimulation of the mTOR signaling pathway.

Notably, treating cells with rapamycin, a potent mTOR inhibitor, cannot relieve cells from HCMV-mediated autophagy suppression. Furthermore, HCMV-infected cells appear to also be resistant to mTOR-independent autophagy induction by lithium chloride (61), suggesting an mTOR-unrelated pathway is involved in HCMV infection. However, the *in vivo* relevance of these findings has not been investigated, which represents an important direction for understanding the mechanism of autophagy evasion after HCMV infection. Nevertheless, the capability of HCMV to thwart this antiviral defense highlights autophagy as an important player in herpesviral infection.

Lymphotropic γ-herpesvirus

Being sophisticated oncogenic viruses, γ-herpesviruses establish life-long persistency in lymphoid cells by blunting almost every aspect of host cell immunity (32). The involvement of autophagy in γ-herpesviruses infection and pathogenesis is just beginning to be appreciated. Among many virus-designed or pirated immuno-modulators, one critical virulence factor for γ-herpesviruses persistence and oncogenicity are the viral homologs of the Bcl-2 protein (referred to as vBcl-2) encoded by all γ-herpesviruses, including EBV, Kaposi's sarcoma-associated herpesvirus (KSHV), herpesvirus saimiri (HVS), and murine γ-herpesvirus 68 (γ-HV68) (62). The traditional view of vBcl-2 focused on its ability to abrogate cellular apoptotic response, allowing completion of viral replication and favoring the spread of progeny virus during acute infection (63~66). These *in vitro* observations, however, may not accurately reflect the real task of vBcl-2 *in vivo*, since loss of vBcl-2 of γ-HV68, somewhat paradoxically, did not affect acute infection but rather impaired the virus' ability to establish chronic infection in the host (66). It is now clear that the Bcl-2 family members also fine-tune cellular autophagy balance, for instance the anti-apoptotic Bcl-2 and Bcl-xL proteins inhibit, whereas the pro-apoptotic BH3-only molecules (e.g. Bad) activate it (67, 68). Similar to cellular Bcl-2, we and others found that the vBcl-2 encoded by KSHV and γ-HV68 effectively attenuates autophagy through a direction interaction with Beclin1, surprisingly in a manner more potently than their cellular counterpart (66, 67, 69, 70). Structural analyses further implicated that the two functions of vBcl-2, anti-apoptosis and anti-autophagy, engage the similar if not the same structural cassette, the hydrophobic BH3-binding groove on the surface of vBcl-2 (66, 69). Yet, the affinity of vBcl-2 to Beclin1 is apparently higher than to pro-apoptotic molecules, suggesting that Beclin1 is a prime target of vBcl-2 for chronic infection and/or pathogenesis of γ-herpesviruses (66, 69). Indeed, evidence has recently been provided showing that targeted elimination of vBcl-2's anti-autophagic activity severely attenuated the ability of γ-HV68 to maintain a latent reservoir in splenocytes, a prerequisite for persistent infection and transmission (20, 71). In conjunction with this, the mutant virus that lacks the anti-apoptotic property of vBcl-2 showed defects in viral reactivation frequency *ex vivo* (20, 71). Thus, γ-HV68 vBcl-2 confers distinct mode of actions in different stages of infection, with autophagy clearly implicated in restricting long-term viral persistence. Since persistent infection is critical for γ-herpesvirus-associated malignancy and autophagy functions in tumor suppression (11), vBcl-2 antagonism of Beclin1 function and autophagy thereof might contribute to the oncogenic potential of the γ-herpesviruses.

Besides targeting Beclin1, γ-herpesviruses have evolved a second strategy to subvert autophagy by expressing a latency-associated protein viral FLICE-like inhibitor protein (vFLIP) (72). Being well characterized as a potent activator of the NFκB pathway (73~75), the herpesviral FLIPs (KSHV and HVS) were found to disturb the Atg3-mediated LC3-PE conjugation and, therefore, impair the elongation of autophagosome membrane and cells' overall autophagy activity (72). As expected, vFLIP expression rendered the virus-infected B lymphocytes resistant to rapamycin-induced autophagic cell death *in vitro* as well as in nude mice *in vivo* (72). However, functional importance regarding the anti-autophagy role of vFLIP in the context of the γ-herpesvirus infection is still lacking. It is noteworthy that autophagy is recently shown to limit the role of NFκB activation (76). Given that NFκB activation is an important aspect of vFLIP function and KSHV pathogenesis, it is

probable that, during a long-term persistent infection wherein most of the viral genome is silenced, reshaping cellular autophagy by vFLIP may tilt the balance to a pro-inflammatory response that favors viral persistence and spread; it may also prevent the antigen presentation of latent viral proteins to evade host antiviral immune responses. Strikingly, a peptide derived from vFLIP acts in a diagonally opposite way by targeting vFLIP itself, leading to a significant autophagy induction and autophagy-related death towards KSHV-infected cells (72). The potent effects and functional specificity of the herpesvirus-derived anti-viral peptides might be useful in the treatment or prevention of herpesviral infection.

Autophagy evasion is not always the mechanism of choice of γ-herpesviruses. The EBV-encoded latent membrane protein 1 (LMP1) is shown to stimulate the autophagic degradation of itself, as overexpression and accumulation of LMP1 triggers cytostasis and dampens overall survival of transformed cells (77). In the case of KSHV, the lytic switch protein replication and transcription activator (RTA) is recently found to induce autophagy to facilitate viral lytic replication, as blunting cellular autophagy reduces the virus's ability to reactivate from latency (78). Yet, the mechanism of RTA boosting autophagy in the lytic phase is unclear; it is also unclear whether induced autophagy is reflective of a viral-specific process or of the secondary effects of host defense.

VI. Conclusions

After all is said and done, reshaping cellular autophagy seems to be a common strategy shared by the herpesvirus family. Yet, much remains unknown regarding how this might relate to the regulation of the lytic/latent lifecycle balance and viral pathogenesis, and whether the findings of both positive and negative effects of virus on autophagy can be easily reconciled. Further studies will be required to clarify the precise mechanism(s) by which autophagy restricts herpesviral infection and by which the viruses evade or hijack autophagy. It is also envisioned that different modes of autophagy in terms of induction, cargo selection, and lysosomal degradation may be affected in specific context of viral infection, and understanding such complexity and specificity of the autophagy pathway and viral regulation should enable us translate this knowledge into new therapeutic interventions for viral therapy.

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