Review

Xenophagy-Evasion Mechanisms by Intracellular Pathogens in Bacteria, Viruses, and Parasites

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Abstract: Autophagy is an essential process for maintaining cellular homeostasis. Xenophagy, a key defense mechanism, selectively degrades and eliminates pathogens such as bacteria, viruses, and parasites that have invaded the host. Host cells mark pathogens through ubiquitination. These marked pathogens are then recognized by autophagy receptors and sequestered within autophagosomes. The autophagosomes then fuse with lysosomes for degradation. However, many pathogens have evolved strategies to evade or suppress xenophagy at each step to survive the host defense system. This review outlines the molecular mechanisms of autophagy and summarizes recent research on how bacteria, viruses, and parasites evade xenophagy to cause disease. Pathogens utilize various proteins and mechanisms to do so, including removing ubiquitin chains, blocking access to autophagy receptors, and interfering with autophagosome formation and fusion. Understanding these host-pathogen interactions provides important clues for discovering new therapeutic targets for preventing and treating infectious diseases and for developing strategies to overcome drug resistance.

Keywords: autophagy; xenophagy; infectious disease; xenophagy evasion

1. Introduction

Autophagy is a process that maintains cellular homeostasis by degrading damaged or dysfunctional intracellular components via a lysosome-dependent pathway. Depending on its mechanism of action, autophagy is categorized into three types: macroautophagy, chaperone-mediated autophagy (CMA), and microautophagy [1]. Macroautophagy has been the most intensively studied of these. Macroautophagy can be divided into non-selective autophagy, which degrades bulky cellular components, and selective autophagy, which degrades specific cargo [2]. Selective autophagy mediated by soluble autophagy receptors (SARs), such as p62, optineurin (OPTN), neighbor of BRCA1 gene 1 (NBR1), and nuclear dot protein 52 kDa (NDP52), involves an E3 ligase attaching a ubiquitin tag to cargo to be degraded. Then, SARs bind to the ubiquitin tag. The cargo is then enveloped by an isolation membrane called a phagophore, which closes to form a double-membrane autophagosome [3]. The autophagosome then fuses with a lysosome for degradation [4]. Depending on the cargo being degraded, this selective autophagy is named differently: aggrephagy for removing aggregates, melanophagy for removing melanosomes, mitophagy for removing mitochondria, and xenophagy for removing pathogens that have entered from outside [5–8]. Xenophagy is unique among these various forms of selective autophagy because it removes substances that have entered the cell from outside, rather than substances that originate within the cell. Xenophagy is derived from the Greek words xeno (stranger) and phagein (to eat) and refers to the process of selectively breaking down pathogens, such as bacteria, viruses, and parasites, that invade host cells [9]. However, many pathogens have evolved to evade or disrupt these processes; those that survive ultimately cause infectious diseases [10,11].

According to some reports, deaths caused by antimicrobial resistance (AMR) pathogens have already been identified as one of the major causes of death. Thus AMR pathogens are considered one of the most dangerous potential future disease [12,13]. Consequently, strategies to bolster the body's own defense mechanism for treatment have been investigated, and approaches to eliminate pathogens via xenophagy are under active research [14].

In order for a pathogen to cause an infectious disease with meaningful symptoms in humans, it must first proliferate to a certain dose [15–17]. Subsequently, cell lysis occurs during toxin secretion or host cell escape, damaging surrounding tissues [18–20]. Therefore, to effectively limit pathogen proliferation and survival, which are prerequisites for infectious diseases, a rapid clearance mechanism is necessary at the cellular level. In this context, the host appropriately performs this process through xenophagy [21,22]. The importance of xenophagy is reflected by its ubiquity in non-immune cells, such as epithelial cells [23,24], and by the fact that pathogens have evolved various strategies to evade, suppress, and even utilize xenophagy-related molecules [25].

The goal of this review is to improve our understanding of the mechanisms by which pathogens interact with host defense mechanisms. To achieve this, the review explains the concept of xenophagy and summarizes pathogen-specific diseases and xenophagy evasion strategies. This expanded knowledge will provide valuable insights for developing new strategies to prevent and treat infectious diseases.

2. Molecular Mechanism of Selective Autophagy

Selective autophagy is a mechanism that maintains cellular homeostasis by degrading intracellular protein aggregates, pathogens, and damaged organelles. Unlike non-selective autophagy, which randomly degrades cytoplasmic components, SARs-mediated selective autophagy degrades specific cargo, which is recognized by autophagy receptors [4,26]. Ubiquitination involves the attachment of poly-ubiquitin chains to the surface of cargo by E3 ligases, such as RING finger and CHY zinc finger domain-containing protein 1 (RCHY1), leucine rich repeat and sterile alpha motif containing 1 (LRSAM1), and SMAD ubiquitination regulatory factor 1 (SMURF1) [27–29]. These poly-ubiquitin chains act as a kind of “eat-me” signal and are recognized by soluble autophagy receptors [30]. These receptors include p62, NBR1, NDP52, and OPTN. They have two domains in common: One is the microtubule-associated protein 1A/1B-light chain 3 (LC3)-interacting region (LIR) domain, which binds to LC3 on the phagophore membrane. The other is the ubiquitin-binding domain (UBD), which recognizes and binds to poly-ubiquitin chains on cargo [31]. Although the endoplasmic reticulum (ER) is known to be a major membrane source, it is now widely understood that phagophores can be generated from various different membrane sources inside the cell [32]. The autophagic process is orchestrated by a highly conserved set of autophagy-related (ATG) proteins. Membrane initiation primarily occurs at a specialized, phosphatidylinositol 3-phosphate (PI3P)-enriched subdomain of the ER, known as the omegasome. When omegasomes form in the ER, ATG9 vesicles supply lipids in a Rab1-dependent manner, leading to membrane elongation [33–35]. The formation of these phagophores is regulated by intracellular energy status and signaling pathways. While autophagy is induced by diverse cellular stresses, energy depletion specifically elevates the AMP/ATP ratio, which activates AMP-activated protein kinase (AMPK) to subsequently phosphorylate and activate Unc-51-like autophagy activating kinase 1 (ULK1) [36]. The ULK1 complex (ULK1, ATG13, FIP200, and ATG101) then recruits and activates the class 3 phosphoinositide 3-kinase (PI3K) complex (Beclin-1, VPS34, VPS15, and ATG14) through phosphorylation [37]. Vacuolar protein sorting 34 (VPS34) within the activated PI3K complex produces PI3P at the omegasome, providing a docking platform for WD repeat domain phosphoinositide-interacting protein 1/2 (WIPI1/2) localization [38]. WIPI1/2 recruits the ATG12-ATG5-ATG16L1 complex and is involved in LC3 lipidation. LC3 initially exists in the pro-LC3 form, which is cleaved by ATG4 to form LC3-I. The ATG12-ATG5-ATG16L1 complex then lipidates LC3-I to form LC3-II, which is anchored to the phagophore membrane [39]. The LC3 protein on the phagophore membrane then binds to the LIR domain of the autophagy receptor, sequestering the cargo. Once the phagophore has completely engulfed the cargo, it matures into an autophagosome. The autophagosome then fuses with a lysosome to form an autolysosome, where the cargo is degraded [32]. (Figure 1).

This selective autophagy system is used to remove both damaged cellular organelles and pathogens that have invaded the cell. Pathogens exposed to the cytoplasm are marked by a process called ubiquitination, which is specifically recognized by autophagy receptors. The process by which these pathogens are delivered to the phagophore for removal is called xenophagy and functions as a core defense mechanism of the cell.

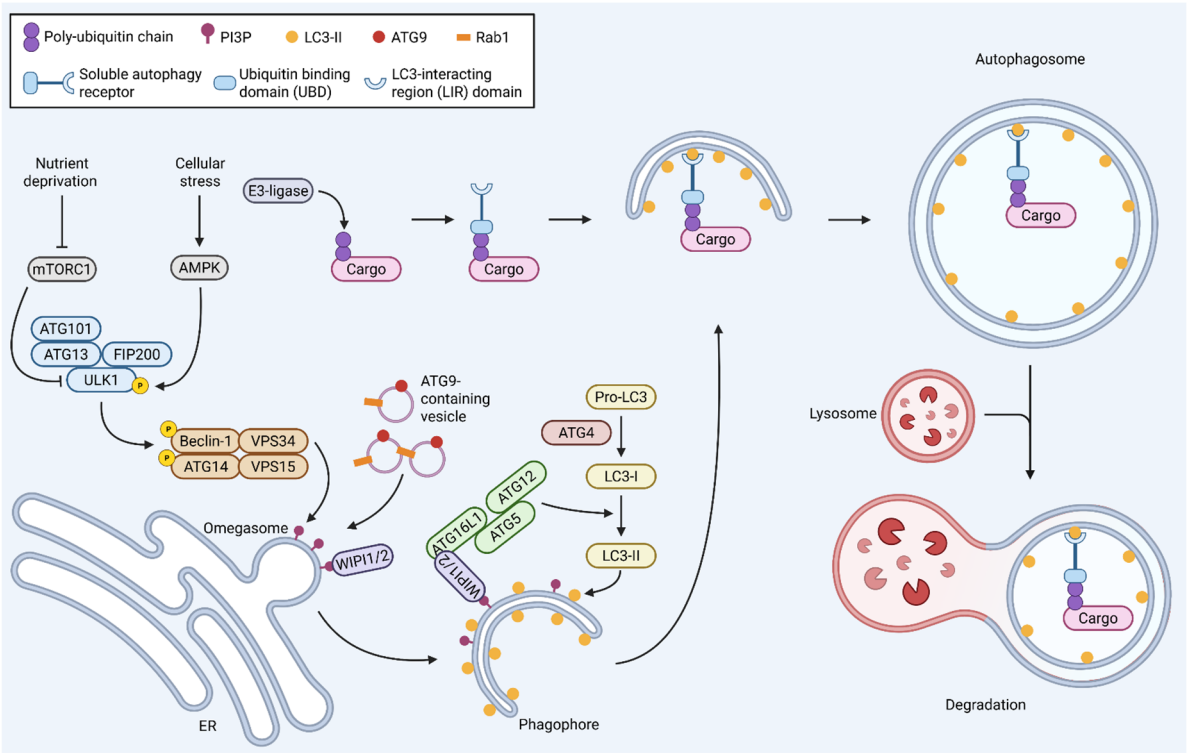

Figure 1. Overview of selective autophagy. Autophagy can be induced by diverse cellular stresses including nutrient deprivation, hypoxia, and energy depletion. Under energy stress, AMPK is activated and, together with mTORC1 inhibition, sequentially activates the ULK1 and class 3 PI3K complexes to form a phagophore. LC3-I is formed by ATG4 and then converted to LC3-II through the lipidation of the ATG12-ATG5-ATG16L1 complex. LC3-II is then anchored to the phagophore. Cargo that has been ubiquitinated by an E3 ligase is recognized by a soluble autophagy receptor and engulfed by the phagophore. The fully mature autophagosome then fuses with the lysosome to degrade the cargo. mTORC1: mechanistic target of rapamycin complex 1; AMPK: AMP-activated protein kinase; ATG: autophagy-related; FIP200: FAK family kinase-interacting protein of 200 kDa; ULK1: Unc-51-like autophagy activating kinase 1; VPS: Vacuolar protein sorting; WIPI1/2: WD repeat domain phosphoinositide-interacting protein 1/2; PI3P: phosphatidylinositol 3-phosphate. Created in BioRender. Kim, M. (2026) https://BioRender.com/ghz990k (accessed on 10 March 2026).

3. Xenophagy Evasion Mechanisms of Bacteria

Xenophagy is a key host defense mechanism that selectively recognizes and eliminates intracellularly invasive bacteria. However, many bacteria have evolved mechanisms to evade or disrupt xenophagy. Failure to eliminate bacteria due to these mechanisms can lead to severe infectious diseases. (Table 1).

Table 1. Xenophagy evasion mechanisms of bacteria.

Bacteria	Evasion Mechanism	Diseases	Reference
Salmonella enterica	SseL removes ubiquitin chains. SifA stabilizes SCV membrane	Salmonellosis, Typhoid fever	[40,41]
Shigella flexneri	IcsB blocks IcsA-Atg5 interaction. VirA blocks the supply of membrane sources	Shigellosis	[42–45]
Listeria monocytogenes	ActA and InlK coat the bacterial surface, physically blocking ubiquitination.	Listeriosis	[46,47]
Mycobacterium tuberculosis	Eis induces the degradation of LC3-II by inhibiting ROS production. miR-33 inhibits ATG5 expression.	Tuberculosis	[48–50]
Streptococcus pyogenes	SLO damages the autophagosome membrane. SpeB induces the degradation of autophagy receptors.	Pharyngitis, Necrotizing fasciitis	[51,52]
Legionella pneumophila	LotA removes ubiquitin chains. RavZ cleaves LC3-II.	Legionnaires' disease	[53,54]
Escherichia coli	Upregulates miR-30c/miR-130a to suppress ATG5/ATG16L1. Upregulates miR-18 to impair SUMOylation via PIAS3	Crohn's disease	[55,56]

3.1. Salmonella enterica

Salmonella enterica is a bacterium that causes salmonellosis and typhoid fever in humans [57]. Through the Type III secretion system (T3SS), *Salmonella* injects effector proteins, such as *Salmonella* outer protein E (SopE) and *Salmonella* outer protein E2 (SopE2), into host cells. This process induces membrane ruffling in the host cell, allowing *Salmonella* to enter the host cell and form *Salmonella*-containing vacuoles (SCVs) [58]. *Salmonella* primarily multiplies in SCVs, but escapes into the cytoplasm when the membrane is damaged by the T3SS. Galectin-8 then binds to glycans on the damaged SCV membrane and recruits the autophagy receptor NDP52 [59]. The exposed bacterial surface, particularly lipopolysaccharide (LPS), is ubiquitinated by E3 ligases such as LRSAM1 and ring finger protein 213 (RNF213). Notably, RNF213 directly ubiquitylates the lipid A moiety of bacterial LPS, generating a unique non-protein "eat-me" signal that facilitates xenophagy [60]. These ubiquitinated *Salmonella* are recognized by autophagy receptors, including NDP52, p62, and OPTN [61]. NDP52 then recruits FAK family kinase-interacting protein of 200 kDa (FIP200), activating the ULK1 complex and promoting phagophore formation. [62]. However, *Salmonella* secretes proteins, such as *Salmonella*-secreted effector L (SseL) and *Salmonella*-induced filament A (SifA), to evade xenophagy. SseL is a deubiquitinase that removes ubiquitin chains from the Salmonella surface, thereby blocking access to autophagy receptors [40]. SifA stabilizes the SCV membrane structurally, which inhibits membrane damage and prevents recognition by Galectin-8 [41]. (Figure 2A) Additionally, endomembrane damage also triggers the V-ATPase-ATG16L1 axis, which initiates both canonical xenophagy and non-canonical LC3 lipidation on single membranes (CASM) [63]. However, the effector protein *Salmonella* outer protein F (SopF) potently blocks xenophagy and CASM. SopF, activated by host ADP-ribosylation factor (ARF) GTPases, ADP-ribosylates the V0c subunit of host V-ATPase at Gln124. This modification disrupts the V-ATPase-ATG16L1 interaction, preventing ATG16L1 recruitment to damaged membranes and inhibiting autophagic clearance [64]. Furthermore, Salmonella targets ER-phagy (reticulophagy) by inhibiting the ER-phagy receptors Family with sequence similarity 134 member B (FAM134B) and reticulophagy regulator 1 (RETREG1), thereby preventing ER fragmentation and turnover that would otherwise restrict bacterial replication [65,66]. These layered mechanisms allow Salmonella to evade both cytosolic xenophagy and ER-derived membrane stress responses.

3.2. Shigella flexneri

Shigella flexneri is a bacterium that causes shigellosis in humans [67]. It passes through M cells in the intestine, migrates to the lamina propria, and attaches to the basolateral membrane of epithelial cells. Then, using the T3SS, *Shigella* injects effector proteins, including invasion plasmid antigen B (IpaB) and invasion plasmid antigen C (IpaC), into the host cell. IpaC then induces membrane ruffling, enabling *Shigella* to enter the host cell. IpaB disrupts the vesicle membrane containing *Shigella*, enabling it to escape into the cytoplasm [68]. *The Shigella* surface protein intracellular spreading A (IcsA) induces actin polymerization, facilitating the spread of Shigella into neighboring cells. Simultaneously, host ATG5 recognizes IcsA through a ubiquitin-independent pathway by directly binding to it, forming a phagophore [42,69]. However, *Shigella* evades xenophagy by secreting IcsB, which competitively binds to IcsA and ATG5 [42,43]. Additionally, *Shigella* secretes virulence protein A (VirA), which blocks the membrane source required for phagophore formation [44,45]. Phagophore formation requires a continuous supply of ATG9-containing vesicles, a process managed by Rab1. However, VirA inactivates Rab1, thereby blocking ATG9 vesicle trafficking and consequently inhibiting phagophore formation [45]. (Figure 2B).

3.3. Listeria monocytogenes

Listeria monocytogenes is a bacterium that causes listeriosis in humans [70]. It attaches to host cells using the surface proteins called internalin A (InlA) and internalin B (InlB). These proteins bind to E-cadherin or c-Met, which induces endocytosis of the host cell [71]. Once inside the cell, *Listeria* secrete the pore-forming toxin listeriolysin O (LLO), which forms pores in the vesicle membrane, allowing *Listeria* to escape into the cytoplasm [72]. In the cytoplasm, E3-ligases such as LRSAM1 and Parkin ubiquitinate *Listeria*, and p62, NDP52, etc., recognize the ubiquitinated *Listeria* and induce xenophagy [73]. However, *Listeria* evades xenophagy by utilizing the surface proteins actin assembly-inducing protein A (ActA) and internalin K (InlK). ActA recruits the host actin-related protein 2/3 (Arp2/3) complex and vasodilator-stimulated phosphoprotein (VASP), which induces host actin polymerization and forms an actin tail on the Listeria surface. This actin tail interferes with ubiquitination and physically blocks access to autophagy receptors [46]. InlK proteins bind to the host's major vault protein (MVP) and coat the bacterial surface, physically blocking access to ubiquitination and autophagy receptors [47]. (Figure 2C).

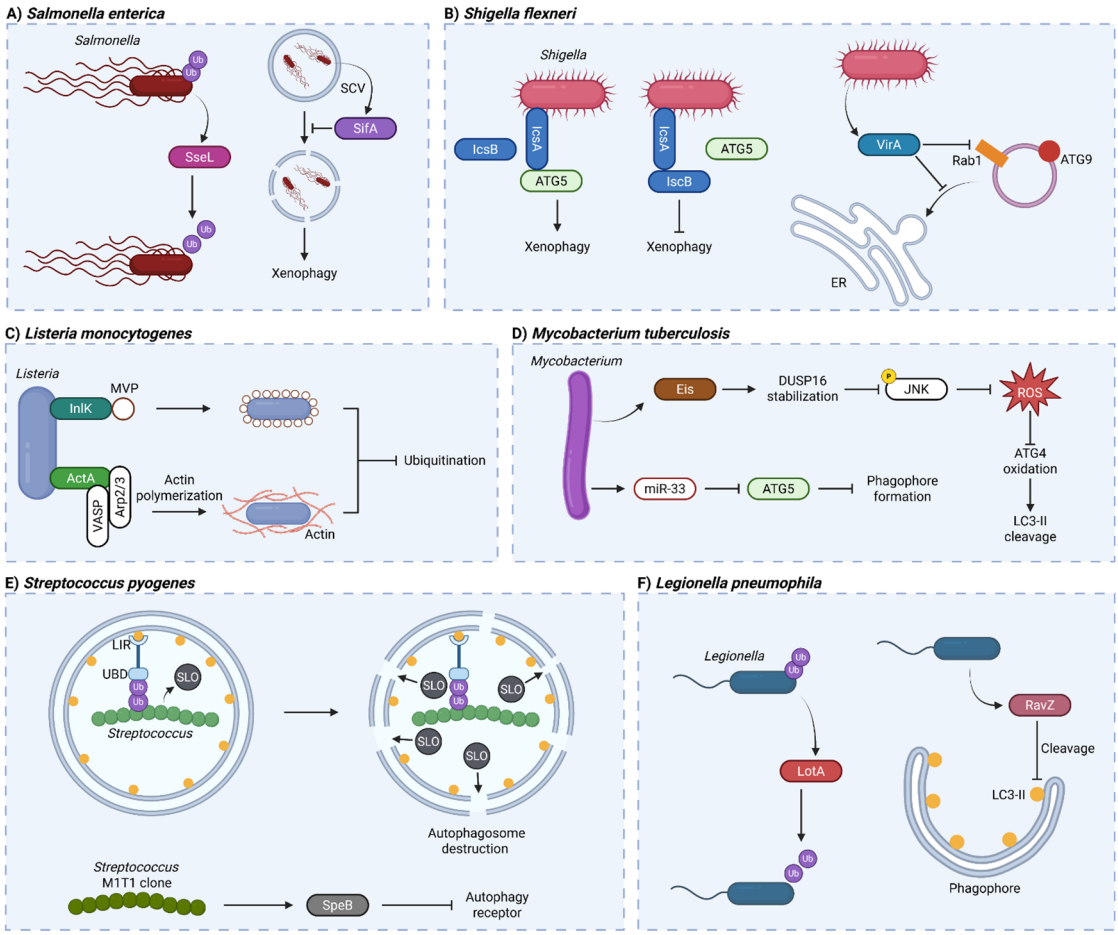

Figure 2. Overview of xenophagy evasion mechanisms of various bacteria. (**A**) *Salmonella* removes polyubiquitin chains through SseL and SCV through SifA, thereby preventing exposure to the cytosol. (**B**) *Shigella* secretes IcsB, which binds to and inhibits the binding of ATG5 to IcsA. *Shigella* also secretes VirA, which inhibits Rab1. Rab1 is responsible for trafficking ATG9 vesicles. (**C**) *Listeria* physically inhibits ubiquitination by binding to the host MVP through its surface InlK and to the host Arp2/3 and VASP through its ActA, thereby coating the surface. (**D**) *Mycobacterium* stabilizes DUSP16 via Eis, which inhibits JNK activity. This inhibits ROS generation, leading to decreased ATG4 oxidation and inducing the cleavage of LC3-II. Furthermore, mycobacterial infection upregulates host miR-33 expression, which represses ATG5 expression. (**E**) *Streptococcus* secretes SLO to destroy autophagosomes. The Streptococcus M1T1 clone secretes SpeB, which directly degrades autophagy receptors. (**F**) *Legionella* removes polyubiquitin chains through LotA and directly cleaves LC3-II through RavZ. SseL: *Salmonella*-secreted effector L; SCV: *Salmonella*-containing vacuoles; SifA: *Salmonella*-induced filament A; IcsA: intracellular spreading A; IcsB: intracellular spreading B; ATG5: autophagy-related 5; VirA: virulence protein A; MVP: major vault protein; InlK: internalin K; Arp2/3: ActA recruits the host actin-related protein 2/3; VASP: vasodilator-stimulated phosphoprotein; ActA: assembly-inducing protein A; DUSP16: dual-specificity phosphatase 16; Eis: enhanced intracellular survival; JNK: c-Jun N-terminal kinase; ROS: reactive oxygen species; SLO: streptolysin O; SpeB: Streptococcal pyrogenic exotoxin B; LotA: *Legionella* OTU-like effector A; RavZ: region allowing vacuole colocalization protein Z. Created in BioRender. Kim, M. (2026) https://BioRender.com/pntvvsw (accessed on 10 March 2026).

3.4. Mycobacterium tuberculosis

Mycobacterium tuberculosis is a bacterium that causes tuberculosis in humans [74]. It enters host cells by inducing phagocytosis and primarily multiplies within the phagosomes of alveolar macrophages [75]. *Mycobacterium* secretes the proteins, early secreted antigenic target of 6 kDa (ESAT-6), and culture filtrate protein 10 kDa (CFP-10) via the type VII secretion system (T7SS). This process forms pores in the phagosome membrane, allowing the bacterium to escape into the cytoplasm [76,77]. Once in the cytoplasm, the bacteria are ubiquitinated by E3 ligases, such as Smad ubiquitination regulatory factor 1 (Smurf1), Parkin, and tripartite motif-containing protein 32 (Trim32), and recognized by autophagy receptors [29,78,79]. The bacterium evades xenophagy using proteins such as enhanced intracellular survival (Eis) and microRNA. Eis is an N-acetyl transferase that stabilizes

the host dual-specificity phosphatase 16 (DUSP16) [48]. This inhibits the activity of c-Jun N-terminal kinase (JNK) and suppresses reactive oxygen species (ROS) production. Suppressing ROS production reduces the oxidation of ATG4, which leads to the cleavage of LC3-II and consequently evades xenophagy [49]. Upon *Mycobacterium* infection, the expression of miR-33 increases in host cells, and miR-33 suppresses ATG5 expression, thereby inhibiting phagophore formation [50]. (Figure 2D) Additionally, membrane Atg8ylation (the conjugation of ATG8 family proteins such as LC3 directly to single membranes or damaged organelles) has emerged as a broader host-protective mechanism against *Mycobacterium* beyond canonical double-membrane autophagy. Atg8ylation acts as an immediate response to phagosomal membrane damage and remodeling, restricting bacterial escape into the cytosol and coordinating multiple antimicrobial outputs. Genetic studies with complete ATG gene inactivation now clearly demonstrate that multiple ATG proteins involved in Atg8ylation are essential for host defense against *Mycobacterium* [80].

3.5. Streptococcus pyogenes

Streptococcus pyogenes is a bacterium that causes various human diseases, ranging from simple pharyngitis to necrotizing fasciitis [81]. *Streptococcus* uses its M protein surface protein to attach to and invade host cells by inducing endocytosis [82]. Once inside the cell, the bacteria secrete the pore-forming toxin streptolysin O (SLO), which forms pores in the vesicle membrane, allowing the bacteria to escape into the cytoplasm [51]. *Streptococcus* that are exposed to the cytosol are recognized and ubiquitinated by E3 ligases. However, *S. pyogenes* evades xenophagy by damaging the autophagosome membrane through SLO[51]. Furthermore, *Streptococcus* M1T1 clone secretes streptococcal pyrogenic exotoxin B (SpeB), a cysteine protease that degrades autophagy receptors such as p62, NBR1, and NDP52. This allows the bacteria to evade xenophagy [52]. (Figure 2E).

3.6. Legionella pneumophila

Legionella pneumophila is a bacterium that causes Legionnaires' disease [83]. It enters host cells by inducing phagocytosis [84]. After invading a host cell, *Legionella* forms a *Legionella*-containing vacuole (LCV) inside which it becomes sequestered. The bacterium then secretes over 300 effector proteins into the host cell via the type IV secretion system (T4SS), which disrupts the LCV membrane and allows the bacterium to escape into the cytoplasm [85]. Once in the cytoplasm, *Legionella* is ubiquitinated by E3 ligases, such as RNF213 and LRSAM1, and recognized by autophagy receptors [86]. However, *Legionella* evades xenophagy using proteins such as the *Legionella* OTU-like effector A (LotA) and region allowing vacuole colocalization protein Z (RavZ) proteins. LotA is a deubiquitinase that removes ubiquitin chains from the surface of *Legionella*, thereby blocking access to autophagy receptors [53]. Additionally, RavZ specifically cleaves LC3-II, thereby inactivating LC3 and blocking autophagosome formation [54]. (Figure 2F) *Legionella* further employs a unique non-canonical ubiquitination strategy. The SidE family effectors (SdeA, SdeB, SdeC, SidE) catalyze phosphoribosyl-linked serine ubiquitination (PR-ubiquitination) on host proteins. Specifically, they PR-ubiquitinate the deubiquitinase ubiquitin-specific peptidase 14 (USP14) at multiple serine residues, impairing its activity and disrupting its interaction with p62. This modification prevents p62 recruitment to the LCV, effectively excluding the autophagy receptor from the bacterial phagosome [87]. The bacterial deubiquitinases deubiquitinases for PR ubiquitination A and B (DupA and DupB) reverse PR-ubiquitination, allowing fine-tuned regulation during infection [88]. These mechanisms allow *Legionella* to camouflage itself from the host autophagy machinery while establishing a replication-permissive vacuole.

3.7. Escherichia coli

Adherent-invasive *Escherichia coli* (AIEC) is strongly associated with Crohn's disease and can invade and replicate within intestinal epithelial cells and macrophages [89]. Unlike typical commensal *Escherichia*, AIEC strains efficiently enter host cells and survive inside phagosomes or in the cytosol. Host cells rely on immunity-related GTPase M (IRGM) and nucleotide-binding oligomerization domain-containing protein 2 (NOD2) to orchestrate antimicrobial autophagy against intracellular *Escherichia*. IRGM directly interacts with the core autophagy machinery, including ULK1 and Beclin-1, and promotes their co-assembly to initiate autophagosome formation. NOD2 senses bacterial peptidoglycan at the site of bacterial entry and recruits ATG16L1, further enhancing K63-linked ubiquitination of IRGM and amplifying the autophagic response [90]. However, AIEC actively subverts this xenophagy pathway. It upregulates host microRNAs miR-30c and miR-130a, which suppress the expression of ATG5 and ATG16L1, thereby inhibiting autophagosome formation [55]. Additionally, AIEC actively impairs host SUMOylation by upregulating the host microRNA miR-18, which targets and downregulates the small ubiquitin related modifier (SUMO) E3 ligase protein inhibitor of activated STAT protein 3 (PIAS3).

SUMOylation is essential for the stability and proper function of key autophagy proteins such as Beclin-1 and ATG16L1, enabling their assembly into the autophagy initiation complex. Consequently, the resulting decrease in SUMO-conjugated proteins inhibits autophagosome formation, allowing AIEC to evade lysosomal degradation and replicate intracellularly [56].

4. Xenophagy Evasion Mechanisms of Viruses

Host cells recognize the viral capsid and nucleic acids, ubiquitinate them, and recruit adapter proteins to isolate them in an autophagosome. Xenophagy, the process by which viruses are eliminated through lysosomal fusion, is an evolutionarily conserved innate defense mechanism. In response, viruses have evolved strategies to evade or disrupt xenophagy to ensure their survival. Failure to eliminate viruses can result in disease. (Table 2).

Table 2. Xenophagy evasion mechanisms of viruses.

Viruses	Evasion Mechanism	Diseases	Reference
HCMV	TRS1, IRS1 bind to Beclin-1, Inhibiting autophagosome initiation	Central nervous system disease, Congenital malformations	[91–95]
HSV-1	ICP34.5 binds to Beclin-1, inhibiting autophagosome formation	Herpes simplex encephalitis (HSE)	[96–99]
SARS-CoV-2	ORF7a mediates caspase-3-dependent SNAP29 degradation, blocking autophagosome-lysosome fusion	COVID-19	[100–103]
HPV	E7 mediates CAPN2-dependent AMBRA1 degradation, destabilizing PI3K complex	Cervical cancer	[104–109]
HIV-1	Nef promotes TFEB cytosolic sequestration, suppressing autophagy-related gene expression	Acquired immunodeficiency disorder (AIDS)	[110–112]

4.1. Human Cytomegalovirus (HCMV)

Human cytomegalovirus (HCMV) is the leading cause of increased mortality in immunocompromised patients, inducing central nervous system diseases and congenital malformations. Upon HCMV infection, the protein kinase R (PKR) protein in host cells binds to viral double-stranded RNA (dsRNA), undergoes dimerization, and auto-phosphorylates. This subsequently phosphorylates eukaryotic translation initiation factor 2A (eIF2α). Phosphorylated eIF2α inhibits guanine nucleotide exchange factor eukaryotic initiation factor 2B (eIF2B), thereby suppressing protein synthesis in the host cell's ribosomes and inhibiting virus production. HCMV encodes two non-canonical dsRNA-binding proteins: terminal repeat short protein 1 (TRS1) and internal repeat short protein 1 (IRS1). These proteins antagonize PKR autophosphorylation by competitively binding to dsRNA or directly interacting with PKR [91]. This process prevents the inhibition of eIF2B and activates viral replication [92,93]. Furthermore, TRS1 and IRS1 independently inhibit xenophagy; both proteins contain a common N-terminal Beclin-1-binding domain (BBD) that allows them to directly interact with Beclin-1, blocking autophagosome initiation and evading xenophagy [94]. (Figure 3A) Although HCMV actively suppresses autophagy via TRS1 and IRS1, host cells can still target HCMV components for autophagic degradation when these inhibitors are overwhelmed. Autophagy limits HCMV genome replication and virion production, highlighting its role as an antiviral defense [95].

4.2. Herpes Simplex Virus Type 1 (HSV-1)

Herpes simplex virus type 1 (HSV-1) causes herpes simplex, and can infect central nervous system, leading to herpes simplex encephalitis (HSE) in severe cases. During an HSV-1 infection, the PKR in host cells detects the viral double-stranded RNA (dsRNA) and undergoes autophosphorylation, which leads to the phosphorylation of eIF2α. Phosphorylated eIF2α then binds to the translation initiation factor eIF2B protein, which stops protein synthesis in host cells and blocks viral replication [96]. However, the HSV-1 neurovirulence protein infected cell protein 34.5 (ICP34.5) recruits protein phosphatase 1α (PP1α), which dephosphorylates eIF2α despite PKR activation. Consequently, eIF2B is released from eIF2α, enabling viral replication to continue [97]. Additionally, ICP34.5 binds to Beclin-1, which recruits initiation factors and adapter proteins during the early stages of autophagosome formation. This blocks complex assembly and inhibits autophagosome formation [98]. (Figure 3A) Despite ICP34.5-mediated inhibition, xenophagy contributes to the degradation of HSV-1 particles and viral proteins. This autophagic clearance mechanism is particularly important in neuronal cells and explains why ICP34.5 is a critical neurovirulence factor [99].

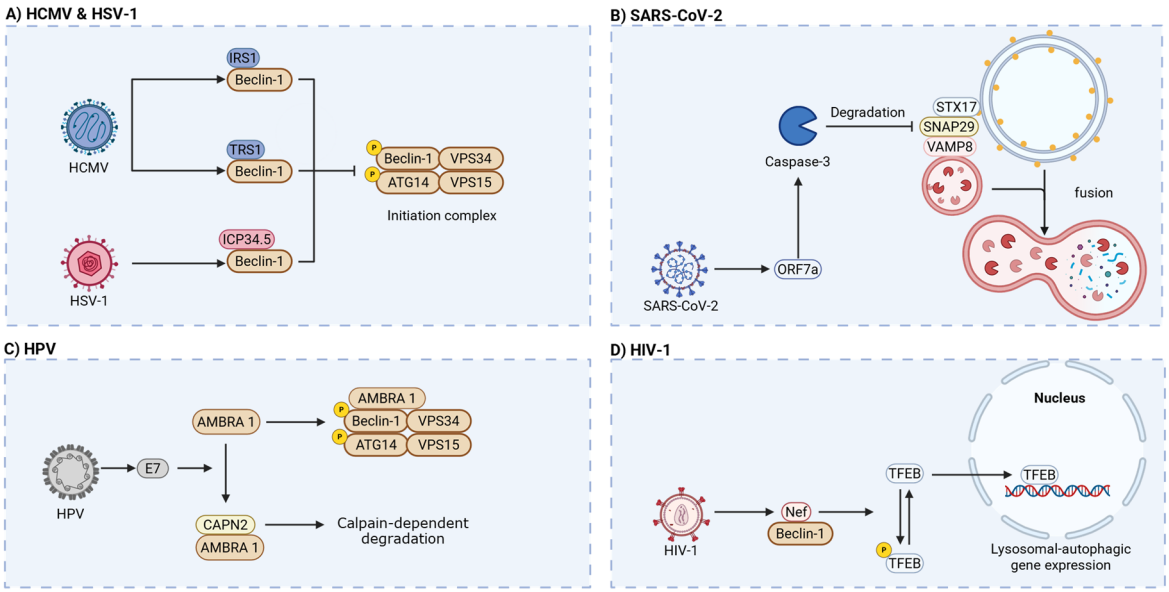

Figure 3. Overview of xenophagy evasion mechanisms of various viruses. (**A**) HCMV-encoded proteins IRS1 and TRS1, as well as the HSV-1 protein ICP34.5, competitively bind to Beclin-1. This interaction prevents the assembly of the autophagy initiation complex (Beclin-1/VPS34/ATG14/AMBRA1) and blocks the formation of autophagosomes. (**B**) The viral protein ORF7a induces the degradation of the soluble N-ethylmaleimide-sensitive-factor attachment protein receptor (SNARE) protein SNAP29, which is essential for membrane fusion. This inhibits the fusion of autophagosomes with lysosomes and prevents the degradation of viral components. (**C**) The HPV protein E7 promotes the calpain-dependent degradation of AMBRA1. The loss of AMBRA1 destabilizes the Beclin-1 complex, leading to its dissociation and subsequent inhibition of autophagy initiation. (**D**) The HIV-1 protein Nef promotes the phosphorylation of the transcription factor TFEB, sequestering it in the cytoplasm. This prevents TFEB from translocating to the nucleus and suppresses the transcriptional activation of lysosomal and autophagy-related genes. IRS1: internal repeat short protein 1; TRS1: terminal repeat short protein 1; ICP34.5: infected cell protein 34.5; ORF7: open reading frame 7; SNAP29: synaptosomal-associated protein 29; AMBRA1: activating molecule in Beclin1-regulated autophagy 1; Nef: negative regulatory factor; TFEB: transcription factor EB. Created in BioRender. Kim, M. (2026) https://BioRender.com/pcsi1o5 (accessed on 10 March 2026).

4.3. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a severe acute respiratory syndrome coronavirus that caused the COVID-19 pandemic worldwide in 2019 [100]. In addition to structural proteins that form viral particles, SARS-CoV-2 encodes open reading frame (ORF) proteins (ORF3-10) that modulate host responses to facilitate viral activity [101]. Although precise mechanism of ORF7a is not known, ORF7a activates caspase-3, and caspase-3 cleaves synaptosomal-associated protein 29 (SNAP29) by targeting SNAP29 aspartic acid residue 30 (Asp30) [102]. Since SNAP29 mediates fusion between autophagosomes (via syntaxin 17(STX17)) and lysosomes (via vesicle-associated membrane protein 8 (VAMP8)), its cleavage by ORF7a impairs autophagosome-lysosome fusion. Through this mechanism, the virus evades lysosomal degradation and promotes its proliferation [102,103]. (Figure 3B).

4.4. Human Papillomavirus (HPV)

Human papillomavirus (HPV) is a major cause of cervical cancer and has also been linked to non-melanoma skin cancer [104,105]. During an HPV infection, host cells inhibit the mTOR-mediated inhibitory phosphorylation of ULK1 at Ser757 by suppressing AKT, also known as protein kinase B (PKB), phosphorylation at Ser473/Thr308 [60,106]. De-phosphorylated ULK1 then recruits autophagosome complexes, inducing the formation of autophagosomes. However, HPV interacts with epidermal growth factor receptor (EGFR) via host cell membrane heparan sulfate proteoglycans (HSPGs), which causes AKT activation. This ultimately triggers mTOR-mediated ULK1 phosphorylation, thereby blocking autophagosome formation [104]. Additionally, HPV's E7 protein competitively binds to activating molecule in Beclin1-regulated autophagy 1 (AMBRA1), displacing Beclin-1 and inducing its calpain-dependent degradation [107,108]. AMBRA1 normally activates ULK1 via non-degradative ubiquitination and promotes the recruitment of the ULK/Beclin-1-VPS34 complex to initiate autophagy. Therefore, E7-mediated

degradation of AMBRA1 impairs the recruitment of the ULK-mediated autophagy initiation complex and effectively blocks autophagosome initiation [109]. (Figure 3C).

4.5. Human Immunodeficiency Virus-1 (HIV-1)

Human immunodeficiency virus-1 (HIV-1) targets T-lymphocytes, a type of white blood cell. It utilizes them as hosts and subsequently destroys them, leading to acquired immunodeficiency syndrome (AIDS). During HIV-1 infection, the mTOR in host cells is suppressed. This results in the dephosphorylation of transcription factor EB (TFEB) and its translocation into the nucleus. There, TFEB upregulates the expression of autophagy and lysosomal genes [110]. The HIV-1 protein negative regulatory factor (Nef) binds to Beclin-1, a key autophagy regulator, and promotes TFEB phosphorylation. Nef also sequesters TFEB in the cytoplasm [111]. This blocks TFEB-mediated transcription, which inhibits both the initiation of autophagosomes and the fusion of mature autophagosomes with lysosomes [112]. (Figure 3D).

5. Xenophagy Evasion Mechanisms of Parasites

Different parasite species have evolved a variety of strategies to evade host xenophagy. These strategies include targeting different molecules to inhibit the formation of autophagosomes or phagophores to prevent sequestration or the formation of autolysosomes to prevent degradation. (Table 3).

Table 3. Xenophagy evasion mechanisms of parasites.

Parasites	Evasion Mechanism	Diseases	Reference
Leishmania donovani	miR-30a-3p inhibits autophagosome formation by degrading Beclin-1	Visceral leishmaniasis	[113]
Toxoplasma gondii	Inhibition of autolysosome formation by regulating PV membrane components, unlike the host plasma membrane	Toxoplasmosis	[114]
Trypanosoma cruzi	Inhibition of autolysosome formation by interfering with the recruitment of STX17, an autophagosome membrane component	Chagas disease	[115]
Plasmodium spp.	UIS3 competitively binds to LC3, thereby inhibiting phagophore formation.	Malaria	[116]

5.1. Leishmania donovani

Leishmania donovani is a protozoan parasite known to infect host macrophages and cause visceral leishmaniasis in humans [117,118]. In the THP-1 macrophage-like cell line, *L. donovani* infection increases the expression of microRNA miR-30a-3p, which induces the degradation of Beclin-1 mRNA. Beclin-1 is a member of the class 3 PI3K complex formed during autophagy. Thus, miR-30a-3p interferes with the formation of these complexes and suppresses autophagosome formation [113]. (Figure 4A).

5.2. Toxoplasma gondii

Toxoplasma gondii is a parasite that causes toxoplasmosis, which can cause neurological damage and even fetal death in pregnant women [119]. In mice, immunity-related GTPases (IRGs) and guanylate-binding proteins (GBPs) are recruited to the parasitophorous vacuole (PV) membrane that contains the parasite. This causes membrane lysis, and toxoplasma exposed to the cytoplasm are captured by phagocytes and eliminated by lysosomes. However, humans are genetically deficient in IRGs and GBPs, so *T. gondii* is not eliminated [120–122]. Upon *T. gondii* infection, human cells reportedly recruit ubiquitin, autophagy adapters (p62 and NDP52), and LC3 around the PV by interferon-gamma (IFN-γ) activation. These proteins then form multiple membranes through the action of ATG16L1 and ATG7, which function in phagophore elongation. This results in the inhibition of parasite growth [114,123,124]. This may be because the multiple layers limit the space necessary for replication and activity, as well as physically inhibiting the movement of substances, such as nutrients, through the membrane. However, the multiple membranes surrounding the PV do not lead to fusion with late endosomes or lysosomes; thus, the parasite continues to survive. This has been confirmed by immunofluorescence: ubiquitin-positive PVs were lysosomal-associated membrane protein 1 (LAMP-1) negative. However, the molecular mechanism by which *T. gondii* inhibits lysosome fusion remains unclear [114]. (Figure 4B) However, several studies analyzing PV membrane components have shown that, although *T. gondii* forms PVs using the host cell plasma membrane during phagocytosis, the levels of various host cell membrane-derived transmembrane proteins (e.g., CD44, Na+/K+ ATPase, β1-integrin, caveolin-1, transferrin receptors, and mannose-phosphate receptors) are reduced. This

suggests that *T. gondii* selectively excludes host cell-derived transmembrane proteins during PV formation to create a non-fusion compartment and avoid clearance through late endosome and lysosome fusion [125,126].

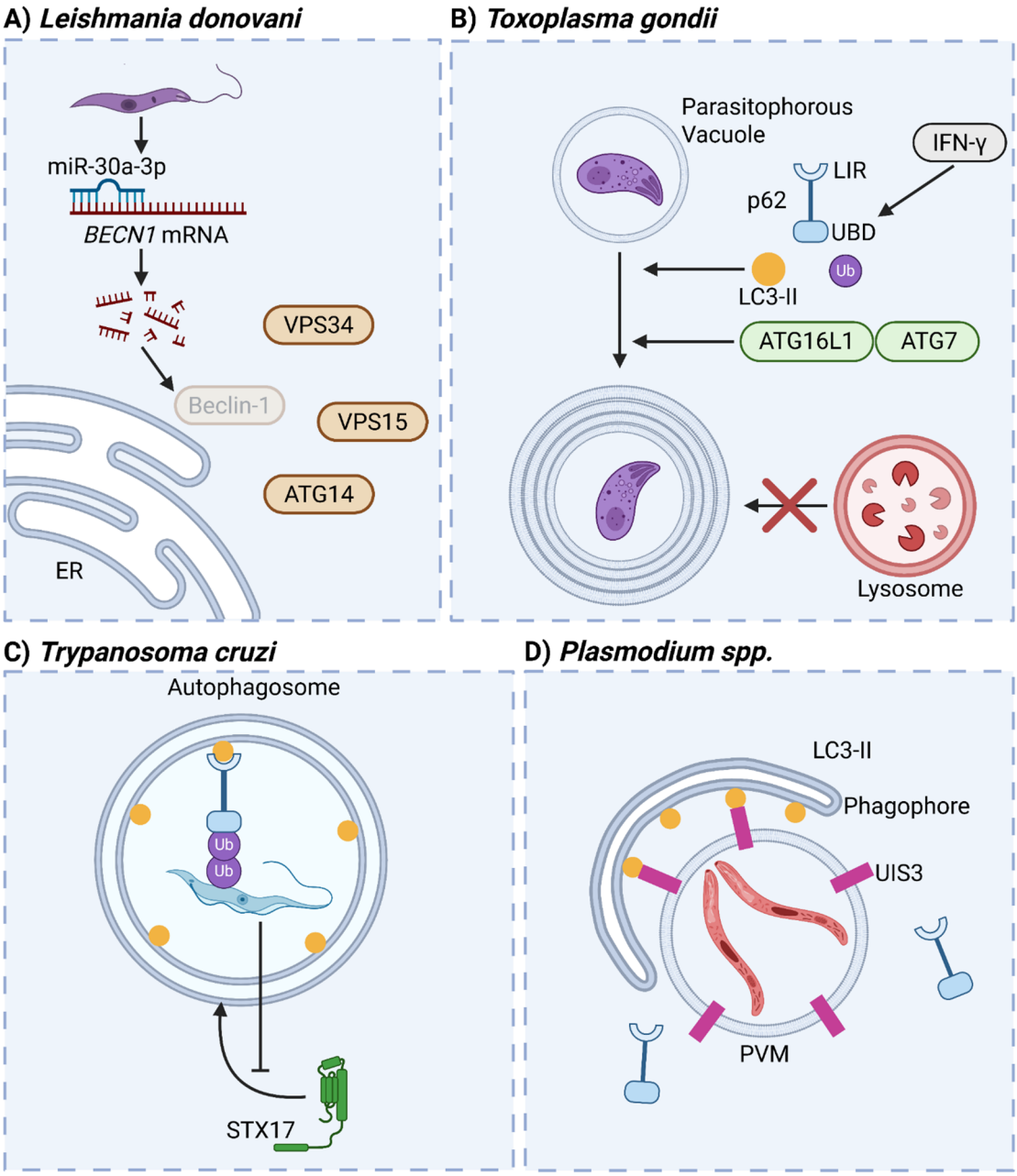

Figure 4. Overview of xenophagy evasion mechanisms of various parasites. When a parasite forms PV and invades a host cell, the host cell breaks down the PV, exposing the parasite to the cytoplasm. The parasite is then ubiquitinated and delivered to a downstream phagophore of selective autophagy via several adaptor proteins (p62, NDP52, OPTN). Finally, the parasite is eliminated by lysosome fusion. However, some parasites evade host xenophagy, survive, and cause infectious diseases in humans. (**A**) *Leishmania donovani* upregulates miR-30a-3p in host cells, preventing the production of Beclin-1. (**B**) *Toxoplasma gondii* survives by interfering with autolysosome formation, but the mechanism is not yet understood. However, the host cell forms multiple membranes around the PV containing *T. gondii,* which inhibits parasite growth. (**C**) *Trypanosoma cruzi* survives by preventing STX17, which is involved in autophagosome-lysosome fusion, from being recruited to the autophagosome. (**D**) *Plasmodium spp.* evade xenophagy by expressing UIS3 on the PVM. UIS3 directly binds to host LC3 on the cytosolic side of the PVM, preventing its interaction with the autophagy receptor p62. VPS: vacuolar protein sorting; ATG: autophagy-related; IFN-γ: interferon-gamma; LC3: microtubule-associated protein 1A/1B-light chain 3; LIR: LC3-interacting region; UBD: ubiquitin-binding domain; STX17: syntaxin 17; UIS3: upregulated in infective sporozoites 3; PVM: parasitophorous vacuole membrane. Created in BioRender. Kim, M. (2026) https://BioRender.com/i2n05ys (accessed on 10 March 2026).

5.3. Trypanosoma cruzi

Trypanosoma cruzi, the parasite that causes Chagas disease, can lead to megasyndromes in some individuals, resulting in enlarged hearts and livers [127]. *T. cruzi* appears to utilize the host autophagy system in the early stages of infection. Its infection rate increases under conditions of starvation or artificially induced autophagy. Conversely, the infection rate decreases with the deletion of ATG5 or Beclin-1 [128–130]. During *T. cruzi* infection, LC3-II levels increase to induce autophagosome formation. However, STX17, a SNARE protein that mediates lysosome fusion, fails to be recruited to the autophagosome membrane. This results in the failure of autophagosome maturation and autolysosome formation [115]. (Figure 4C) Although the molecular mechanism has not been elucidated, another parasite species, *Leishmania major*, inhibits autolysosome formation by removing VAMP8, a subfamily of SNAREs, from phagosomes through the secretion of glycoprotein 63 (GP63), a parasite surface metalloprotease. *T. cruzi* expresses a GP63 ortholog, TcGP63 [131,132].

5.4. Plasmodium spp.

Plasmodium spp. are transmitted through female mosquitoes and initially invade and proliferate in hepatocytes. They then invade and destroy red blood cells, causing malaria in humans [133,134]. The upregulated in infective sporozoites 3 (UIS3) protein, located on the parasitophorous vacuole membrane (PVM) of *Plasmodium spp.*, binds directly to host LC3 on the cytosolic face of the PVM and competitively inhibits the interaction between LC3 and autophagy receptors such as p62, thereby preventing xenophagy and allowing parasite survival. Parasites lacking UIS3 cannot proliferate in hepatocytes. However, the proliferation ability of UIS3-deficient parasites was rescued in hosts that have lost autophagy capacity due to ATG5 or Rab7 deficiency, suggesting a mechanism by which *Plasmodium spp.* evade autophagy recognition [116]. (Figure 4D).

6. Conclusions

Xenophagy is a key host defense mechanism that selectively eliminates invading pathogens. This review comprehensively examines the sophisticated evasion strategies that diverse pathogens have evolved. Bacteria, viruses, and parasites can disrupt multiple steps in the xenophagy pathway. These disruptions include blocking ubiquitination, inhibiting autophagy initiation, interfering with autophagosome formation, and inhibiting autophagosome-lysosome fusion. Antibiotic and antiviral drug resistance is one of the most serious threats to human health today. The World Health Organization (WHO) has identified superbugs as one of the most dangerous causes of disease in the future. In this context, existing therapies that directly attack pathogens are facing limitations. Host-targeted therapeutic strategies that pharmacologically enhance xenophagy activity or block the effector proteins that pathogens use to evade xenophagy could offer powerful alternatives to overcome drug resistance. However, such xenophagy modulation must be carefully balanced to avoid disrupting basal autophagy, which is essential for cellular homeostasis and may lead to unintended immunopathology. Furthermore, these approaches are expected to synergize with existing antimicrobials, providing novel strategies to combat the escalating global threat of antimicrobial resistance while minimizing host toxicity. In conclusion, a molecular understanding of pathogen-host interactions, particularly xenophagy evasion mechanisms, is essential for elucidating the pathophysiology of infectious diseases. The diverse, pathogen-specific evasion mechanisms presented in this review will serve as a foundation for discovering new targets for the prevention and treatment of infectious diseases. Furthermore, these mechanisms are expected to accelerate research into innovative therapeutics through the modulation of xenophagy.

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