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Decoding the parvovirus life cycle: Molecular mechanisms of cellular entry, trafficking, and replication

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ABSTRACT

Parvoviruses exhibit a broad host spectrum and possess the potential of cross-species transmission. This evolutionary adaptability raises concerns regarding the potential expansion of their host range into human populations, thus posing a significant public health threat. This review systematically summarizes the current knowledge regarding the molecular interactions between parvoviruses and host cellular components, elaborating on the entire viral life cycle—encompassing cellular entry, intracellular trafficking, nuclear transport, DNA replication, and nuclear egress. It aims to lay a foundation for advancing research on parvovirus pathogenesis and identifying novel targets for vaccine and drug development.

1. Introduction

As a public health concern, parvoviruses have garnered increasing attention in recent years. Numerous evidence indicates their prevalence in natural ecological cycles, a phenomenon significantly driven by cross-species transmission facilitated by viral mutations (Lina et al., 2022; Temeeyasen et al., 2022; Wang et al., 2020). The rapid evolutionary capacity of parvoviruses enables them to adapt to new hosts and evade host immune responses. Understanding viral population dynamics during intra- and interspecific transmission is therefore crucial for studying emerging viruses (Fay et al., 2022). The emergence and prevalence of new pathogens often result from ancestral viruses adapting to new hosts through a cycle of mutation, adaptation, and further evolution (Debbink et al., 2014; Tsetsarkin et al., 2016; Zhao et al., 2011). Cross-species transmission is a pivotal force in virus evolution (Geoghegan et al., 2017). Viruses that overcome species barriers—through mutations affecting cell receptor binding or key amino acid sites—can trigger severe outbreaks in humans and animals (Chen et al., 2023b; Cui et al., 2023b).

The interaction between parvoviruses and host cell receptors is a critical determinant of cellular infection, tissue tropism, and host range (Chen et al., 2023b; Cui et al., 2023b). Specific virus-receptor interactions mediate cell attachment and initiate entry, typically via receptor-mediated endocytosis (Boisvert et al., 2010). This process can induce conformational changes in the viral capsid, which are essential for successful infection (Chen et al., 2023a). Variability in host receptors can impose barriers to infection, and viral adaptation to these receptors may facilitate the expansion of the virus's host range (Li, 2013; Ohishi et al., 2014). Parvoviruses employ multiple pathways to infect cells, each involving a series of specific and coordinated interactions. Their broad host range, encompassing rodents, bats, and insectivorous mammals, along with confirmed cross-species transmission capabilities, underscores their significant public health threat (Chesnut et al., 2025).

At the genomic level, most parvoviruses possess palindromic inverted terminal repeat (ITR) sequences or telomere-like structures at both ends. These act as unique *cis*-acting elements essential for viral replication, initiating DNA synthesis and resolving single-stranded viral DNA (ssDNA) (Campbell et al., 2022; Shen et al., 2021). The parvovirus genome is compact and functionally specialized, typically containing two major open reading frames (ORF1 and ORF2). These are transcribed

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independently from early and late promoters and share a common polyadenylation site (Mietzsch et al., 2019). ORF2, located on the genome's right side, encodes the viral capsid proteins (Cap/VP). Beyond forming the virion structure, the ORF2-encoded region harbors critical functional elements such as a phospholipase A_2 (PLA_2) domain, a calcium-binding loop, and nuclear localization signals (NLS) (Jager et al., 2021; Li et al., 2026). The PLA_2 domain, located within the unique N-terminal region of VP1 (VP1u), becomes exposed in acidic endosomes to facilitate endosomal escape and genome release, processes vital for infectivity (Girod et al., 2002). ORF1, situated at the genome's left end, encodes the non-structural proteins NS1 and NS2 (analogous to Rep78 and Rep68 in adeno-associated viruses) (Girod et al., 2002). NS1, the largest and most functionally critical non-structural protein, contains three conserved domains: an N-terminal DNA-binding/endonuclease domain, a central helicase domain, and a C-terminal transactivation domain (Xie et al., 2023).

This review examines the interactions between parvoviruses and host cells, encompassing cellular entry, cytoplasmic trafficking, nuclear transport, DNA replication, and egress. It aims to lay a foundation for further research into parvovirus pathogenesis and the exploration of novel targets for vaccine and drug development.

2. Parvovirus cellular entry and trafficking toward the nucleus

Parvoviruses demonstrate a remarkably broad host range, infecting virtually all vertebrate and invertebrate species, including mammals (humans among them), birds, fish, and insects (Figure-1). Cellular entry is mediated by specific cell surface receptors on the cell surface, which facilitate viral translocation across the membrane. Once internalized, the viral particles undergo conformational changes that allow them to escape from endosomes. With the aid of microtubules, actin networks, and other cytoskeletal components, the virions are then transported through the cytoplasm. Successful entry into the nucleus enables the initiation of viral DNA replication, thereby establishing infection.

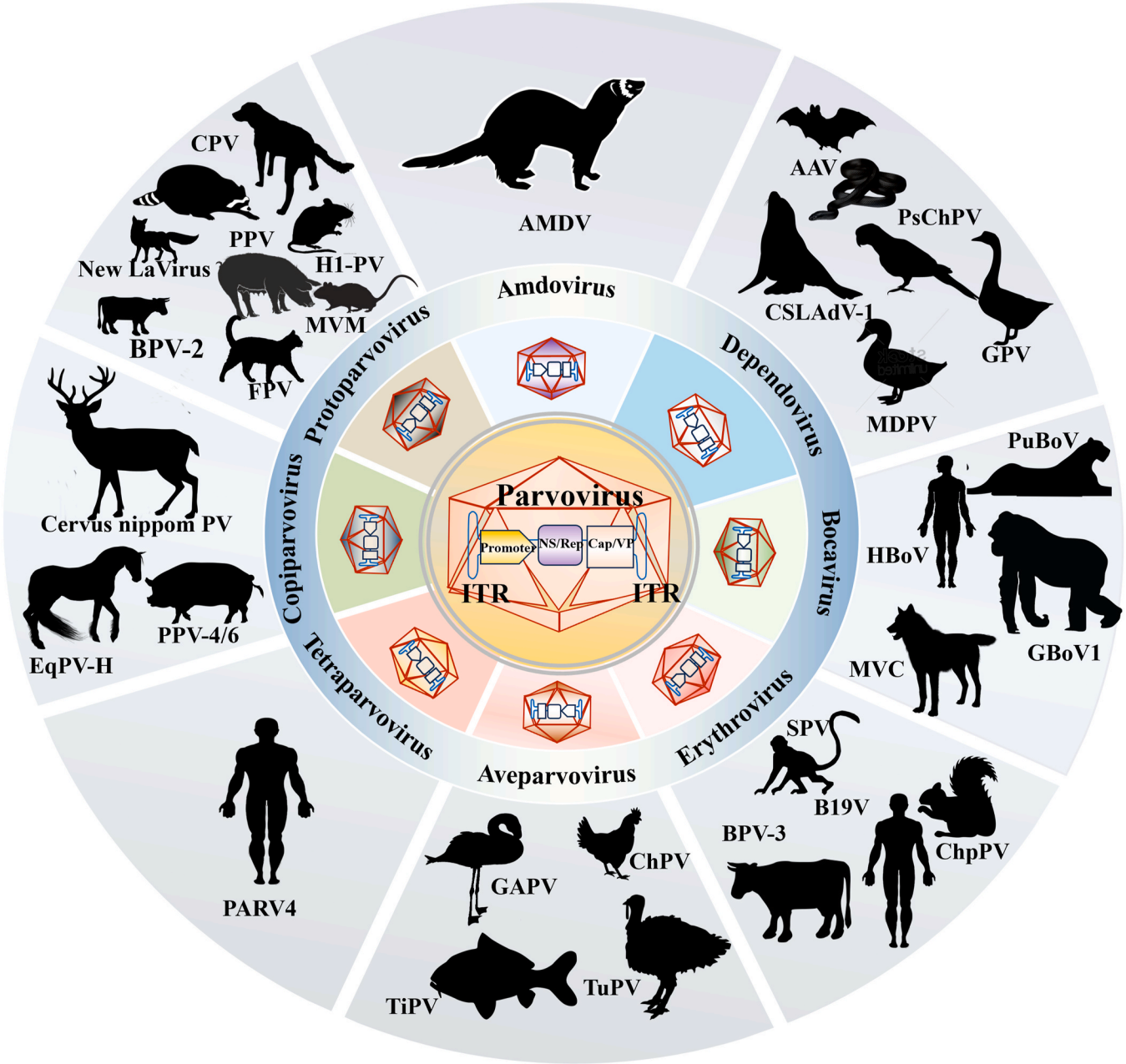

Figure-1. Host range and tissue tropism of parvovirus.

2.1. Parvovirus traverse cellular barriers through receptor-mediated binding

The interaction between the parvovirus capsid and host cell receptors plays a pivotal role in facilitating viral invasion and establishing infection. Different parvoviruses utilize distinct receptors for infection, including both broadly recognized universal receptors and more specific ones, such as globotetraosylceramide and tyrosine protein kinase receptor UFO(AXL) (Table-1).

Target cell recognition by parvoviruses involved two principal mechanisms. For example, studies have shown that the primary receptor for human pathogenic parvovirus B19V on erythroid progenitor cells is the P-antigen (Brown et al., 1993; Kerr, 1996). Interestingly, although mature human erythrocytes express the P-antigen, they do not support B19V infection because they lack the integrin receptor α5β1. Both Ku80 and α5β1 are required to mediate B19V adhesion to the cell surface (Sundin et al., 2008; Weigel-Kelley et al., 2003). Furthermore, silencing the receptor tyrosine kinase AXL significantly reduces B19V internalization in erythroid progenitor cells (Ning et al., 2023). Similarly, KIAA0319L, commonly known as the adeno-associated virus receptor (AAVR), has been identified as a crucial host factor for capsid-mediated entry of multiple adeno-associated virus (AAV) serotypes both *in vivo* and in *vitro* (Pillay et al., 2016, 2017). AAVR is a glycosylated transmembrane protein containing five polycystic kidney disease (PKD) repeat domains (Large and Chapman, 2023). AAV2 primarily interacts with the second immunoglobulin-like PKD domain (PKD2) in the extracellular region of AAVR (Zhang et al., 2019). In contrast, AAV5 transduction depends mainly on binding to the membrane-distal PKD1 domain. Other serotypes, such as AAV1 and AAV8, require simultaneous engagement of both PKD1 and PKD2 to achieve optimal transduction efficiency (Zengel et al., 2025). These findings indicate that different AAV serotypes have evolved distinct binding strategies toward the same receptor, AAVR, resulting in serotype-specific entry mechanisms. Following the identification of AAVR, haploid genetic screens revealed GPR108 as a second highly conserved cellular entry factor required for most primate AAVs *in vitro* and *in vivo* (Dudek et al., 2019) (Table-S1). The reduced quantity of internalized viral genomes and the decreased proportion of nuclear-localized genomes in AAVR and GPR108 knockout cells demonstrate that both proteins are essential for early entry steps prior to nuclear import (Dudek et al., 2020). Additionally, AAV2 can attach to cells via heparan sulfate proteoglycans (HSPGs)and fibroblast growth factor receptor-1 (FGFR1), integrin αVβ5, and hepatocyte growth factor receptor (MET) as coreceptors in a coordinated entry process (Walters et al., 2001; Wu et al., 2025) (Table-S1). Collectively, these studies illustrate that different viral serotypes can engage the same receptors through unique interaction modes, and that viral entry often relies not on a single receptor but on cooperative interactions among multiple receptors and coreceptors to establish effective host entry portals.

At the same time, parvovirus from different species recognize distinct cellular receptors (Table-1). Aleutian mink disease virus, porcine parvovirus, bovine parvovirus (Walters et al., 2004), CPV-2 (Löfling et al., 2013), AAV-5, and minute virus of mice (MVM) all bind to sialic acid receptors (Calvo-López et al., 2023). Specifically, AAV-5 interacts with sialic acid residues linked via α2, 3 and α2, 6 glycosidic bonds, whereas MVM recognizes α2, 3, 6, 8 glycosidic chains, porcine parvovirus attaches to the terminal O-linked and N-linked sialic acid moieties of cell surface glycoproteins (Mészáros et al., 2017). Meanwhile, bovine parvovirus binds to α2, 3-O-linked and α2, 3-N-linked sialic acids and can enter host cells through distinct transport pathways following attachment (Dudleenamjil et al., 2010). These observations indicate that when receptors are expressed on cells, they exhibit distinct interactions with viral capsids, and specific binding sites for parvovirus invasion are localized to different regions of the receptors. Therefore, the second mechanism-whereby parvoviral ligands directly utilize host cell-specific receptors to mediate viral entry-appears to be the more common one.

Along similar lines, it is well established that CPV is a natural variant of feline panleukopenia virus (FPV) that emerged during the 1978 influenza pandemic. Additional evidence shows that the canine transferrin receptor (TfR) differs from other host receptors in its amino acid sequence and possesses an additional (i.e., fourth) glycosylation site within the apical domain, which is attached to Asn384 in the canine TfR sequence (Cureton et al., 2012). CPV utilizes the uniquely glycosylated canine TfR to mediate capsid attachment to the cell surface and subsequent rapid uptake via clathrin-dependent endocytosis (Cureton et al., 2012).

The dynamic binding process between the viral capsids and receptors is mutually interactive. CPV strains isolated from dogs, wolves, and coyotes all harbor a glycine (Gly) residue at position 300 of the capsid protein VP2, whereas raccoons-derived CPV contains an aspartic aid (Asp) residue at this position (Lee et al., 2016). Furthermore, recent amino acid sequence analyses of VP2 suggest that residues 426E/D, 305H/D, and 297S may be critical for viral binding to distinct host receptors. Beyond this, the receptor-binding loop region and specific amino acid sites including 87L, 93N, 232I, and 305Yhave been linked to the cross-species transmission of CPV-2. To date, the homology of TfR sequences among different hosts infected with CPV-2 ranges from 77.2% to 99.0%. In particular, porcine TfR shares 80.7% homology with feline

Table 1
Different receptors in parvovirus.

Parvovirus	Virus	Receptor	Receptor Category	Reference
Protoparvovirus	CPV, FPV/MVM, PPV, H-1PV	TfR1/sialic acid (Neu5Gc)/Sialic acid (α2,3 - linked, N - acetylneuraminic acid); Heparan sulfate proteoglycan (HSPG, some strains)/Sialic acid (α2,3 - linked Neu5Ac); Laminin γ1 (SIA - dependent)	Protein/ Glycan	(Callaway et al., 2016; Calvo-López et al., 2023; Hartmann et al., 2023; Kaelber et al., 2012; Kim et al., 2016; Kulkarni et al., 2021; Lee et al., 2016; López-Astacio et al., 2023; Majumder et al., 2020; Robert et al., 2023; Wasik et al., 2016)
Erythrovirus	B19V	Gb4Cer/AXL	Glycan/ Protein	Bieri et al. (2021); Bircher et al. (2022); David (2024); Ganaie and Qiu (2018); Ning et al. (2023); Zo
Amdoparvovirus	AMDV	Sias acids	Glycan	Lakshmanan et al. (2022); Vahedi et al. (2023); Walter
Bocavirus	HBoV, MVC	Specific receptors are still unknown	unknown	(Dong et al., 2018; Guo et al., 2024; Mietzsch et al., 2017; Mohammadi, 2023; Tuteja et al., 2022; Xu et al., 2021)
Dependovirus	AAV2, AAV3, AAV6, AAV13, AAV1, AAV4, AAV5, AAV6, AAV9, AAV13	Heparan sulfate/N or O-linked sialic acid/Sialic acid terminal galactose/KIAA0319L/GPR108(For detailed information, see Supplementary Table S1)	Glycan/ Protein	(Dudek et al., 2019; Meisen et al., 2020; Mietzsch et al., 2020a; Pillay et al., 2017; Summerford and Samulski, 1998; Walters et al., 2004; Zengel et al., 2025; Zhang et al., 2019)
Tetraparvovirus	Parvovirus 4 (PARV4)	Specific receptors are still unknown	unknown	Karlin (2024); Lazutka et al. (2020); Vahedi et al., 2
Aveparvovirus	ChPV, TuPV	Specific receptors are still unknown	unknown	(Cui et al., 2023a; Finkler et al., 2016; Nuñez et al., 2020)
Copiparvovirus	BPV	Sias acids	Glycan	Johnson et al. (2004)

TfR, 80.4% with canine TfR, and 77.2% with human TfR (Chen et al., 2024b). Several studies have also demonstrated that CPV frequently mutates its VP2 residues to adapt to the resistant receptors of diverse hostsa maladaptive mechanism that enables CPV to dominate cross-species transmission cycles within forest ecosystems (Allison et al., 2014).

However, as observed in oncolytic virotherapy, the entry mechanism of the parvovirus H-1PV may differ from the two pathways described above. Studies investigating H-1PV infection in 59 cancer cell lines and 3D organotypic spheroid cultures with varying sensitivities to H-1PV revealed that cells with elevated laminin γ1 expression in the extracellular matrix are more susceptible to H-1PV invasion. Although laminins are not transmembrane receptor proteins, they can act as attachment factors for H-1PV, coordinating interactions with sialic acid receptors or other as-yet-unknown multiple cell surface receptors. This facilitates H-1PV traversal of the plasma membrane and cellular penetration (Kulkarni et al., 2021).

In summary, the dynamic interaction between parvoviral capsids and host cell receptors is a complex process that serves as a critical determinant of cellular infection, tissue tropism, and host range (Callaway et al., 2018). While attachment factors and functional receptors have been identified for some parvovirus members, current understandings of how the kinetics of viral capsid–receptor binding regulate cellular infection, drive disease pathogenesis, and influence transmission to new hosts remain limited.

2.2. *Parvovirus undergo endosomal trafficking within the cytoplasm*

The parvovirus capsid protein (VP) is crucial for viral entry host cell (Dai et al., 2022). Upon binding to specific receptors, the viral capsid is internalized via receptor-mediated endocytosis (Figure-2A). Clathrin-mediated endocytosis (CME—the most common entry pathway for parvovirus infection—is initiated when clathrin is recruited to the plasma membrane through the AP2 adaptor complex (Ferreira et al., 2020b). As CME assembly processed, it induces gradual invagination of the plasma membrane, leading to the formation of clathrin-coated pits (Ros et al., 2017). The neck of each coated pit then forms a ring structure that mediates membrane scission, pinching off clathrin-coated vesicles from the plasma membrane (McMahon and Boucrot, 2011) (Figure-2B). These newly formed vesicles rapidly shed their coats and fuse with early endosomal vesicles near the cell periphery, thereby delivering the viral cargo into the endosome compartment. With increasing endosomal acidity, the specific endoysosomal microenvironment triggers a critical rearrangement of the capsid structure (Cotmore and Tattersall, 2007). This conformational change promotes the externalization of the unique functional extension at VP1u. The PLA_2 motif within the VP1u enables parvoviruses to efficiently penetrate the endosomal membrane (Figure-2C). The functional efficiency of B19V is constitutively exposed on the capsid surface, homologous regions in other parvoviruses—such as AAV and MVM—remain concealed within the capsid interior. Indeed, in AAV and MVM, VP1u only externalizes under the acidic pH conditions encountered during endosomal trafficking.

Recent studies have revealed that the conformational change of the AAV capsid is regulated by the intracellular calcium environment. While most evidence indicates that endosomal escape requires acidic conditions and that acidification shortly after internalization promotes infection, virus particles unable to escape from late endosomes into the cytoplasm are ultimately degraded by lysosomes (Figure-2D). In contrast, parvovirus particles released into the cytoplasm rely primarily on the cytoskeletal transport system—including microtubules and the actin network—to move toward the nucleus (Figure-2E). Notably, recent work on AAV has challenged aspects of the previously described entry

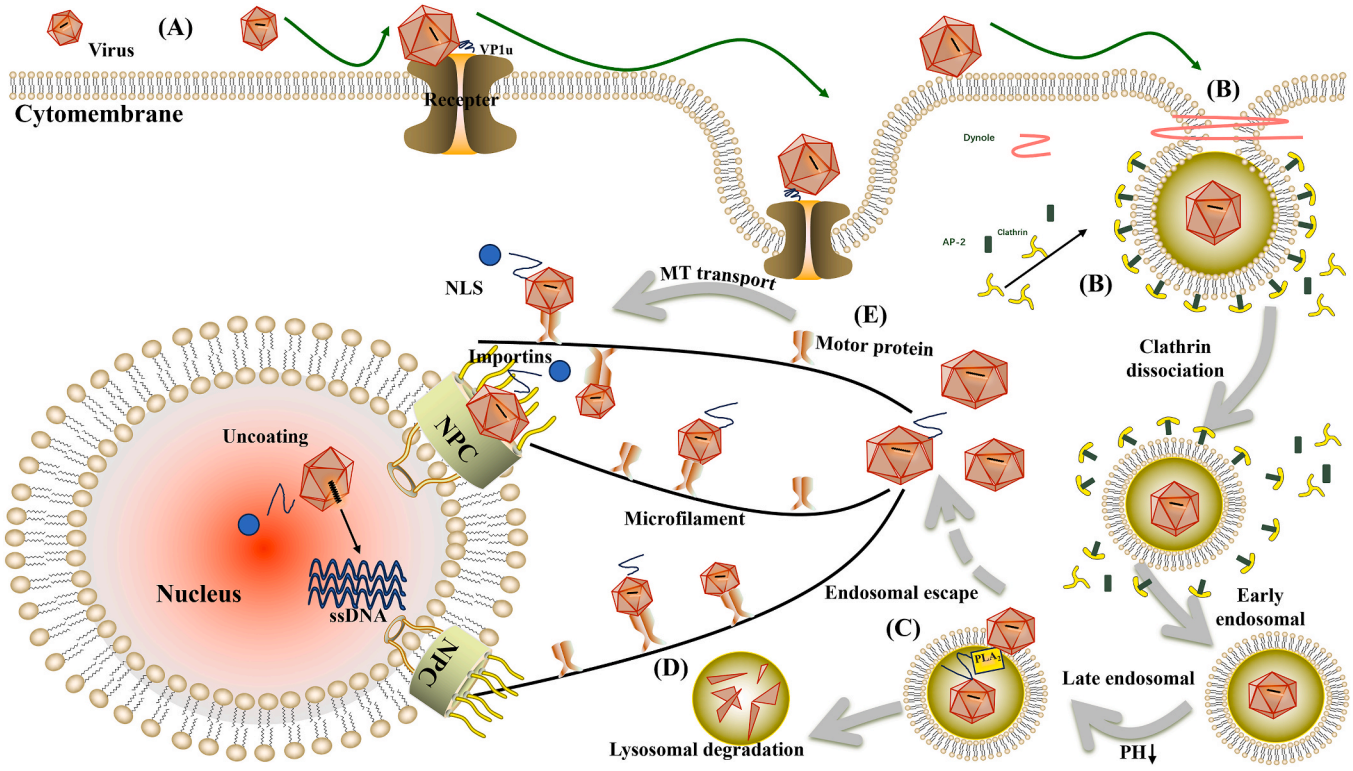

Figure-2. Molecular mechanisms of parvovirus host cell invasion. (A) Initial attachment: Parvoviruses recognize and bind to specific cell surface receptors through viral capsid proteins. **(B)** Cellular entry: Viral internalization occurs via clathrin-mediated endocytosis, facilitated by the assembly of AP2 adaptor protein complexes. **(C)** Endosomal maturation: Acidification of the endosomal compartment induces conformational changes in the viral capsid structure. **(D)** Lysosomal degradation: The endocytic pathway directs most internalized virions to lysosomes for enzymatic degradation and clearance. **(E)** Nuclear targeting: A small subset of intact virions escapes endosomal confinement, hijacks the host cell's cytoskeletal transport system (utilizing motor proteins), and undergoes nuclear translocation through nuclear pore complexes to initiate viral genome replication.

model. It is now recognized that AAV employs a multifactorial entry mechanism (Dudek et al., 2019). The AAVR receptor binds to intact AAV capsids and directs them to the trans-Golgi network (TGN) (Pillay et al., 2016). Subsequent endosomal acidification induces capsid conformational changes and exposure of the VP1/2 unique region, allowing engagement of GPR108via the VP1u domain (Dudek et al., 2019; Meisen et al., 2020). Although the exact mechanism remains unclear, GPR108 is hypothesized to facilitate endosomal escape—either by stabilizing the extruded VP1u domain or by forming pores in the endosomal membrane to enable genome release (Dudek et al., 2019). If AAV particles indeed remain shielded within membrane-bound compartments deep in the endocytic pathway, maintaining their integrity until they reach the TGN, and potentially use this subcellular route to enter the nucleus (Nicolson and Samulski, 2014), this could help explain why AAV typically triggers only weak innate immune activation. By contrast, viruses that escape early from endosomal often activate cytoplasmic DNA sensors. Moving forward, genetic engineering of parvovirus capsids to reduce neutralizing antibody titers may represent a key direction for improving parvovirus-based applications in cancer and gene therapy.

2.3. *Parvovirus interaction with the nuclear membrane barrier*

Nuclear import of the parvovirus genome depends on capsid interaction with nuclear transport mechanisms, including members of the importin-β superfamily and nuclear pore complex (NPC) proteins—collectively referred to as nucleoporins. To date, two pathways for parvovirus nuclear entry have been identified. The first involves classical interaction between VP proteins and the NPC (Panté and Kann, 2002), which allows intact capsids to enter the nucleus through the pore without disassembly (Mantyla et al., 2020). The other pathway may rely on activation of mitotic factors and local transient disruption of the nuclear envelope to enable viral entry (Shi et al., 2023). As the sole bidirectional gateway for nucleocytoplasmic transport, the NPC consists of approximately 30 distinct proteins (Tamura and Hara-Nishimura, 2013). The viral capsid interacts with at least three nucleoporins—Nup358, Nup153, and Nup62. Most parvoviruses follow the classical nuclear import pathway, in which importin α recognizes the NLS-containing substrate protein, followed by binding to importin β. Once inside the nucleus, the complex is dissociated by Ran–GTP, allowing the cargo to diffuse deeper into the nucleoplasm. The import receptor–Ran–GTP complex is then exported through the NPC, ready for another round of transport (Shi et al., 2023) (Figure-3B). However, MVM, CPV, and AAV2 do not utilize this pathway.

CRISPR-mediated knockout of the *ATP2C1* gene, which encodes a Golgi-resident calcium ATPase pump, significantly reduces nuclear transduction across multiple AAV serotypes. It also disrupts the conformational changes required for externalization of the VP1-u phospholipase A2 domain during cellular trafficking (Madigan et al., 2020). Indeed, intracellular calcium plays a critical role in the redundant transduction pathways of parvoviruses (Popa-Wagner et al., 2012). Studies further indicate that calcium release from intraluminal and extraluminal compartments of the nuclear membrane is closely linked to an alternative pathway that induces local, transient nuclear membrane rupture. Such rupture occurs within minutes after capsid exposed to the nucleus consistent with rapid entry and the observed rise in perinuclear Ca^{2+} levels prior to nuclear envelope breakdown during infection (Mantyla et al., 2020). Parvovirus-induced nuclear membrane rupture resembles mitosis events in that Ca^{2+} released from the perinuclear space is critical for PKCα activating. PKCα subsequently activates cyclin-dependent kinase 1 and/or 2 (CDK1/2), which then induce caspase-3 kinase activation, leading to hyperphosphorylation of lamin B (Mantyla et al., 2020). This hyperphosphorylation is required for local disassembly of the nuclear lamina beneath the envelope, enabling the formation of pores up to 190 nm in diameter and facilitating viral entry

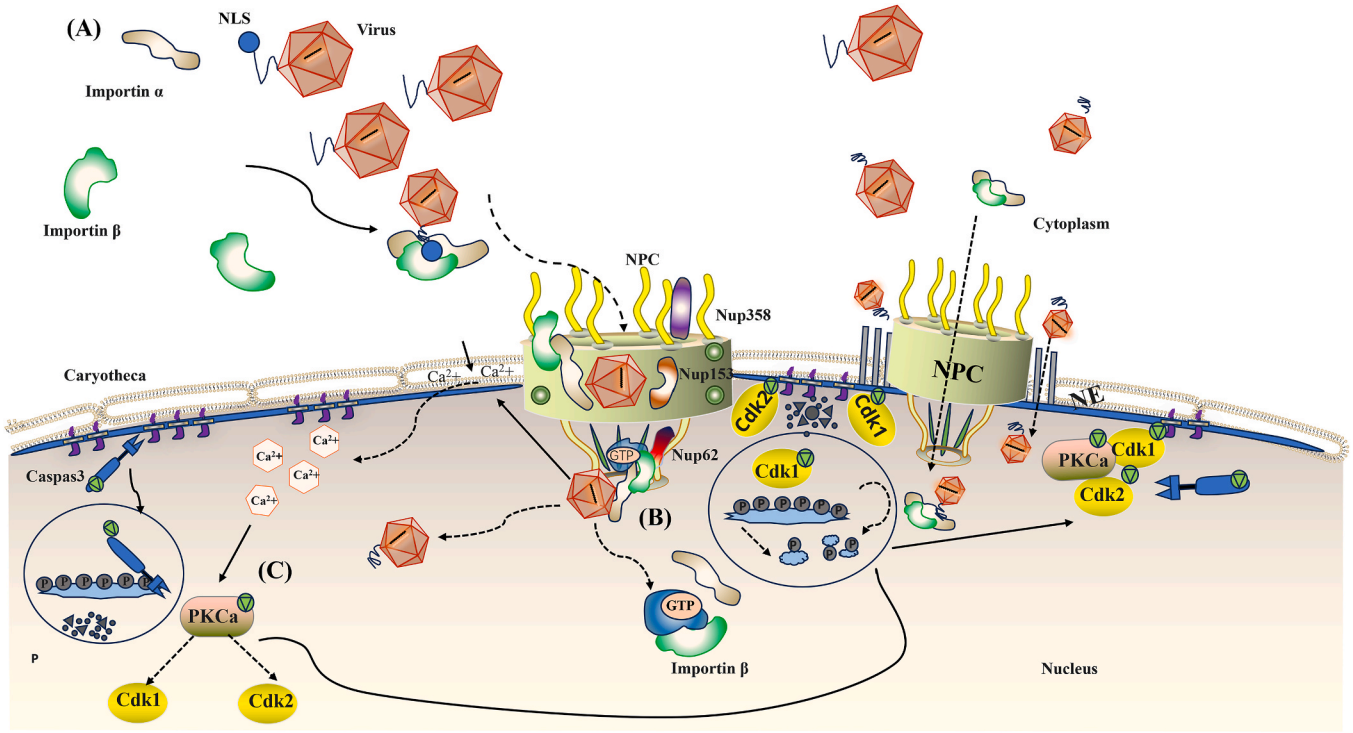

Figure-3. Nuclear import mechanism of parvoviruses. (A) Nuclear entry via the importin pathway. Structural remodeling enables parvoviruses to escape endosomal compartments and bind importin-α/β, forming a trimeric import complex. This complex traffics through the nuclear pore complex (NPC) and disassembles at the nuclear basket, releasing viral capsids into the nucleoplasm. **(B)** Recycling of import machinery. The importin receptor-RanGTP complex is exported back through the NPC to sustain subsequent rounds of nuclear transport. **(C)** Nuclear envelope remodeling facilitates capsid entry. Parvovirus infection triggers calcium release, activating PKCα and downstream effectors (Cdk1/Cdk2 and caspase-3). Hyperphosphorylation of lamin B by PKCα and its cleavage by caspase-3 induce localized nuclear lamina degradation, forming transient pores. These pores permit entry of NPC-bound capsids or cytoplasmic capsid-importin complexes.

into the nucleus (Cohen et al., 2011; Mattola et al., 2022a) (Figure-3C).

The core controversy between the two current nuclear import models remains unresolved, and three key scientific questions urgently require systematic clarification: First, do different AAV serotypes inherently prefer specific nuclear import mechanisms? Existing studies have confirmed that capsid proteins of different AAV serotypes exhibit significantly different binding affinities for the nuclear transport protein importin-β, suggesting potential specificity in transport protein selection [3]. However, it is still unclear whether such differences are sufficient to drive fundamental changes in the core nuclear import mechanism—a question that directly determines the feasibility of universal strategies for optimizing nuclear transport through vector modification. Second, the correlation between the timing of viral nuclear entry and the host cell cycle is not well understood. AAV demonstrates efficient infectivity in quiescent cells such as cardiomyocytes and hepatocytes—cells that lack mitosis-related physiological NEBD (Lux et al., 2005; Miguel--Dos-Santos et al., 2025). How the virus precisely regulates the occurrence and repair of pathological NEBD in such cells, or whether it switches to an NPC-dependent nuclear import mechanism, remains mechanistically unexplored in a systematic manner (He et al., 2022; Hou et al., 2023). Third, there is substantial controversy regarding the functional localization of the AAV capsid VP1u. Some studies propose that the phospholipase A2 domain within VP1u only mediates endosomal escape and is irrelevant to nuclear import (Li et al., 2015), whereas others have confirmed through mutational analysis that the basic amino acid sequence at the VP1u can function as a NLS to mediate nuclear transport (Hou et al., 2023). It therefore remains to be clarified whether VP1u serves a dual role in both endosomal escape and nuclear localization during nuclear entry, and what molecular switches—such as phosphorylation or conformational changes—govern the transition between these functions (Hou et al., 2023; Li et al., 2015).

To address these unresolved issues and mechanistic controversies, future research should advance along three core directions to achieve a precise understanding of parvovirus nuclear import: First, employ dynamic super-resolution imaging to track single viral particles in living cells, combined with cryo-electron tomography, to directly visualize the interactions between AAV particles and the NPC or nuclear envelope, and to determine pathway preferences across different cell cycle stages (Jang et al., 2022; Tan et al., 2018). Second, integrate CRISPR-Cas9 screening with proteomics to systematically identify host factor networks associated with the two import mechanisms, clarify the regulatory pathways and crosstalk between NPC-mediated transport and NEBD-dependent entry, and uncover potential nodes that control pathway switching (Ramani et al., 2025). Third, focus on serotype differences and VP1u functionality by constructing and characterizing capsid mutants. This approach would reveal preferential differences in nuclear import mechanisms among AAV serotypes, elucidate the precise roles and regulation of VP1u in nuclear entry, and thereby provide a theoretical foundation for developing next-generation gene therapy vectors through targeted capsid modifications that enhance nuclear transport efficiency and overall vector performance (Mietzsch et al., 2020b).

3. Parvovirus nuclear transport and DNA replication

After entering host cells through receptor-mediated endocytosis, parvoviruses release their ssDNA into the nucleus (Gualtiero et al., 2025). Host DNA polymerases then convert the viral ssDNA_typically the negative strand, into double-stranded replicative form DNA (dsDNA), generating a replicative intermediate (RF DNA) that serves as a template for subsequent replication. The viral NS1 (Rep) protein recognizes specific palindromic sequences, particularly terminal hairpin structures, on the dsDNA. Following dimerization, NS1 cleaves the replication origin on the positive strand, which is complementary to the newly synthesized negative strand, generating a free 3′-OH end. Utilizing host replication machinery, the virus initiates rolling-circle replication (RCR) during late S phase and early G2 phase (Tompkins et al., 2021). Host DNA polymerases such as Pol δ/ε extend the positive strand using the negative strand as template, starting from the 3′-OH end, while displacing the original positive strand. During this process, the negative strand of the dsDNA forms a circular intermediate, and the displaced positive strand continues to elongate, forming linear concatemeric DNA. The Rep protein cleaves the palindromic sequences at the termini of the nascent strand, releasing unit-length viral genomes. The cleaved ssDNA ends then refold into hairpin structures, preserving genomic integrity. Finally, the newly synthesized positive-strand ssDNA is packaged by capsid proteins to assemble mature viral particles.

3.1. Minute Virus of Mice (MVM)

The genome of MVM undergoes vigorous replication within host cells during the S phase through a rolling hairpin replication (RHR) mechanism, which ultimately leads to cell cycle arrest. Unlike AAV, the MVM genome features two inverted palindromic terminal sequences (i.e., heterotelomeres) at both ends that serve as origins of replication. NS1, the core regulatory protein of MVM replication (Cotmore and Tattersall, 2014), participates in the transcriptional regulation of the capsid protein P38 promoter (Xie et al., 2022), exhibits helicase and ATPase activities, and induces DNA damage responses (DDR). Moreover, NS1 can localize to DNA damage sites to establish viral replication centers, referred to as “autonomous parvovirus replication factories” or “APAR bodies”. These bodies recruit various DDR factors, including phosphorylated H2AX (γ-H2AX), NBS1, replication protein A 32 (RPA32), Chk2, p53, mediator of DNA damage checkpoint 1 (MDC1), the MRN complex, and PCNA, to coordinate viral DNA replication (Mattola et al., 2021). Cellular DNA polymerases, typically DNA Pol δ, convert the ssDNA genome into RF DNA, which then serves as a template for viral gene transcription. Throughout this process, the host RPA from the DDR pathway stabilizes single-stranded regions to prevent nuclease degradation (Majumder et al., 2018) (Figure-4A).

While the above processes are relatively well understood, how MVM localizes to DNA damage sites remains an unanswered question. Kinjal Majumder et al. (2020) found that NS1 can localize to DNA damage sites induced by laser micro-irradiation and can transport heterologous DNA molecules containing NS1-binding elements (NSBEs). This suggests that NS1 may act as a bridging molecule, facilitating the localization of the MVM genome to cellular DNA damage sites. Interestingly, transient treatment of cells with ATR inhibitors reduces NS1 re-localization to cellular DDR sites, thereby attenuating MVM replication and promoting greater dissociation of NS1 from cellular γ-H2AX. These results demonstrate that although ATM is the primary kinase required for DDR signaling induced by MVM infection, NS1 localization to DDR sites depends on early ATR signaling (Larsen and Majumder, 2023). Nevertheless, to date, studies directly validating the replication mechanism through which the NS1 protein interacts with the early ATR pathway to localize to DDR sites are still lacking.

The recruitment of DDR repair factors depends on the specific signals generate by recognized DNA break, which are marked by the γH2AX. The dephosphorylation of γH2AX facilitate the recruitment of MDC1, which in turn recruits the double-strand break sensor MRN complex (i.e., MRE11–RAD50–NBS1) to DDR sites (Majumder et al., 2017) (Figure-4A). MRE11 alone can interacts with the P4 and P38 promoters, and in the absence of cellular MRE11, MVM replication is attenuated and APAR bodies become smaller. However, MVM replication can still proceed in MRE11-deficient cells, indicating that the virus utilizes redundant host pathways (Bunke et al., 2023). The redistribution of the MRN complex at DNA damage sites inevitably recruits the ataxia-telangiectasia mutated (ATM) kinase. In uninfected cells, ATM signaling activates checkpoint response through phosphorylation of the kinase CHK2, which subsequently activates p53, ultimately leading to induction of p21a key regulator of the G1-S checkpoint (Boftsi et al., 2022; Majumder et al., 2017).

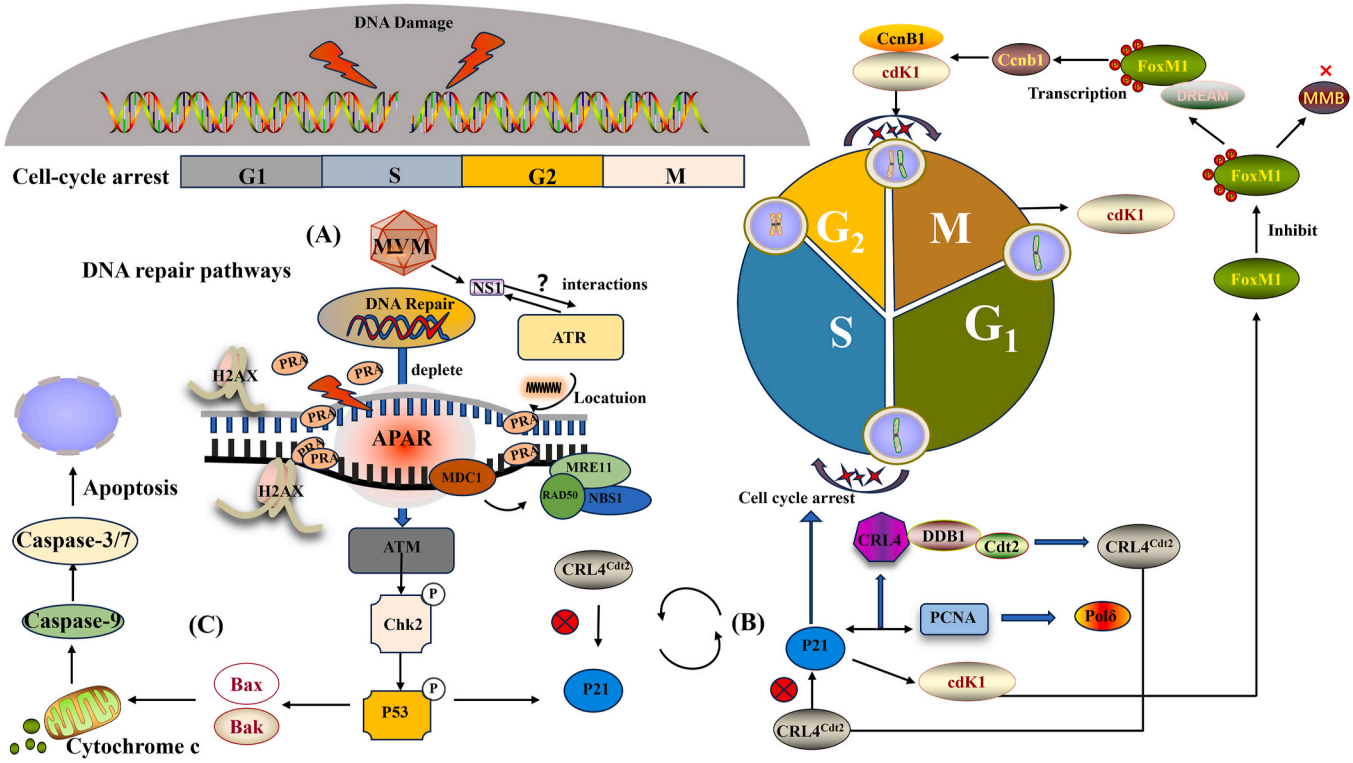

Figure-4. Host-parvovirus interactions during viral replication. (A) Viral replication center formation via DNA damage response (DDR) hijacking MVM NS1 protein recruits the ATR pathway to DNA damage sites, establishing viral replication centers (APAR) and co-opting DDR factors (e.g., γ-H2AX, RPA, MDC1, MRN). The precise NS1-ATR interaction mechanism remains unresolved. **(B)** Cell cycle manipulation. G1/S arrest: The CRL4 ubiquitin ligase complex (Cul4-Rbx1-DDB1) binds Cdt2 to degrade p21, blocking G1/S progression; G2/M dysregulation: CDK1 disrupts FOXM1 transcriptional networks, destabilizing the FOXM1-DREAM-MMB equilibrium and inducing G2/M arrest. **(C)** Apoptotic induction in late infection p53 upregulates pro-apoptotic genes (e.g., *Bax*, *Bak*), triggering mitochondrial outer membrane permeabilization (MOMP). Cytochrome *c* release activates the apoptosome, which recruits and cleaves caspase-9 to initiate a caspase cascade (caspase-3/7), executing apoptosis.

Numerous studies have shown that after MVM infection, the CRL4 complex (e.g., Cul4, Rbx1, and DDB1) binds to Cdt2 to mediate p21 degradation. This process, which requires p21 interaction with PCNA for targeting by the CRL4Cdt2 ubiquitin ligase (Adeyemi et al., 2014), is partly achieved through CDK1-mediated dysregulation of the transcription factor FOXM1. Reduced FOXM1 activity impairs the function of the MMB complex, while simultaneously enhancing the inhibitory effect of the DREAM complex (Fuller et al., 2017). This disruption in the balance between FOXM1, DREAM, and MMB prevents the cyclin B1–CDK1 complex from reaching the threshold activity required for cell cycle progression (Fuller et al., 2017),thereby inducing an effective pre-mitotic G2/M arrest (Figure-4B).

In the late stages of infection, host cell death serves as a key mechanism for viral survival, proliferation, and dissemination. Although various forms of cell death can be induced, apoptosis is the predominant mode triggered by most parvovirus infections (Afumba et al., 2022; Mattola et al., 2022b), and occurs in close association with cell cycle arrest and the DDR. If DNA damage is too severe or not promptly repaired, persistent DDR signaling can lead to premature apoptosis or cellular senescence (Chen et al., 2024a). Prolonged mitotic arrest also activates apoptotic pathway.

Both in cell cycle arrest and apoptosis, p53 plays a critical synergistic role. Early in infection, p53 induces cell cycle arrest by upregulating p21, which interferes with cyclin-dependent kinases such as cyclin B1–CDK1. Later, p53 transcriptionally activates pro-apoptotic genes (e.g., Bax and Bak), leading to mitochondrial outer membrane permeabilization. The subsequent release of cytochrome *c* and formation of the apoptosome with caspase-9 activate executioner caspases (e.g., caspase-3 and -7) to carry out apoptosis (Fig. 4C). Importantly, regardless of the specific mechanism by which MVM induces apoptosis, it increases nuclear envelope permeability, thereby facilitating the release of viral progeny (Mattola et al., 2022b).

In summary, parvovirus replication is a complex process involving multiple interconnected cellular pathways. The virus has evolved mechanism to exploit the DDR, cell cycle arrest, and apoptotic pathways to support its own replication. Nevertheless, the precise roles of DDR proteins in viral replication and the sequence of interactions with cellular components remain to be fully elucidated.

3.2. *Adeno-Associated Virus (AAV)*

AAV is a group of small, non-pathogenic dependoviruses. The 145-base pair ITRs flanking its genome serve as core elements that mediate viral replication, and the precise regulation of the host DDR pathway constitutes a key mechanism for completing its life cycle. Together, thesecomponents form a highly efficient replication network through synergistic interaction between viral and host factors. The ITRs of AAV can self-anneal into double-hairpin structures, which act as 3′-OH primers to initiate the conversion of ssDNA to dsDNA without enzymatic catalysis. This results in the formation of double-stranded intermediates with one open end and one covalently closed end (Meier et al., 2021b). The viral core regulatory proteins Rep 68/78 covalently bind to the 5′-end of the cleavage site in ITRs via phosphotyrosine linkages, generating free 3′-OH substrates that provide essential conditions for replication initiation (Young and Samulski, 2001). Notably, AAV replication depends on helper viruses. In the presence of adenovirus type 5 (AdV5), it follows a RHR mechanism, where by ITR hairpin structures initiate dsDNA synthesis. DNA polymerases provided by AdV or the host extend the hairpins to form double-stranded RF DNA. After Rep proteins cleave the terminal resolution site, progeny ssDNA is released through multiple

rounds of hairpin formation and strand displacement (Meier et al., 2021a). In contrast, when co-infected with herpes simplex virus type 1 (HSV-1), rolling circle replication (RCR) predominates (Table 2). Early HSV-1 genes encode proteins such as the helicase-primase complex (UL5–UL8–UL52), DNA polymerase (UL30), and nuclease (UL12), which promote the formation of head-to-tail linked dsDNA intermediates from the AAV genome. Continuous synthesis and cleavage then produce monomeric ssDNA, resulting in higher infection efficiency (Forrester et al., 1992; Weerasooriya et al., 2019; Weindler and Heilbronn, 1991).

The replication process of AAV is closely linked to activation and regulation of the DDR pathway: the hairpin structures formed by ITRs can mimic cellular DNA damage intermediates (Nash et al., 2008) and directly recruit DDR initiation factors, including the MRN complex (Mre11-Rad50-Nbs1). Meanwhile, Rep68/78, through its endonuclease, helicase, and ATPase activities, further activates ATM/ATR/DNA-PK-mediated DDR signaling while cleaving ITRs and unwinding viral DNA (Boftsi et al., 2022). Helper viruses play a dual role in this process. AdV5 activates host DNA synthesis and promotes strand displacement via gene products such as E1a, E2, and E4, while E4orf6 blocks non-homologous end joining (NHEJ)-mediated recombination to stabilize the viral genome and maintain the RHR replication mode (Lkharrazi et al., 2024). In contrast, HSV-1 assists ITR pairing and cyclization through its DNA repair protein ICP8, and its helicase complex unwinds dsDNA to form replication forks, facilitating DDR factor recruitment (Meier et al., 2021b; Weerasooriya et al., 2019). Under DDR signals regulation, Rep 68/78 can specifically localize to host cell DNA damage sites and mediate the formation of viral replication centers (VRCs). These centers recruit key factors such as γ-H2AX, RPA, DNA polymerase δ, and PCNA to stabilize ssDNA regions, promote RF DNA formation, and support viral gene transcription (Summers et al., 2025). Additionally, DDR pathway activation induces p53-dependent cell cycle arrest (predominantly at the S phase or G2/M phase), providing sufficient host factors and time windows for viral replication. However, excessive DDR activation can lead to RPA exhaustion and DNA damage accumulation, triggering the mitochondrial apoptotic pathway and STING-IL-1R-mediated inflammatory responses. This not only facilitates viral particles release but also limits excessive infection, reflecting AAV's precise regulation of host cell fate (Costa-Verdera et al., 2025; Lovric et al., 2012).

In summary, AAV replication centers on the structural features of ITRs and the multifunctional activities of Rep proteins. By sensing the helper virus type, it initiates either RHR or RCR mechanisms, and through activation and regulation of the DDR pathway, it constructs a highly efficient replication network. This process not only illustrates the evolutionary strategy by which dependoviruses exploit host pathways to complete their life cycles, but also provides a theoretical foundation for improving AAV gene therapy vectors—by targeting key DDR factors or optimizing helper virus combinations—to enhance transduction efficiency and safety.

3.3. *Human parvovirus B19 (B19V)*

Human parvovirus B19 (B19V), a representative pathogen of the genus *Erythroparvovirus*, possesses a linear ssDNA genome flanked by ITRs at both ends. These ITRs serve as replication origins and endow the virus with a unique regulatory basis for replication (Zou et al., 2018a). B19V exhibits strict tropism for human erythroid progenitor cells (EPCs) in the bone marrow and fetal liver, with its replication tightly coupled to host cell cycle progression and the induction of the DDR (Pietsch et al., 2020). During the replication initiation phase, the 3′-OH group of the ITR hairpin structure serves as a primer to convert the viral ssDNA genome into the double-stranded replicative form (dsRF DNA). As a core regulatory factor, the viral nonstructural protein NS1 specifically binds to NSBEs within the ITRs and introduces a nicks at the terminal resolution site via its DNA-binding, endonuclease, helicase, and ATPase activities, thereby triggering strand displacement synthesis—a hallmark of the RHR mechanism (Ganaie and Qiu, 2018). The efficient replication of B19V is dependent on a diverse array of host factors. Key DNA replication factors, including proliferating cell nuclear antigen (PCNA), replication factor C subunit 1 (RFC1), the minichromosome maintenance (MCM) complex, and DNA polymerases α/δ—are all recruited to viral replication centers. Among these factors, DNA polymerases α and δ mediate the conversion of ssDNA to dsRF DNA and strand extension, respectively, whereas PCNA and RFC1 act to enhance polymerase activity (Xu et al., 2017b). The erythropoietin (EPO)-JAK2-STAT5 signaling pathway and hypoxic microenvironment collectively act to further optimize viral replication efficiency. Phosphorylated STAT5 binds to the ITRs and recruits the MCM complex, whereas hypoxia fosters a favorable microenvironment by upregulating STAT5 activity and downregulating ERK signaling. UT7/Epo-S1 cells necessitate exogenous EPO supplementation and exposure to a hypoxic environment to robustly support viral replication (Luo et al., 2013).

B19V replication elicits robust activation of the DDR signaling pathway, a process characterized by the engagement of three phosphatidylinositol 3-kinase-related kinases (PI3KKs): ATM, Rad3-related (ATR), and DNA-dependent protein kinase catalytic subunit (DNA-PKcs). However, only ATR and DNA-PKcs are indispensable for viral replication (Lou et al., 2012). Unlike the canonical model in with individual viral proteins independently induce the DDR, DDR activation by B19V is strictly dependent on intermediates generated during viral genome replication. These intermediates mimic replication fork stalling or single-strand break structures, thereby recruiting the MRN complex to trigger a downstream signaling cascade (Qiu et al., 2017). Among the activated kinases in this cascade, ATR sustains cell cycle arrest at the late S phase via the ATR-CHK1-CDC25C pathway, thereby promoting the enrichment of DNA replication factors within the cell, whereas DNA-PKcs stabilizes the viral genome by suppressing NHEJ-mediated recombination events (Chen et al., 2010a). Notably, although B19V infection elicits hyperphosphorylation of replication protein A32 (RPA32) at residues S4/8, T21, and S33, this modification is dispensable for viral replication. Both phosphorylation-deficient (alanine-substituted) and phosphorylation-mimetic (aspartic acid-substituted) RPA32 mutants can fully support viral genome amplification (Xu et al., 2017b). Meanwhile, the C-terminal transactivation domain 2 (TAD2) of the viral NS1 mediates G_2/M phase arrest. Activation of the ATR-CDC25C-CDK1 pathway promotes the phosphorylation of CDC25C, which is subsequently sequestered in the cytoplasm by 14-3-3 proteins; this event blocks the activation of the cyclin B1-CDK1 complex in a p53-independent manner (Chen et al., 2011). The dual arrest at the late S phase and G_2/M phase not only ensures the continuous supply of host replication factors but also prevents mitosis from disrupting the viral replication centers (Luo et al., 2011).

As a specialized intranuclear substructure, the B19V replication center employs NS1 as a scaffold to recruit a repertoire of DDR factors, thereby orchestrating the coordinated regulation of viral replication. γ-H2AX, a canonical marker of DDR activation, colocalizes with NS1 and the replicating viral genome. However, NS1-induced ATR activation does not elicit substantial γ-H2AX phosphorylation, a phenomenon that reflects the unique DDR regulatory paradigm adopted by B19V (Wan et al., 2010). The MRN complex, MDC1, and PCNA are recruited to the replication center to maintain genomic stability (Qiu et al., 2017). Notably, NS1 can localize to laser-induced DNA damage foci and function as a bridging molecule to mediate the association between the viral genome and the host DDR machinery. This process is dependent on early ATR signaling, ATR inhibition diminishes NS1-γ-H2AX colocalization and compromises viral replication efficiency (Morita et al., 2001). In the late stage of infection, sustained DDR signaling cooperates with NS1 and the 11-kDa protein to induce apoptosis: NS1 upregulates pro-apoptotic genes such as TNF-α and IL-6, while the 11-kDa protein activates the caspase-10 pathway (Chen et al., 2010b). Meanwhile, p53 induced by DDR mediates cell cycle arrest through p21 in the early stage and promotes mitochondrial apoptosis by activating Bax and Bak in the late

Table 2
The replication mechanisms of different viruses.

Virus	Viral Serotype	Specific replication mechanism	Critical molecules/conditions	Core characteristics	Reference
HBoV1	*Bocaparvovirus*	Regulates replication through its own non-structural proteins, with no need for helper viruses	Non-structural proteins NP1, NS1, NS2; long non-coding RNA BocaSR	Independent Replication: Replication is driven independently of helper viruses, relying on its own non-structural proteins (NS1, NS2, NP1) and the long non-coding RNA (BocaSR). NP1 Function–RNA Processing: The NP1 protein is an essential replication factor that regulates viral precursor mRNA processing. As a virus-specific RNA-processing factor, NP1 targets intronic regions and polyadenylation signals of viral pre-mRNAs, promoting accurate splicing and enhancing polyadenylation efficiency of transcripts from the viral late transcription unit. NS1 Function–Replication Initiation: NS1 acts as the core replication initiator. Possessing intrinsic helicase and nuclease activities, it binds to the Inverted Terminal Repeats (ITRs) of the viral genome to trigger rolling-circle replication. BocaSR Function–Polymerase Recruitment: The long non-coding RNA BocaSR promotes efficient viral DNA replication by recruiting the Y-family DNA polymerase to the replication center.	(Deng et al., 2016; Ning et al., 2024; Shao et al., 2021; Shen et al., 2016)
AAV	*Dependovirus*	Strictly relies on helper viruses or exogenous DNA damage signals	Helper virus factors (e.g., UL5/UL8/UL52, ICP8 of HSV-1; E1A/E2A/E4orf6 of AdV, etc.); AAVR receptor; Rep protein.	Helper Virus/Damage Dependence: Replication is strictly dependent on co-infection with helper viruses (e.g., AdV, HSV-1) or on the induction of exogenous DNA damage. Entry and Replication Initiation: Following viral entry mediated by the essential receptor AAVR, the endonuclease and helicase activities of the Rep proteins (Rep68/78) are required to initiate replication via the inverted terminal repeats (ITRs). Dependence on Cellular DNA Damage Response: Replication relies on signals from the cellular DNA damage response (DDR) regulated by the DNA-PK pathway, with viral replication centers (VRCs) colocalizing with DDR foci. Replication Mechanism: Viral DNA replication can proceed via rolling circle replication or strand displacement mechanisms, a process that is dependent on helper virus factors (e.g., HSV-1 ICP8, adenovirus E2A).	(Abrahams and Majumder, 2025; Boftsi et al., 2021; Meier et al., 2020; Seyffert et al., 2017; Yuan et al., 2024)
MVM	*Parvovirus*	Autonomous replication (without the need for helper viruses) and dependence on the host DNA Damage Response (DDR)	Non-structural protein NS1; Host ATR signaling pathway; Replication Protein A (RPA)	Helper Virus-Independent Replication: Capable of initiating autonomous replication without the assistance of helper viruses. Essential Role of NS1: The NS1 protein is critical for replication. It binds to viral ITRs, mediates strand cleavage, and simultaneously activates the host DNA Damage Response (DDR). Induction of Replication Stress: Induces replication stress by depleting host Replication Protein A (RPA), thereby creating a cellular state that promotes viral replication. Formation of APAR Bodies: Viral replication centers (termed Autonomous Parvovirus Associated Replication bodies, or APAR bodies) colocalize with cellular DNA damage sites. Modulation of ATR Signaling: Inhibits the phosphorylation of downstream substrates in the ATR signaling pathway, thereby	(Adeyemi et al., 2010; Etingov and Pintel, 2024; Haubold et al., 2023; Larsen and Majumder, 2023; Majumder et al., 2020)

(*continued on next page*)

Table 2 (*continued*)

Virus	Viral Serotype	Specific replication mechanism	Critical molecules/conditions	Core characteristics	Reference
				establishing a cellular environment conducive to viral replication.	
B19V	*Erythrovirus*	Exhibits extremely high host specificity and depends on the differentiation status of erythroid cells	Erythroid lineage-specific receptor (P antigen); Co-receptor integrin α5β1; DNA-dependent Protein Kinase (DNA-PK) pathway-related factors; Non-structural protein NS1	Strict Host and Cell Cycle Specificity: It exhibits extremely strong host specificity and replicates exclusively in human erythroid progenitors during the S phase. Dependence on Erythroid-Specific Factors: Its replication relies on: Transcriptional Regulation: Erythroid lineage-specific transcription factors to regulate viral promoters. Cellular Entry: The erythroid lineage-specific receptor (P antigen) and co-receptor integrin α5β1. Role of NS1 and Helper Virus Independence: Replication is initiated by the non-structural protein NS1, which activates the DNA-PK pathway. No helper virus is required, but replication is dependent on the specific differentiation state of erythroid lineage cells.	(Alvisi et al., 2023; Bonvicini et al., 2017; Ganaie and Qiu, 2018; Ganaie et al., 2017; Gigi and Anumba, 2021; Ning et al., 2023; Xu et al., 2017; Zhang et al., 2025; Zou et al., 2018)

stage (Zhi et al., 2006). This finely regulated apoptotic process facilitates the release of viral progeny while limiting excessive infection, ensuring efficient viral proliferation. Despite significant progress in current research on B19V, several issues remain unresolved. The precise molecular interactions mediating the targeting of DDR sites between NS1 and the ATR pathway require further validation. Additionally, the redundancy of host pathways hijacked by B19V-for instance, the partial dependence of replication center biogenesis on MRE11-merits in-depth investigation. Elucidating these mechanisms not only advances our understanding of parvovirus-host interactions but also identifies potential targets for the development of antiviral therapeutics against B19V-associated disorders (e.g., transient aplastic crisis and pure red cell aplasia).

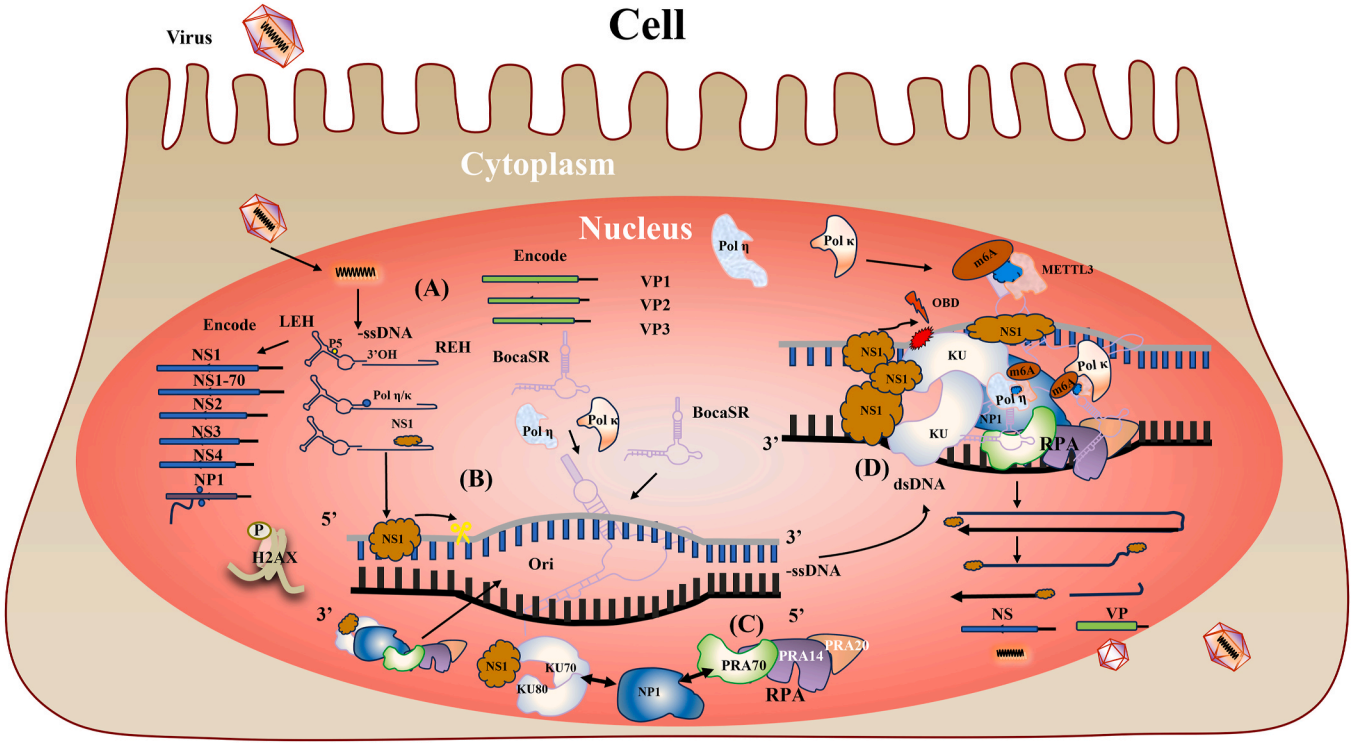

Figure-5. Replication mechanism of Human Bocavirus 1 (HBoV1). (A) Viral gene expression profile. HBoV1 encodes six non-structural proteins (NS1, NS1-70, NS2, NS3, NS4, NP1), a regulatory non-coding RNA (*BocaSR*), and three structural capsid proteins (VP1–VP3). **(B)** Replication initiation at the origin (Ori). NS1 introduces site-specific nicks at Ori and unwinds dsDNA via its helicase domain, inducing DNA damage and recruiting repair machinery (γ-H2AX, RPA, KU complex). **(C)** Replisome assembly NP1 serves as a scaffold bridging NS1 to the KU (KU70/KU80) and RPA (RPA70/RPA32/RPA14) complexes. The NS1-Ku70-NP1-RPA70 supercomplex facilitates extensive Ori unwinding. **(D)** DNA synthesis switch & m6A-mediated regulation. During ssDNA(−)→dsDNA conversion: *BocaS* recruits m6A methyltransferase METTL3 and Y-family DNA polymerases (Pol η/κ) to Ori. Replication initiates at the 3′-OH of the left-end hairpin (LEH), forming a replication initiation complex (RIC) with DDR proteins (KU, RPA) and NP1. RIC drives dsDNA transcription, viral protein expression, and *BocaSR* production to sustain replication.

3.4. Human bocavirus (HBoV)

Human bocavirus 1 (HBoV-1) is a ssDNA virus discovered in 2005 in nasopharyngeal samples from children with respiratory illnesses (Mohammadi, 2023). Similar to other parvovirus, bocaviruses replicate their DNA using an RHR mechanism. The left-end hairpin of the HBoV-1 genome is 140 nt long and can form a Y-shaped rabbit ear structure, which is hypothesized to be involved in the packaging of the HBoV1 genome. The left end of the genome also contains a single promoter, P5, which generates a unique precursor mRNA during viral transcription. The mRNA encodes various nonstructural proteins (e.g., NS1-70, NS1, NS2, NS3, NS4, and NP1) as well as the capsid proteins VP1, VP2, and VP3 (Shen et al., 2016). The right-end hairpin, meanwhile, contains a 46 nt region that interacts with the replication origin and serves as the minimal replication origin of HBoV1. It primarily includes the NS1 binding and cleavage sites (Yang et al., 2024) (Figure-5A).

The replication mechanism of HBoV1 is unique. Unlike other parvovirus, HBoV1 does not rely on cell cycle arrest and is the only parvovirus known to involve the activation of three PI3KKs to facilitate DNA replication (Deng et al., 2016). Moreover, during HBoV1 infection, no NS1 protein-induced DNA break ends are observed, which suggests that the HBoV1 NS1 protein recruits DDR damage proteins to form pseudo-DDR foci and activates PI3KKs without causing chromosomal DNA damage (Deng et al., 2017). Further studies have shown that HBoV1 induces DDR markers in HEK293 cells, including the phosphorylation of H2AX and RPA, as well as the recruitment of DNA damage repair proteins such as the KU complex (i.e., KU70 and KU80) (Deng et al., 2017; Ning et al., 2022) (Figure-5B).

Because NS1 does not directly interact with RPA or NP1, how do they interact to promote viral replication initiation? Research has revealed that HBoV1 directly interacts with the Ku70 protein of the KU complex and the RPA70 protein of the RPA complex (i.e., RPA70, RPA32, and RPA14). In the process, NP1 acts as a bridge that facilitates the recruitment of the RPA complex to the viral DNA replication origin through NS1–Ku70–NP1 interactions (Ning et al., 2022) (Figure-5C). Moreover, HBoV1 transcribes a unique small non-coding RNA (i.e., BocaSR) from the non-coding region at the 3' end of the genome via intragenic RNA polymerase III, which plays a direct role in viral replication (Wang et al., 2017). Nevertheless, the mechanism by which BocaSR promotes viral genome replication remains unclear.

A model of N6-methyladenosine (m6A)-regulated HBoV1 DNA replication involving BocaSR has recently been proposed. BocaSR undergoes m6A modification at multiple sites and interacts with m6A processing protein complexes. It may also interact with the negative strand of the HBoV1 genome at the replication origin located within the right-end hairpin. The replicative origin of the viral replicative form RF DNA is recognized and bound by the N-terminal domain of the viral large nonstructural protein NS1, which includes the DNA-binding or endonuclease domain and the central helicase domain, thereby forming the origin-binding domain. NS1 nicks the origin and unwinds it through its helicase activity (Mohammadi, 2023) (Figure-5B).

Subsequently, the complex formed by m6A-modified BocaSR and METTL3 (potentially in coordination with other m6A processing-related proteins) specifically recruits Y-family DNA polymerases Pol η and Pol κ to the 3′-OH primer site within the left-end hairpin of the viral genome, initiating the conversion of the ssDNA genome into dsRF DNA (Ning et al., 2024) (Figure-5D). Following the formation of dsRF DNA, the viral non-structural protein NS1 recognizes and binds to the terminal resolution site (trs) within the right-end origin of replication via its N-terminal endonuclease domain. Simultaneously, it exerts helicase activity to unwind the dsRF DNA duplex and cleaves the trs site through its endonuclease activity, initiating strand displacement synthesis via the RHR mechanism. During this process, the KU complex (KU70/KU80) rapidly binds to the DNA break ends to maintain the stability of the replication fork; the RPA complex continuously associates with the nascent ssDNA to prevent non-specific reannealing; and the viral NP1 protein acts as a bridging molecule, cooperating with host replication factors to further promote replication fork progression. Concurrently, DNA damage repair-related proteins, the KU complex, RPA, and NP1 gradually localize to the origin of replication region, assembling into a functionally intact replication initiation complex. This complex not only ensures the sustained progression of viral DNA replication but also facilitates the transcription of the dsRF DNA template, providing support for the continuous expression of viral proteins (e.g., NS1, VP family proteins) and the non-coding RNA BocaSR. Ultimately, a large number of progeny ssDNA are generated for the assembly of new viral particles (Ning et al., 2022, 2024) (Figure-5D). Recent insights suggest that HBoV-1 replication may alter epithelial barrier function, trigger the DDR, and activate the NLRP3 inflammasome, which leads to pyroptosis. Moreover, because HBoV-1 infection upregulates the expression of anti-apoptotic genes BIRC6 and IFI6, it may favor chronic infection through pyroptosis instead of apoptosis, because the mechanism may be more conducive to its own replication.

In recent years, HBoV-1 has been widely studied for its potential applications in oncolytic anticancer drugs, antiviral therapies, and vaccine vectors (Hartley et al., 2020). However, a deeper understanding of how HBoV infects host cells is a prerequisite for its effective development and utilization. Researchers can identify drug targets based on the underlying molecular mechanisms of viral infection, better elicit human immune responses, and provide a theoretical foundation for the treatment and prevention of HBoV infections. Notably, as members of the Parvoviridae family, HBoV-1 and AAVs differ markedly in their helper dependency profiles—a distinction that directly influences vector development and production. AAVs are categorized as helper-dependent defective viruses, requiring gene products (e.g., E2A, E4, VA) from helper viruses (e.g., adenoviruses [AdVs]) or, alternatively, a cellular environment induced by genotoxic agents to support efficient replication and progeny production. In contrast, the autonomously replicating HBoV-1 can function as a novel helper virus for AAV replication. Its helper function depends on the synergistic action of non-structural proteins NP1 and NS2 as well as the non-coding RNA BocaSR, without relying on its own replication or the DDR pathway. At the vector production level, recombinant AAV (rAAV) generated using the HBoV-1 helper system displays comparable transduction efficiency to that produced with the AdV helper system, yet its initial yield is reduced by 1–2 orders of magnitude, primarily due to insufficient expression of AAV Rep52 and capsid proteins. However, exogenous enhancement of the expression of these key proteins or construction of a dual-helper system by fusing the Ad*V**E2A* gene can increase the vector yield to 50%–70% or even higher compared with the AdV helper system. This provides a novel strategy for developing AdV-independent rAAV production systems and expanding the range of applicable cell types for vector propagation.

4. Parvovirus nuclear egress

During the late stage of parvovirus infection, the nuclear assembly of progeny capsids is accompanied by virus-induced G_2/M phase cell cycle arrest (Mattola et al., 2022b). The cell cycle regulatory protein Cdk1 and the inhibitor of pro-apoptotic caspase 3 have been shown to reduce nuclear envelope permeability and the nuclear export of non-phosphorylated capsids (Mühlbauer et al., 2015). This observation suggests that apoptosis can passively release a subset of non-phosphorylated viral particles (Figure-6A). Although this nuclear export pathway is thoroughly documented, the underlying mechanisms remain elusive. We propose that apoptosis-mediated nuclear export is closely associated with the caspase-dependent activation of initiator caspases 8/9 and effector caspases 3/7 (Figure-4C). Moreover, Cdk1-mediated activation of the G2/M checkpoint, which leads to mitotic dissolution of the nuclear envelope and increased nuclear permeability, also plays an indispensable role in the process.

Other studies have revealed that parvovirus utilize the nuclear export receptor CRM1 (i.e., exportin 1) to mediate active transport

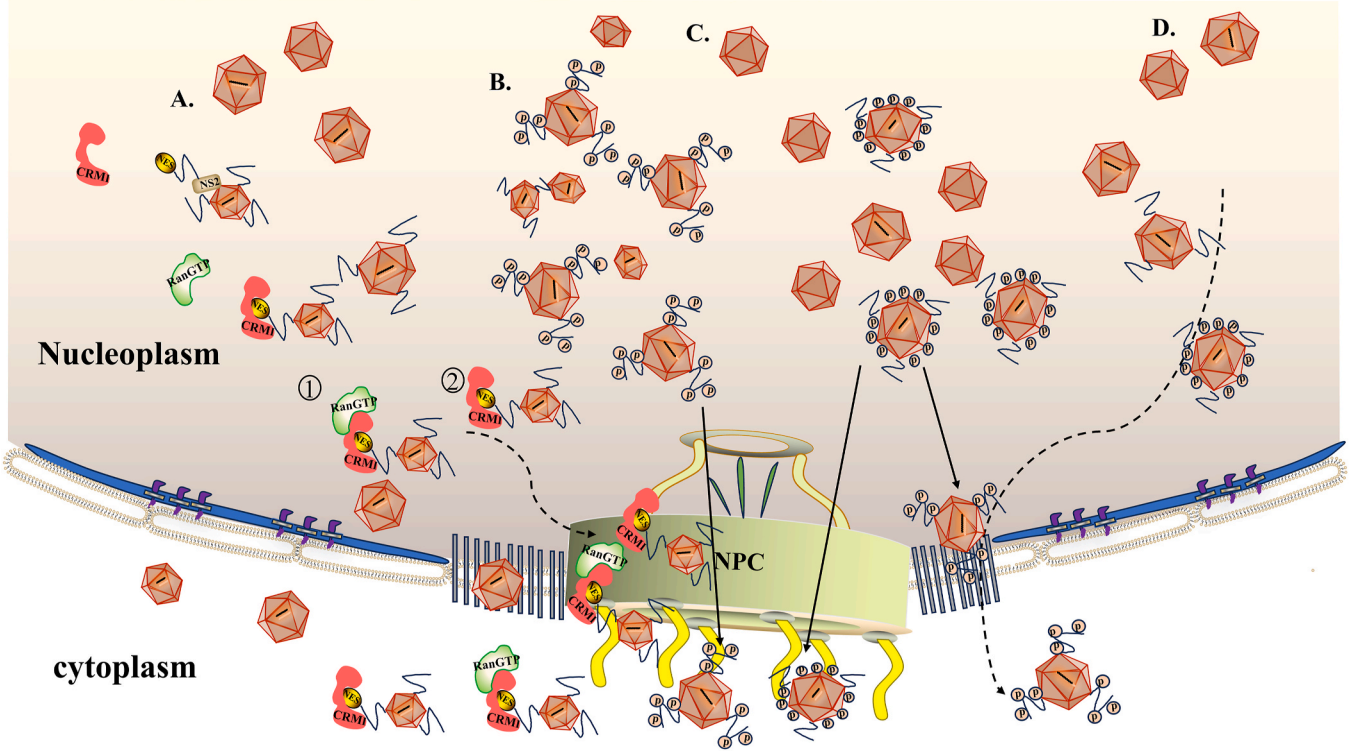

Figure-6. Nuclear egress of parvoviral capsids. (A) Apoptosis-mediated leakage. Late-stage apoptosis increases nuclear envelope permeability, enabling passive capsid release into the cytoplasm. **(B)** CRM1-dependent export (MVM model). NS2's NES binds CRM1, forming a RanGTP-CRM1-NES ternary complex for NPC-mediated nuclear export. **(C)** Active NPC trafficking. NES-CRM1 interactions direct capsid translocation through NPCs in an energy-dependent manner. **(D)** Phosphorylation-regulated export. VP2 N-terminal phosphorylation generates an auxiliary NES, augmenting capsid nuclear export efficiency.

through the NPC [83]. This nuclear export mechanism has been validated in a mutant model (NS2-Crm1Δ), in which the mutant viral particles accumulated in the nucleus (Bodendorf et al., 1999). Consistent with this finding, treatment the CRM1 inhibitor leptomycin B yielded the same conclusion (Mattola et al., 2022b). Similarly, point mutations in NS2 protein variants (e.g., T88A, K96E, L103P, and L153M) enhance binding to CRM1, thereby improving the nuclear export capacity of capsids—supporting the critical role of CRM1 in the nuclear export process. Additionally, the virus may modify its own functional sites to interact with host factors, thus alleviating stress under different environmental conditions. The binding of CRM1 to its cargo is driven by RanGTP, and the formation of a RanGTP–CRM1–nuclear export signal (NES) trimeric complex, mediated by the NES in NS2, facilitates transport through the NPC to the cytoplasm (Ferreira et al., 2020a). Interestingly, in MVM, CRM1 has been found to interact with NS2 in a RanGTP-independent manner (Eichwald et al., 2002; Fu et al., 2018; Mattola et al., 2022b; Wolfisberg et al., 2016) (Figure-6B), which suggests the possibility of a mechanism in which CRM1 directly binds to the NES surface to mediate parvovirus nuclear export (Figure-6C). When the CRM1-mediated nuclear export pathway is blocked by LMB, viral capsids are reduced but not completely suppressed (Cao et al., 2022), which suggests that parvovirus capsids may utilize redundant nuclear export pathways.

Evidence from multiple studies supports the existence of a CRM1-independent capsid nuclear export pathway. In support of this notion, two distinct populations of full capsid viral particles (FC-P1 and FC-P2) were isolated from the nuclei of MVM-infected cells, and FC-P2 was found to undergo active nuclear export in infected host cells, independent of CRM1 activity (Wolfisberg et al., 2016). It was also observed that Raf-1 kinase-mediated phosphorylation of three serine residues at the N-terminus of VP2 on the MVM capsid surface enhances nuclear export (Figure-6D). The diverse strategies employed by parvovirus to mediate nuclear export of viral particles highlight their cunning adaptability in navigating the nuclear export mechanisms in host cells.

5. Conclusion and future directions

The dynamic interaction between parvovirus and host proteins adds to the complexity of research. Although many issues appear to have been reported, these interactions are not actually related to the virus replication and infection process. The exact mechanisms of how parvovirus induces the DDR response, how DDR damage protein factors interact with the viral genome, the precise mechanisms of immune evasion, and the structures and pathways involved in nuclear entry remain unclear. As these questions are answered, the mechanisms behind parvovirus's continuous transmission in the ecological environment will be unveiled. This will enable us to fully harness parvovirus's potential, transforming it from a waste into a valuable asset. As parvovirus is increasingly utilized as a safer, broader-spectrum, and more efficient therapeutic or delivery vector, its clinical applications will become more widespread, benefiting humanity.

In the future, researchers should continue to address challenges including parvovirus capsid modification, hybrid vector construction, regulatory element insertion, adaptive mutant selection, and the development of armed recombinant parvovirus vectors. As these challenges are answered, the mechanisms underlying the persistent transmission of parvoviruses in ecological niches will be elucidated, enabling researchers to fully harness viral potential by engineering them into valuable biotherapeutic assets. Altogether, this review has revealed the molecular mechanisms behind the interactions between parvovirus and host cells that promote viral infection, which offers a foundation for further research on the widespread transmission of parvovirus in nature and the development of universal vaccine targets.

CRediT authorship contribution statement

Aofei Yang: Writing – review & editing, Writing – original draft. **Jian Chen:** Writing – review & editing. **Chengshui Liao:** Data curation, Conceptualization. **Bichen Miao:** Writing – review & editing, Formal analysis, Data curation. **Songbiao Chen:** Writing – review & editing, Resources, Project administration, Methodology, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.virol.2026.110819.

Data availability

No data was used for the research described in the article.

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