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Progress on Interactions between Cellular Autophagy and Picornavirus

Qinglu Zhao[1,a], Weiding Cheng[1,b], Zhanying Hu[1,c], Ruizhe Li[1,d], Rui Zhang[1,e,*]

[1]Key Laboratory of Veterinary Medicine in Universities of Sichuan Province, Southwest Minzu University, Chengdu, 610041, China
[a]3278153307@qq.com, [b]1124420146@qq.com, [c]2891645167@qq.com, [d]2925521691@qq.com, [e]zhangrui.caas@foxmail.com
[*]Corresponding author

Abstract: *Cellular autophagy is a self-protection mechanism that exists universally in eukaryotes to renew intracellular substances and maintain the homeostasis of the internal environment. Recent studies have shown that cellular autophagy can be involved in the infection process of Picornavirus. When small RNA viruses infect cells, autophagy pathway is activated rapidly and autophagy can play the function of antiviral natural immunity by delivering viral antigens. At the same time, autophagy provides replication-associated proteins and non-cellular cleavage release pathway for part of Picornavirus to promote the replication of the viruses. In this paper, we review the progress of the interaction between Picornavirus and cellular autophagy in recent years, and provide reference for further elucidation of the mechanism of Picornavirus involved in the regulation of autophagy.*

Keywords: *Cellular Autophagy, Picornavirus, Interactions, Viral Replication*

1. Introduction

Cellular autophagy is a lysosome-dependent degradation pathway present in eukaryotes that degrades intracellular misfolded proteins and damaged organelles by phagocytosis to maintain cellular homeostasis and organelle renewal. Autophagy, as a defense mechanism of the organism, plays an important role in resisting pathogen infection and regulating innate and adaptive immune responses [1]. As an intracellular pathogen, viruses are completely dependent on host cells for the replication of their viral genomes and the assembly and release of viral particles. Recent studies have shown that cellular autophagy plays an important role in viral infection. On the one hand, autophagy plays an antiviral role by promoting viral clearance. On the other hand, many picornavirus have evolved certain mechanisms to cope with host cell evolution and even use autophagy to promote viral replication. Autophagy can promote viral invasion, decapsidation, and release. The autophagosome can act as a viral replication site, meanwhile, autophagy can also inhibit apoptosis, regulate cellular metabolism, and inhibit the host's antiviral natural immunity [2]. Currently, there are many studies on foot-and-mouth disease virus (FMDV), poliovirus (PV), Coxsackievirus (CV), human rhinovirus (HRV), human rhinovirus (HRV), and human rhinovirus (HRV). virus (HRV), Enterovirus A71 (EV-A71), Echovirus (ECHO) and Encephalomyocarditis virus (EMCV) have shown that the use of autophagy mechanism is a key process of picornavirus infection. In this paper, we mainly introduce the interaction relationship between the above picornavirus and cellular autophagy.

2. Replication of Picornavirus

Picornaviruses are non-enveloped, single-stranded, positive RNA viruses that are divided into 35 genera and 80 species, including enterovirus, rhinovirus, cardiovirus, hepatitis virus, and foot-and-mouth disease virus. Picornavirus can cause a wide range of diseases. Foot-and-mouth disease virus infection causes foot-and-mouth disease in even-toed hoofed animals, human rhinovirus infection causes colds and asthma, and poliovirus infection causes poliomyelitis. Picornaviruses infecting host cells can be recognized by cell surface receptors and enter into the cytoplasm through endocytosis, the viral genome is internalized, disassembled and synthesized into a poly-protein under the action of the host protein synthesis system, which consists of structural proteins in the P1 region and non-structural proteins in the P2 and P3 regions. P1 is broken down into four types of coat proteins, namely, VP1, VP2, VP3 and VP4,

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by proteolytic enzymes. P2 and P3 are broken down into four types of coat proteins and P2 and P4 are broken down into four types of coat proteins. P2 and P3 are decomposed into 2A, 2B, 2C, 3A, 3B, 3C and 3D non-structural proteins. These mature viral proteins are involved in the transcription and replication of the RNA genome, as well as in the process of assembly and release of the virus. Viral proteases are not only involved in the maturation of viral proteins, but also act on cytokines, leading to the shutdown of the host cell and increasing viral replication [3].

3. Mechanisms of Cellular Autophagy

Cellular autophagy is a widespread mechanism of programmed death in eukaryotes. By engulfing intracellular proteins or damaged organelles, encapsulating them into vesicles and fusing them with lysosomes to form autophagic lysosomes, which degrade their encapsulated contents, thus maintaining the cell's own metabolic needs and organelle renewal. Autophagy is classified as macroautophagy, microautophagy, and molecular chaperone-mediated autophagy according to the route of entry of cellular substances into lysosomes. Macroautophagy is one of the most widely researched pathways in viruses. It refers to the process in which the autophagosome with double membrane structure wraps the intracellular proteins or damaged and necrotic organelles, and the fusion of the autophagosome membrane and lysosome membrane degrades the substrate proteins under the action of hydrolases.

The formation of autophagy is usually divided into four stages: ① Induction: When autophagy induction occurs, a crescent-shaped double-membrane vesicle, called an isolation membrane or phagocytic vesicle, is formed in the cytoplasm to isolate misfolded proteins and damaged organelles. ② Extension: The phagocytic vesicle extends continuously and fuses at both ends to form a dense spherical structure called autophagosome. ③ Fusion: the outer membrane of autophagosome fuses with lysosome to form autophagolysosome. ④Degradation: The inner membrane of autophagosome and its wrapped contents are hydrolysed by lysosomal enzymes and the products are returned to the cytoplasm through the lysosomal membrane for cell recycling. More than 30 autophagy genes (Atg) have been shown to be involved in the autophagy process. The key proteins involved in autophagosome formation include: ① The Atg1/ULK complex composed of ULK1, ULK2, FIP200, Atg13, and Atg101, which regulates the formation of autophagosomes at the initiation stage. (ii) The PI3KIII complex, containing Vps34, p150, beclin-1, and Atg14, promotes early autophagosome formation. ③ Two ubiquitinated conjugation systems, consisting of Atg4, Atg12, Atg5, Atg16L1, Atg7, Atg10, Atg3, and microtubule-associated protein 1 light chain 3 (LC3), which are involved in the elongation and maturation of autophagosome membranes [4].

4. Picornavirus and Autophagy

4.1 Foot-and-Mouth Disease Virus (FMDV)

Foot and mouth disease virus (FMDV) belongs to the genus Foot and mouth disease virus, which infects even-toed ungulates and causes fever, lameness and vesicular macules on the skin and mucous membranes, leading to the development of foot and mouth disease. Early in the course of FMDV infection, FMDV is capable of rapidly inducing lipidation of LC3 to promotes viral replication. Studies have shown that FMDV infection causes nuclear translocation of GFP-tagged LC3 molecules from the cytoplasm to the perinuclear region and co-localisation with viral non-structural proteins 2B, 2C and 3A, and that the viral capsid protein VP1 co-localizes with LC3 and autophagy-associated protein ATG5, resulting in a large number of LC3 punctate aggregates [5]. During FMDV infection, a large number of autophagosomes with double-layer vesicle structure were induced in the cytoplasm by electron microscopy. In the early stage of FMDV infection, the viral protein 3C could degrade ATG5-ATG12, which led to a gradual decrease in the expression levels of LC3II and ATG5-ATG12 and inhibited cellular autophagy. Silencing of ATG5-ATG12 promoted the proliferation and replication of FMDV, while overexpression of ATG5-ATG12 inhibited viral replication. In addition, ATG5-ATG12 inhibited viral replication by regulating antiviral natural immunity. Studies have shown that ATG5-ATG12 can activate the NF-kB signalling pathway by promoting the expression of the antiviral protein PKR, which in turn promotes the phosphorylation of IKKα/β, the degradation of IκB and the entry of p65 into the nucleus. ATG5-ATG12 also inhibits TRAF3 degradation, promotes TBK1 phosphorylation, which in turn activates IRF3, induces the type I IFN signalling pathway and inhibits viral replication. However, FMDV has evolved a mechanism to escape the host cellular natural immune response by degrading the ATG5-ATG12 complex, the host NEMO protein and the KPNA1 protein through the 3C protein, thereby

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inhibiting the host's natural antiviral immune response to promote its own replication. Currently, it has been shown that during FMDV infection, viral protein L can degrade the natural immune transcription factors p65, IRF3, and IRF7 to suppress the antiviral innate immune response [6]. It was found that FMDV coat protein VP2 could interact with HSPB1 and activate the EIF2S1-ATF4 signalling pathway to induce autophagy and promotes viral infection and replication [7].

4.2 Poliovirus (PV)

Poliovirus (PV), a member of the genus Enterovirus, is the causative agent of poliomyelitis, and the viral infection is capable of damaging the central nervous system, resulting in flaccid paralysis of the limbs. PV infection induces cellular autophagy, which also promotes viral replication and proliferation. Studies have shown that the autophagy inducer rapamycin promotes PV replication, and the autophagy inhibitor 3-MA down-regulates the expression of autophagy-related genes, inhibiting cellular autophagy and PV proliferation. In the early stage of PV replication, viral proteins 2BC and 3A can induce the maturation of autophagosomes, and LC3 co-localises with viral protein 3A and PV double-stranded RNA replicates. In the late stage of PV infection, LAMP1 and LC3 can be induced to co-localize to form double-layer vesicle structures similar to autophagosomes [8]. Studies have shown that PV uses autophagy to promote viral maturation and release. After autophagy occurs, autophagosomes and endosomes fuse to form autophagic endosomes, which contain the vesicular enzyme ATPase, and the vesicles are acidified when the material in autophagosomes is transported to the lysosome, and vesicle acidification promotes the maturation of the PV viral particles. The levels of the ULK1, ULK2, ATG13, RB1CC1, and ATG101 proteins were decreased after PV infection, and with the reduction of ULK1 protein levels, autophagic signals were significantly increased, suggesting that PV induces autophagy in a manner that is not dependent on the ULK1 complex [9]. In addition, binding of phosphatidylserine (PS) to the viral receptor facilitates PV-induced autophagy and PS-enriched autophagosome vesicles wrapped around PV particles enhance the non-cleavage cellular release of mature viral particles [10].

4.3 Coxsachie Virus (CV)

Coxsackie virus (CV) is an enterovirus that is classified into two groups according to its biological characteristics: group A, which mainly causes skeletal muscle damage, and group B, which can cause damage to the central nervous system and internal organs. Coxsackie viruses can either induce autophagy to promote their own replication or inhibit the formation of autophagosomes, which in turn inhibits viral replication. Coxsackievirus B3 (CV-B3) utilizes an autophagic mechanism to promote its maturation within autophagosomes. Under transmission electron microscopy, a large number of double-membrane vesicles were observed to form in CV-B3-infected Hela and HEK293T cells, and the ratios of GFPLC3 and LC3II/LC3I were increased, but the level of p62 was not affected by the viral infection. These results suggest that CV-B3 induces LC3 lipidation and accumulation of autophagosomes and blocks autophagic lysosomal degradation [11]. Phosphorylation of eukaryotic initiation factor 2α (eIF2α) plays an important role in endoplasmic reticulum (ER) stress-induced autophagy, and the PERK pathway participates in autophagy by positively regulating autophagosome formation through activation of eIF2α and by facilitating co-localisation of LC3 and LAMP1. When autophagy occurs, extracellular microvesicles encapsulate CV-B3, which provides both a site for viral replication and a protective barrier for CV-B3 to escape host degradation [12]. Treatment with 3-MA as well as knockdown of Beclin1, Atg7 and Vps34 decreased the viral titre and expression of coat protein VP1. However, treatment with rapamycin promoted the expression of VP1 and replication of CVB3. It was found that the 2B protein of CV-B3 induces autophagy using its transmembrane hydrophobic sequence, CV-B3 can regulate autophagy by regulating AMPK/MEK/ERK and Ras/Raf/MEK/ERK signalling pathways and the PI3K/Akt/mTOR signalling pathway is involved in the autophagy process induced by CV-B3 infection [13-14]. During CV-B3 infection, 2A protein favors the autophagy pathway to degrade host protein SQSTM1 in large quantities, and low levels of SQSTM1 can activate the NF-κB signaling pathway and induce the production of large quantities of III-IFN and IL-6, which leads to the inhibition of CV-B3 replication. -B3 replication inhibition. Studies have shown that iNOS is a molecular marker of oxidative stress. iNOS expression levels were significantly upregulated in CV-B3 infection-induced myocarditis in mice, and the regulation of autophagy and JNK signalling pathways through inhibition of iNOS expression reduced CV-B3-induced cardiomyocyte damage [15].

Infection of primary rat neuronal cells with CV-B4 has been reported to have a similar effect to that of infection with CV-B3. CV-B4 induces autophagy in a calpain-dependent manner, causing accumulation of LC3 lipids and autophagic vesicles. LC3 is modified during infection and treatment with

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3-MA inhibits autophagosome formation and viral replication [16]. Treatment by a calpain inhibitor caused a decrease in VP1 expression and viral titre, while autophagosome formation was inhibited, suggesting that calpain plays a role in CVB4-induced autophagy. CV-A16 induces early autophagy, and the nonstructural proteins 2C and 3C trigger autophagosome accumulation by blocking autophagosome-lysosome fusion, and the 2C protein augments the immunity related GTPaseM (IRGM) promoter activation, thereby increasing IRGM expression and inducing autophagosome formation, in addition, CV-A16 infection can induce autophagy through inhibition of the Aktm-TOR signalling pathway and activation of the ERK signalling pathway [17].

4.4 Enterovirus A71

Enterovirus A71 (EV-A71) belongs to the genus Enterovirus and is one of the major pathogens causing hand, foot and mouth disease in infants and young children. EV-A71 infection induces the onset of autophagy, which facilitates viral replication. EV-A71 infected cells in transfected GFP -LC3 in mouse neuronal cells transfected with GFP. Apparent LC3 punctate aggregation occurred in EV-A71-infected cells and autophagosome-like vesicle formation was observed in EV-A71-infected cells, accompanied with co-localisation of LC3 and clathrin VP1 occurred in the vesicles. The viral titre of EVA71 was significantly increased by treatment with rapamycin, while decreased by treatment with 3-MA. EV-A71 is released from cells in a non-soluble manner using the secretory autophagy pathway, which increases the production of infectious viral particles [18]. It has been shown that EV-A71 is involved in autophagy regulation mainly by regulating the activities of p-mTOR and pp70S6K. In EV-A71-infected SK-N-SH cells, mTOR and p70 S6K expression decreased in association with the activation of autophagy, but this result did not occur in EV-A71-infected RD cells, suggesting that EV-A71 may activate autophagy in different cell types using different signalling pathways. The non-structural proteins of EV-A71, 2BC and SNARE, STX17, and SNAP29 protein interactions can induce autophagy lysosome formation to promote its replication. After blocking autophagosome-lysosome fusion with chloroquine, viral RNA replication was inhibited, and the viral titer, viral RNA copy number, and expression of viral proteins were reduced in EV-A71 [19]. Autophagy induced by V-A71 infection of 16HBE cells inhibited TLR7-dependent I-IFN production to promote viral replication [20].

4.5 Human Rhinovirus (HRV)

Human rhinovirus (HRV) belongs to the genus Rhinovirus, which is the main pathogen of human colds. It can cause acute and chronic respiratory infections and even serious complications such as asthma and capsular fibrosis. HRV-B14 and HRV-A2 infections have been shown to induce autophagy, which is dependent on intracellular adhesion molecule 1 (ICAM-1) and low-density lipoprotein receptor (LDLR) family proteins, respectively, to enter cells [21]. Infection with HRV-A2 and HRV-B14 induces intracellular GFP-LC3 punctate aggregation and co-localisation with LAMP1. Treatment with rapamycin significantly increases HRVA2 viral titres. Whereas, 3-MA decreases viral titres and autophagy promotes HRV-A2 replication [22]. Similar to PV and CV-B3, HRV-A2 is encapsulated in autophagosome-like vesicles enriched with PS lipids and released into the extracellular matrix in a non-soluble manner.

4.6 Echovirus Type 7 (ECHO-7)

Echovirus type 7 (ECHO-7) belongs to the genus Enterovirus, which causes acute chest pain and cardiomyopathy and is highly infectious and pathogenic. ECHO-7 requires the participation of several core components of the autophagy-related proteins Beclin-1, Atg12, Atg14, Atg16L1, and LC3 when it enters Caco-2-polarised intestinal epithelial cells through lattice protein-mediated endocytosis. Silencing of autophagy-related genes such as Beclin-1, Atg12, Atg14, Atg16L1 and LC3 inhibited ECHO-7 infection and invasion but had no effect on virus adsorption [23].

4.7 Encephalomyocarditis Virus (Emcv)

Encephalomyocarditis virus (EMCV) belongs to the genus Cardiovirus and is an important zoonotic pathogen that causes an acute infectious disease characterised by encephalitis and myocarditis in mammals, rodents and even humans. Upon infection of BHK-21 cells with EMCV, the expression level of LC3-II and the number of autophagosome-like vesicles were significantly increased and the co-localisation of LC3 with structural protein VP1 and non-structural protein 3A indicated that EMCV infection induced autophagy. EMCV non-structural proteins 2C and 3D regulated the expression of proteins related to the UPR pathway through the activation of the endoplasmic reticulum stress signalling

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pathway and induced autophagy [24]. Treatment with rapamycin resulted in a significant increase in EMCV viral titre. 3-MA treatment resulted in impaired LC3 modification as well as GFP-LC3 patch formation [25]. Silencing of LC3 or ATG7 resulted in a decrease in viral titre and a decrease in the expression level of the viral protein VP1, suggesting that autophagy promotes EMCV replication. Studies have shown that TRIM23 protein plays an important role in autophagy induced by EMCV infection. TRIM23 activates the activity of TBK1 and phosphorylates P62 through ubiquitination of its K-27 chain and ubiquitination of ARF. The interaction between TRIM23, TBK1, and P62 promotes the autophagy process [26].

5. Conclusions

Cellular autophagy is a highly conserved self-protective mechanism prevalent in eukaryotes and plays an important role in maintaining cell survival, organismal stability, and homeostasis of the internal environment. When viruses infect host cells, autophagy can activate adaptive immune response through antigen presentation and activate antiviral natural immunity to fight against viruses. On the other hand, autophagy can provide a site for viral replication and facilitate the replication and expression of viral genes. On the other hand, picornavirus have evolved a natural immunity mechanism to escape from the host and promote their own replication by blocking or exploiting the autophagy of the host cells. Due to the different mechanisms involved in autophagy regulation of different picornavirus and the differences in the mechanisms of autophagy on different viral infections, the development of current antiviral drugs and novel vaccines is constrained, which poses a serious threat to human health and the development of animal husbandry around the world. In conclusion, the in-depth understanding of the interaction between picornavirus and host cellular autophagy and its mechanism, as well as the analysis of the temporal and spatial relationship between different picornavirus and autophagy, will provide new ideas for the development of new and effective antiviral drugs as well as disease prevention and control methods.

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