# Life Cycles and Mechanism of Viral Replication in Various DNA and RNA Viruses

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## Abstract

Viruses are obligate intracellular particles that make use of host biosynthetic machinery in order to cause diseases in humans, animals, and plants. The most prevalent type of life, viruses, affect almost all living things. Subsequently, human suffering and economic loss are major causes of these obligatory parasites. The viral DNA genome has a wide interaction with the cellular pathway, which detects and repairs damage to the cell's DNA. The contacts take place throughout the viral life cycle and result in a variety of effects for effective viral DNA replication. To create and spread viral particles, viruses, which are inherently infectious agents, take advantage of the molecular infrastructure of host cells. Since the viral infection mechanism is modular, synthetic biology methods are best adapted to address it. Since several ion channel-blocking drugs are currently available for the treatment of other human diseases, some of these drugs also have *in vitro* and occasionally *in vivo* antiviral activity, and targeting host ion channels is a promising therapeutic strategy.

Keywords: Viruses, Genome, Replication, Infectious, Drugs

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## Introduction

The most prevalent type of life, viruses, affect almost all living things. Subsequently, human suffering and economic loss are major causes of these obligatory parasites (Gergerich & Dolja, 2006). In Biology, the organization and origin of such a huge virosphere is an extremely important issue. Viruses that infect evolutionarily diverged organisms, such as bacteria and humans, have generally been viewed as being distinct. The number of particles in the biosphere is estimated to be $10^{31}$– $10^{32}$ particles (Bamford et al., 2005; Zhang et al., 2018).

The sequencing of the genome revealed that only about 5% of their DNA contains details for eukaryotes. It is believed that viral or transposon origin accounts for a large part of the remainder (Wei et al., 2017). There are not so many extra genes in a bacterium's genome, but they do contain the genomes of a virus or its remnants. Despite their small size, viruses undoubtedly perform a significant function as obligate cellular parasites, ensuring their own production and influencing the host cells (Harvey & Holmes, 2022).

A wealth of information that could be used for the creation of viruses' genetic and chromosomal phylogenies, as well as to analyze complex relationships between virus genomes, was generated by genotyping and gene comparison, e.g., studies on the tail bacteriophages (Hendrix et al., 1999; Strachan & Read, 2018). Viruses have long been a preferred model system for the study of structures and functions because they are essentially easy-living beings that can, in principle, be produced very readily and usually possess an ordinary structure. In the past few months, major advances have been made in identifying the crystal structure of very complex viruses (Caspar & Klug, 1962; Stuart & Grimes, 2006).

Viral capsids have a protective effect on the genetic sequence of nucleic acid and thus produce capsid proteins (Harrison et al., 2023). Using the capsid protein of viruses, the development of icosahedral capsids is easy (Lucas & Knipe, 2001; Mateu, 2013; Harrison et al., 2023). There are similarities between the capsid protein-coding areas of viruses that infect cells from all three domains of life at the nucleotide level, reproducing a previously proposed structure-based categorization of icosahedral viral capsids (Koonin et al., 2015; Sinclair et al., 2017). A variety of DNA replication strategies for viruses have been developed due to the abundance of genetic diversity in virus genomes (Koonin & Dolja, 2013). A specific group of proteins involved in the genome replication process is encoded by each virus. The smaller the genome of a virus, the less able it is to code and the more cellular processes it will have to be exploited (Adriaenssens & Cowan, 2014). To guarantee optimal fidelity and connectivity with the rest of chromatin, replication of eukaryotic DNA is itself subject to an extensive set of controls (Zeman & Cimprich, 2014).

In addition to affecting cellular function and the immune system, interactions between the host and the virus, as well as the way

that viruses react to one another during evolution, have also had an impact on the countermeasures that viruses employ (Gutiérrez-González & Santos-Mendoza, 2019). Accordingly, it is no surprise that they are able to evade detection and modify host physiology by manipulating the normal cellular pathways to their gain (Sanjuán & Domingo-Calap, 2016). Apoptosis, cysteinylated signalling, intracellular protein transmission, MHC-restricted antigen presentation, cell cycle regulation, and humoral immune responses are among them (Krump & You, 2018). In addition, viruses are commonly able to manipulate host cell cycles to produce an advantageous environment for replication, much of this based on deregulating cellular cycle checkpoints (Bagga & Bouchard, 2014; Fan et al., 2018; Jane Flint et al., 2020).

When DNA injury is identified, it activates cellular factors to fix the injury and synchronizes with cell cycle seize (Mjelle et al., 2015). In order to avoid the harmful finding of their genome by this host gene repair machine, DNA viruses are evolving strategies for limiting its detrimental replication and utilizing the machinery of these pathways in order to be able to maintain a consistent reproduction of their genomes (Maréchal & Zou, 2013).

Viral genome detection and DDR signaling activation may take place during viral genome entry into the nucleus, active viral DNA synthesis, integration into the host genome, or persistence of extra-chromosomal viral genomes (McKinney et al., 2015; Weitzman & Fradet-Turcotte, 2018). By directly interacting with cell components, by altering the progression and stress on replication cells, viral proteins may have an impact on damage sensing and repair machinery (Saldivar et al., 2017). Cellular DNA damage response keeps the integrity of the genome intact and protects the cell from DNA damage induced by endogenous and exogenous agents (Heijink et al., 2013; Gomez & Hergovich, 2016; Hustedt & Durocher, 2017).

DNA replication of the host cell is a highly synchronized process involving intricate apparatus, including helicases, which split the DNA duplex, priming enzymes, and polymerases, which make new strands.(Afonin et al., 2014; Nikoomanzar et al., 2020). Inability to fix damage causes apoptosis or senescence, whereas inaccurate repair results in the acquisition of cancer hallmarks that allow tumor cells to multiply and spread (Weitzman & Fradet-Turcotte, 2018).

There is a whole range of viruses out there. Some of them, for example, the influenza virus, etc., are entirely dependent on host cells for the completion of the replication cycle (Dimmock & Easton, 2014). For Influenza, there are around 11 different proteins that need to be obtained at major steps of the virus duplication round. Influenza viruses enter the cell via receptors that moderate endocytosis, which transports them to a late endosome where they fuse and discharge their genetic material into the cells (Dubois et al., 2014). The segments of the genome will then be transferred to a nucleus where viral polymerases, which stimulate together transcription and replication reactions, generate new virus proteins as well as newly synthesized genetic copies. New segments of the chromosomes are released from the nucleus and inserted into the cell membrane, mutually with key virus protein components that make up the virion (McDonald et al., 2016; Rampersad & Tennant, 2018). The developing viral constituent part is removed from its cell membrane and disseminated to the external surroundings at the end of each step. The contents of this chapter are concentrated on the current understanding of the molecular components of cell cycle regulation that are frequently impacted by viruses.

## RNA Virus

RNA viruses have a special mechanism of action for host attachment (Simpson & Yamauchi, 2020). Firstly, the RNA virus, i.e., influenza virus, is bound to its receptor, sialic acid, by an envelope protein named H-agglutinin HDA. The virus primarily enters cells through clathrin-mediated endocytosis in the next move, but there are also other, less common, integrated uptake mechanisms (McMahon & Boucrot, 2011). The transition of the endosome from early to late endosome is the third phase, and the fusion of the viral. There is a fourth step where the endosomal membrane fuses with viral proteins. The release of the viral ribonucleoprotein (vRNP) complexes from the layer of matrix protein M1 is referred to as viral uncoating in the next stage. Finally, the unconfined vRNPs are carried into the nucleus of the host cell, which is a sign of winning entry.

## Influenza Virus Life Cycle

Influenza viruses replicate and transcribe their DNA into a cell's nucleus (Samji, 2009). Viral RNP containing vRNAs with negative-sense function as a guide for transcription and duplication after entering the nucleus. Its nucleus has a special mechanism of priming transcription called "cap-snatching." This method is used by the heterotrimeric polymerase complex (PB1, PB2, PA) that is linked with each RNP ( Velthuis & Fodor, 2016). Furthermore, replication is initiated without a prioritization in comparison to transcription. The latest structural data show that the polymerase complex undergoes significant rearrangement, though it is still unclear what causes the polymerase to switch between transcriptional and reproductive modes (Blanchard et al., 2020). It is sufficient to say that host functions are directly involved in the production of both viral transcripts and new copies of the viral genome. pp32 and APRIL, both of which are also called ANP32a and ANP32B, represent the only factors to date that have been suggested as a key factor in promoting virus genome replication. These two factors have been found in fractionated uranium, and the synthesis of vRNA has been demonstrated to be supported by a CRNA template (Shaw & Stertz, 2018).

A vibrant and membrane-confined multi-protein congregation, named the replication complex, induces the synthesis of RNA during the replication process of the virus. The receptor, which is located close to the nucleus, consists of both virus and host cell proteins that are assembled into sacs with a membrane consisting of an endoplasmic reticulum (Lescar et al., 2018).

Virus-determined proteins are crucial for the duplication of the virus. A number of studies have shown that the UPS acts as an antiviral system by dephosphorylating virus proteins. The UPS has been reported to degrade a variety of HBV proteins until now (Sompayrac, 2013). Innate immunity of the host cell provides the first line of defense against infections caused by viruses. Viral PAMPs molecules possess a receptor site named pattern recognition receptor site (PRRs) which stimulates the production of stimulator of interferon genes (STING) and a receptor site called RIG-like receptor (RLPs), and nucleic acid sensing PRRs, enabling host cells to start the production of interferons, cytokines, and the activation of intracellular pathways in order to eradicate the virus (Kumagai & Akira, 2010; Kong et al., 2019).

HCV Life Cycle

The first step is the attachment of the virus to the cell. There are many cellular factors that facilitate the ingress of HCV constituents in hepatocytes, such as proteins, lipids, and glycans (Kim & Chang, 2013). HCV primarily attaches itself to surface proteoglycans, for example, a scavenger receptor BI or tetraspanin CD81. Claudin1 and occluding proteins have become indispensable for HCV entry after lateral migration to tight junctions (Treyer & Müsch, 2013). In low pH conditions, HCV constituents are ingested by clathrin-mediated endocytosis and then amalgamated to the endosomal membrane. In turn, the cytoplasm is opened up by viral genomic RNA (Wommack & Colwell, 2000).

The HCV genomic RNA is then utilized for both viral RNA proliferation and protein translation. Replication of the HCV occurs inside the endoplasmic reticulum. Finally, HCV constructs viral particles and leaves cells by using the biosynthetic pathway for very low-density lipoproteins (Zeman & Cimprich, 2014; Stoeck et al., 2018). 96000 nucleotides of the HCV genome have a single reading frame and 50 and 30 untranslated sections on either side of it. The translation of viral RNAs results in the production of a polyprotein, which is processed through both cellular and viral protease enzymes to produce specific viral proteins (Dougherty & Semler, 1993). The major components of HCV particles are the Structural proteins, e.g., core and outer glycoproteins E1 and E2, whereas viroporin p7 and a nonstructural protein 2NS2 take part in a vital role in viral assembly (Hustedt & Durocher, 2017). The duplication complex consists of the remaining unstructured proteins NS3, NS4A, NS4B, NS5A, and NS5B, which have a definite job in viral genome expansion (Staufer et al., 2022).

A protein family known as APOBEC deaminates cytosines found in nucleic acids. It is composed of apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like (APOBEC) proteins (Nabel et al., 2012). The numerous mechanisms that viruses use to prevent APOBEC function and the initiation of ApoBEC proteins by type I interferons, NKPNs, which induce antiviral status in contaminated or neighbouring cells, illustrate this inhibitory relationship (Pecori et al., 2022). First, the ability for APOBEC to inhibit viral replication has been demonstrated in studies with HIV 1, where there was a be short of expression of an infectious factor known as VPV, encoded by a gene originally called sor (Abdulrahman Ashy & Agustí, 2020).

DNA Virus Life Cycle

When it carries HBV envelope proteins, the HDV virion enters cells by an identical mechanism. The virus specifically interacts with the Na+-taurocholate co-transporting polypeptide (NTCP) and the epidermal growth factor receptor (EGFR) after attaching to heparan sulphate proteoglycans on the surface of the hepatocytes (Zakrzewicz & Geyer, 2023). For HDV mRNA transcription from circular HDV RNAs, it is essential that you have SAgHD to start, but only small quantities are required (Lucifora & Delphin, 2020). Various mechanisms that could include Pol I-like polymerases may regulate the synthesis of HDVANG RNA, which was described to be produced in the nucleolus. The assembly, release, and infection rate of HDV particles are influenced by the sequences and HBsAg levels (Hill et al., 2018).

Foamy Viruses

Unlike other retroviruses and hepadnaviruses, foamy viruses (FVs) have a different reproduction method. There are two steps to the retrovirus replication cycle. The receptor-mediated entry, reverse transcription of the RNA genome to produce cDNA, transport of the pre-integration complex to the nucleus, and integration of the provirus are all steps in the early phase (Targett-Adams et al., 2008). The entire proviral gene expression process, the production and modification of viral proteins, the packing of the diploid RNA genome, the construction of capsids, and their release via budding from the cell membrane are all included in the late phase (Jeeva et al., 2019). The maturation of the Gag and Pol precursor molecules is thought to take place late in the budding phase or after virus release. The discovery of DNA in external virions led us to the hypothesis that the point at which reverse transcription of the RNA genome takes place in HFV may differ from that in the retroviral replication cycle (Wilhelm & Wilhelm, 2001).

During their replication cycles, long terminal repeat (LTR) retrotransposons and retroviruses both utilize cellular tRNAs as primers for reverse transcription. Primer tRNAs are specifically packaged into the virion of retroviruses, where it is bound to the viral RNA genome's primer binding site (PBS) and used to prime reverse transcriptase's (RT) catalyzed production of minus-strand cDNA (Wilhelm & Wilhelm, 2001).

LTR retrotransposons and retroviruses exhibit striking parallels in their replication cycles. The proteins Gag and Gag-Pol are encoded by both retroviruses and retrotransposons. The sequences for matrix (MA), capsid (CA), and nucleocapsid (NC) proteins are found in retroviral Gag proteins, whereas the sequences for CA and, occasionally, NC proteins are found in retrotransposon Gag proteins (Olson & Musier-Forsyth, 2019). For protease (PR), RT, and integrase (IN), the retroviral and retrotransposon pol genes are both responsible. When the envelope protein (Env) is present, several different types of retroviruses enter an extracellular stage of their life cycle. A VLP without Env protein is created throughout the replication cycle of the majority of retrotransposon elements (Boeke & Corces, 1989). Some gipsy elements do have an extracellular stage, and this is connected to the presence of Env protein. The precursor proteins Gag and Gag-Pol, as well as low-molecular-weight tRNAs, are encoded by the full-length RNA that is synthesized from proviral or retrotransposon elements. These particles in the cytoplasm package the full-length mRNA. A viral protease cleaves the Gag and Gag-Pol precursor proteins into the final mature proteins in both particle types. Both retroviruses and retrotransposons employ cellular tRNAs to prime the reverse transcription of the packaged RNA, and the double-stranded cDNA that results is then integrated into the host cell DNA by virally or retrotransposon-encoded IN (Moebes et al., 1997).

HIV -1 Life Cycle

The life cycle of this virus is divided into an initial and a late phase of replication. The genetic material, such as the DNA of the provirus, is integrated into the genome of the host when the early phase ends, which starts with the virion adhering to the cell surface (Nisole & Saïb, 2004). The initiation of the transcription indicates the end stage of the replication of the virus, which concludes with the discharge of fully infectious offspring virions. HIV needs the CD4+ receptor site to bind to the host cell and is associated with apoptosis of both infected and uninfected cells. High mutation rate is observed, 1 mistake per 10,000 nucleotides in HIV, and viral load varies from person to person, known

as quasi-species (Domingo, 2003). Finally, CD4+ helper T cells, which are essential for the upkeep of a functional immune system, are infected by HIV and killed (Hokello et al., 2019). Different cell types can become infected, where viral replication takes different times, and the outcomes of infected cells can differ. For instance, macrophages have the ability to manufacture HIV over a period of weeks and retain infectious virions inside their cells (Wilen et al., 2012).

## Mechanism of Replication

### Attachment

Binding of the virus to its host cell is mediated by the cell membrane with several proteins that serve as a receptor site binding facilitator, and an ion transporter. The viral attachment proteins of the virus interact with the host receptor site. Virus, after attachment, takes control of the site for its exploitation. Rhinovirus binds to intracellular adhesion molecule, ICAM-1, which allows attachment from one cell to another. Herpes simplex Virus makes reversible binding to glycosaminoglycans (GAGS) for making its attachment to the cell surface receptor. HIV uses the CD4 receptor site for its attachment to the host cell (Burrell et al., 2016; Louten, 2016).

### Penetration

After successfully entering the cell, the virus enters the host cell by avoiding the flow of mucus. Virus uses the endocytosis mechanism to cross the cell membrane barrier of the cell. In this process, cell surface receptors are occupied by the ligands and internalized in pits coated by clathrin to make endocytic vesicles. At the sudden, these vessels lose their coating and make fusion with early endosome (decreased acidity 6-6.5pH) and late endosome (increased acidity 5- 6pH) and then transport it to lysosome, such as dengue virus and hepatitis C virus (Louten, 2016).

### Uncoating

Removal of the capsid for the incorporation of the viral genome into the cell, where replication of the virus takes place called uncoating. For example, haemagglutinin (HA) proteins are embedded in the viral capsid of the influenza virus. It uses respiratory epithelial cells to bind to the cell surface and receptor receptor-mediated endocytosis pathway for penetration into the cell. This causes conformational changes in the early endosome due to low pH, revealing the fusion peptide of the two membranes with each other. Fusion of the viral envelope occurs with the endosomal membrane with the facilitation of HA proteins. The released RNA genome is transported to the nucleus of the cell via nucleopores, such as the influenza virus. In the polio virus, it is not transported to the nucleus (Burrell et al., 2016; Louten, 2016).

### Replication

Viral genome directs the synthesis of viral proteins. Expression of viral genes is required for the incorporation of viral proteins into the virion in order to synthesize new virions. The mechanism of viral replication typically relies on the nucleic acid of its genome. Virus uses different strategies for its classification as discussed in the Baltimore classification system of viral replication (Jane Flint et al., 2020). For example, in the case of ssDNA viruses, after entering the nucleus of the host cell, the ssDNA genome is converted to dsDNA in the presence of DNA polymerase because parvoviruses contain hairpin ends that complementarily bind to the cell and fold back, called self-priming. After that, transcription of viral genes occurs with the help of RNA polymerase II, which is then translated into viral proteins. DNA polymerase will then help in the replication of the genome, releasing new virions (Jane Flint et al., 2020).

### Assembly

After replication, newly synthesized cells are released from the cell and undergo assembly. The viral assembly may occur on different sites depending upon the type of virus, such as in the Golgi complex, the nucleus, or the plasma membrane. In cases of picornaviruses and parvoviruses, self-assembly of the viruses occurs within capsid proteins. Scaffolding proteins, also known as chaperone proteins, are the site of assembly of complex viruses like adenoviruses and herpesviruses. Assembly of non-enveloped viruses occurs through nucleocapsid (Louten, 2016; Jane Flint et al., 2020).

### Maturation and Release

When HIV proteins come in contact with the plasma membrane of the cell, they form a fusion bud. After that, the packaging of the diploid RNA genome occurs in the assembling capsid. This process causes the release of the virus from the cell, but Gag proteins remain unencapsulated. The protease enzyme contained by the HIV accomplishes the cleavage of polyproteins, inducing the cleavage of capsid and matrix proteins and hence completes the infection cycle (Louten, 2016).

After maturation, viruses are released into the extracellular environment in order to complete their infectious cycle. The release of the virus happens in different ways depending on the type of virus. Enveloped viruses assemble in their plasma membrane and embed their proteins inside it. Viral capsid protein and membrane-associated viral proteins interact with each other, forming a curve around each other until the membrane is wrapped fully and the virus is released, called budding. For example, Rubella virus (Louten, 2016).

Infections are the most abundant organic substances in the seas, and a large proportion of them are bacteriophages. Two major classes of viral contamination can be classified: lysogenic and lytic. In the lysogenic cycle, phage DNA integrates stably cooperations inside the host cell, described as a mild phage, and it permits the phage genome to replicate in the host cells until being prompted by specific signals to become lytic (Figure 1). The infection replicates in the lytic cycle, finally leading to the destruction of the host cell and the formation of virions (Abdulrahman Ashy & Agustí, 2020).

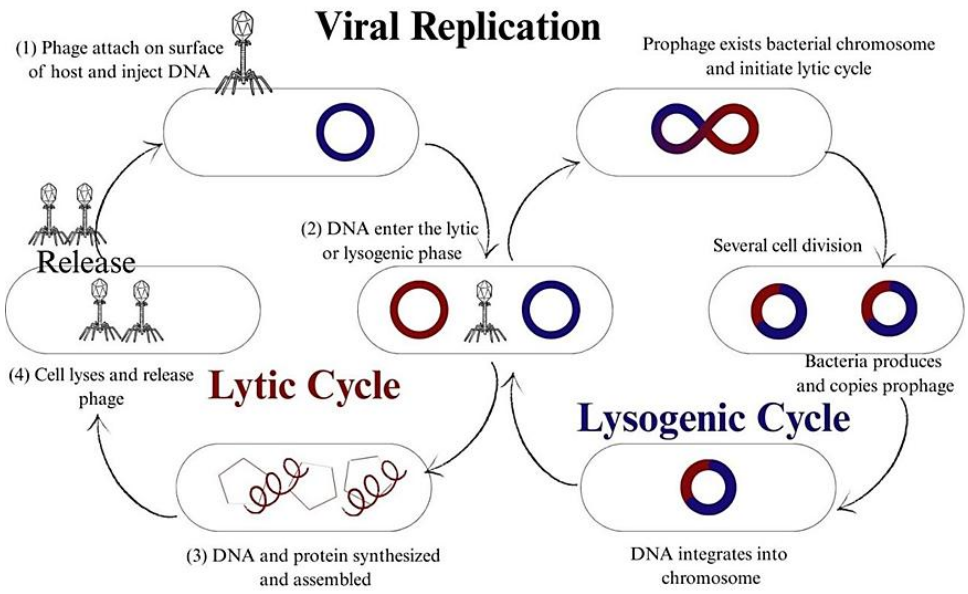


Fig. 1: Showing an overview of the lytic and lysogenic cycle of replication of viruses (image created at canva.com)

Role of Ion Channels in Viral Replication

Ion channels are necessary for the effective reproduction of a wide range of viruses, such as the influenza A virus, human immunodeficiency virus, the Middle East respiratory syndrome coronavirus, and severe acute respiratory syndrome coronavirus (Dyall et al., 2017). In order to reduce viral replication and aid in the treatment of viral infections, focusing on host ion channels may be a useful strategy. Since several ion channel-blocking drugs are currently available for the treatment of other human diseases, some of these drugs also have in vitro and occasionally in vivo antiviral activity, and targeting host ion channels is a promising therapeutic strategy (Kumari et al., 2023). It may therefore be possible to repurpose ion channel inhibitors for the treatment of viral illnesses by identifying the precise ion channels implicated in replicative cycles. Ca2+, Cl-, K+, and Na+ ions are the most common ions to pass through channels. For instance, Ca2+ plays a part in the viral life cycle's entry phase for the following viruses: Rota virus, the Ebola virus, the influenza A virus, and other Coronaviridae species (Russell et al., 2022).

Conclusion

Viruses are obligate intracellular particles that make use of host biosynthetic machinery in humans, animals, and plants. They contain nucleic acid and a capsid made up of capsomeres. Viral capsids have a protective effect on the genetic sequence of nucleic acid and thus produce capsid proteins. Only the nucleic acid causes damage to host cells. The virus uses several strategies and molecular targets to circumvent host cellular processes at the same time as evading detection. Apoptosis, cysteinylated signalling, intracellular protein transmission, MHC-restricted antigen presentation, cell cycle regulation, and humoral immune responses are among them. Each DNA and RNA virus has its own mechanism of replication.

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