

VIROLOGIA 2006/2007

APRESENTAÇÃO 10

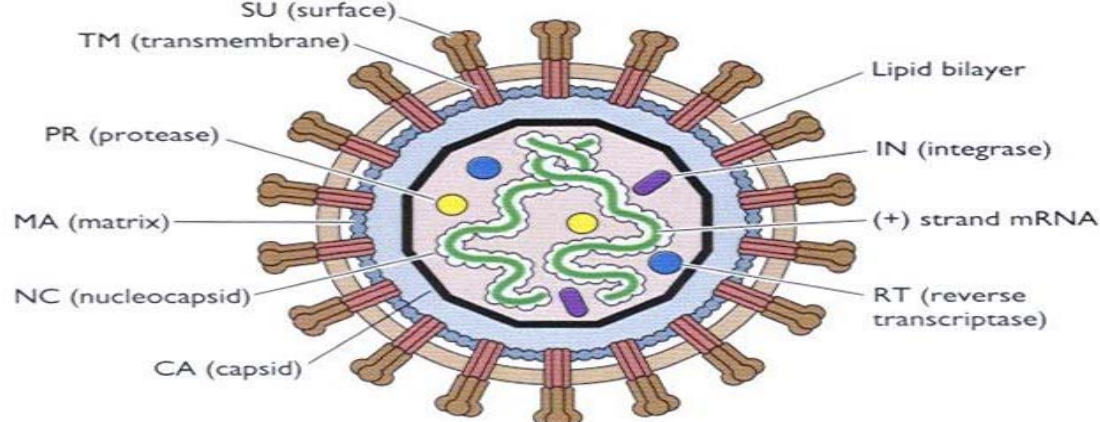
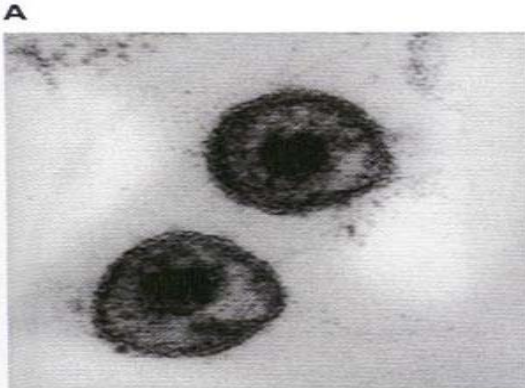
(Vírus com transcriptase reversa)

Maria Filomena Caeiro

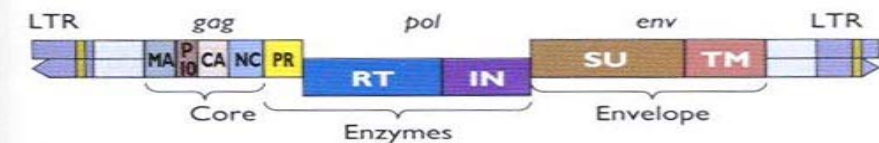
Quadro 21.1

Descrição sumarizada dos diversos retrovírus conhecidos, género a que pertencem e tipo de hospedeiro e afecções que provocam

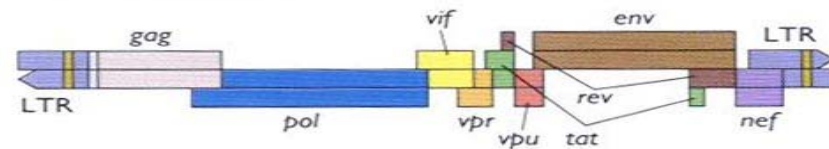
Nome do Vírus	Acrónimo	Classificação (Género)	Hospedeiro	Doença
V. Leucémia Aviária	ALV	<i>Alpharetrovirus</i>	Aves (Galinhas)	Linfomas, Leucémias, Anemia, Osteopetrose
V. Sarcoma Aviário	ASV	<i>Alpharetrovirus</i>	Aves (Galinhas)	Sarcomas
V. Sarcoma de Rous	RSV	<i>Alpharetrovirus</i>	Aves (Galinhas)	Sarcomas
V. Eritroblastose Aviária	AEV	<i>Alpharetrovirus</i>	Aves (Galinhas)	Eritroblastose, Sarcomas
V. Reticuloendoteliose Aviária	REV	<i>Gammaretrovirus</i>	Aves (Galinhas)	Linfoma, Anemia, Sarcoma
V. Leucémia Felina	FeLV	<i>Gammaretrovirus</i>	Felinos	Leucémia, Anemia, Imunodeficiência
V. Sarcoma Felino	FeSV	<i>Gammaretrovirus</i>	Felinos	Sarcoma
V. Sincicial Felino	FSFV	<i>Spumavirus</i>	Felinos	Não-conhecida
V. Imunodeficiência Felina	FIV	<i>Lentivirus</i>	Felinos	Imunodeficiência, lesões no SNC
V. Leucose Bovina	BLV	<i>Deltaretrovirus</i>	Bovinos	Leucose, Linfoma
V. Imunodeficiência Bovina	BIV	<i>Lentivirus</i>	Bovinos	Linfocitose, Imunodeficiência (?)
V. Anemia Equina Infecciosa	EIAV	<i>Lentivirus</i>	Equinos	Anemia
V. <i>Maedi-Visna</i>	(MVV)	<i>Lentivirus</i>	Ovinos	Pneumonia progressiva/ /Encefalite, Desmielinização SNC
V. Artrite/Encefalite Caprina	CAEV	<i>Lentivirus</i>	Caprinos	Artrites, Encefalomielites
V. Leucémia dos Gibões	GALV	<i>Gammaretrovirus</i>	Macaco Gibão	Leucémia
V. Imunodeficiência dos Símios	SIV (vários)	<i>Lentivirus</i>	Primatas não-humanos (várias espécies)	Imunodeficiência (experimental)
V. Mason-Pfizer do Macaco	MPMV	<i>Betaretrovirus</i>	Macaco <i>rhesus</i>	Não conhecida
V. Leucémia Murina	MuLV	<i>Gammaretrovirus</i>	Murinos (Ratos e Murganhos)	Linfomas, Leucémias, Eritroblastose, Sistema Nervoso
V. Tumor Mamário Murino	MMTV	<i>Betaretrovirus</i>	Murinos (Murganhos)	Carcinomas Mamários
V. Sincicial (vários)	—	<i>Spumavirus</i>	Humano, Bovídeos, Felinos e Símios	Não conhecida (contaminantes de cultura de tecidos)
V. Leucémia Humana de Células T (1 e 2)	HTLV (1 e 2)	<i>Deltaretrovirus</i>	Homem	Leucémias, Parésia Espástica Tropical (TSP)
V. Imunodeficiência Humana	HIV (1 e 2)	<i>Lentivirus</i>	Homem	Imunodeficiência, lesões no SNC



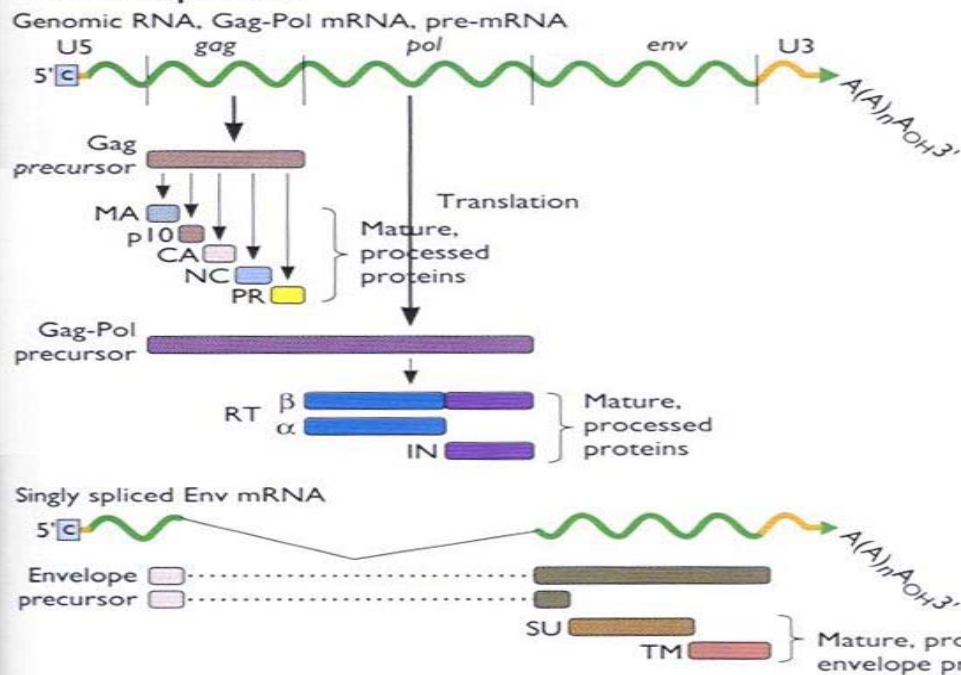
B Simple retrovirus (ALV)



Complex retrovirus (HIV-1)



Genome expression



Genome expression

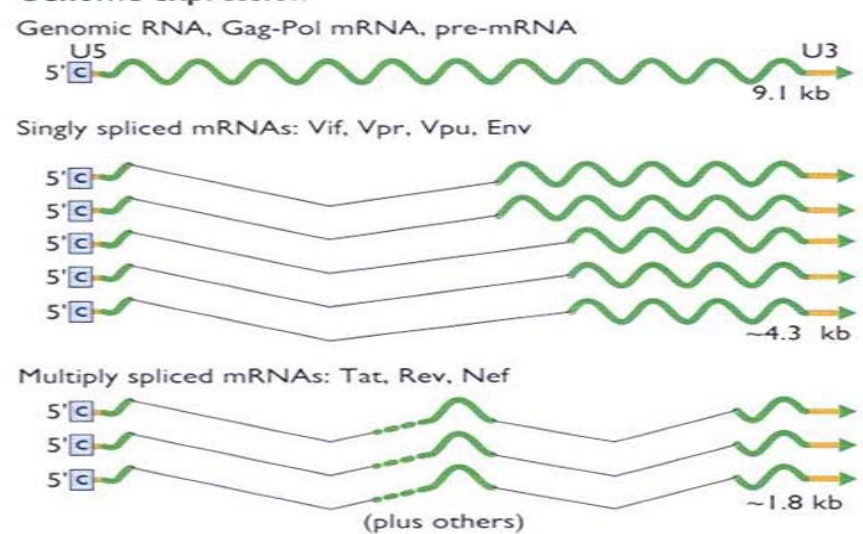


Figure 9 Structure and genomic organization of retroviruses.

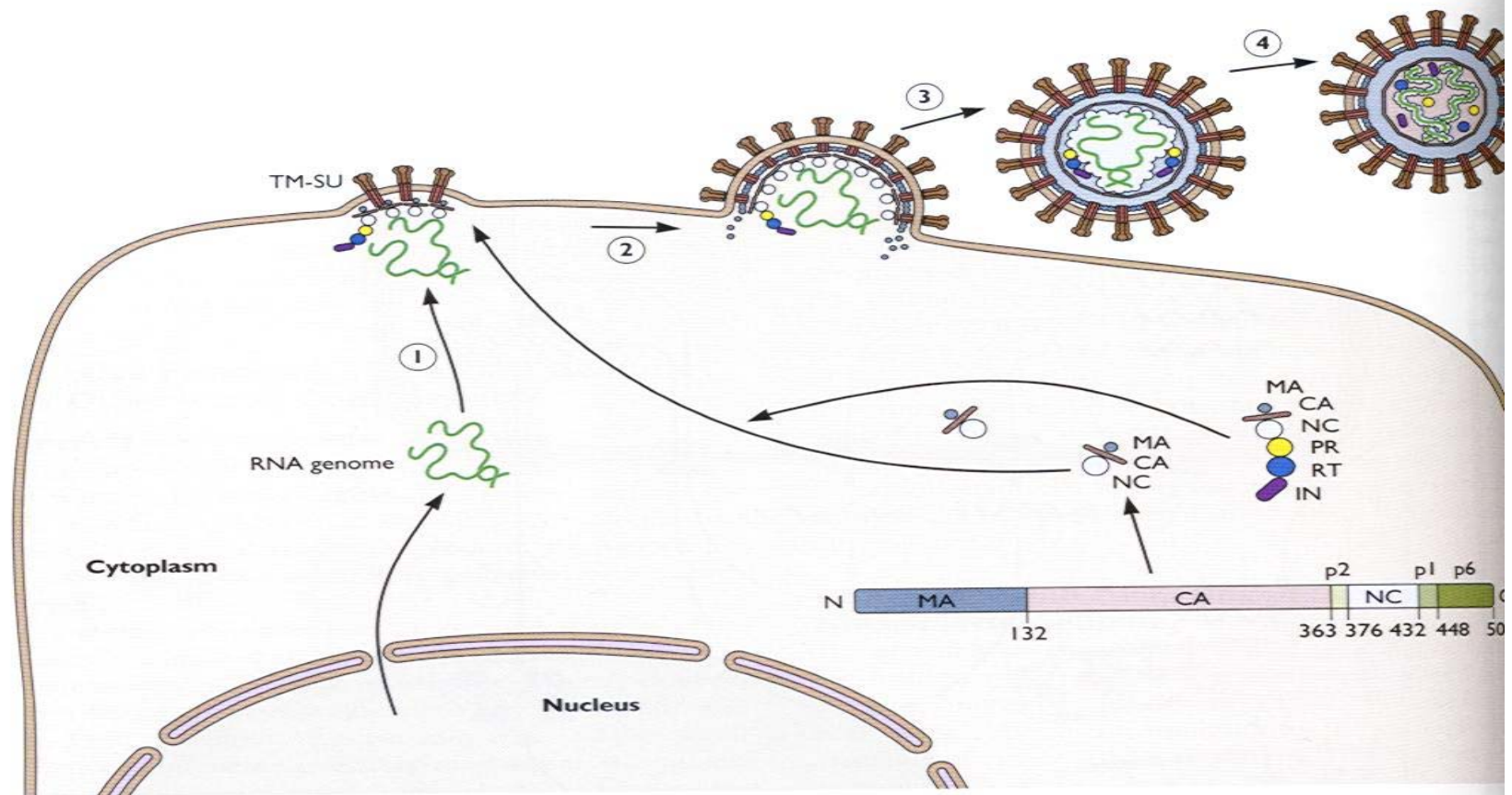
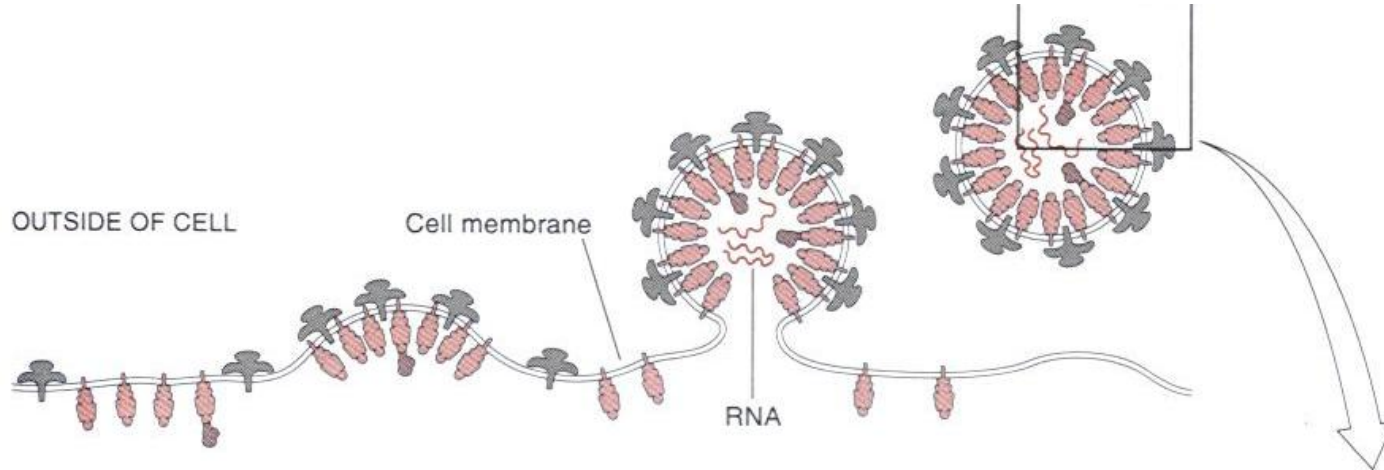


Figure 13.8 Assembly of a retrovirus from polyprotein precursors. The Gag polyprotein of all retroviruses contains the MA, CA, and NC proteins linked by spacer peptides that are variable in length and position. The proteins are in the order (from N to C terminus) of the protein shells of the virus particle, from the outer to the inner. The organization of human immunodeficiency virus type 1 Gag is summarized on the right. A minor fraction, about 1 in 10, of Gag translation products carry the retroviral enzymes, denoted by PR, RT, and IN, at their C termini. The association of Gag molecules with the plasma membrane, with one another, and with the RNA genome via binding of NC segments initiates assembly at the inner surface of the plasma membrane (step 1). In some cases, such as human immunodeficiency virus type 1, the MA segment also binds specifically to the internal cytoplasmic domain of the TM-SU glycoprotein, whose synthesis, processing, and transport to the plasma membrane are described in chapter 12. Note that no discrete intermediates are formed, as assembly of the particle continues by incorporation of additional molecules of Gag (step 2). This pathway is typical of many retroviruses, but some (e.g., D-type retroviruses) complete assembly of the core in the interior of the cell prior to its association with the plasma membrane. The dimensions of the assembling particle are determined by interactions among Gag polyproteins. Eventually, fusion of the membrane around the budding particle (step 3) releases the immature noninfectious particle. This fusion process is not well understood. Cleavage of Gag and Gag-Pol polyproteins by the viral protease (PR) produces infectious particles (step 4) with a morphologically distinct core (see Fig. 13.18).

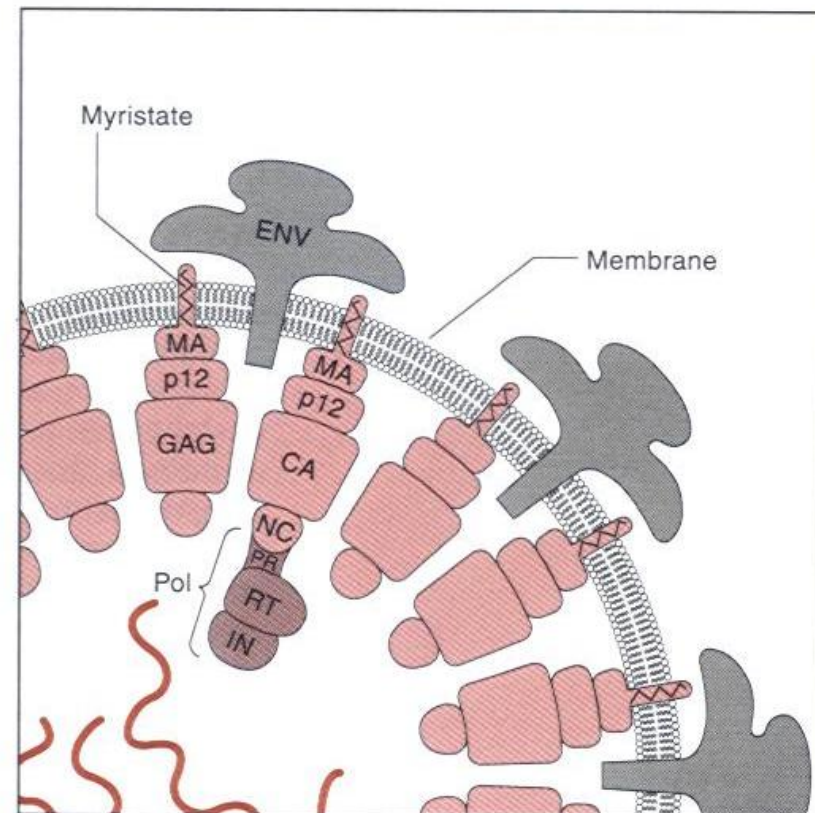


INSIDE OF CELL

(a)

Figure 3.21

Assembly of the retroviral virion particle. The gag and gag-pol precursors are largely cytoplasmic and are retained in the membrane by their N-terminal fatty acid modification. The envelope protein is an integral membrane glycoprotein. The virion particle is formed by the side-to-side aggregation of the gag and gag-pol precursor proteins; as the particle grows, curvature is induced in the membrane. The env protein is attracted to the site of the bud, probably by contacts with gag. The RNA genome is incorporated, also through contacts with gag. At the end of the budding process the membrane is pinched off, and the gag and gag-pol precursors are processed to their mature products.



(b)

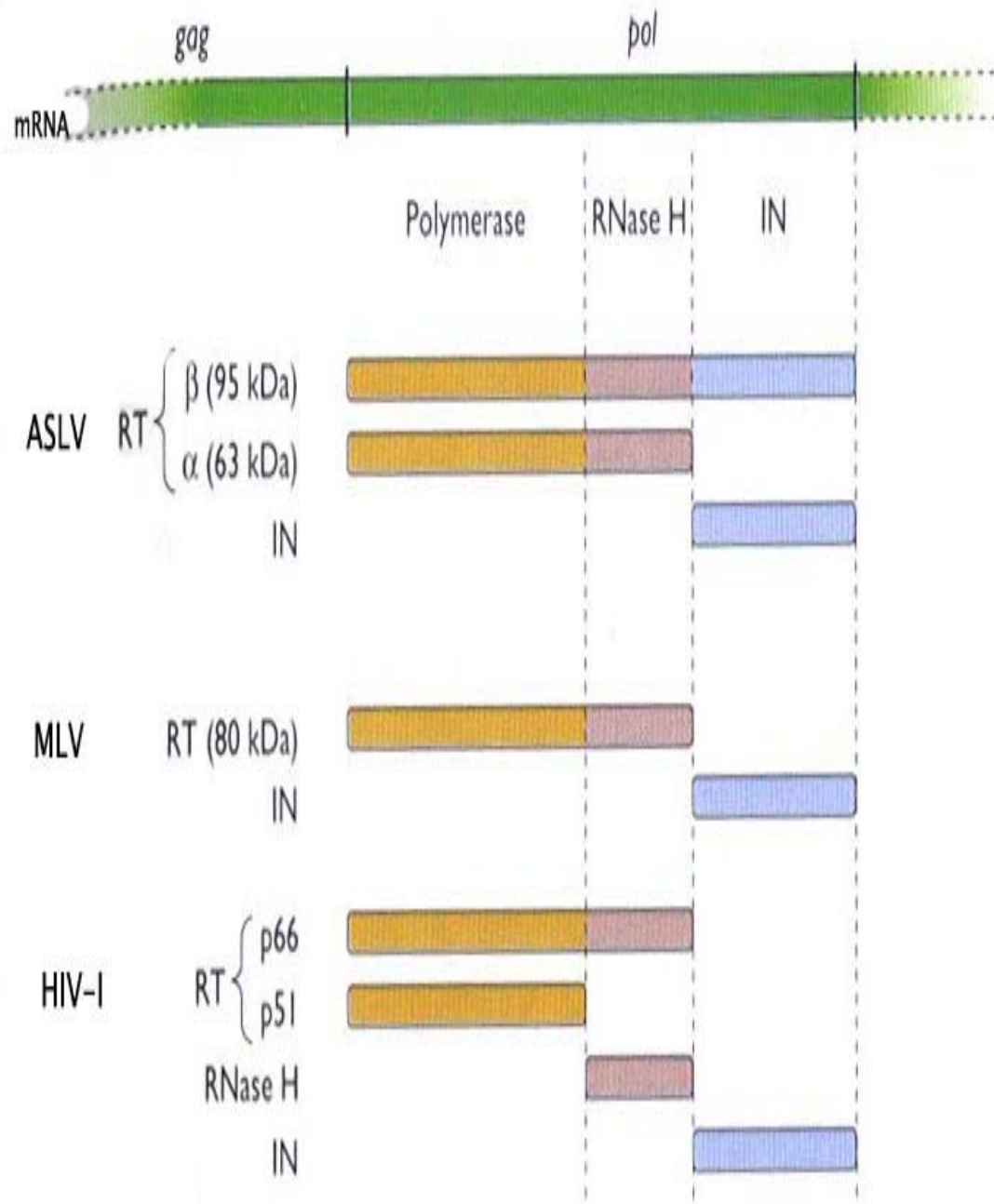
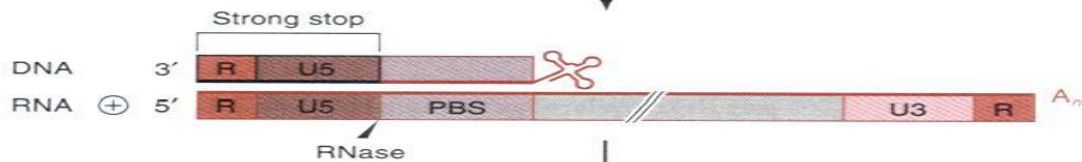


Figure 7.6 Domain and subunit relationships of RTs from different retroviruses. The RT of ASLV includes sequences corresponding to integrase in its largest subunit, β . Both subunits of this enzyme include RNase H sequences. MLV RT functions as a homodimer; both subunits contain the RNase H domain, but neither includes IN sequences. Like that of ASLV, the HIV-1 RT is a heterodimer. However, in this case only one subunit includes the RNase H domain, and neither includes IN sequences. Adapted from R. A. Katz and A. M. Skalka, *Annu. Rev. Biochem.* **63**:133–173, 1994, with permission.



tRNA is extended to form DNA copy of 5' end of genomic RNA.



RNase removes hybridized RNA.

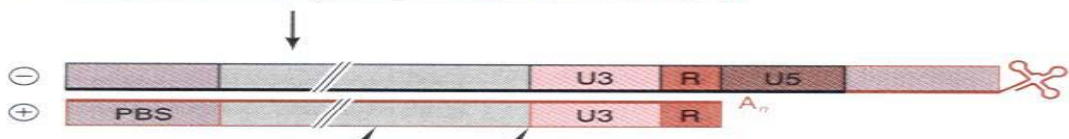
First jump: DNA hybridizes with remaining RNA R sequence.



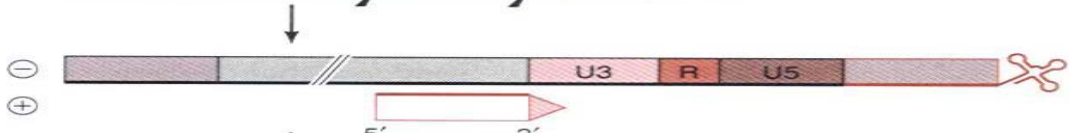
DNA strand is extended.



Most hybrid RNA is removed.



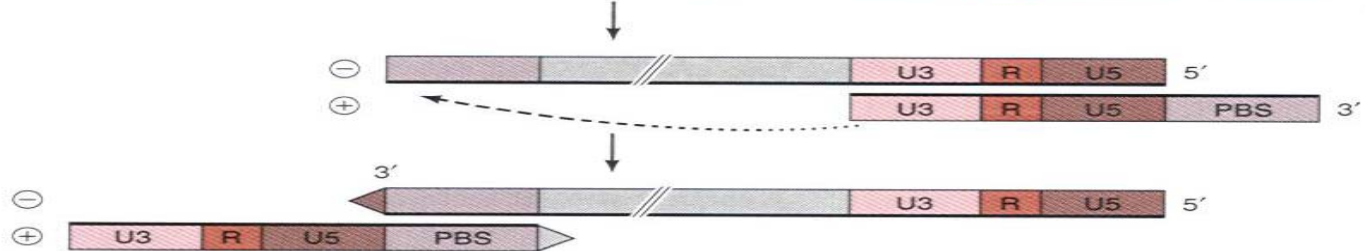
5' end of second DNA strand is synthesized.



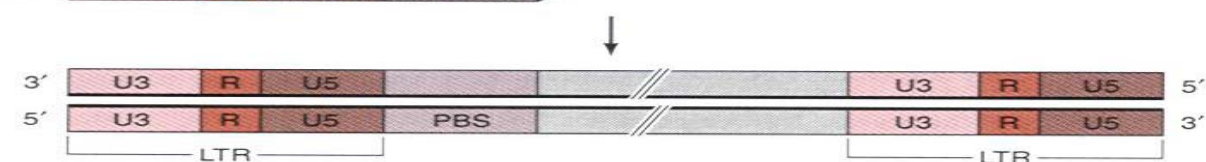
RNA and tRNA are removed.



Second jump occurs.



Both strands are completed.



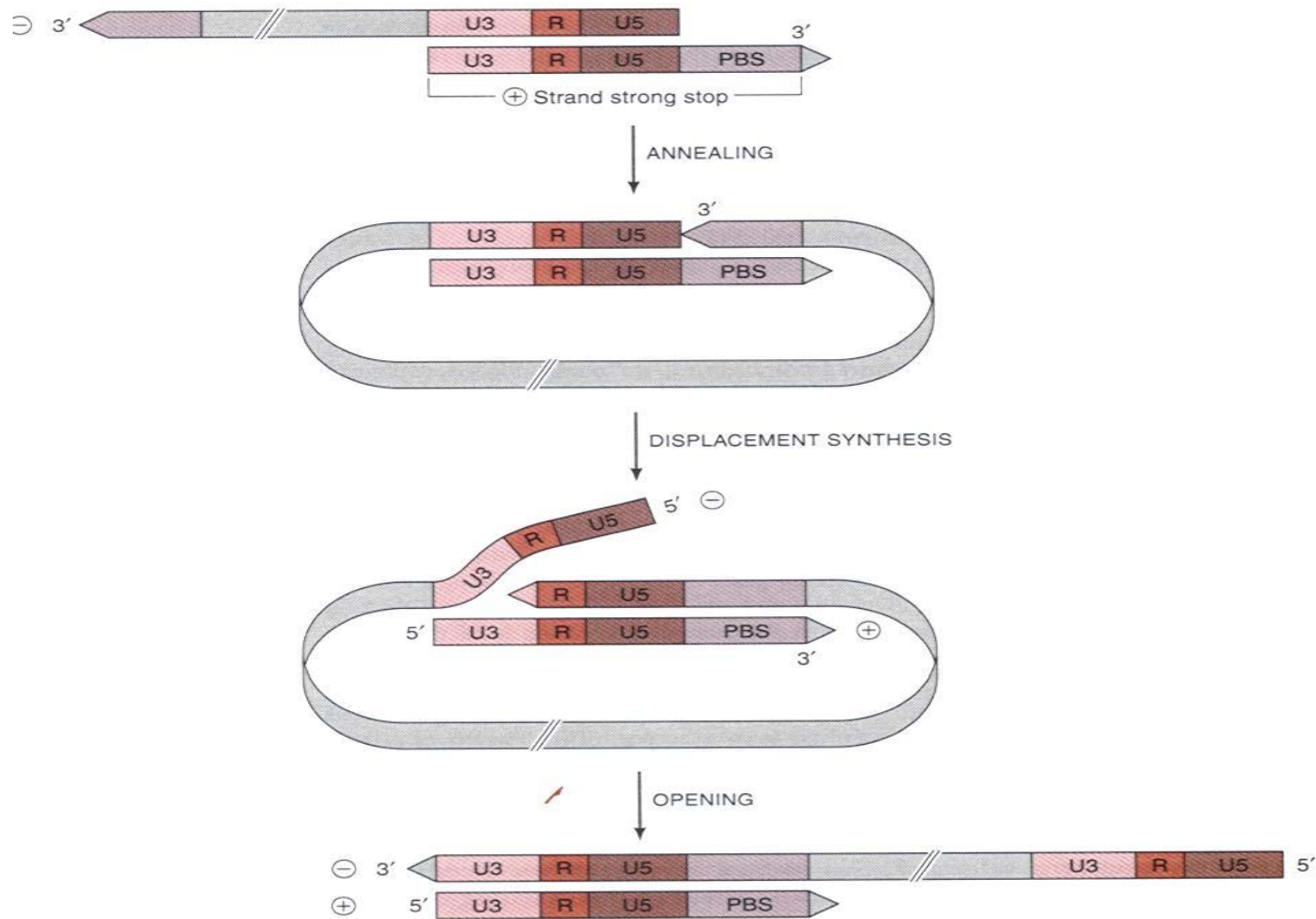


Figure 3.8

Detail of the translocation of the plus-strand strong stop DNA. The translocation of the plus-strand strong stop DNA is thought to proceed through a circular intermediate formed by annealing of complementary sequences at the 3' ends of the minus and plus strands. Elongation of the minus strand coupled to displacement of the 5' end of the minus strand from the plus-strand template results in the opening of the circle into a linear DNA. The net effect is the "jumping" of the plus-strand strong stop from the 5' end to the 3' end of the minus strand.

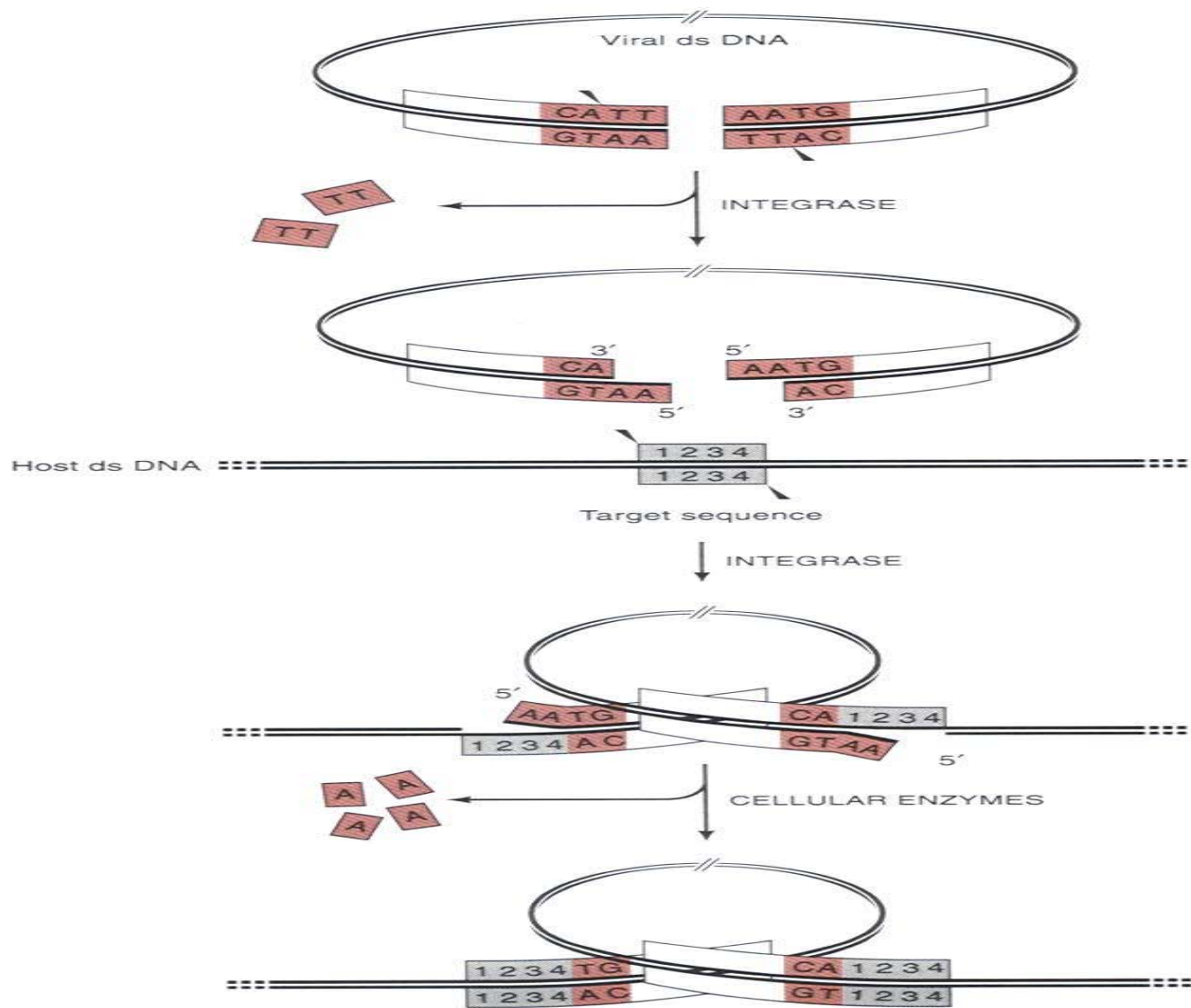


Figure 3.10

Structures of intermediates formed during the integration of the viral DNA into the host DNA. In a prefatory step, the termini of the full-length blunt-ended linear DNA are brought together and then cleaved by the endonuclease activity of the integrase protein to form recessed 3' termini. In a second joining step, the recessed 3' hydroxyl ends of the viral DNA are used by the integrase to attack phosphodiester bonds of the target DNA (arrows). The 3' OH ends of the viral DNA are joined to the 5' phosphates with displacement of the host 3' OH. In the resulting intermediate, only one strand of the viral DNA is joined to the host DNA of each junction; two gaps and two unpaired protruding 5' ends remain. Host enzymes are presumed to repair these discontinuities.

FIGURE 6.9

Gene map and the transcription (TC), translation (TL), and posttranslational cleavage (PTC) and processing strategies of Rous sarcoma virus.

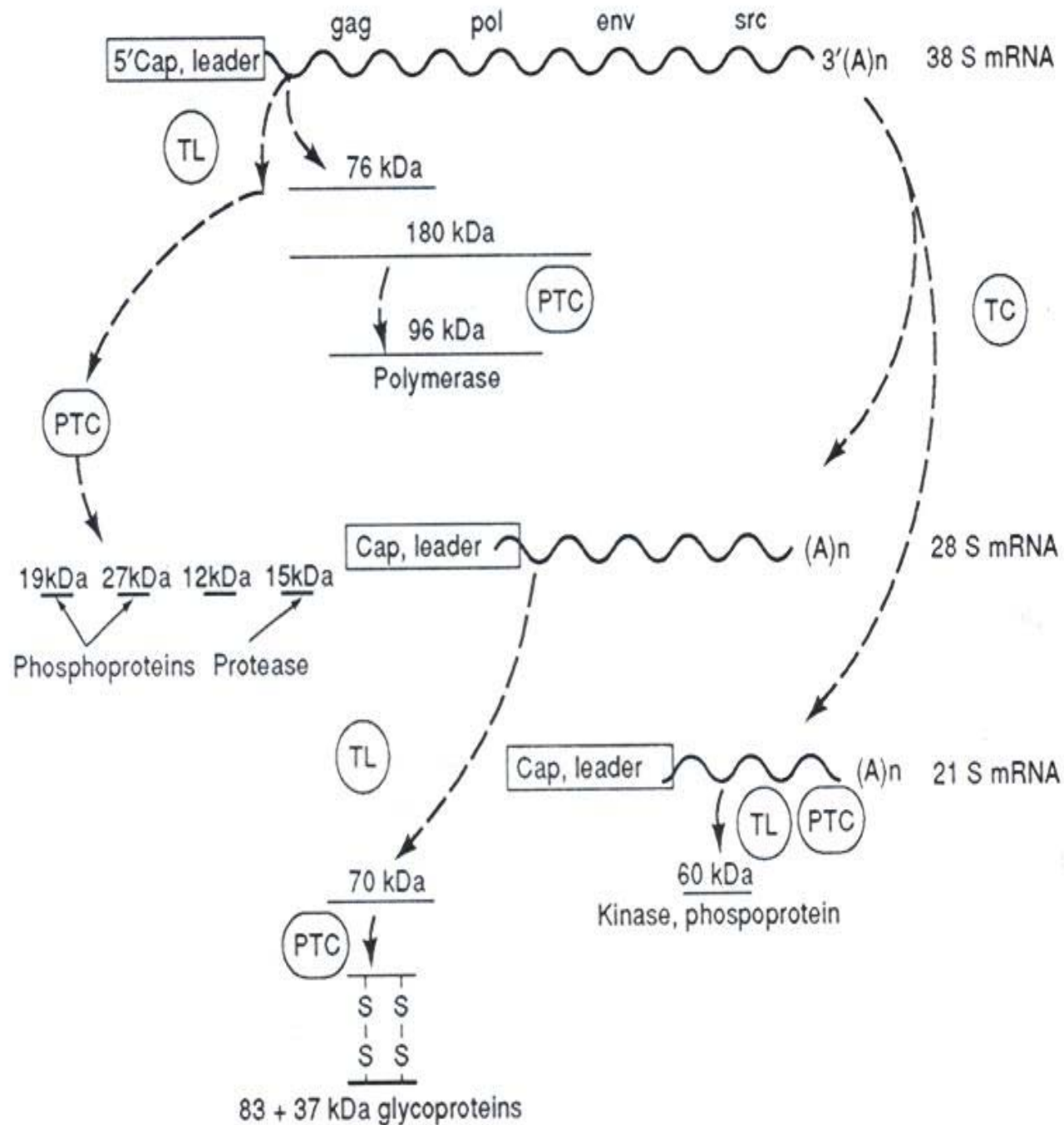
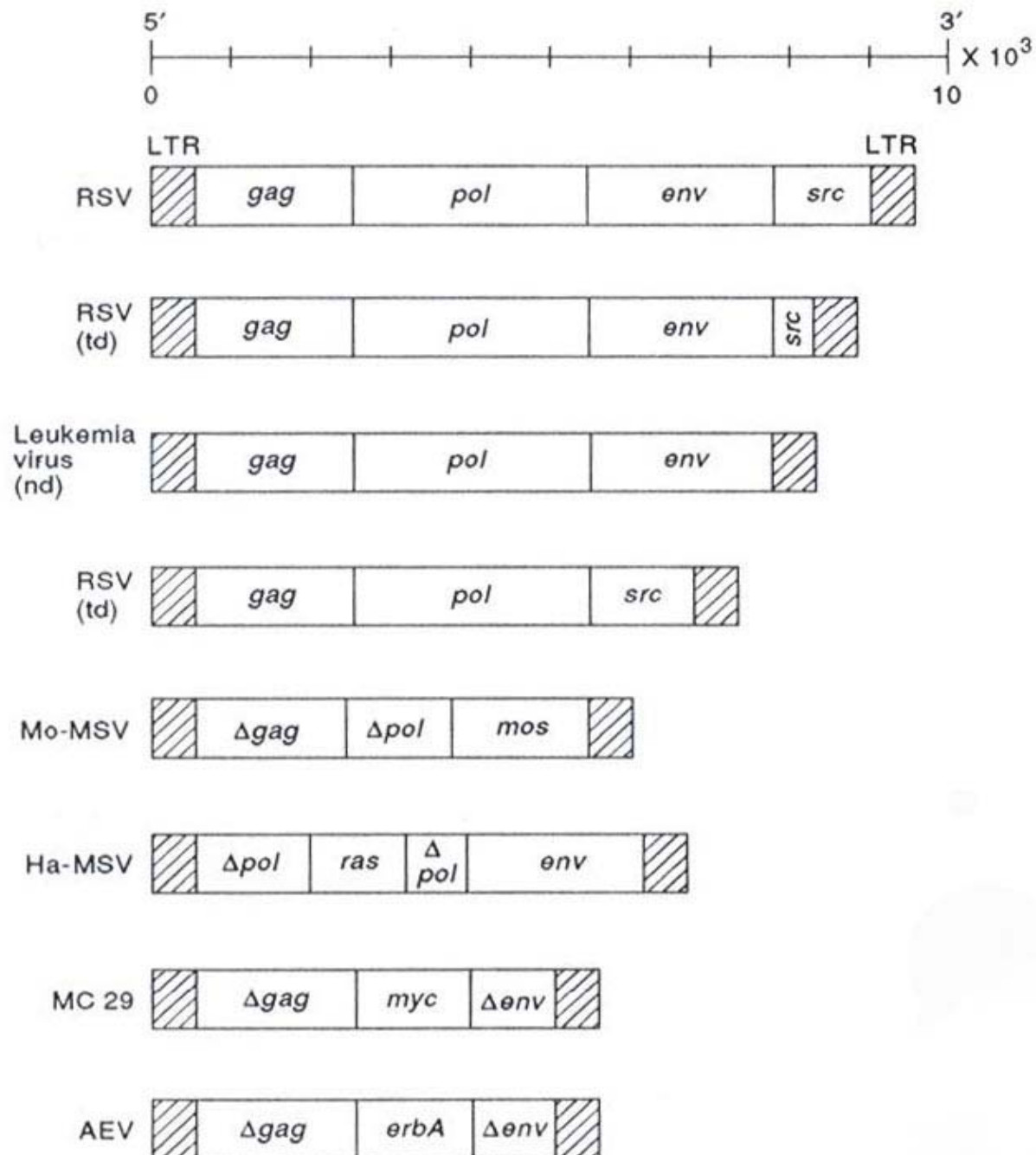


FIGURE 6.8

Genetic maps of oncogenic retroviruses. The shaded segments are the parts of the genome responsible for malignancies: td, transformation-defective; nd, nondefective; rd, replication-defective; RSV, Rous sarcoma virus; Mo-MSV, Ha-MSV, Moloney and Harvey mouse sarcoma viruses; MC-29, avian myelocytoma virus; AEV, avian erythroblastosis virus. The Δ indicates defective genes. (Modified from P. Duesberg and K. Bister. (1980) Proc. 3d Internat. Feline Leukemia Virus Meeting)



Known oncogenes transduced by retroviruses

Protein function	Type of tumour
Tyrosine kinase	Pre-B-cell leukemia/sarcoma
?	T-cell lymphoma/sarcoma
Activator of tyrosine kinase	
Thyroid hormone receptor	
Epidermal growth factor receptor	Erythroleukemia/fibrosarcoma
Nuclear protein	
Tyrosine kinase	Sarcoma
Tyrosine kinase	Sarcoma
Tyrosine kinase; macrophage colony stimulating factor receptor	Sarcoma
Nuclear transcription factor	Osteosarcoma
AP-1 transcription factor	Fibrosarcoma
Tyrosine kinase	Sarcoma
Serine/threonine kinase	Sarcoma
Serine/threonine kinase	Sarcoma
Nuclear protein	Myeloblastosis
Nuclear protein	Sarcoma/myelocytoma/carcinoma
G protein	Sarcoma/erythroleukemia
G protein	Sarcoma/erythroleukemia
Nuclear protein	Reticuloendotheliosis
Tyrosine kinase	Sarcoma
Tyrosine kinase	Sarcoma/leukemia
Platelet-derived growth factor	Sarcoma
Nuclear protein	Carcinoma
Tyrosine kinase	Sarcoma
Tyrosine kinase	Sarcoma

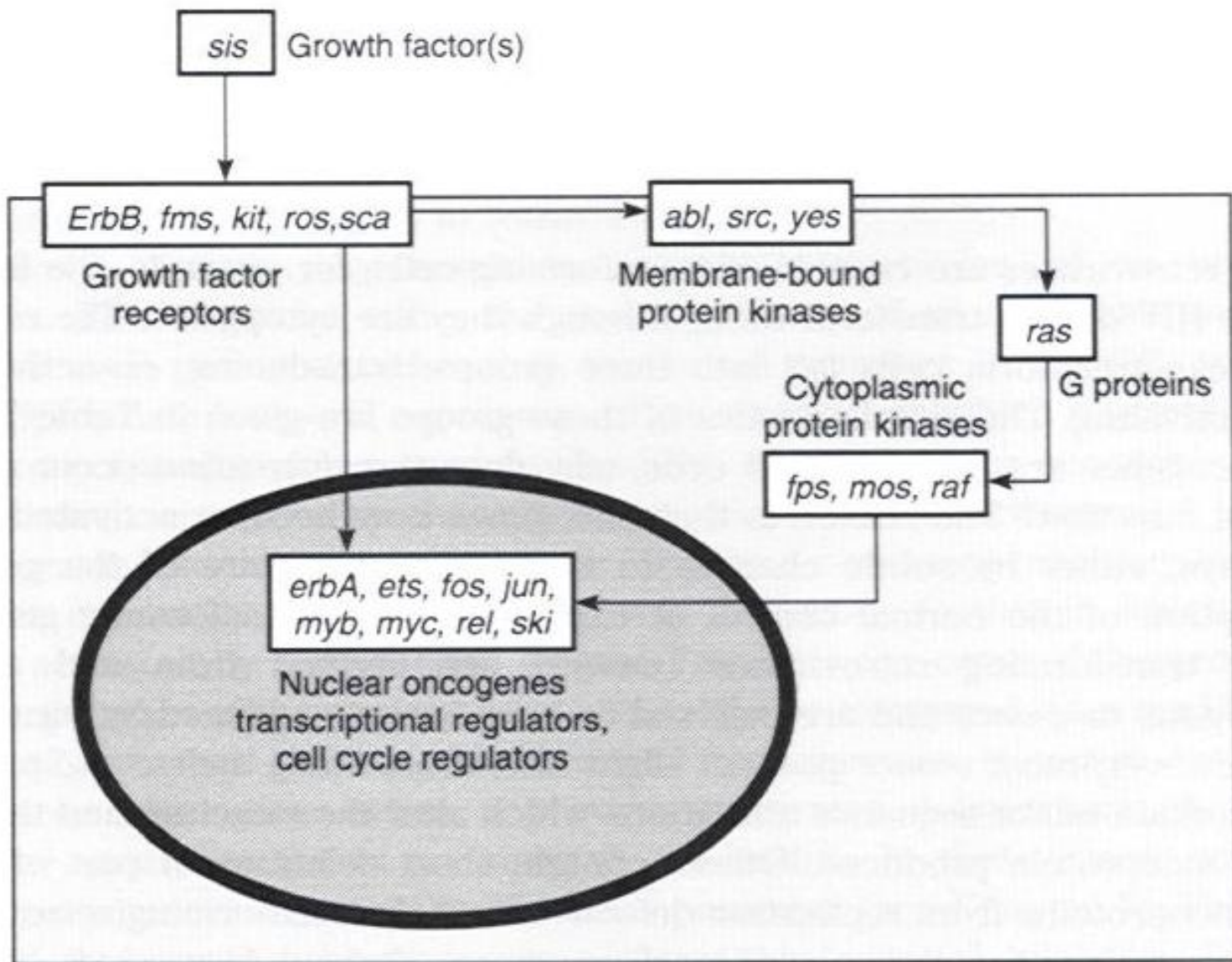
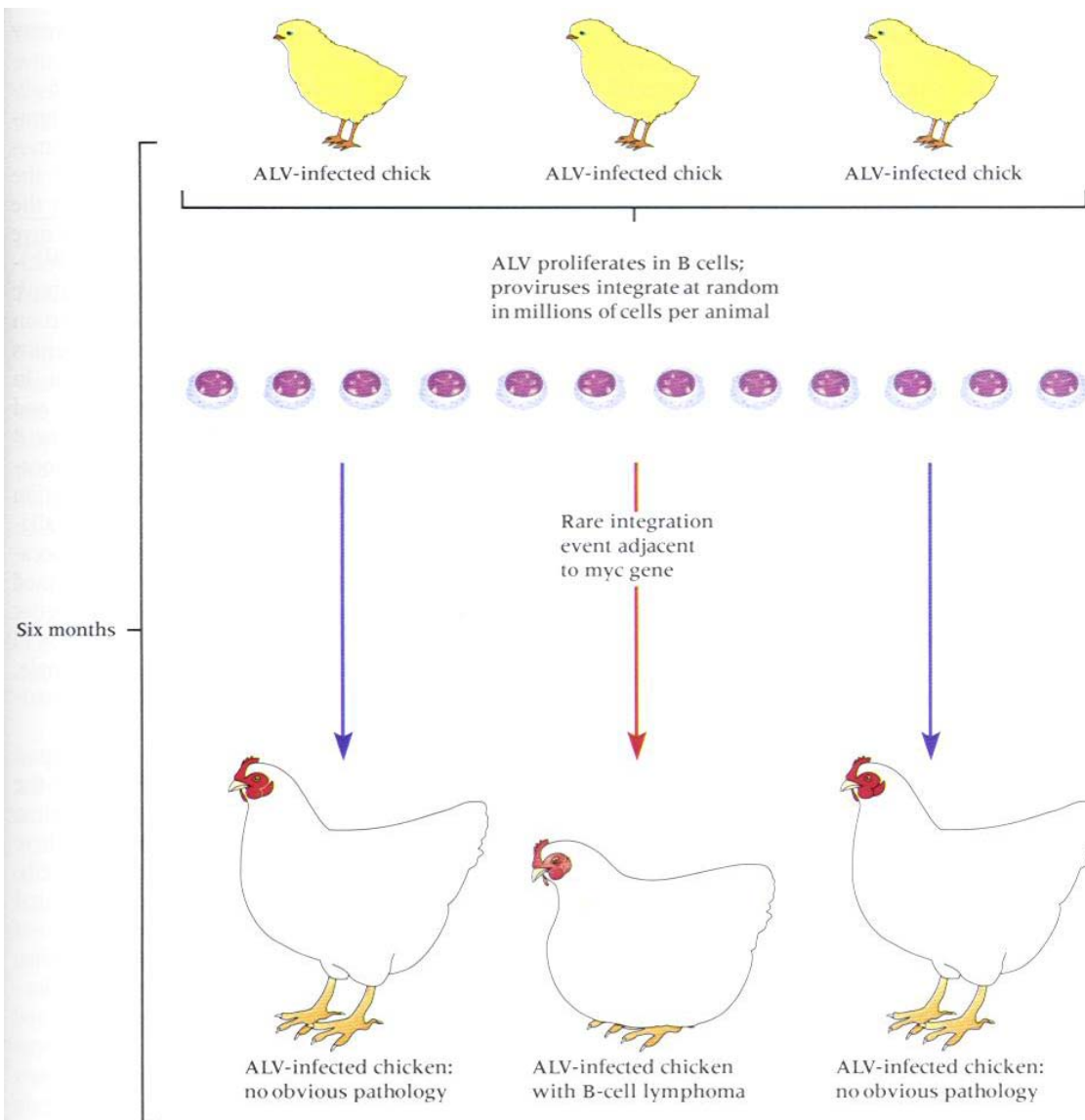
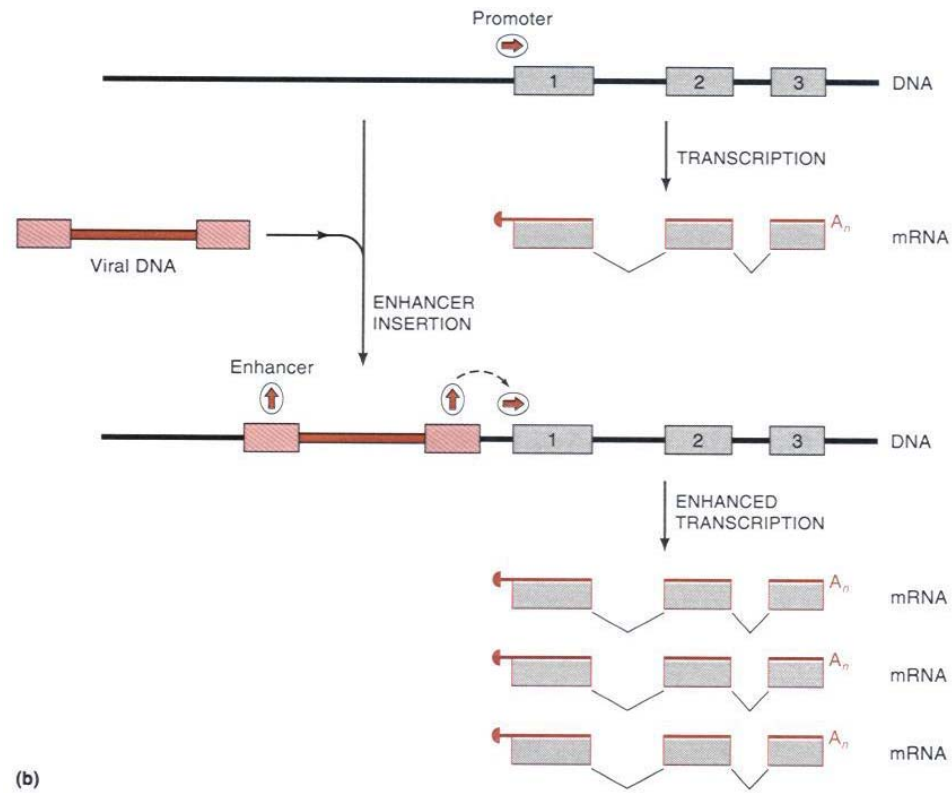
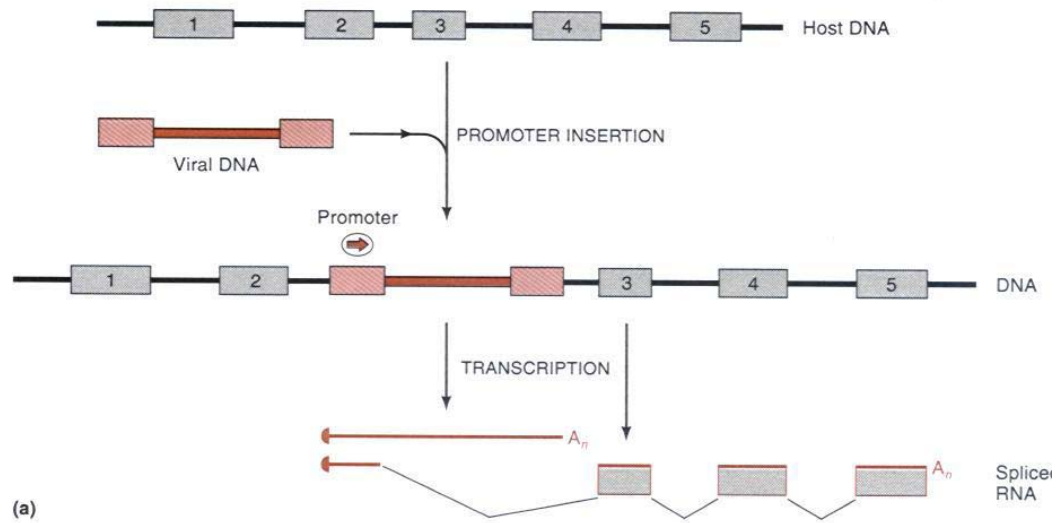


Figure 7.4 Subcellular location of oncoproteins.



Schematic representation of events that lead to long-latency B-cell lymphomas in chickens infected with ALV. When an ALV provirus integrates adjacent to the *myc* gene of a B cell, the viral LTR promotes the transcription of *myc* mRNA, increasing the level of *myc* protein and contributing to abnormal cell replication. These rare clones are selected for because they increase so efficiently.



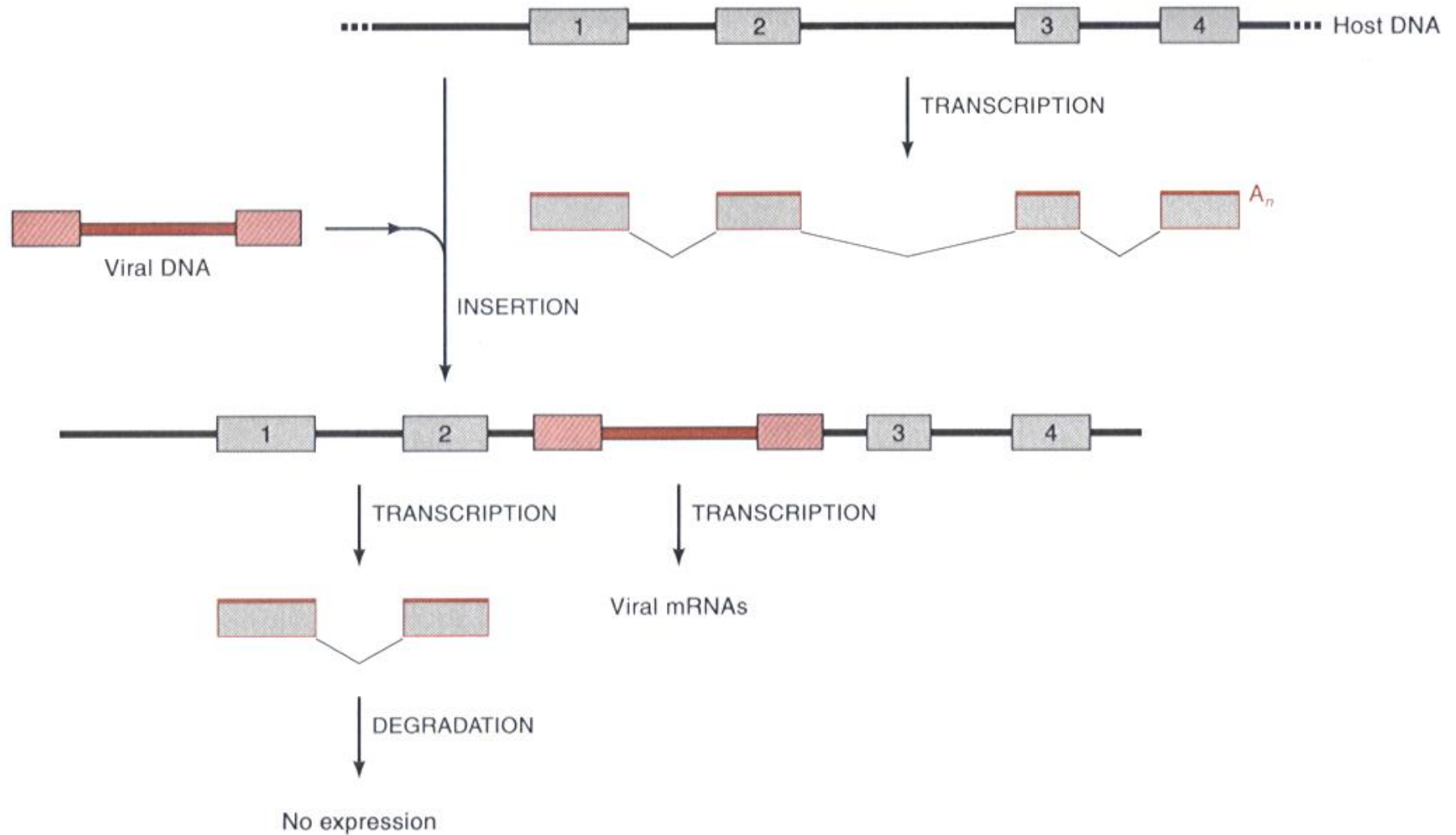
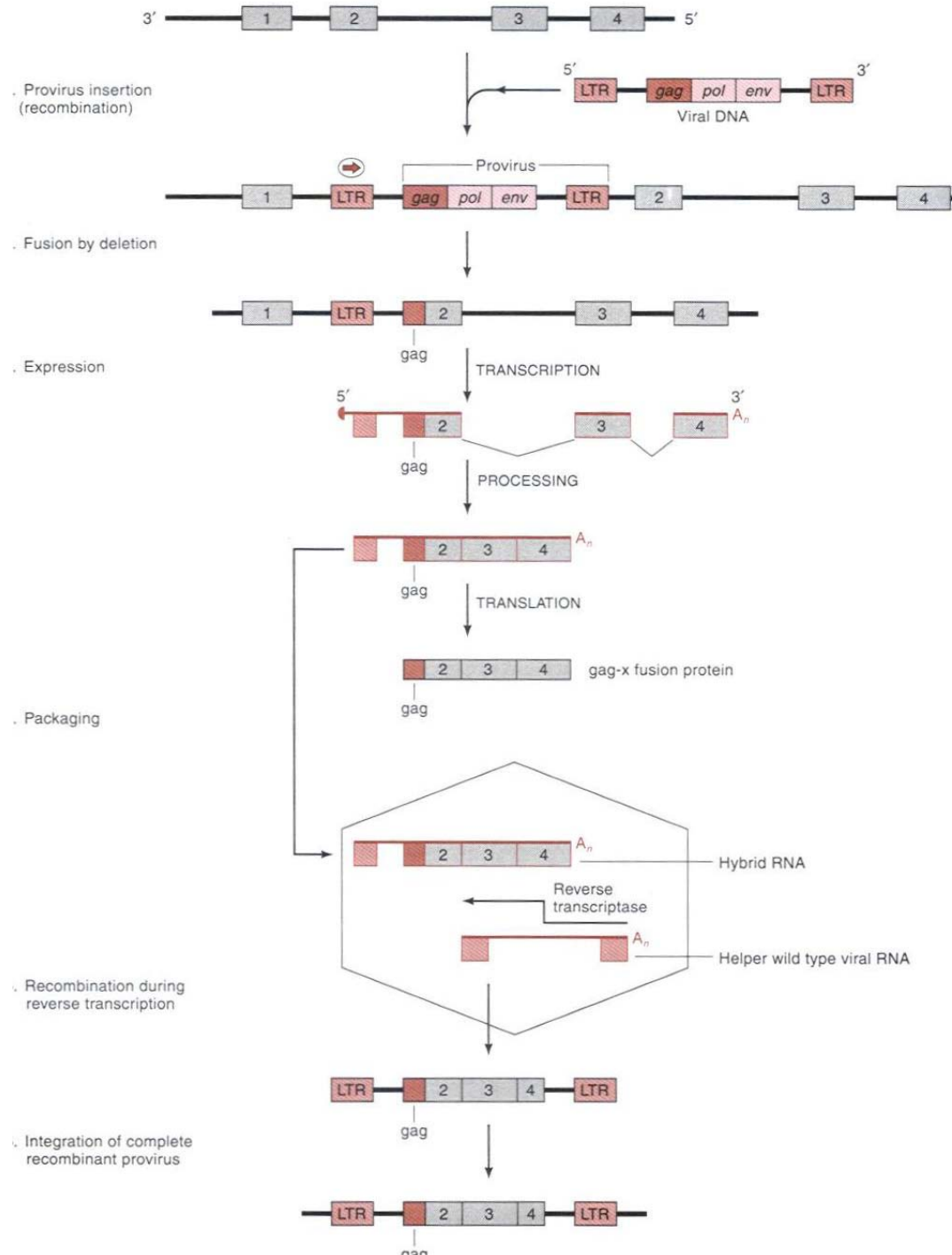
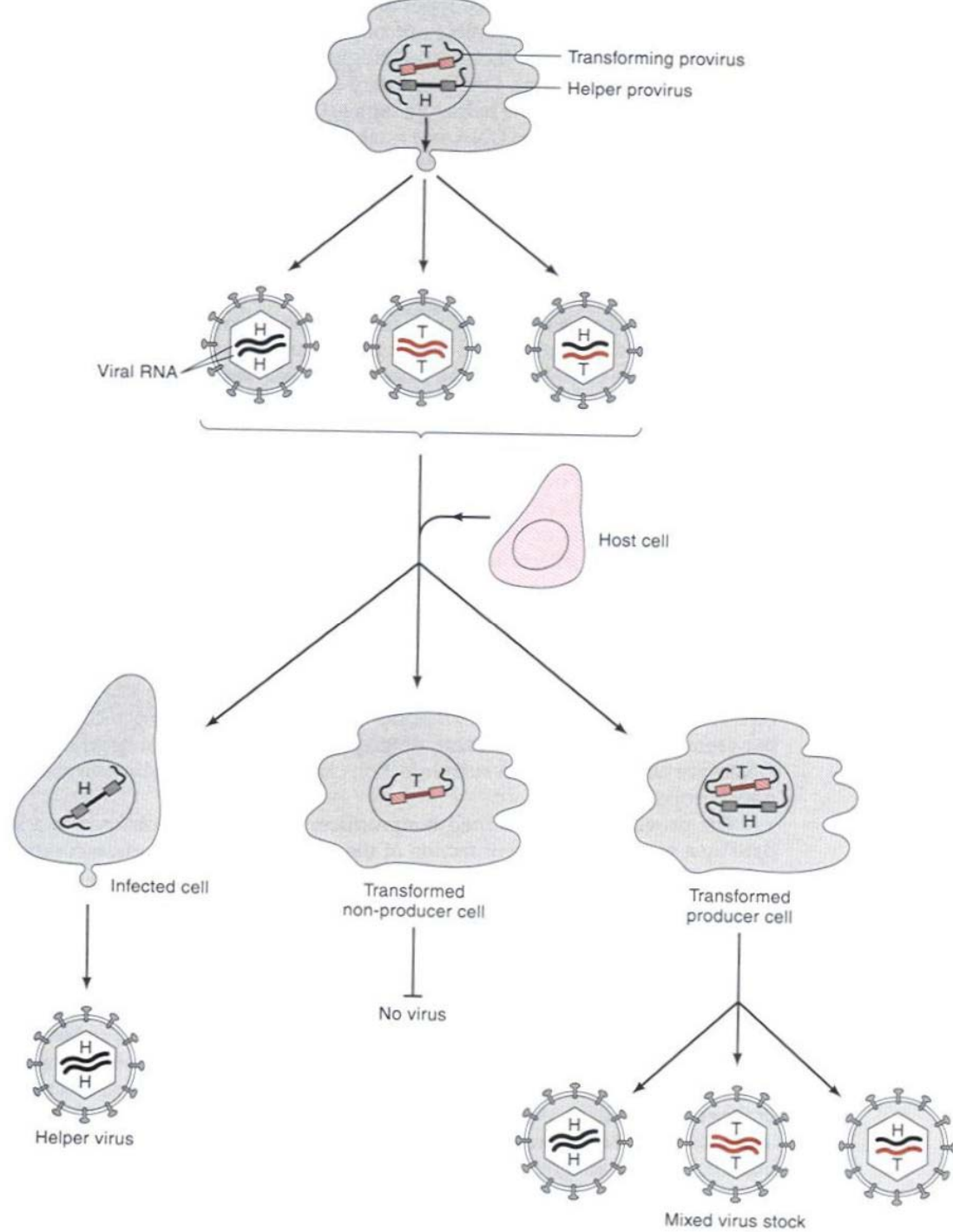
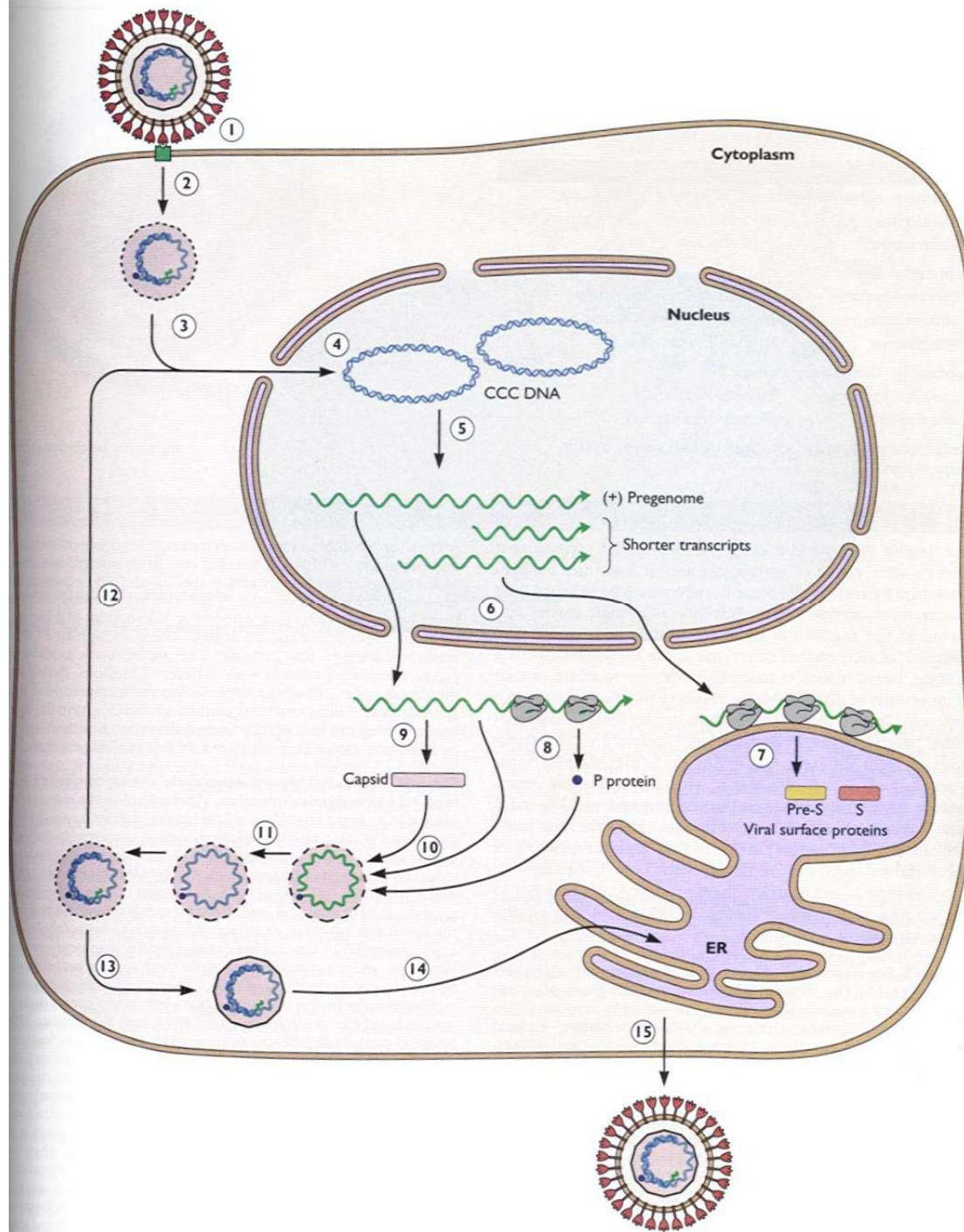


Figure 3.23

Gene disruption by retroviral insertion. Retroviral integration can block expression of the target gene. Even when insertion occurs in an intron sequence, the presence of the viral promoter and polyadenylation sites can affect the structure of the RNA formed at the locus such that the pre-mRNA is not successfully completed, processed, or exported from the nucleus.







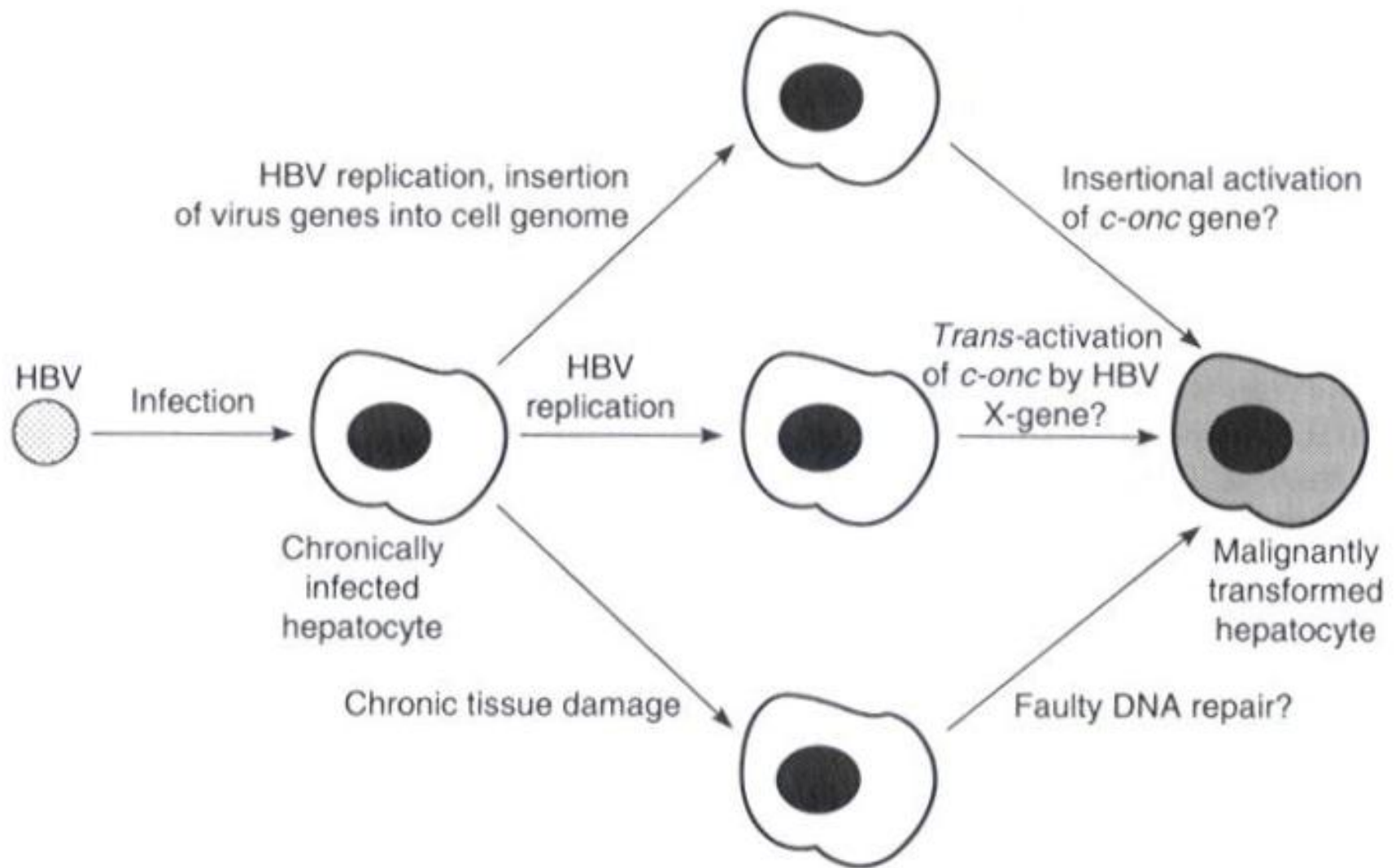


Figure 7.10 Possible mechanisms of hepatocellular carcinoma formation due to hepatitis B virus infection.

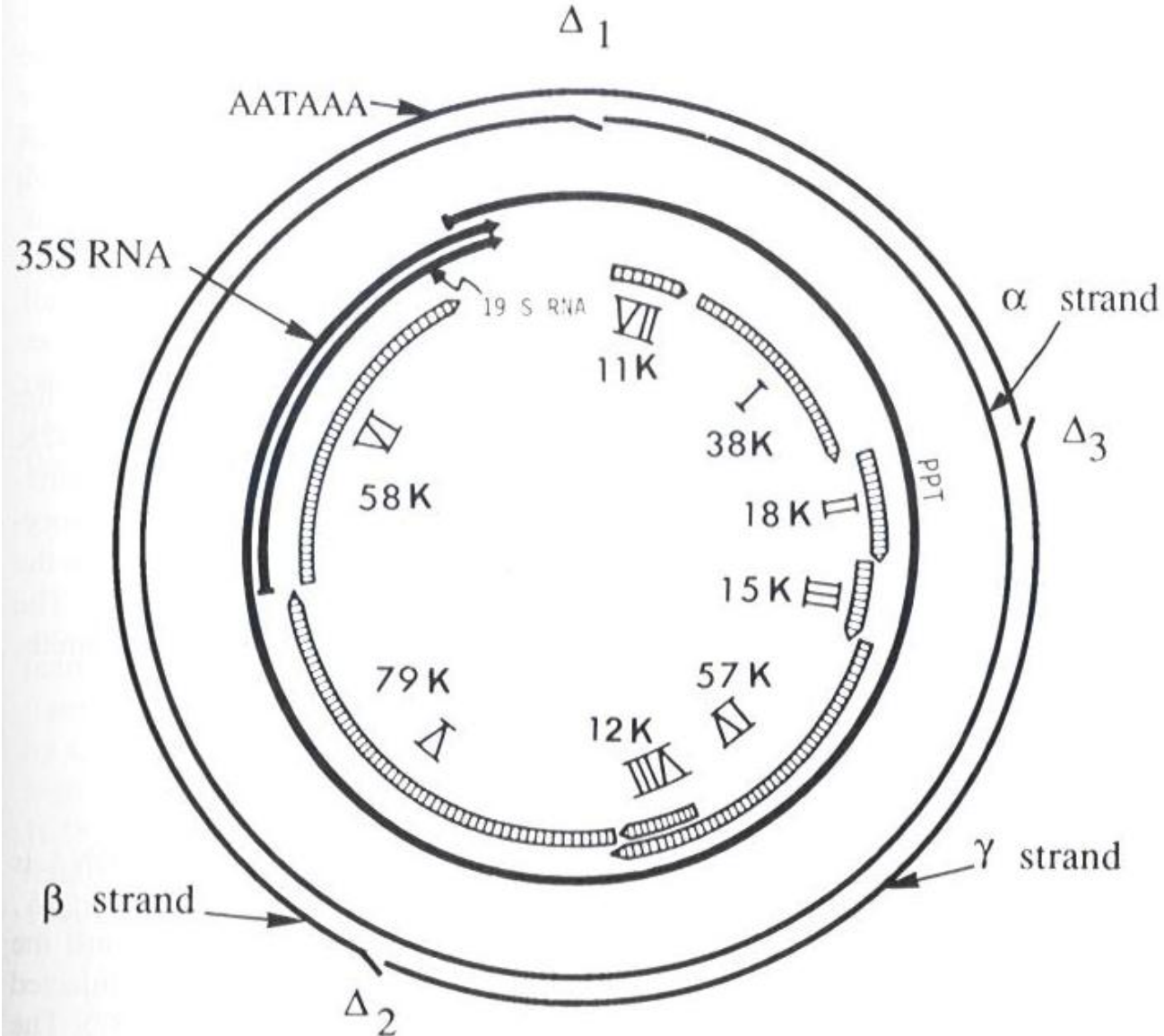


Figure 8.1 Genetic organization of CaMV. The 8-kbp viral DNA features three single-stranded interruptions, one (Δ_1) in the α (or coding) strand and two (Δ_2 and Δ_3) in the noncoding strand, defining the β and γ DNA species. The DNA encodes eight potential ORFs. The MWs of the predicted proteins are indicated. The capped and polyadenylated 19 S and 35 S RNAs have different promoters, but share the same 3' termini. The two mRNAs are translated from a fully ds form of the DNA and not from the gapped form shown here. (From Pfeiffer *et al.*, 1987.)

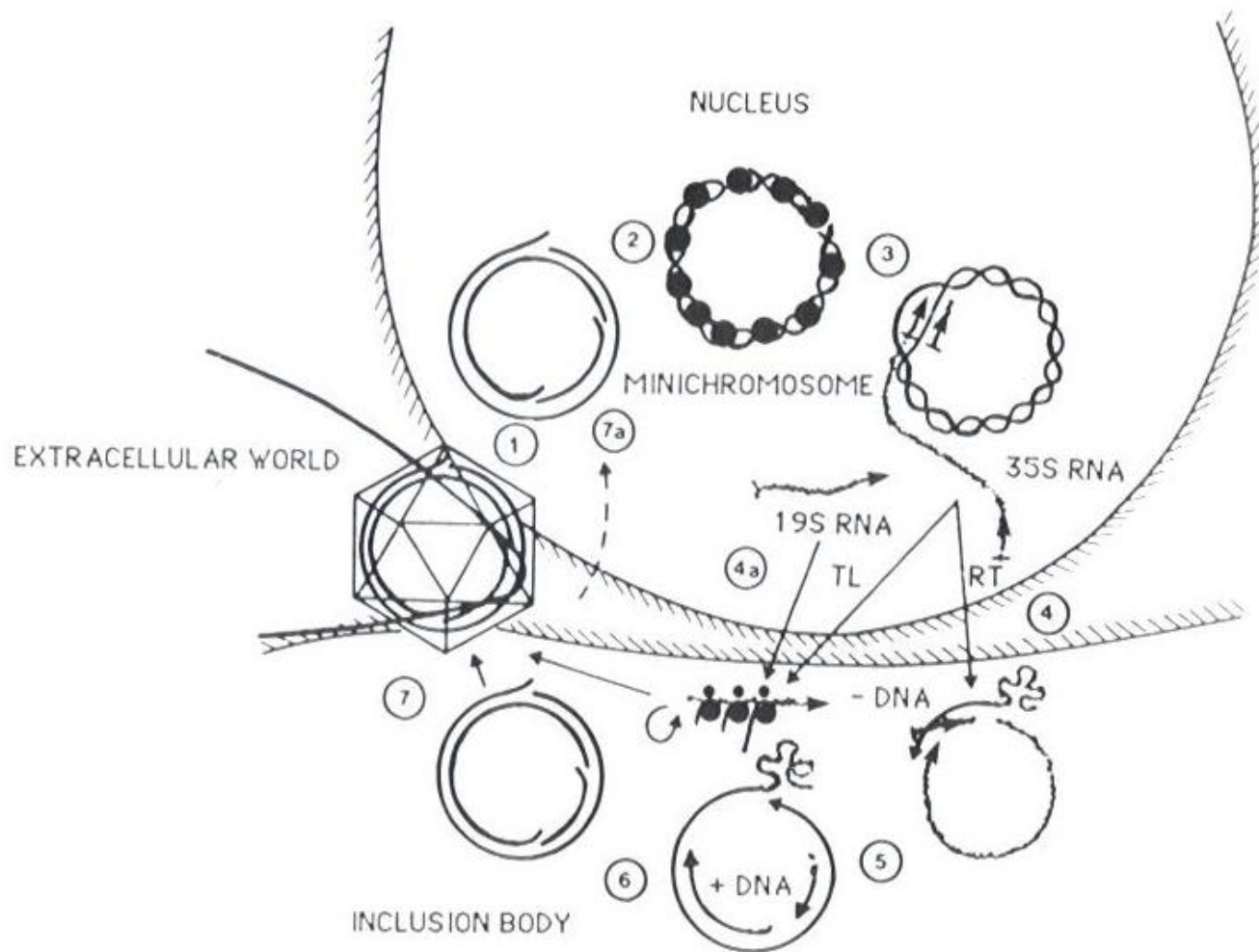


Figure 8.2 A current model of the life cycle of CaMV. Upon infection, the CaMV virus particles release their DNA (1), which gets repaired and sealed in the nucleus (2), where it associates with histones to generate a transcribing minichromosome (3). The 19 S and 35 S RNA are exported to the cytoplasm for translation (4a). Some of the 35 S RNA goes to the viroplasms, where it associates with a met-tRNA molecule (4) to get reverse transcribed into DNA. After digestion of the RNA template and synthesis of the second strand of DNA (5), the viral DNA (6) is packaged into virions (7). Two pathways may coexist: the 35 S RNA may be encapsidated as early as step 4 and DNA synthesis occur in (pre)particles, or it may produce replication complexes that generate free viral DNA that is directed back into the nucleus for amplification (shunted pathway 7a). (From Pfeiffer *et al.*, 1987.)