Review

Pingdong Jia*

Autophagy and virus infection

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Abstract: Autophagy is a highly conserved pathway for physiological metabolism. Bilayer vesicles transport their contents to lysosomes for degradation. Autophagy is therefore a means of removing intracellular viruses and other pathogens in mammalian cells. However, the role of autophagy in virus infection is complex. Several viruses have developed a way to escape autophagy-dependent degradation and replicate themselves through autophagy. This article summarizes the fundamental mechanism and function of autophagy and its role in infection with viruses such as HIV, HTLV-1, and other retroviruses.

Keywords: autophagy, virus infection, retrovirus

1 Introduction

Autophagy, a biological phenomenon in eukaryotic cells, is a self-balancing process for self-protection of cells. Autophagy is also a procedural death mechanism that coexists with apoptosis and necrosis. The three autophagic approaches are macroautophagy, microautophagy, and chaperone-mediated autophagy [1,2]. This article discusses the role of macroautophagy in virus infection (especially, retroviral infection) and the possible underlying mechanism.

2 Mechanism and role of autophagy in organisms

Autophagy, which plays a key role in maintaining homeostasis, is formed in autophagosomes with a bilayer vesicle structure and is related to subsequent degradation of the lysosome-dependent pathway of damaged or excessive cell components [3,4]. Autophagy starts from a segment of independent membranes (generally from the endoplasmic reticulum). Autophagosome formation relies on autophagy-related gene (ATG) family [5]. Approximately 40 kinds of ATG have been found in yeast. Various homologs have also been found in mammals [6]. However, ~50% of family members need to form in classic autophagosomes and include ATG1, ATG2, ATG3, ATG4, ATG5, ATG6, ATG7, ATG8, ATG9, ATG10, ATG12, ATG13, ATG14, ATG16, ATG17, ATG18, ATG29, and ATG31 [7]. Classic autophagic signal pathway includes two kinds of ubiquitin-like binding systems, namely, ATG12 binding system and ATG8 lipid system. ATG12 and ATG8 are activated by the same E1 ubiquitin enzyme analog ATG7 [8]. In the ATG12 binding system, ATG7 helps ATG12 to bind to ATG5 to form the ATG12–ATG5 compound [9]. In the ATG8 lipid system, the activated Type I ATG8 is moved to ATG3 to finally bind to phosphatidylethanolamine [10]. The ATG8–phosphatidylethanolamine compound generally called as Type II ATG8 is the most recognized sign of autophagy. Another highly recognized autophagy marker is autophagic receptor p62, whose degradation can reflect autophagy lysosome activity [11].

Autophagy exerts important physiological functions in organisms. First, autophagy can resist metabolic pressure. In cases of nutrient deprivation, lack of growth factors, and hypoxia, autophagy can be activated to be an adaptive catalytic pathway. The autophagic body is degraded to a large quantity of release-free and reused amino acids and fatty acids [12]. Second, autophagy can remove defective proteins and organelles,

prevent abnormal protein concentration, and remove intracellular pathogens. With these functions, autophagy can mediate the resistance of an organism to aging, tumor formation, neurodegenerative diseases, and infection. Although these functions overlap with those of the ubiquitination–proteasome system, autophagy has its own uniqueness, that is, it can degrade organelles, such as mitochondria, peroxisomes, and endoplasmic reticula [13]. Autophagy can also limit DNA damage and chromosome instability. However, the specific mechanism remains unclear [14]. Autophagy can be also regarded as a non-apoptotic programmed cell death process [15].

3 Autophagy and virus infection

Autophagy can eliminate invading pathogens in a process called as autophagocytosis. For several virus infections, autophagy can keep its titer in the body at low levels [16]. Several studies have shown that autophagy can weaken encephalitis induced by Sindbis virus [17]. The capsid protein of Sindbis virus is recruited on autophagosome through p62 to facilitate full-genome screening for capsid restriction of the virus. Numerous members of Parkin-dependent degradation pathway of the mitochondria have been identified. Scholars had reported a significant similarity between virus and mitochondria through autophagy degradation [18]. Ubiquitin ligase Smurf1 is a key component in the autophagic clearance of Sindbis virus and mitochondria. The capsid protein of Smurf1 Sindbis virus is ubiquitinated and degraded through autophagy. The autophagic degradation is also mediated by p62 in chikungunya virus [19]. However, autophagic restriction in chikungunya virus is reflected in mouse cells. In human cells, chikungunya virus replicates in the reverse Golgi mesh structure through binding of NDP52 to ATG8. Inhibiting autophagy thus weakened the replication of chikungunya virus [20]. Similar to chikungunya virus, other viruses have developed strategies to combat autophagy. Herpes viruses often carry Bcl-2 homologs, which can prevent the induction of autophagy by beclin-1 [21,22]. Influenza A virus can prevent the fusion of lysosomes and autophagosomes [23]. Autophagy can inhibit the replication of several viruses in cells, but some strains of viruses have developed mechanisms to escape this process.

4 Autophagy and HIV-1 infection

HIV-1 is the pathogen responsible for acquired immunodeficiency syndrome. More than 30 million people are infected with HIV worldwide. Approximately 3 million of infected individuals die annually [24,25]. HIV-1 can infect CD4⁺ T cells and macrophages and replicate in cells [26,27]. After HIV-1 enters cells, its replication is affected by autophagic degradation and host-cell limiting factors, such as APOBEC3G T2/tether-in, TRIM5a, SAMHD1, and microRNA [28]. However, HIV-1 has developed various ways to escape these defense mechanisms to overcome cell limitation. For example, HIV-1 promotes the degradation or exclusion of APOBEC3G into virus particles through the auxiliary protein Vif, the Vpu protein can resist the effect of BST-2/tetherin, and the Tat protein can adjust the activity of miRNA in cells. For autophagy, HIV-1 evidently evades the cell defense process, thereby promoting replication. In macrophages, the virus auxiliary protein Nef inhibits the maturity of autophagy by binding to Beclin-1 to prevent damage to the virus [29]. Bafilomycin A1 inhibits the mixture of autophagosomes and lysosomes. Bafilomycin A1 can promote the occurrence of HIV-1. Moreover, immune-associated guanosine triphosphatase family M can interact with ATG5 and ATG10, and Nef can promote the accumulation of autophagic body and the occurrence of HIV-1 [30]. HIV-1 without Nef cannot overcome autophagic degradation, resulting in low replication efficiency [31]. In general, early steps in autophagy contribute to HIV-1 replication. Furthermore, HIV-1 Gag protein colocalizes with autophagosomes with abundant ATG8; using the autophagic inhibitor 3-methyladenine to treat HeLa cells or siRNA to silence Beclin-1 or ATG7 can significantly inhibit the occurrence of HIV-1, whereas the autophagic inducer Sirolimus can promote viral production [31]. Vitamin D can also inhibit HIV-1 replication by initiating and promoting autophagy maturation. Using bafilomycin A1 to treat or silence Beclin-1 and ATG5 can reduce the inhibition

of vitamin D [32]. These results show that enhancing the fusion of autophagosomes and lysosomes may be an effective strategy for anti-HIV-1 therapy. HIV-1-infected human acute T lymphoblastic leukemia cells, namely, MOLT-4 and CD4⁺ T-cell, inhibit autophagy, and ATG8 or Beclin-1 protein expression is reduced [33]. Another study reported that autophagy may negatively regulate HIV-1 replication in T cells [34]. HIV-1-infected CD4⁺ T cells can induce autophagy, as indicated by the increased protein expression of Beclin-1 and ATG8 [35]. Moreover, the levels of ATG1, ATG4D, and ATG5–ATG12 increase after HIV-1 or HIV-2 infection. The autophagic inhibitor 3-methyladenine and the siRNA of Beclin-1 can inhibit HIV-1 replication in Jurkat T cells [35]. Stable silencing of ATGs such as ATG5 and ATG16 can inhibit the occurrence of HIV-1 in human T lymphocytic series SupT1 cells [36]. Hence, autophagic activation positively regulates HIV-1 in T cells. The relationship between HIV-1 and autophagy in T cells remains unclear and must be further investigated.

5 Autophagy and HTLV-1 infection

HTLV-1 is the first retrovirus that confers diseases to human beings. Thus far, no effective method has been developed to treat adult T-cell leukemia and its resulting rigidity of lower limb paresis [36]. Incomplete statistics in 2005 showed that 10–20 million people are HTLV-1 virus carriers worldwide [37].

HTLV-1 infection can promote autophagosome accumulation, thereby inducing HTLV-1 replication [38]. The Tax protein of HTLV-1 can prevent the fusion of autophagosomes and lysosomes and reduce autophagosome degradation by using lysosomes to promote autophagosome accumulation; the inhibitor for intracellular fusion of autophagosomes and lysosomes, namely, bafilomycin A1, can improve the stability of the Tax protein. This finding indicates that the degradation of partial intracellular Tax protein is completed through autophagy [38].

T-cell receptor signal will activate the inhibitor of nuclear factor kappa-B kinase (IKK) and phosphatidylinositol 3-kinase C1 (PI3KC1) and induce autophagy. This condition is crucial for T-cell proliferation. The Tax protein can also activate IKK and PI3KC1 [39,40]. T cells are converted from HTLV-1 expressing Tax protein, accompanied by high-level autophagy. In adult T-cell leukemia cells without Tax expression, the incidence of autophagy is very low. The Tax protein can interact with important molecules in autophagic signal (Beclin-1 and PI3KC3) and Bax-interacting factor 1 and isolate autophagic molecules into the fat raft. This process depends on the IKK complex. In HTLV-1-transformed T cells, knockdown of Beclin-1 can lead to reduced autophagy and cell survival rate. Hence, the Tax protein coupled with the IKK complex and autophagy signaling pathway can promote the survival and proliferation of HTLV-1-transformed T cells [41].

6 Summary

Viruses have developed a defensive strategy to overcome autophagy by escaping or using this process. Blocking the fusion of autophagosomes and lysosomes is a common mechanism for the production of virus-induced autophagosome membranes. These viruses have developed methods for blocking the fusion of autophagosomes and lysosomes to prevent autophagosome damage. Viruses can also use the autophagic membrane to efficiently replicate their viral genome. An in-depth study of the interaction between virus and cell must be conducted to develop drugs for enhancing the fusion of autophagosomes and for clinical applications. Cytokines involved in autophagy, signal transduction, and pathophysiological significance must also be elucidated. The precise role of autophagy in immune responses to the virus still needs to be established. Research on the double-edged sword of autophagy will certainly bring new hope for human intervention and ultimate treatment of antiretroviral diseases.

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