Retroviruses

Family: *Retroviridae*

Genus	Type species
Subfamily *Orthoretrovirinae*	
Alpharetrovirus	Avian leukosis virus
Betaretrovirus	Mouse mammary tumor virus
Gammaretrovirus	Murine leukemia virus
Deltaretrovirus	Bovine leukemia virus
Epsilonretrovirus	Walleye dermal sarcoma virus
Lentivirus	Human immunodeficiency virus type 1
Subfamily *Spumavirinae*	
Spumavirus	Chimpanzee foamy virus

Retrovirus particles contain the enzyme reverse transcriptase, which mediates synthesis of a double-stranded DNA copy of the viral RNA genome. Although once thought to be unique to this family, similar enzymes are now known to be encoded in other viral genomes (i.e., hepadnaviruses and caulimoviruses), and the term **retroid viruses** has been coined to include these families. Retrovirus particles contain a second enzyme, integrase, that mediates the insertion of the viral DNA into essentially random sites in host DNA. The retroviruses can be propagated as integrated elements (called proviruses) that are transmitted in the germ line or as exogenous infectious agents. They infect a wide range of animal hosts and can cause cancer by multiple mechanisms. Some retroviruses, i.e., alpha-, beta-, and gammaretroviruses, have **simple** genomes that encode only the three genes common to all retroviruses—*gag*, *pol*, and *env*. All of the others have more **complex** genomes, which include auxiliary or accessory genes that encode nonstructural proteins that affect viral gene expression and/or pathogenesis.

Figure 21 Structure and genomic organization. (A) The virion. (Left) Electron micrograph of a negatively stained alpharetrovirus, Rous sarcoma virus. Courtesy of R. Katz and T. Gales, Fox Chase Cancer Center. The method of preparation for electron microscopy (staining of thin sections) does not allow visualization of the envelope protein projections. (Right) Diagram of the alpharetrovirus, avian leukosis virus (ALV), indicating the names and locations of the component proteins, genomic RNA, and envelope. **(B) Genomic organization.** (Left) A retrovirus with a simple genome, here denoted "simple retrovirus." (Top) Genetic map of the avian leukosis virus provirus. Colored boxes delineate open reading frames, which, as indicated, are overlapping. (Bottom) The map of genomic RNA shows the genes common to all replication-competent retroviruses, *gag*, *pol*, and *env*. The ends of the RNA include short terminal repeats. Near the termini of the genomic RNA, sections containing *cis*-acting sequences that are required in replication are also shown (in orange): U5 (unique to the 5′ end) and U3 (unique to the 3′ end). In the integrated proviral DNA, the U5 and U3 sections are duplicated and comprise long terminal repeats (LTRs) at the borders between cellular and viral DNA. Initiation of DNA transcription and polyadenylation of pre-mRNA occur within the LTRs to produce progeny viral genomes and mRNAs. The viral mRNAs are translated to produce the indicated polyprotein precursors, which are eventually processed proteolytically to form the mature viral proteins. (Right) A retrovirus with a more complex genome, here denoted "complex retrovirus." (Top) Genetic map of the lentivirus human immunodeficiency virus type 1 (HIV-1) provirus. Genes are encoded in all three reading frames, as indicated by the overlaps. (Bottom) Human immunodeficiency virus type 1 mRNAs, which fall into one of three classes. The first type is an unspliced transcript of 9.1 kb, identical in function to that of the simple retrovirus. The second type consists of five singly spliced mRNAs (average length, 4.3 kb) that result from splicing from a 5′ splice site upstream of *gag* to any one of a number of 3′ splice sites near the center of the genome. Among these mRNAs is one specifying the Env polyprotein precursor, as illustrated for the simple retrovirus. The others specify the human immunodeficiency virus type 1 accessory proteins Vif, Vpr, and Vpu. Both unspliced RNA and singly spliced mRNAs require the Rev protein for transport out of the nucleus. This transport is mediated by the binding of Rev to the Rev-responsive element (RRE) in the *env* gene. The third type of mRNAs, multiply spliced molecules, average 1.8 kb in length; all lack the region of *env* that includes the RRE. This group includes a complex class of 16 mRNAs derived by exhaustive splicing from 5′ and 3′ splice sites throughout the genome. Such multiply spliced products are the first mRNAs to accumulate after infection; they specify the regulatory proteins Tat and Rev and the accessory protein Nef. As Rev protein accumulates, more and more of the 9.1- and 4.3-kb mRNAs are exported from the nucleus, allowing the production of virion proteins and formation of progeny virus.

Figure 22 Single-cell reproductive cycle of a simple retrovirus. The virus attaches by binding of SU and TM to specific receptors on the surface of the cell **(1)**. The identities of receptors (which are normal components of the cell surface) are known for several retroviruses. The viral core is deposited into the cytoplasm **(2)** following viral protein-assisted fusion of the virion and cell envelopes. The viral RNA genome is reverse transcribed by the virion RT **(3)** within a subviral particle. The product is a linear double-stranded viral DNA with ends that are shown juxtaposed in preparation for integration. The viral preintegration complex, which includes viral DNA and IN, enters the nucleus **(4)**, where it gains access to the host chromatin. Integrative recombination **(5)**, catalyzed by IN, results in site-specific insertion of the viral DNA ends, which can take place at numerous (essentially random) sites in the host genome. Integrated viral DNA is called the provirus. Transcription of proviral DNA by host cell RNA polymerase II **(6)** produces full-length RNA transcripts, which are used for multiple purposes. Some full-length RNA molecules are

exported from the nucleus and serve as mRNAs **(7)**, which are translated by cytoplasmic ribosomes to form the viral Gag and Gag-Pol polyprotein precursors **(8)**. Some full-length RNA molecules become encapsidated as progeny viral genomes following transport into the cytoplasm **(9)**. Other full-length RNA molecules are spliced within the nucleus **(10)** to form mRNA for the Env polyprotein precursor proteins. Env mRNA is translated by ribosomes bound to the endoplasmic reticulum (ER) **(11)**. The Env proteins are transported through the Golgi apparatus **(12)**, where they are glycosylated and cleaved to form the mature SU-TM complex. These mature envelope proteins are then delivered to the surface of the infected cell **(13)**. Virion components (viral RNA, Gag and Gag-Pol precursors, and SU-TM) assemble at budding sites **(14)** with the help of *cis*-acting signals encoded in each. Type C retroviruses (e.g., alpharetroviruses and lentiviruses) assemble at the inner face of the plasma membrane, as illustrated. Other types (A, B, and D) assemble on internal cellular membranes. The nascent virions bud from the surface of the cell **(15)**. Maturation (and infectivity) requires the action of the virus-encoded protease (PR), which is itself a component of the core precursor polyprotein. During or shortly after budding, PR cleaves at specific sites within the Gag and Gag-Pol precursors **(16)** to produce the mature virion proteins. This process causes a characteristic condensation of the virion cores.