Microbiology

Subject :

Lec no : 24

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وقل رب زدني علما

Viral life cycle

Virology Lecture 2

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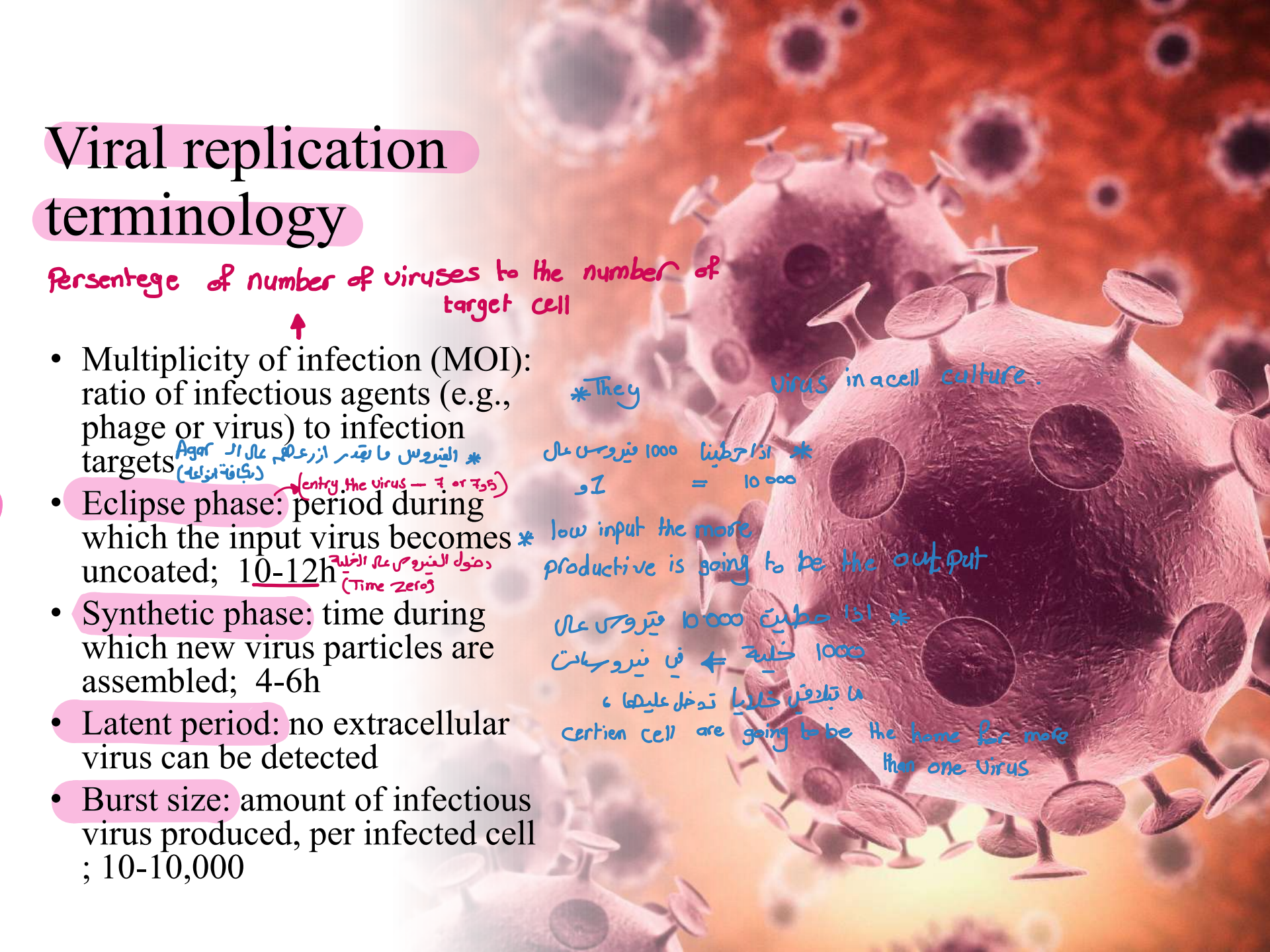
Viral replication terminology

Persentege of number of viruses to the number of target cell

- Multiplicity of infection (MOI): ratio of infectious agents (e.g., phage or virus) to infection targets
- Eclipse phase: period during which the input virus becomes uncoated; 10-12h
- Synthetic phase: time during which new virus particles are assembled; 4-6h
- Latent period: no extracellular virus can be detected
- Burst size: amount of infectious virus produced, per infected cell ; 10-10,000



host cell (replication) → بتصير بالنواة

need of DNA virus for their replication enzyme is less than RNA virus

all DNA replicate in nucleus except → pox virus (لأنها كبيرة)

" RNA " " cytoplasm " → HIV and Infelonza

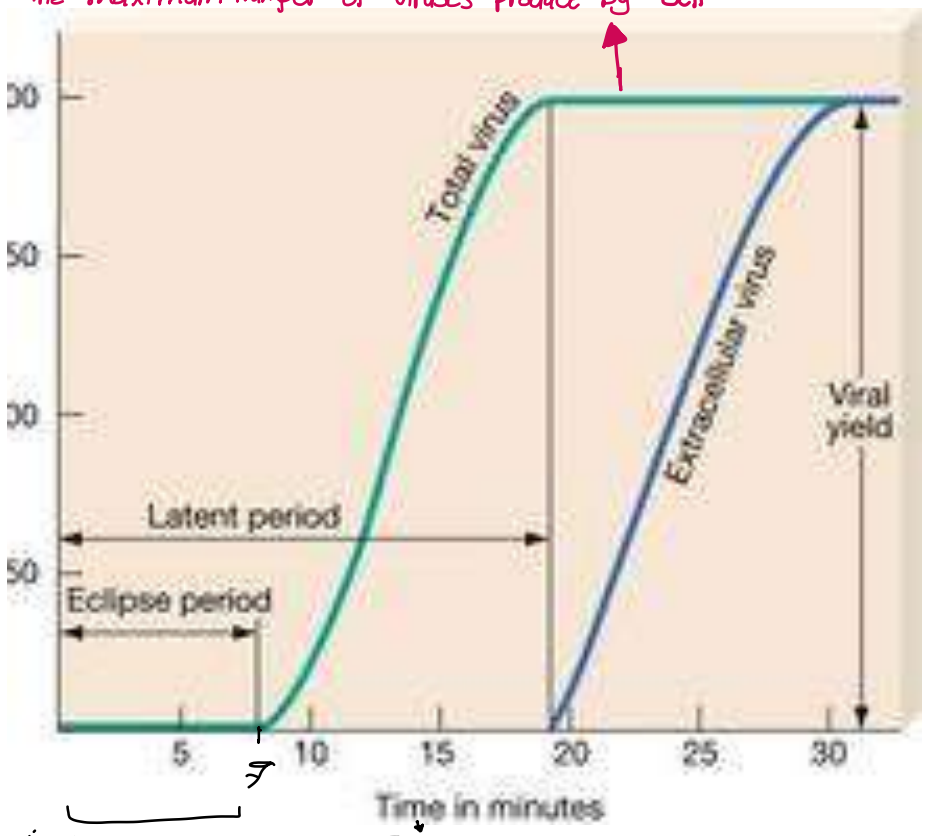
One-step virus growth curve

latent period → also start with entry the virus of target cell but it include five step of DNA replication

protein → structural (capsid, glycoprotein)
→ Non " (enzyme)

نبقدم الـ nonstructural عن الـ structural ليش!

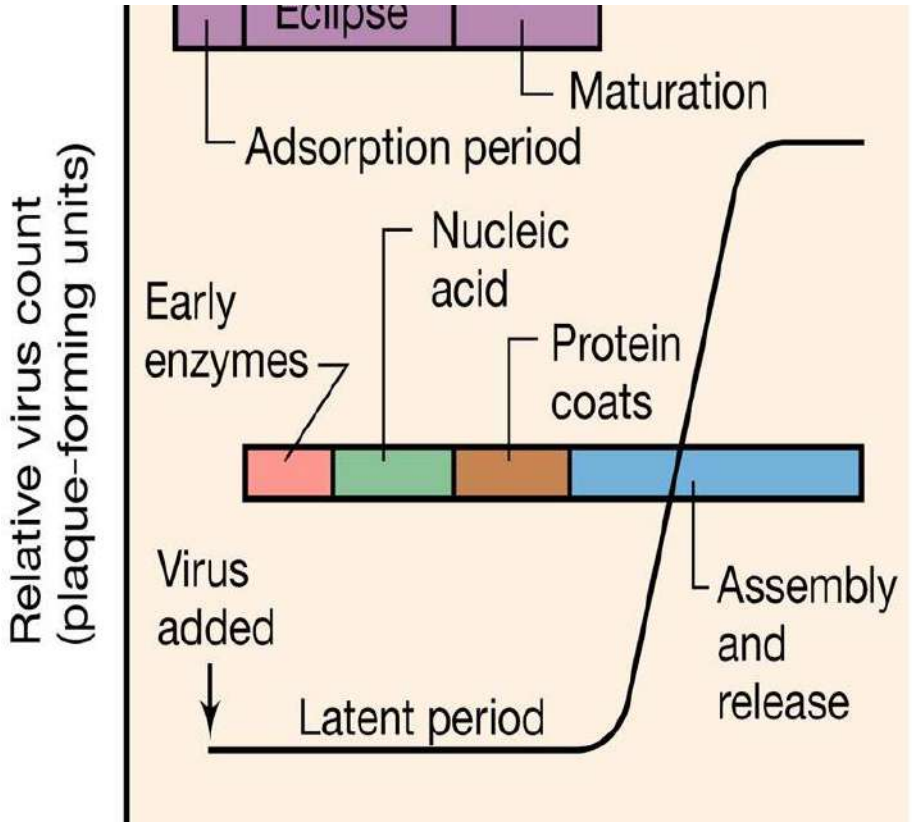
The maximum number of viruses produce by cell



Time

مافي فيروسات صحوفي بكون تفكك . uncoated →

coated حواليها genitic material بدخل الفيروس على الخلية ك capsid نفسها بدخل بشيل الـ (capsid)



من تعريفي
بردجس

* لتوضيح الافكار

Viral replication terminology

- **Multiplicity of infection (MOI): ratio of infectious agents (e.g. phage or virus) to infection targets**

ثاني مصطلح هو ال MOI و اللي يعني فيه النسبة بين ال
infectious agent اللي سبب العدوى
ل ال infectious target اللي صار عليه العدوى

ممكن يجيلك سؤال هون يعطيك ال MOI
و يعطيك عدد الخلايا و يطلب الفايروسات او العكس
موضوعها سهل بس حط MOI = agents / target و بتنحل عادي

بما اني بقسم الفيروسات ع الخلايا المصابة
لو حكالك انه ال MOI = 10
هذا معناه لكل 100 خلية في 1000 فيروس
لو قلنا انه ال MOI = 0.1
يعني لكل 1000 خلية في 100 فيروس

- **Eclipse phase: period during which the input virus becomes uncoated; 10-12h**

ال eclipse phase ثالث مصطلح
الفترة من اول ما الفايروس يدخل ال genetic material
لل host cell لحد قبل ما يتكون اول فايروس جوا الخلية
فهل في فايروس ممكن نلاقيه بهاي ال phase ؟؟
الجواب لا لانه الفايروس لما يدخل مادته الوراثية بتحلل و بعدها بتكون باقي النسخ

- **Synthetic phase: time during which new virus particles are synthesized ; 4-6h**

المصطلح الرابع ال synthetic phase
في عنا شغلتين بيصروا بنفس الوقت
اول اشي genetic material لل duplication
ثاني اشي formation of new viral proteins
اللي راح نستخدمهم ل assembly proscess

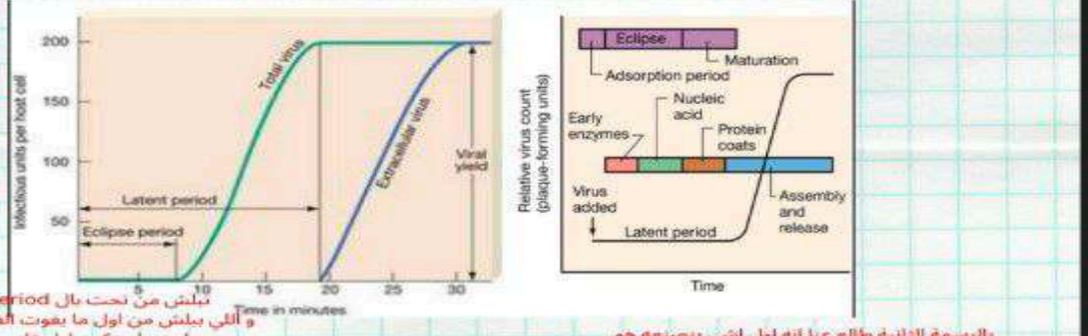
- **Latent period: no extracellular virus can be detected**

خامس مصطلح ال latent period
و اللي هي الفترة اللي بتبلش من اول ما يفوت عندي الفيروس للخلية لحد ما يتكون عندي فايروسات جديدة بس لسا ما صار release للفيروسات الجديدة

- **Burst size: amount of infectious virus produced, per infected cell ; 10-10,000**

اخر مصطلح هو ال burst size و اللي معناه قديش فيروس راح يتصنع من الخلية
و هذا الحكي بعتمد على نوع الفايروس و نوع الخلية يعني
في خلايا بتتحمل 10 فيروسات و خلايا بتتحمل 10000 فيروس

One-step virus growth curve



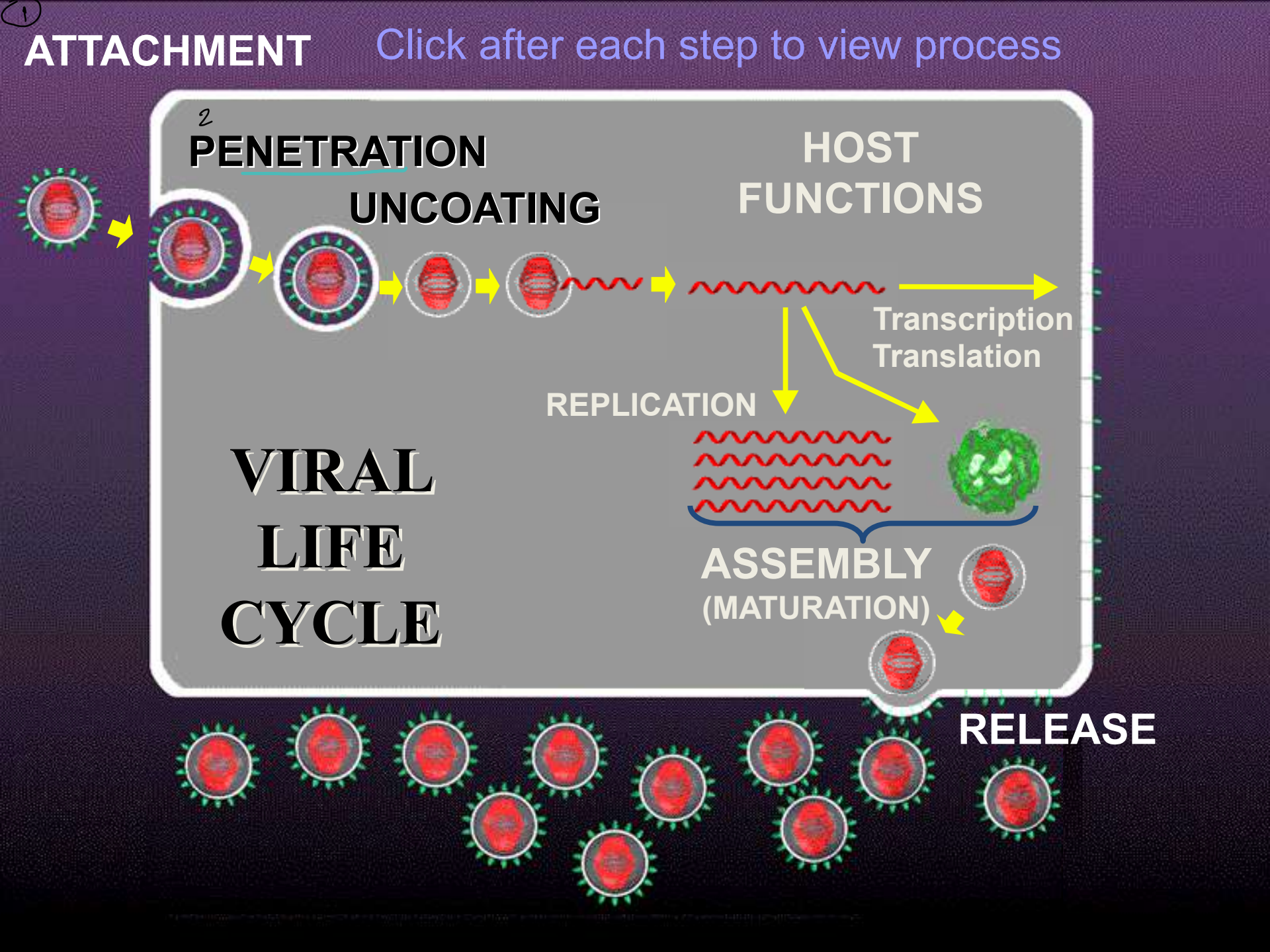
تبلش من تحت بال eclipse period
و اللي بتبلش من اول ما يفوت الفايروس ع ال cell
لحد ما يتكون اول فايروس جديد
و حكينا انه بهاي الفترة ما يكون في فايروس جوا الخلية و بقدروا تلاحظوا هالاشي ع الرسم البياني انه المحور العامودي بتكون قيمه صفر بفترة ال eclipse phase
بالنسبة لل latent period
جزء منها هو ال eclipse period و ال synthetic period
و بهاي الفترة بنقدر نلاقي الفيروس جوا الخلايا مش برا

بالرسمة الثانية طالع عنا انه اول اشي بتصنعه هو early protein synthesis
و اللي همه ال enzymes مثل DNA polymers
الانزيمات هاي راح تصنع ثاني اشي و هو ال nucleic acid
بعدها بتنتج عنا ال structural proteins زي glycoprotein و capsid

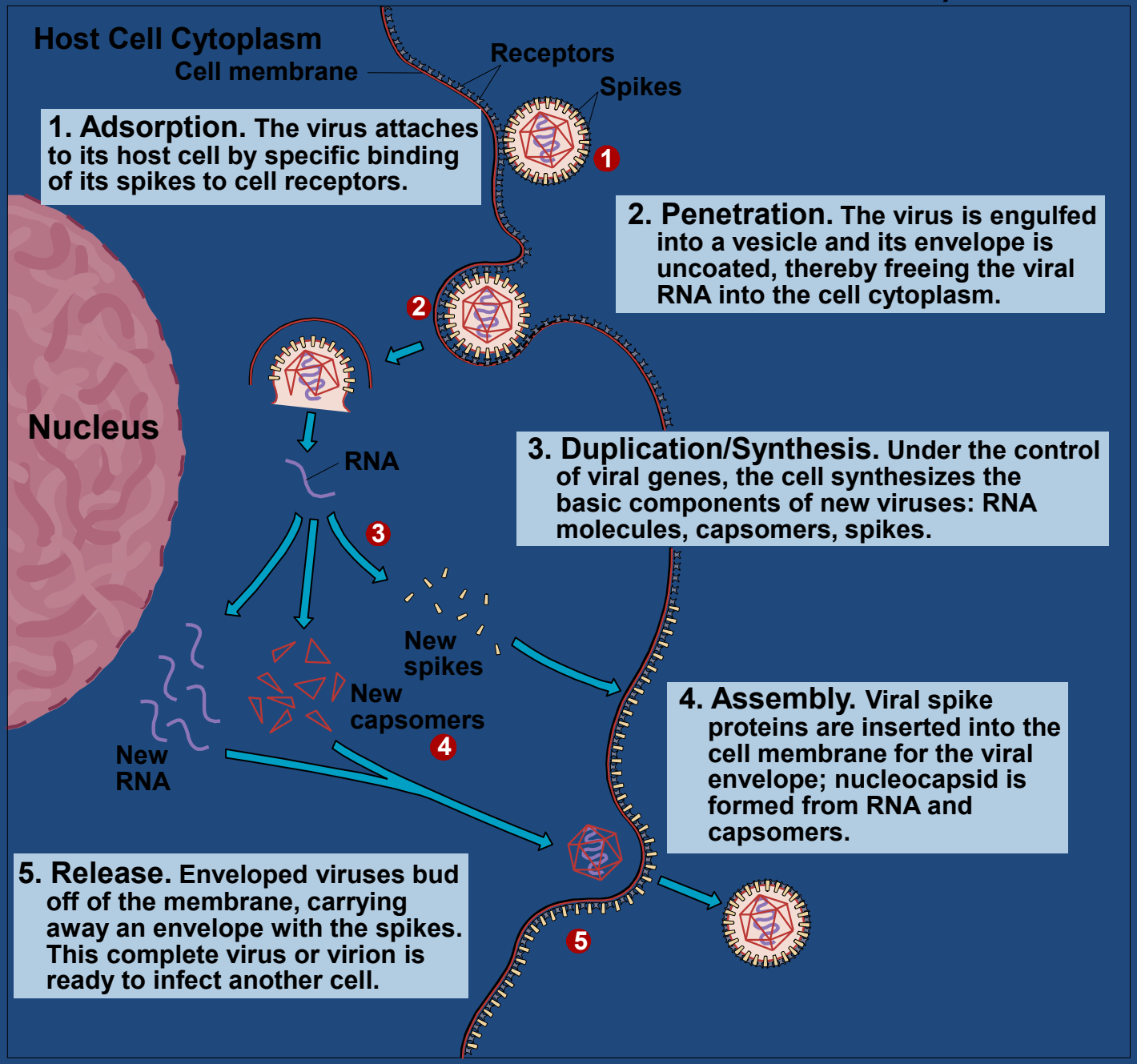
The Replication Cycle

- Virus replication can be divided into eight arbitrary stages.
- Regardless of their hosts, all viruses must undergo each of these stages in some form to complete their replication cycle. all virus go through all these steps in order to produce new viruse
- Not all the steps described here are detectable as distinct stages for all viruses.

stages الـ
متداخلة
مش ضروري اخلص
واحد بعدين اخش ٣
وهكذا


ATTACHMENT
Click after each step to view process
2
PENETRATION
UNCOATING
HOST
FUNCTIONS
Transcription
Translation
REPLICATION
VIRAL
LIFE
CYCLE
ASSEMBLY
(MATURATION)
RELEASE

Life cycle – Animal virus



بين الـ receptor تاع الخلية
مع الـ glycoprotein تاع الفيروس

Attachment

لازم يصير عنا
Attachment

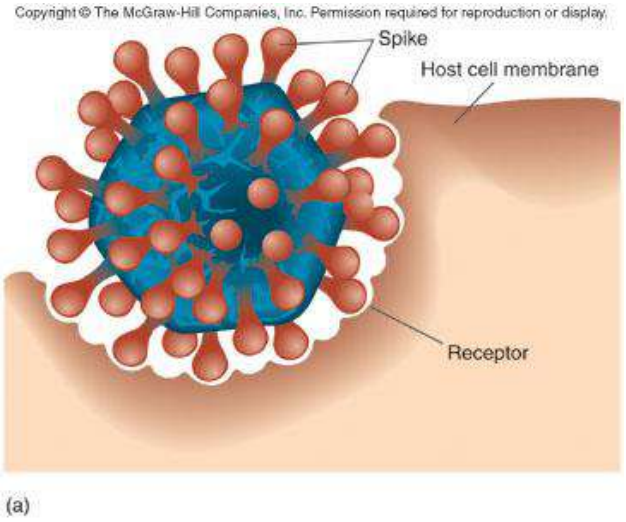
- Virus attachment consists of specific binding of a virus-attachment protein (or 'antireceptor') to a cellular receptor molecule.
- Target receptor molecules on cell surfaces may be proteins (usually glycoproteins), or the carbohydrate residues present on glycoproteins or glycolipids.
- Some complex viruses (e.g. poxviruses, herpesviruses) use more than one receptor and have alternative routes of uptake into cells.

Enveloped = Lipid bilayer

Adsorption

glycoprotein و spike

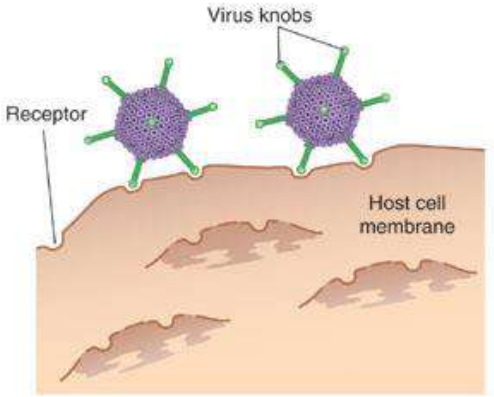
Enveloped
With prominent spikes



groove
Surface protein ← مثل adenovirus

Naked; with capsid spikes

* Can resist and tolerat enviromental condetion (envelop اكثر من ال)



- Host range: the collection of hosts that an organism can utilize as a partner
- Cellular (tissue) tropism: the cells and tissues of a host which support growth of a particular virus

Adsorption

هذا enveloped virus عليه عال surface تاعته spikes اللي بتعمل attachment
للفيروس مع ال receptors و بتفوته جوا الخلية

كم نوع ال receptors اللي بنحتاجها مشان الفيروس يفوت ع الخلية ؟؟
غالبا نوع واحد بكفي مثلا ال influenza بس بده نوع receptors اسمه sialic acid receptors
لكن بعض الفيروسات بدها اكثر من مثل ال HIV و ال hepatitis B بدهم اكثر من نوع مشان
يقدروا يعملوا ارتباط و يدخلوا جوا الخلية
كمان سؤال
how many glycoprotein-receptor interaction
we need at the same time in order to initiate virus entry in the target cell ??

يعني بتعبير ثاني هل لو ربطت receptor واحد مع glycoprotein واحد
راح يدخل الفيروس ع الخلية ؟

غالبا لا و ع الاقل مشان نقدر نحفز دخول الفيروس ع الخلية لازم يكون عنا اكثر من ربطة بين
ال receptor و ال glycoprotein بنفس الوقت
مثلا ال HIV بده ع الاقل 3 ل5 glycoprotein-receptor interactions at the same time

kes

ال naked ما عندهم spikes لانه ما عندهم envelope اصلا
لكن عندهم اما projections (اللي اسمهم بالرسمة virus knobs) او grooves
اللي همه تجاويف برضو بعملوا attachment ل receptors على ال cell

من تفريغ
برجس

TABLE 6–6. Examples of Viral Receptors

Virus	Target Cell	Receptor*
Epstein-Barr virus	B cell	C3d complement receptor CR2 (CD21)
Human immunodeficiency virus	Helper T cell	CD4 molecule and chemokine co-receptor
Rhinovirus	Epithelial cells	ICAM-1 (immunoglobulin superfamily protein)
Poliovirus	Epithelial cells	Immunoglobulin superfamily protein
Herpes simplex virus	Many cells	Immunoglobulin superfamily protein
Rabies virus	Neuron	Acetylcholine receptor
Influenza A virus	Epithelial cells	Sialic acid
B19 parvovirus	Erythroid precursors	Erythrocyte P antigen (globoside)

*Other receptors for these viruses may also exist.
ICAM-1 = Intercellular adhesion molecule.

Coreceptor: CCR5
CRCX4

TABLE 6–5. Examples of Viral Attachment Proteins

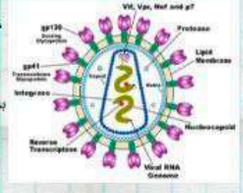
Virus Family	Virus	VAP
Picornaviridae	Rhinovirus	VP1-VP2-VP3 complex
Adenoviridae	Adenovirus	Fiber protein
Reoviridae	Reovirus	σ-1
	Rotavirus	VP7
Togaviridae	Semliki Forest virus	E1-E2-E3 complex
Rhabdoviridae	Rabies virus	G Protein
Orthomyxoviridae	Influenza A virus	HA
Paramyxoviridae	Measles virus	HA
Herpesviridae	Epstein-Barr virus	gp350 and gp220
Retroviridae	Murine leukemia virus	gp70
	Human immunodeficiency virus	gp120

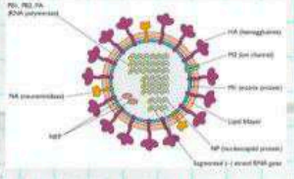
gp = glycoprotein; VAP = viral attachment proteins. HA: Hemagglutinine

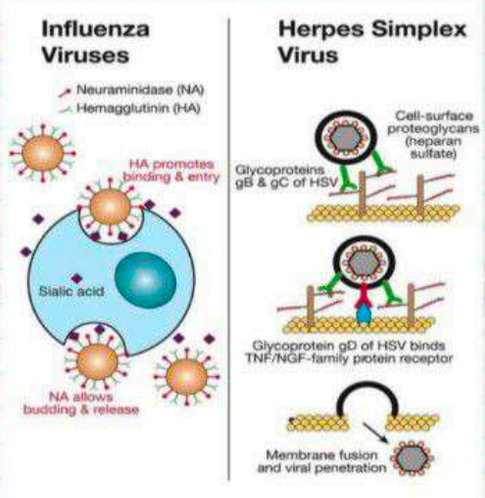
ال glycoprotein ممكن يتكون من one unit و ممكن يتكون من multiple units
احد الامثلة عنا ال HIV اللي بتكون من gp160 و اللي بنقسم ل outer unit gp120 و transmembrane unit gp 41
برضو عنا ال influenza A و Measles بكون البروتين تاعهم HA (hemagglutinin)

هذول الصورتين انا ضفتهم مشان نشوف كيف ال HIV بتكون من 2 units اللي همه gp120 and gp41

بينما ال influenza يكون عليه ال HA برضو عليه نوع تاني اسم هال NA لكن اغلب الاعتماد بكون ع ال HA







How does an animal virus infect its host? Examples of Animal Virus Entry

- **Host range: the collection of hosts that an organism can utilize as a partner**

المقصود فيها عدد ال species يلي يقدر الفيروس يعمللها infection مثالً عنا
فيروسات تكون قادرة تعمل عدوى للانسان والحيوانات والنباتات مثال
influenza can infect humans birds and pigs

- **Cellular (tissue) tropism: the cells and tissues of a host which support growth of a particular virus**

عدد الانسجة و الخلايا اللي ممكن يصرلها growth لنوع فيروس

مثل ال influenza virus غالبا بتسبب عدوى بال upper respiratory tract infection
او مثلا ال hepatitis بتعمل infection for liver cells

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*Other receptors for these viruses may also exist. Coreceptor: CCR5
ICAM-1 = Intercellular adhesion molecule. CXCR4

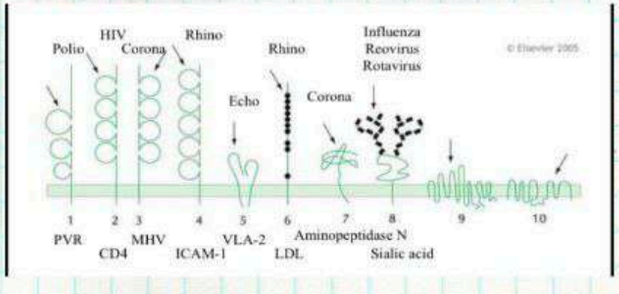
كل نوع من الفيروسات يرتبط على نوع receptor مثلا
influenza virus the glycoprotein is the hemagglutinin protein witch attaching to sialic acid receptors
the sialic acid receptors found on the target cell
هل ممكن لانواع اخرى انها تستخدم نفس ال receptors ؟؟
نعم نفس نوع ال receptors بقدر يستخدمه اكثر من نوع من الفيروسات

هذول الجرهستين الدكتور ما حكاهم. وبرق عليهم مرورلس

Virus Receptors

Many examples of virus receptors are now known. Schematic representation of some virus receptors - arrows indicate virus attachment site:

زي ما حكينا فوق في فيروسات بشتركوا بنفس ال receptor و لكن بكون في فرق بال structure تاعهم
الدكتور ما جاب سيرة حفظهم بس ركز كتير على ال HIV
و على الانواع اللي بتشترك بال receptor زي ال influenza and rotavirus



Virus Receptors

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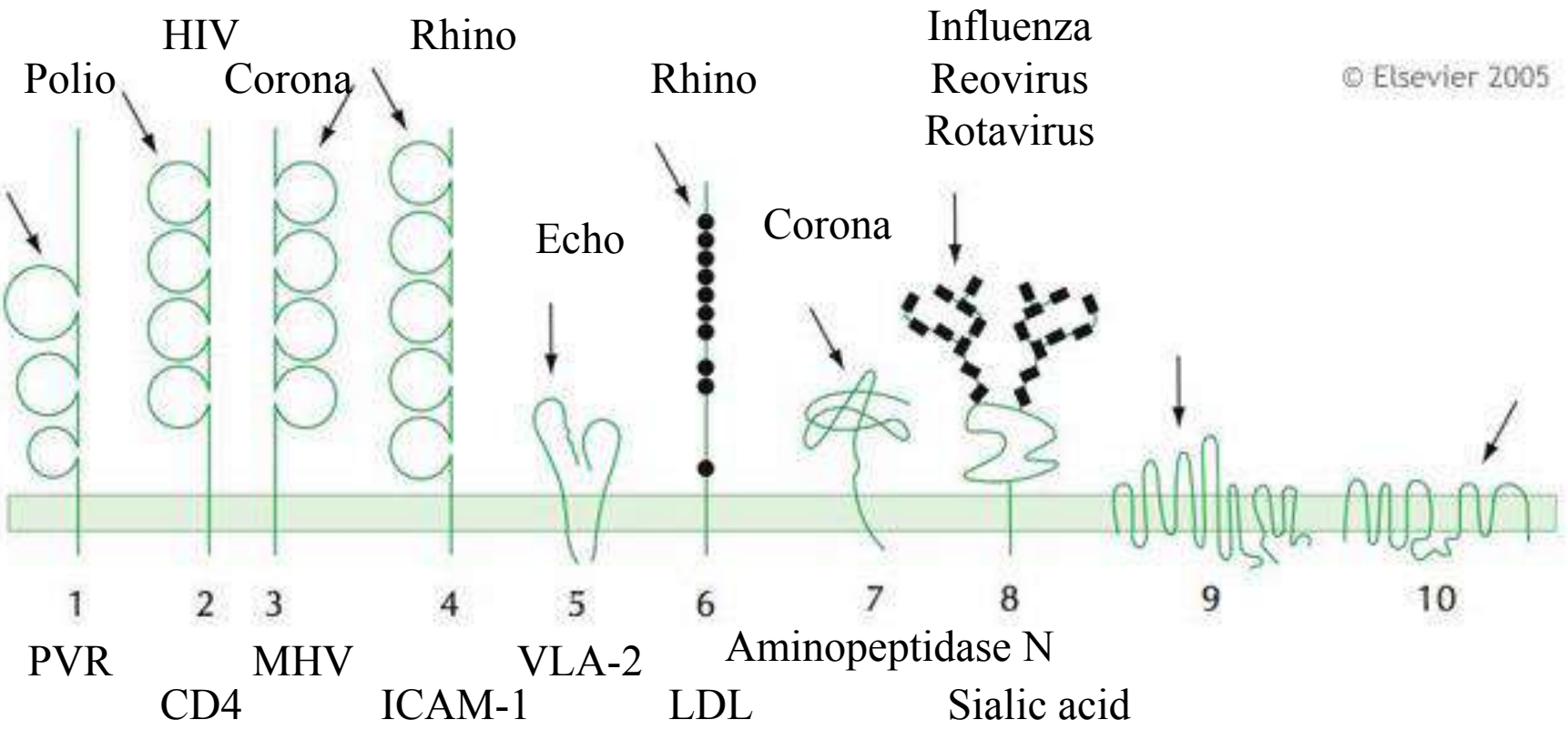
Schematic representation of some virus receptors

- arrows indicate virus attachment site:



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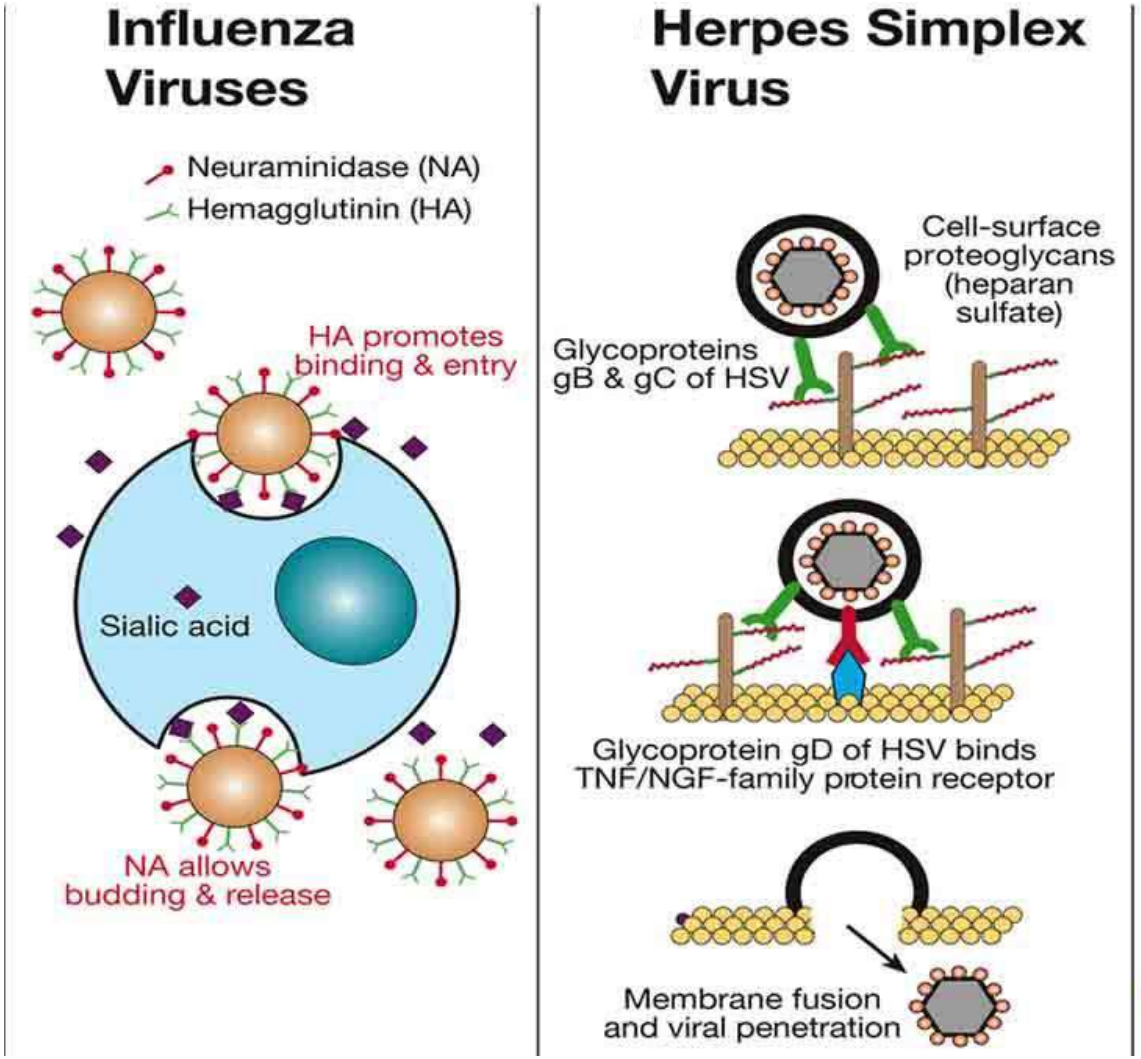

How does an animal virus infect its host?

Examples of Animal Virus Entry

Influenza Virus Receptor Binding

- The influenza haemagglutinin protein is one of two types of glycoprotein spike on the surface of influenza virus particles, the other type being the neuraminidase protein.
- Each haemagglutinin spike is composed of a trimer of three molecules, while the neuraminidase spike consists of a tetramer.
- The haemagglutinin spikes are responsible for binding the influenza virus receptor, which is sialic acid (N-acetyl neuraminic acid).
- As a result, there is little cell-type specificity imposed by this receptor interaction and therefore influenza viruses bind to a wide variety of different cell types.

Influenza Virus Receptor Binding

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- The influenza haemagglutinin protein is one of two types of glycoprotein spike on the surface of influenza virus particles, the other type being the neuraminidase protein.

ي ما قلنا ال influenza بتكون على سطحه لوعين من ال glycoproteins ال HA و ال NA

- Each haemagglutinin spike is composed of a trimer of three molecules, while the neuraminidase spike consists of a tetramer.

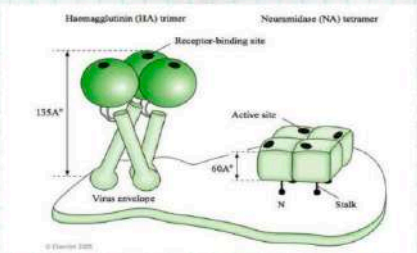
ال HA بتكون من ال 3 molecules بينما ال NA بتكون من 4 molecules زي ما حتشوف بعدين ع الصورة

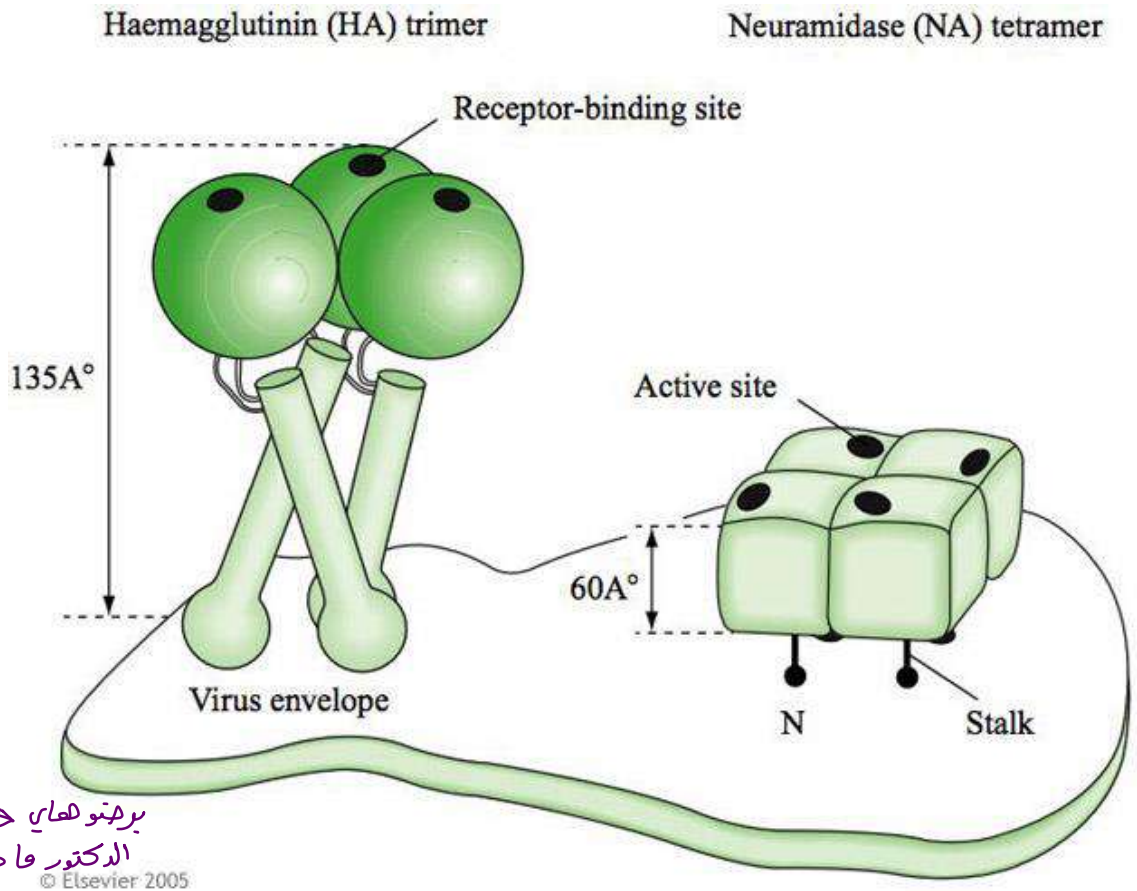
- The haemagglutinin spikes are responsible for binding the influenza virus receptor, which is sialic acid (N-acetyl neuraminic acid).

ال HA بترتبطوا على ال sialic acid مثلاً بقدر الفيروس يدخل ماشية الوراثية

- As a result, there is little cell-type specificity imposed by this receptor interaction and therefore influenza viruses bind to a wide variety of different cell types.

بما انه ال influenza virus قليلة ال specificity بتقدر ترتبط على عدد كبير من الخلايا





برجعتو هاي ع الدكتور فاحكاها

Multiple Receptors

- In some cases, interactions with more than one protein are required for virus entry - neither protein alone is a functional receptor.
- Adenovirus receptor-binding is a two stage process involving an initial interaction of the virion fibre protein with a range of cellular receptors, including MHC class I molecule and the coxsackievirus-adenovirus receptor (CAR).
- Another virion protein, the penton base, then binds to the integrin family of cell surface heterodimers allowing internalization of the particle via receptor-mediated endocytosis.

- The primary receptor for HIV is the T cell antigen, CD4.
- These are Several members of a family of proteins known as b-chemokine receptors play a role in the entry of HIV into cells, and their distribution may be the primary control for the tropism of HIV for different cell types (lymphocytes, macrophages, etc).

2

Penetration

دخول الفيروس لجوا الخلية

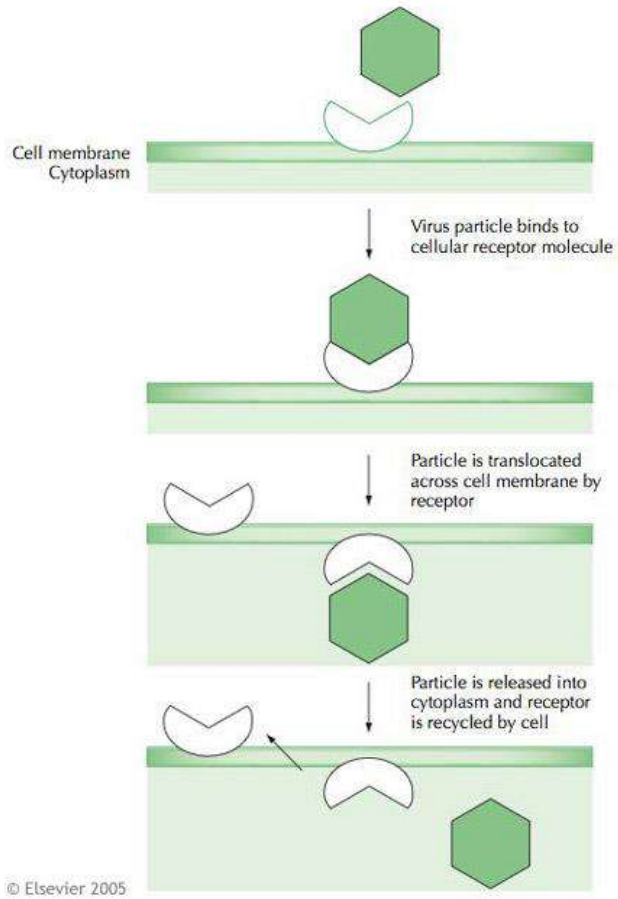
- Penetration of the target cell normally occurs a very short time after attachment of the virus to its receptor in the cell membrane.
- Unlike attachment, cell penetration is generally an energy-dependent process, i.e. the cell must be metabolically active for this to occur.
- Three main mechanisms are involved. الي 2 mechanism هما بتخص الاسئلة

① Translocation

ما بتهمنا لأنه ما بتحدث مع الفيروسات اللي بتصيب البشر.

1) Translocation of the entire virus particle across the cytoplasmic membrane of the cell.

- This process is relatively rare among viruses and is poorly understood.
- It is mediated by proteins in the virus capsid and specific membrane receptors.

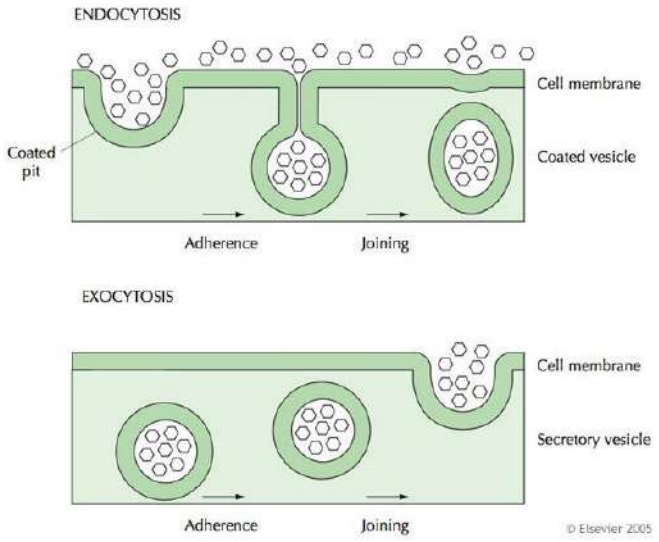


2 Endocytosis

Naked or enveloped

2) Endocytosis of the virus into intracellular vacuoles is probably the most common mechanism.

- Does not require any specific virus proteins (other than those utilized for receptor binding) but relies on the formation and internalization of coated pits at the cell membrane.
- Receptor-mediated endocytosis is an efficient process for taking up and concentrating extracellular macromolecules.

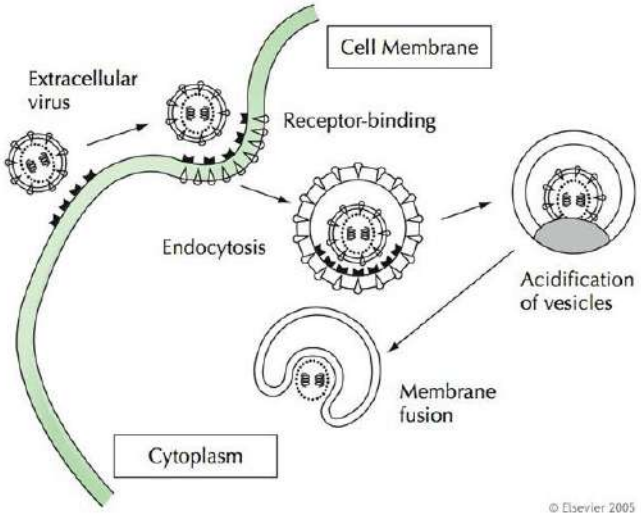


Fusion

Envelope

3) Fusion of the virus envelope with the cell membrane, either directly at the cell surface or in a cytoplasmic vesicle.

- Fusion requires the presence of a fusion protein in the virus envelope which promotes joining of the cell and virus membranes, resulting in the nucleocapsid being deposited directly in the cytoplasm.
- There are two types of virus-driven membrane fusion: pH-dependent and pH-independent.



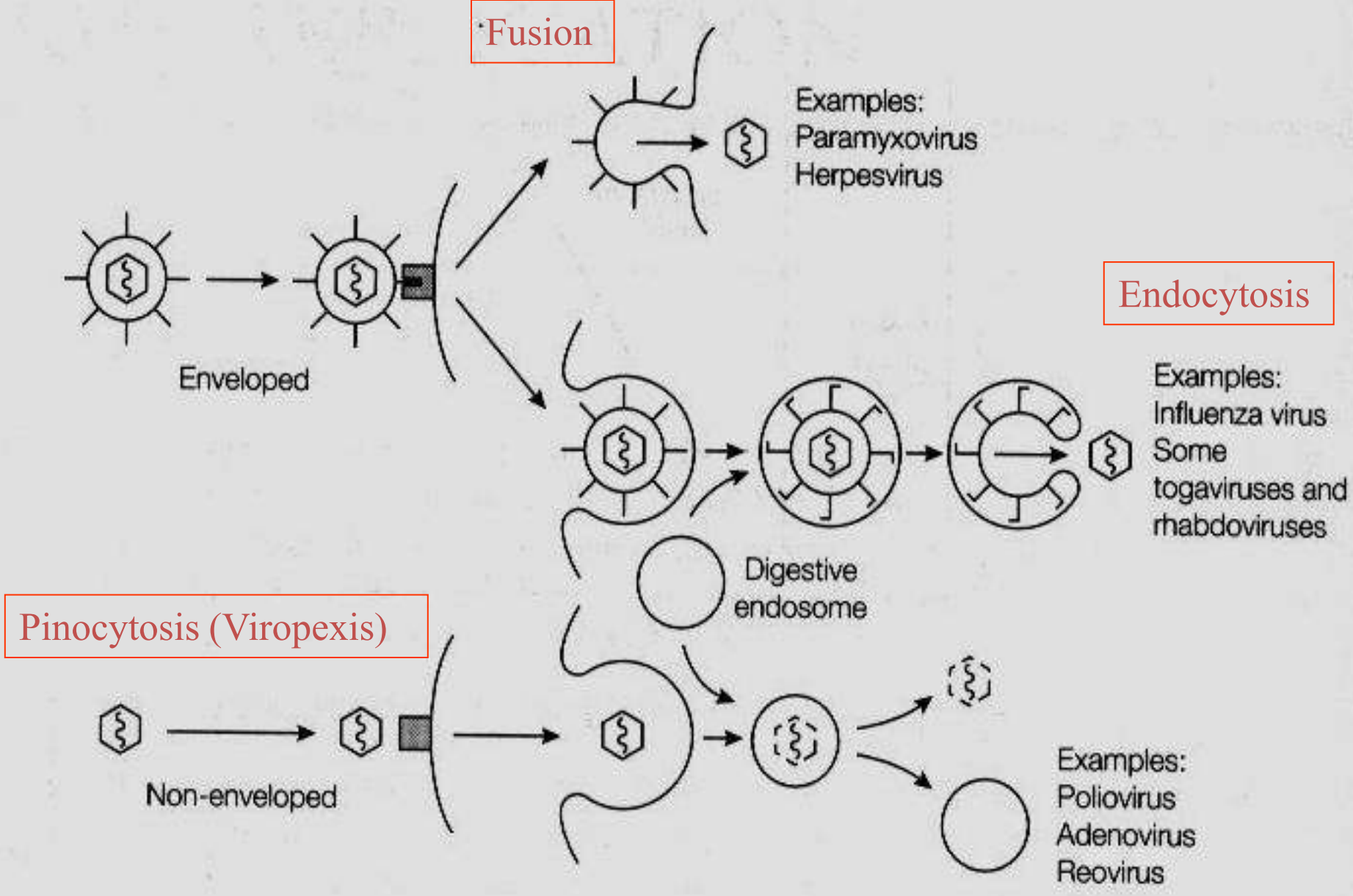


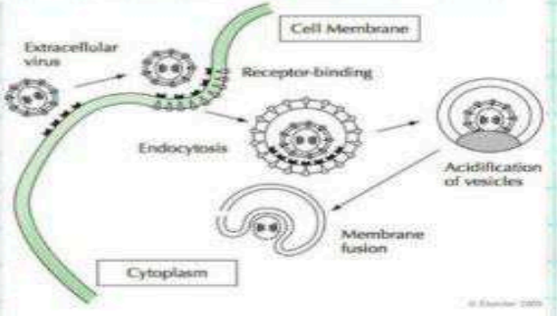
Fig. 2. Methods of virus entry. From Harper, D., Molecular Virology, 2nd edn, © *BIOS Scientific Publishers Limited, 1998.*

Fusion

3) Fusion of the virus envelope with the cell membrane, either directly at the cell surface or in a cytoplasmic

ثالث طريقة ال fusion برضو عنا ال receptors و ال glycoproteins مرتبطي مع بعض
بعدها ممكن يصير عنا 2 processes اما يصير fusion followed by endocytosis
or fusion occur between the target cell and the envelope of the virus
and this fusion between viral envelope and plama membrane will lead to form small pore and the capsid only enter

- **Fusion requires the presence of a fusion protein in the virus envelope which promotes joining of the cell and virus membranes, resulting in the nucleocapsid being deposited directly in the cytoplasm.**



في فرق بين ال endo و ال fusion انه ال endo ما بحتاج غير البروتينات اللي بتعمل attachment لكن ال fusion بده بروتينات تساعده في العملية

- **There are two types of virus- driven membrane fusion: pH- dependent and pH- independent.**

كيف ممكن يصير عندي release للفيروس من ال endostatic vesicle ؟؟
ال triggering step مشان اعمل release هي drop في ال ph
لما يصير عندي drop في ال ph ال endostatic vesicle راح تصير more acidic و هذا راح يحفز خروج الفيروس

بس لسا هون بس عملنا triggering ما طلع الفيروس

ال naked راح يطلع certain enzymes راح تحلل ال endostatic vesicle و يتحرر الفيروس او ممكن يطلع المادة الوراثية لحالها لانه هي اللي بتهمنا انها توصل داخل الخلية

اما ال envelope راح يصير fusion بين ال endostatic vesicle و ال envelope و يحرر الفيروس

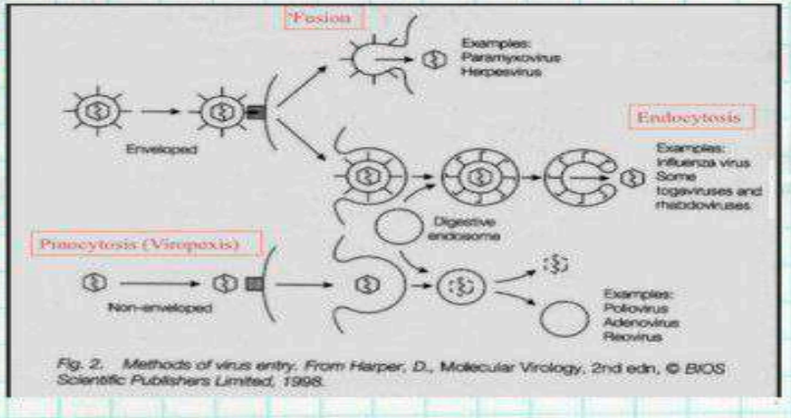


Fig. 2. Methods of virus entry. From Harper, D., Molecular Virology, 2nd edn, © BIOS Scientific Publishers Limited, 1998.