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Mechanobiology of viruses

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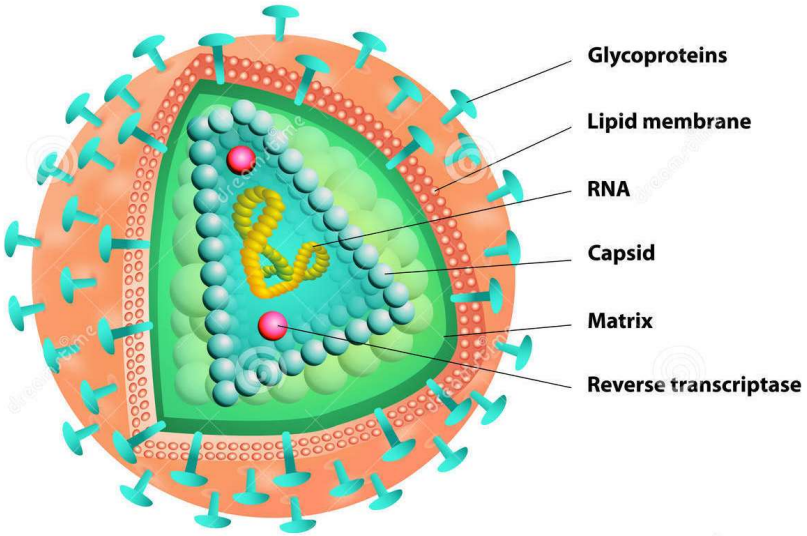
INTRODUCTION

- Life cycle of a generic virus.
- Virus of HIV.
- The process of receptor-mediated endocytosis (particle size).

Viruses structure



- capsid (made of lipids, proteins etc.)
- nucleic acid
- enzymes

Viruses classification

Viruses can be classified in two categories:

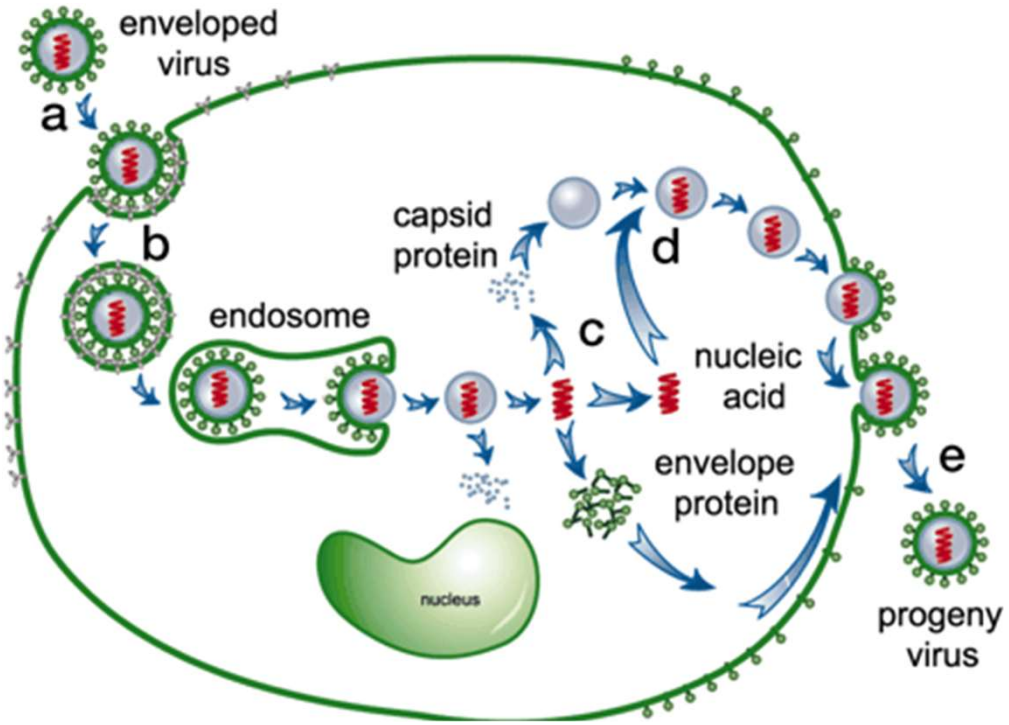
DNA virus: the information of the virus is stored into the DNA filament inside nucleic acid

RNA virus (retro-virus): the information is stored into a RNA filament and thus it needs the reverse transcriptase to convert the genome from RNA to DNA filament

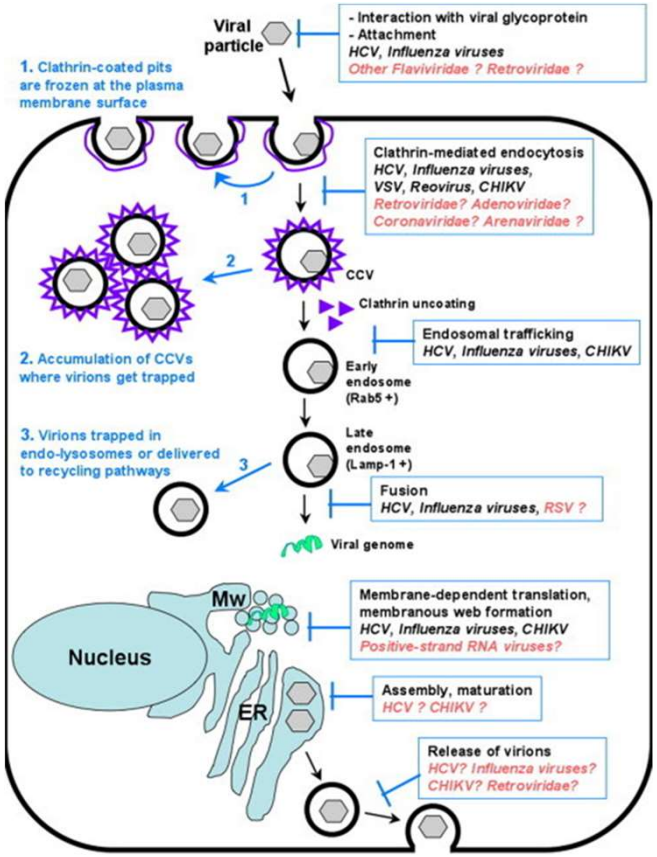
Life cycle of a virus

- Tropism
- Entrance into the cell
- Replication
- The exit of a virus

Entrance into the cell

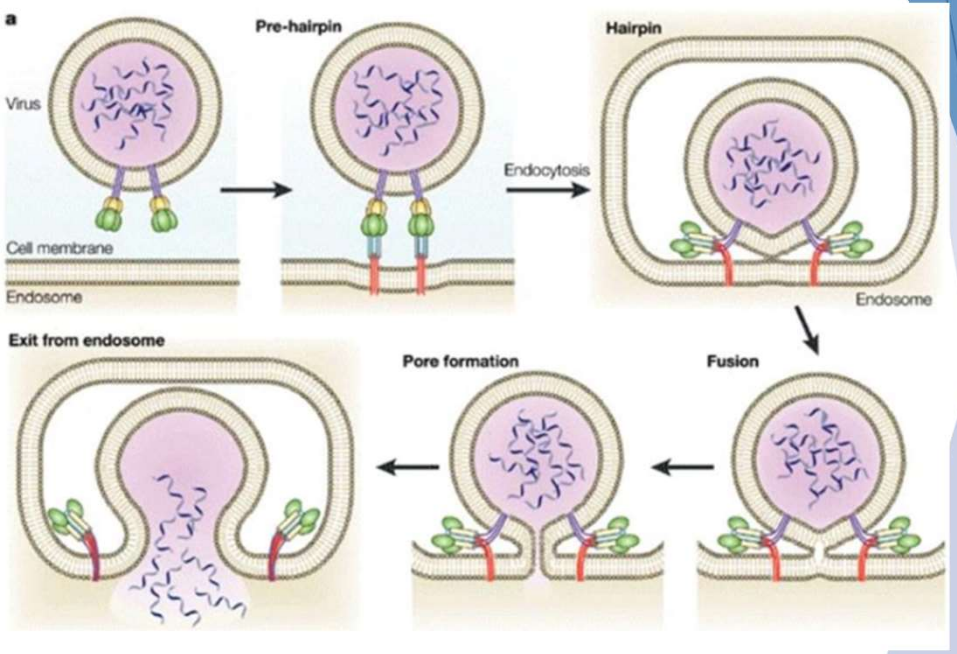


- Endocytosis: the membrane gets bent by the virus at the point where it gets incorporated into the cell.



Endocytosis is generally associated with the formation of a clathrinid coat (clathrinid-mediated endocytosis) around the virus.

Receptor-mediated endocytosis does not require the formation of a clathrinid coat.



- Fusion of membrane: the cell and virus membranes blend together, so that they become one, allowing the nucleic acid to enter the cell.
- Translocation of the entire virus particle across the cytoplasmic membrane of the cell.

Replication

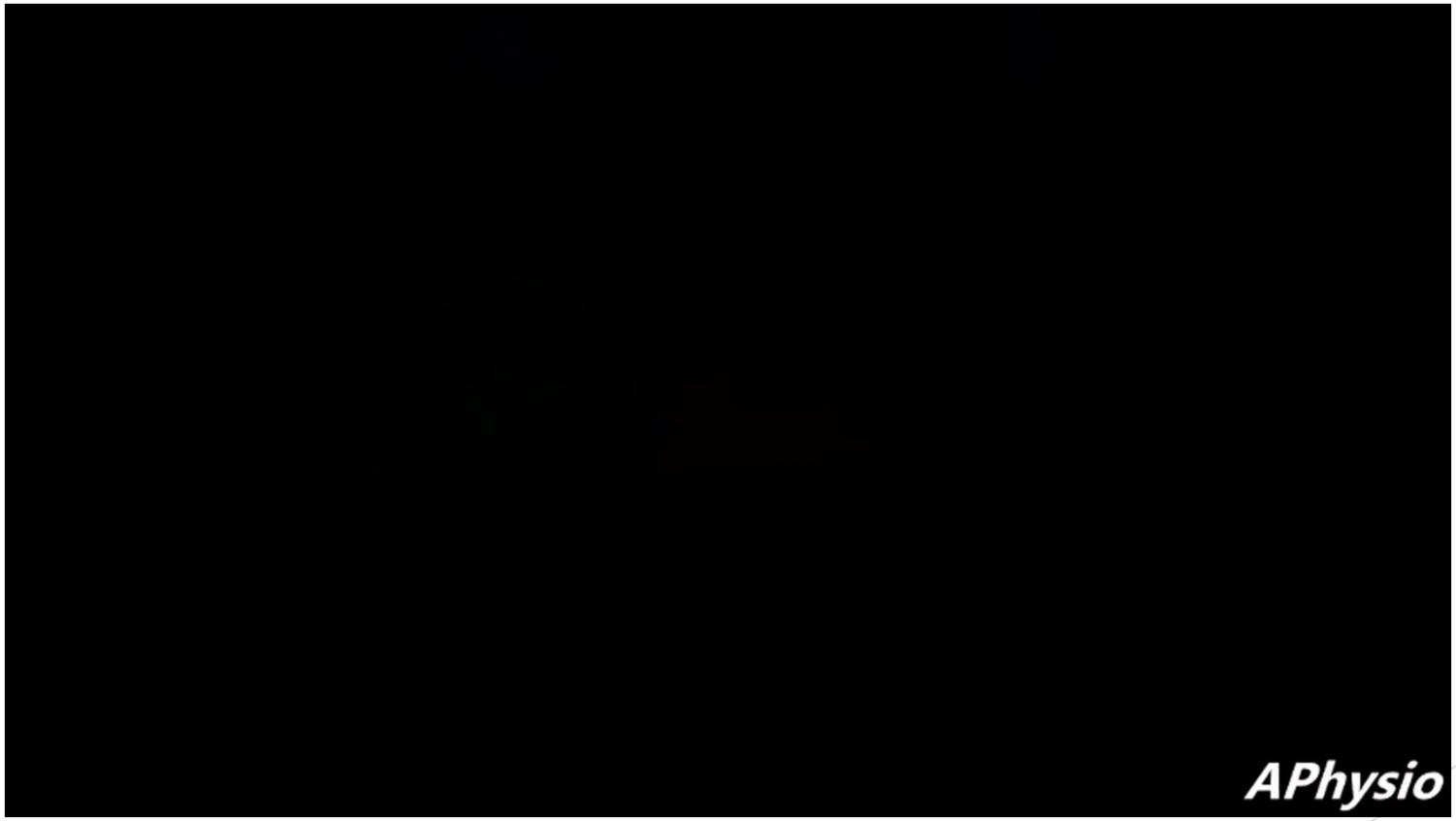
- Once the virus has entered the cell it starts replicating. The virus takes control of the cell and starts producing the genome and the proteins necessary to the recreation of the capsid.
- Afterwards, the genome and the capsid proteins are assembled, thus forming a progeny virus almost completely identical to the original virus.

Exit of a virus

The newly formed viruses can exit the cell in two different ways:

- Budding: the virus is expelled actively by the cell and it takes with it a part of the plasmatic membrane of the host. Virus envelopes are acquired during budding;
- Lysis: the cell dies after the collapse of the cellular membrane that allows the progeny viruses to exit;

Cycle of HIV



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Complete replication of HIV virus necessarily involves a cycle that can be divided in a few stages.

- **absorption and penetration**

The main targets for HIV infection are cells with some specific receptors on their surface such as CD4 (the most important).

The entry of HIV virus in the target cells requires the fusion between cell membrane and the viral one. This event allows the virus genome to be transported into the host cell cytoplasm.

- **transcription of RNA in DNA**

Viral RNA is transcribed into the cytoplasm in a double DNA chain, thanks to reverse transcriptase RT (DNA polymerase-RNA dependent).

Provirus resides permanently in the host cell genome, activating from time to time to produce new virions.

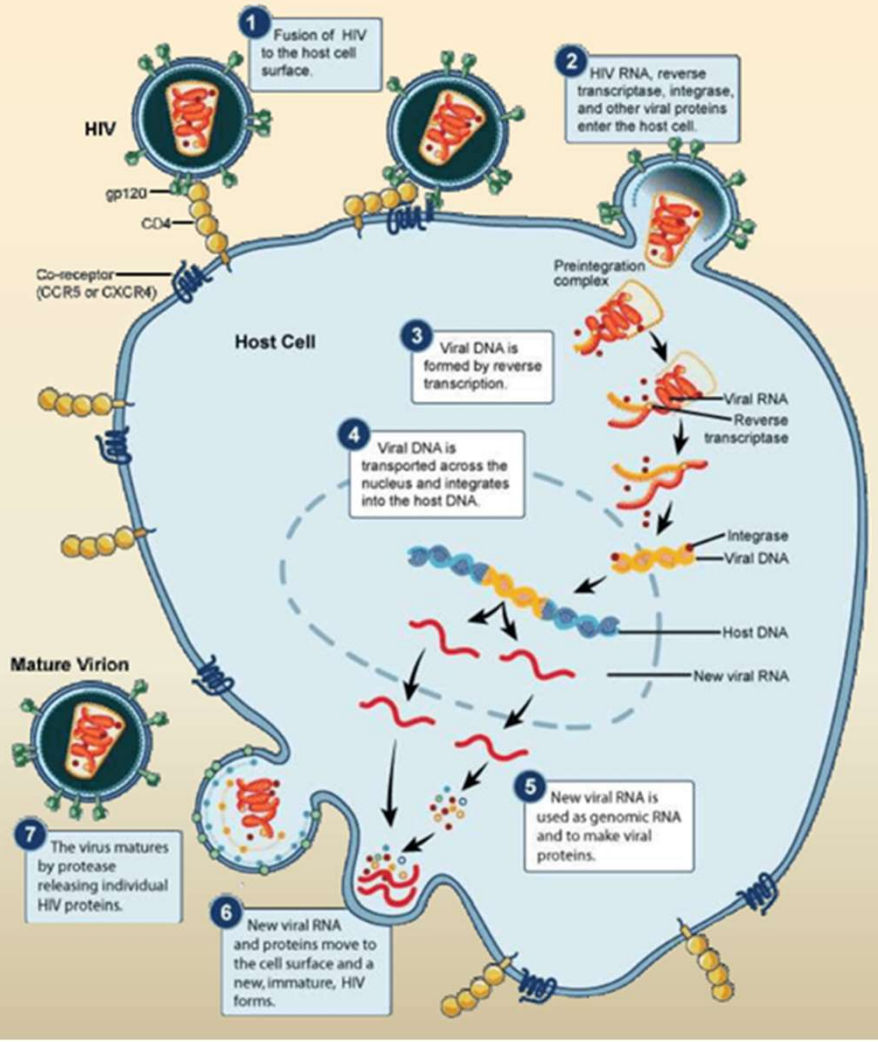
- **The release** of virions from the host cell occurs by a gemmation process very similar to exocytosis.

Ciclo replicativo

HIV: Replicazione

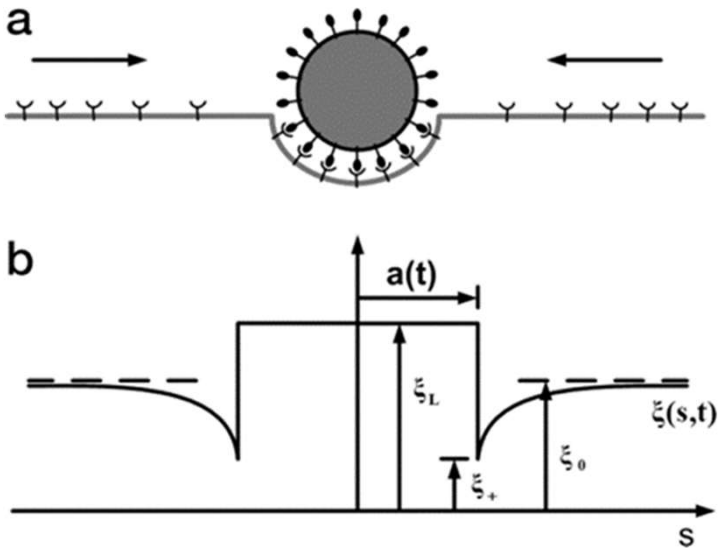
1^ fase: enzimi del virus (1-4)

2^ fase: macchinario cellulare (5-7)



Receptor-mediated endocytosis

We consider how a cell membrane containing diffusive mobile receptors wraps around a cylindrical particle coated with compatible ligands. The ligands are assumed to be immobile and uniformly distributed on the particle surface.



- The receptor-ligand binding causes the membrane to locally wrap around the viral particle
- Previous studies have shown that particle size has an important role in cellular uptake of nanomaterials.
- We want to write a mathematical model of receptor-mediated endocytosis.

Assuming that the total number of receptors in the membrane remains constant during the wrapping process, we can write a global conservation condition for the receptor density ξ (*s*, *t*) as:

$$\frac{d}{dt}\left[\int_0^{a(t)} \xi_L ds + \int_{a(t)}^{\infty} \xi(s,t) ds\right] = 0, \qquad [1]$$

Using Fick's Law and the continuity equation we obtain

$$(\xi_L - \xi_+)\dot{a} + j_+ = 0, \quad \text{on } s = a(t), \qquad [3]$$

The receptor density ξ (s, t) is determined from the diffusion equation:

$$\frac{\partial \xi(s,t)}{\partial t} = D\nabla^2 \xi(s,t), \quad a(t) < s < \infty. \qquad [4]$$

The appropriate solution has the form:

$$\xi(s,t) = A\,\mathrm{Erfc}\left(\frac{s}{2\sqrt{Dt}}\right) + \xi_0\,\mathrm{Erf}\left(\frac{s}{2\sqrt{Dt}}\right), \qquad [5]$$

We can now substitute the solution in Eq. 5 into the conservation condition in Eq. 3, obtaining:

$$\left[\xi_L - AErfc\left(\frac{a(t)}{2\sqrt{Dt}}\right) - \xi_0 Erf\left(\frac{a(t)}{2\sqrt{Dt}}\right)\right]\dot{a} + \frac{D}{\sqrt{\pi Dt}}e^{-\left(\frac{a(t)^2}{4Dt}\right)}(A - \xi_0) = 0 \qquad \mathbf{[6]}$$

which can be satisfied only if

$$a(t) = 2\alpha\sqrt{Dt} \qquad \mathbf{[7]}$$

We can substitute Eq. 7 into Eq. 6 and find the constant *A*.

We consider a simplified free energy function for a curved cell membrane in adhesive contact with a substrate:

$$F(t)/k_BT = \int_0^{a(t)} \left(-\xi_L e_{RL} + \xi_L \ln\frac{\xi_L}{\xi_0} + \frac{1}{2}Bk_p^2\right) ds + \int_{a(t)}^{\infty} \xi \ln\frac{\xi_L}{\xi_0} ds \qquad \textbf{[9]}$$

Differentiating Eq. 9 with respect to time leads to:

$$\frac{\dot{F}(t)}{k_BT} = -\left(\xi_L e_{RL} - \frac{1}{2}Bk_p^2 - \xi_L \ln\frac{\xi_L}{\xi_+} + \xi_L - \xi_+\right)\dot{a}(t) - \int_{a(t)}^{\infty} D\xi \left(\frac{\partial \chi}{\partial s}\right)^2 ds \qquad \textbf{[10]}$$

where

$$\chi(s,t) = \ln(\xi/\xi_0) + 1 \qquad \textbf{[11]}$$

If we require that the rate of free energy reduction gained from the wrapping process exactly balances the rate of energy dissipation consumed during receptor transport, the first term in Eq. 10 must vanish so that

$$\xi_L e_{RL} - \frac{1}{2} B k_p^2 - \xi_L \ln \frac{\xi_L}{\xi_+} + \xi_L - \xi_+ = 0 \qquad [12]$$

Substituting Eq. 5, 7 and 8 into the power balance relation of Eq. 12 allows us to determine the speed factor α:

$$\left[e_{RL} - \frac{\frac{1}{2} B k_p^2}{\xi_L} + ln \frac{\tilde{\xi} - g(\alpha)}{1 - g(\alpha)} \right] [1 - g(\alpha)] + 1 - \tilde{\xi} = 0 \qquad [13]$$

where

$$g(\alpha) = \sqrt{\pi} \alpha e^{\alpha^2} \mathrm{Erfc}(\alpha) \qquad [14]$$

and $\tilde{\xi} = \frac{\xi_0}{\xi_L}$.

Once α is known, the particle wrapping time is obtained as:

$$\alpha(t_W) = \pi R \quad \text{or} \quad t_W = \left(\frac{\pi R}{2\alpha \sqrt{D}} \right)^2 \qquad [15]$$