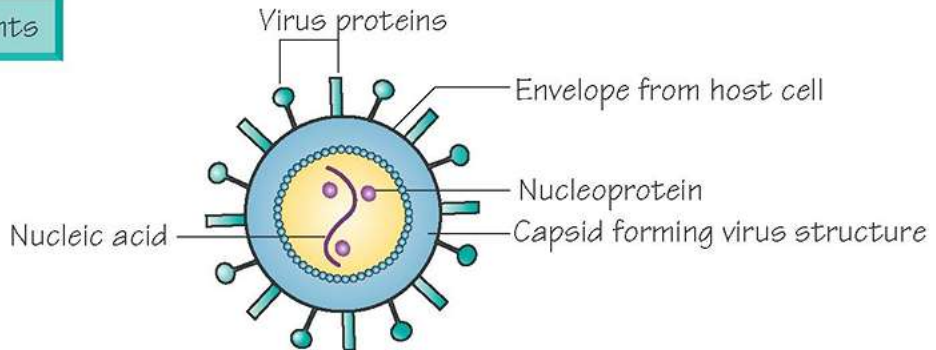
Positive-strand RNA viruses (**+ssRNA viruses**) are a group of related viruses that have positive-sense, single-stranded genomes made of ribonucleic acid. The positive-sense genome can act as messenger RNA (mRNA) and can be directly translated into viral proteins by the host cell's ribosomes. Positive-strand RNA viruses encode an RNA-dependent RNA polymerase (RdRp) which is used during replication of the genome to synthesize a negative-sense antigenome that is then used as a template to create a new positive-sense viral genome.

Possible structural components



ds DNA
Herpesvirus
Pox virus
Adenovirus
Hepadnavirus

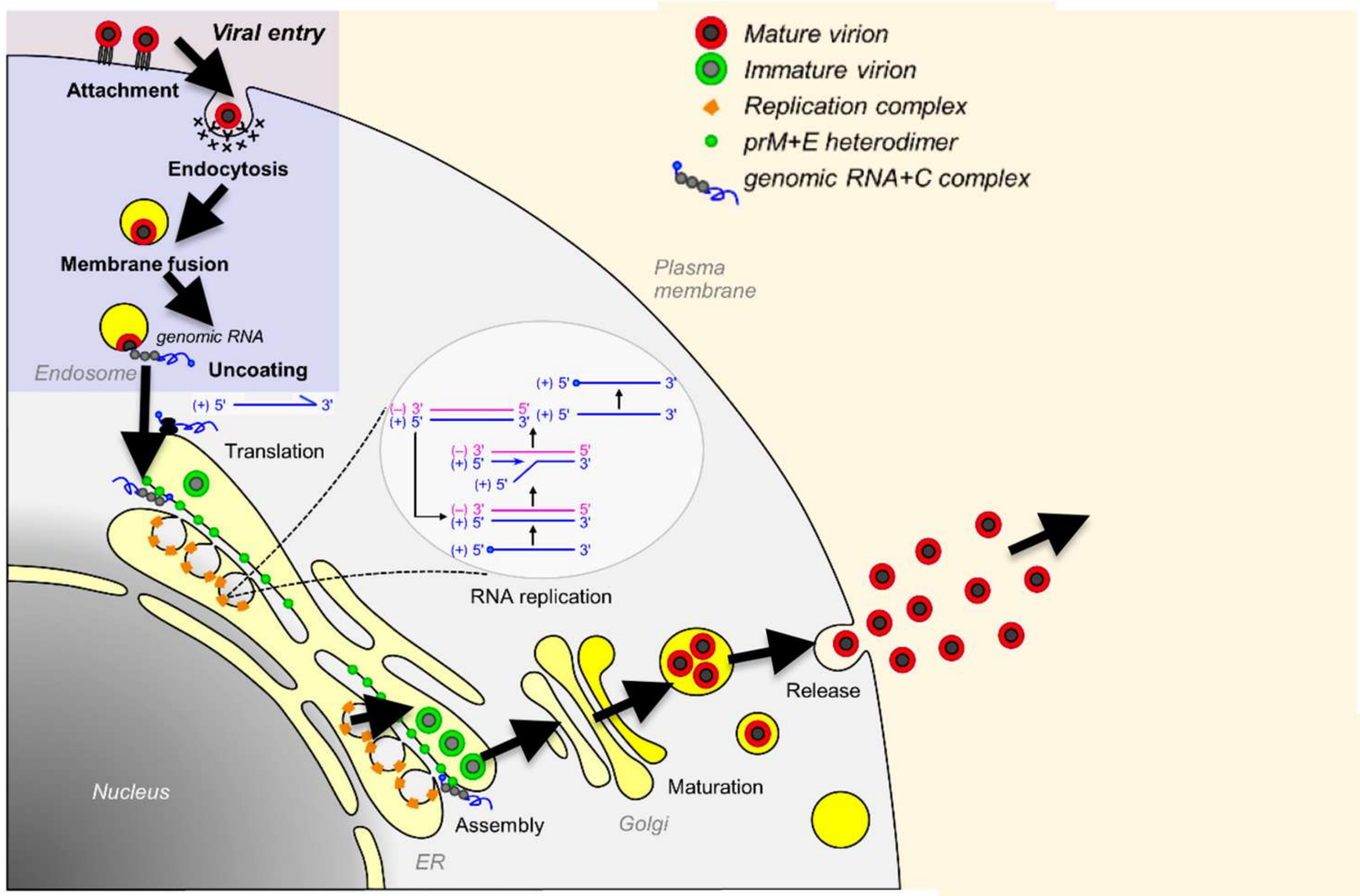
ss DNA
Parvovirus

+ss RNA
Picornaviridae
Calicivirus
Togavirus & flavivirus
Coronavirus
+ss RNA → Viral proteins
New virus

−ss RNA
Paramyxoviridae
Orthomyxoviridae
Arenavirus
Rhabdoviridae
−ss RNA → +ss RNA
−ss RNA
New virus
Viral proteins

+ss RNA
Retroviridae (HIV)
+ss RNA → DNA
RNA
New virus
Host membrane
Enveloped virus
Viral proteins

Positive-strand RNA viruses have genetic material that can function both as a genome and as messenger RNA; it can be directly translated into protein in the host cell by host ribosomes.[7] The first proteins to be expressed after infection serve genome replication functions; they recruit the positive-strand viral genome to viral replication complexes formed in association with intracellular membranes. These complexes contain proteins of both viral and host cell origin, and may be associated with the membranes of a variety of organelles—often the rough endoplasmic reticulum, but also including membranes derived from mitochondria, vacuoles, the Golgi apparatus, chloroplasts, peroxisomes, plasma membranes, autophagosomal membranes, and novel cytoplasmic compartments.[3]



Viral entry
Attachment
Endocytosis
Membrane fusion
genomic RNA
Uncoating
Endosome
Mature virion
Immature virion
Replication complex
prM+E heterodimer
genomic RNA+C complex
Plasma membrane
(+) 5'
3'
Translation
(–) 3'
5'
RNA replication
Nucleus
ER
Assembly
Golgi
Maturation
Release

The replication of the positive-sense RNA genome proceeds through double-stranded RNA intermediates, and the purpose of replication in these membranous invaginations may be the avoidance of cellular response to the presence of dsRNA. In many cases subgenomic RNAs are also created during replication.[7] After infection, the entirety of the host cell's translation machinery may be diverted to the production of viral proteins as a result of the very high affinity for ribosomes by the viral genome's internal ribosome entry site (IRES) elements; in some viruses, such as poliovirus and rhinoviruses, normal protein synthesis is further disrupted by viral proteases degrading components required to initiate translation of cellular mRNA.[5]

All positive-strand RNA virus genomes encode RNA-dependent RNA polymerase a viral protein that synthesizes RNA from an RNA template. Host cell proteins recruited by +ssRNA viruses during replication include RNA-binding proteins, chaperone proteins, and membrane remodeling and lipid synthesis proteins, which collectively participate in exploiting the cell's secretory pathway for viral replication.[3]

Plus-sense, single-strand RNA virus

Translation

Protein cleavage

Transcription

Replication

Assembly

Release

Minus-sense, single-strand RNA virus

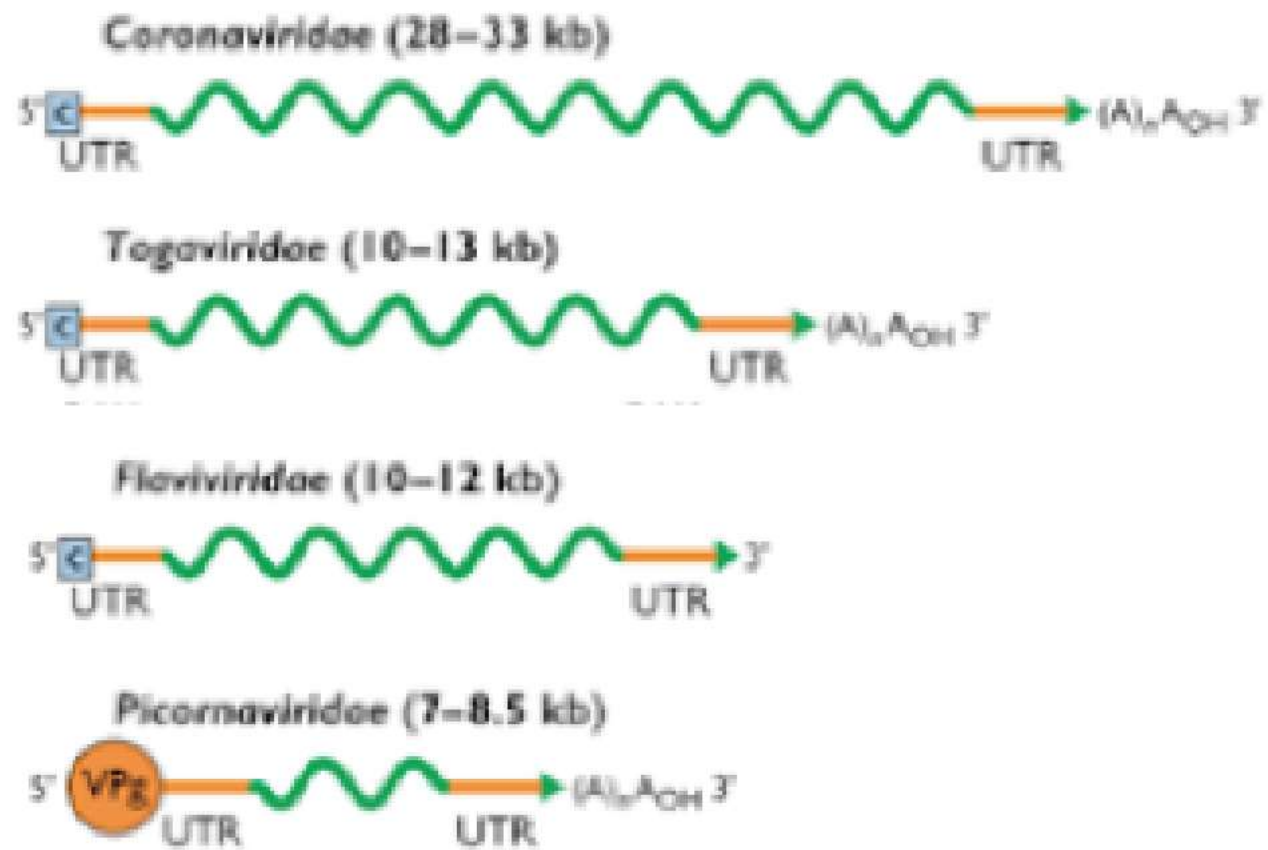
mRNA transcription

Replication

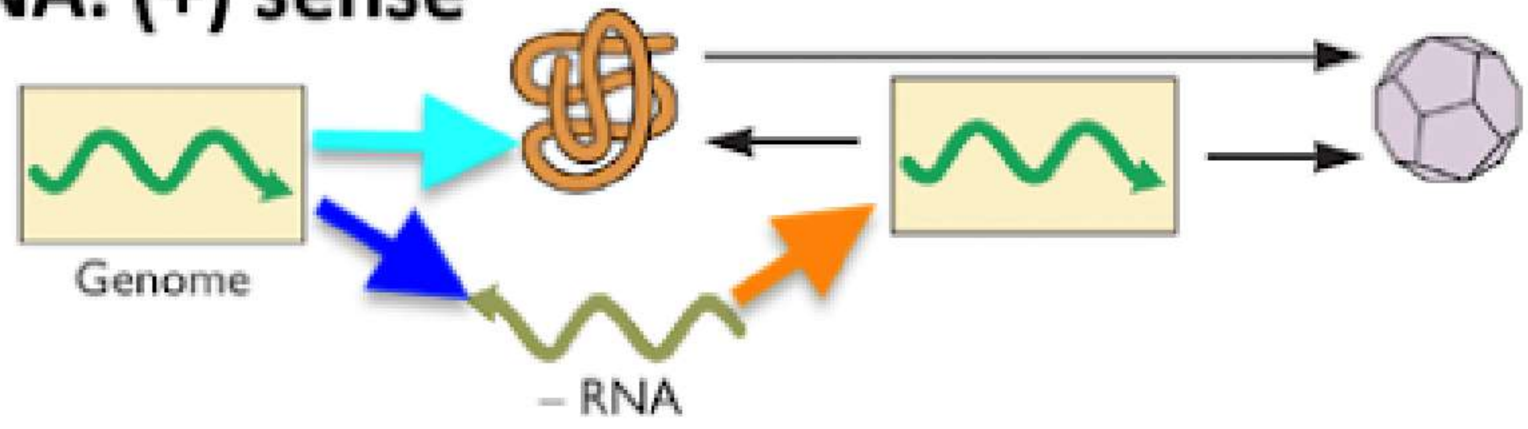
Translation

Assembly

Release



ssRNA: (+) sense



Numerous positive-strand RNA viruses can undergo genetic recombination when at least two viral genomes are present in the same host cell.[8] The capability for recombination among +ssRNA virus pathogens of humans is common. RNA recombination appears to be a major driving force in determining genome architecture and the course of viral evolution among *Picornaviridae* (e.g. poliovirus).[9] In the *Retroviridae* (e.g. HIV), genome damage appears to be avoided during reverse transcription by strand switching, a form of recombination.[10][11][12] Recombination occurs in the *Coronaviridae* (e.g. SARS).[13]

Recombination in RNA viruses appears to be an adaptation for coping with genome damage.[8] Recombination can also occur infrequently between +ssRNA viruses of the same species but of divergent lineages. The resulting recombinant viruses may sometimes cause an outbreak of infection in humans, as in the case of SARS and MERS.[13]

Positive-strand RNA viruses are common in plants. In tombusviruses and carmoviruses, RNA recombination occurs frequently during replication.[14] The ability of the RNA-dependent RNA polymerase of these viruses to switch RNA templates suggests a copy choice model of RNA recombination that may be an adaptive mechanism for coping with damage in the viral genome.[14] Other +ssRNA viruses of plants have also been reported to be capable of recombination, such as Brom mosaic bromovirus[15] and Sindbis virus.[16]

Positive-strand RNA viruses are divided between the phyla *Kitrinoviricota*, *Lenarviricota*, and *Pisuviricota* (specifically classes *Pisoniviricetes* and *Stelpavirictes*) all of which are in the kingdom *Orthornavirae* and realm *Riboviria*. They are monophyletic and descended from a common RNA virus ancestor. In the Baltimore classification system, +ssRNA viruses belong to Group IV.[1]

Positive-sense RNA viruses include pathogens such as the hepacivirus C, West Nile virus, dengue virus, and the MERS, SARS, and SARS-CoV-2 coronaviruses,[2] as well as less clinically serious pathogens such as the coronaviruses and rhinoviruses that cause the common cold.[3][4][5]

ssRNA: (+) sense

Viruses from eight families infect mammals:

- *Picornaviridae* (*Poliovirus*, *Rhinovirus*)
- *Caliciviridae* (gastroenteritis)
- *Astroviridae* (gastroenteritis)
- *Coronaviridae* (SARS)
- *Arteriviridae*
- *Flaviviridae* (*Yellow fever virus*, *West Nile virus*, *Hepatitis C virus*)
- *Retroviridae* (HIV)
- *Togaviridae* (*Rubella virus*, *Equine encephalitis virus*)

Hepatitis C Virus

- RNA virus of Flaviviridae family
- Parenteral, perinatal, and sexual transmission
- Accounts for ~ 20% of cases of acute hepatitis
- Only 10-15% of infected individuals develop symptomatic acute hepatitis
- If untreated, ~ 85% of infected patients develop chronic infection

Hepatitis A Virus

- Single-stranded RNA virus in Picornaviridae family
- Usually spreads via oral or fecal-oral transmission
    - Community outbreaks related to contaminated food or water
- Accounts for ~ 1/2 of acute viral hepatitis cases in USA
- At least 4 genotypes described, but only 1 serotype exists
    - Infection with one genotype confers immunity against all genotypes
- Never results in chronic infection

Hepatitis D Virus (Delta Agent)

- Defective RNA virus
- Parenteral and sexual transmission
- Requires coinfection with hepatitis B virus or superinfection in patient with chronic hepatitis B virus infection

Hepatitis E Virus

- Single-stranded, nonenveloped RNA virus in Caliciviridae family
- 4 routes of infection
  - Vertical transmission
  - Parenteral transmission
  - Consumption of raw or undercooked meat of infected animals
  - Contaminated water supply

Retroviruses are single-stranded RNA viruses that can integrate into the genome of cells, which results in stable replication and transmission to all the progeny of these cells. Retroviruses continue to be employed as gene delivery vehicles, although recent adverse events following retroviral gene therapy have raised concerns about potential insertional mutagenesis (Hacein-Bey-Abina et al., 2003).

Human T Lymphotropic Virus-1

Retroviruses, single-stranded RNA viruses with the capacity for reverse transcription into DNA, are another virus family whose oncogenic potential was initially recognized through pioneering studies in animal systems. Interestingly the first human retrovirus, the human T lymphotropic virus-1 (HTLV1) discovered in 1980 (Poiesz et al., 1980), remains the only such agent directly linked to malignancy in man.

HTLV1 is rare in many human populations but is more common in certain parts of Japan, equatorial Africa, the Caribbean, and South America, where 2–3% infected individuals eventually go on to develop a distinct adult T cell leukemia/lymphoma (ATL) and a slightly lower number suffer inflammatory disorders, particularly a chronic progressive myelopathy (Matsuoka and Jeang, 2007; Tattermusch and Bangham, 2012; Cook et al., 2013).

HTLV1 preferentially infects T cells, most often the $CD4^+$ subset, and is transmitted not as a free virus but within latently infected T cells present in breast milk, semen, or blood. After transmission, such cells activate to produce infectious virions which then enter host T cells either through tight T cell–T cell synapses or via dendritic cell surfaces as an intermediary (Matsuoka and Yasunaga, 2013). As with all retroviruses, the RNA genome is then reverse-transcribed to a double-stranded DNA proviral copy that integrates into the cellular genome and acts as a permanent template for viral RNA synthesis.

HTLV1 is a complex retrovirus which, besides the standard virion components (gag, pol, env), encodes six regulatory and/or accessory proteins. Of these, the key players are the transcriptional activator Tax and its regulator HBZ, which together drive the clonal proliferation of latently infected cells *in vivo* (Matsuoka and Yasunaga, 2013). This strategy (Figure 2) allows the virus to first enter and then colonize the naïve host as a cell-associated latent infection, against which neutralizing antibodies (whether induced by infection or by vaccination) would offer little defense.

First, several reports describe rapid progression to high proviral loads/ATL in HTLV1-infected patients receiving T cell–suppressive drugs. Second, in asymptomatic virus carriers there is a clear inverse relationship between proviral load (i.e., the number of HTLV1-infected cells) in the blood and the strength of the virus-specific $CD8^+$ T cell response as measured in *ex vivo* functional assays. Third, certain HLA class I alleles found to protect against progressive HTLV1 infection/inflammatory disease also show the most avid binding of HBZ peptides recognized by $CD8^+$ T cells.

While multiple HTLV1-positive T cell clones each with unique proviral integration points are detectable in the blood during asymptomatic virus carriage, progression to full-blown ATL involves the evolution of a single malignant clone (Bangham et al., 2014). The details of that evolution, and the virus' contribution to malignant growth, are still not fully understood. However, while the proviral Tax gene is often inactivated by mutation or hypermethylation and only around 30% of ATLs continue to express the protein, HBZ is always present and likely contributes both to growth and the tumor's antiinflammatory, Th2-like, phenotype (Sugata et al., 2012).

Lentiviral vectors can transduce both proliferating and quiescent cells. Advantages of retroviral vectors for gene therapy include potential long-term transgene expression due to integration into the target tumor cells or host genome and low immunogenicity. However, most retroviruses demonstrate low levels of transduction efficiency and only infect dividing cells during mitosis (Adamina, Daetwiler, Rosenthal, & Zajac, 2005).

Like other single-stranded RNA viruses, LCMV mutates frequently, and these mutants vary in their tropism and disease-producing potential. A single passage of a cloned LCMV variant into mice will soon segregate into clear neurotropic and turbid viscerotropic plaque variants, which can be recovered from the brain and spleen, respectively. A single amino acid change in the LCMV glycoprotein (residue 260) can convert the immunostimulatory Armstrong strain of LCMV into an immunosuppressive (clone 13) variant, and these genotypes rapidly intraconvert during *in vivo* passage.

The presence of two virion RNAs allows for high-frequency recombination due to reassortment of viral genomes. The technique of generating reassortants has led to the assignment of viral-encoded proteins to the appropriate RNA and has facilitated the mapping of genes required for disease-producing potential. The ease of producing reassortants in the laboratory suggests that they also occur in nature and probably play roles in enhancing the genetic diversity of arenaviruses.

Viral isolation and PCR are commonly used to identify viremic animals. A variety of PCR assays have been developed and are commercially available (Lerche et al., 1997; Liska et al., 1997; Wilkinson et al., 2003; Hara et al., 2005). It is important for the PCR assay to use primers specific enough to not identify endogenous retroviral sequences which are ubiquitous in many species of primates but are nonpathogenic (Morton et al., 2008).

Nonhuman Primates Retroviruses

Retroviruses are single-stranded RNA viruses. NHPs are natural hosts for six known retroviruses: simian retrovirus type D (SRV-D), simian immunodeficiency virus (SIV), simian T-lymphotropic virus (STLV), simian foamy virus (SFV), simian sarcoma virus, and Gibbon-Ape leukemia virus (Lerche and Osborn, 2003). Historically, these viruses have caused significant morbidity and mortality in NHP colonies, especially macaques.

Unlike SRV-D, SIV is not a natural infection of Asian macaques. SIV naturally infects African species (i.e. vervets) and chimpanzees and in these animals causes subclinical disease. Virus can be transmitted to macaques via contact with infected African species or artificially in a laboratory setting and, once infected, Asian macaques can transmit virus to other macaques. Similar to SRV-D, disease in Asian macaques is quite serious and leads to an AIDS-like condition. SIV is a target agent for eradication in SPF macaque colonies.

SIV viral screening of macaque colonies is performed using immunoassays. The ideal immunoassay uses whole virus preparations to ensure that all SIV variants are identified (Morton et al., 2008). It is unlikely that animals will seroconvert unless they are exposed experimentally, housed with or exposed to African species, or exposed through fomites. Therefore, confirmation of indeterminate or positive immunoassay results should be confirmed using PCR or Western Blot (Lairmore et al., 1990; Lerche et al., 1994; Berry et al., 2011).

confirmation of indeterminate or positive immunoassay results should be confirmed using PCR or Western Blot (Lairmore et al., 1990; Lerche et al., 1994; Berry et al., 2011). PCR should target conserved regions of the viral sequence in order to identify all possible SIV variants. In general, the genetic variation increases from LTR → *gag* → *pol* → *env*. SIV is also included in an available multiplex microbead immunoassay and this can be used to screen large numbers of animals for SIV antibodies (Khan et al., 2006).

Simian T-lymphotropic virus (STLV) is the fourth virus included as a target for eradication from specific pathogen free breeding colonies. Many macaque colonies historically had high seroprevalence rates but the virus causes subclinical infection in these animals. In contrast, in African species, including vervets, gorillas, and baboons (Lerche and Osborn, 2003), the virus may cause lymphoproliferative disease.

Screening for STLV is important primarily to form and maintain SPF colonies but may also be beneficial as this agent is a potential confounder of experimental research (Lerche and Osborn, 2003). The virus shares significant sequence homology with human T-lymphotropic virus (HTLV) and HTLV specific immunoassays can be used to screen for disease (Meertens et al., 2001). PCR or Western Blot can be used to confirm positive test results.

Polioviruses are single-stranded RNA viruses belonging to the family Picornaviridae. They have a naked protein capsid with a dense central core. The capsid consists of four structural proteins, VP1, VP2, VP3, and VP4. The genomic RNA is approximately 7440 to 7500 nucleotides in length. Three serotypes of poliovirus are antigenically distinct, but all three have 70% nucleotide identity.[1] Polioviruses are stable and can be stored indefinitely at –20°C and are inactivated by formaldehyde, chlorination, and ultraviolet light.

Humans are the only known natural host; however, poliovirus can replicate in other primates. The virus is exclusively propagated in cultured cells of primate origin because other cell lines lack a functional receptor molecule. Since identification and molecular cloning of the viral receptor, transgenic mice have been developed that are susceptible to all three serotypes of poliovirus.[2]

Poliovirus is transmitted primarily by the fecal–oral route and replicates in the pharynx and lower intestinal tract (Table 235-1). Only small amounts of infectious virus are needed to cause infection.

Virus is shed in the pharynx for 1 to 3 weeks and in the gut for 4 to 8 weeks after primary infection. During reinfection, pharyngeal shedding is rare and fecal shedding is reduced to less than 3 weeks. The incubation period generally is 7 to 14 days but can be as short as 3 days and as long as 35 days. The virus spreads quickly from the alimentary tract to regional lymph nodes. After several days, a minor viremia ensues, and a number of sites, such as muscle, fat, liver, spleen, and bone marrow, become infected. If virus is contained at this point, subclinical infection occurs.

Poliovirus replicates within neurons; the anterior horn cells of the spinal cord are involved most often. Neurons in nuclei of the medulla, vermis of the cerebellum, midbrain, thalamus and hypothalamus, palladium, and motor cortex of the cerebrum also can be involved. Rarely, the posterior horn cells and dorsal root ganglia are infected. Although poliovirus infection usually destroys neurons, injury occasionally is reversible.

Serum neutralizing antibody develops after about 1 week and protects against paralysis but not reinfection. Immunity to poliovirus infection is type specific, without any cross-protection, and persists for life. Local antibody appears 1 to 3 weeks after infection and limits virus replication at the mucosal level. Reinfection occurs; however, the duration of shedding is reduced and viremia does not occur. Immunodeficient individuals are at considerable risk of disseminated infection.