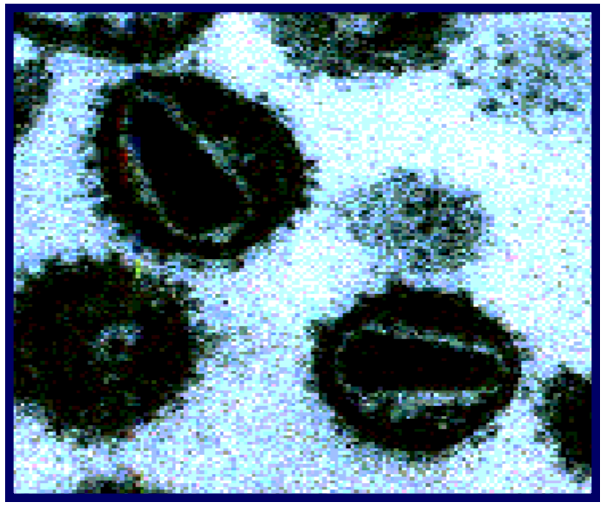
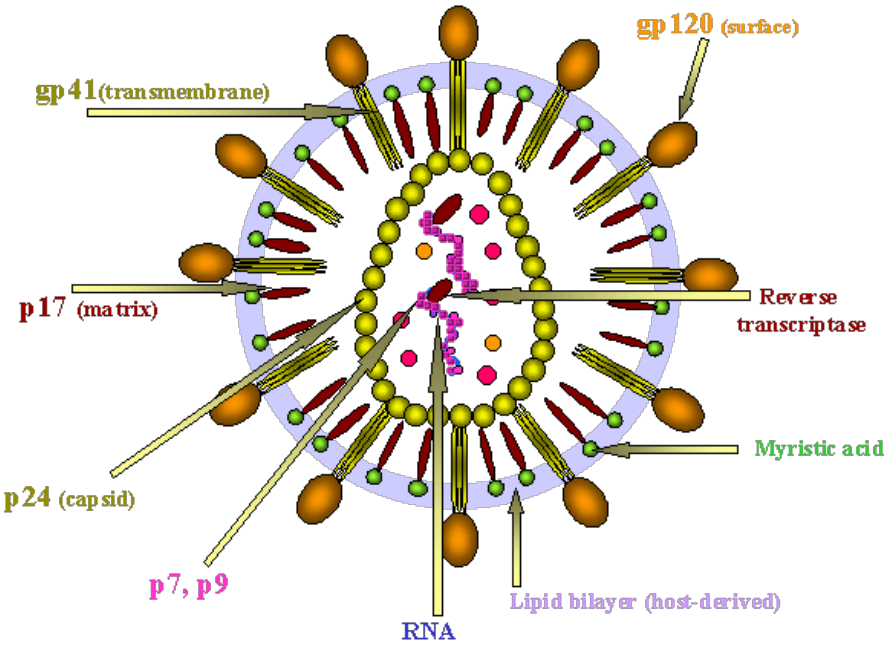
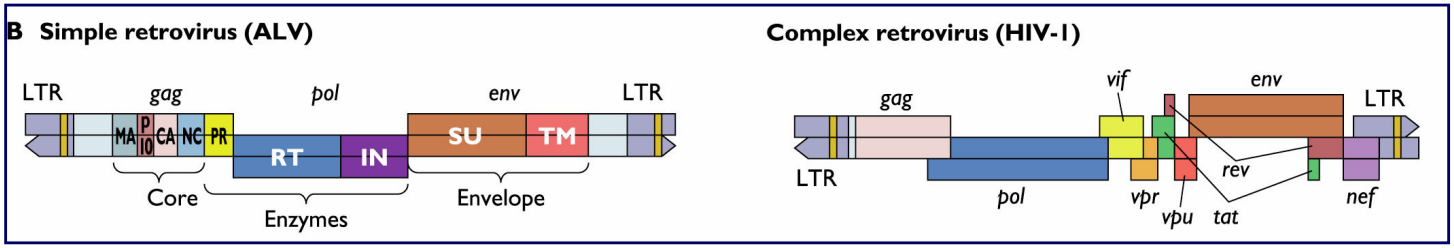
Human Immunodeficiency Virus biology

The virion



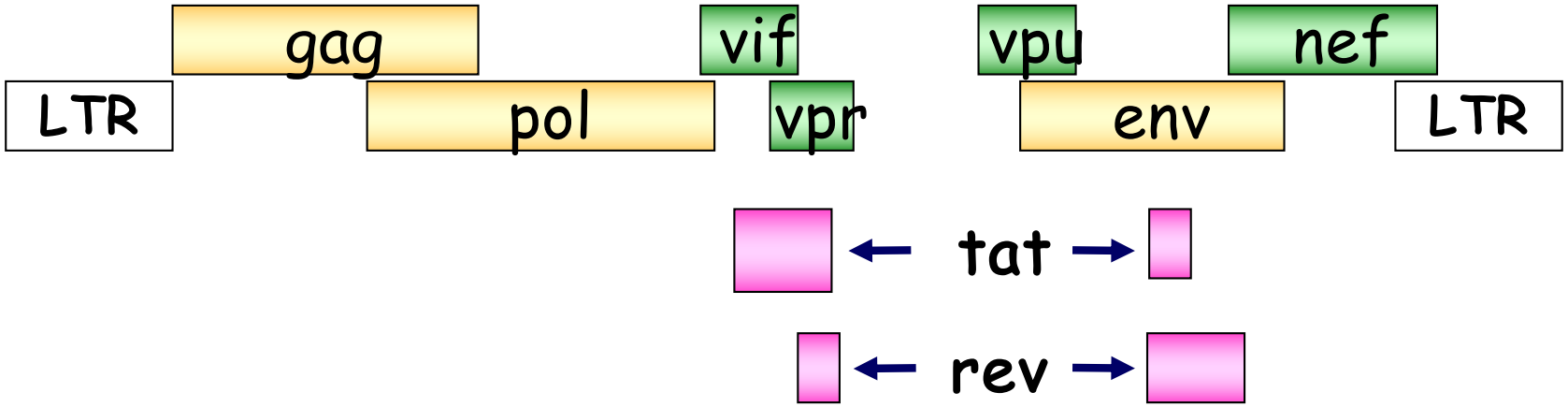


Multiple copies of the accessory proteins Vpr, Vif and Nef are also found within the virion



From Flint et al. *Principles of Virology* (2000), ASM Press

HIV-1 genome

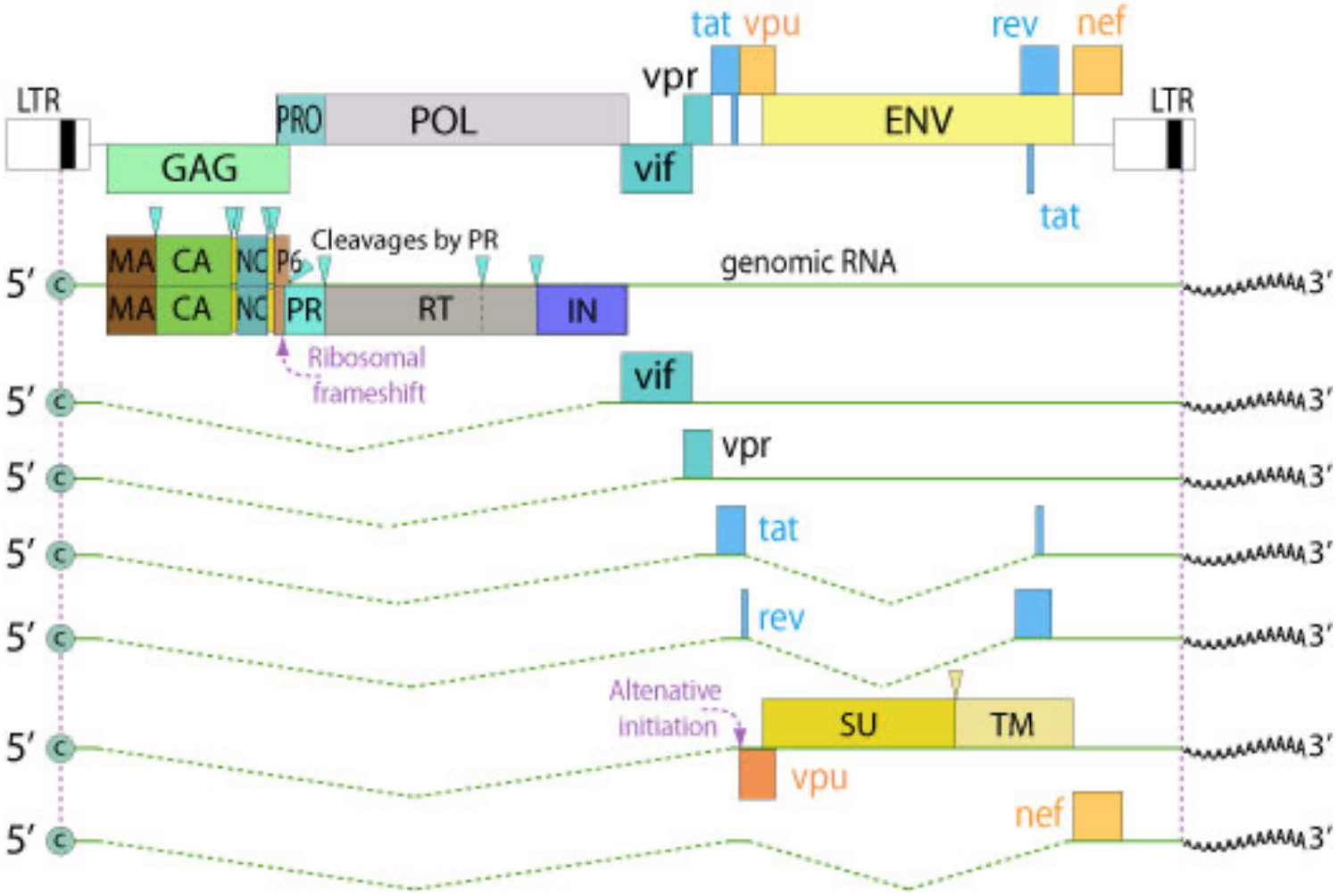


Structural genes

Transactivation genes

Accessory genes

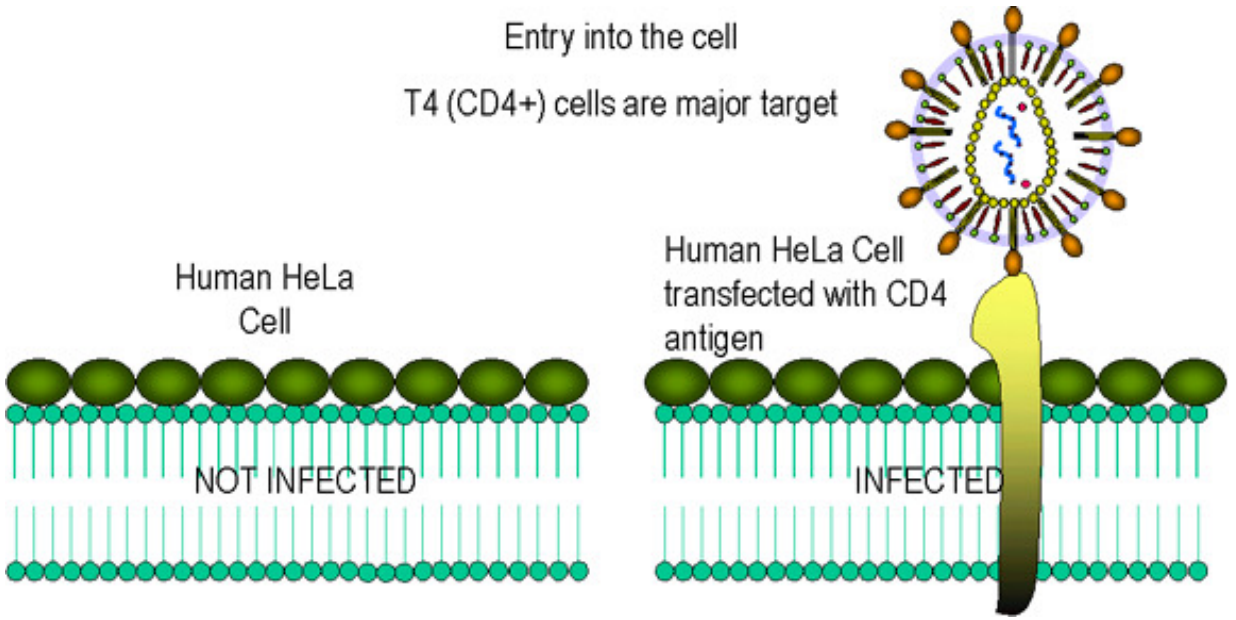
HIV-1 transcripts and proteins



HIV-1 transactivation and accessory proteins

- TAT: ***T***rans-***A***ctivator of ***T***ranscription
- REV: ***Re***gulator of ***V***irion protein expression
- NEF: ***Ne***gative *R*egulatory ***F***actor
- VIF: ***V***irion ***I***nfectivity ***F***actor
- VPU: ***V***iral ***P***rotein ***U***
- VPR: ***V***iral ***P***rotein ***R***

CD4 ANTIGEN IS THE HIV RECEPTOR

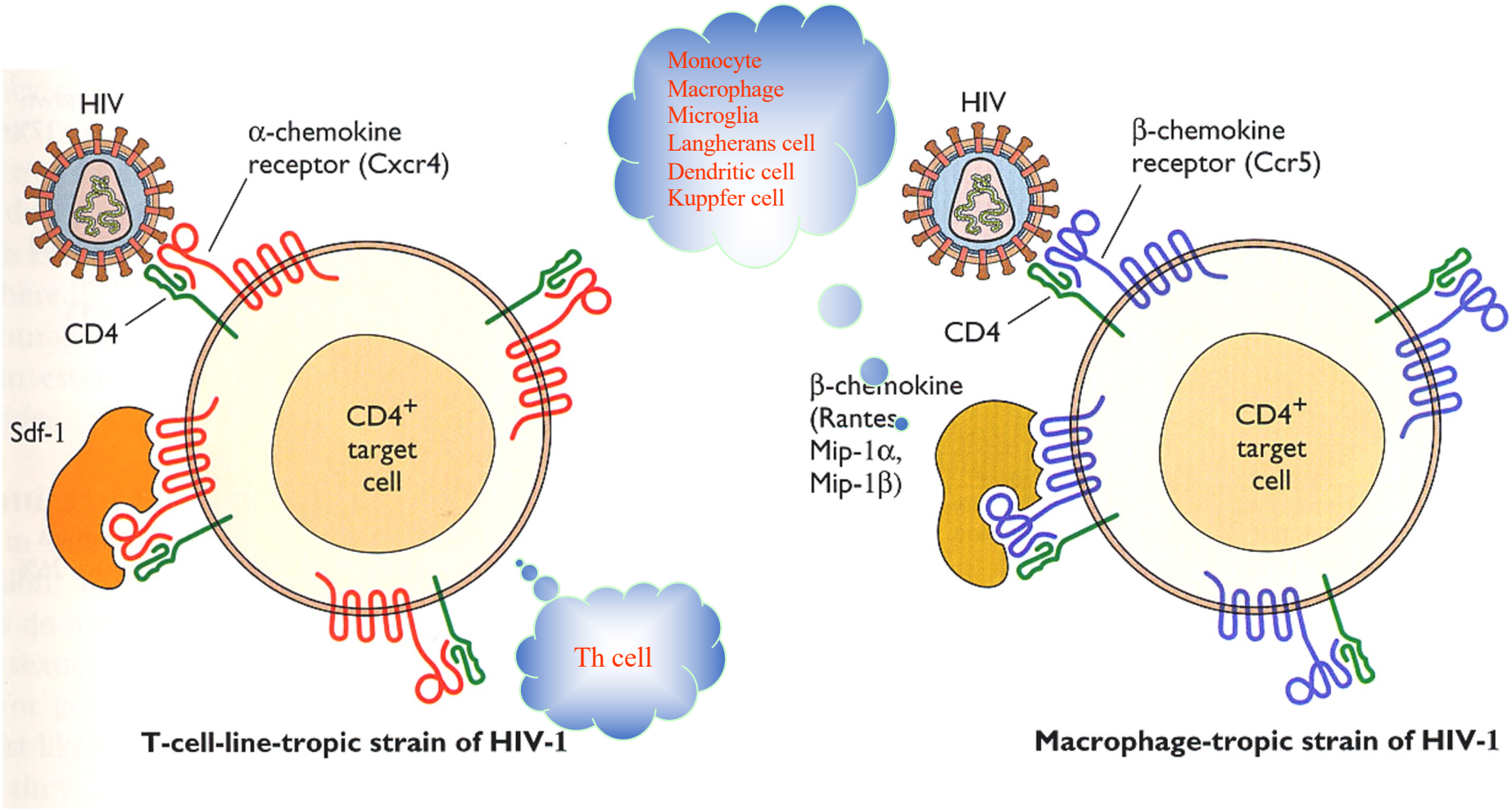


The necessity for CD4 antigen expression for entry of HIV into a human cell. HeLa cells do not have CD4 antigen and are not infected. HeLa cells transfected with CD4 gene are infected

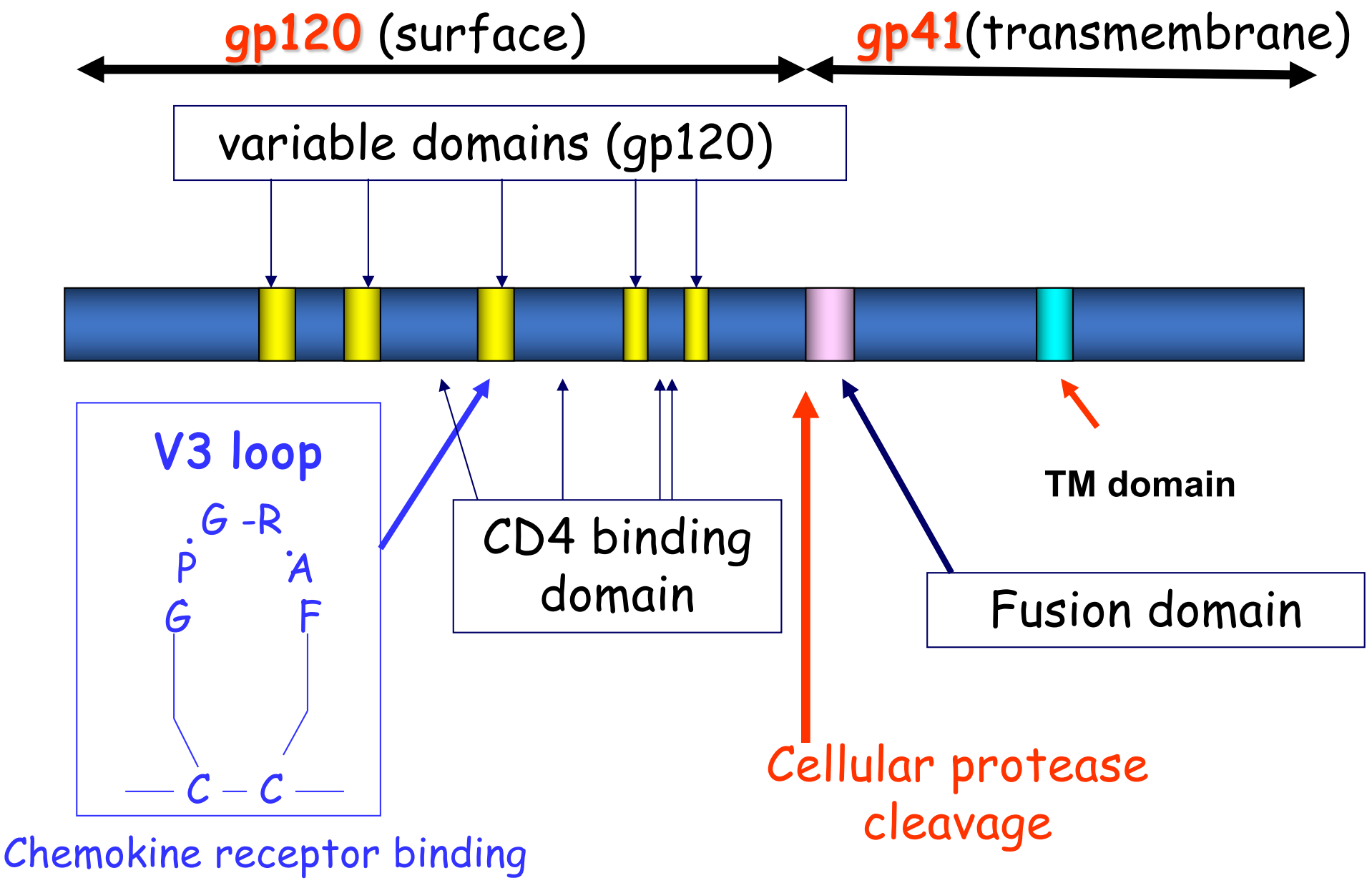
A CO-RECEPTOR FOR INFECTION BY HIV

Some strains of HIV (those adapted for life in T cells) could infect and replicate in activated human T cells but not in monocytes or macrophages. Conversely, those adapted for life in macrophages are less efficient in replicating in activated T cells. Yet both macrophages and T4 cells possess CD4 antigen. The differences in tropism of the viral strains mapped to the V3 region of Gp120 suggesting that molecules other than CD4 antigen have an important role in infection and this role is CD4+ cell type-specific

Chemokine receptors seem to be the key to the gateway of the cell



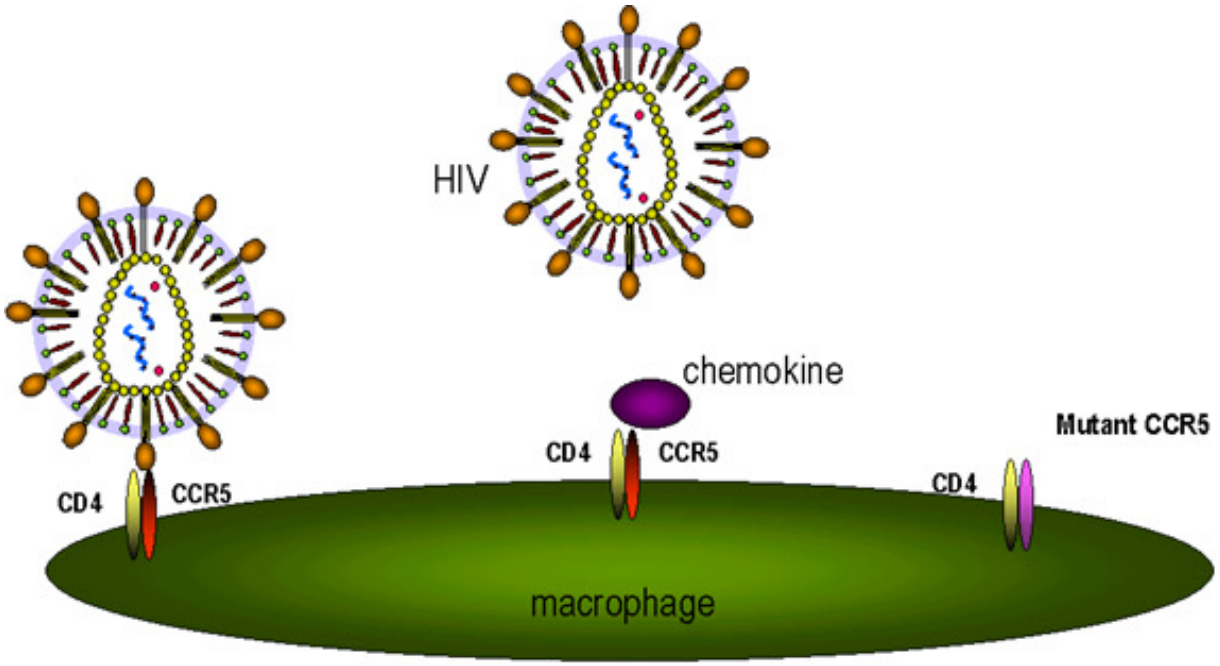
The env proteins



Chemokine receptors seem to be the key to the gateway of the cell

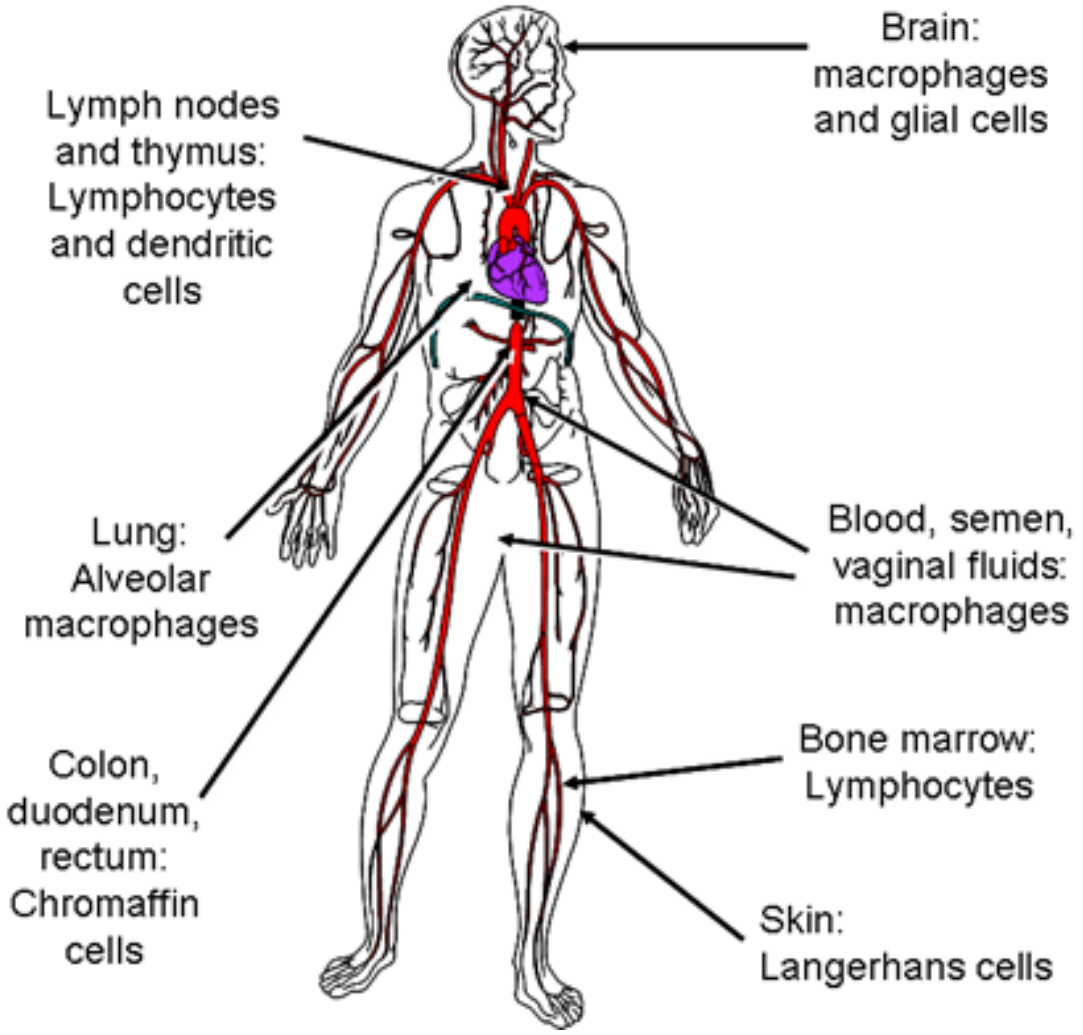
These co-receptors may explain the phenotypic switch during infection. Changes in the amino acid sequence of Gp120 occur in the progression of the disease. It is likely that HIV uses CCR5 in the early stages of disease and then switches to CXCR4, perhaps avoiding the suppressive activity of chemokines. This also explains the transition from non-syncytium-inducing to syncytium-inducing phenotype. CXCR4 and CCR5 are members of a large family of receptors and the spread of HIV through subtypes of T cells may reflect subtle changes on the variable loops of Gp120 allowing the infection of new CD4+ cells with different co-receptors.

A CO-RECEPTOR FOR INFECTION BY HIV

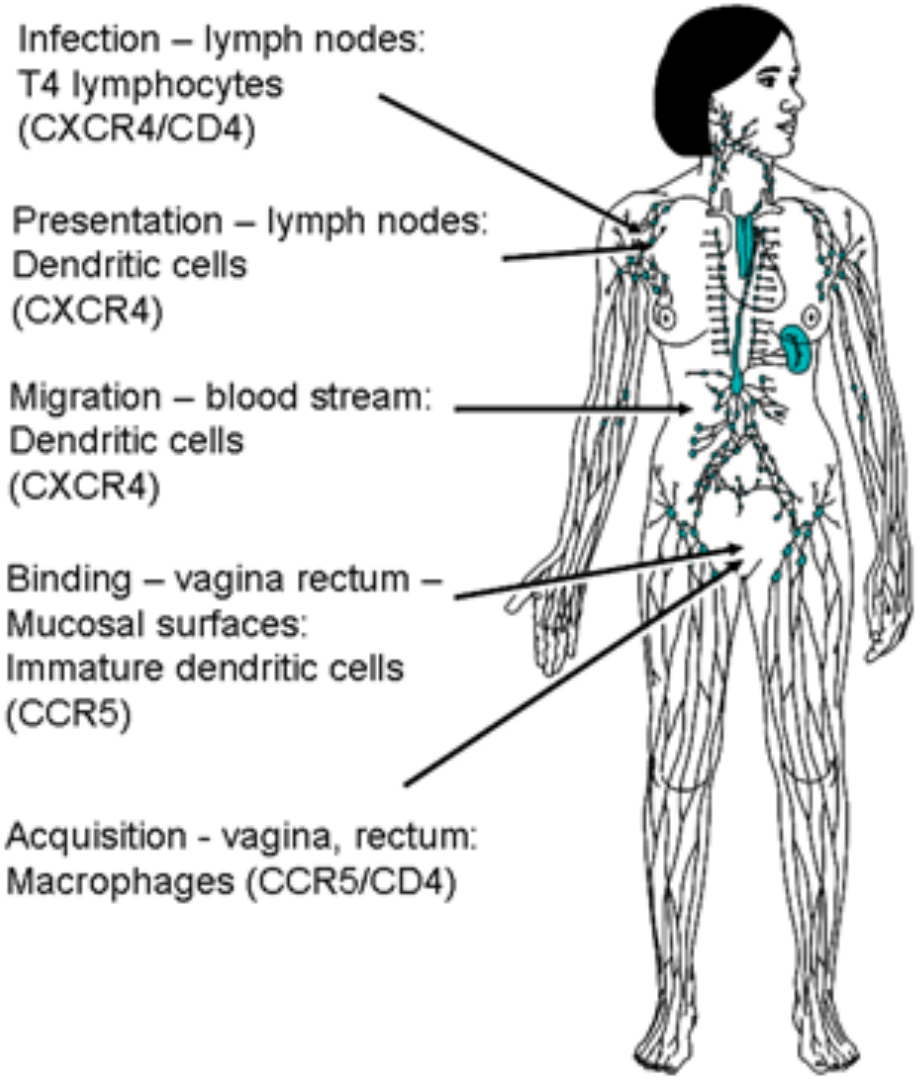


Chemokine receptors are involved, in association with CD4 antigen, in infection by HIV. The chemokine can block attachment of the virus to its receptors (i.e. RANTES, MIP-1a and MIP-1b secreted by CD8 T lymphocytes). Mutations in the chemokine receptor can lead to resistance to HIV infection

Cells that are infected by HIV

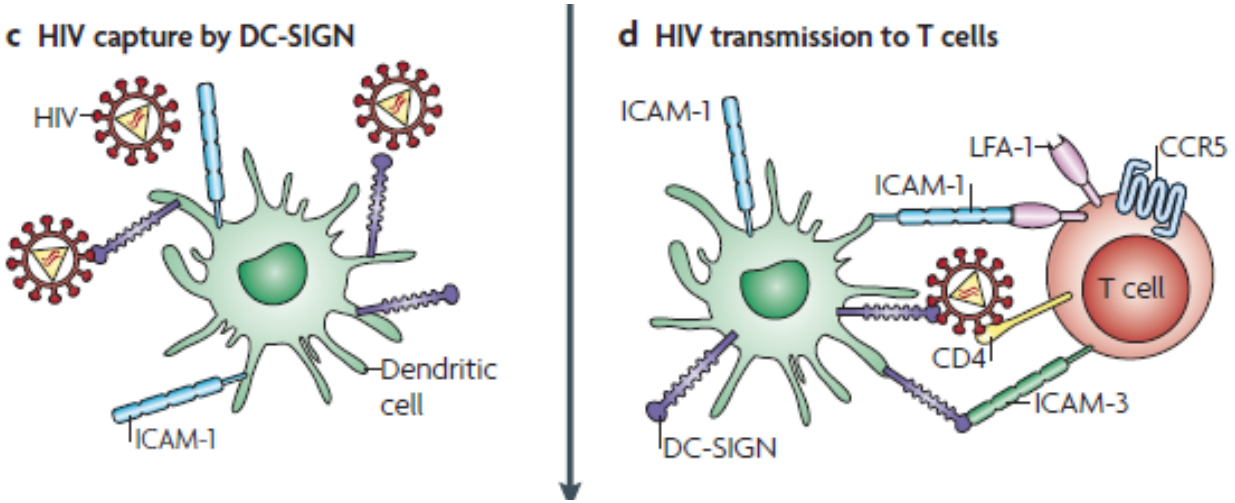


Entry of HIV via the mucosal route and transit via dendritic cells to the lymph nodes



HIV-1 and Dendritic cells

When HIV enters the body via the mucosal route (epithelia of the vagina, penis or rectum), it is bound by DCs that migrate to the lymphonodes; here the DCs present HIV to T4 cells, which become infected.

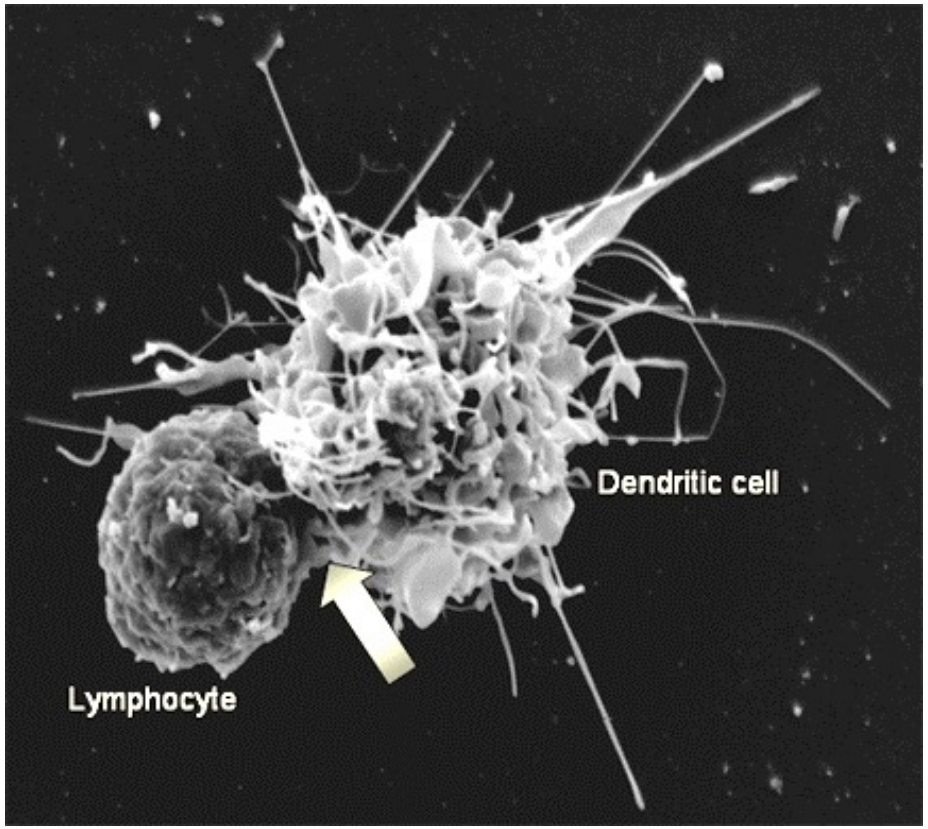


The capture of HIV particles by dendritic cell (DC)-specific intercellular adhesion molecule 3 (ICAM-3)-grabbing non-integrin (DC-SIGN)-expressing cells such as DCs (c), and DC-SIGN-captured HIV transmission to T cells (d).

HIV-1 and Dendritic cells

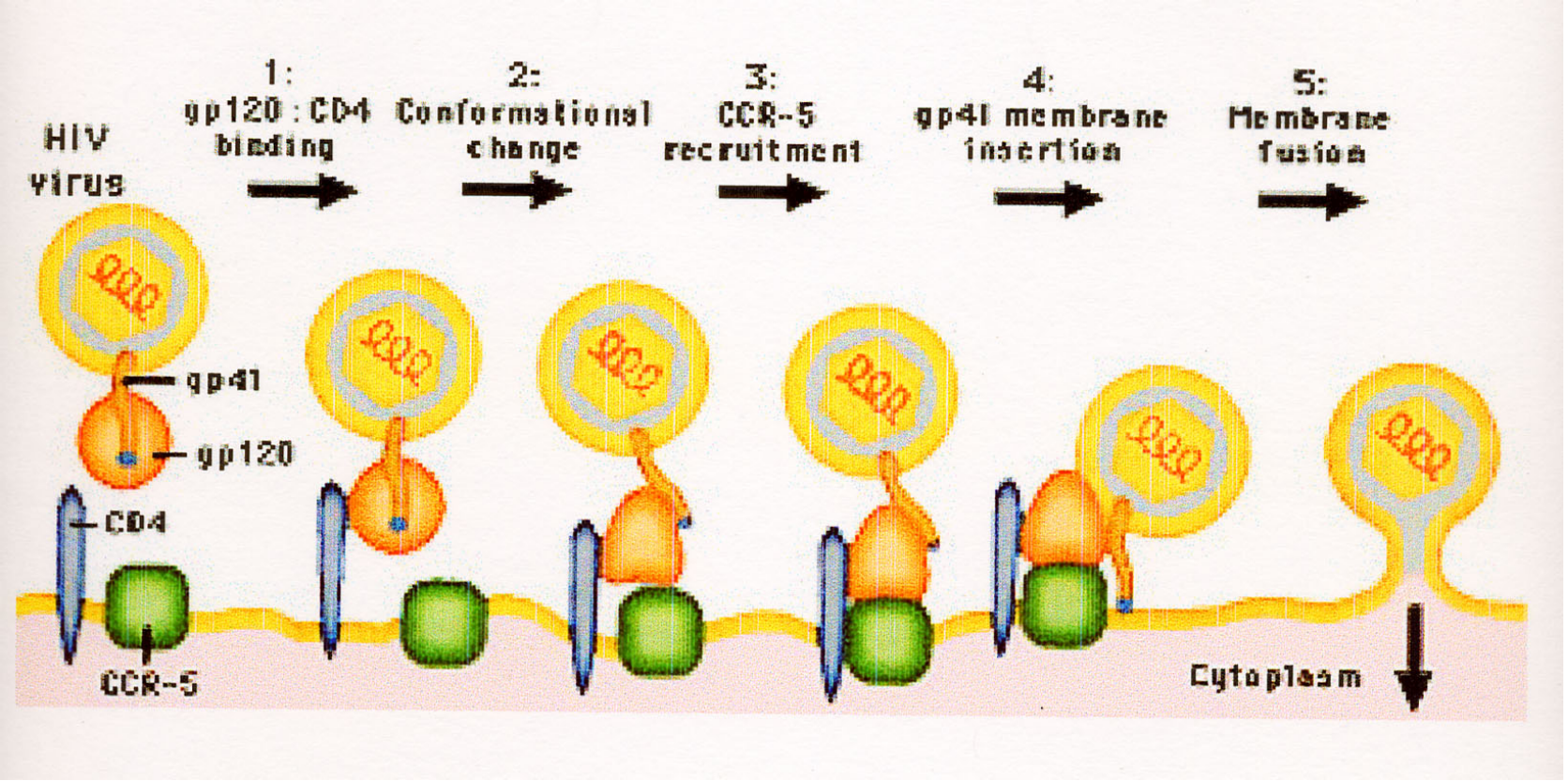
DCs are not readily infected by HIV, though they can be productively infected as a result of having low levels of HIV receptors (CD4 antigen and the co-receptors CCR5 and CXCR4). Importantly, these cells trap HIV on their surfaces since they possess a surface lectin (called dendritic cell-specific intercellular adhesion molecule 3-grabbing non-integrin or DC-SIGN) that binds to the carbohydrate components of HIV gp120. Binding by DC-SIGN does not allow fusion of the membrane of the virus with the DC (which requires CD4 antigen) and so infection does not occur by this route; however, this protein also participates in the association of DCs with lymphocytes and clusters at the sites of DC-lymphocyte interactions. Thus, the bound virus is concentrated just at the site of interaction of the DC with the CD4+ cell.

HIV-1 and Dendritic cells

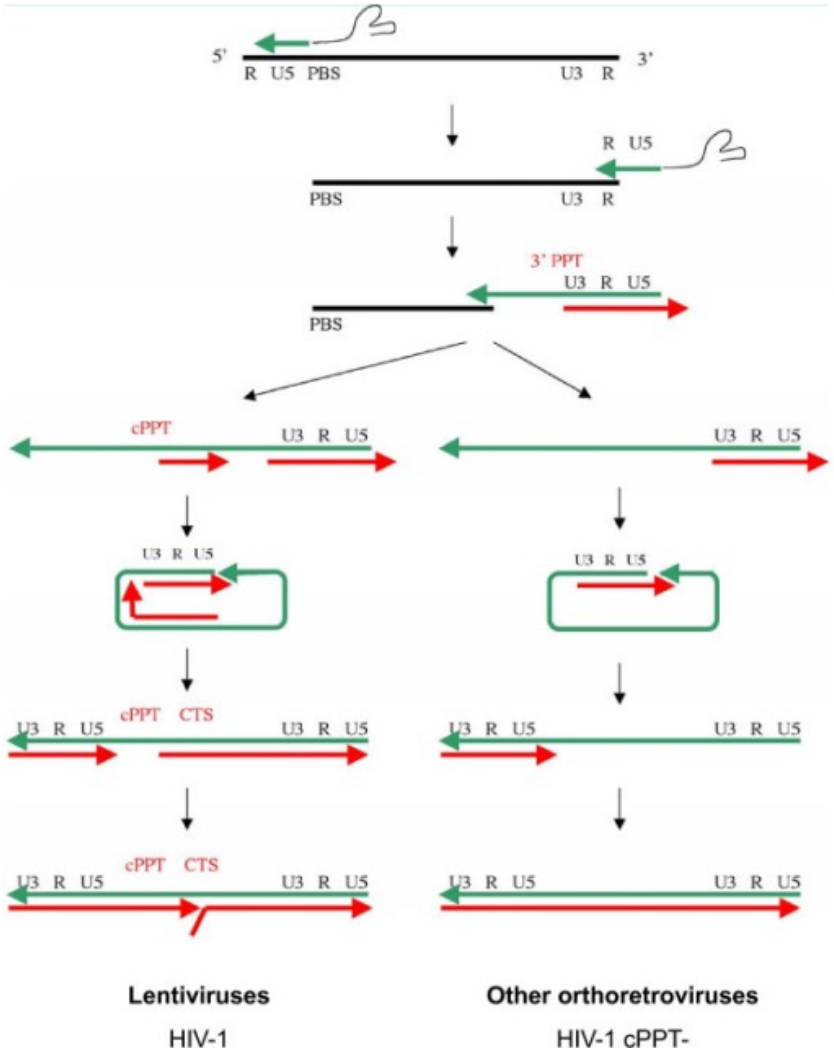


The interaction of a dendritic cell (right) with a lymphocyte (left). HIV bound to the surface of the dendritic cell is clustered at the site of interaction between the two cells (arrow), thereby facilitating the infection of the lymphocyte. On T4 cells, HIV receptors also concentrate here

HIV-1 attachment and membrane fusion



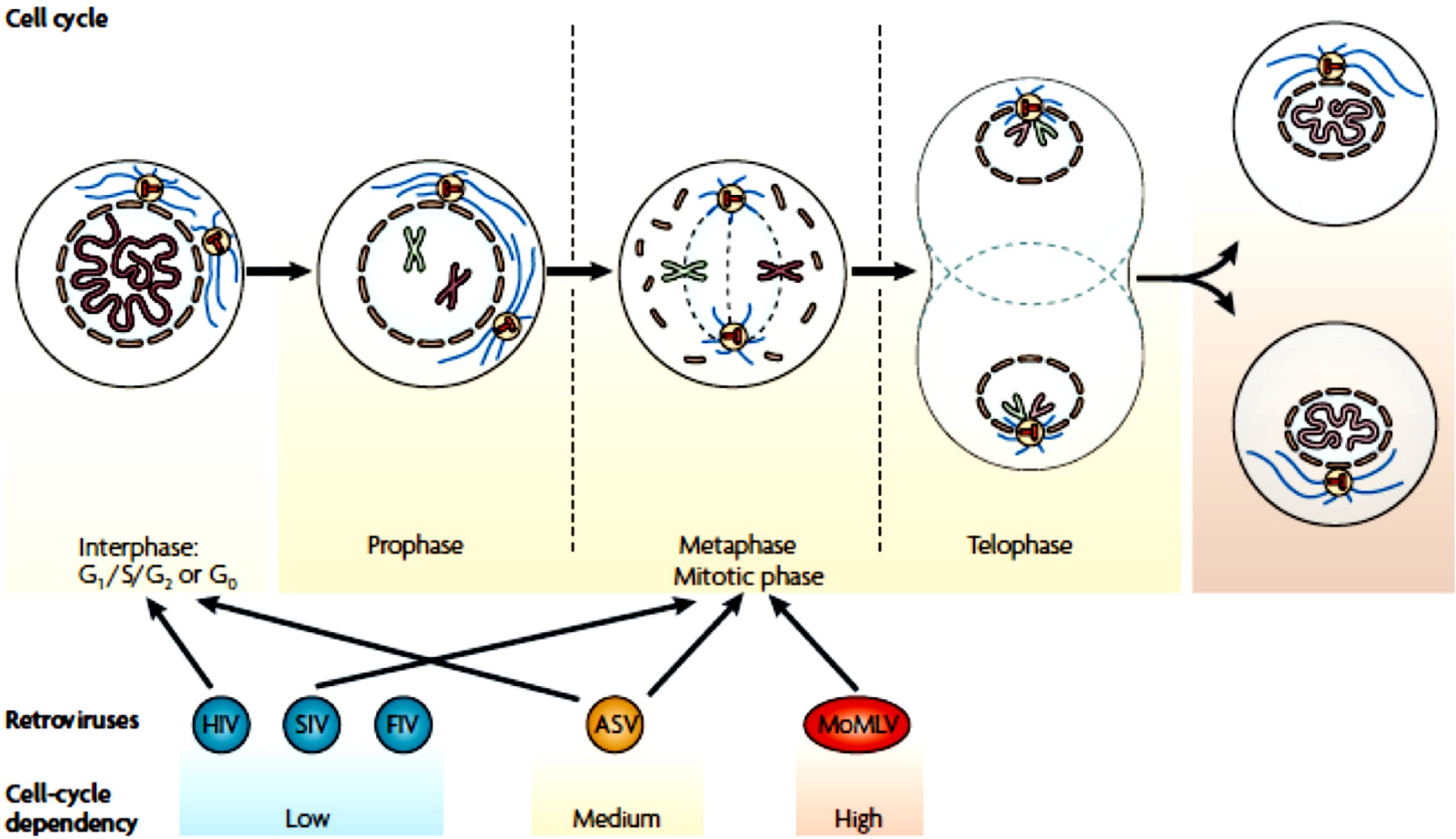
HIV-1 reverse transcription

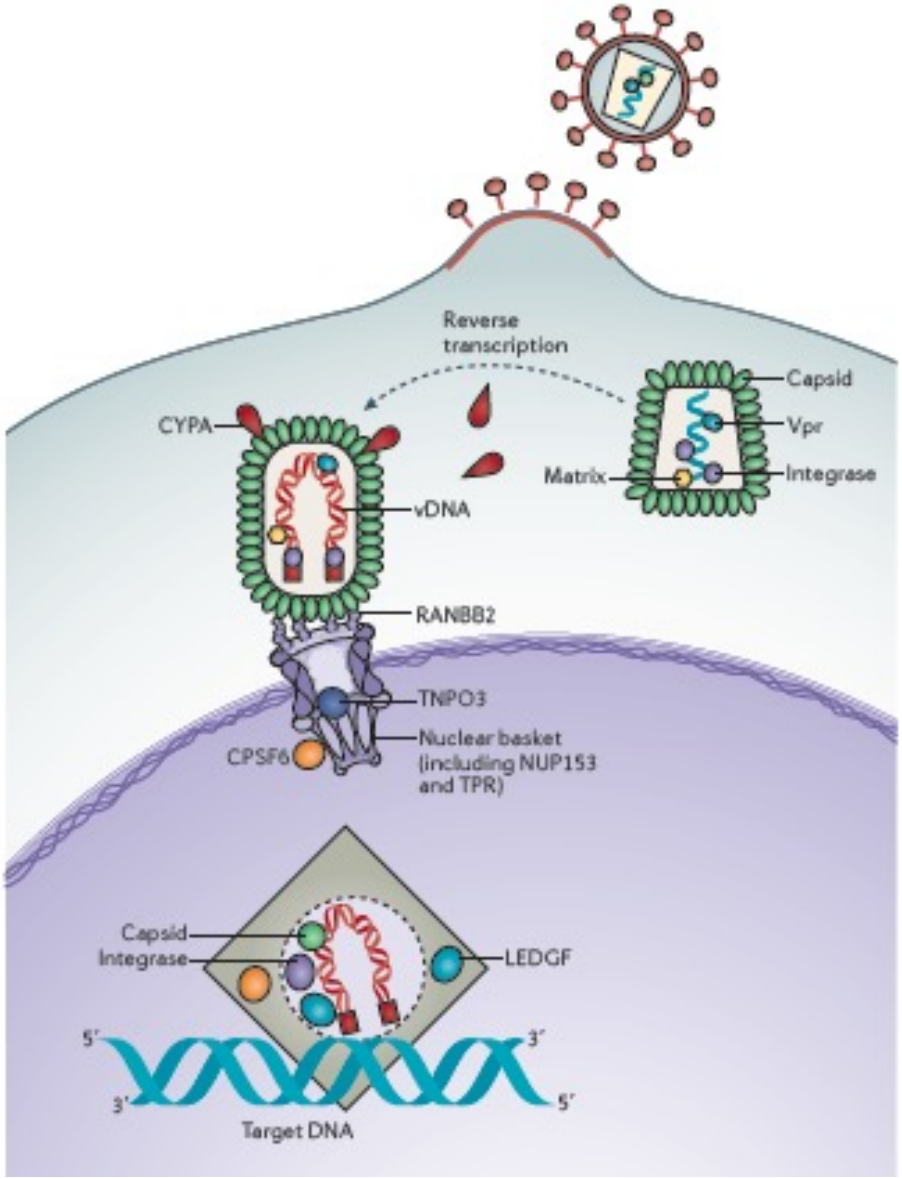


Comparison of retroviral and lentiviral reverse transcription. Retroviral DNA synthesis is initiated by a host-encoded tRNA primer that anneals the primer binding site. Copying of the genomic RNA template until the 5' cap is reached, results in the formation of a short minus-strand DNA, usually called minus-strand strong-stopDNA (-sssDNA). This -sssDNA anneals to the 3' end of the viral RNA. The jump from one end of the RNA copy to the other end is referred to as 'strand transfer'. After the first jump, the 3' end of the minus strand can be extended to produce the minus-strand DNA. Termination occurs near the PBS region of the genomic RNA. During synthesis of the minus-strand DNA, RNase H digests the RNA template. However, upstream of the U3 region, the RNA template is not digested and serves as a primer for plus-strand DNA synthesis (3' PPT). The initial plus-strand DNA product is termed plus-strand strong-stop DNA (+sssDNA). This process also produces a DNA copy of the PBS allowing second strand transfer to occur. The DNA copy of the viral genome is completed by RT that copies the entire plus and minus strands. The final product is a blunt-ended linear duplex DNA with a long terminal repeat (LTR) at each end. Formation of the plus strand of lentiviruses proceeds differently. **In these viruses, next to the 3' PPT, a second central polypurine tract (cPPT) is present in the pol open reading frame in the center of the genome. As a consequence, plus strand DNA synthesis is initiated both at the 3' PPT and the cPPT. When the DNA strand initiated by the 3' PPT reaches the DNA stretch initiated by the cPPT, strand displacement takes place until the central termination sequence (CTS) is reached. A single-stranded gap and a single-stranded overlapping DNA of 90 or 99 nucleotides, the DNA flap, are formed.**

Retrovirology 2010, 7:96

Nuclear import of pre-integration complexes and the cell cycle.



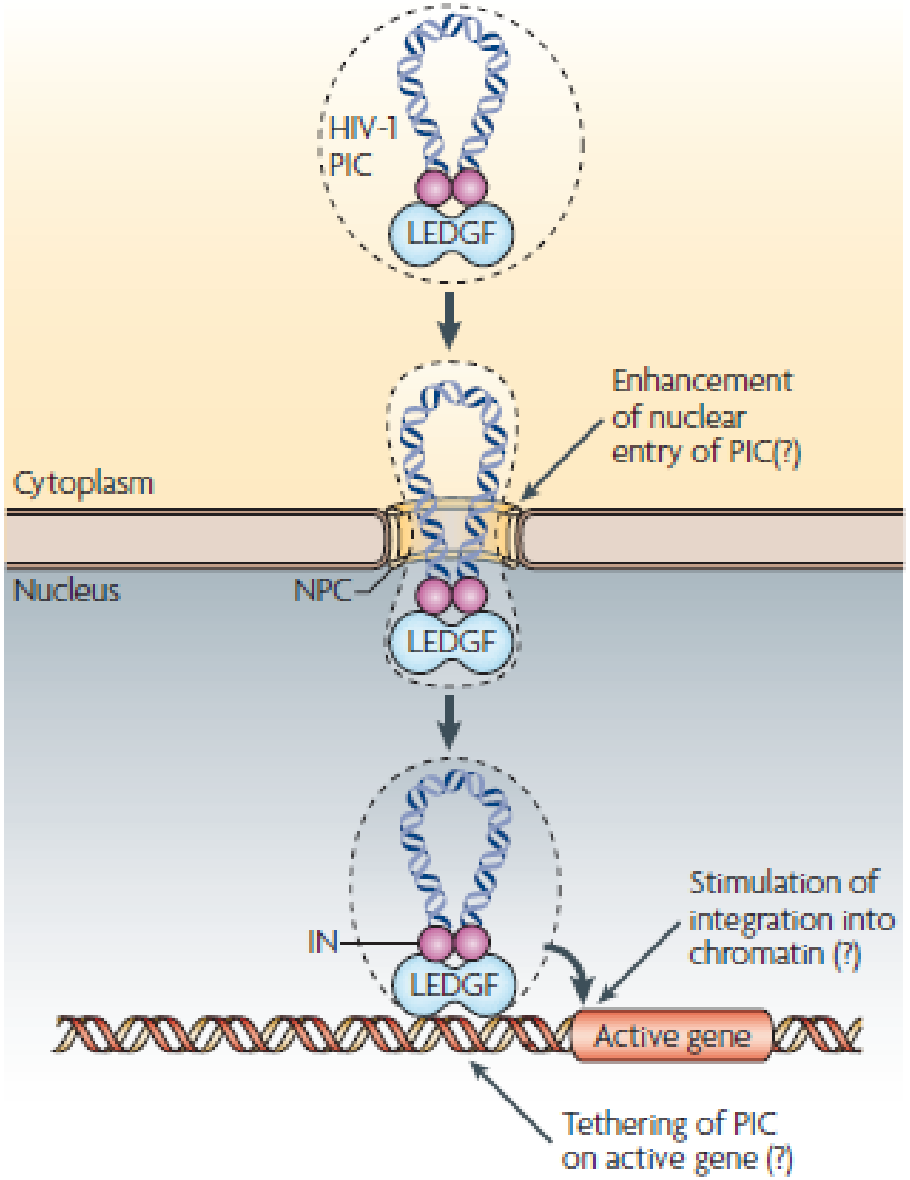


Nuclear entry and the selection of integration site

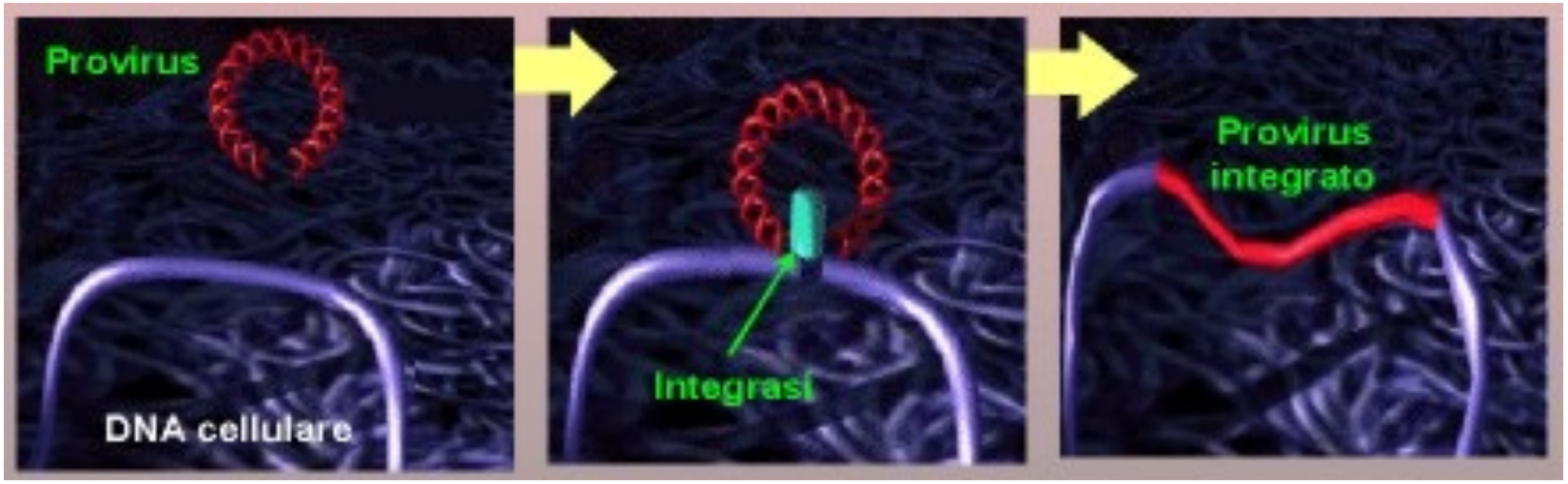
The capsid of HIV-1 seems to be a crucial viral factor for both uncoating and the entry of the pre-integration complex (PIC) into the nucleus. Other than capsid, the viral factors Vpr and matrix, as well as different cellular partners are involved in the process of nuclear entry on the cytosolic side of the nuclear pore complex (NPC). Cyclophilin A (CYPA; also known as PPIA) and RANBP2 have roles in the nuclear entry of the PIC on the cytosolic side of the NPC, transportin 3 (TNPO3) is involved in shuttling through the NPC, and nucleoporin 153 (NUP153) and cleavage and polyadenylation specificity factor 6 (CPSF6) are involved in the import of HIV-1 into the nucleus. Both NUP153 and CPSF6 have a role in target site selection, together with lens-epithelium-derived growth factor (LEDGF), which is the most prominent chromatin-tethering factor that is involved in HIV-1 integration.

LEDGF/p75 and nuclear entry of PICs.

Several roles for lens-epithelium-derived growth factor (LEDGF/p75) have been proposed for human immunodeficiency virus 1 (HIV-1) DNA integration.
LEDGF/p75 might regulate HIV-1 replication through the tethering of integrase protein (IN) and chromatin. NPC, nuclear pore complex; PIC, pre-integration complex.

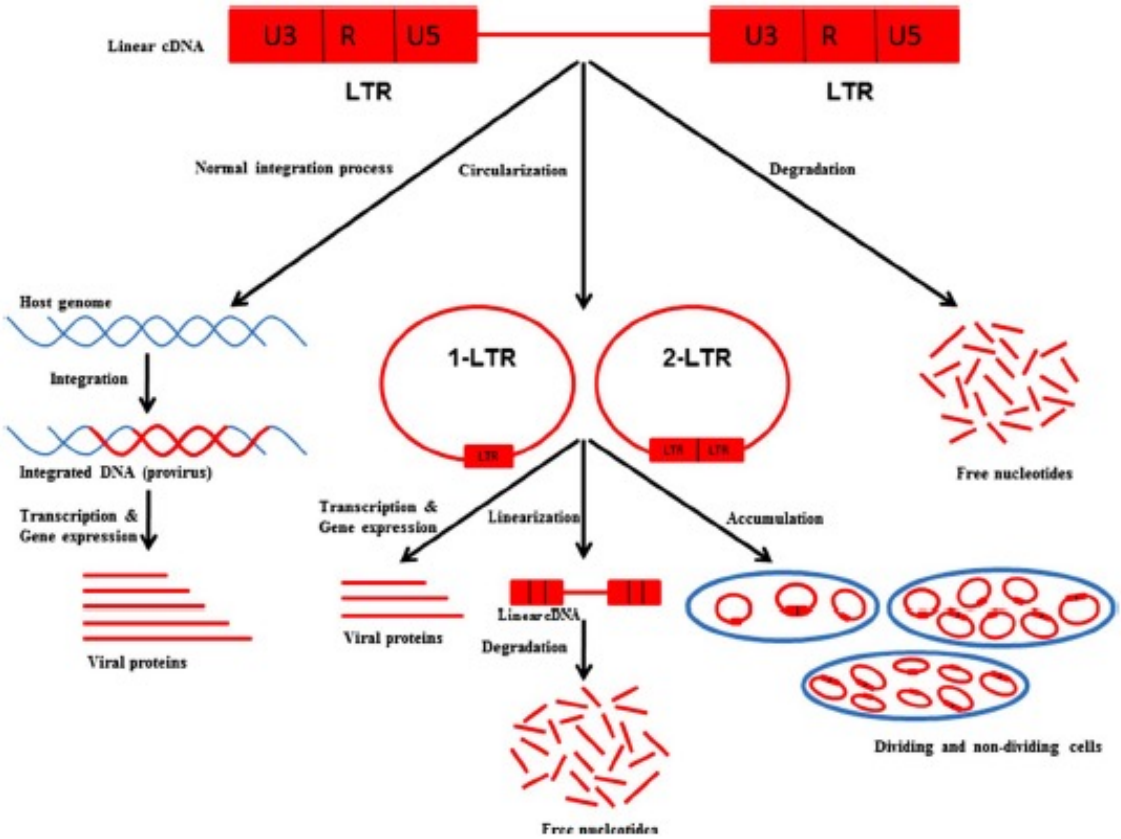


Viral DNA integration requires at least four steps



IN associates with the viral DNA in the cytoplasm to form the pre-integration complex (PIC).
In a first catalytic step IN cuts a dinucleotide from both ends of the viral DNA to produce hydroxylated 3' ends in the PIC
In the nucleus IN binds the host DNA, catalyses a staggered cleavage in the cellular target DNA, The 3' recessed ends of viral DNA are joined to the 5' "overhanging" termini of the cleaved cellular DNA.
Finally, gaps and any mismatched bases at the newly created junctions are repaired by host DNA repair machinery⟶irreversible integration.

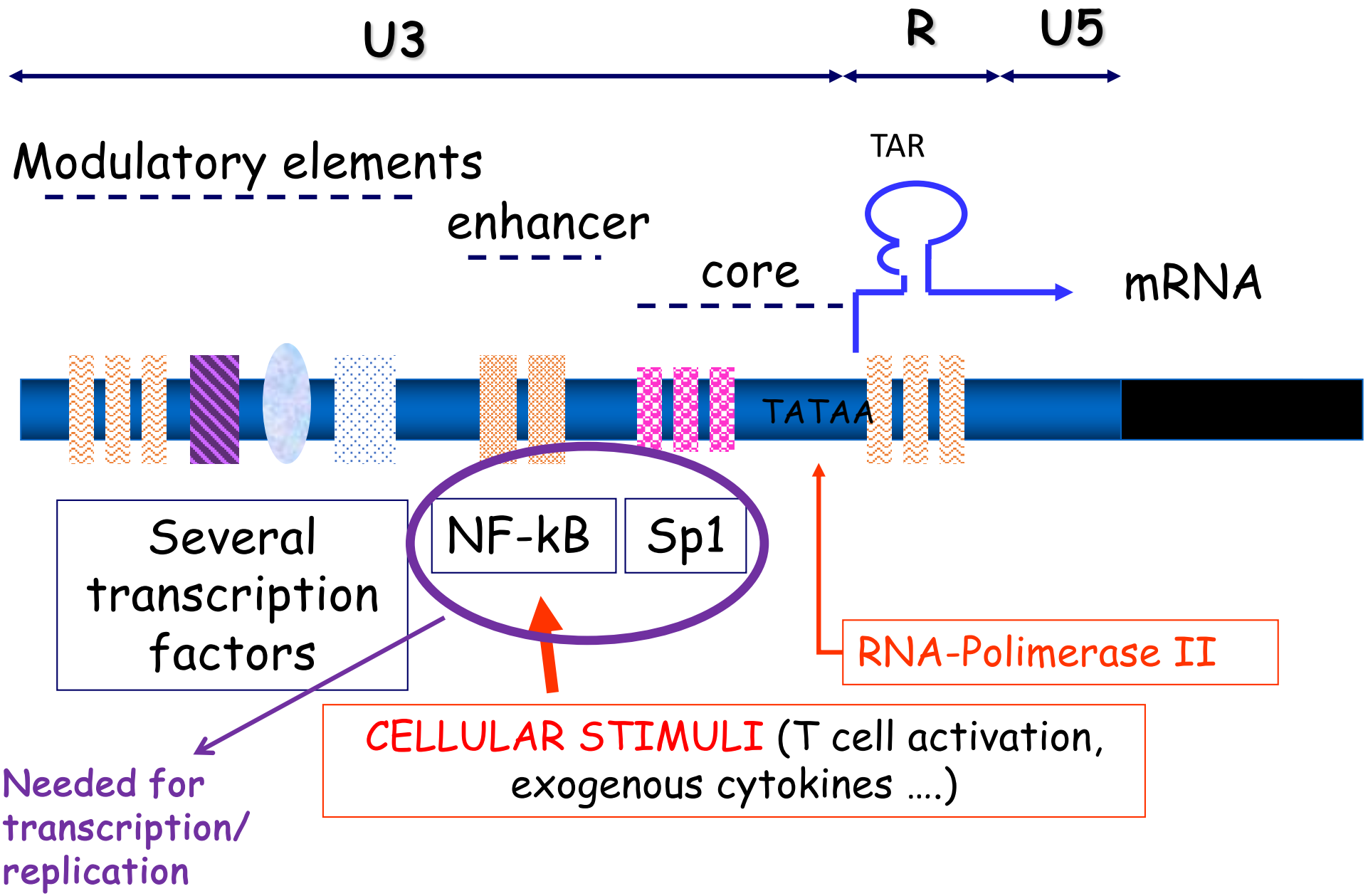
Fates of viral cDNAs after reverse transcription.



After reverse transcription, HIV-1 produces cDNAs that may either be integrated into host genome or circulate themselves. Otherwise, they are degraded into free nucleotides. Circular DNAs have been reported to actively participate in current gene expression similar to the integrated DNAs followed by linearization. They can also undergo to degradation, or accumulation as a reservoir. HIV-1 IN required for linearization of 2-LTR circles was found at the palindromic junction, recognized as integration site, and subsequently executed a de novo integration process.

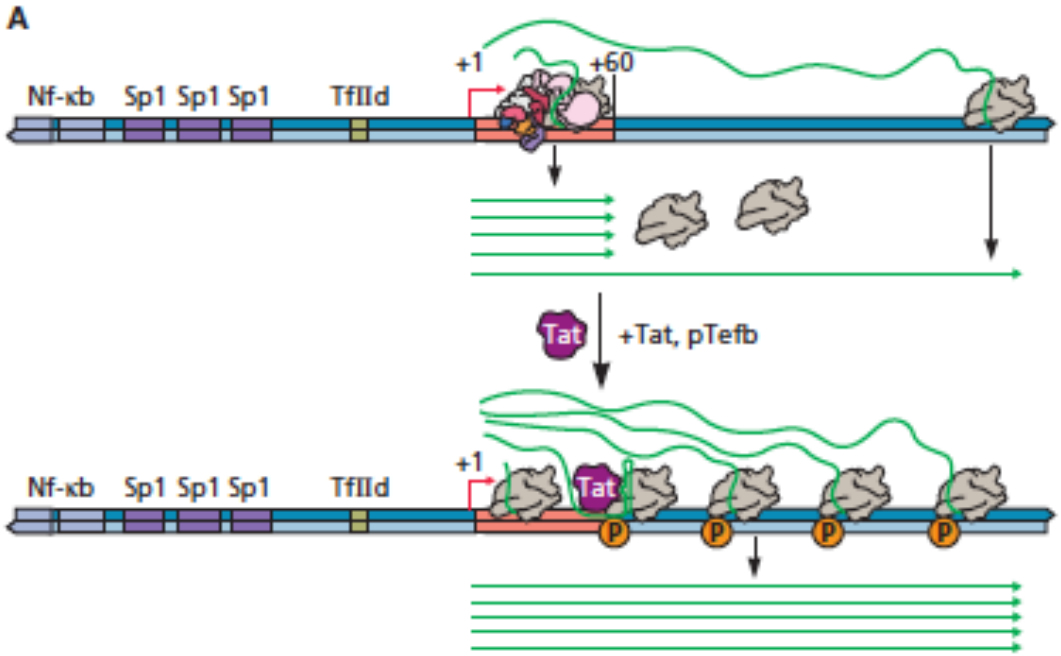
AIDS Research and Therapy 2017 **14**:9

HIV-1 LTR ORGANIZATION



HIV provirus transcription

Tat plays a crucial role in synthesis of full-length HIV-1 mRNA transcripts

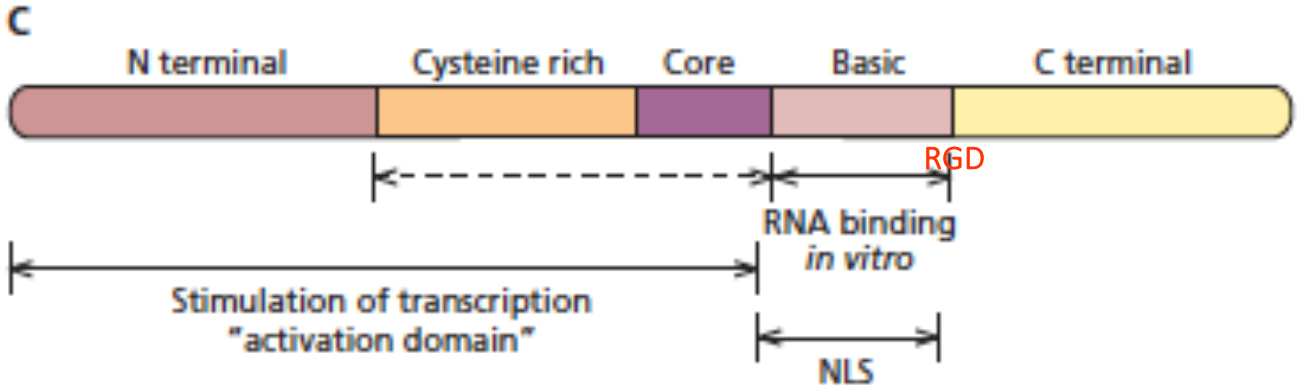


In the absence of Tat, transcription complexes are poorly processive, and the great majority (9 of 10) terminate within 60 bp of the initiation site, releasing transcription components and short transcripts.

Production of the Tat protein upon translation of mRNAs spliced from rare, full-length transcripts and its recruitment of p-Tefb and other regulators of elongation to nascent RNA allow transcriptional complexes to pass through the elongation block and synthesis of full-length viral RNA.

From Flint et al. *Principles of Virology* (2015), ASM Press

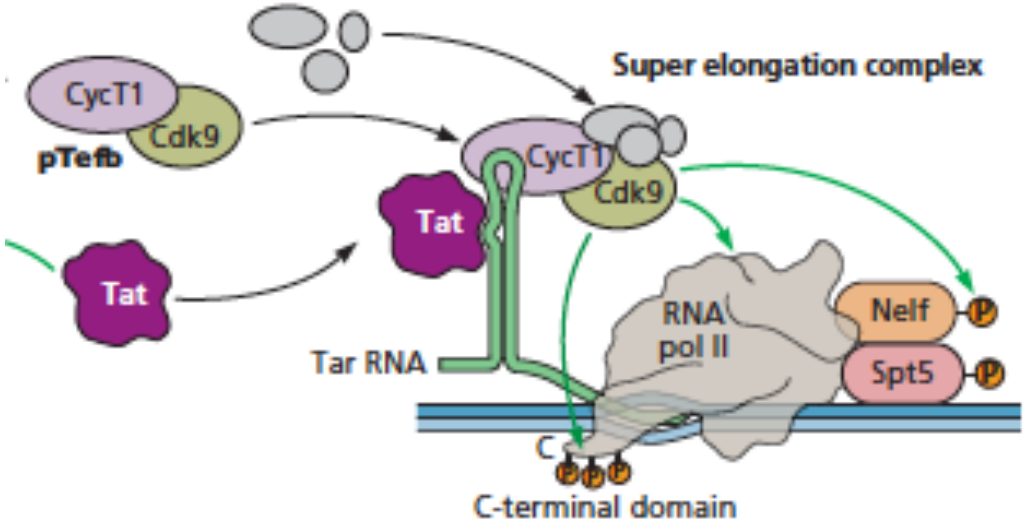
Tat - Trans-Activator of Transcription (14-16kDa)



The Tat protein is made from several different, multiply spliced mRNAs and therefore varies in length at its C terminus. The regions of the protein are named for the nature of their sequences (basic, cysteine rich) or greatest conservation among lentiviral Tat proteins (core). Experiments with fusion proteins containing various segments of Tat and a heterologous RNA-binding domain identified the N-terminal segment as sufficient to stimulate transcription. **The basic region, which contains the nuclear localization signal (NLS), can bind specifically to RNA containing the bulge characteristic of TAR RNA. However, high-affinity binding, effective discrimination of wild-type TAR from mutated sequences in vitro, and RNA-dependent stimulation of transcription within cells require additional N-terminal regions of the protein, shown by the dashed arrow.**
TAT interacts with the ciclina T1/cdk9 complex through the cysteine rich domain.

From Flint et al. *Principles of Virology* (2015), ASM Press

Model for the stimulation of elongation by Tat

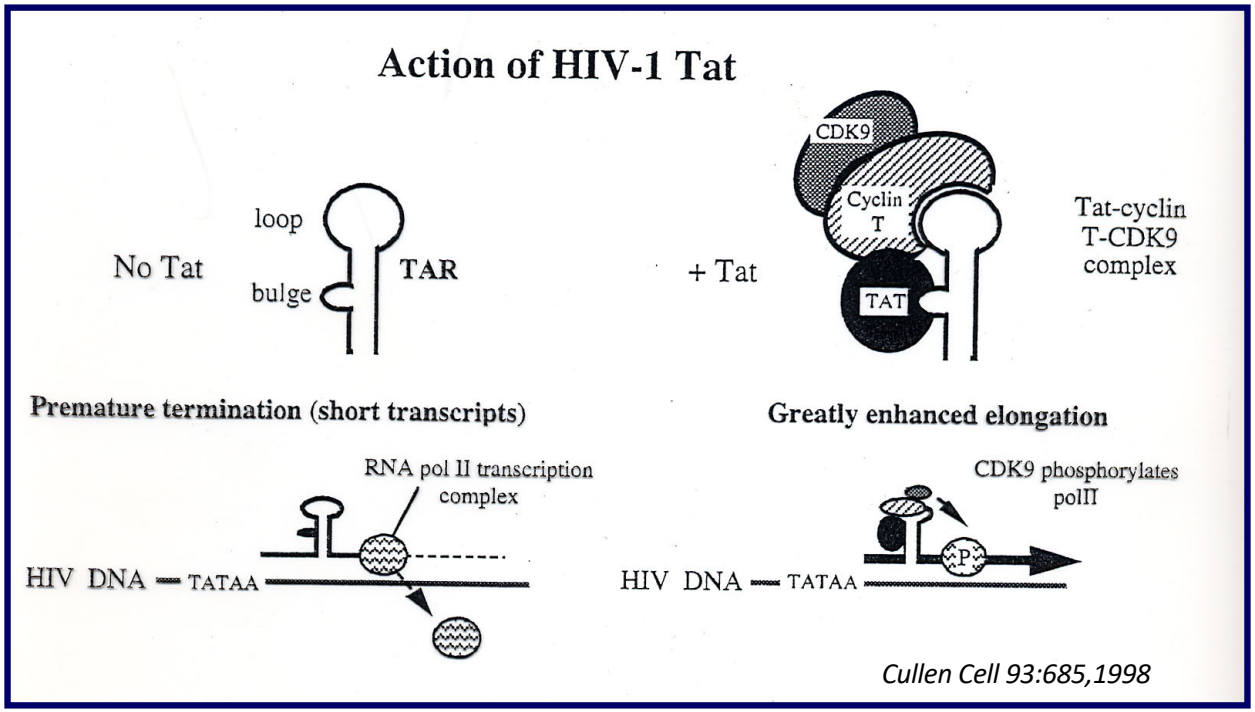


Cooperative binding to TAR of Tat and p-Tefb (via its cyclin T1 subunit) leads to phosphorylation (P) of the C-terminal domain of the largest subunit of RNA polymerase II by the Cdk9 kinase subunit of p-Tefb. This enzyme also phosphorylates and inactivates negative regulators of transcriptional elongation (e.g., transcription elongation factor [Spt5] and negative elongator factor complex [Nelf]). Positive regulators of elongation, such as RNA polymerase II elongation factor 2 (Ell2), are also recruited to form a super elongation complex. The net result is that transcriptional complexes become competent to carry out highly processive transcription. Adapted from M. Ott et al., Cell Host Microbe 10:426–435, 2011, with permission.

From Flint et al. *Principles of Virology* (2015), ASM Press

Action of TAT

- Nuclear activity
- Recognizes and binds the TAR sequence (Tat-responsive element) located in the R region of the nascent viral RNA
- Interacts with the RNA polymerase II complex by increasing the efficiency of the elongation



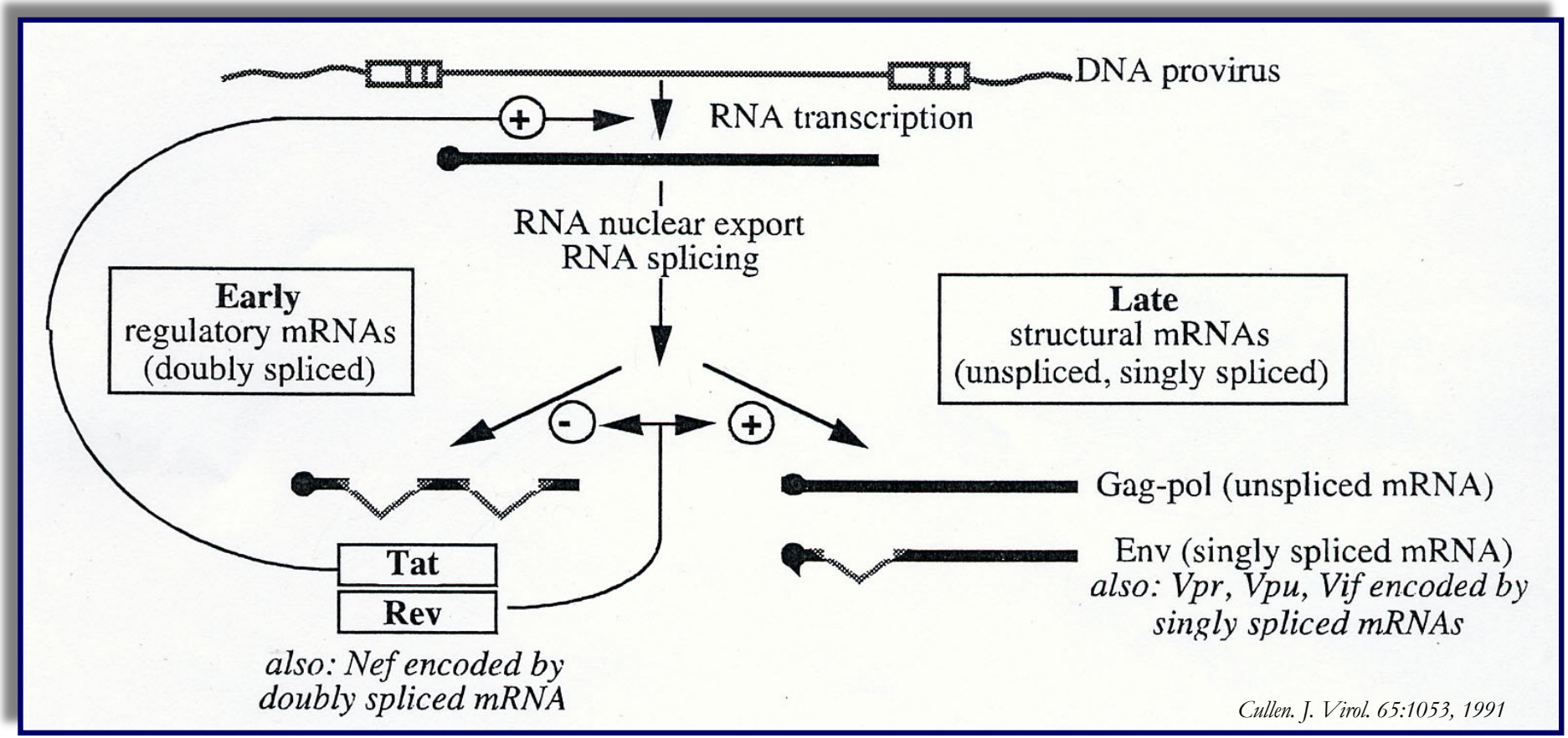
1. Establishes a cooperative interaction with the TAR sequence and the human cyclin T1 (the regulative component of the elongation factor b, P-TEFb)
2. Recruitment of the hCycT1/ CDK9 complex on the TAR sequence allows phosphorylation of Pol II C-terminus by CDK9, resulting in productive transcription

TAT is much more than just a HIV transactivator

- ✓ Released in soluble form is able to enter into uninfected cells by interacting with and crossing the membrane and affect the expression of target genes also in uninfected cells
- ✓ Interacts with fibronectin receptor and other integrins through the RGD motif

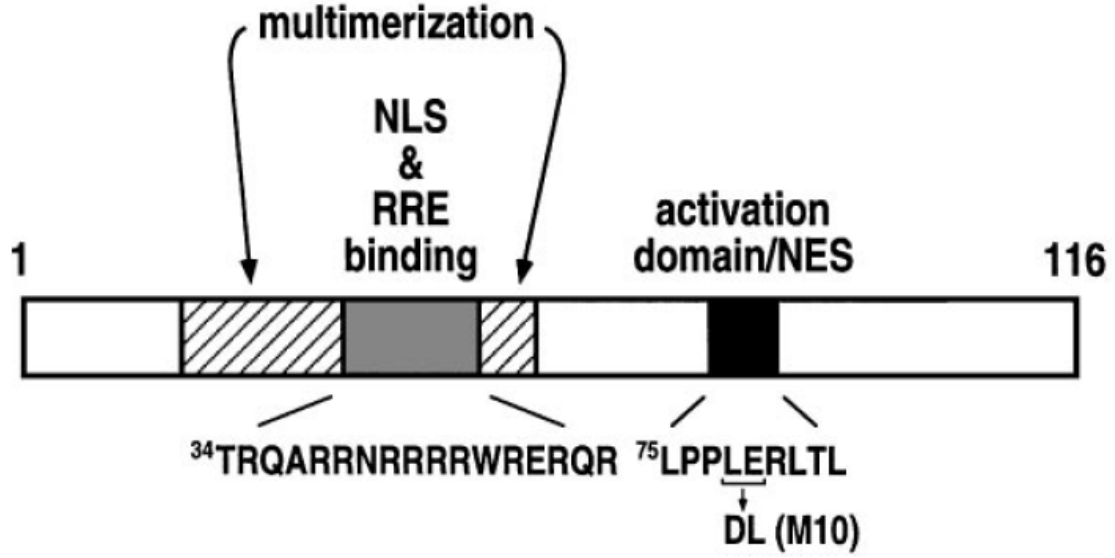
- ✓ Stimulates the expression of immunoregulatory cytokines: TNF, IL-2, IL-6, TGF-a, TGF-b, IL-8 [immunomodulation]
- ✓ Induces the expression of adhesion molecules such as fibronectin and collagen type I and III [migration of infected cells]
- ✓ Regulates the expression of proteins involved in apoptosis: the CD95 ligand (FasL) and Bcl-2 [apoptosis of activated T cells]
- ✓ Inhibits the transcription of p53 and MnSOD (manganese superoxide dismutase) [cancer and oxidative stress]
- ✓ Represses the expression of MHC class I [escape from IS]

HIV-1 Gene Expression



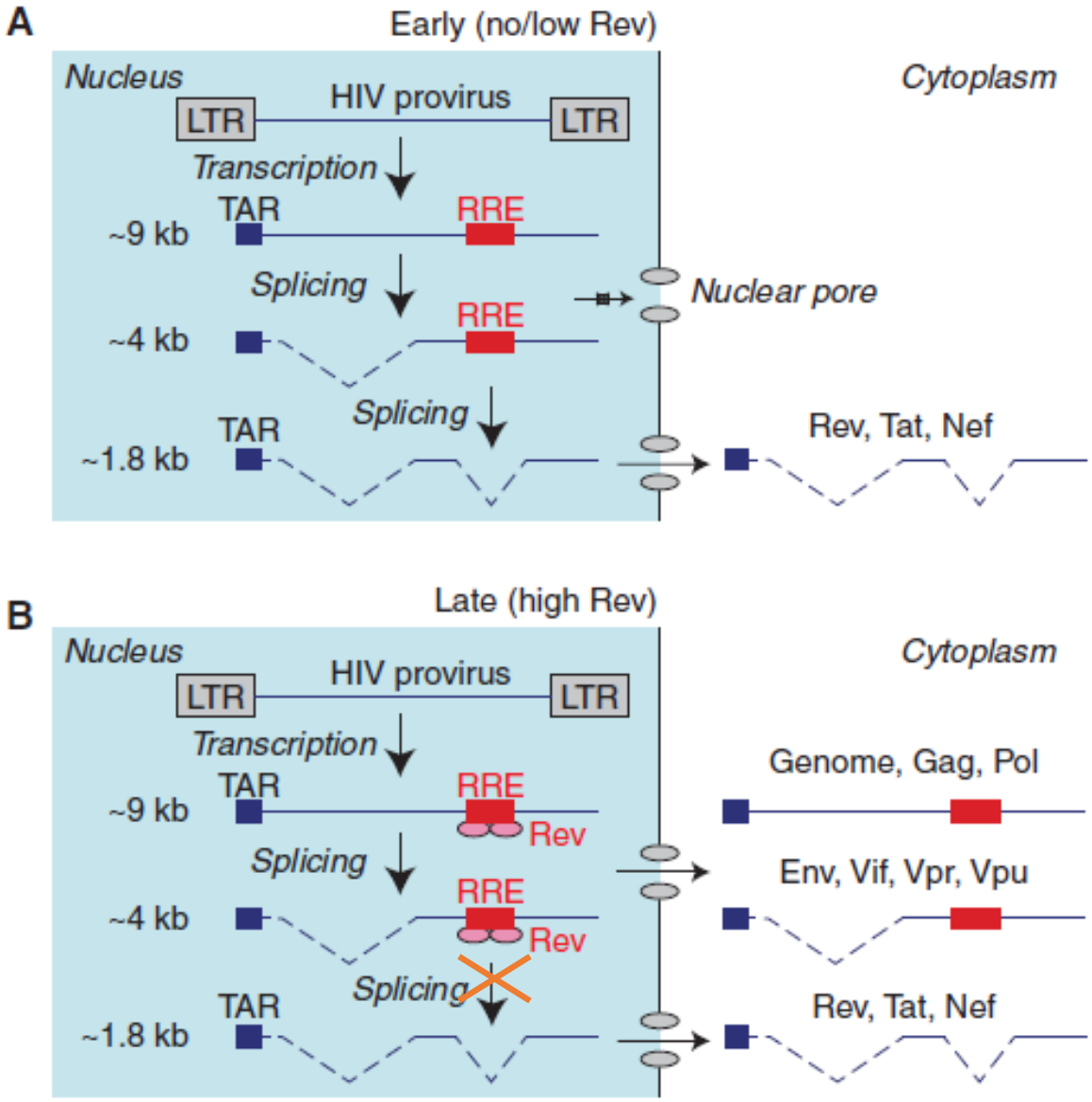
REV

Regulator of virion protein expression: regulates the splicing and transport of viral RNA. Rev facilitates the transport of intron-containing viral RNA (unspliced or singly spliced) out of the nucleus, promoting viral structural protein synthesis.



- The arginine rich, N-terminal domain harbors regions that mediate RNA (RRE) binding through the RRE (Rev-responsive element) sequence on the *env* gene and nuclear localization (NLS, gray box), and regions required for protein multimerization (hatched boxes).
- The leucine rich central domain harbors the NES (nuclear export signal)/activation domain (solid box).

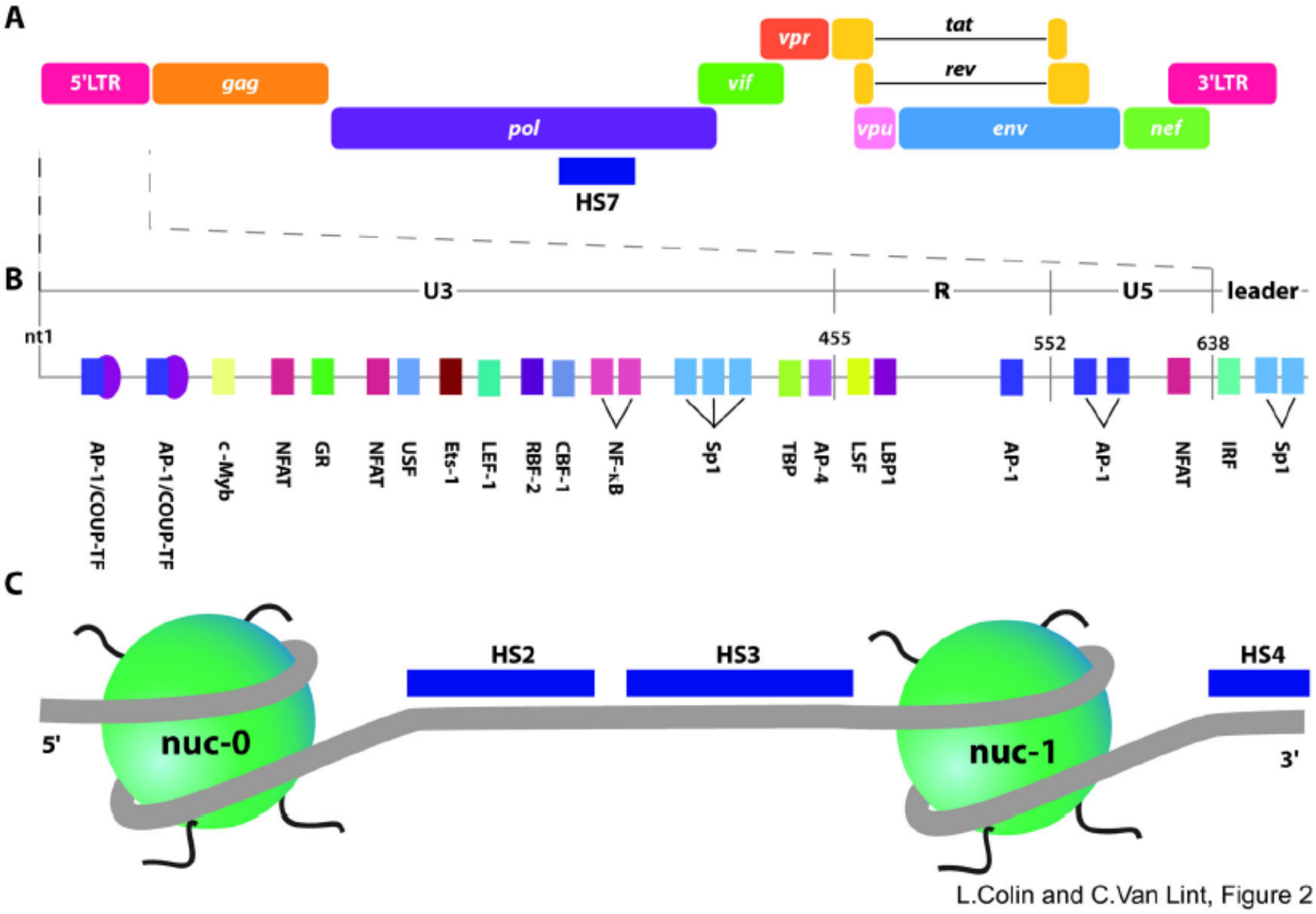
Early and late phases of HIV-1 mRNA expression



Full-length unspliced 9-kb, incompletely spliced 4-kb mRNA, and completely spliced 1.8-kb mRNAs are transcribed at both early and late times. (A) In the absence of Rev or when Rev is below the threshold necessary for it to function, the 9-kb and 4-kb mRNAs are confined to the nucleus and either spliced or degraded. Completely spliced 1.8-kbmRNAs are constitutively exported to the cytoplasm and translated to yield Rev, Tat, and Nef. (B) When the levels of Rev (shown as a pink oval) in the nucleus exceed the threshold necessary for function, the 9-kb and 4-kb mRNAs are exported to the cytoplasm and translated. The Rev-response element (RRE) is shown as a red rectangle.

Cold Spring Harb Perspect Med 2012

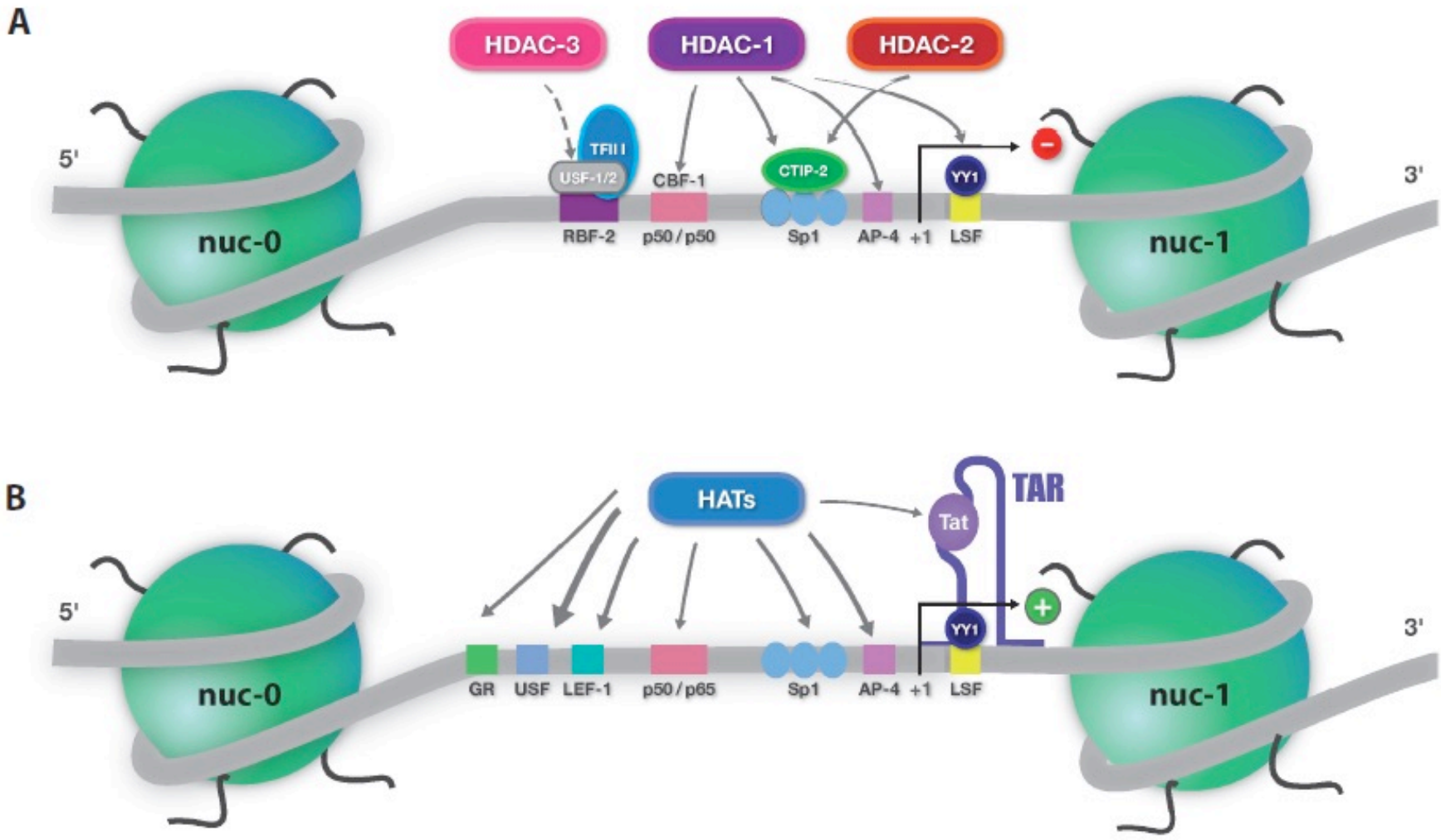
Molecular mechanisms that allow or restrict HIV proviral expression in quiescent T cells



L.Colin and C.Van Lint, Figure 2

Transcription factor binding sites and chromatin organization in the 5'LTR and leader region of HIV-1. (A) Representation of the HIV-1 genome. The intragenic hypersensitive site HS7 located in the *pol* gene is indicated. (B) Schematic representation of the main transcription factor binding sites located in the 5'LTR and in the beginning of the leader region of HIV-1. The U3, R, U5 and leader regions are indicated. Nucleotide 1 (nt1) is the start of U3 in the 5'LTR. The transcription start site corresponds to the junction of U3 and R. (C) Schematic representation of the nucleosomal organization of the HIV-1 genome 5' region. Hypersensitive sites HS2, HS3 and HS4 are indicated. The assignment of nucleosome position in this region is based on DNase I, micrococcal nuclease and restriction enzyme digestion profiles. During transcriptional activation, a single nucleosome, named nuc-1 and located immediately downstream of the transcription start site, is specifically and rapidly remodeled.

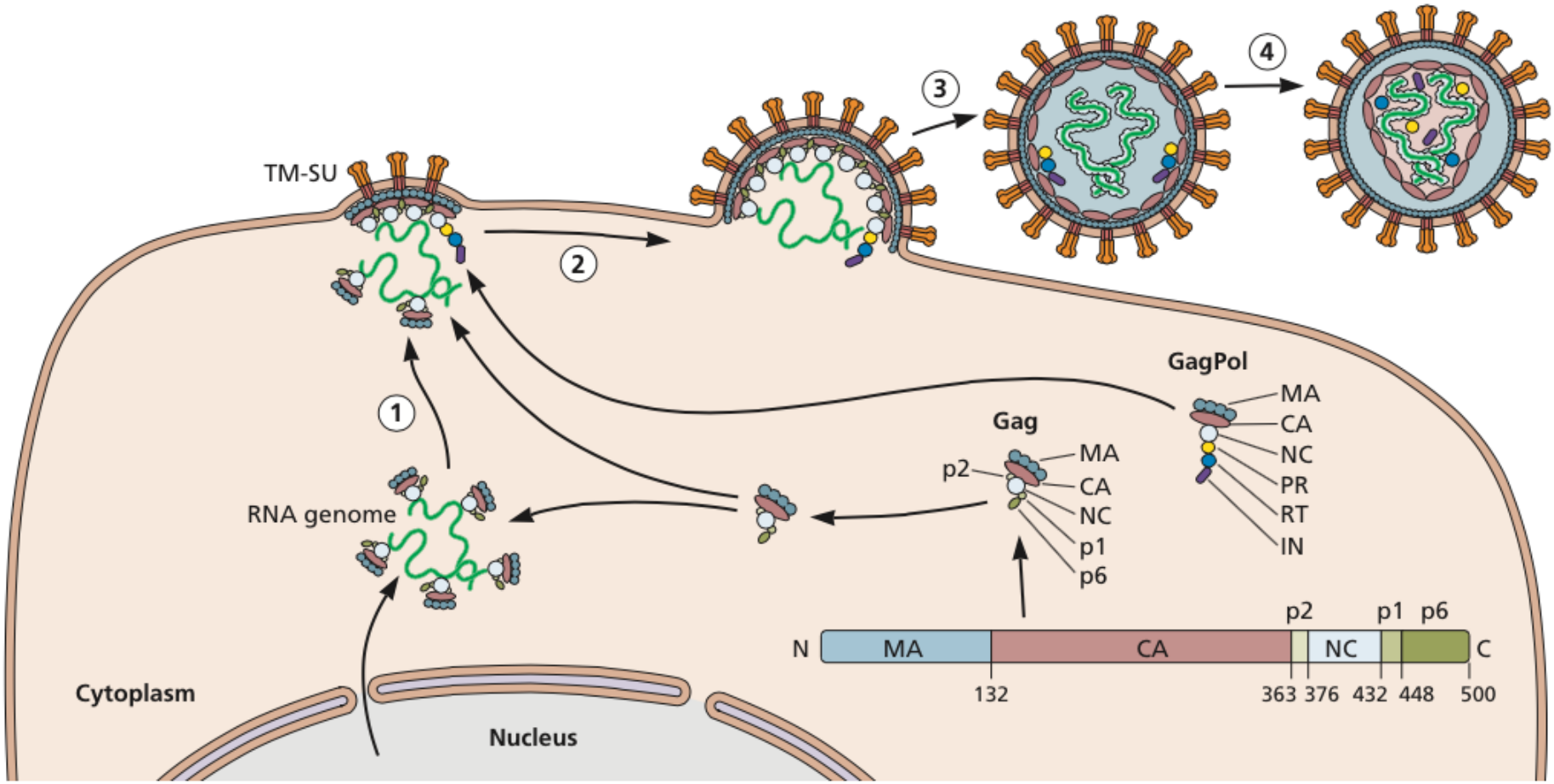
Molecular mechanisms that allow or restrict HIV proviral expression in quiescent T cells



*Retrovirology*2009

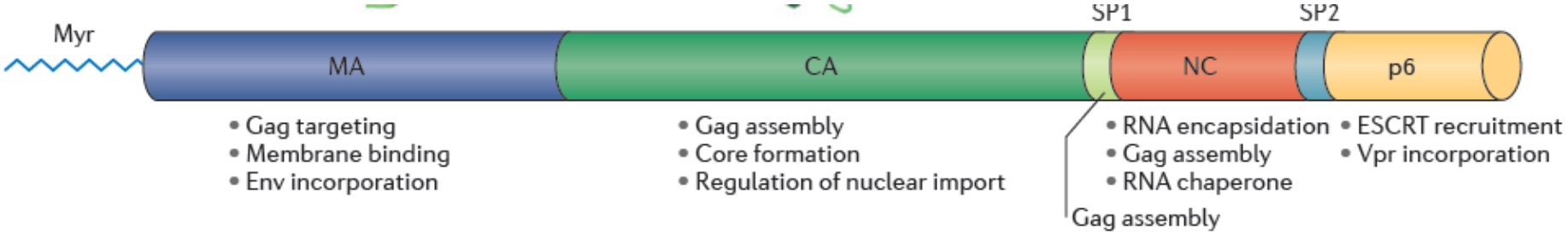
HDAC and HAT recruitment to the HIV-1 5'LTR. (A) During latency, nuc-1 blocks transcriptional initiation and/or elongation because it is maintained hypoacetylated by nearby recruited HDACs. The targeting of nuc-1 by these HDACs is mediated by their recruitment to the 5'LTR via several transcription factor binding sites. Thin arrows indicate that the implicated transcription factors were demonstrated to recruit HDACs to the 5'LTR (by ChIP experiments or following knockdown of the corresponding transcription factor). The dotted arrow indicates that the USF transcription factor could potentially recruit HDAC-3 to the nuc-1 region based on its interactome partners in the literature, but this recruitment has not been demonstrated so far in the specific context of the HIV-1 promoter. (B) Nuc-1 is a major obstacle to transcription and has to be remodelled to activate transcription. This disruption could happen following local recruitment of HATs by DNA-binding factors, and/or by the viral protein Tat, which binds to the neo-synthesized TAR element. This would result in nuc-1 hyperacetylation and remodelling, thereby eliminating the block to transcription at least for certain forms of viral latency. This acetylation-based activation model has been validated notably regarding the involvement of the transcription factors NF-kB p65 and Tat.

Assembly and release



Assembly and release

Endosomal sorting complex required for transport (ESCRT). A multi-complex machinery that comprises ESCRT-0, ESCRT-I, ESCRT-II and ESCRT-III, and that promotes membrane scission reactions (for example, during vesicle budding, cytokinesis and enveloped-virus budding).



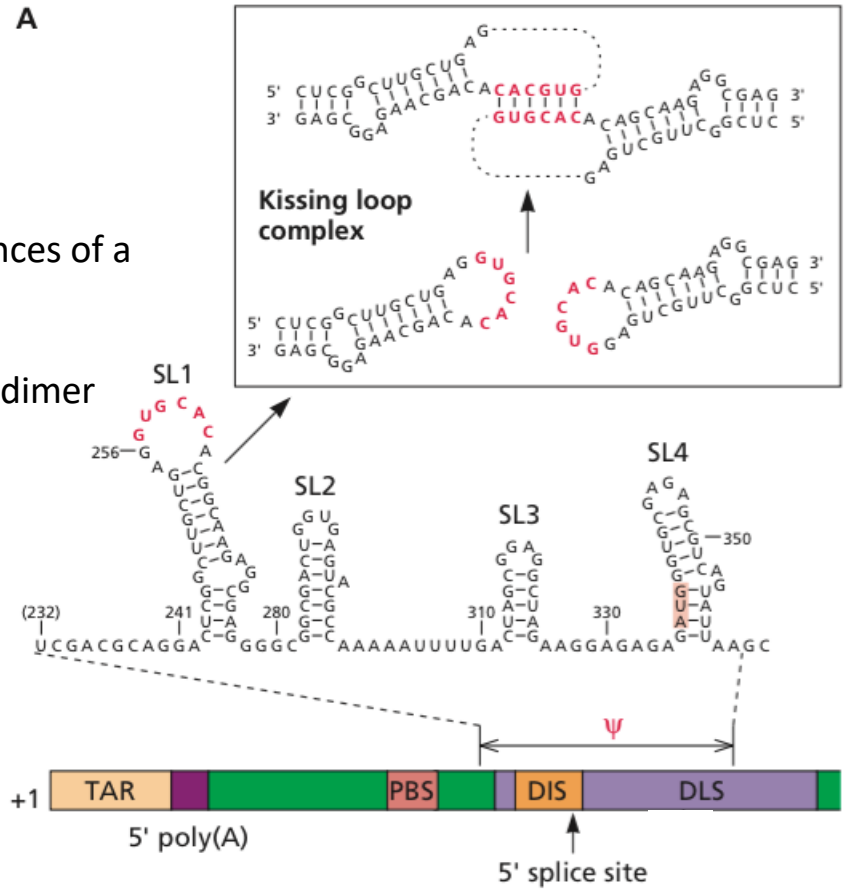
The NC domain of Gag is the primary viral determinant that drives RNA packaging.
Gag NC domains direct the packaging of viral genomic RNA by binding to the packaging signal (ψ site).
An RNA dimer is the recognition unit for packaging into assembling virions.

Assembly and release

In virions, the dimeric genome is held together by many noncovalent interactions between the RNA molecules.

In vitro – Evidence for base pairing between loop sequences of a specific herpin (SL1) within the DIS.

Mutations in this sequence – inhibition of genomic RNA dimer formation in vivo

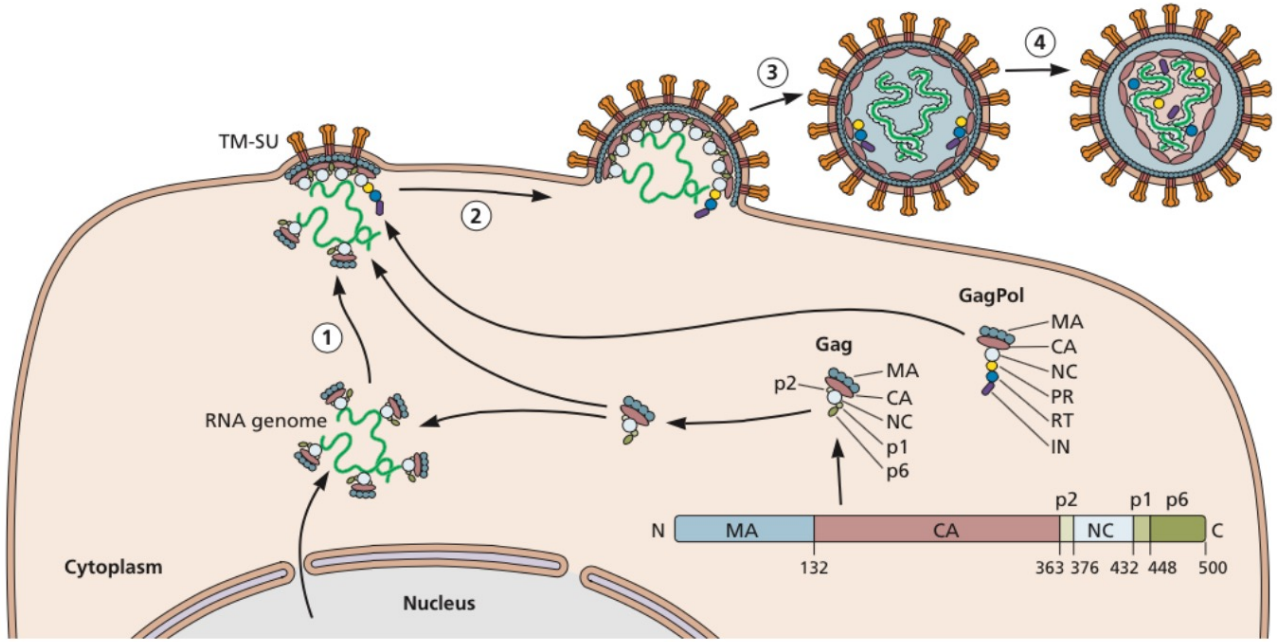


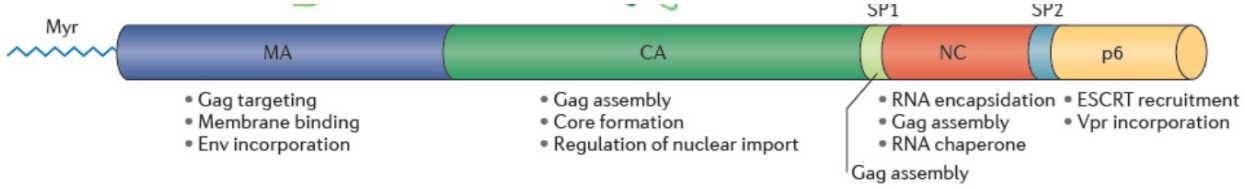
DIS - dimer initiation site
DLS – dimer linkage structure

Assembly and release

MA drives GAG targeting to the plasma membrane (1)

CA promotes GAG multimerization (2)

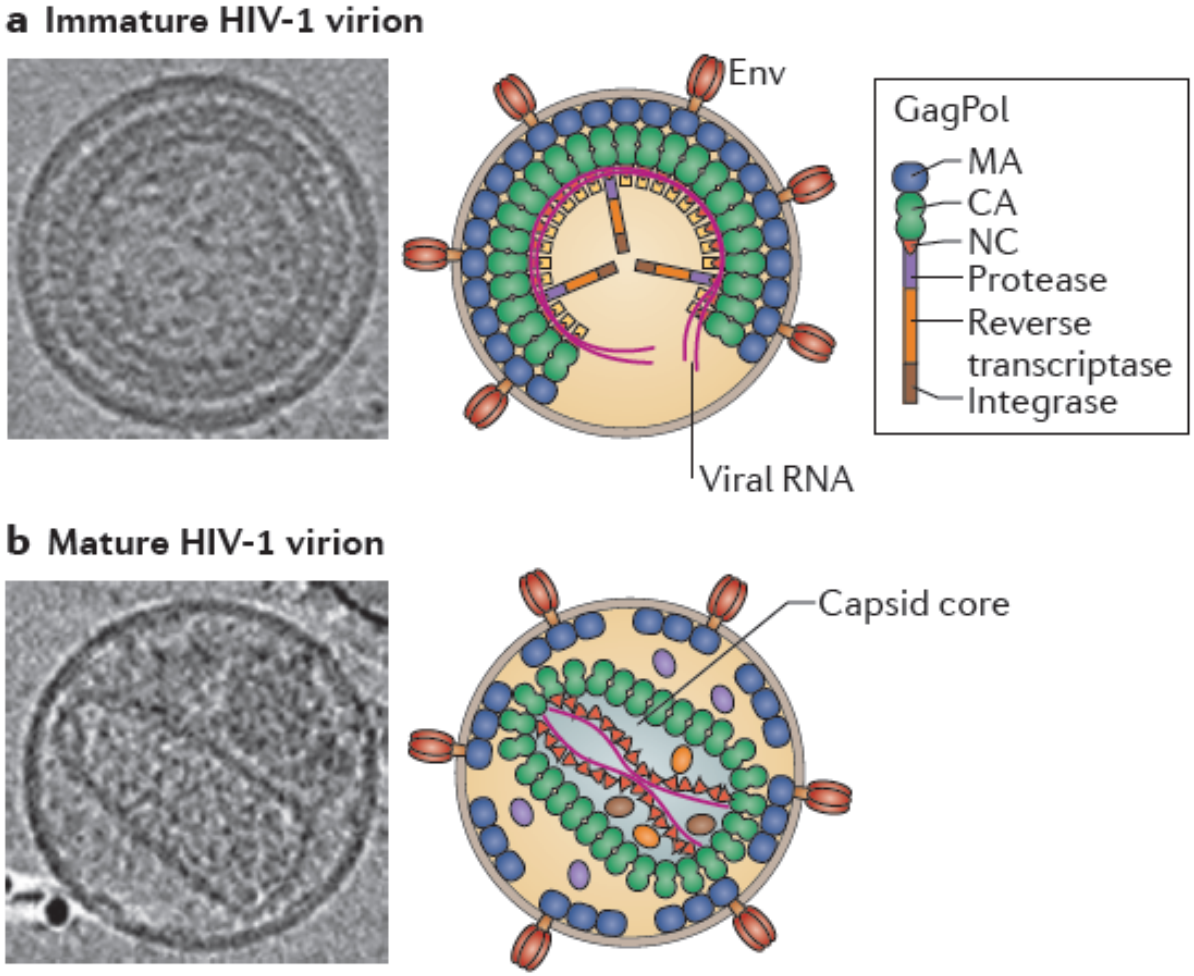




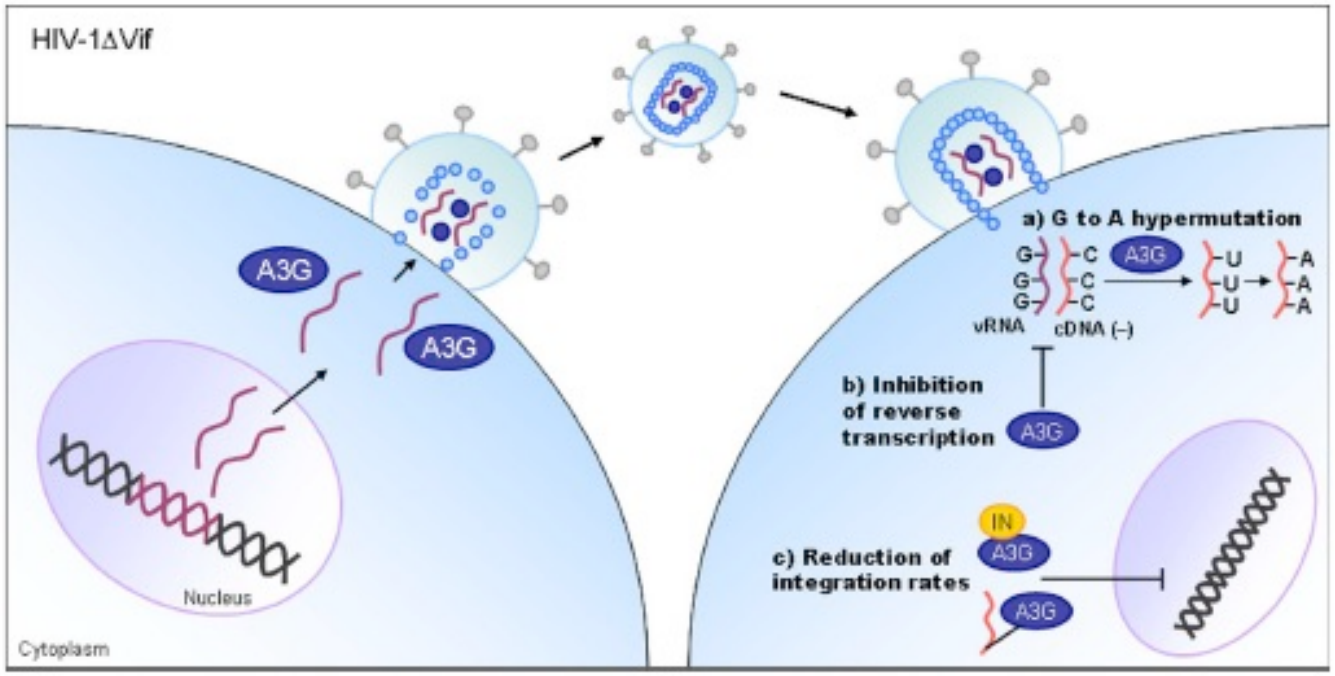
Maturation

The virus buds and the protease cuts itself free of the GAG-POL polyprotein

Further proteolytic cleavage occurs and the virion matures



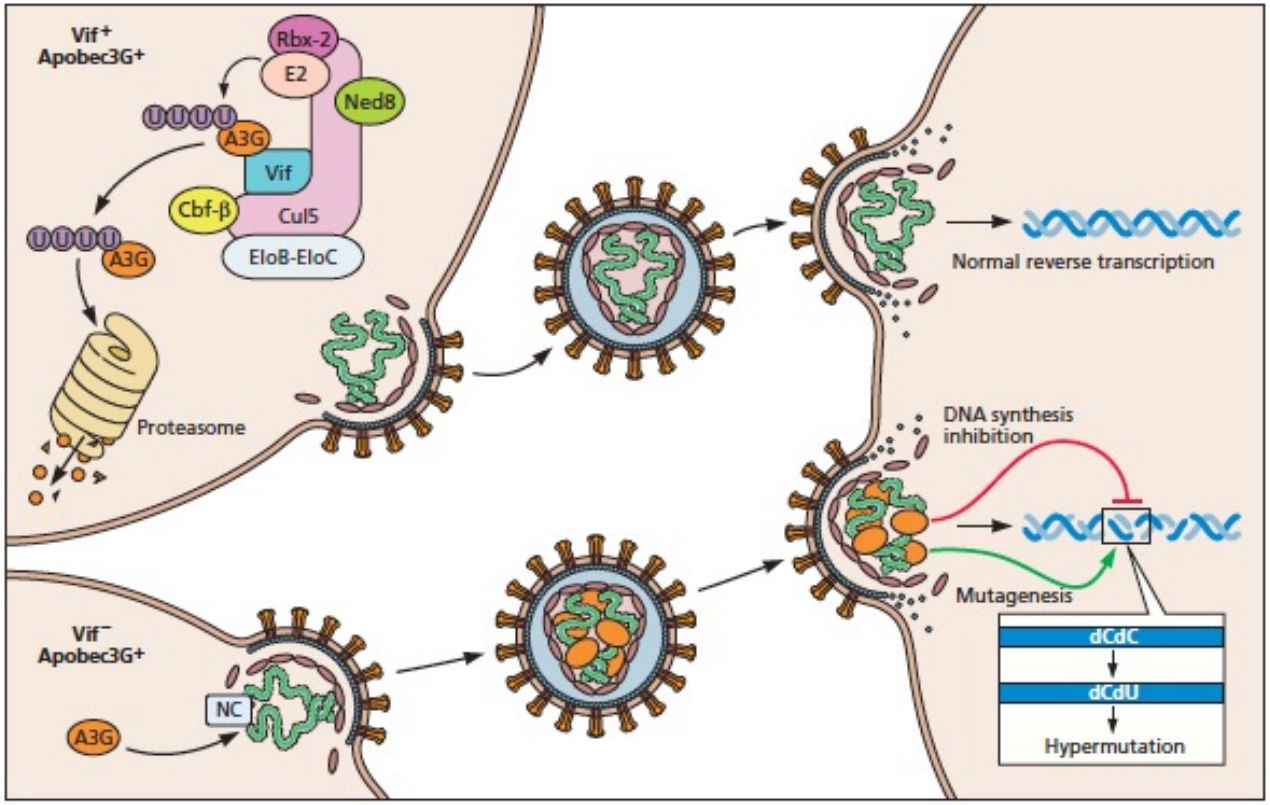
VIF: *Virion Infectivity Factor (23 kDa)*



Apobec3G (member of an RNA-binding family of cellular cytidine deaminases) is incorporated into progeny virus particles via interactions with the viral RNA and possibly NC protein. Apobec3G appears to inhibit virus reproduction in a number of ways. It has been proposed that binding to viral RNA may account, in part, for the deaminase-independent inhibition of reverse transcription in newly infected cells. The deaminase activity of Apobec3G leads to formation of deoxyuridine (dU), most frequently at preferred deoxycytidine (dC) sites in the first (-) strand of viral DNA to be synthesized by reverse transcriptase. Consequently, the (+) strand complement of the deaminated (-) strand will contain deoxyadenosine in place of the normal deoxyguanosine at such sites. Indeed, the frequency of G→A transitions is abnormally high in the genomes of vif -defective particles produced in nonpermissive cells, and incomplete protection from Apobec3 proteins by Vif may explain why such transitions are the most frequent point mutations in HIV genomes. It has been suggested that the Apobec3 proteins represent an ancient intrinsic cellular defense against retroviruses.

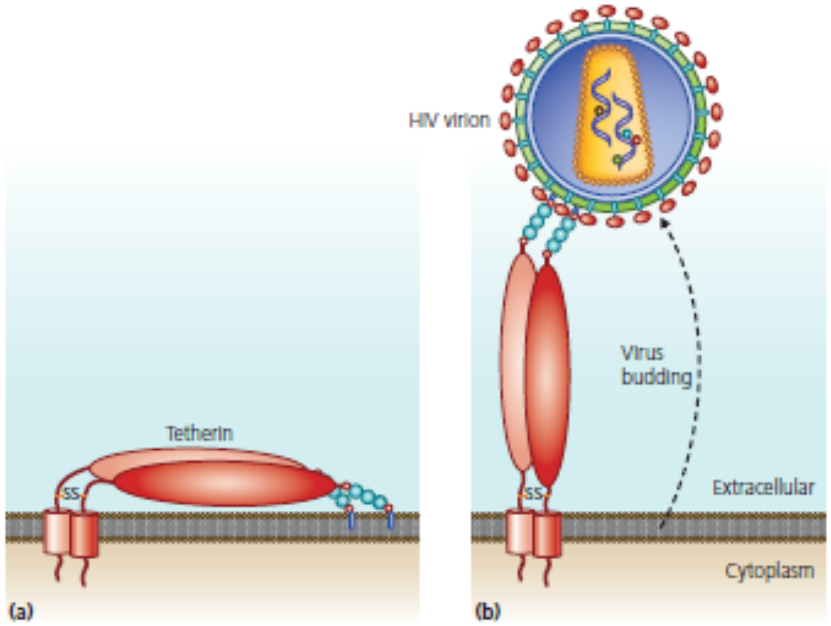
Front. Microbiol., 26 July 2012

VIF: *Virion Infectivity Factor (23 kDa)*



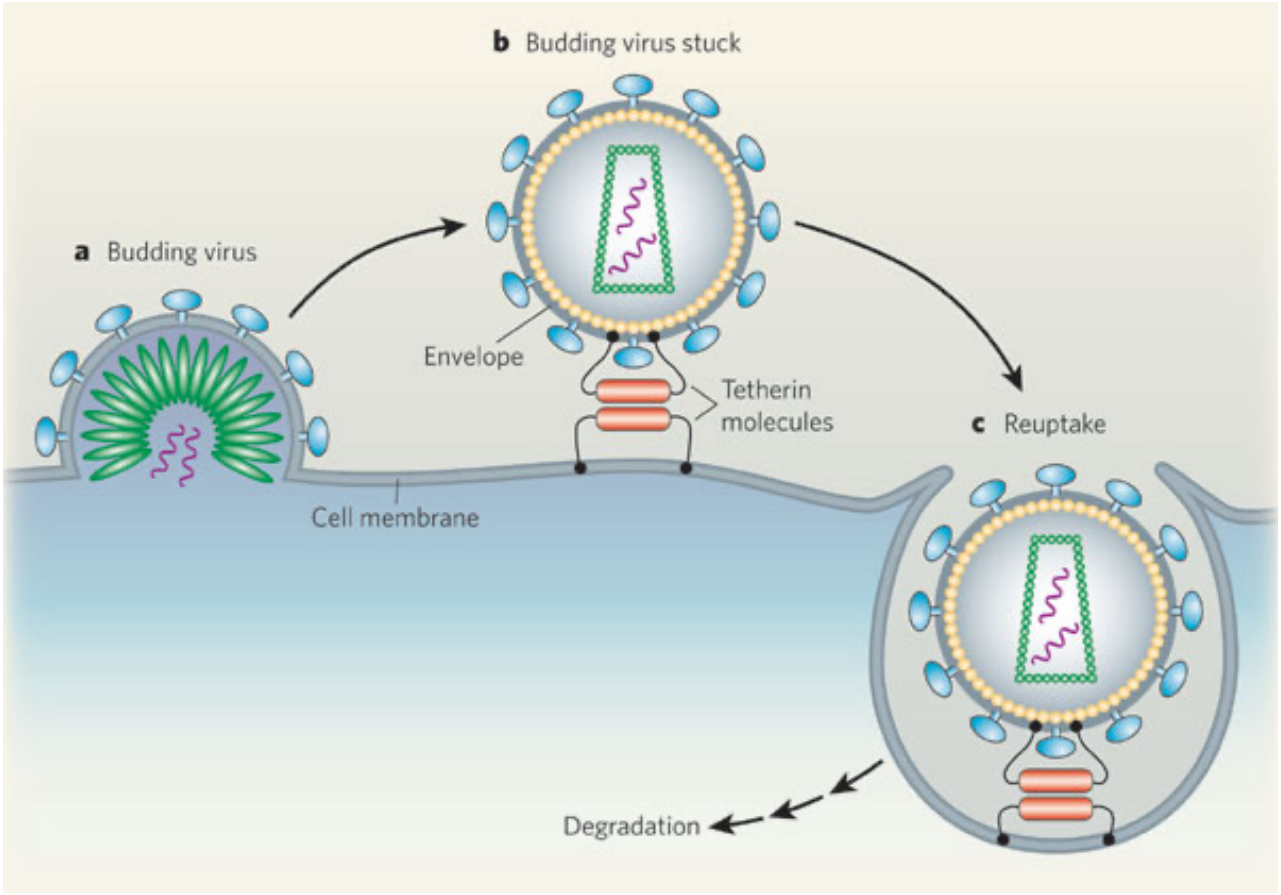
(Top) Vif counteracts the antiviral effects of Apobec3G (A3G) by mediating its polyubiquitination, which leads to proteosomal degradation. (Bottom) In the absence of Vif, A3G is incorporated into newly formed virus particles through interaction between viral RNA and NC protein. In the newly infected cell, reverse transcription is inhibited by A3G, and cytosines in the newly synthesized DNA are converted to uracil, causing hypermutation through eventual C to A transversions.

Tetherin has been recognized as a potent repressive factor for HIV-1 replication**. It is a cell-surface protein that, in addition to being anchored in the plasma membrane by a hydrophobic membrane-spanning region, also has a second membrane anchor in the form of a GPI (glycosyl phosphatidyl inositol) modification at the C terminus of its extracellular domain**; it also dimerizes via its extracellular domains which become linked by disulphide bonds. Possession of a GPI anchor causes the protein to locate in lipid rafts within the plasma membrane, which are known to be sites for budding of HIV and several other enveloped viruses. Thus, when HIV particles exit the cell, they carry with them the tetherin GPI anchor and so remain attached to the cell by a tetherin bridge.



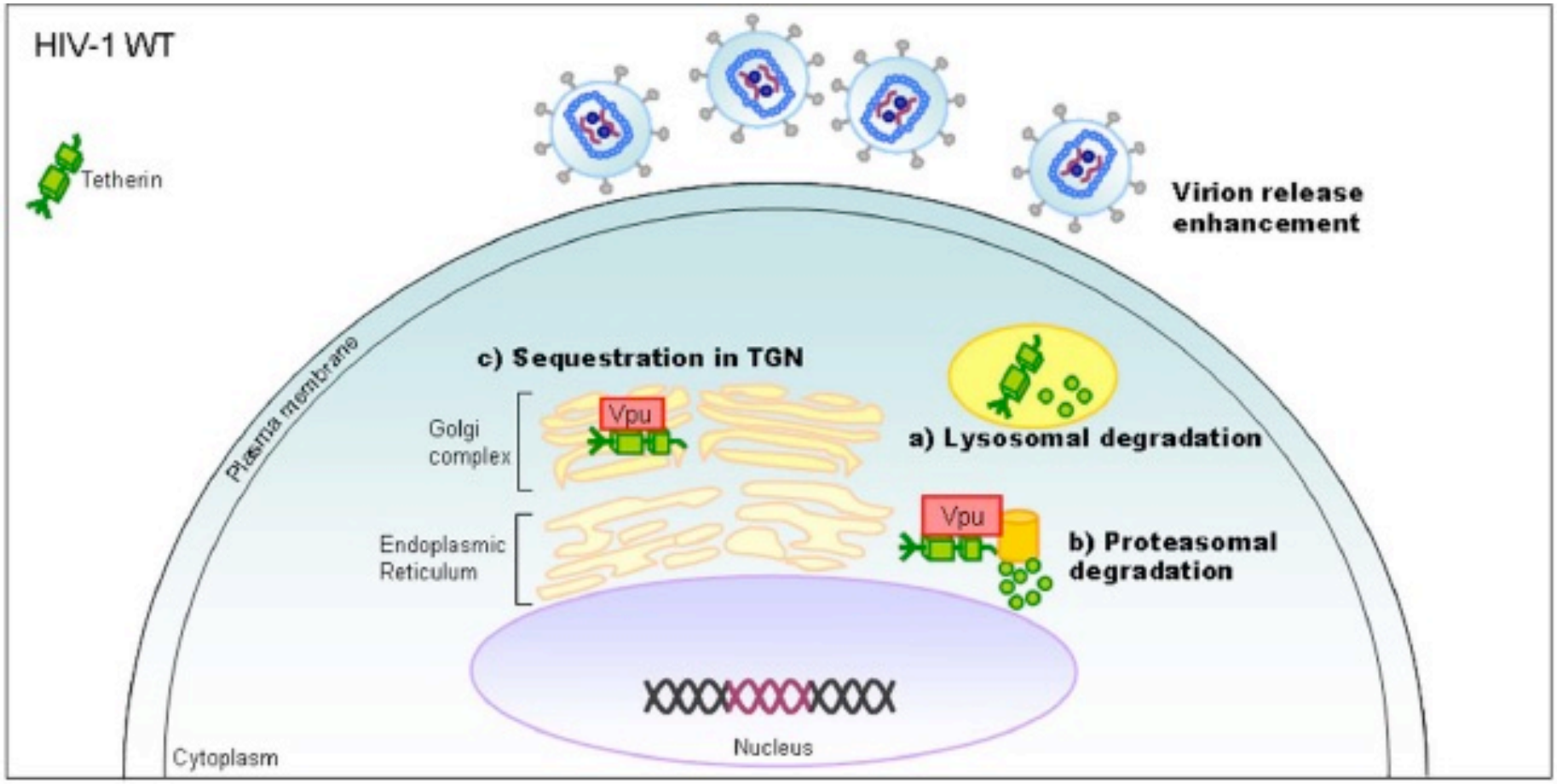
Schematic representation of the topology of tetherin protein dimers in (a) an uninfected cell and (b) an HIV-infected cell, in which it prevents virus release by anchoring exiting virions to the producer cell. In HIV-1 infection, this effect is opposed by the action of the viral **Vpu** protein to allow more efficient spread of virus between cells.

VPU: *Viral Protein Unknown (9,2 kDa)*



Nature **451**, 406-408(24 January 2008)

VPU: *Viral Protein Unknown (9,2 kDa)*



Front. Microbiol., 26 July 2012

Accessory genes

VPU: ***Viral Protein Unknown (9,2 kDa)***

- Promotes the degradation of the CD4/gp160 complex in the endoplasmic reticulum, facilitating the gp160 transport to the plasma membrane for assembling of new viral particles.

- Reduces CD4 and MHC-I expression promoting the virion budding and the escape of the virus from IS

VPR : ***Viral Protein, Regolatory (15 kDa)***

- Is a late HIV product packaged into the virion nucleocapsid

- Contains a nuclear localization signal (NLS) and is involved in the pre-integration complex (PIC) formation and nuclear transport

- Induces cells to arrest in the G2 phase of the cell cycle (LTR promoter is more active in G2-arrested cells)

- Negatively modulates the expression of CD4 on the cell surface

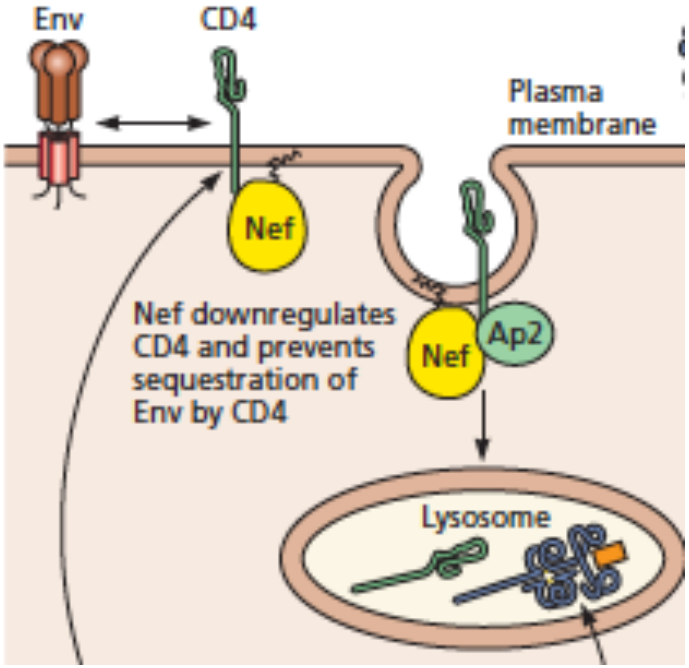
- Acts as a weak transactivator of viral transcription. It is important for proviral DNA expression occurring before integration

NEF: *Negative Factor (27 kDa)*

- Nef protein is synthesized early in infection.
- Nef is a myristoylated protein localized at the cell membrane of infected cells.
- NEF is important for HIV replication *in vivo* but there seems to be much less effect of NEF in an in vitro cell culture situation.

Attenuated HIV-1 strains exist that lack nef

NEF: *Negative Factor (27 kDa)*

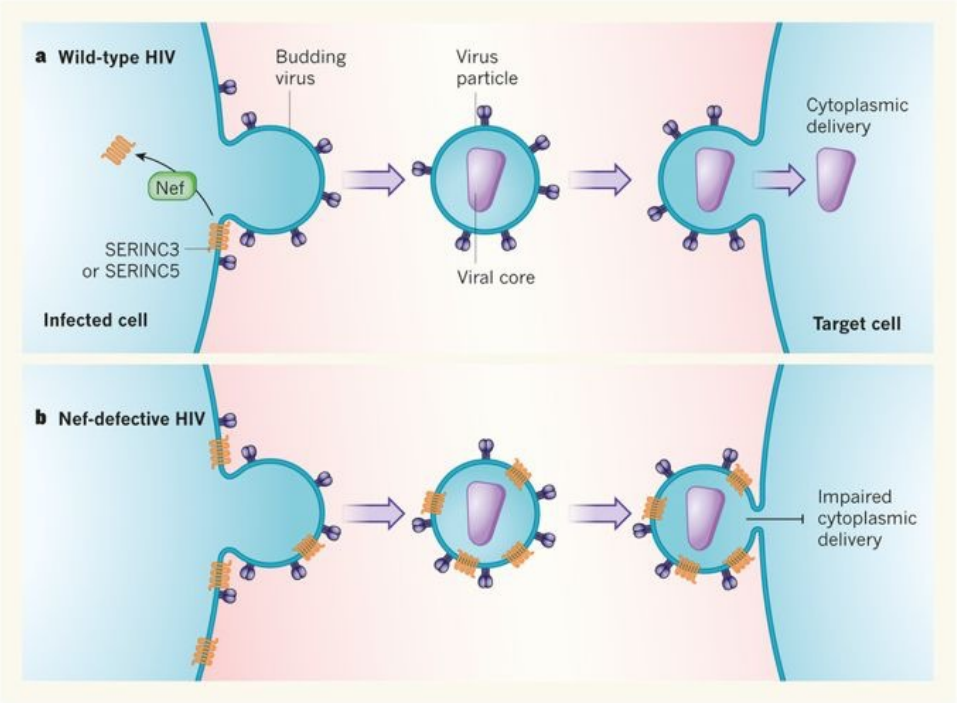


NEF causes the internalization of CD4 antigen from the cell surface and its destruction in lysosomes, enhancing Env incorporation into budding virus particles.

NEF reduces surface expression of MHC class I molecules. This alters antigen presentation by the infected cell and is proposed to protect the infected cell from attack by cytotoxic T cells.

Antiviral action countered by Nef

Both SERINC3 and SERINC5 are members of a family of proteins named for a putative activity on membranes ('serine incorporator'). The SERINC proteins are integral membrane proteins that form scaffolds for enzymes involved in the synthesis of specific membrane phospholipid molecules. How do SERINC3 and SERINC5 lower HIV infectivity? It has been showed that, at high levels of expression, these proteins reduce the efficiency of virus fusion with target cells. Nef induces SERINC5 to move from the cell surface to an intracellular compartment, preventing it from being incorporated into the budding virus.



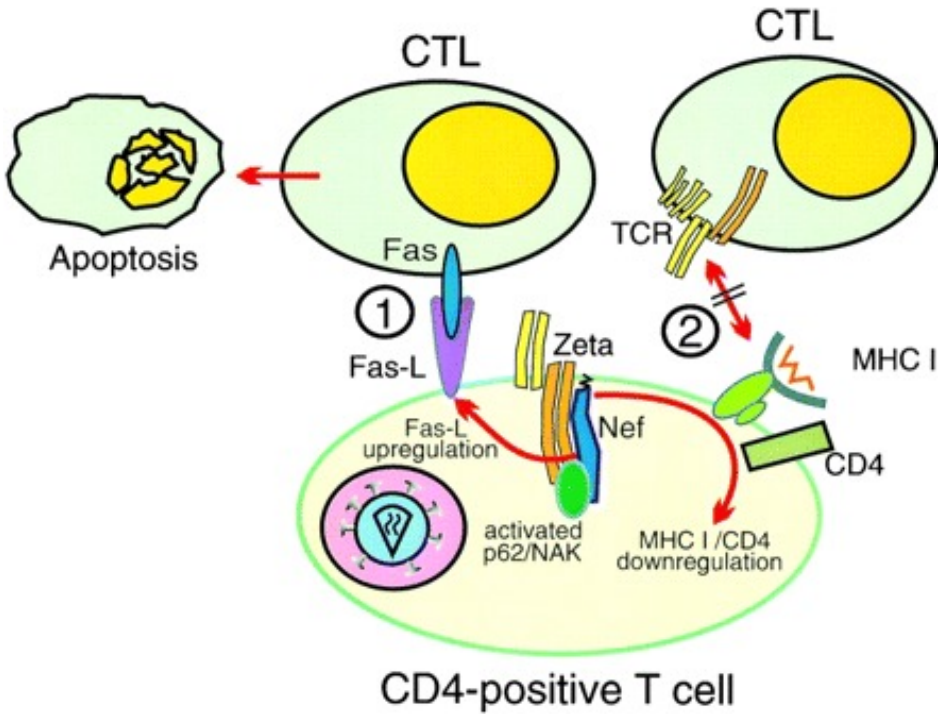
SERINC3 and SERINC5 are membrane proteins found to have antiviral activity against HIV. **a**, HIV protein Nef prevents the SERINC proteins from being incorporated into a growing virus particle as it buds from the membrane of an infected cell. The resulting virus particle is able to correctly fuse with another target cell and deliver its viral core to the host-cell cytoplasm. **b**, It has been proposed that, in the absence of Nef, SERINC3 and SERINC5 are successfully incorporated into viral particles, and prevent delivery of the viral core by inhibiting the expansion of the fusion pore.

Nature **volume 526**, pages 202–203 (08 October 2015)

Nef and apoptosis

Pro-apoptotic Role

Nef stimulates expression of FasL on the surface of infected cells (the mechanism involves the signaling pathway of the TCR). This results in the protection of infected cells from CTL attack by killing Fas+ viral-specific CTLs in the process (1)

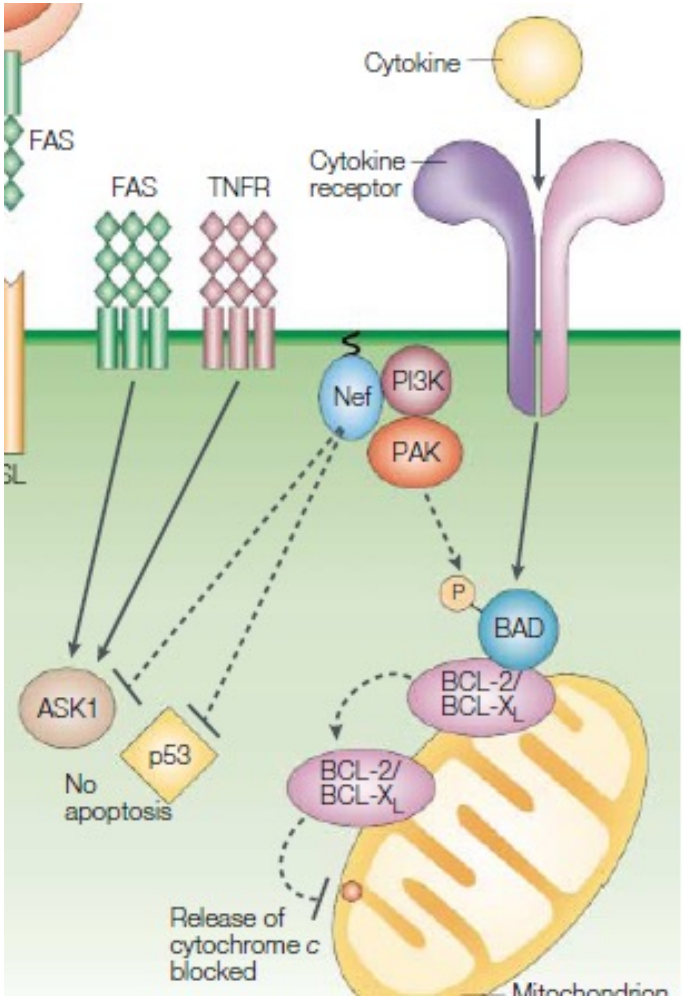


Xu X et al. J Exp Med 1999;189:1489-1496

Nef and apoptosis

Anti-apoptotic role

In infected cells, Nef blocks apoptotic pathways mediated by FAS and tumour-necrosis factor receptor (TNFR) (through inhibition of apoptosis signal-regulating kinase 1, ASK1) and by p53 (through direct binding), and unleashes the anti-apoptotic effects of BCL-2 and BCL-XL (by inducing the PAK-mediated phosphorylation of BAD, releasing the anti-apoptotic effectors, and thereby mimicking cytokine-induced signals).



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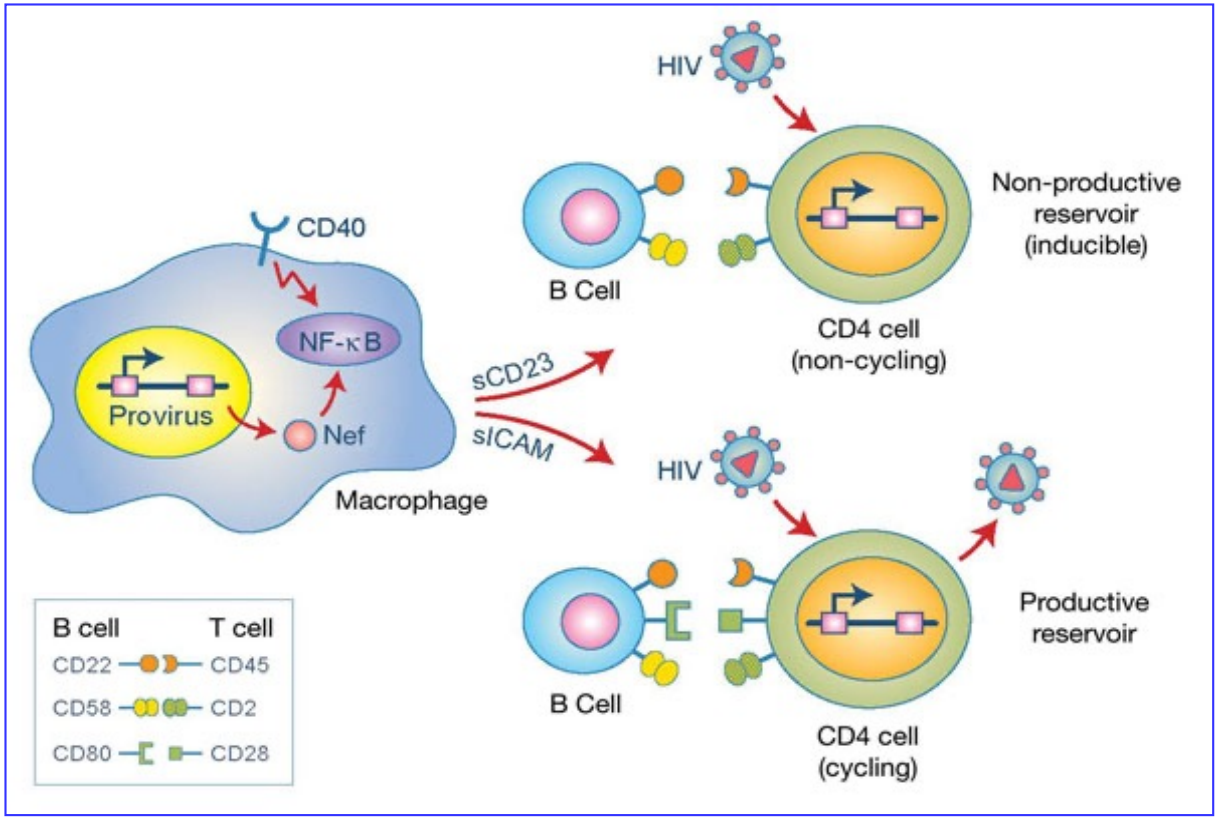
Nef induces T resting lymphocytes permissivity to HIV-1 infection



Physiological stimulation of CD40 in macrophages leads to NF-kappaB activation. This signalling pathway is intersected by HIV-1 Nef. In macrophages, activation of CD40 or expression of Nef induces the release of sCD23 and sICAM, which upregulate the expression of co-stimulatory receptors on B lymphocytes. These, in turn, interact with their corresponding ligands on T lymphocytes, rendering them permissive to HIV-1 infection. The types of receptor that are upregulated on B cells dictate the outcome of the infection. The induction of CD22 and CD58 on B cells is mediated primarily by sCD23. The action of these receptors on T cells does not lead to T-cell proliferation, but is sufficient to permit virus entry, but not virion release. Induction of CD80 on B cells, as mediated primarily by sICAM, provides signals that promote entry of T cells into the cell cycle, thereby allowing the productive infection of these cells.

Swingler S, *et al.* Nature 2003