· Review ·

Interplay between borna disease virus and host autophagy: implications for pathogenesis and therapeutic strategies

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Abstract

Borna disease virus (BDV) is a nonsegmented, single-stranded, negative-sense RNA virus with strict neurotropism, capable of infecting a wide range of warm-blooded animals and humans. BDV establishes persistent, nonlytic infections in the central nervous system, leading to neurological and behavioral disorders, including cognitive deficits and psychiatric conditions. Recent studies have shown that BDV interacts with host autophagy, an essential cellular degradation process, to facilitate its replication and persistence. BDV infection upregulates autophagy-related proteins, such as LC3, and activates HMGB1-mediated autophagy, whereas viral proteins suppress the innate immune responses, including interferon signaling and apoptosis pathways. These mechanisms allow BDV to evade immune clearance and sustain chronic infection. Therefore, autophagy is a double-edged sword, acting as both a host defense mechanism and a process exploited by BDV for its survival. Understanding the interplay between BDV and autophagy will provide insights into its pathogenesis and potential therapeutic targets. Advances in BDV vaccine development, including recombinant protein and virus-like particle vaccines, are also promising, but challenges such as immune evasion and subtype diversity remain. Further research is required to address these challenges and develop effective prevention and treatment strategies.

Keywords: Borna disease virus, autophagy, infection, vaccine

In the mid-19th century, European scientists isolated borna disease virus (BDV) from infected equine tissues. Researchers subsequently identified BDV in countries outside Europe, and demonstrated that it is capable of infecting both animals and humans [1]. This led to surges in scientific interest and research.

Molecular Biological Characteristics of BDV

Borna disease virus is an enveloped, nonsegmented, single-stranded negative-sense RNA virus belonging to the order *Mononegavirales*, the family *Bomaviri-*

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dae, and the genus *Bomavirus*. BDV shares structural similarities with viruses such as paramyxoviruses, rabies virus, and Ebola virus. The full genome of BDV is 8910 nucleotides (nt) long and encodes six functional proteins: the five structural proteins nucleoprotein (N, 40 kDa), phosphoprotein (P, 24 kDa), matrix protein (gp18, 18 kDa), glycoprotein (G, 94 kDa), and RNA-dependent RNA polymerase (L, 190 kDa), and one nonstructural protein (X, 10 kDa) [2]. These six proteins work synergistically during BDV infection and are essential to its pathogenic mechanism. The genomic structure of BDV is shown in Figure 1. The overlapping regions between proteins reflect their functional interdependence. BDV transcription and replication occur in the host cell nucleus during infection. As shown in Figure 1, the protein-coding genes of BDV have overlapping regions. The modification of the BDV subgenomic RNA occurs posttranscriptionally, and the protein-coding sequences of BDV cultured in different host tissues are significantly conserved.

BDV Infection and Pathogenesis

Studies have shown that nearly all warm-blooded animals throughout the world are susceptible to BDV infection. The virus enters the central nervous system (CNS) directly through the neural terminals of the host. After infection, clinical symptoms often take a long time to appear, although viral replication in CNS cells is rapid [3]. BDV-infected cells include neurons, ependymal cells, astrocytes, and oligodendrocytes. BDV is highly neurotropic and neurotoxic, and can remain latent in the CNS throughout the lives of infected individuals. Infected hosts develop various neurological disorders, including immune dysregulation and

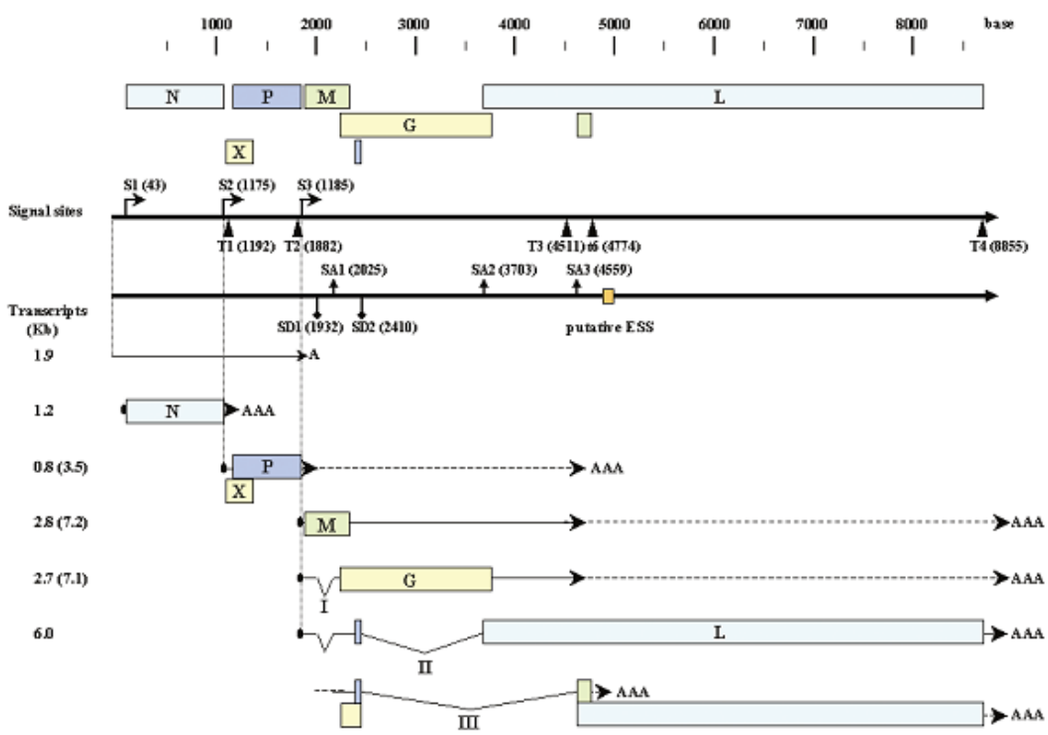

Figure 1. Genomic organization and transcription map of BDV [2].

behavioral changes, such as deficits in learning and social behavior. The virus displays strict neurotropism, causes nonlytic infections, and shows low-replicative persistence during infection. Consistent with its strong neurotropism, it has been repeatedly shown that BDV is closely associated with the onset of neuropsychiatric disorders. BDV disrupts neuron formation and causes neurological dysfunction. It has been reported that glutamate and the hippocampal lipid metabolism are disturbed in asymptomatic BDV-infected horses [4]. BDV infection is also associated with diseases such as schizophrenia, chronic fatigue syndrome, and autism. Its primary mode of infection is persistent infection, producing asymptomatic carriers [5].

At present, no primary pathogenic mechanism of BDV has been identified, but it probably involves the innate immunity of its host, which may reduce the viral capacity for transmission.

BDV Infection and Innate Immunity

During pathogen infection, the immune system of the host is usually activated to combat exogenous invasion. The host's innate immune system is considered to block the transmission of incoming viruses to prevent their invasion. However, changes in the interferon levels in the brains of BDV-infected animals indicate that BDV affects the synthesis of induced interferons through the innate immune pathway, preventing the efficient clearance of the virus by the host cells. The BDV P protein suppresses the activity of TBK-1 kinase, significantly reducing its antiviral effect, and thus inhibiting the host's innate immune response [6]. Furthermore, recent studies have shown that BDV X protein colocalizes with mitochondrial antiviral signaling protein (MAVS) inside the cell to suppress the apoptotic pathways, thus facilitating infection [7,8]. These mechanisms could explain how BDV establishes a persistent infection in its host.

Factors such as the characteristics of the pathogen, the infection intensity, the host cell status, and the regulation of the survival and apoptosis signaling pathways within the cell can also greatly influence the fate of the host cell. Affected individuals usually develop fever, accompanied by headaches in humans, followed by a broad range of behavioral and neurological disorders, including apathy, compulsive movements, seizures, ataxia, and blindness [9]. Because the mechanism underlying BDV's persistent infection may involve the aforementioned pathways and it is well-known that cell death can occur through apoptosis, autophagy, or necrosis, it is important to investigate whether these processes play a role in the persistence of BDV.

Autophagy and Viruses

Autophagy, also known as 'type II programmed cell death', is a biological process widespread in eukaryotic cells. The autophagic pathway is shown in Figure 2. Autophagy begins with the nucleation of the autophagic isolation membrane, which ultimately engulfs cytoplasmic material or microorganisms for degradation in the lysosome [10]. The mTOR kinase plays an essential role in inducing autophagy by inhibiting the ULK1–ATG13–FIP200 complex and hyperphosphorylating ULK1 and ATG13 [11-13].

Autophagy is stimulated by conditions such as nutrient deprivation and the binding of MTOR to the ULK1–ATG13–FIP200 complex, which facilitates the expansion of the isolation membrane [14]. The nucleation of the autophagic vesicle can also occur through the activation of the PIP3–VPS34 complex, which includes the essential mammalian autophagy proteins beclin 1 and ATG14 [15]. The second major step in autophagy

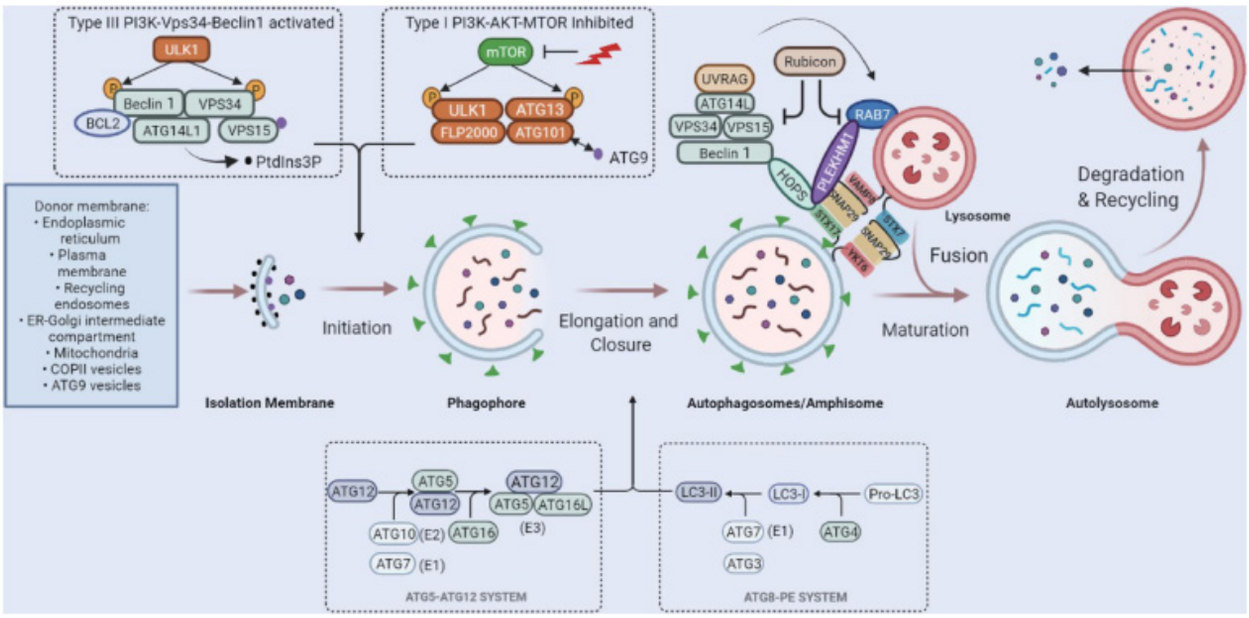

Figure 2. Autophagic pathway [10].

involves the elongation of the isolation membrane, leading to the formation of the autophagosome. This structure is generated by the selective enclosure of substances within two phospholipid bilayers and an inner membrane. Two ubiquitin-like conjugation systems regulate this step by modifying the ubiquitin-like molecules ATG5 and LC3, which are associated with the isolation membrane, to promote its curvature and expansion. In the final step, the autophagosome fuses with the lysosome, and enzymatic reactions within the lysosome degrade the autophagosome's membrane and its components [16]. Intracellular autophagy is regulated by various factors, including nutrient availability, growth factor signaling, and the generation of immune signals after microbial infection [17]. Autophagy provides regenerative resources for the cell and plays a critical role in regulating the lipid metabolism. For instance, Dengue virus modulates the lipid metabolism through an autophagic process [18,19]. Autophagy also functions as a defense mechanism by engulfing and degrading exogenous pathogens, helping to resist their invasion and infection.

Studies have shown that autophagy plays a crucial role in herpes simplex virus (HSV) infections. Autophagy can target and degrade viral proteins, and the interaction between the HSV-1 ICP34.5 protein and beclin 1 inhibits autophagy, allowing the virus to persist within the host [20,21]. Similarly, human immunodeficiency virus (HIV) utilizes autophagosomes to promote its replication [22,23]. Hepatitis C virus (HCV) evades the host immune response by interacting with autophagic processes, suppressing autophagy, and benefiting from the cellular autophagic responses [24]. According to current data, autophagy affects the later stages of HBV replication in humans, leading to an increase in HBV production [25]. The suppression of autophagy reduces the synthesis of HBV DNA, suggesting that autophagy facilitates HBV DNA replication [26]. Other viruses, such as coxsackievirus (CVB), accumulate autophagosomes, and CVB infection inhibits the fusion of autophagosomes with lysosomes [27].

Enterovirus 71 (EV71), a member of the genus Enterovirus, manipulates the autophagic machinery to facilitate its replication. Zhang Xiaoyan et al. [28] demonstrated that EV71 infection leads to the switching of LC3 isoforms and the degradation of P62, a selective auto-

phagy receptor, indicating a complex interplay between the virus and the host's autophagic pathways. However, other studies have shown that the 3C protein of EV71 inhibits autophagosome formation, thereby allowing the virus to evade the host's immune response [29]. Similarly, avibirnavirus is targeted by selective autophagy, and the autophagy cargo receptor P62 mediates the degradation of the viral capsid protein VP2. This process is dependent on the ubiquitination of VP2, which allows P62 to recognize it and promote its autophagic degradation, thus inhibiting viral replication [30]. The regulation of autophagy and its influence on viral replication is summarized in Table 1, based on the relevant literature. Certain viruses interact with the autophagic process, as shown in Table 2.

Autophagy is an evolutionarily conserved degradation process in which cytoplasmic components are broken down through a complex pathway in the lysosome. Autophagy eliminates damaged materials, maintaining

Table 1. Role of autophagy in viral replication [28,31].

Autophagy	Virus	Viral replication
A	HIV-1/ HBV /HCV/ EV71/ DENV/ IAV/ ARVs/ CVB3/KSHV/ CHIKV/ Rotavirus/ Poliovirus	Up
A	HSV-1/ HCMV/ SIV 1	Down
S	Tobacco mosaic virus/VSV	Up
S	HBV	Down

Notes: S, suppressor; A, activator.

Table 2. Roles of viral proteins in the regulation of autophagy [31].

Viral protein	Virus	Viral species	Viral effect(s) on autophagy
DP71L	ASFV	dsDNA	S
P17	ARV	dsRNA	A
3C	EV71	dsRNA	S
E7	HPV16	dsDNA	A
E5	HPV16	dsDNA	S
nsP2	CHIKV	RNA	A
nsP4	CHIKV	RNA	S
LMP-1	EBV	dsDNA	A
HBs	HBV	dsDNA	A
HBx	HBV	dsDNA	A
TRS1	HCMV	dsDNA	S
PUL38	HCMV	dsDNA	A
E1 protein	HCV	ssRNA	S
Nef	HIV-1	dsRNA	A
Glycoprotein B	HSV-1	dsDNA	S
ICP34.5	HSV-1	dsDNA	S
Us11	HSV-1	dsDNA	S
vFLIP	HVS/KSHV/MCV	DNA	S
M2 protein	IAV	ssRNA	A
v-cyclin	KSHV	dsDNA	A
vBcl-2	KSHV/γHV-68	DNA	S
m142&m143	MCMV	dsDNA	S
IE180	PRV	dsDNA	S
nsP4	Rotavirus	dsRNA	A
Small T antigen	SV40	dsDNA	A

Notes: S, suppressor; A, activator.

cellular homeostasis. It helps the immune system capture and remove invading nonself elements, acting as a defense mechanism [32,33]. However, autophagy is a double-edged sword for viruses. On the one hand, autophagy is part of the host's stress response, activated by the innate immune system to degrade and process viral invaders. On the other hand, viruses can hijack autophagosomes and utilize the metabolic products and energy derived from autophagy to replicate, thus supporting their own survival.

A distinctive feature of BDV is its ability to establish chronic, persistent, nonlytic infections in humans. However, the mechanism by which BoDV-1 evades the host's antiviral immune defenses and replicates within cells remains unclear. Autophagy-related assays have shown that the expression of autophagy-related proteins and the autophagy marker LC3 in neuronal cells is significantly upregulated after BoDV-1 infection. Autophagic flux experiments and transmission electron microscopic observations have corroborated the activation of HMGB1-mediated autophagy by BoDV-1. Moreover, the experimental modulation of miR-505 expression revealed that the overexpression of miR-505 markedly suppressed HMGB1-mediated autophagy [34]. These findings offer novel insights into the pathogenic mechanisms of BoDV-1 and potential strategies for the prevention and treatment of BDV-1 infections. Viruses can modulate autophagic activity during infection, and the suppression of the innate immunity by BDV probably facilitates its persistent infection within the host. Whether BDV interacts with the autophagic process during chronic infection requires further experimental confirmation.

Vaccine Development for BDV

Despite the significant attention directed toward BDV-1 infections of both animals and humans, the development of a vaccine for this virus is at a relatively early stage. The key advances made and the challenges encountered in BoDV-1 vaccine research are summarized below.

Animal Model Studies

Research has shown that immunizing Lewis rats with recombinant vaccinia virus expressing the BoDV N protein partially protected them from BoDV infection, but these animals subsequently developed severe encephalitis and more-aggressive clinical symptoms [35]. In another study, rats were immunized with cell-cultured Orf virus strain D1701-V expressing the BoDV N protein via intramuscular injection, which induced a long-term humoral immune response and prevented the development of borna disease for an extended period after challenge [36]. However, no vaccine is currently available for the prevention of staggering disease [37].

Types of Candidate Vaccines

Recombinant protein vaccines: These vaccines are prepared by expressing specific BDV proteins, such as the nucleoprotein (N) and phosphoprotein (P), that induce specific immune responses in the host.

DNA vaccines: Some research has examined the potential of DNA vaccines, which involve the direct injection of DNA fragments encoding viral proteins into host cells to induce immune responses.

Virus-like particle (VLP) vaccines: VLPs are noninfectious, empty shells that mimic the structures of viruses and induce strong immune responses. Although this approach has shown promise in vaccines directed against other viruses, more research is required to apply it to a BDV vaccine [38].

Immune Mechanism Studies

Cellular and humoral immunity: Studies have suggested that effective immune protection against BDV probably requires the activation of both cellular and humoral immune responses. Therefore, any vaccine design must consider how both types of immune response can be induced simultaneously.

Immune evasion mechanisms: BDV has certain immune evasion capabilities, which pose a challenge for vaccine development. Therefore, researchers are investigating ways to overcome these mechanisms to enhance the effectiveness of vaccines.

Preclinical and Clinical Studies

Most BDV vaccine research is currently in the preclinical phase, primarily conducted in laboratories and animal models. These studies aim to confirm the safety and efficacy of vaccines. Although large-scale clinical trials have not yet been initiated, some preliminary clinical trials are underway to assess the safety of and immune responses induced by the vaccines.

Future Directions

Multivalent vaccines: Because there are multiple BDV subtypes, the development of a multivalent vaccine that targets different subtypes will be a significant aim of future research.

Combination therapies: Combining vaccines with other antiviral treatments (e.g., antiviral drugs and immunomodulators) could improve treatment outcomes.

Interdisciplinary collaboration: Effective BDV vaccine development requires interdisciplinary collaboration, involving experts from virology, immunology, molecular biology, and other fields.

Conclusion

The in-depth study of BDV and its interactions with the autophagic mechanisms of its host cells will provide valuable insights, allowing the development of more-effective vaccines and antiviral strategies. The reverse genetics technology has great potential utility in BDV vaccine development, especially for the development of recombinant VLPs and genetic vectors expressing specific viral proteins, which offer enhanced protection in animal models. Successful studies will not only control the spread of borna disease in both animals and humans but will also offer new avenues for the prevention and treatment of other neurotropic viruses.

Acknowledgments

We thank Janine Miller, PhD, from Liwen Bianji (Edanz) (www.liwenbianji.cn) for editing the English text of a draft of this manuscript.

Author Contributions

Lan Sun wrote the manuscript.

Conflicts of Interests

The author declares no conflict of interest.

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