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# Inter-regulation between Autophagy and Innate Immunity in Antiviral Responses

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***Abstract:*** *The innate immune system in the body can defend against viral infections through a variety of mechanisms, and autophagy has recently been found to be effective in defending against viral particles that infect cells. Viral infection can promote autophagy through pattern recognition receptors, which are located in the cell membrane and cytoplasm and are initiators of the cell's natural immune responses. Autophagy regulates the natural antiviral response mediated by pattern recognition receptors and plays an important role in maintaining immune homeostasis. However, some viruses have evolved to establish the ability to evade autophagy or to use autophagy to evade antiviral immune responses. The mutual regulation between viruses, autophagy and natural immune responses against viral infections is a hot area of research. The aim of this paper is to provide an overview of recent advances in this field and to raise important questions to be solved for relevant researchers.*

***Keywords:*** *Viral Infection, Innate Immunity, Autophagy, Antiviral Responses*

## 1. Introduction

Innate immunity is the body's first line of defense against pathogenic microbial infections and can be activated quickly to defend against invading microbes. Innate immune response is mediated by pattern recognition receptors (PRRs), and viruses can be recognized by a variety of PRRs located both at the cell membrane and intracellularly. PRRs recognise conserved molecules of pathogens, termed pathogen-associated molecular patterns (PAMPs), and initiate the cellular natural immune signalling pathway. The Toll-like receptors (TLRs), the membrane-located PRRs, most of which are located in the cytoplasmic membrane, recognize PAMPs from a wide range of microorganisms. Whereas TLR3/7/8/9, are located on intronic membranes in the cytoplasm and recognize viral nucleic acids into [1]. With the exception of TLR3, all TLRs can transmit signals through Myeloid Differentiation Factor 88 (MyD88), which is a β-interferon TIR structural domain interface protein (TRIF). TLR4, which can activate innate immune signalling pathways through MyD88 and TRIF simultaneously. The MyD88 pathway activates nuclear factor κB (NF-κB), which induces the expression of inflammatory factors, while the TRIF pathway activates interferon regulatory factor (IRF), which induces the expression of type I interferon (IFN-α/β) [2]. During viral infection, IFN-α/β can also be induced through the MyD88-dependent signalling pathway. IFN-α/β are the main cytokines that defend the host against viral infection, and they can induce the production of a large number of antiviral proteins, which can directly disrupt viral replication [3].PRR-mediated production of IFN-α/β is essential for antigen-specific expression of IFN-α/β, and it is also important for the development of the IFN-α/β pathway. IFN-α/β mediated by PRR also plays an important regulatory role in the generation of antigen-specific acquired immunity [4].

In addition to membrane-anchored TLRs, a variety of virus-recognizing PRRs are also present in the cytosol, notably the retinoic acid-inducible gene I (RIG-I)-like receptor (RLR), the NOD-like receptor (NLR) and the DNA receptor. The RLR receptors including RIG-I and MDA5, are expressed in a variety of cells and recognize viral double-stranded RNA. In response to ligand stimulation, RIG-I and MDA5 bind to the mitochondrial junction protein -Interferon β initiating stimulatory factor 1 (IPS-1), which initiates signalling and activates IRF and NF-κB, which in turn induces the expression of inflammatory factors and IFN-α/β [5].NLR receptors can recognize PAMPs of a wide range of pathogens. Some NLRs can initiate IPS-1-mediated antiviral responses [6]. Many NLRs, such as NLRP3 and NLRC4, can aggregate with related proteins to form inflammatory vesicles, activate caspase-1, shear certain

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inflammatory factor precursors, and transform them into biologically active cytokines [7]. For example, the maturation of IL-1β is dependent on the activation of inflammasomes, and mature IL-1β amplifies the inflammatory response by autocrine and paracrine secretion, while inflammasomes also promote the maturation of IL-18. Recently, a variety of cytoplasmic PRRs recognizing viral genomic DNA, termed DNA receptors, have been found to initiate innate antiviral responses, and the antiviral signalling pathway initiated by DNA receptors is dependent on a splice molecule, the activator protein of the interferon gene (STING).

Although the innate immune response can be initiated immediately after viruses infect cells, the virus cannot be suppressed immediately because it takes time to induce gene expression. Autophagy, on the other hand, is a continuous process that can capture and degrade pathogens in a timely manner and may be the fastest natural defense mechanism. Autophagy can also regulate the PRR-initiated innate antiviral response at various levels [8].

## 2. Autophagy

Autophagy is a lysosome-dependent intracellular degradation process and can be divided into three categories [9]. Molecular chaperone-mediated autophagy, which directly translocates target molecules to the lysosome. Microautophagy, which degrades target molecules by capturing them through the invagination of lysosomal membranes. Macroautophagy, which can capture large cytoplasmic fractions as well as foreign pathogens to form autophagic vesicles, which then fuse with lysosomes. Autophagy generally refers to macroautophagy. Firstly, the free intracellular membrane structure starts to form an open autophagosome to capture other components, and then wraps its captured components to form a closed double-layer membrane structure called autophagosome. The autophagosome then fuses with lysosomes to form autophagic lysosomes, which degrade the inner membrane of the autophagosome and its captured components. Autophagy is a tightly regulated process involving a series of autophagy-associated proteins (ATGs), which can be divided into four stages: initiation, closure, fusion, and maturation. The membrane structures that form autophagosomes can be derived from the endoplasmic reticulum, Golgi apparatus, mitochondria or plasma membrane structures.

The phenomenon of cellular autophagy was first identified in yeast cells as a survival mechanism for yeast cells against starvation. More than 30 genes involved in the formation of autophagy have been identified through the study of yeast autophagy, and most of these genes are highly conserved and can be used as the molecular mechanism of autophagy. In recent years, with the deepening of the research, the study of the mechanism of mammalian cellular autophagy has progressed very rapidly, and the homologues of many autophagy-related genes in yeast have been found in mammals and identified and cloned successfully. Currently, autophagy has become one of the hotspots in cell biology research, attracting more and more scholars' attention, and is known as a new mode of programmed cell death-type II apoptosis.

As a central molecule in the negative regulation of autophagy, TOR (target of rapamycin) is a key protein in the control of cellular autophagy, sensing a wide range of cellular signals of change to enhance or reduce the level of autophagy occurring. Cellular signals such as intracellular ATP levels, hypoxia, and viral infection can be integrated directly or indirectly through TOR, thus altering the autophagy occurrence of cells in response to different external environmental stimuli. The whole process of autophagy is regulated by different proteins encoded by ATGs. These autophagy genes are either absent or mutated, resulting in different degrees of autophagy failure or abnormality.

ATGs can form multiple protein complexes that regulate autophagy. For example, ULK1/Beclin-1/ATG14 is involved in signalling autophagy, ATG12/ATG16L1/ATG15 complex promotes the extension of the autophagosome in the initiation phase and ATG2/ATG9 complex regulates the formation of closed autophagosomes with LC3. Syntaxin17 protein contributes to the fusion of the autophagosome with lysosomes, and finally, Beclin-1 and LC3 function in the maturation of autophagic lysosomes. Initially, autophagy was thought to regulate cellular metabolism and homeostasis by capturing certain cytoplasmic components under nutrient-deficient conditions for use in generating energy, which is beneficial to cell survival, and by removing senescent or damaged organelles from the cell. Recently, it has been found that autophagy is also able to selectively degrade microorganisms that invade the cell, becoming an independent natural defense mechanism. Pathogen infection can induce autophagy, and autophagy can also regulate PRR-mediated natural immune signalling pathways, which plays important functions in regulating immune responses [10].

Cellular autophagy is widely present in the physiological and pathological processes of eukaryotic

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cells, and autophagy can either protect or destroy cells. Recent studies have found that cellular autophagy also plays an important regulatory role in the process of pathogenic microbial infection. In the process of pathogen infection, the host can remove intracellular parasites through autophagy on the one hand; on the other hand, some pathogens can induce autophagy to encapsulate them and promote their own propagation in the cell, so cellular autophagy plays a dual role in the infection of pathogens. Viruses, as strict intracellular parasites, have attracted attention with the increasing research on cellular autophagy and the mutual regulatory role of viral infection and cellular self.

## 3. Inter-regulation between Autophagy and Innate Antiviral Immunity

Innate immunity is the body's antiviral line of defense and has an active role in fighting viruses and recognizes receptors for relevant viral molecular patterns that initiate immune signalling (cellular) pathways. Cellular autophagy is more closely related to the inflammatory response, necrosis and other immunity. The core of natural antiviral immunity is the inflammatory response, which occurs when receptors recognize damaged molecules or associated pathogens and then trigger a response, and is a major function of the intrinsic immune system. Necrosis is an unprogrammed death and is subject to programmed control during unprogrammed death. Poly ADP Ribose Polymerase (PARP) is closely related to the mechanism of necrosis. When PARP is activated, ATP is consumed; when PARP is over-activated, cell death may occur due to energy depletion, or necrosis may occur due to apoptosis induced by poly ADP Ribose (PARP product).

The relationship between autophagy and the natural antiviral response has recently made great progress [11]. Autophagy and the natural antiviral response initiated by PRR promote each other and amplify the antiviral response. Some TLRs are able to recognize viral components, for example, TLR4 recognizes certain viral surface proteins, whereas TLR3/7/8/9 recognizes viral nucleic acids to promote autophagy in cells [12-14]. Initial studies suggested that pathogen-induced autophagy was not dependent on the MyD88 signalling pathway [12], but recent studies have demonstrated that this junction protein also mediates autophagy [14]. The autophagy regulator Beclin-1 forms a complex with MyD88 and TRIF to promote autophagy and requires the involvement of TLR [13]. NOD2 recognizes viral ssRNA and promotes autophagy by recruiting ATG16L1 [15]. Herpesvirus (HSV-1) and human cytomegalovirus (HCMV) were recently found to induce autophagy [16]. Further evidence that viral DNA can promote autophagy suggests that intracellular DNA receptors can promote autophagy, but the mechanism remains to be investigated. Unlike bacterial infections, direct degradation of pathogens is not the main pathway of autophagy against viral infections, and few reports have found viral particles in autophagosomes. Autophagy may simply remove certain components of the virus, such as substances essential to the viral life cycle [17].

The above evidence suggests that innate immune mechanisms can promote autophagy. In turn, autophagy can regulate the natural immune response initiated by PRR [18]. Autophagy regulation of the innate immune response was first identified in rat plasma dendritic cells (pDC) [19], where autophagy captures RNA from Sendai virus, delivers it to endosomes, and induces IFN-α/β synthesis by activating the PRR. Autophagy is also involved in HIV-1-induced IFN-α/β expression [20].TLR7 is activated to induce autophagy first, which in turn promotes the TLR7 signalling pathway to activate IRF and induce interferon expression. Besides pDC, autophagy is also involved in regulating interferon production in other cells. Recently, in rat myeloma-derived dendritic cells, autophagy has been shown to promote respiratory syncytial virus-induced IFN-α/β production [21]. However, autophagy does not always promote interferon production in some cell types, but sometimes inhibits interferon expression instead, which is related to the type of virus infecting it, the mechanisms of which are discussed below. In rat embryonic fibroblasts, autophagy promotes IFN-γ expression due to the fact that autophagy inhibits the production of reactive oxygen species (ROS) by mitochondria, which in turn inhibits the production of IFN-γ [22]. IFN-γ can exercise its function in the IFN-α IFN-γ can exert antiviral effects when the IFN-α/β pathway is blocked [23].

## 4. Viruses Exploits Autophagy to Evade Innate Immune Response

When viruses invade, animal cells initiate the autophagy system, and the cells undergo self-phagocytosis to protect the organism and minimize viral damage. However, the relationship between cellular autophagy and animal virus invasion is more complex. In addition to the influence of cellular autophagy, viruses also use cellular autophagy to accelerate intracellular replication. Thus, the relationship between cellular autophagy and animal virus infection is very complex and diversified.

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Although autophagy and innate antiviral mechanisms regulate each other to amplify resistance to viruses, some viruses establish the ability to evade autophagy, as well as to use autophagy to inhibit the innate antiviral response, and such viruses often cause chronic disease. Although this phenomenon is not universal, it is particularly important to study its detailed mechanisms, as it may provide new strategies for antiviral therapy. Many advances have been made in this direction recently, notably in the following areas.

### *4.1 Viruses Suppress Inflammatory Responses through Autophagy*

While autophagy promotes natural antiviral responses, some viruses are able to evade innate immune responses through autophagy, favoring viral replication. For example, the M45 protein of rat cytomegalovirus can interact with NF-κB regulatory subunit and degrade it through autophagy, thereby reducing NF-κB activity and inhibiting the expression of antiviral cytokines [24]. Cytomegalovirus can also inhibit the maturation of autophagosomes, thereby inhibiting autophagy-mediated antiviral responses [25]. Activation of inflammasome is also a natural antiviral mechanism that induces the maturation and secretion of inflammatory factors. For example, the precursor of IL-1β can be sheared into biologically active molecules by activated inflammasome. It has been found that inhibition of autophagy promotes IL-1β production, whereas promotion of autophagy hinders inflammasome activation [26]. Activation of inflammasome induces autophagy, which in turn inhibits the activation of inflammatory factors, thus controlling the balance of inflammatory response. In influenza virus infection, TLR7 signalling promotes the transcription of the precursor IL-1β and the synthesis of its precursors, and the virus also activates the NLRP3 inflammasome, which shears the IL-1β precursor into active IL-1β [27]. Influenza A virus prevents the fusion of autophagosomes with lysosomes, thereby inhibiting autophagosome maturation [28]. Whether this is related to the activation of inflammatory vesicles still lacks direct evidence. Recently, it was found that autophagy inhibits IL-1β production, not dependent on the activation of inflammatory vesicles, but by inhibiting IL-1β transcription [29]. Viruses may use this pathway to evade the antiviral response, but the detailed mechanism is unknown. HIV inhibits autophagy early in the infection of dendritic cells, and this inhibition is a result of viral capsid proteins initiating an inhibitory autophagy signal, which requires the mediation of the CD4 receptor. During endocytosis, HIV-1 escapes degradation by inhibiting autophagy. Inhibition of autophagy favors intracellular HIV-1 survival and promotes HIV-1 infection of CD4+ cells. Moreover, the inhibition of autophagy by HIV-1 interferes with the natural immune response of cells and suppresses TLR-mediated TNF-α expression [30].

### *4.2 Autophagy Hinders IFN Synthesis*

In some cells, autophagy promotes virus-induced IFN-α/β expression. Whereas in other cells, autophagy proteins inhibit RLR-mediated IFN-α/β production. It has been shown that ATG5/12 can interact with RIG-I and its connector IPS-1, thereby inhibiting the RIG-I signalling pathway and subsequent IFN-α/β expression [31]. However, it is unclear whether this process is related to autophagy, or perhaps ATG5/12 is not autophagy-dependent. Autophagy can inhibit the RIG-I signalling pathway in mouse macrophages by scavenging mitochondria-generated ROS, which promote intracellular IPS-1 expression, thereby amplifying RIG-I signalling and inducing the production of IFN-α/β [32]. The regulatory function of autophagy on natural antiviral responses is cell-specific.

Hepatitis C virus (HCV) inhibits IFN-α/β production by promoting autophagy. In infected human hepatocytes, HCV promotes HCV RNA replication through the activation of autophagy, a role that is achieved by inhibiting IFN-α/β expression [33]. Autophagy is associated with IFN-β promoter activation, and when autophagosome maturation is inhibited, IFN-β promoter activity is elevated. Conversely, under conditions that promote autophagy, IFN-β promoter activity is reduced, so that autophagy contributes to the persistence of HCV infection. Indeed, in autophagy-deficient cells, HCV infection or HCV-NS5A overexpression induced the production of more IFN-α/β [34]. Moreover, HCV proteases are able to scavenge IPS-1 thereby inhibiting antiviral signalling [35]. The recent finding that HCV inhibits apoptosis by promoting mitochondrial autophagy also favors viral survival [36]. Thus, HCV evades the innate antiviral response through multiple mechanisms.

### *4.3 Autophagy and Apoptosis in Viral Infections*

Viral infection induces apoptosis, thereby limiting viral replication in cells [37]. In contrast, autophagy inhibits apoptosis and favors virus survival. Human dengue virus and mouse flavivirus infection of epithelial cells can inhibit cell death by inducing autophagy [38], and inhibition of autophagy reduces the

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level of viral replication. However, this phenomenon was not observed in macrophages, suggesting that this mechanism is cell-specific. Interestingly, dengue virus and mouse flavivirus infections also prevented influenza virus-induced cell death to the detriment of influenza virus clearance, and influenza virus infection alone promotes cell death by inhibiting autophagic maturation [28]. Autophagy virus-induced apoptosis and the reciprocal regulation between antiviral responses are important study fields.

## 5. The Promise of Autophagy in Therapeutic Strategies

Drugs such as antibiotics and interferons have long played a very important role in fighting infectious diseases. However, as more and more antibiotics are being misused, bacterial resistance is becoming more and more serious, and viruses are constantly undergoing new mutations and gradually acquiring drug resistance. What is urgently needed is to find a new way to fight infections that, unlike antibiotics, is less likely to develop resistance and has a highly effective antibacterial effect. For example, the use of drugs to regulate the cellular autophagy signalling pathway has been shown to be an effective way to combat intracellular infections, but its specific mechanism and application prospects require further in-depth study; the complexity of the interaction between some pathogenic microorganisms and autophagy has also limited the application of autophagy in therapy.

## 6. Conclusions

When the cells are invaded by a virus, in order to ensure the relative stability of the intracellular environment, it will effectively inhibit viral replication through autophagy, so that the viral concentration is maintained at a low level. The effect of autophagy can be enhanced by silencing autophagy-related factors through RNA interference technology. Cellular autophagy can also inhibit the replication of viral diarrhea viruses and reduce the effects of viruses on individual animals .

Cellular autophagy not only inhibits viral replication, but also promotes viral replication due to the stability of the host cell's protective defense mechanism, which evolves when certain viruses survive for a long period of time in an individual, adapting to the cell's defense mechanism and transforming cellular autophagy into a favorable factor for its own development. When Tembusu Virus (TMUV) infects the organism, it can induce autophagy in the cells and use cellular autophagy to achieve its replication. When BHK21 cells are infected with TMUV, cellular autophagy markers can be measured and the occurrence of cellular autophagy can be analyzed by applying relevant detection instruments. After the activation of autophagy by rapamycin in BHK21 cells, followed by TMUV, it was found that TMUV replication was increased, indicating that cellular autophagy could promote viral replication to a certain extent. In addition to TMUV, classical swine fever virus (CSFV), newcastle disease virus (NDV), porcine reproductive and respiratory syndrome virus (PRRSV) and other viruses can replicate rapidly after the appearance of autophagy in cells.

The invasion of viruses into cells triggers cellular autophagy, which stimulates cellular self-protection and defense mechanisms. The occurrence of cellular autophagy is mainly associated with endoplasmic reticulum stress caused by a combination of protein accumulation and receptor-ligand interaction modalities. Some viruses stimulate cellular autophagy signalling upon invasion. When the cells were infected with UV-inactivated vesicular stomatitis virus (VSV), it was observed that elevated intracellular LC3-domain content. When the cells were transfected with GFP-LC3-domain, green dotted fluorescence was detected. Virus-like particles, virus-infected cells, and co-incubation of cells may lead to autophagy. This process can inhibit AKt activity, resulting in suppression of mTOR activity and contributing to the emergence of cellular autophagy. Endoplasmic reticulum stress-mediated cellular autophagy is mainly caused by the destruction of the environment of the endoplasmic reticulum lumen when the cells are stimulated, which results in the disruption of endoplasmic reticulum function, causing obvious deviation of protein folding and accumulation of proteins in the endoplasmic reticulum, which leads to the cellular stress effect. The endoplasmic reticulum stress effect may be induced by viral infections. Viral proteins can induce cellular autophagy on cellular autophagy, and matrix M2 protein (influenza virus A) alone can promote the formation of autophagosomes and stimulate cellular autophagy.

Cellular autophagy is one of the host's immune mechanisms. Cellular autophagy can inhibit viral replication, but some viruses can inhibit cellular autophagy. There are 2 ways in which cellular autophagy is affected by viruses leading to inhibition of autophagy: When A549 cells were infected with influenza A virus, autophagosomes could be observed through fluorescence microscopy and the number of which was relatively large. The relatively small amount of GFP-LC3, associated membrane protein 1, and

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lysosomes observed were important markers for the maturation of autophagosomes, and when the level of these substances decreased, indicating that autophagosome maturation was blocked. For example, influenza A virus would prevent the formation of phagolysosomes. The other is the inhibition of autophagy formation in virus-infected cells. Herpes simplex virus (HSV) can inhibit the formation of autophagosomes by binding Bclin-1 and blocking the stimulation of the transcription initiation factor eIF2.

Undoubtedly, autophagy performs an important regulatory function in the immune response and defense against pathogen infections, and understanding of the inter-regulatory relationship between cellular antiviral responses and autophagy is still scarce. Innate antiviral immune signalling pathways can induce autophagy, but the detailed mechanisms are poorly understood. In turn, autophagy can regulate the natural antiviral response initiated by PRR and work together to defend against viral infection, and future studies should pay more attention to the interrelationship between autophagy and PRR signalling pathway in antiviral innate immunity. However, some viruses escape autophagy and use autophagy for self-replication, and an in-depth understanding of their mechanisms could provide new ideas for intervention against viral infections. Depending on the sensitivity of different pathogens to autophagy, infection with commensal pathogens may be used to block harmful viral infections. Studying the mutual regulation of infection by different pathogens and cell-specific autophagy and natural immune responses has the potential to reveal the key mechanisms by which viruses escape the natural immune response.

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