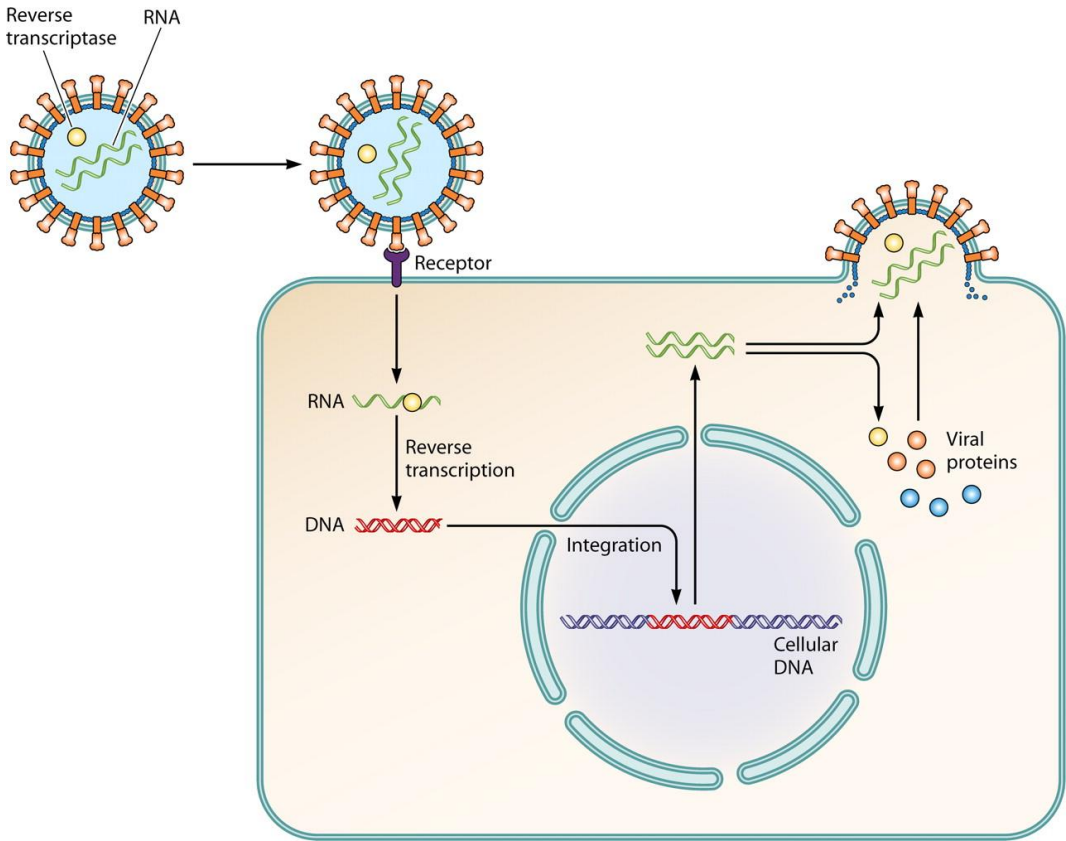
Retroviruses

- Virion
- Genome
- Genes and proteins
- Viruses and hosts
- Diseases
- Distinctive characteristics

Viruses and hosts

- Retroviridae from *re*verse *tr*anscriptase, characteristic of these viruses
- Retroviruses have a unique replication cycle based on reverse transcription and integration of their genomes
  - **Reverse transcriptase** produces a DNA copy of the RNA genome
  - RSV induces tumors by acquisition of an **oncogene** from the cell
  - The discovery of HIV, responsible for a worldwide epidemic of AIDS, in the mid-1980s led to an explosion of work on retroviruses



Viruses and hosts

- Seven genera are recognized: *Alpha-* to *Epsilonretroviruses, Lentivirus, Spumavirus*
  - Simple retroviruses: *Rous sarcoma virus* (chickens), *mouse mammary tumor virus, Jaagsietke sheep retrovirus*
  - Lentiviruses: human, feline, bovine and avian immunodeficiency viruses
  - Spumaviruses: simian foamy virus

Table 28.1 Retrovirus genera

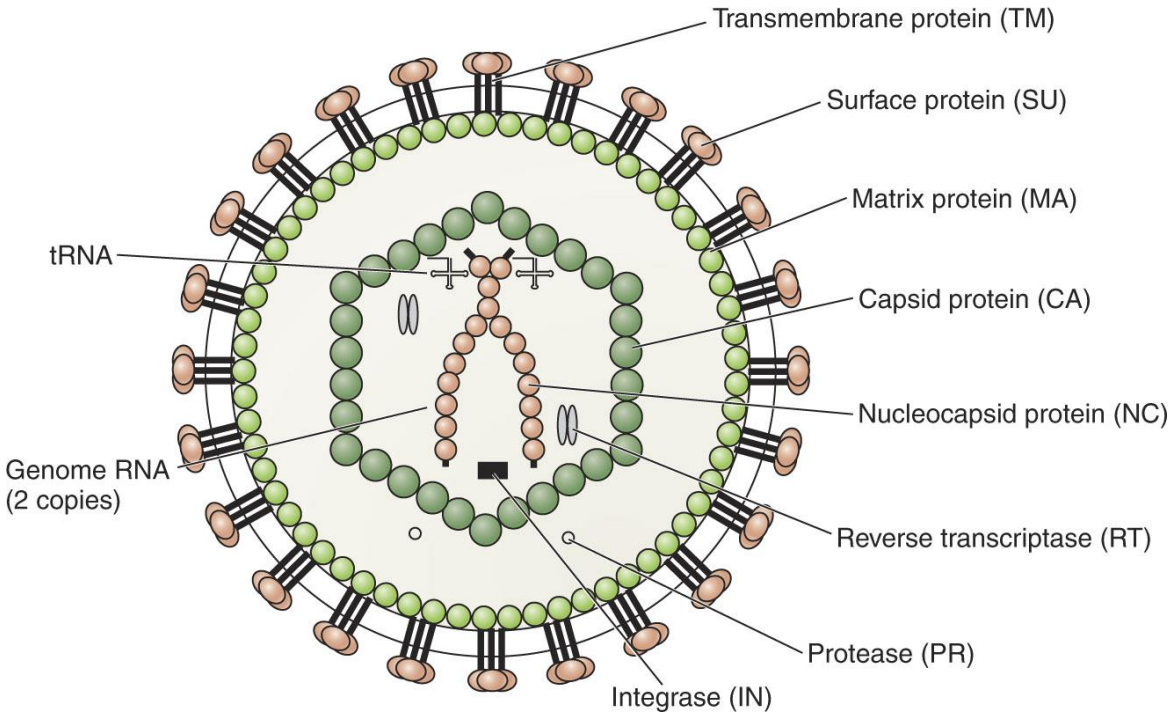
Genus	Examples of virus	Host
Alpharetrovirus	Rous sarcoma virus	Chickens
Betaretrovirus	Mouse mammary tumor virus	Mice
Gammaretrovirus	Murine leukemia virus	Mice
Deltaretrovirus	Human T-cell leukemia virus type 1	Humans
Epsilonretrovirus	Walleye dermal sarcoma virus	Fish
Lentivirus	Human immunodeficiency virus type 1	Humans
	Simian immunodeficiency virus	Monkeys
	Feline immunodeficiency virus	Cats
Spumavirus	Simian foamy virus	Monkeys

Diseases

- Humans: AIDS, leukemia
- A variety of cancers in monkeys, mice, cats, sheep, birds, etc.
- RNA tumor viruses

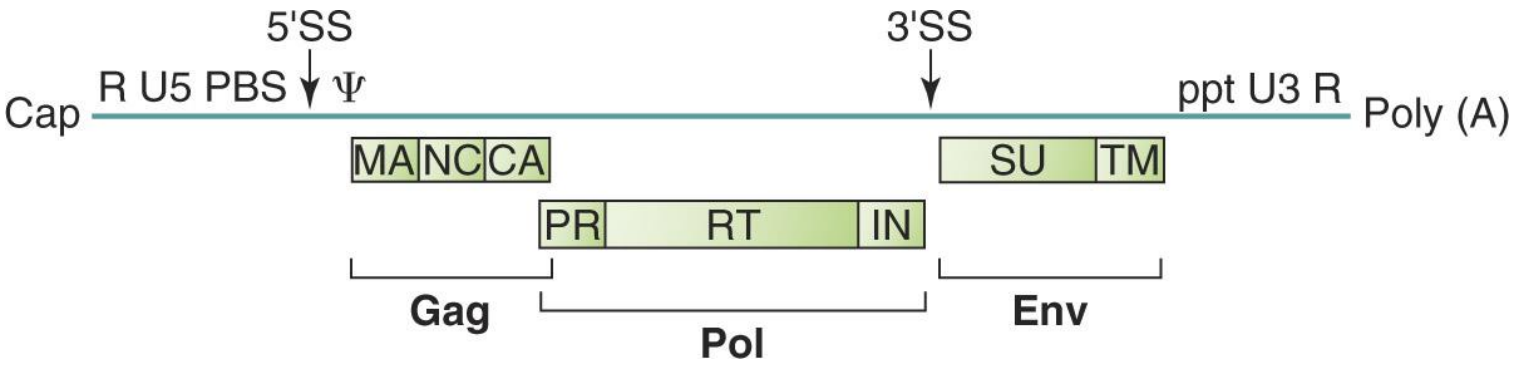
Virion

- Spherical enveloped particle; Diameter 100 nm; Envelope assembled at plasma membrane
- Icosahedral or conical capsid
- Viral proteins derived from the gag, pol and env genes are incorporated in virions



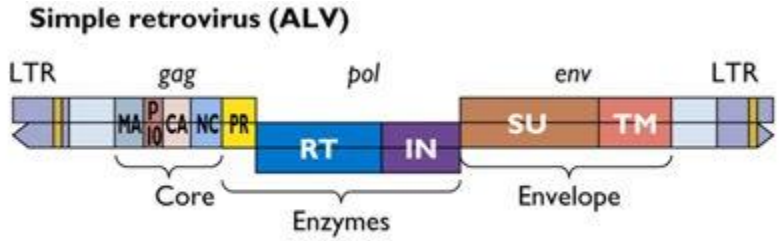
Genome

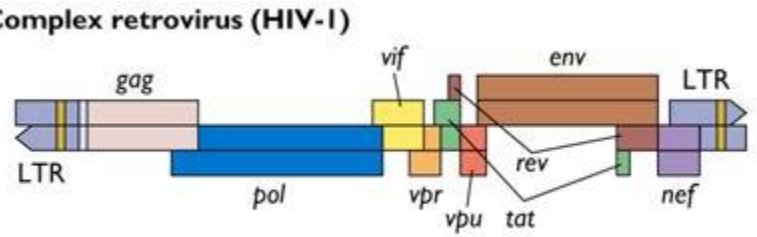
- Linear single-stranded RNA, positive sense
- Two identical molecules, 7-10 kb, complexed with NC protein
- 5’ cap and 3’ poly(A) tail



Genes and proteins

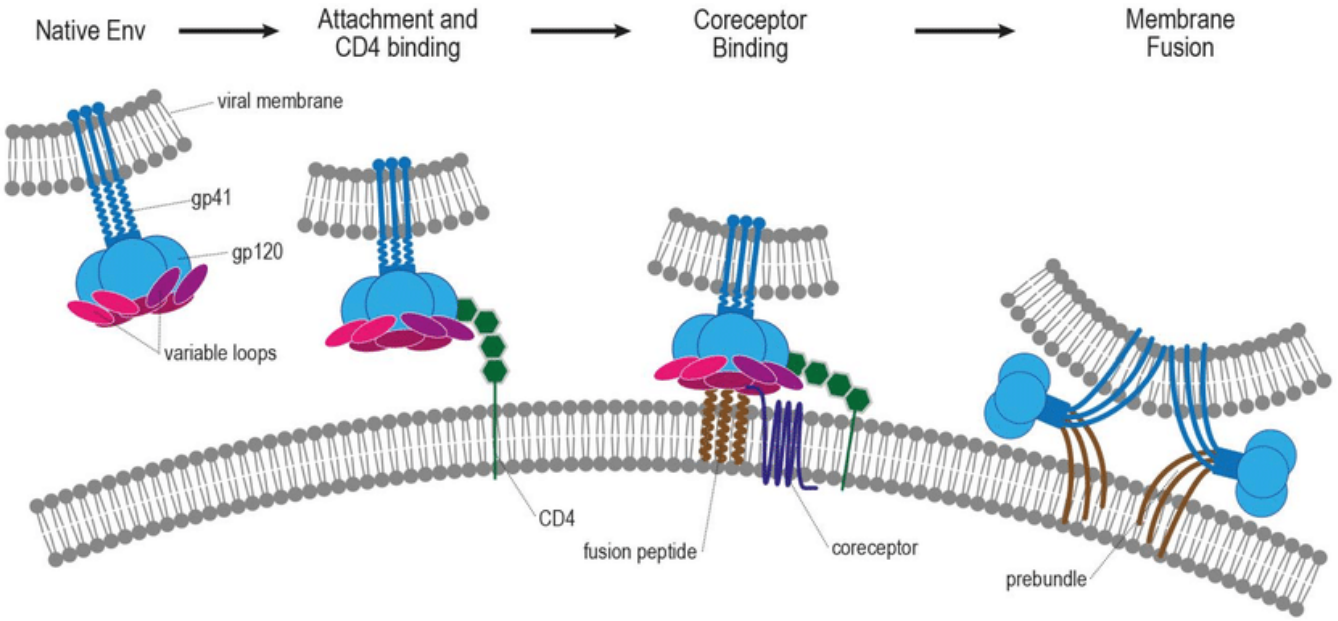
- mRNAs are transcribed from integrated provirus DNA by RNA pol II
- Gag and Pol proteins are made from unspliced mRNA
- Env proteins are made from singly spliced mRNA
- Three major genes, each translated as a polyprotein and cleaved into mature proteins
  - Gag: nucelocapsid protein
  - Pol: reverse transcriptase, protease and integrase
  - Env: envelope proteins
- Complex retroviruses have additional regulatory genes expressed from multiply spliced mRNAs





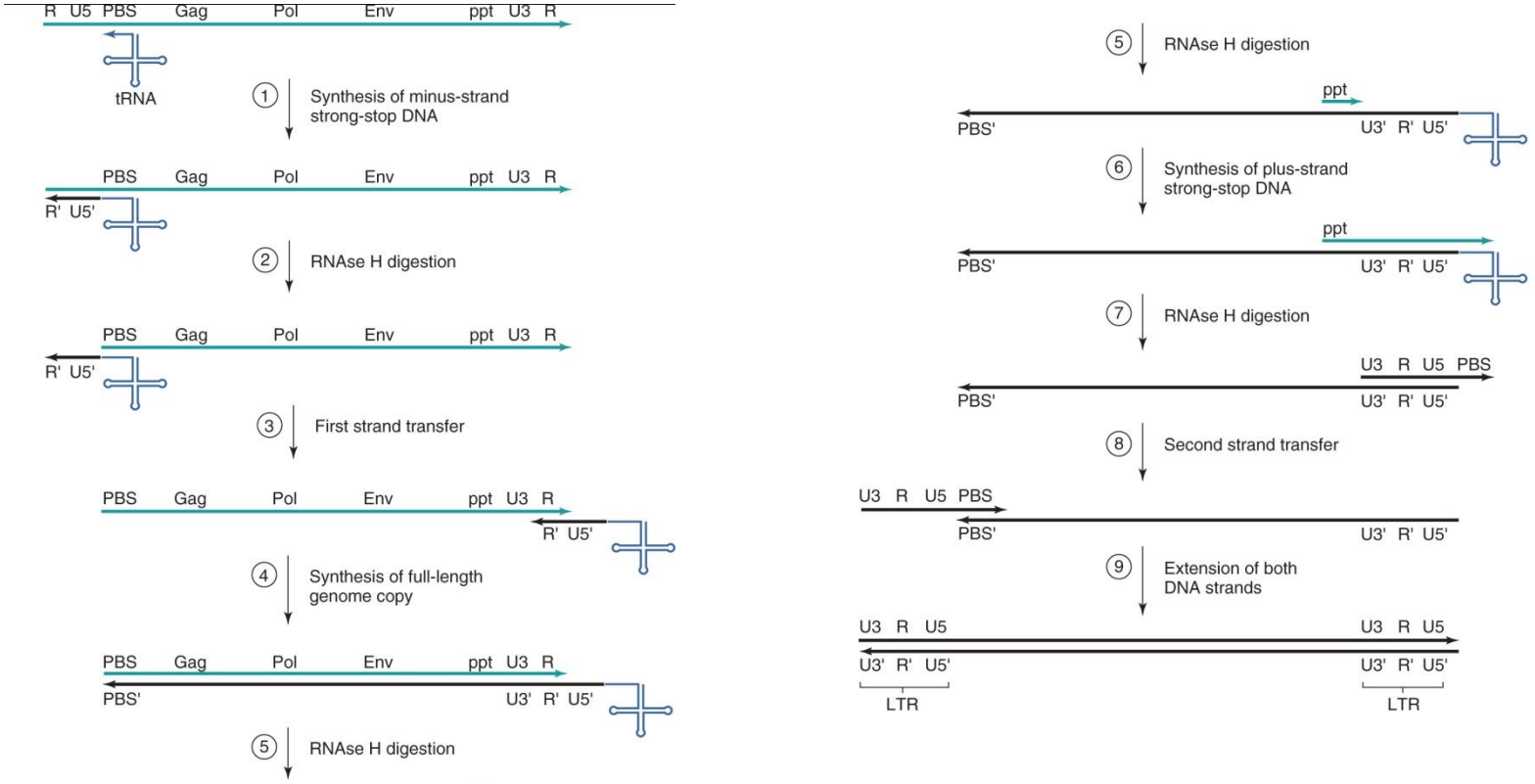
Entry

- Retroviruses enter cells by the fusion pathway
  - Receptors include: CD4 and the **chemokine** receptors CCR5 and CXCR4 (for HIV-1)
  - Envelope fuses with plasma membrane or is endocytosed followed by fusion
  - Early phase includes entry, making a DNA copy of its RNA genome, and integrating it into cellular genome



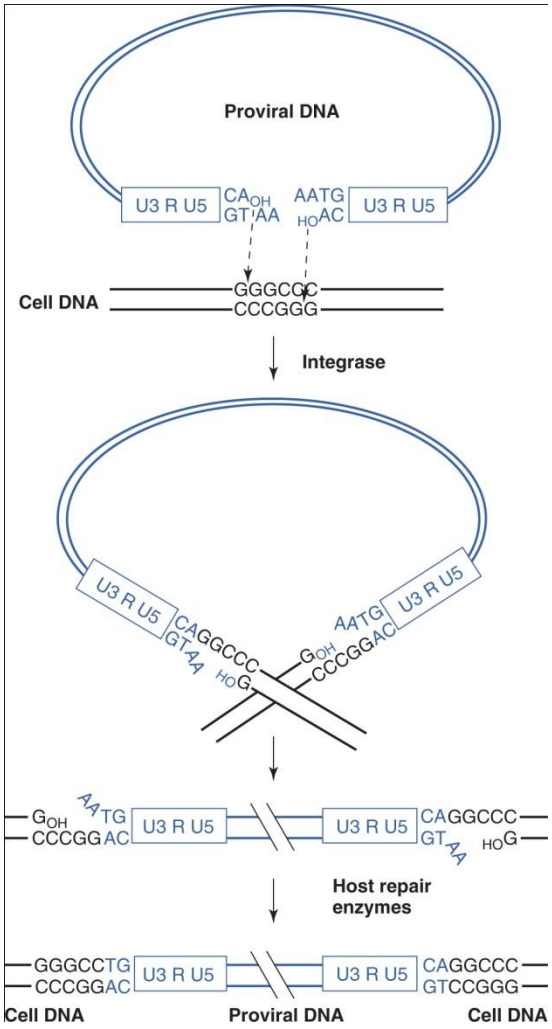
Reverse transcription

- Viral RNA is converted into dsDNA copy by reverse transcription
  - RT is a dimer that has RNA-dependent DNA polymerase activity and **ribonuclease H** activity
  - Production of **proviral DNA** which is found in a **preintegration complex**
  - Lack of proofreading capability leads to high mutation rate and generation of **quasispecies**



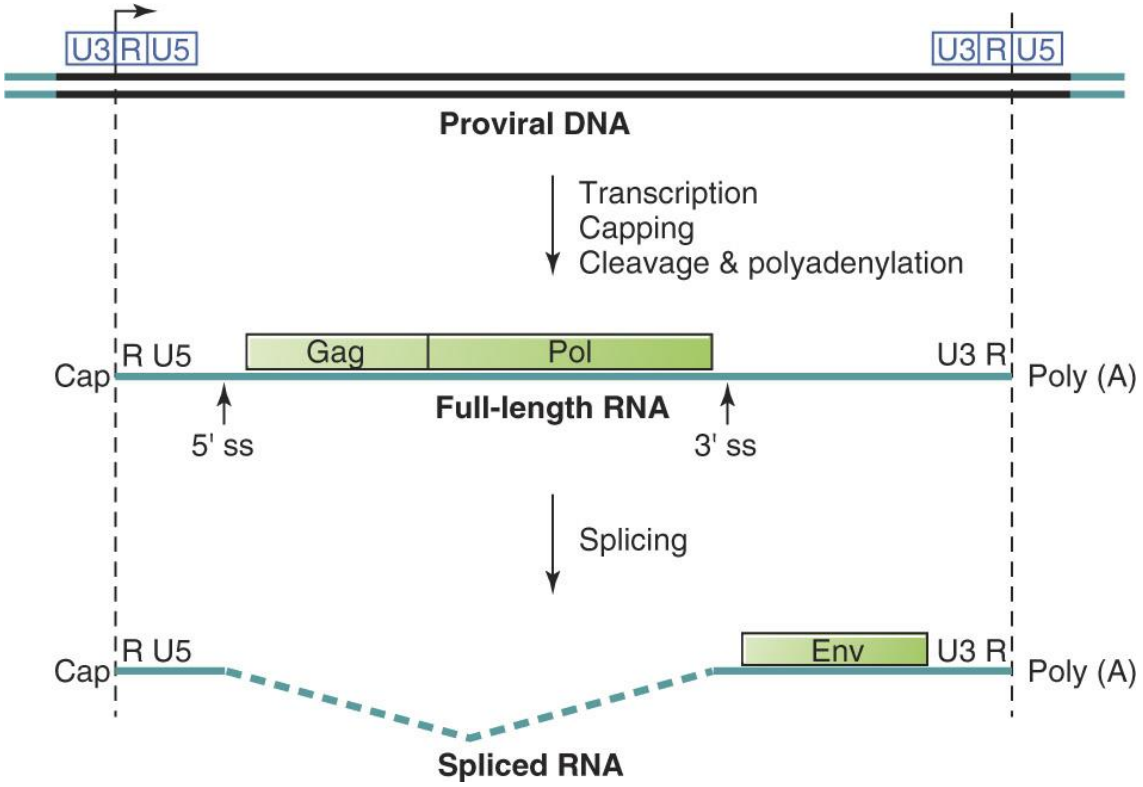
Proviral Integration

- A copy of proviral DNA is integrated into the cellular genome at a random site
  - Carried out by enzyme integrase



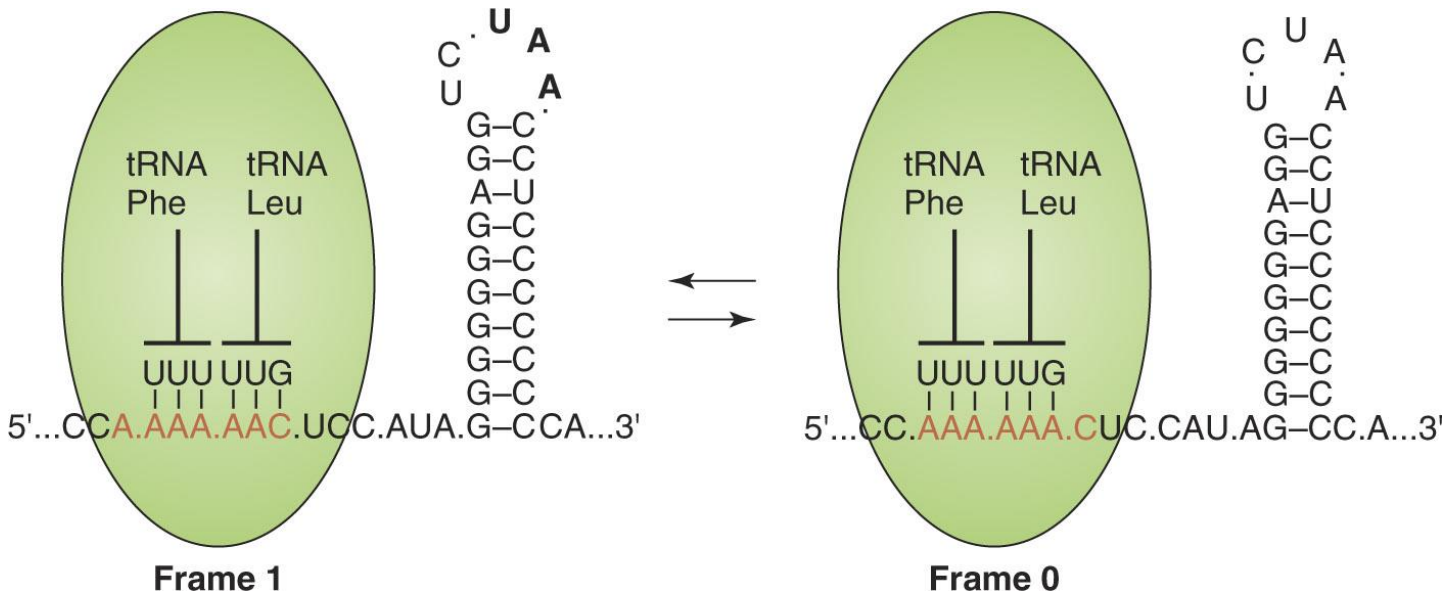
Gene expression

- Sequence elements in the long terminal repeats direct transcription and polyadenylation by host cell enzymes
- Differential splicing generates multiple mRNAs



Gene expression

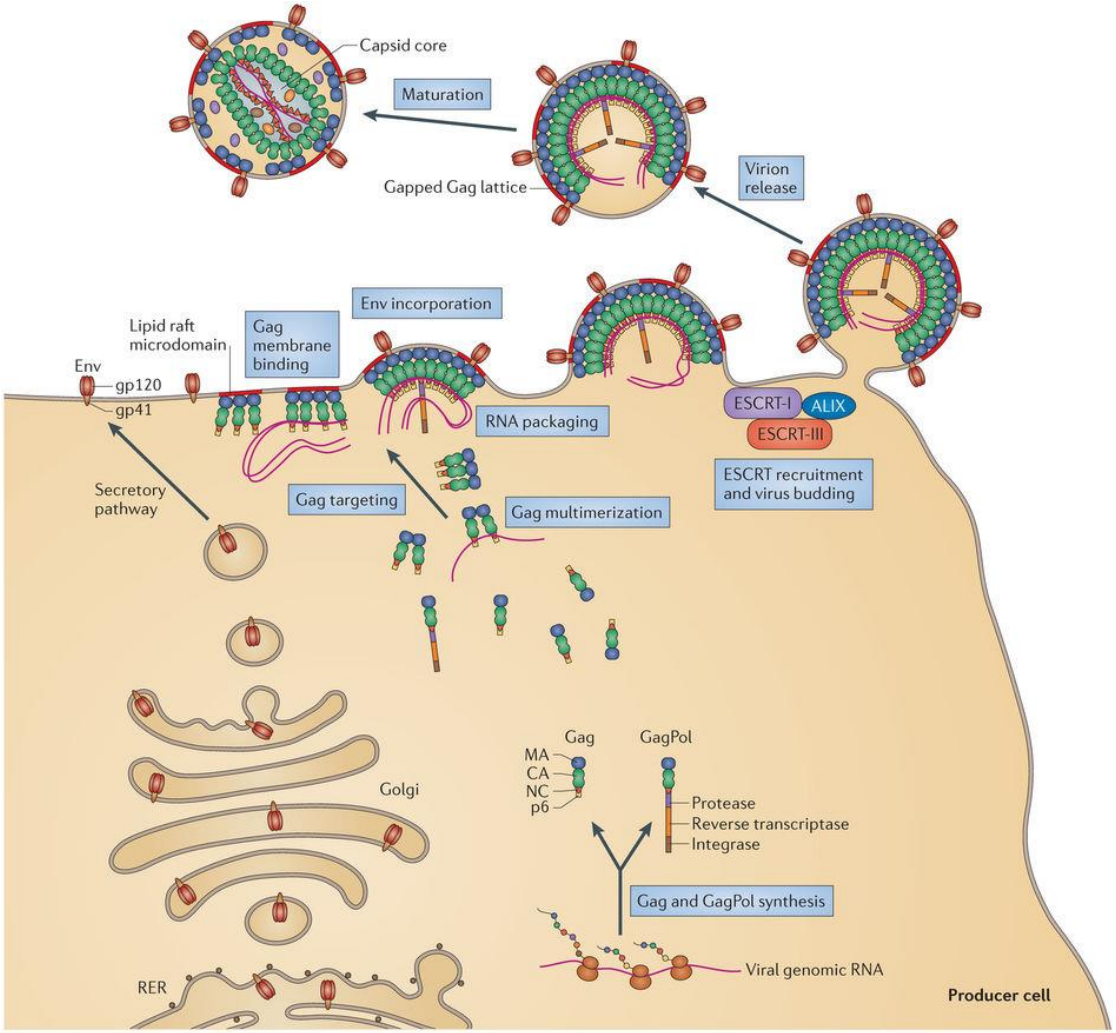
- The Gag/Pol **polyprotein** is made by suppression of termination and use of alternative reading frames
  - Misreading of the UAG codon is promoted by a **pseudoknot** and results in readthrough
  - Sequence elements can initiate ribosome stalling and frameshifting



Ribosome frameshifting

Assembly

- Virions mature into infectious particles after budding from the plasma membrane
  - Env protein is translocated into the **lumen** of ER then through Golgi, and directed to plasma membrane
  - Gag/Pol are released into **cytosol**
  - Gag is targeted to plasma membrane via **myristate**. NC portion binds to a **packaging signal** on the viral RNA
  - Protease cleaves Gag/Pol into mature proteins after assembly



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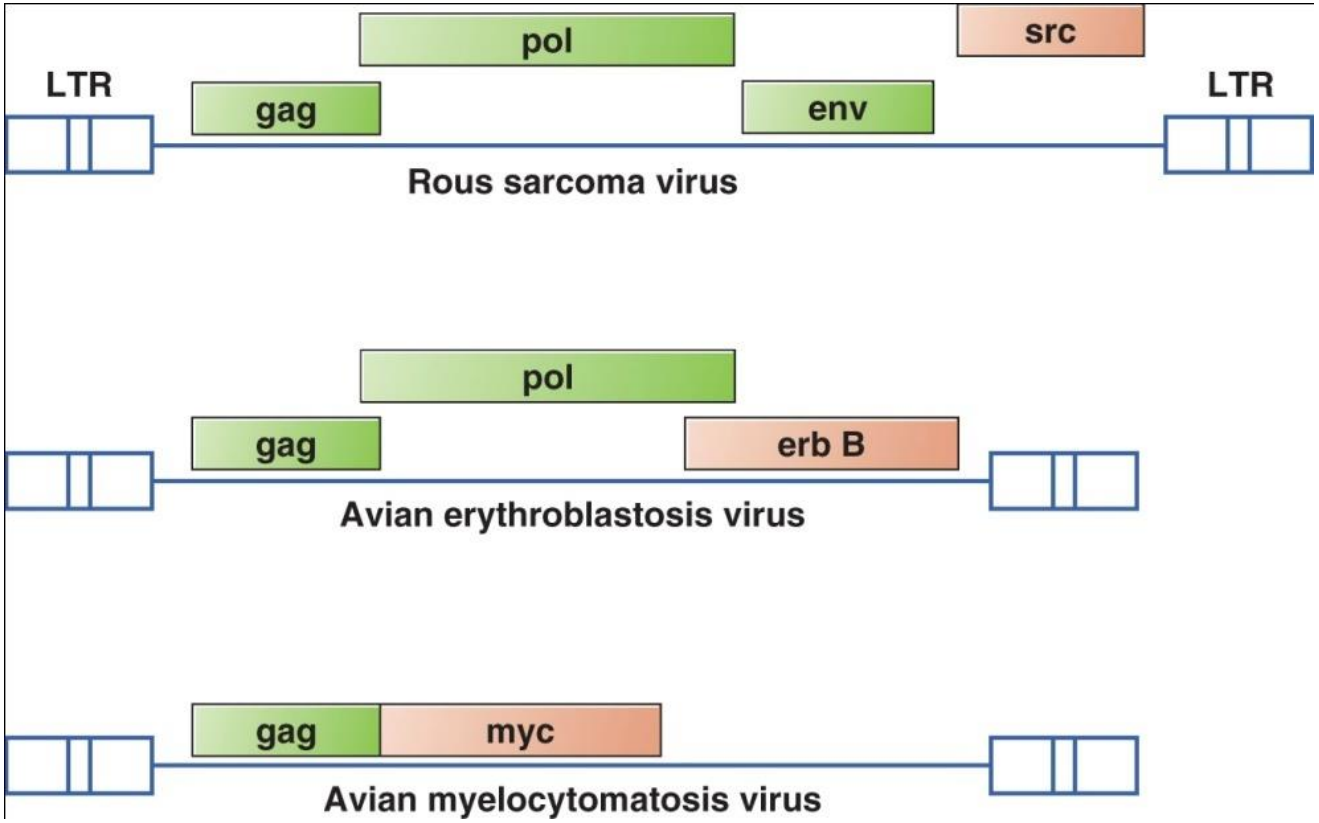
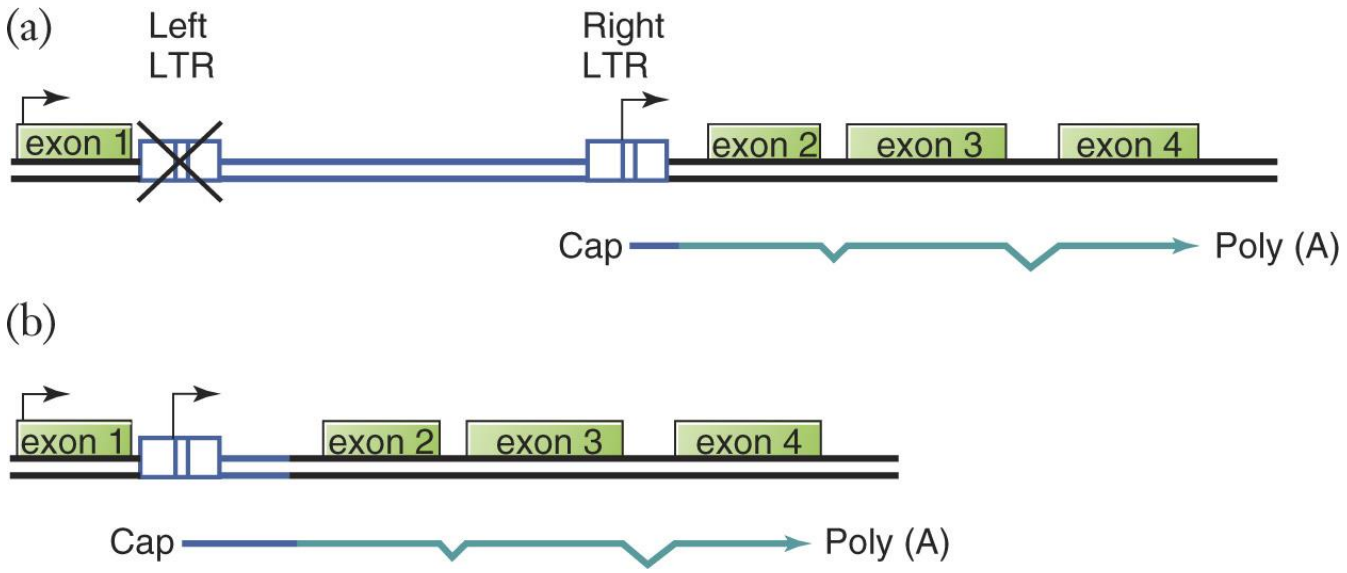
Oncogenic retroviruses

- **Acute transforming retroviruses** express mutated forms of cellular growth signaling proteins
  - Viral Src is nearly identical to cellular **proto-oncogene** c-src

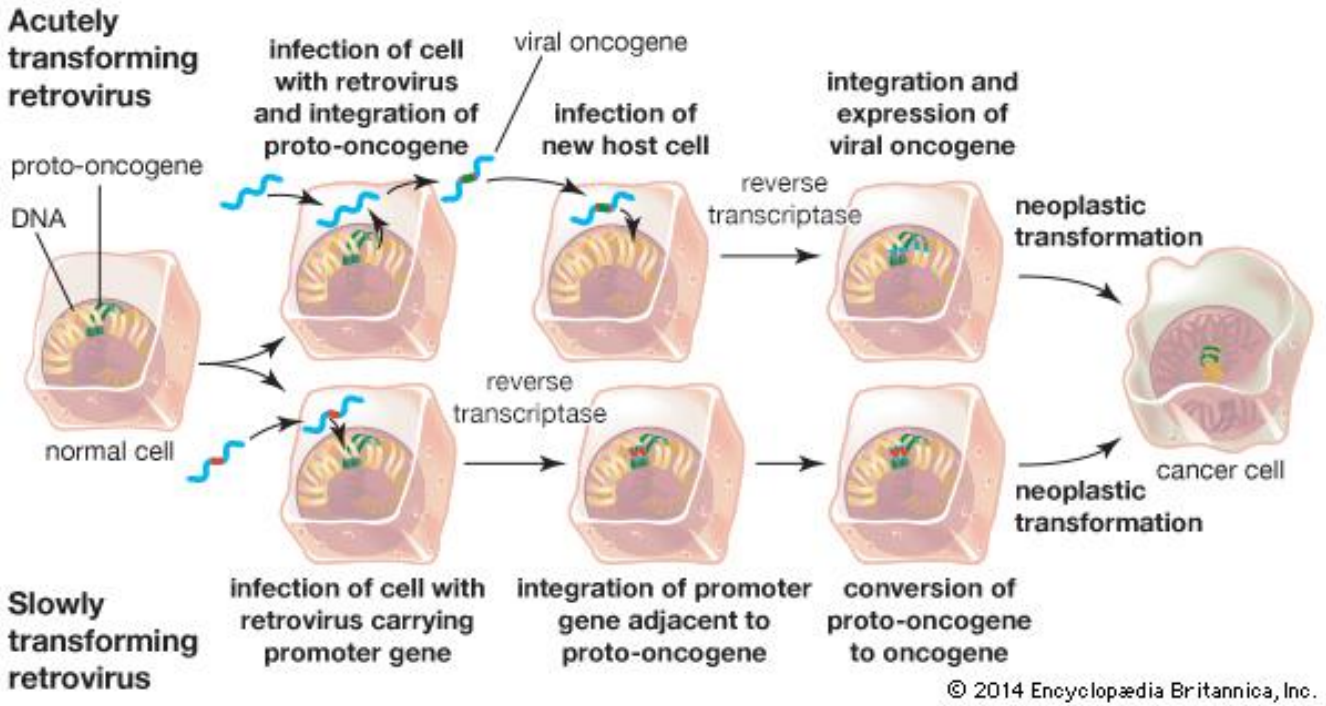


Oncogenic retroviruses

- Slowly transforming retroviruses lacking oncogenes can transform cells by insertion of proviral DNA near a proto-oncogene



Oncogenic retroviruses



Virus category	Tumor latency period	Efficiency of tumor formation	Oncogenic effector	Infecting viral Genome	Transform cultured cells?
Transducing retrovirus	Short (days)	High (can reach 100% of animals)	Cell-derived oncogene carried in viral genome	Viral-cellular chimera, replication defective	Yes
Cis-acting/ nontransducing	Long (wk, mo)	Low	Cellular oncogene activated in situ by provirus insertion	Intact, replication competent	No

Endogenous retroviruses

- Endogenous retroviruses and retrotransposons
  - 8% of the human genome is composed of retroviral DNA
  - Results from insertion of viral genes into germ line cells
  - 41% of human genome is composed of **retrotransposons**