The Viral Subversion of Neuronal Autophagy: Mechanisms, Pathogenesis, and Neurodegenerative Convergence

1. Introduction: The Autophagic Imperative in the Central Nervous System

The central nervous system (CNS) operates under a unique set of biological constraints. Its primary functional units, the neurons, are post-mitotic cells that must endure for the lifespan of the organism. Unlike epithelial or hematopoietic cells, neurons cannot dilute intracellular damage, protein aggregates, or invading pathogens through cell division. Consequently, they rely heavily on the ubiquitin-proteasome system (UPS) and, more critically, the autophagy-lysosomal pathway (ALP) to maintain cellular homeostasis. In the complex morphological landscape of a neuron—where axonal volumes can exceed the somatic volume by orders of magnitude—autophagy is not merely a waste disposal mechanism; it is a vital logistical operation involving the retrograde transport of autophagosomes from distal synaptic terminals to the lysosome-rich soma. The failure of this system is pathognomonic of neurodegeneration, characterizing diseases ranging from Alzheimer's (AD) and Parkinson's (PD) to Amyotrophic Lateral Sclerosis (ALS).

Into this delicate homeostatic balance enter neurotropic viruses. These pathogens, which have evolved to invade and replicate within the neural architecture, face a potent innate immune defense: virophagy, the selective autophagic degradation of viral components. To survive, neurotropic viruses have developed sophisticated molecular strategies to manipulate the autophagic machinery. This manipulation is rarely a simple inhibition; rather, it is a dynamic, often biphasic modulation where viruses hijack the early nucleation machinery to generate membrane scaffolds for replication organelles, while simultaneously arresting the late-stage fusion or degradative capabilities of the lysosome to prevent their own destruction.

This report provides an exhaustive analysis of the mechanisms by which neurotropic viruses—including members of the *Herpesviridae*, *Flaviviridae*, *Picornaviridae*, *Rhabdoviridae*, *Togaviridae*, and *Retroviridae* families—interfere with neuronal autophagy. By synthesizing

data on viral virulence factors, host protein interactions, and signaling dysregulation, we elucidate how this viral subversion contributes to acute encephalitis and acts as a potential etiological trigger for chronic neurodegenerative proteinopathies.

2. The Cellular Biology of Neuronal Autophagy and Viral Vulnerability

To appreciate the magnitude of viral disruption, one must first delineate the specialized nature of neuronal autophagy. The process begins with the nucleation of the phagophore, driven by the Unc-51-like kinase 1 (ULK1) complex and the Class III PI3K complex (comprising Beclin-1, VPS34, and ATG14). In neurons, this initiation frequently occurs in the distal axon or at the synapse, often in response to local stress or bioenergetic demands. Once formed, the autophagosome recruits motor proteins, specifically dynein-dynactin complexes, to traverse the microtubule tracks of the axon in a retrograde fashion toward the cell body.[1]

During this transport, autophagosomes undergo maturation, a process involving acidification and fusion with late endosomes to form amphisomes, before finally fusing with lysosomes in the soma to form autolysosomes. This extreme spatial segregation of biogenesis and degradation renders neurons uniquely vulnerable to "traffic jams." A viral block at any stage—initiation, transport, or fusion—can lead to the rapid accumulation of autophagic vacuoles (AVs) within the axon, causing swellings (spheroids) that physically impede synaptic transmission and trophic signaling, eventually leading to "die-back" axonopathy.

Neurotropic viruses exploit this dependency. By targeting key regulatory nodes such as the Beclin-1 complex, the mTOR signaling pathway, or the SNARE fusion machinery, they effectively turn the neuron's logistical complexity against itself. The resulting accumulation of undegraded cargo not only facilitates viral egress and replication but also creates a cytotoxic environment ripe for the aggregation of host proteins like β-amyloid, α-synuclein, and TDP-43, thereby bridging the gap between infectious disease and neurodegeneration.[3]

3. Alphaherpesvirinae: The Paradigm of Latency and Beclin-1 Sequestration

Herpes Simplex Virus type 1 (HSV-1) represents the archetype of a neurotropic virus that has

mastered the modulation of neuronal autophagy. As a virus capable of establishing lifelong latency in the trigeminal ganglia, HSV-1 must navigate the balance between silencing the host immune response and maintaining cellular viability.

3.1 The ICP34.5 Neurovirulence Factor

The pivot of HSV-1's anti-autophagic strategy is the neurovirulence protein ICP34.5 (Infected Cell Protein 34.5). This multifunctional protein acts as a molecular antagonist to the host's translational arrest and autophagy induction pathways.

The Beclin-1 Binding Domain (BBD):
ICP34.5 contains a specialized domain that mimics the host protein Bcl-2, allowing it to bind with high affinity to the coiled-coil domain of Beclin-1. Beclin-1 is essential for the nucleation of the autophagic vesicle. By sequestering Beclin-1, ICP34.5 physically prevents the recruitment of the PI3K complex to the phagophore assembly site.4 This blockade is absolute; recombinant viruses lacking the Beclin-binding domain of ICP34.5 are unable to inhibit autophagy and, consequently, exhibit dramatically reduced neurovirulence in murine models. They are rapidly cleared by the host's innate immune response, underscoring that autophagy inhibition is a prerequisite for HSV-1 to cause lethal encephalitis.5
The PKR-eIF2α Axis:
Beyond direct steric hindrance of Beclin-1, ICP34.5 manipulates the signaling landscape via the Protein Kinase R (PKR) pathway. In response to viral double-stranded DNA (dsDNA) and RNA intermediates, neuronal PKR phosphorylates the translation initiation factor eIF2α. This phosphorylation event halts general protein synthesis—a defense mechanism to starve the virus—and simultaneously upregulates ATG gene expression to induce autophagy. ICP34.5 recruits Protein Phosphatase 1α (PP1α) to dephosphorylate eIF2α, thereby reversing the translational arrest and blunting the autophagic signal.7

3.2 Cell-Type Specificity: Neurons vs. Glia

Recent investigations have revealed a dichotomy in how HSV-1 modulates autophagy across different neural cell types. In neurons, HSV-1 infection triggers a robust, immediate induction of autophagy mediated by the innate immune sensors (PKR/cGAS). Consequently, the virus must actively suppress this induced response to survive. However, in glial cells (astrocytes and microglia), the baseline autophagy dynamics differ. The virus suppresses basal autophagy in glia but does not face the same surge of induced autophagy seen in neurons.[9] This differential

modulation suggests that HSV-1 has evolved specific countermeasures for the terminally differentiated, highly defended environment of the neuron, distinct from its strategy in supporting glial cells.

3.3 Mitophagy and the EIF2S1-ATF4 Axis

Deepening the injury to the neuron, HSV-1 also targets mitophagy, the quality control mechanism for mitochondria. The viral proteins ICP34.5 and US11 have been implicated in deregulating the EIF2S1-ATF4 signaling axis. Under normal stress, ATF4 upregulates Parkin (PRKN) and PINK1, the ubiquitin ligase and kinase responsible for tagging damaged mitochondria for degradation. HSV-1 suppresses this expression.8
The consequence is the accumulation of dysfunctional, ROS-generating mitochondria. While this metabolic stress is deleterious to the neuron, the inhibition of mitophagy serves a sinister viral purpose: it prevents the release of mitochondrial DNA (mtDNA) into the cytosol. Cytosolic mtDNA is a potent agonist of the cGAS-STING pathway, which drives Type I interferon production. By blocking the degradation of leaky mitochondria, HSV-1 paradoxically limits the magnitude of the immune alarm, maintaining a "smoldering" level of damage that supports viral persistence without triggering catastrophic clearance.10

4. Flaviviridae: Hijacking Membranes and Metabolic Reprogramming

The *Flaviviridae* family, including Zika Virus (ZIKV), West Nile Virus (WNV), and Dengue Virus (DENV), utilizes the endoplasmic reticulum (ER) membrane system for replication. These viruses do not merely inhibit autophagy; they remodel it to construct replication factories.

4.1 Zika Virus: The "Block and Build" Strategy

ZIKV, particularly associated with microcephaly and damage to neural progenitor cells (NPCs), exemplifies the manipulation of autophagic flux.

Induction via Akt-mTOR Inhibition:
Unlike HSV-1, which blocks initiation, ZIKV actively induces the formation of early autophagic

membranes. The viral non-structural proteins NS4A and NS4B inhibit the Akt-mTOR pathway.12 Since mTORC1 is the master negative regulator of autophagy, its inhibition releases the brake on the ULK1 complex, triggering massive vacuolization. These double-membraned vesicles serve as protected scaffolds for viral RNA replication, shielding dsRNA from cytoplasmic RIG-I-like receptors.

Arrest of Maturation and Egress:

While ZIKV promotes vesicle formation, it strictly prohibits their destruction. ZIKV infection blocks the fusion of autophagosomes with lysosomes.15 Instead of degradation, these vesicles function as transport vehicles. Recent evidence suggests ZIKV utilizes late endosomes and amphisomes for viral egress, turning the waste disposal pathway into a secretory route. Inhibition of the fusion stage—using pharmacological agents like chloroquine—can paradoxically limit viral spread by locking the virus in a non-productive compartment, although the precise timing of such intervention is critical.15

Downregulation of FANCC and Selective Virophagy:

A critical insight into ZIKV pathogenesis is its specific targeting of the Fanconi anemia complementation group C (FANCC) protein. ZIKV infection downregulates the transcription factor E2F4, which controls FANCC expression. FANCC is essential for selective autophagy (virophagy). By suppressing this specific gene, ZIKV effectively blinds the host cell to the presence of viral capsids, preventing them from being tagged for engulfment, even while bulk autophagy is upregulated for membrane synthesis.17

Mitochondrial Dynamics and Metabolic Shift:

ZIKV also induces mitochondrial fragmentation by decreasing the levels of Mitofusin 2 (MFN2), a fusion protein. Concurrently, viral proteins (such as NS4A) block the mitophagy that would normally clear these fragmented organelles.18 This leads to a metabolic shift towards glycolysis, creating an environment rich in biosynthetic intermediates necessary for rapid viral replication, albeit at the cost of neuronal energetic stability and survival.

4.2 West Nile Virus: Proteinopathy Induction

West Nile Virus presents a contrasting mechanism. While it utilizes ER membranes, its interaction with autophagy is characterized by the induction of aggregate-prone toxicity.

Capsid-Mediated AMPK Degradation:

The WNV Capsid (C) protein targets AMP-activated protein kinase (AMPK), a metabolic sensor that activates autophagy during energy stress. The C protein facilitates the ubiquitination and proteasomal degradation of AMPK.20 This degradation uncouples the stress signal from the autophagy response. Specifically, point mutations in the C protein (L51 and A52) have been shown to abrogate this interaction, restoring autophagy and reducing neurovirulence.

The clinical consequence of this blockade is the accumulation of p62/SQSTM1 and ubiquitinated protein aggregates within infected neurons.20 These aggregates are neurotoxic and mimic the pathology of neurodegenerative proteinopathies, suggesting that WNV

encephalitis is, in part, an acute, virus-induced proteinopathy.

5. Picornaviridae: Proteolytic Dismantling of the Fusion Machinery

Enteroviruses (EV), including EV71, Coxsackievirus B3 (CVB3), and the paralyzing EV-D68, employ a direct enzymatic assault on the autophagy machinery. These RNA viruses encode potent proteases, 2A and 3C, which process the viral polyprotein but also cleave specific host factors to disable cellular defenses.

5.1 The Cleavage of SNARE Proteins

The fusion of autophagosomes with lysosomes is mediated by SNARE (Soluble N-ethylmaleimide-sensitive factor Attachment Protein Receptor) complexes. The core complex involves Syntaxin 17 (STX17) on the autophagosome, VAMP8 on the lysosome, and the bridging protein SNAP29.

SNAP29 and SNAP47 Cleavage:
Research has definitively shown that the 3C protease of EV71, CVB3, and EV-D68 cleaves SNAP29.22 This cleavage severs the connection between the autophagosome and the lysosome, resulting in the accumulation of large, mature autophagosomes that cannot be degraded.
Furthermore, EV-D68 has been shown to cleave SNAP47, a distinct SNARE protein. While SNAP29 is critical for general fusion, SNAP47 appears to play a specific role in facilitating viral release or alternative fusion pathways. The differential cleavage of these SNAREs suggests a fine-tuned modulation where the virus blocks degradation while potentially enabling a non-lytic exit pathway known as Autophagosome-Mediated Exit (AME).22
PLEKHM1 Disruption:
In addition to SNAREs, the CVB3 protease 3C cleaves PLEKHM1, an adaptor protein that links the HOPS complex to the fusion machinery. This multipronged attack ensures that no fusion can occur, transforming the neuron’s cytoplasm into a warehouse of viral replication vesicles.23

5.2 Mechanisms of Induction: ROS and ACOX1

While the 3C protease blocks the exit, other viral proteins drive the entry into the autophagy pathway. The EV71 3D polymerase protein interacts with and downregulates Acyl-CoA oxidase 1 (ACOX1), a rate-limiting enzyme in peroxisomal fatty acid oxidation. The reduction of ACOX1 leads to the accumulation of peroxisomal substrates and a surge in Reactive Oxygen Species (ROS). This oxidative stress acts as a potent trigger for autophagy initiation upstream. However, because the downstream fusion is blocked by protease 3C, the neuron is trapped in a futile cycle of stress and vesicle accumulation, culminating in apoptosis.[27]

6. Rhabdoviridae: Rabies and the Retrograde Route

Rabies Virus (RABV) is unique in its absolute dependence on neuronal transport. It enters peripheral motor neurons and travels retrograde to the CNS. Autophagy plays a complex role in this journey.

6.1 The P Protein and Beclin-1

Similar to HSV-1, the RABV phosphoprotein (P) has been identified as an autophagy modulator. The P protein binds to Beclin-1, wrapping immature autophagosomes and inhibiting their fusion with lysosomes.[28] This incomplete autophagy is hypothesized to provide the physical membrane support for the viral Negri bodies—the sites of viral transcription and replication—protecting them from cytosolic degradation.

6.2 Bif-1 and Isoform Specificity

The host protein Bif-1 (SH3GLB1/Endophilin B1) is a positive regulator of autophagy that promotes membrane curvature for phagophore formation. Interestingly, the neuron-specific isoform, Bif-1c, has been identified as a key factor in RABV replication. Silencing Bif-1c significantly inhibits RABV replication, suggesting that the virus specifically exploits the neuronal isoform of this autophagy regulator to support its lifecycle.[29]

6.3 The Role of TRIM44 and IFITM3

The interplay extends to ubiquitin ligases and interferon-stimulated genes. The E3 ubiquitin ligase TRIM44 has been found to promote RABV replication by stabilizing viral proteins or facilitating autophagy initiation; its knockdown reduces viral titers, an effect reversible by autophagy inhibitors.[30] Conversely, the host defense protein IFITM3 (Interferon-induced transmembrane protein 3) inhibits RABV by suppressing mTORC1 and ULK1, effectively shutting down the membrane supply lines the virus requires.[28]

7. Retroviridae: HIV-1 and the Bystander Effect

Human Immunodeficiency Virus (HIV-1) does not productively infect neurons, yet it causes profound neuronal damage, leading to HIV-Associated Neurocognitive Disorders (HAND). This damage is mediated by viral proteins (Tat, Nef, gp120) released from infected microglia and macrophages, which are endocytosed by neurons.

7.1 Nef: The Parkin-Bcl-2 Lock

The HIV accessory protein Nef enters neurons and disrupts autophagy to prevent the degradation of endocytosed viral material. A novel mechanism has been elucidated wherein Nef physically interacts with the E3 ubiquitin ligase Parkin (PRKN). Nef directs Parkin to mono-ubiquitinate Bcl-2. This specific ubiquitin mark increases the affinity of Bcl-2 for Beclin-1. Under normal stress conditions, Bcl-2 dissociates from Beclin-1 to allow autophagy initiation; however, the Nef-induced mono-ubiquitination locks them together, preventing the activation of the PI3K complex and stalling autophagy at the initiation phase.[31]

7.2 Tat: Lysosomal Destabilization

The viral trans-activator Tat penetrates neurons and localizes to the lysosomal membrane.

Evidence suggests Tat interacts with LAMP2A (Lysosome-associated membrane protein 2A), interfering with chaperone-mediated autophagy (CMA) and potentially promoting aberrant fusion events that do not result in degradation.[32] Furthermore, the Antisense Protein (ASP) of HIV-1 has recently been implicated in inducing autophagy in monocytes, suggesting a complex, multi-protein modulation of the pathway that varies by cell type but converges on dysregulation in the CNS.[33]

8. Chikungunya Virus: The ROS-Autophagy Axis

Chikungunya Virus (CHIKV), an alphavirus, induces a robust autophagic response mediated by ER stress and oxidative stress.

8.1 ROS-Mediated mTORC1 Inhibition

CHIKV infection leads to a dramatic increase in Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS). This oxidative burst activates AMPK, which in turn inhibits mTORC1, triggering autophagy.[34]

8.2 The Autophagy-Apoptosis Switch

There is a critical interplay between autophagy and apoptosis in CHIKV infection. They appear to be mutually exclusive processes in the early stages; the induction of autophagy delays caspase-3 activation and apoptosis, acting as a pro-survival mechanism that allows the virus time to replicate. In mice with hypomorphic Atg16L1 (a key autophagy gene), CHIKV infection leads to enhanced lethality and tissue damage, confirming that functional autophagy acts as a buffer against viral virulence. However, the virus eventually overwhelms this system, and the accumulated autophagic membranes may serve as sites for viral RNA capping and assembly.[35]

9. The Viral Origins of Neurodegeneration: A

Convergent Pathology

The mechanisms described above—inhibition of fusion, sequestration of Beclin-1, and cleavage of SNAREs—bear a striking resemblance to the cellular defects observed in "idiopathic" neurodegenerative diseases. This has led to the hypothesis that viral infections may be the environmental triggers for these conditions.

9.1 Alzheimer's Disease (AD) and HSV-1

The accumulation of Amyloid-β (Aβ) and hyperphosphorylated Tau is the hallmark of AD. Autophagy is the primary mechanism for clearing these aggregates. The HSV-1 protein ICP34.5, by inhibiting Beclin-1, directly impairs the clearance of Aβ. Repeated reactivation of HSV-1 in the brain could lead to cumulative autophagic failure, tipping the balance toward plaque deposition. Furthermore, Aβ itself has been proposed to be an antimicrobial peptide that entraps viruses; its overproduction in response to chronic viral presence could drive AD pathology.[3]

9.2 Parkinson's Disease (PD) and Viral Triggers

PD is characterized by the loss of dopaminergic neurons and the accumulation of α-synuclein (Lewy bodies).

- **WNV and Influenza:** These viruses induce α-synuclein aggregation. WNV's inhibition of AMPK and subsequent failure to clear ubiquitinated proteins provides a direct mechanism for Lewy body formation.[3]
- **Human Pegivirus (HPgV):** Recent studies using whole virome sequencing have identified HPgV in the brains of PD patients. Its presence correlates with altered immune signaling (IL-4 suppression) and markers of mitochondrial dysfunction (mitophagy failure), suggesting it may be a novel environmental factor in PD pathogenesis.[37]

9.3 ALS and Enteroviral Proteotoxicity

Amyotrophic Lateral Sclerosis (ALS) involves the aggregation of TDP-43 and the failure of nucleocytoplasmic transport. Enteroviral proteases (2A/3C) cleave components of the nuclear pore complex (Nup62, Nup98), leading to the cytoplasmic mislocalization of TDP-43, mimicking the core pathology of ALS. The cleavage of SQSTM1/p62 by CVB3 further links viral infection to the autophagic deficits seen in ALS patients.[3]

10. Mitophagy, Immunometabolism, and the cGAS-STING Interface

The inhibition of mitophagy by neurotropic viruses (HSV-1, ZIKV) has profound immunological consequences. Mitochondria are evolutionary remnants of bacteria and contain DNA (mtDNA) that is highly immunostimulatory.
Under normal conditions, damaged mitochondria are cleared by mitophagy to prevent the leakage of mtDNA. By blocking this process (via US11 or NS4A), viruses create a pool of damaged organelles. While this prevents the immediate release of mtDNA (which would trigger cGAS-STING and Interferon-β), the chronic accumulation of these organelles leads to a metabolic shift toward glycolysis (the Warburg effect). This shift provides the building blocks for viral replication but leaves the neuron energetically depleted and prone to oxidative damage, contributing to the "brain fog" and cognitive deficits often seen in post-viral syndromes.8

11. Therapeutic Horizons

The identification of specific viral checkpoints in the autophagy pathway opens new avenues for therapy, moving beyond direct antivirals to host-directed therapies.

Target Pathway	Therapeutic Agent	Mechanism	Potential Application	Source
Autophagy Induction	Trehalose	mTOR-independent autophagy activation.	Clearing aggregates in ZIKV/WNV/PD.	41

Autophagy Induction	Rapamycin	mTOR inhibitor.	Reversing Tat/Nef inhibition; WNV.	[30]
Mitophagy Restoration	Necrostatin-1	RIP1 inhibitor; upregulates LONP1/PINK1.	Promoting mitochondrial health in viral infection.	[42]
Mitochondrial Dynamics	Mdivi-1	Inhibits DRP1 (fission).	Restoring mitochondrial morphology in ZIKV infection.	[18]
Viral Protease Inhibition	Rupintrivir analogs	Inhibits 3C protease.	Preventing SNAP29 cleavage in Enterovirus infection.	[23]
Taurine Supplementation	Taurine	Upregulates Parkin (PRKN).	Boosting mitophagy against HSV-1.	[8]

Strategic Considerations:
Therapeutic induction of autophagy must be timed precisely. In the early stages of infection (e.g., ZIKV), inducing autophagy might aid viral replication. However, late-stage induction, particularly with agents like Trehalose that enhance lysosomal biogenesis, could overcome the fusion blockade and clear the pathogen. Conversely, in Enteroviral infections where the fusion machinery (SNAP29) is physically cleaved, inducing upstream autophagy without restoring the SNAREs could be disastrous, leading to massive vesicle accumulation and cell death. Thus, restoration of the flux—not just induction—is the goal.

12. Conclusion

The relationship between neurotropic viruses and neuronal autophagy is a study in molecular opportunism and destruction. Viruses do not simply "stop" autophagy; they dissect it. They exploit the membrane-generating capacity of the early pathway to build their replication

factories, while systematically dismantling the fusion and degradation machinery to ensure their survival. Whether through the steric sequestration of Beclin-1 by HSV-1, the metabolic reprogramming by ZIKV, or the proteolytic cleavage of SNAREs by Enteroviruses, the outcome is a neuron choked by its own waste.

This viral subversion provides a unifying mechanism for the diverse clinical presentations of neuroinvasive disease, from the acute inflammation of encephalitis to the slow degeneration of ALS and Alzheimer's. The viral inhibition of autophagy leads to the accumulation of neurotoxic aggregates, the persistence of dysfunctional mitochondria, and the disruption of axonal transport—the very hallmarks of neurodegeneration. As we unravel the specific molecular interfaces of this blockade, we not only gain insight into viral pathogenesis but also uncover the potential viral etiology of diseases long considered purely genetic or sporadic. Restoring the flow of neuronal autophagy may therefore represent the key to treating both acute viral encephalitis and the chronic neurodegenerative sequelae that follow.

Works cited

1. Unraveling the complexities of neurotropic virus infection and immune evasion | Microbiology and Molecular Biology Reviews, accessed November 19, 2025, https://journals.asm.org/doi/abs/10.1128/mmbr.00185-23
2. Therapeutic targeting of autophagy in neurodegenerative and infectious diseases | Journal of Experimental Medicine | Rockefeller University Press, accessed November 19, 2025, https://rupress.org/jem/article/212/7/979/41860/Therapeutic-targeting-of-autophagy-in
3. Neurotropic virus infection and neurodegenerative diseases: Potential roles of autophagy pathway - PMC - PubMed Central, accessed November 19, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC11163195/
4. Autophagy and viral neurovirulence - PMC - PubMed Central - NIH, accessed November 19, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC2737270/
5. Autophagy in Viral Infection and Pathogenesis - Frontiers, accessed November 19, 2025, https://www.frontiersin.org/journals/cell-and-developmental-biology/articles/10.3389/fcell.2021.766142/full
6. A neuron-specific role for autophagy in antiviral defense against herpes simplex virus - PMC, accessed November 19, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC3454454/
7. When autophagy meets viruses: a double-edged sword with functions in defense and offense - PMC - PubMed Central, accessed November 19, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC3169181/
8. Inhibition of mitophagy via the EIF2S1-ATF4-PRKN pathway contributes to viral encephalitis, accessed November 19, 2025, https://www.researchgate.net/publication/382859786_Inhibition_of_mitophagy_via_the_EIF2S1-ATF4-PRKN_pathway_contributes_to_viral_encephalitis
9. Herpes Simplex Virus type 1 inhibits autophagy in glial ... - Frontiers, accessed

November 19, 2025, https://www.frontiersin.org/journals/microbiology/articles/10.3389/fmicb.2024.1411655/full
10. Inhibition of mitophagy via the EIF2S1-ATF4-PRKN pathway contributes to viral encephalitis, accessed November 19, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC12225914/
11. Pseudorabies virus infection triggers mitophagy to dampen the interferon response and promote viral replication | Journal of Virology, accessed November 19, 2025, https://journals.asm.org/doi/10.1128/jvi.01048-24
12. Role of Autophagy in Zika Virus Infection and Pathogenesis | Request PDF - ResearchGate, accessed November 19, 2025, https://www.researchgate.net/publication/319618561_Role_of_Autophagy_in_Zika_Virus_Infection_and_Pathogenesis
13. Role of Autophagy in Zika Virus Infection and Pathogenesis - PMC - NIH, accessed November 19, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC5844781/
14. Mechanistic Target of Rapamycin Signaling Activation Antagonizes Autophagy To Facilitate Zika Virus Replication - ASM Journals, accessed November 19, 2025, https://journals.asm.org/doi/10.1128/jvi.01575-20
15. Zika virus impairs autophagic flux in trabecular meshwork, and inhibition of autophagy restricts ocular viral transmission and associated pathology - PubMed, accessed November 19, 2025, https://pubmed.ncbi.nlm.nih.gov/40920489/
16. Inhibition of autophagy limits vertical transmission of Zika virus in pregnant mice, accessed November 19, 2025, https://rupress.org/jem/article/214/8/2303/42540/Inhibition-of-autophagy-limits-vertical
17. Zika virus depletes neural stem cells and evades selective autophagy by suppressing the Fanconi anemia protein FANCC - EMBO Press, accessed November 19, 2025, https://www.embopress.org/doi/10.15252/embr.201949183
18. Zika Virus-Induced Neuronal Apoptosis via Increased Mitochondrial Fragmentation, accessed November 19, 2025, https://www.frontiersin.org/journals/microbiology/articles/10.3389/fmicb.2020.598203/full
19. Zika virus modulates mitochondrial dynamics, mitophagy, and mitochondria-derived vesicles to facilitate viral replication in trophoblast cells - NIH, accessed November 19, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC10539660/
20. West Nile virus capsid protein inhibits autophagy by AMP-activated protein kinase degradation in neurological disease development - PubMed Central, accessed November 19, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC6977728/
21. West Nile virus capsid protein inhibits autophagy by AMP-activated protein kinase degradation in neurological disease development - PubMed, accessed November 19, 2025, https://pubmed.ncbi.nlm.nih.gov/31971978/
22. Enteroviruses Remodel Autophagic Trafficking through Regulation of Host SNARE Proteins to Promote Virus Replication and Cell Exit - NIH, accessed November 19, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC5894509/

23. Enteroviral Infection Inhibits Autophagic Flux via Disruption of the SNARE Complex to Enhance Viral Replication - PubMed, accessed November 19, 2025, https://pubmed.ncbi.nlm.nih.gov/29562184/
24. Oh, SNAP! How enteroviruses redirect autophagic traffic away from degradation - PMC - NIH, accessed November 19, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC6103677/
25. The interplay of autophagy and enterovirus - PMC - PubMed Central - NIH, accessed November 19, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC7102577/
26. Coxsackievirus B3 subversion of the autophagy pathway - UBC Library Open Collections, accessed November 19, 2025, https://open.library.ubc.ca/soa/clRcle/collections/ubctheses/24/items/1.0398451
27. Enterovirus 71 induces neural cell apoptosis and autophagy through promoting ACOX1 downregulation and ROS generation - PMC - PubMed Central, accessed November 19, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC7250321/
28. Autophagy and Apoptosis in Rabies Virus Replication - PMC - PubMed Central - NIH, accessed November 19, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC10814280/
29. Bif-1c Attenuates Viral Proliferation by Regulating Autophagic Flux Blockade Induced by the Rabies Virus CVS-11 Strain in N2a Cells | Microbiology Spectrum - ASM Journals, accessed November 19, 2025, https://journals.asm.org/doi/10.1128/spectrum.03079-22
30. TRIM44 Promotes Rabies Virus Replication by Autophagy-Dependent Mechanism - MDPI, accessed November 19, 2025, https://www.mdpi.com/1422-0067/25/9/4616
31. HIV Nef-mediated Ubiquitination of BCL2: Implications in Autophagy and Apoptosis - Frontiers, accessed November 19, 2025, https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2021.682624/full
32. HIV-1 Tat Alters Neuronal Autophagy by Modulating Autophagosome Fusion to the Lysosome: Implications for HIV-Associated Neurocognitive Disorders - PubMed Central, accessed November 19, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC4315828/
33. Friends and Foes: The Ambivalent Role of Autophagy in HIV-1 Infection - MDPI, accessed November 19, 2025, https://www.mdpi.com/1999-4915/16/4/500
34. Chikungunya virus–induced autophagy delays caspase-dependent cell death - PMC, accessed November 19, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC3348111/
35. Role of autophagy during the replication and pathogenesis of common mosquito-borne flavi- and alphaviruses - PMC - PubMed Central, accessed November 19, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC6451359/
36. Role of autophagy during the replication and pathogenesis of common mosquito-borne flavi- and alphaviruses | Open Biology - Journals, accessed November 19, 2025, https://royalsocietypublishing.org/doi/10.1098/rsob.190009
37. Human pegivirus alters brain and blood immune and transcriptomic profiles of patients with Parkinson's disease - JCI Insight, accessed November 19, 2025,

https://insight.jci.org/articles/view/189988
38. Enteroviral Infection: The Forgotten Link to Amyotrophic Lateral Sclerosis? - Frontiers, accessed November 19, 2025, https://www.frontiersin.org/journals/molecular-neuroscience/articles/10.3389/fnmol.2018.00063/full
39. Autophagy and ALS: mechanistic insights and therapeutic implications - PMC, accessed November 19, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC8942428/
40. Full article: Autophagy and ALS: mechanistic insights and therapeutic implications, accessed November 19, 2025, https://www.tandfonline.com/doi/full/10.1080/15548627.2021.1926656
41. Zika Virus Is Transmitted in Neural Progenitor Cells via Cell-to-Cell Spread, and Infection Is Inhibited by the Autophagy Inducer Trehalose - ASM Journals, accessed November 19, 2025, https://journals.asm.org/doi/10.1128/jvi.02024-20
42. Mitophagy-associated programmed neuronal death and neuroinflammation - PMC, accessed November 19, 2025, https://pmc.ncbi.nlm.nih.gov/articles/PMC11479883/