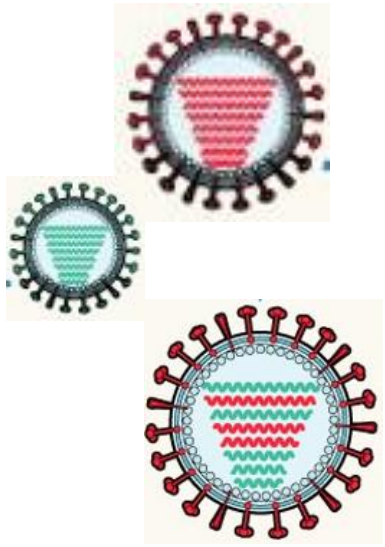
Effetti della replicazione virale sulla cellula ospite

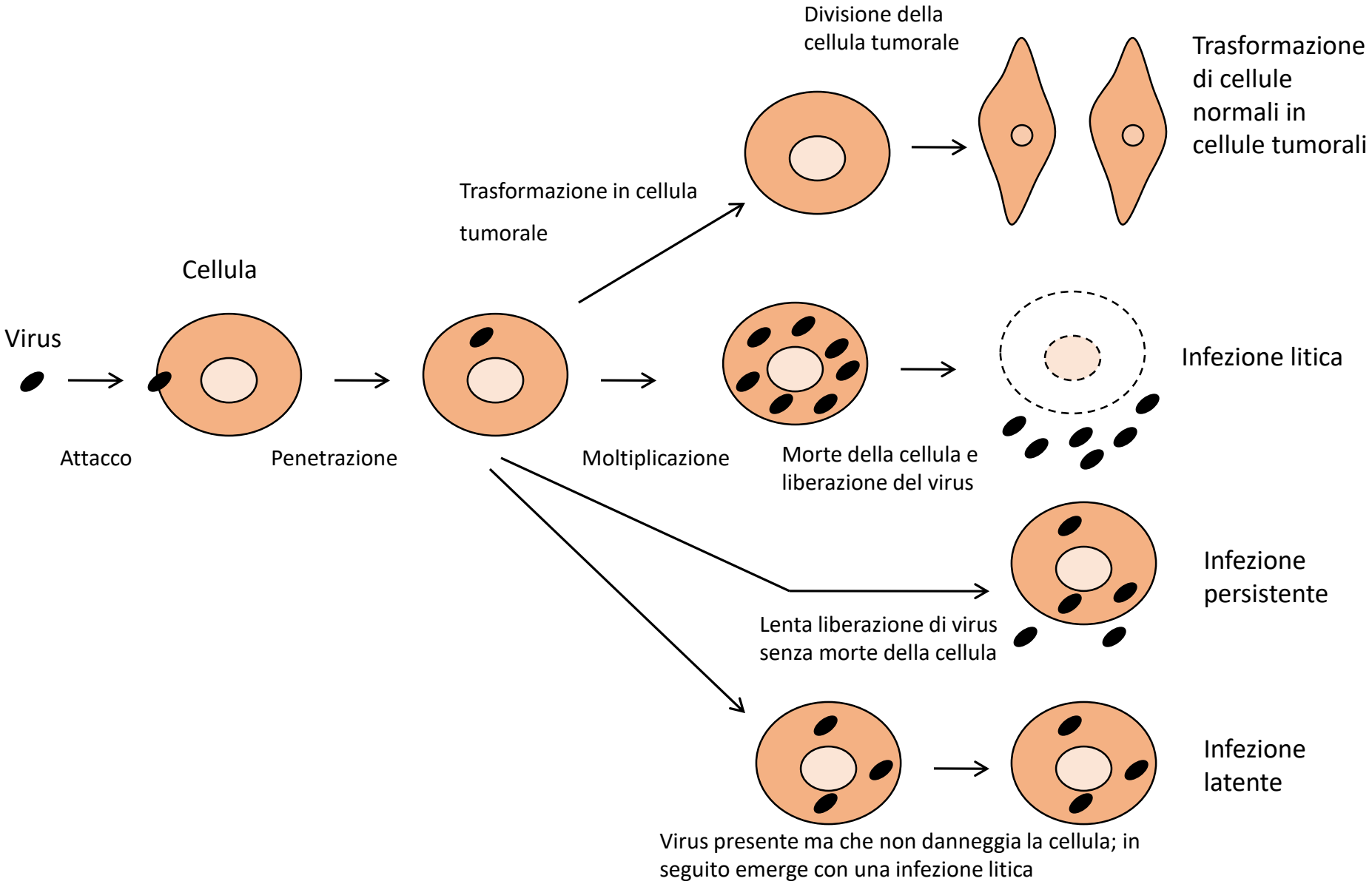
Variabilità genetica dei virus



L’INFEZIONE VIRALE PUO’ ESSERE:

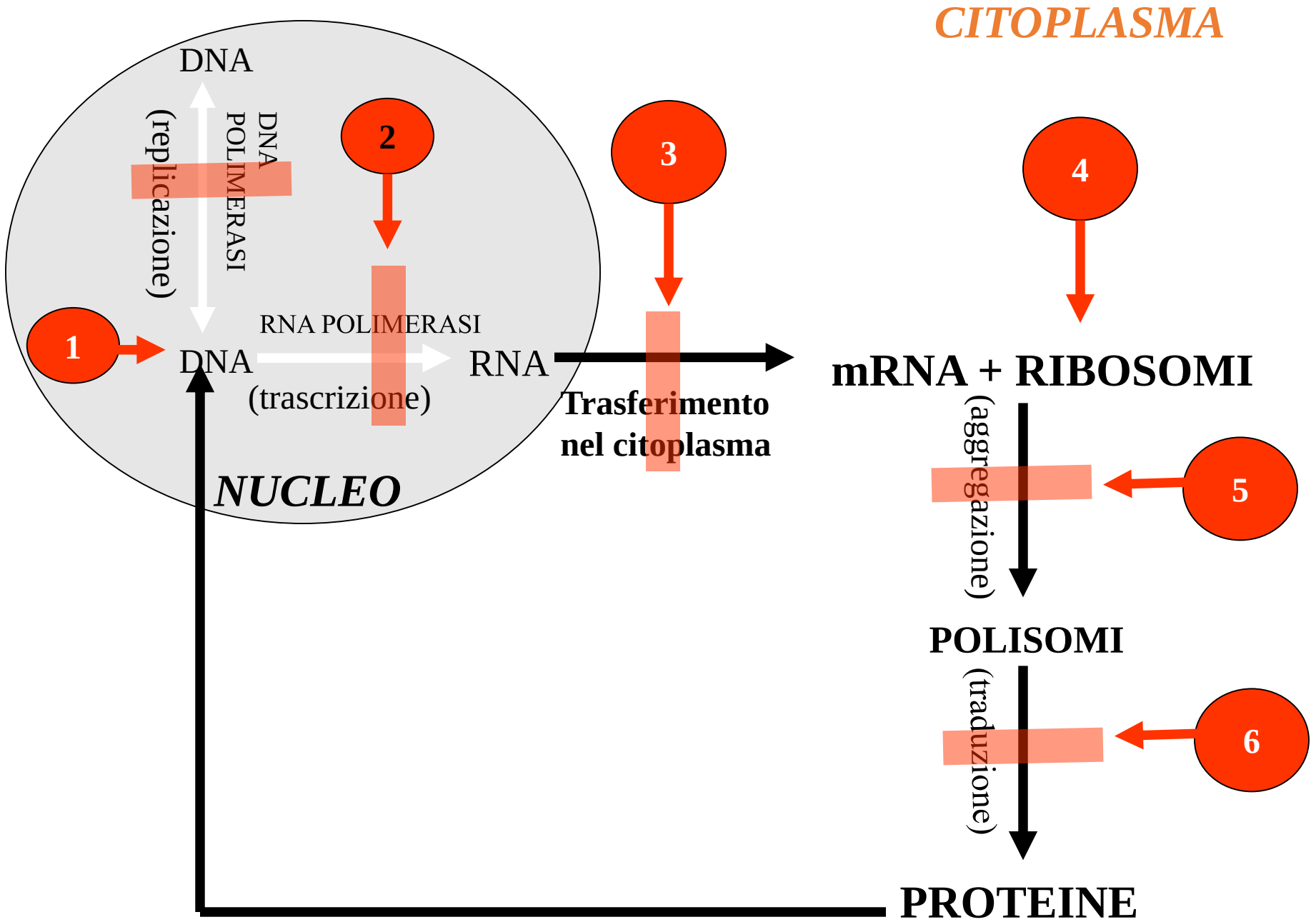
- PRODUTTIVA
- ABORTIVA
- RESTRITTIVA
- LATENTE

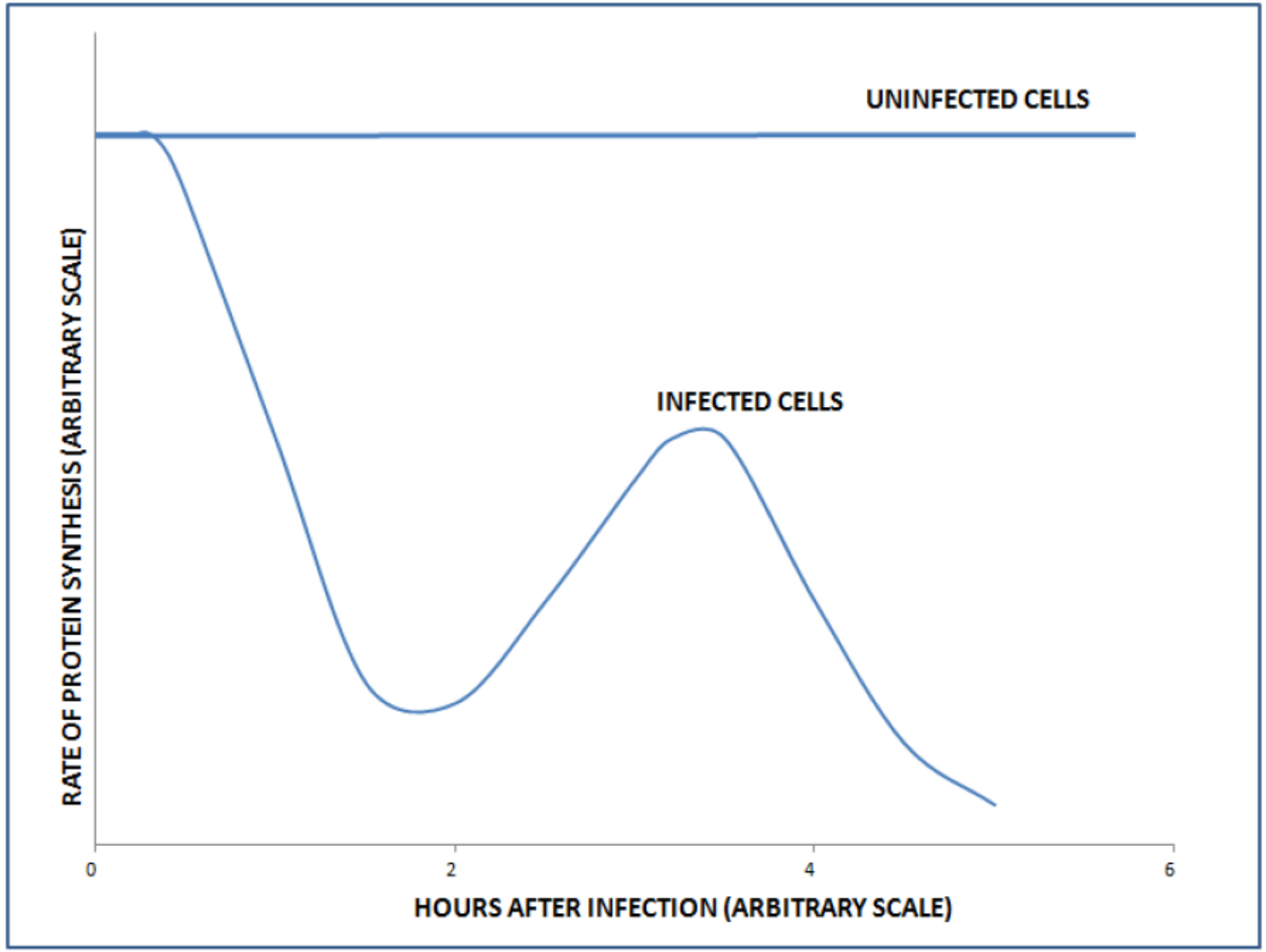
Possibili effetti dei virus sulle cellule animali e tipo di infezione



EFFETTI DELLE INFEZIONI VIRALI SULLA CELLULA OSPITE

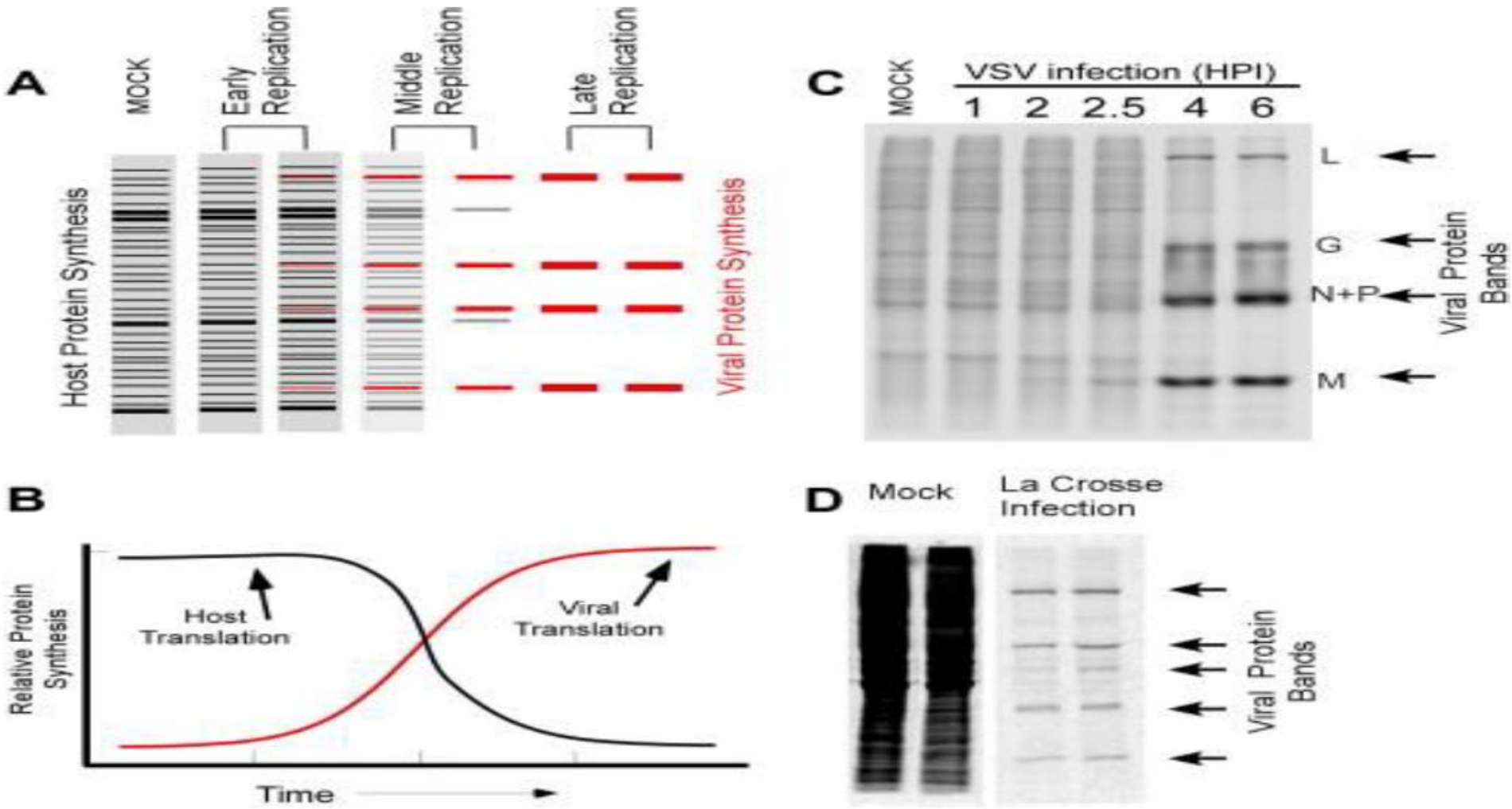
1. Alterazioni nella sintesi delle macromolecole cellulari
2. Alterazione della membrana cellulare
3. Alterazioni morfologiche
4. Alterazione del controllo della proliferazione cellulare


CITOPLASMA
DNA
DNA POLIMERASI
(replicazione)
2
3
4
1
RNA POLIMERASI
DNA
RNA
(trascrizione)
Trasferimento
nel citoplasma
mRNA + RIBOSOMI
(aggregazione)
5
POLISOMI
(traduzione)
6
NUCLEO
PROTEINE

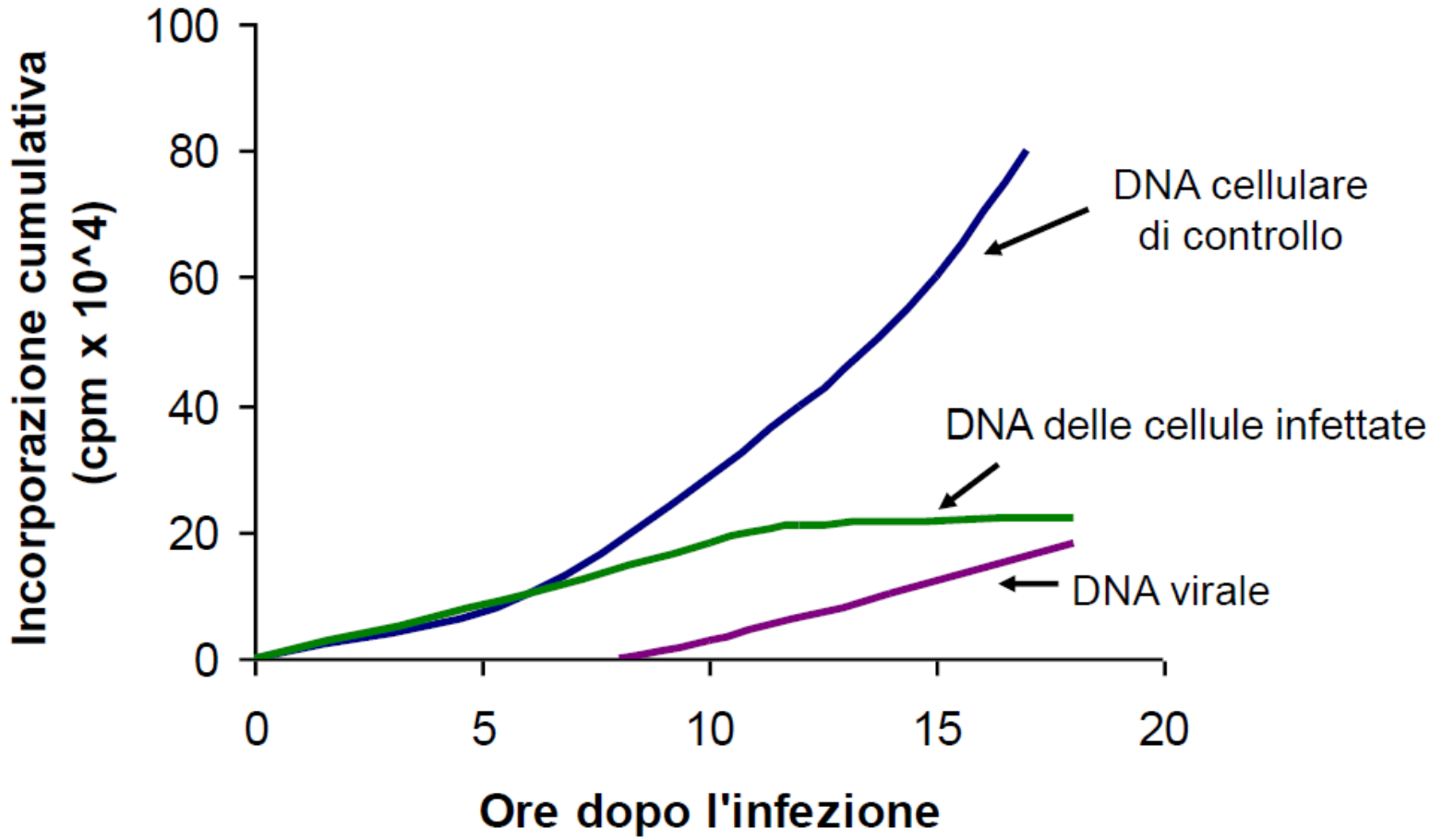

UNINFECTED CELLS
INFECTED CELLS
RATE OF PROTEIN SYNTHESIS (ARBITRARY SCALE)
0
2
4
6
HOURS AFTER INFECTION (ARBITRARY SCALE)

Shutoff

- Most viruses exhibit a phenomenon known as shutoff early in infection
- Shutoff is the sudden & dramatic cessation of most host cell macromolecular synthesis



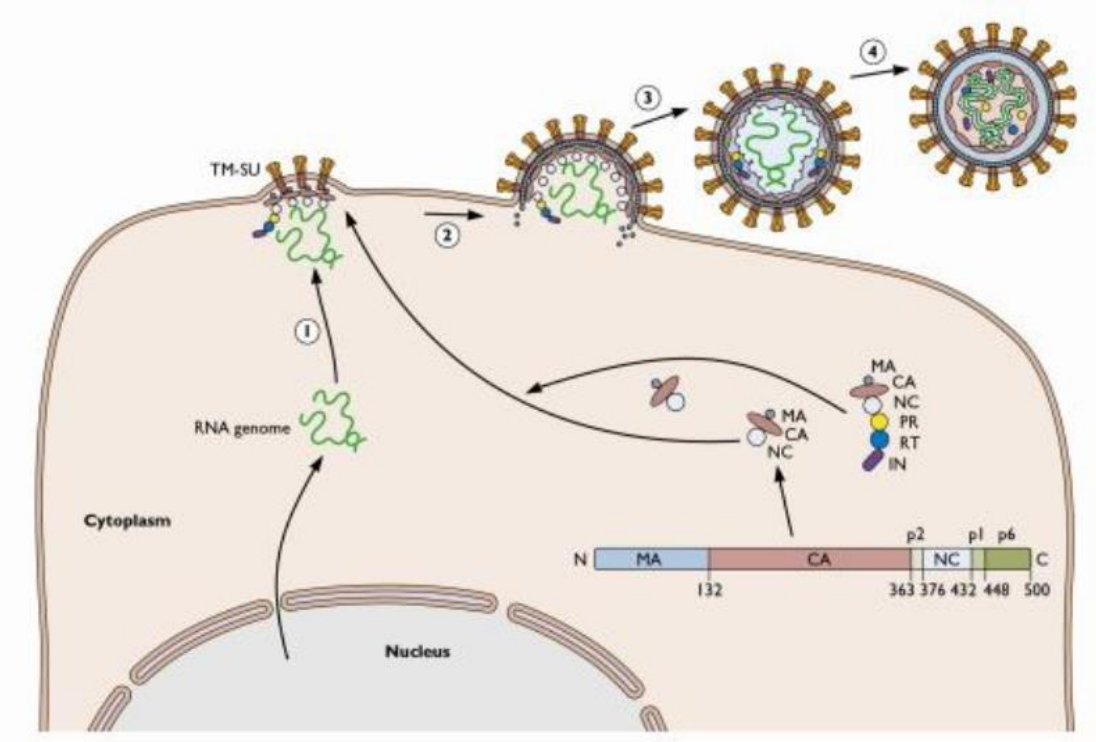
Erin N. Hodges , John H. Connor

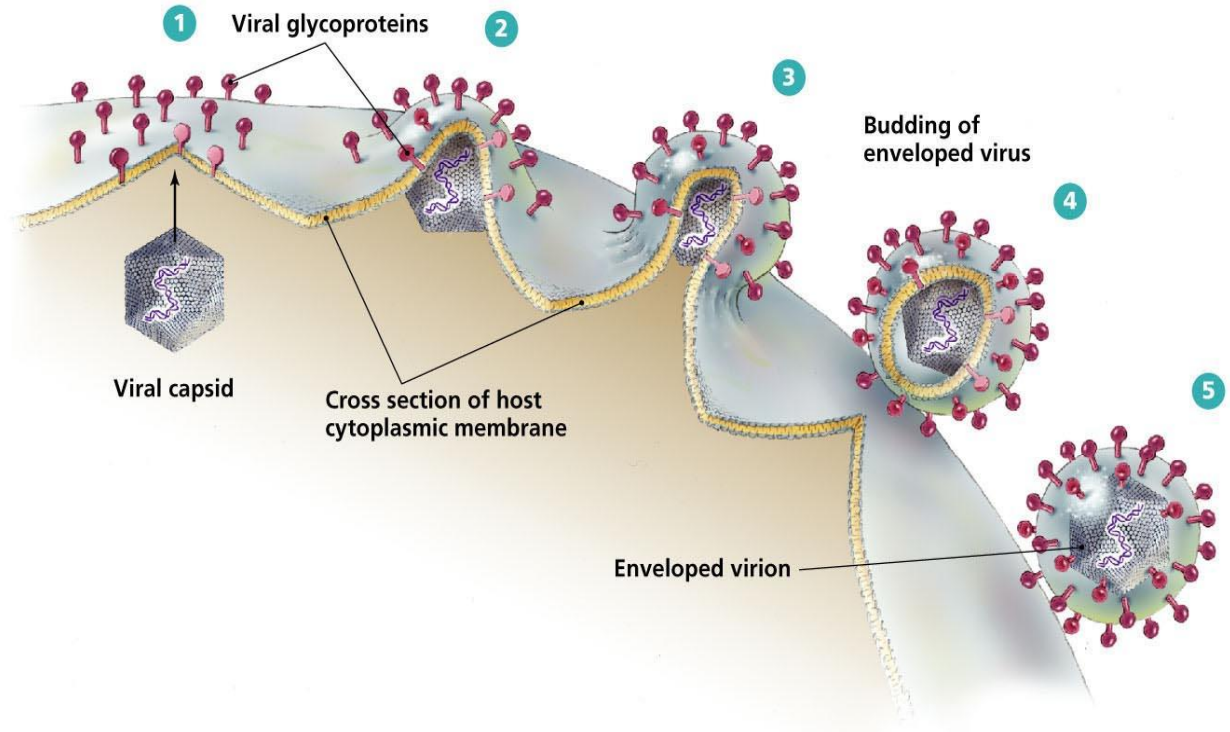


Inibizione della sintesi di DNA cellulare in cellule L infettate con virus dell'aborto equino (un herpesvirus) in presenza di ^{3}H-timidina.

EFFETTI DELLE INFEZIONI VIRALI SULLA CELLULA OSPITE

1. Alterazioni nella sintesi delle macromolecole cellulari
2. Alterazione della membrana cellulare
3. Alterazioni morfologiche
4. Alterazione del controllo della proliferazione cellulare

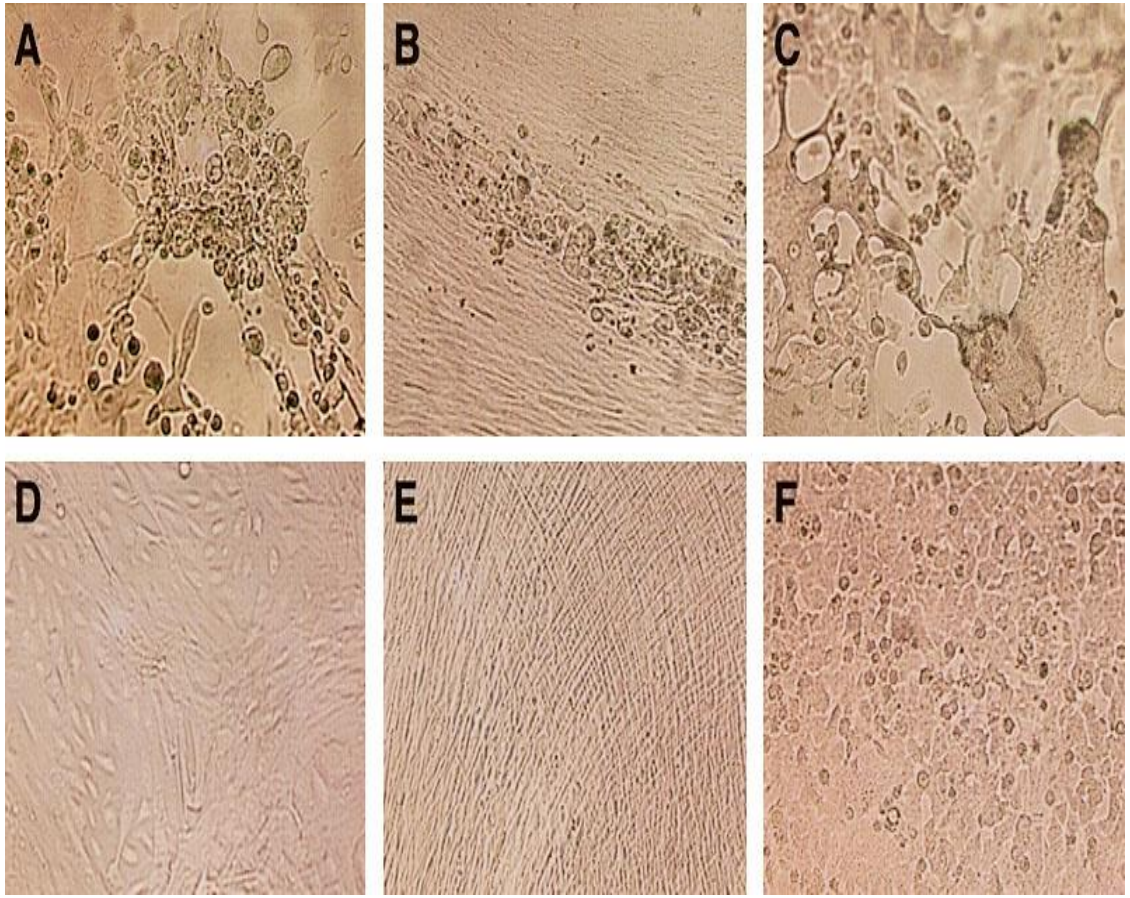




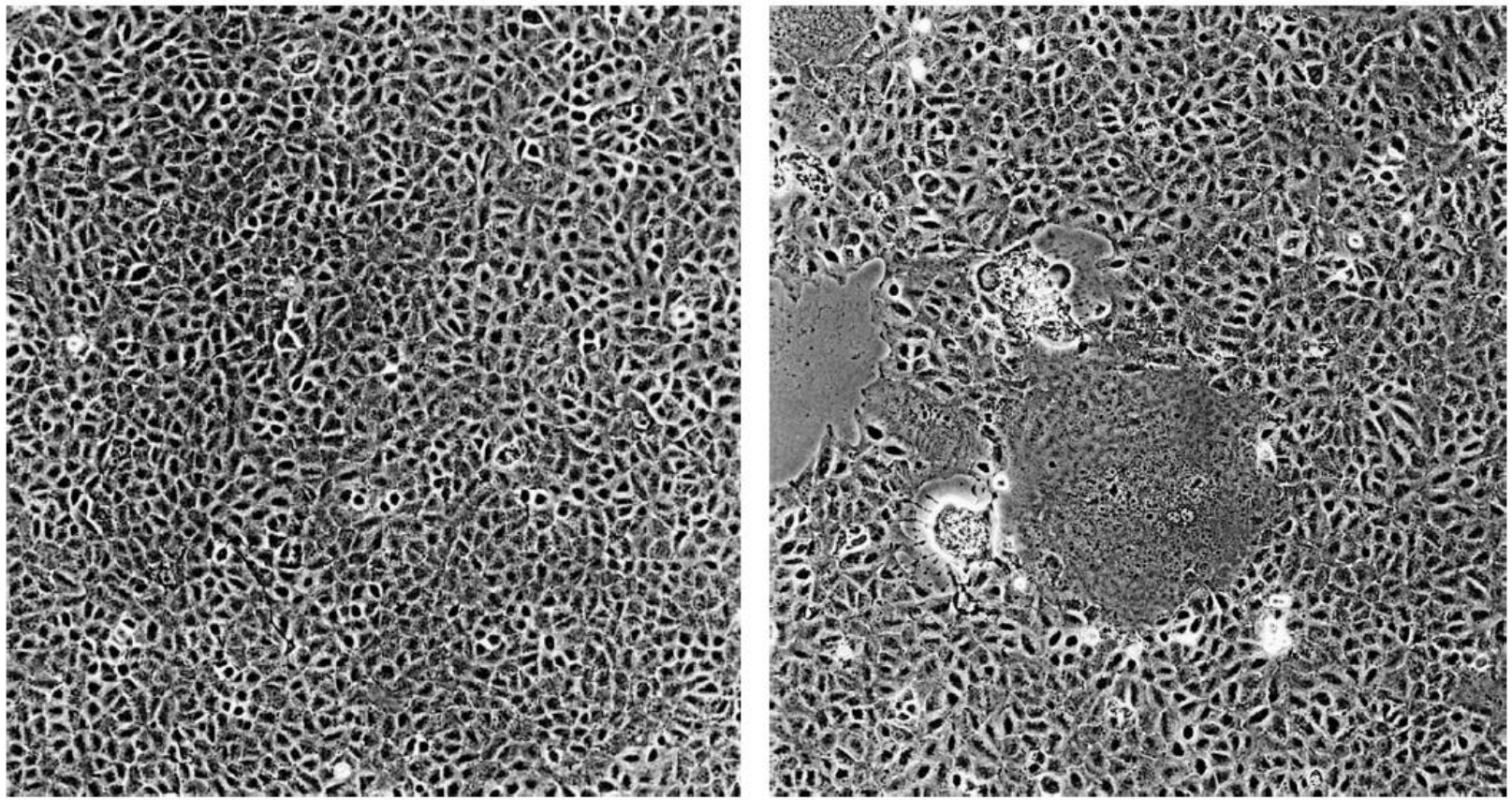
EFFETTI DELLE INFEZIONI VIRALI SULLA CELLULA OSPITE

1. Alterazioni nella sintesi delle macromolecole cellulari
2. Alterazione della membrana cellulare
3. Alterazioni morfologiche
4. Alterazione del controllo della proliferazione cellulare

The destructive consequences of virus infection for the cell are termed **cytopathic effect**, a term most commonly used to describe the consequences of infection in cultured cells

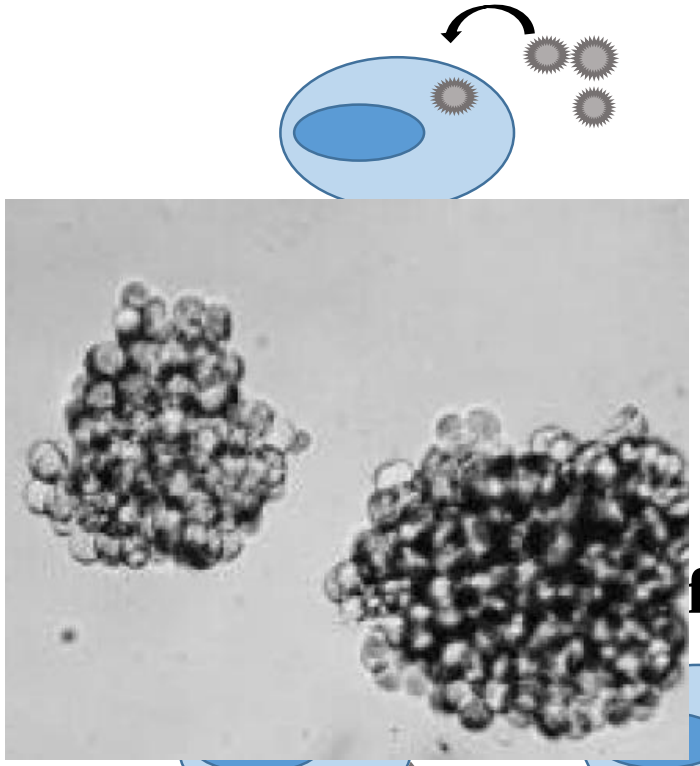


Cytopathic effect caused by viruses growing in cell culture. Herpes simplex virus growing in primary rabbit kidney cells (**A**); uninfected primary rabbit kidney cells (**D**). Cytomegalovirus growing in human embryonic lung fibroblast cells (**B**); uninfected human embryonic lung fibroblast cells (**E**). Respiratory syncytial virus growing in HEp-2 cells (**C**); uninfected HEp-2 cells (F).



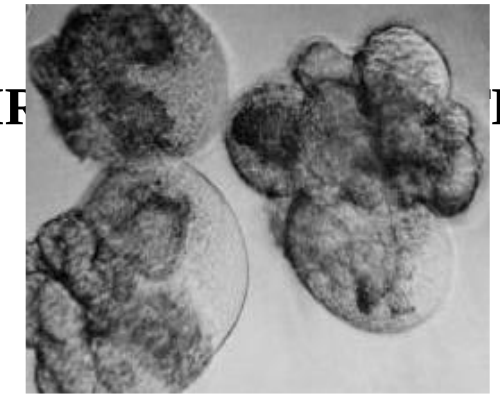
Virus-induced cytopathic effects (CPE). Phase-contrast photomicrographs are shown. *Left:* Uninfected A549 cells, a human lung carcinoma cell line. *Right:* A549 cells infected with measles virus. Measles fuses cells, causing formation of syncytia.

FORMATION OF FUSED MULTINUCLEATED CELLS



1. INFECTION

2. PRODUCTION OF VIR EINS



fected infected

3. FUSION OF CELLS

4. MULTINUCLEATED SYNCYTIAL CELL

RISPOSTA CELLULARE ALL'INFEZIONE

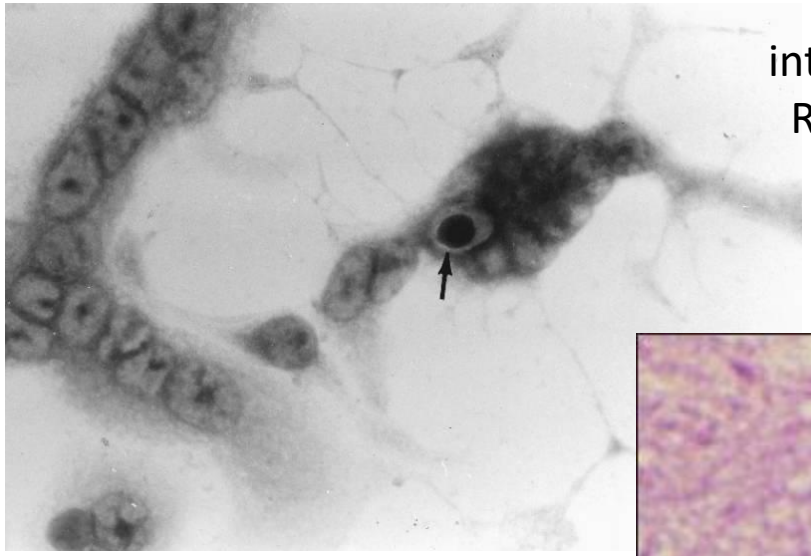
Virus	Tipo di cellule	Risposta cellulare	Inclusioni
Adenovirus	HeLa	Arrotondamento e aggregazione cellulare	Nucleari
	Embrione di ratto	Trasformazione	Nucleari
Herpesvirus (Herpes simplex)	HeLa	Policariociti (alcuni ceppi), arrotondamento cellulare	Nucleari
Poxvirus (vaiolo)	HeLa	Lento arrotondamento, foci iperplastici	Citoplasmatiche
Picornavirus (Poliovirus)	Rene di scimmia	Lisi cellulare	Nessuna
Orthomixovirus (virus influenzali)	Rene di scimmia	Lento arrotondamento	Nessuna
Paramixovirus (virus parainfluenzali)	Rene di scimmia	Fusione delle membrane cellulari, formazione di sincizi	Citoplasmatiche
Coronavirus	Diploidi umane	Minima, raramente sincizi	Nessuna
Togavirus (virus dell'encefalite equina dell'est)	L di topo	Lisi cellulare	Nessuna
Virus della rosolia	Amnios umano	Lento ingrossamento e arrotondamento	Citoplasmatiche
Reovirus	Rene di scimmia	Ingrossamento e formazione di vacuoli	Citoplasmatiche
Virus della rabbia	Rene di hamster	Di solito nessuna	Citoplasmatiche

EFFETTO DELLA REPLICAZIONE SULLA CELLULA OSPITE

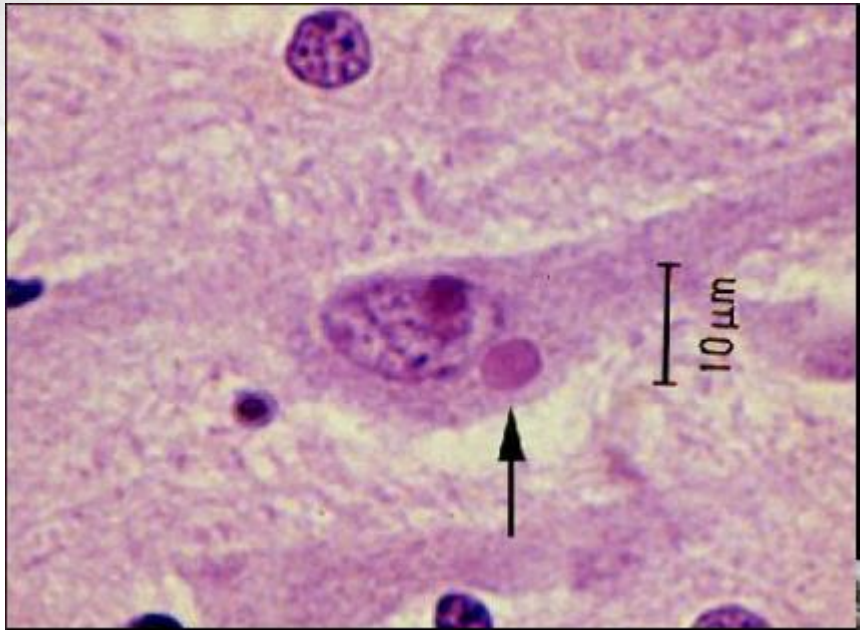
CORPI DI INCLUSIONE CAUSATI DA ALCUNI VIRUS

	Localizzazione nella cellula		
	Nucleo	Citoplasma	
Herpes simplex	+	-	Corpi di Cowdry
Citomegalovirus	+	+	
Virus della rabbia	-	+	Corpi del Negri
Virus del vaiolo	-	+	Corpi del Guarnieri
Adenovirus	+	-	
Morbillo	+	+	
Papovavirus	+	-	
Virus della febbre gialla	-	+	Corpi del Torres

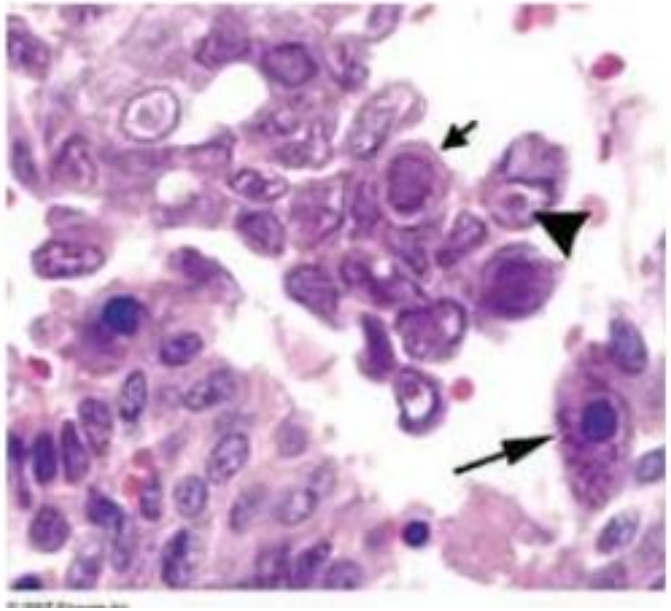
FORMAZIONI DI INCLUSIONI



Inclusioni intracitoplasmatiche da Rabdovirus (corpi del Negri)



Inclusioni intranucleari da HSV-1 (corpi di Cowdry)



Le inclusioni si localizzano nel nucleo o nel citoplasma. Si tratta di masse amorfe costituite da ammassi di proteine virali non montate e/o materiale cellulare alterato

EFFETTI DELLE INFEZIONI VIRALI SULLA CELLULA OSPITE

1. Alterazioni nella sintesi delle macromolecole cellulari
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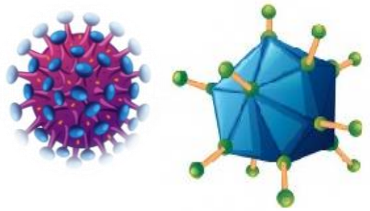
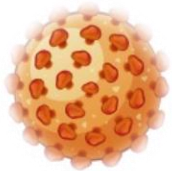
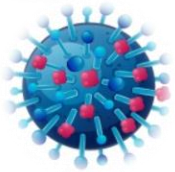






ALTERAZIONI DEL CONTROLLO DELLA PROLIFERAZIONE CELLULARE

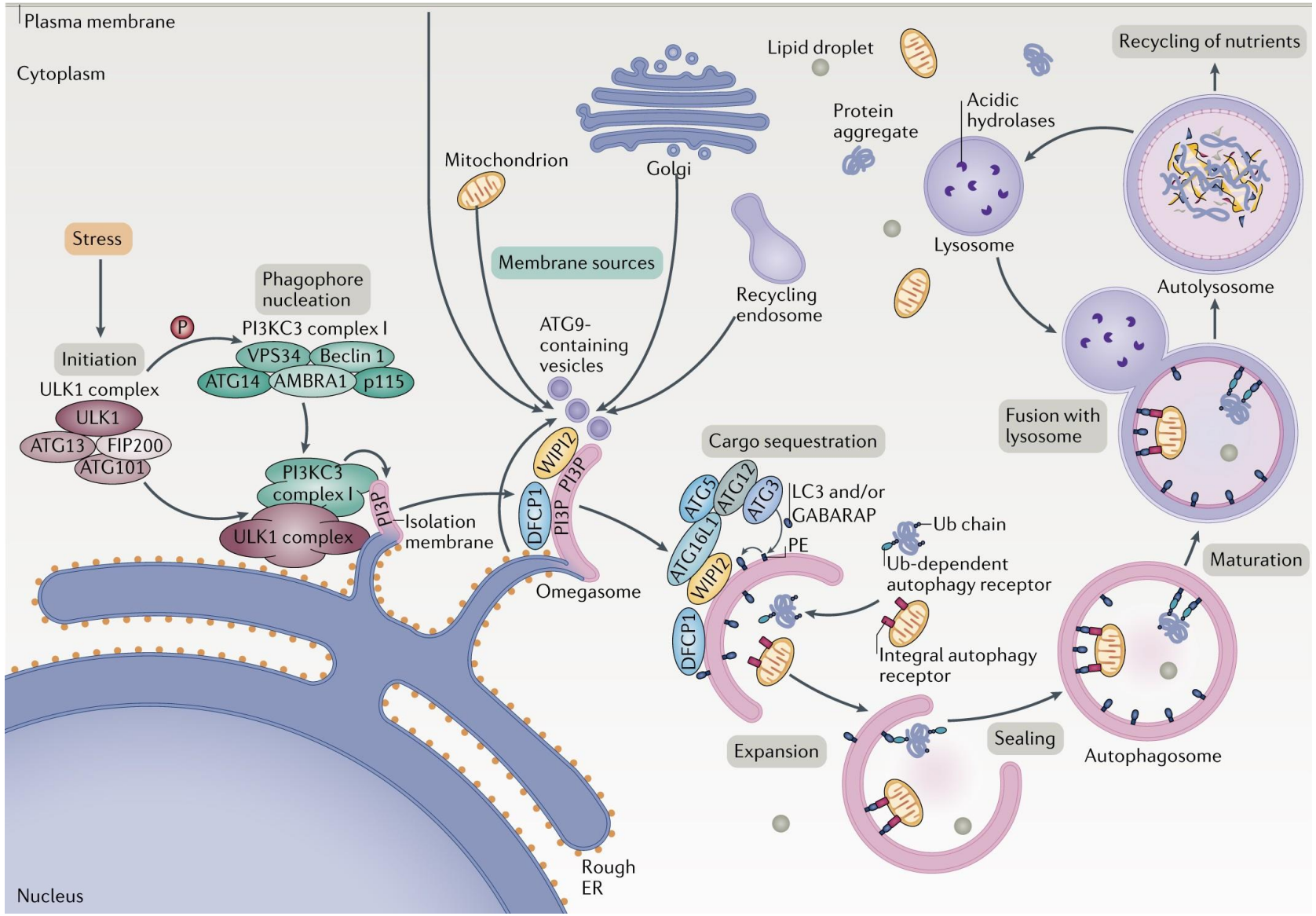
APOPTOSI

AUTOFAGIA

Tabella 37.3 Alcuni meccanismi usati dai virus per contrastare l'apoptosi.

Virus	Meccanismo di inibizione dell'apoptosi
Adenovirus	La proteina E1B-19K forma eterodimeri con varie proteine pro-apoptotiche della famiglia Bcl-2 (Bax, Bak, BNIP3, Bnip3L) stabilizzando la membrana mitocondriale, prevenendone la permeabilizzazione e di conseguenza bloccando il rilascio di una varietà di fattori attivanti le caspasi (citocromo c, AIF, apoptosoma) Le proteine E1B-55k e E4 ORF6 promuovono la degradazione di p53 e di conseguenza diminuiscono l'espressione di membri pro-apoptotici della famiglia Bcl-2
EBV	La proteina LMP-1 interagisce con proteine della famiglia Bcl-2 e up-regola proteine anti-apoptotiche cellulari come A20 e bfl-1. Il virus codifica anche 2 proteine omologhe a Bcl-2: una, detta BHRF-1, funziona in senso anti-apoptotico, l'altra interagisce con Bax e Bak e inibisce l'apoptosi
HHV-8	Codifica una proteina omologa a Bcl-2 che blocca l'apoptosi anche, ma non solo, formando eterodimeri con Bcl-2 L'antigene nucleare LNA-1 lega pRB/E2F e interagisce con p53
HPV	La proteina E6 promuove la degradazione di p53 attraverso il complesso E6-proteina ligasi AP

AUTOFAGIA



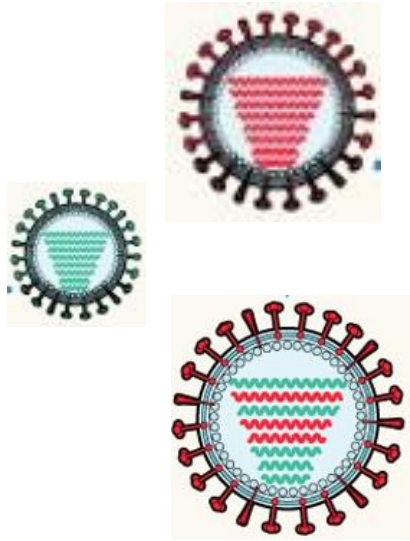
Nature Reviews Molecular Cell Biology ***2018***

Tabella 37.2 **Alcuni meccanismi usati dai virus per contrastare l'autofagia cellulare.**

Virus	Meccanismo di inibizione dell'autofagia	Effetto sull'interazione ospite-patogeno
Virus a DNA		
HSV-1	La proteina virale ICP34.5 inibisce il signaling PKR e lega direttamente la beclina 1 nei neuroni	Determina neurovirulenza
HHV-8	Le proteine virali Bcl-2-like legano direttamente la beclina 1 in molte linee cellulari	Sconosciuto
CMV	Sconosciuto, in fibroblasti primari	Sconosciuto
Virus a RNA		
HIV-1	Sono ridotti i livelli di beclina 1 in linfociti $CD4^+$ primari e in macrofagi della linea cellulare U937	Sconosciuto
SIV-1	L'infezione della microglia induce la produzione di molecole non note inibenti l'autofagia nei neuroni	Accumulo di aggregati proteici nei neuroni con potenziale contributo alla neurodegenerazione

Effetti della replicazione virale sulla cellula ospite

<u>Variabilità genetica dei virus</u>



GENERATION OF GENETIC DIVERSITY

MUTATION

RECOMBINATION

GENERATION OF GENETIC VARIABILITY

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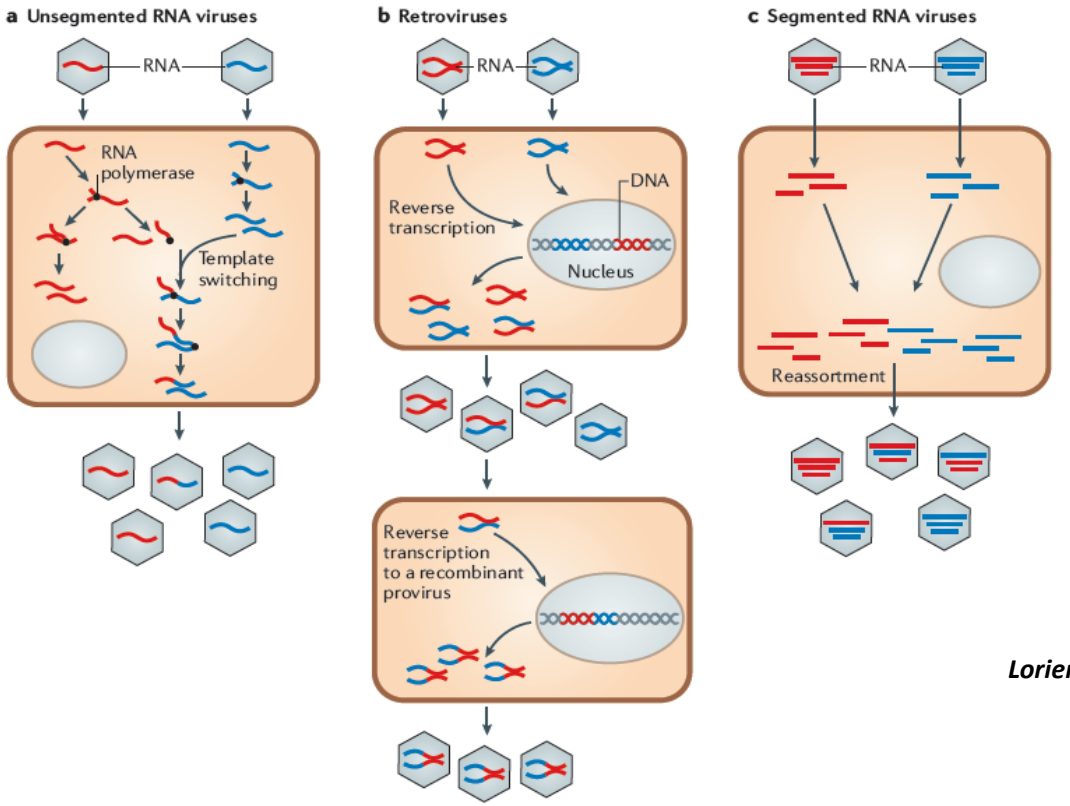
MUTATION

- Mutation refers to the molecular synthesis or modification of a descendant gene that differs from the parental gene because of deletion, insertion or mismatch
- It depends on polymerase fidelity
- It depends on generation time

1 mutation /1,000 - /10,000 bp for RNA viruses
1 mutation/1.000.000- 1.000.000.000 bp for DNA viruses

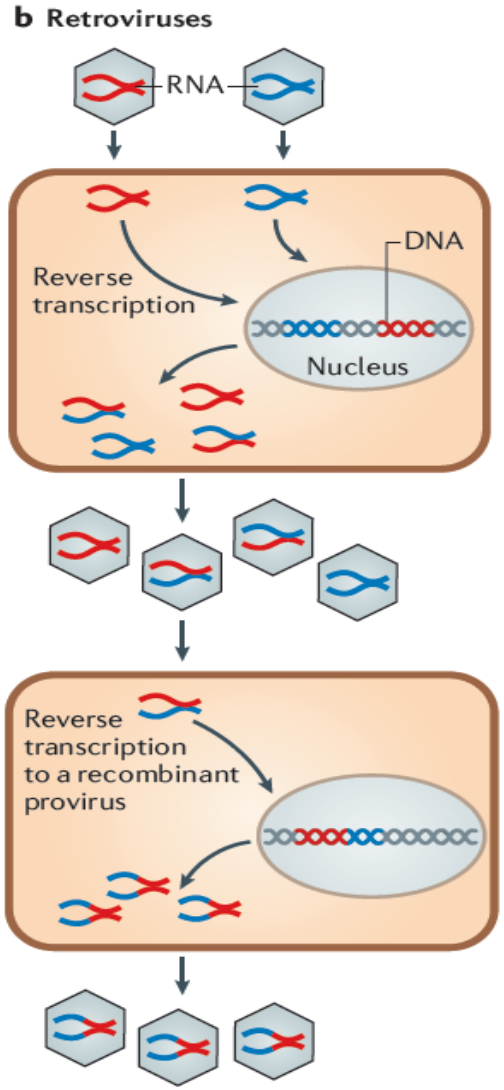
THE GENETIC VARIATION EXIBITED BY A SPECIFIC VIRUS DEPEND ON:

- ✘ The fidelity of its genome replication
- ✘ Frequency of co-infection
- ✘ Population size and structure (both host and virus)
- ✘ Mode of transmission
- ✘ Replication rate

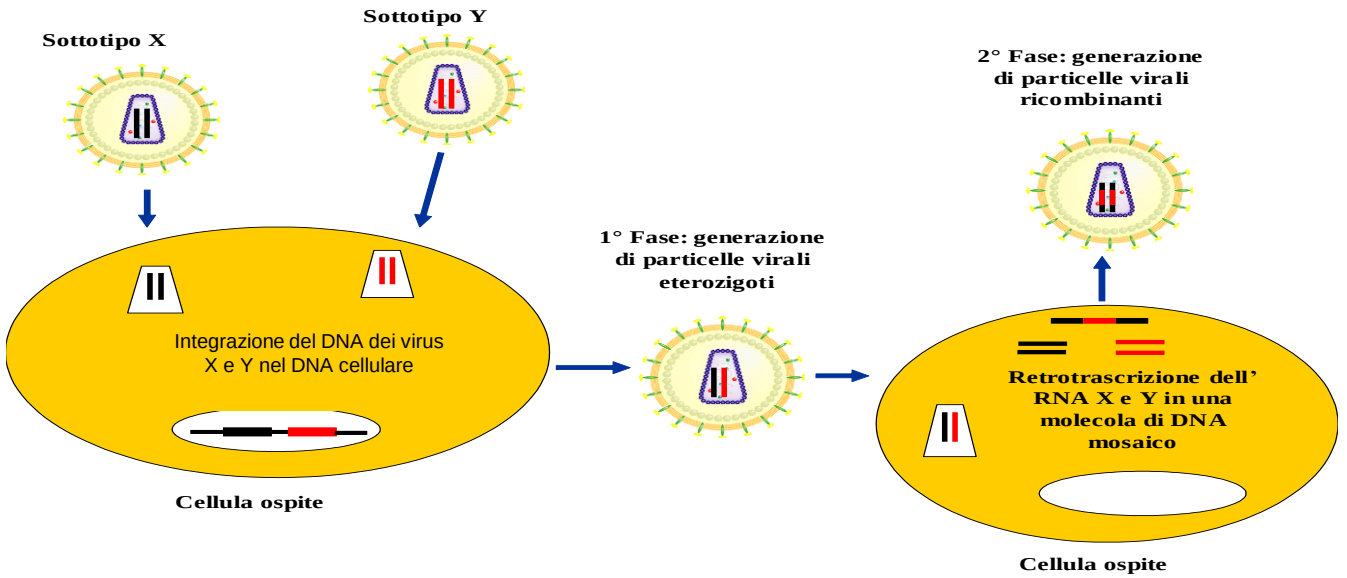


Loriere & Holmes

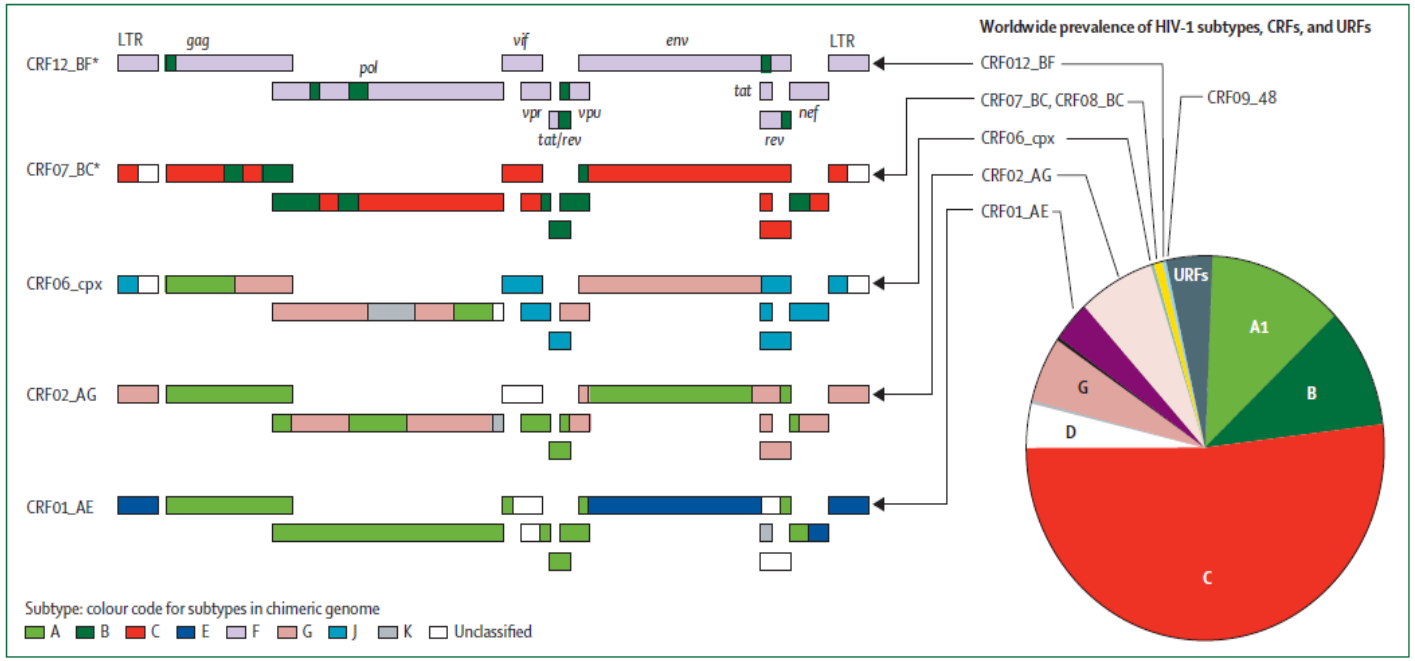
Figure 1 | **Generation of recombinant and reassortant RNA viruses. a** | Co-infection of a cell by genetically distinct viral strains can lead to the generation of recombinant viruses. This process can occur in both non-segmented viruses (as shown here) or within a segment of a segmented virus. **b** | Co-infection of a cell by genetically distinct strains of a retrovirus can lead to the generation of 'heterozygous' virus particles, after which a template-switching event can lead to a recombinant provirus. **c** | Co-infection of a cell by genetically distinct strains of a segmented virus can generate different combinations of reassortant progeny.


b Retroviruses
RNA
DNA
Reverse transcription
Nucleus
Reverse transcription to a recombinant provirus

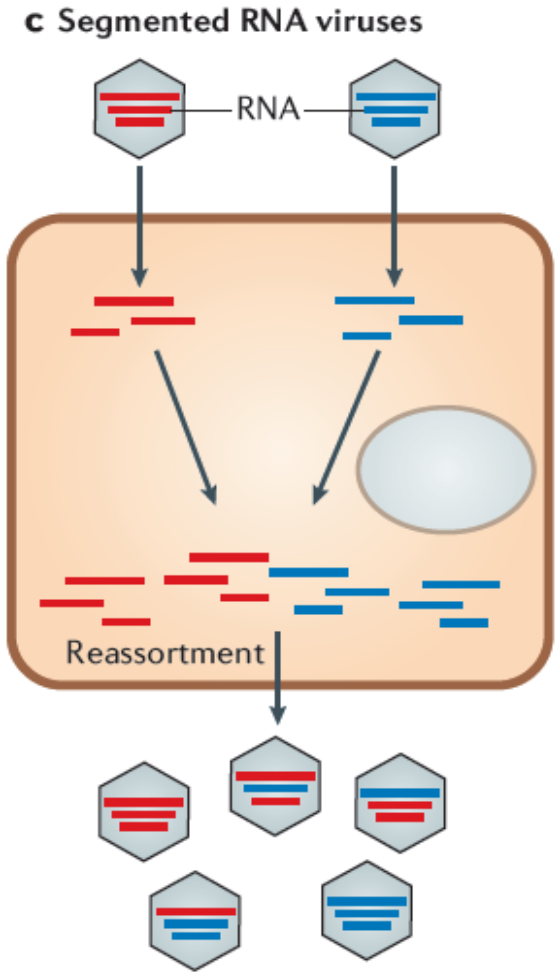
Meccanismi coinvolti nella generazione delle forme ricombinanti



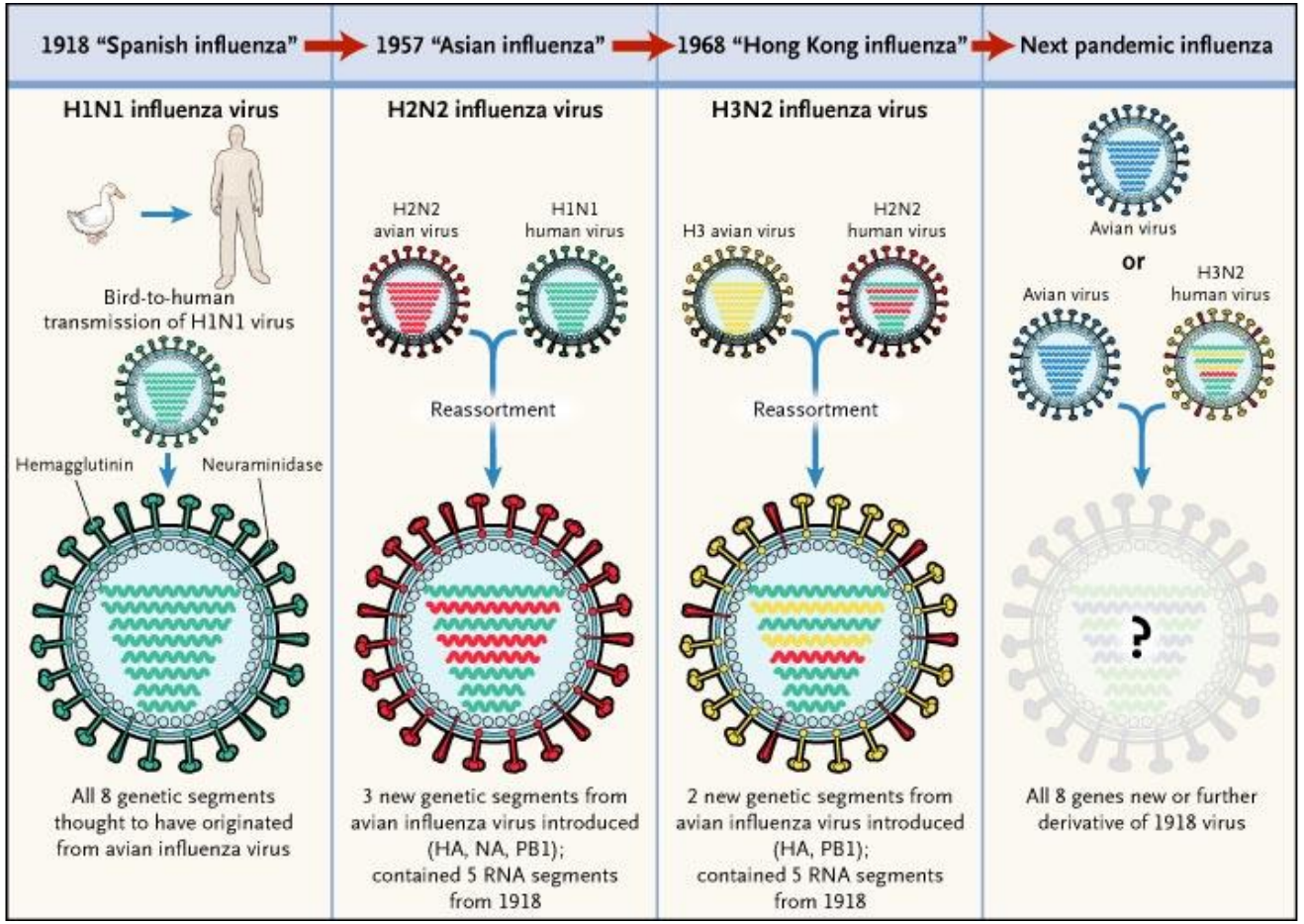
Mosaic structure of the most dominant circulating recombinant forms in the HIV pandemic, and the worldwide prevalence of HIV-1 subtypes, circulating recombinant forms, and



Reassortant RNA viruses



Mechanisms by which pandemic influenza originates



From Belshe RB, NEJM 2005

It is imperative to point out that the mere presence of genetic and phenotypic variation is not sufficient to direct or predict the evolutionary trajectory of any organism

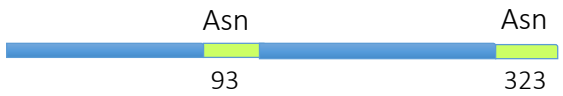
Evolution may be driven by SELECTION

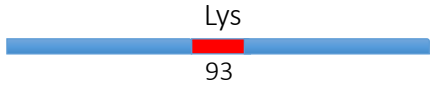
ADAPTATION refers to a character that arise via natural selection and thus confers on its bearer the ability to succed genetically in a specific enviroment.

ADAPTATION

CPV

FPV





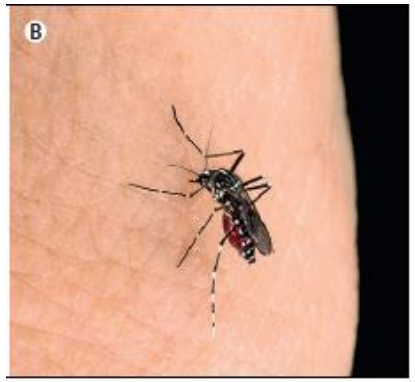
VP2

These two aa change represent a recently acquired adaptation that allowed replication in a new susceptible host species and subsequently enabled the rapid spread of CPV into the world population of canines

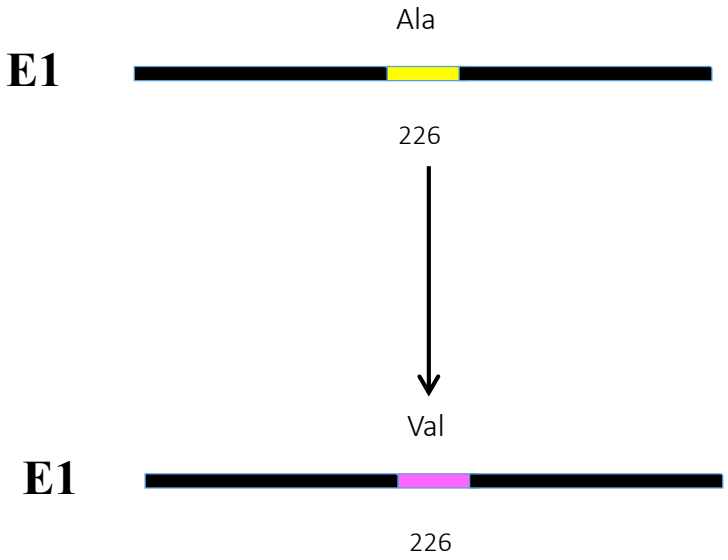
CHIKV is endemic in Africa
A. aegypti is the classical vector for CHIKV

Why did* CHIKV adopt *A.albopictus as its host?

A.albopictus is a good vector



How was CHIKV able to efficiently adapt to *A. albopictus*?

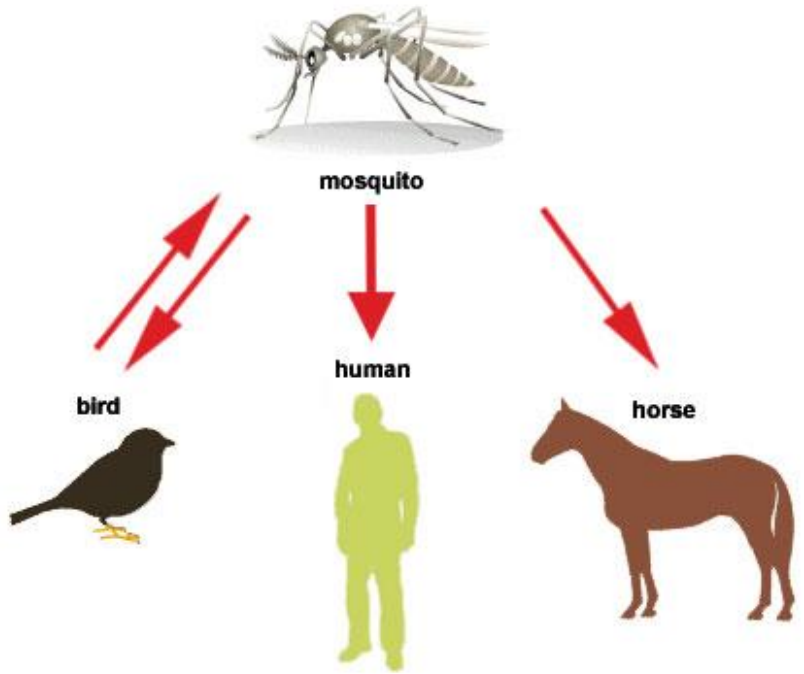


Amino acid residue at position 226 regulates cholesterol dependency during the virus-host cell fusion process

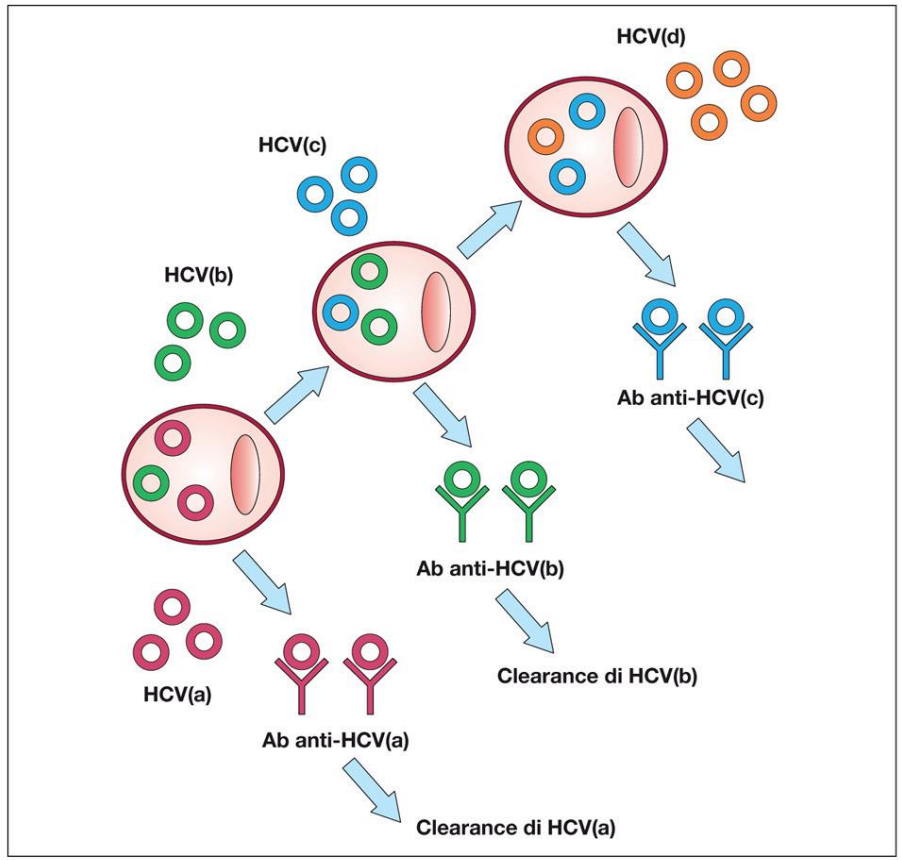
STABILIZING SELECTION

May results in long period of little to no evolutionary change

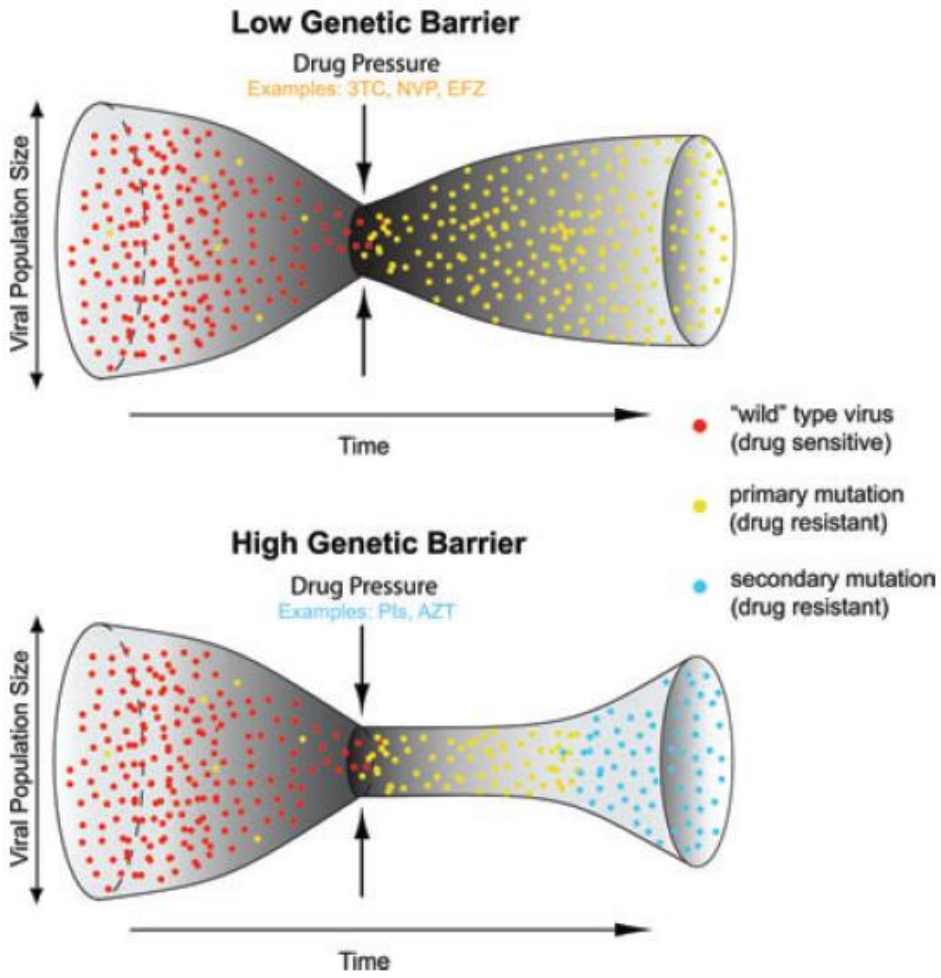
Arthropod-transmitted equine encephalomyelitis viruses (EEV)



Meccanismo di evasione virale dalla risposta immunitaria



G. Antonelli, M. Clementi, G. Pozzi, G.M.Rossolini **Principi di Microbiologia Medica**



Skar et al. Ann.N.Y. Acad Sci 2011

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- The widespread distribution of viruses in the world is a consequence of the highly efficient dissemination of the viruses through different routes of transmission.

- Several characteristics of viral infection, such as long-term persistence, low frequency of symptoms, a long incubation period, virus resistant in the external enviroments, confer adaptive advantages to the spread of viruses and contribute to the maintenance of high incidence rates in the world