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Herpesvírus

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HERPESVÍRUS

- São uma das principais causas de doenças humanas associadas a vírus.
- Quando a infecção acontece é para a vida toda do indivíduo.

O termo *Herpes* vem do grego e significa latente, crônico.

HERPESVÍRUS

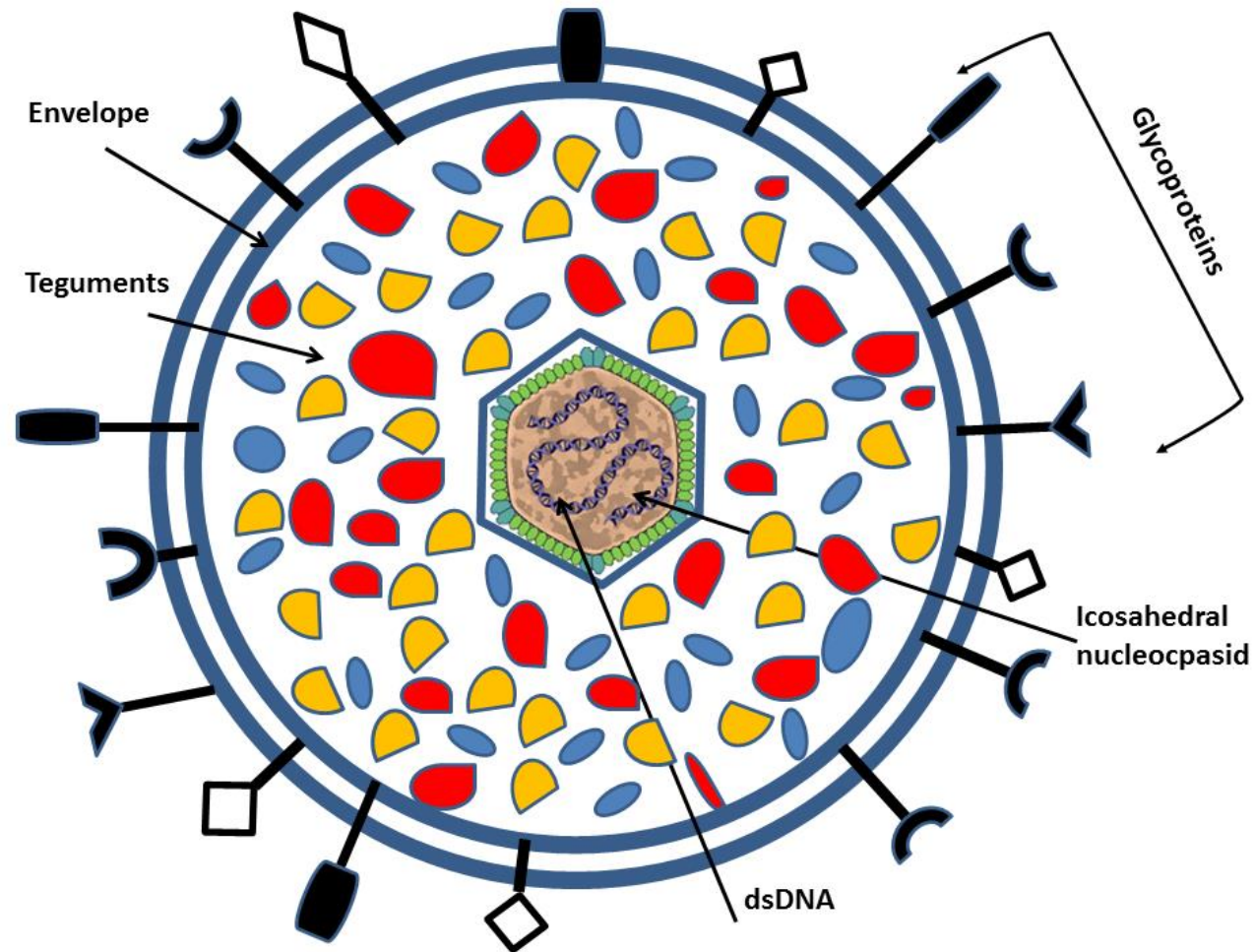
- Vírus envelopados, com capsídeo icosaédrico.
- Partícula de diâmetro entre 180-200nm.
- Genomas de DNA dupla fita, linear, grandes (até 235kbp)
- São vírus complexos (vírions com ~35 proteínas diferentes)
- Codificam uma variedade de enzimas envolvidas no metabolismo e síntese de DNA e no processamento de proteínas.
- Os tipos diferem na sequência do seu genoma e suas proteínas, mas são semelhantes em termos de estrutura do vírion e organização genômica.
- **Replicação: Nuclear.**
- **Montagem: Nuclear.**

HERPESVÍRUS



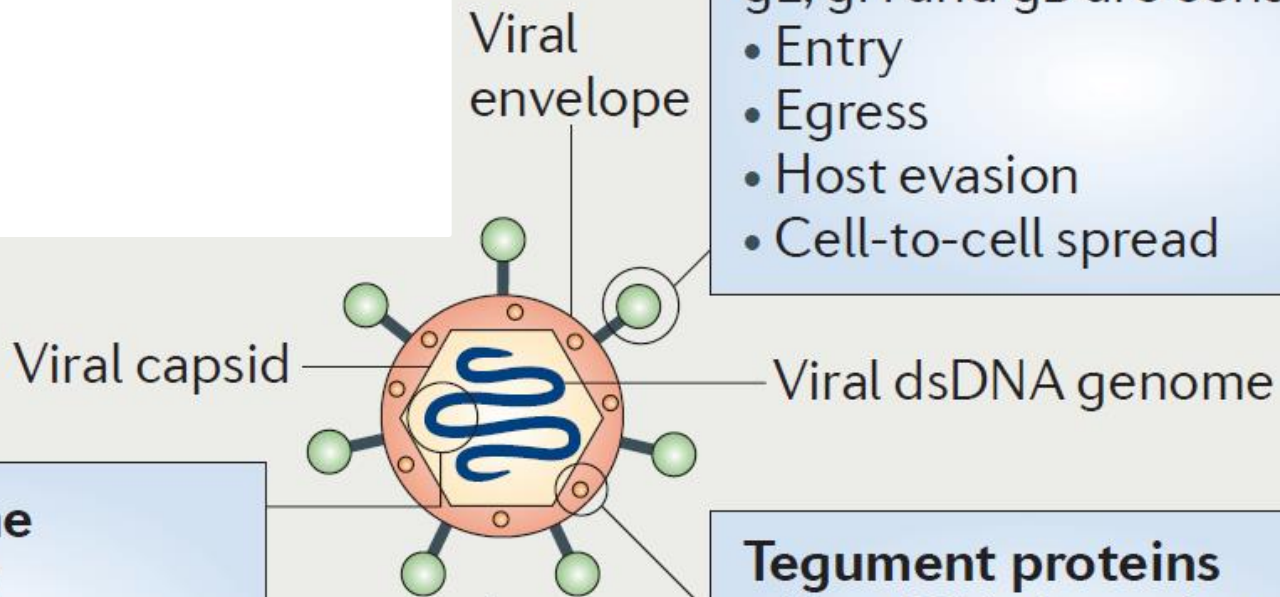
Order: <i>Herpesvirales</i>	(3 Families) < history >	
Family: <i>Alloherpesviridae</i>	(4 Genera) < history >	→ Peixes e anfíbios
Family: <i>Herpesviridae</i>	(3 Subfamilies) < history >	} Mamíferos, aves e répteis
Subfamily: <i>Alphaherpesvirinae</i>	(5 Genera) < history >	
Genus: <i>Iltovirus</i>	(2 Species) < history >	
Genus: <i>Mardivirus</i>	(5 Species) < history >	
Genus: <i>Scutavirus</i>	(1 Species) < history >	
Genus: <i>Simplexvirus</i>	(11 Species) < history >	
Genus: Unassigned	(1 Species) < history >	
Genus: <i>Varicellovirus</i>	(17 Species) < history >	
Subfamily: <i>Betaherpesvirinae</i>	(4 Genera) < history >	
Genus: <i>Cytomegalovirus</i>	(8 Species) < history >	
Genus: <i>Muromegalovirus</i>	(3 Species) < history >	
Genus: <i>Proboscivirus</i>	(1 Species) < history >	
Genus: <i>Roseolovirus</i>	(3 Species) < history >	
Genus: Unassigned	(3 Species) < history >	
Subfamily: <i>Gammapesvirinae</i>	(4 Genera) < history >	
Genus: <i>Lymphocryptovirus</i>	(8 Species) < history >	
Genus: <i>Macavirus</i>	(9 Species) < history >	
Genus: <i>Percavirus</i>	(3 Species) < history >	
Genus: <i>Rhadinovirus</i>	(9 Species) < history >	
Genus: Unassigned	(3 Species) < history >	
Genus: Unassigned	(1 Species) < history >	
Family: <i>Malacoherpesviridae</i>	(2 Genera) < history >	→ Bivalves

HERPESVÍRUS



Herpesvírus

HERPESVÍRUS



Minimum of 11 glycoproteins

gL, gH and gB are conserved

- Entry
- Egress
- Host evasion
- Cell-to-cell spread

DNA genome

- 120–220 kb
- ~100 transcripts
- 47–71% GC content
- Conserved AT-rich regions (such as OriS)

Tegument proteins

- Host RNA degradation
- Viral gene expression
- Host evasion
- Host cell activation

HERPESVÍRUS

- Organização do genoma

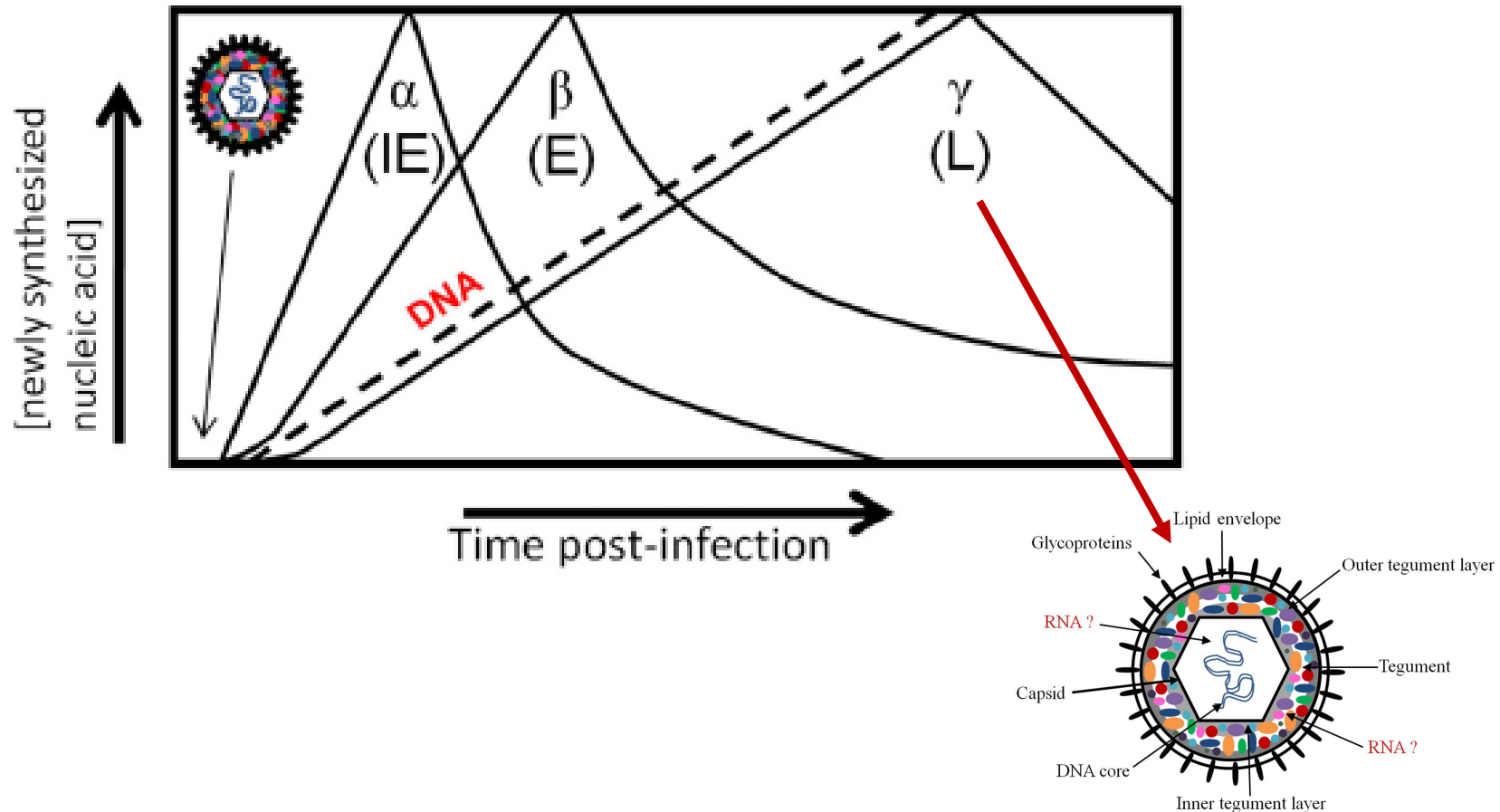
- Genoma formado por fragmento curtos e longos, orientados em “qualquer” direção, gerando 4 isômeros
- Sete blocos de genes conservados.



HERPESVÍRUS

■ Ciclo viral

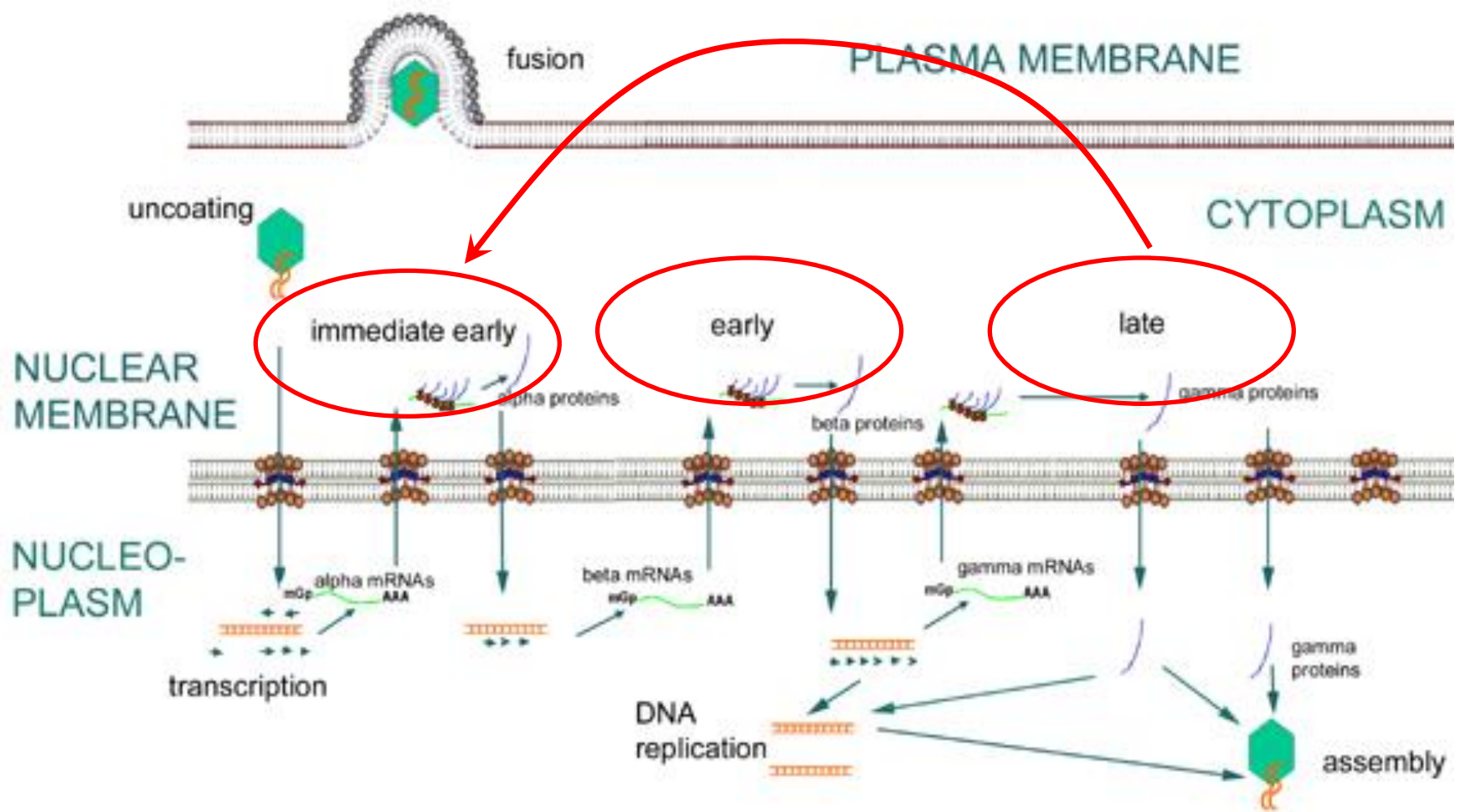
- Expressão dos genes precoces imediatos, precoces e tardios



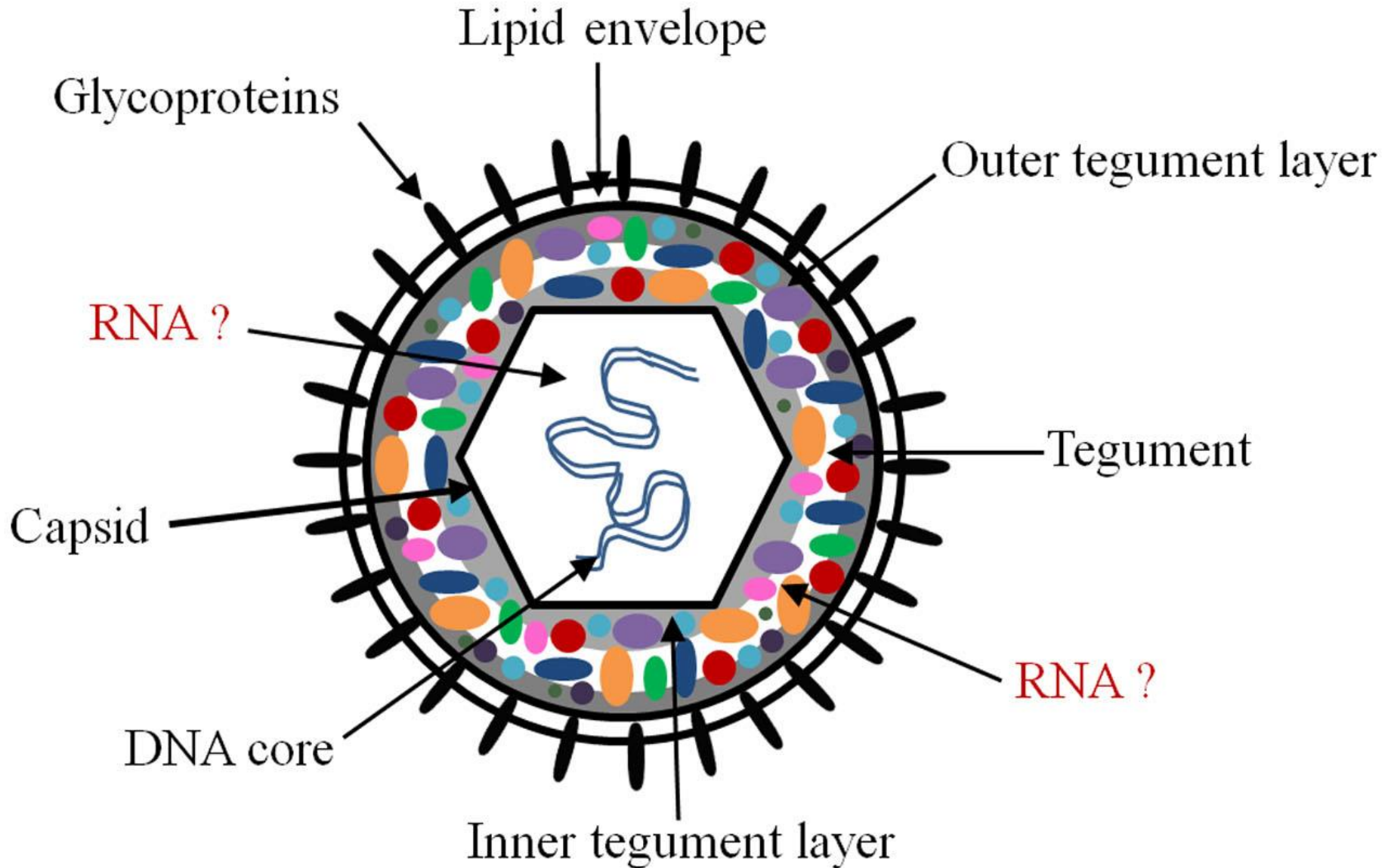
HERPESVÍRUS

■ Ciclo viral

- Expressão dos genes precoces imediatos, precoces e tardios



HERPESVÍRUS

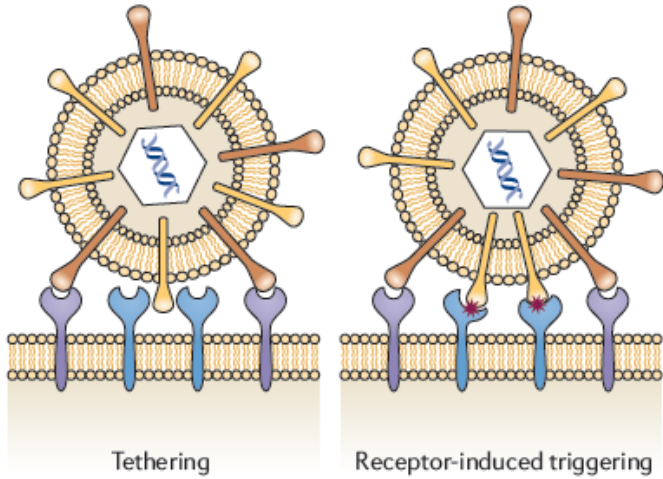


HERPESVÍRUS

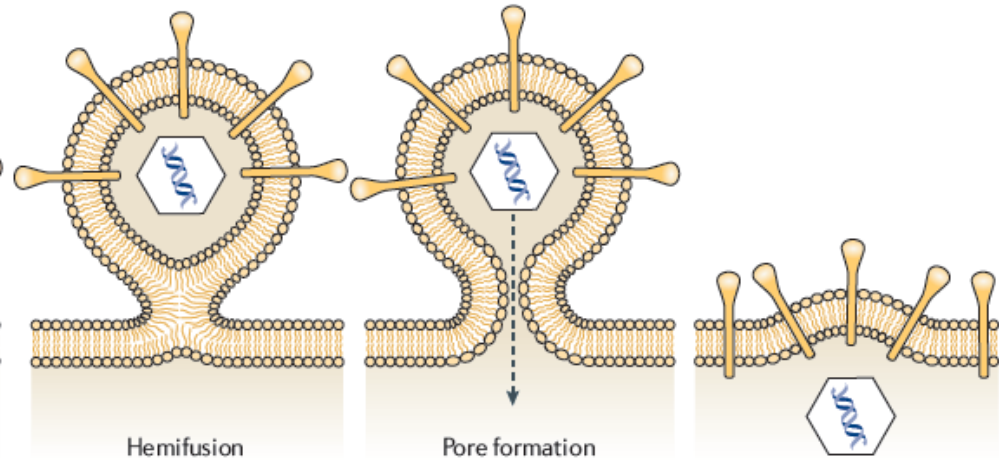
REPLICAÇÃO: ADSORÇÃO E ENTRADA

a

Binding to the host cell

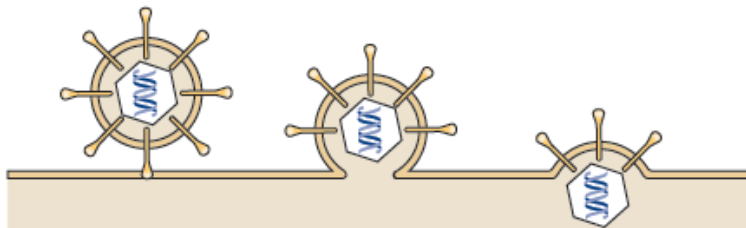


Fusion with the host cell membrane

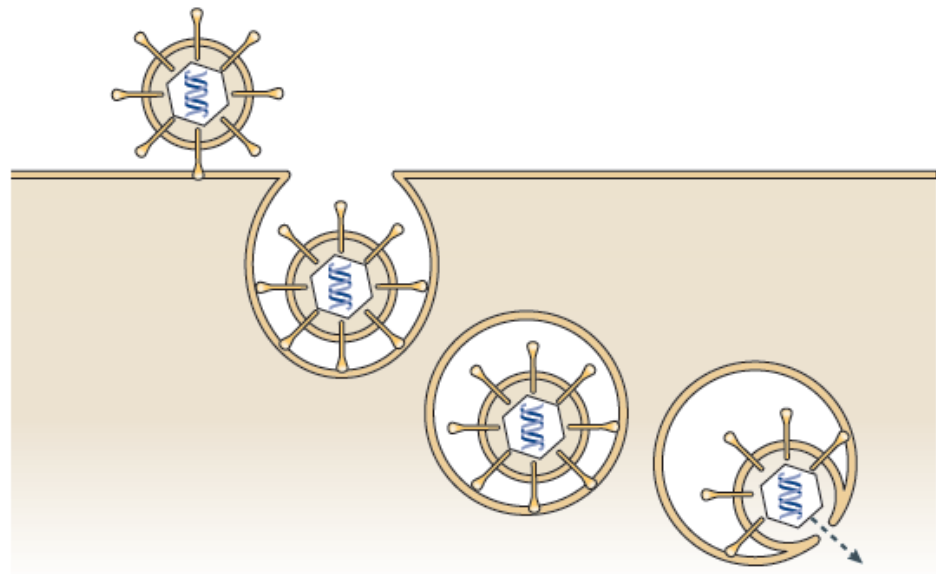


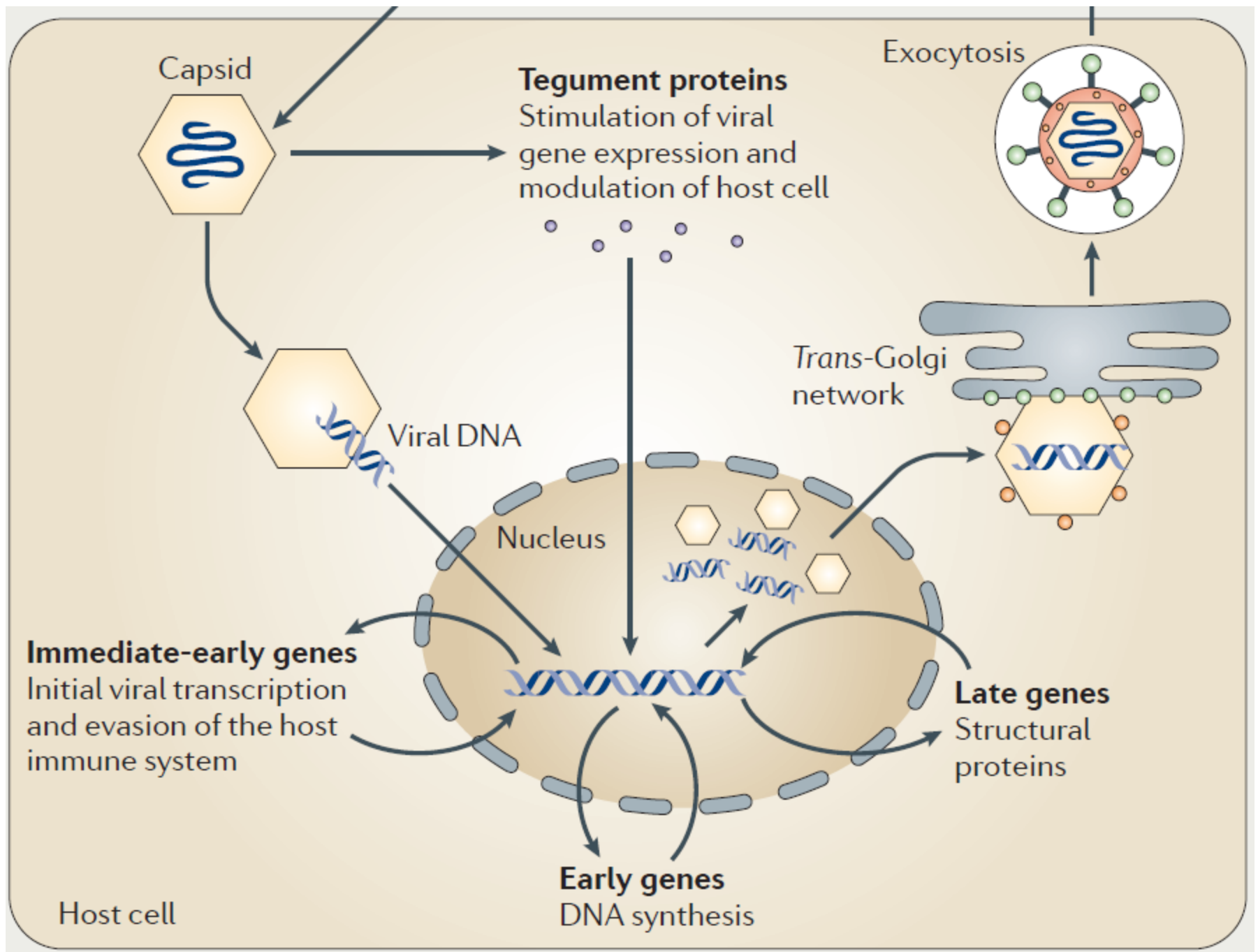
b

Fusion with the plasma membrane



Fusion with the endocytic membrane





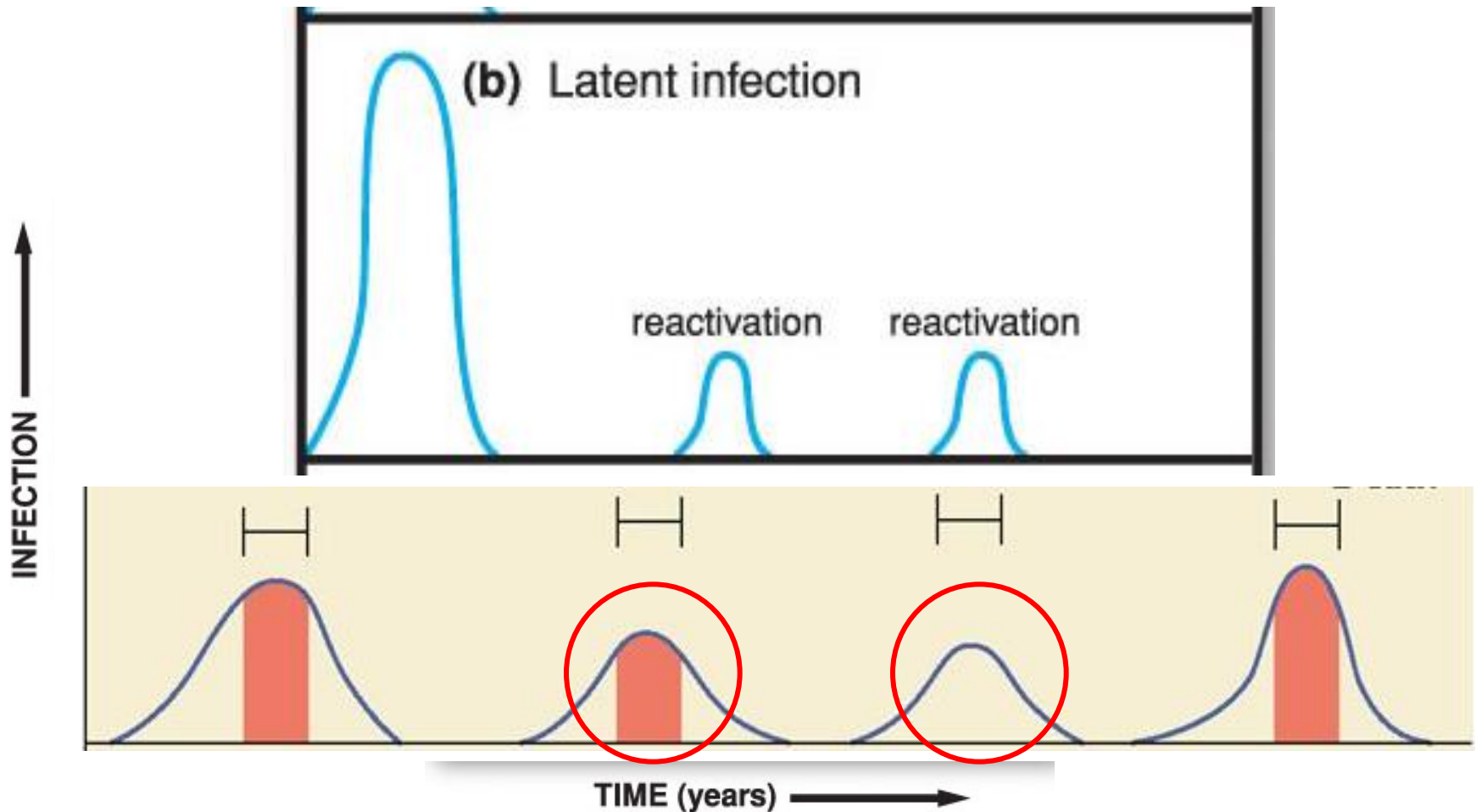
HERPESVÍRUS

- Três subfamílias (Patogénicos em humanos):
 - Alphaherpesviruses (HSV-1/HHV1; HHV2/HSV-2; VZV/HHV-3)
 - Betaherpesviruses (HCMV/HHV-5; HHV-6; HHV-7)
 - Gammaherpesviruses (EBV/HHV-4; HHV-8/KSHV)
- Estabelecem infecções latentes e persistentes após a infecção primária.
- A reativação acontece principalmente em períodos de imunossupressão.
- A infecção primária e a reativação são mais graves em indivíduos imunossuprimidos.

HERPESVÍRUS

INFECÇÃO LATENTE

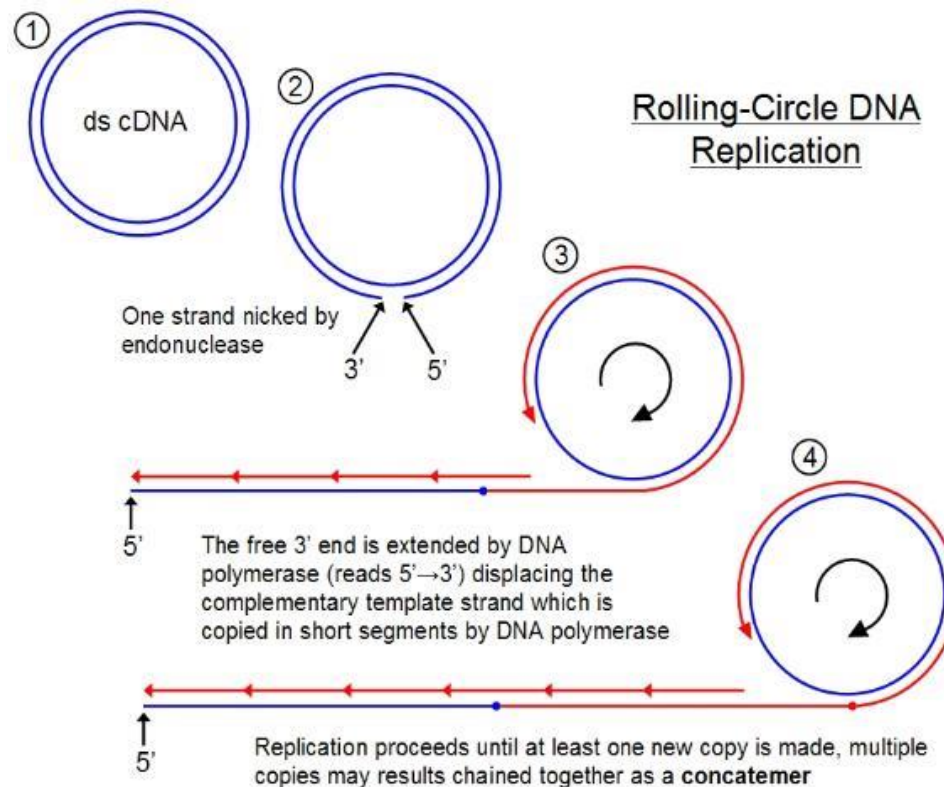
Latência - Estado transcricional e traducional único do vírus. O ciclo produtivo não funciona mas pode ser ativado a qualquer momento.



HERPESVÍRUS

REPLICAÇÃO DO GENOMA

- A replicação acontece pelo mecanismo de “rolling circle” formando repetições em tandem.
- Finalmente estes repetidos são clivados.



Herpes simplex (Herpesvírus 1)

Site of Initial Infection

ACUTE INFECTION

1

Periphery Epithelial Cells

4

Cold Sores
Viral Shedding
Epithelial Cell Death

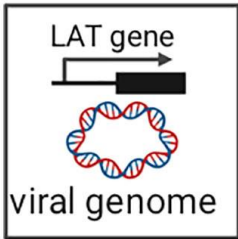
LATENCY

2

Retrograde Transport

Anterograde Transport

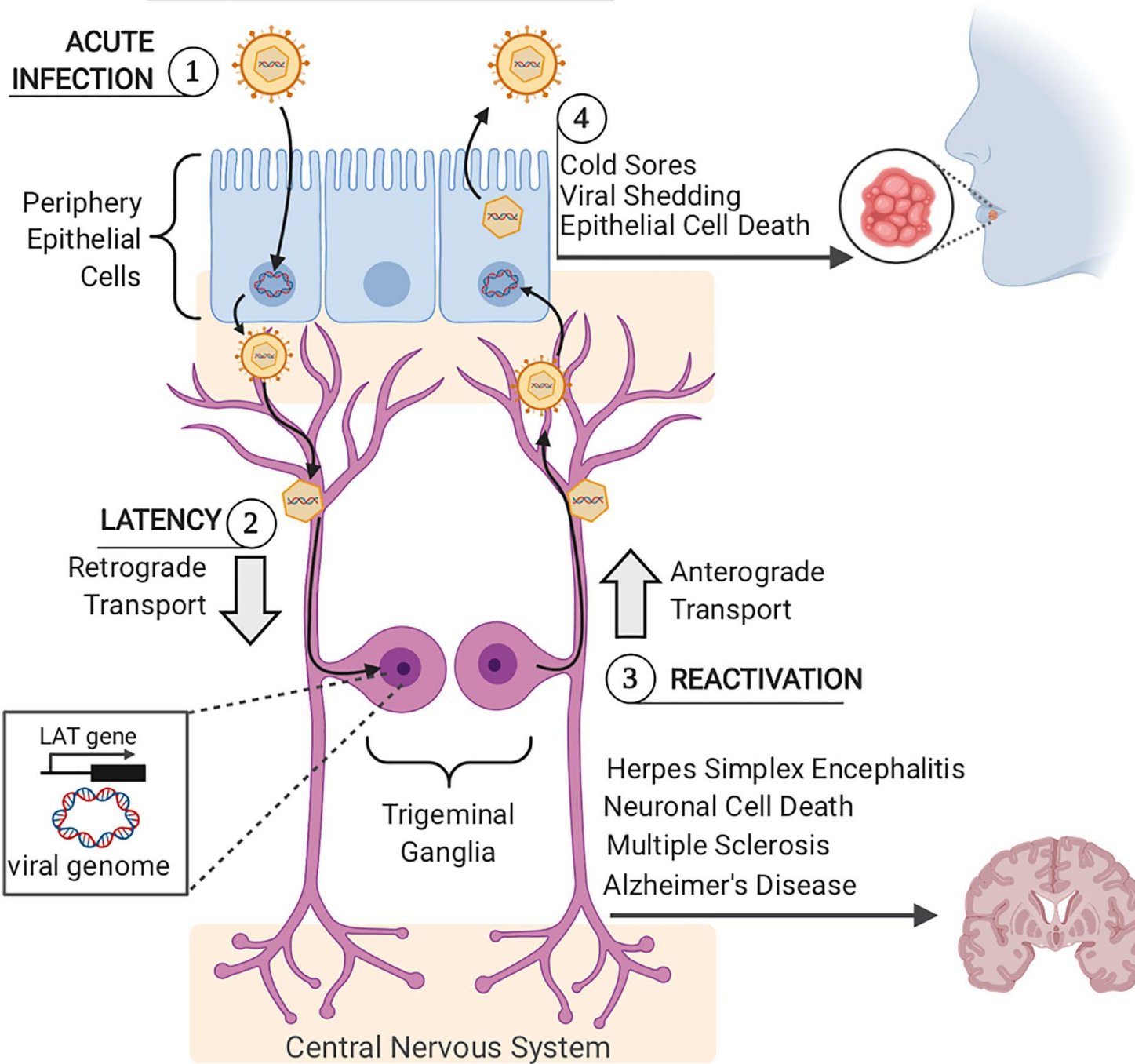
3 REACTIVATION



Trigeminal Ganglia

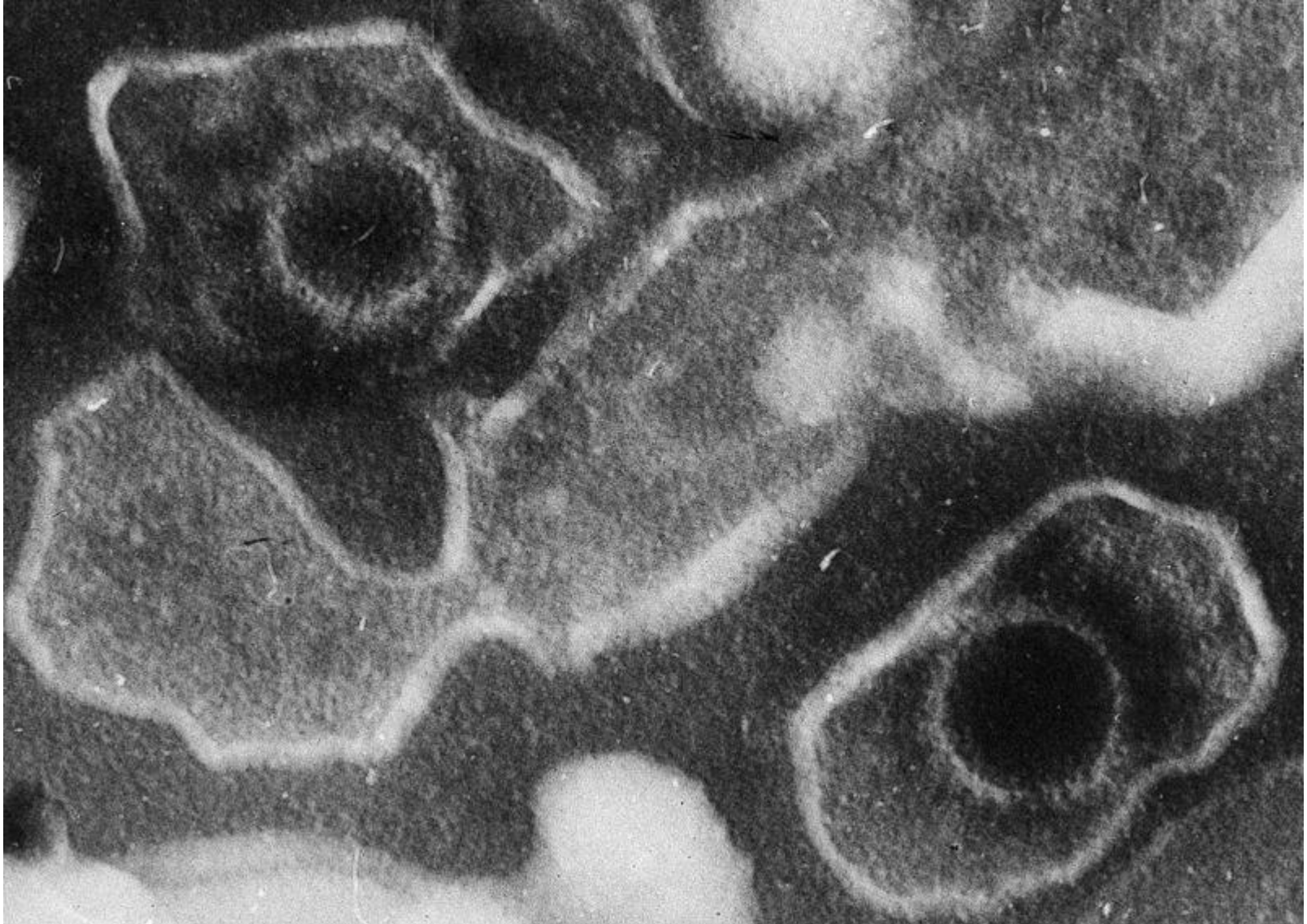
Herpes Simplex Encephalitis
Neuronal Cell Death
Multiple Sclerosis
Alzheimer's Disease

Central Nervous System



Vírus Epstein-Barr (Herpesvírus 4)

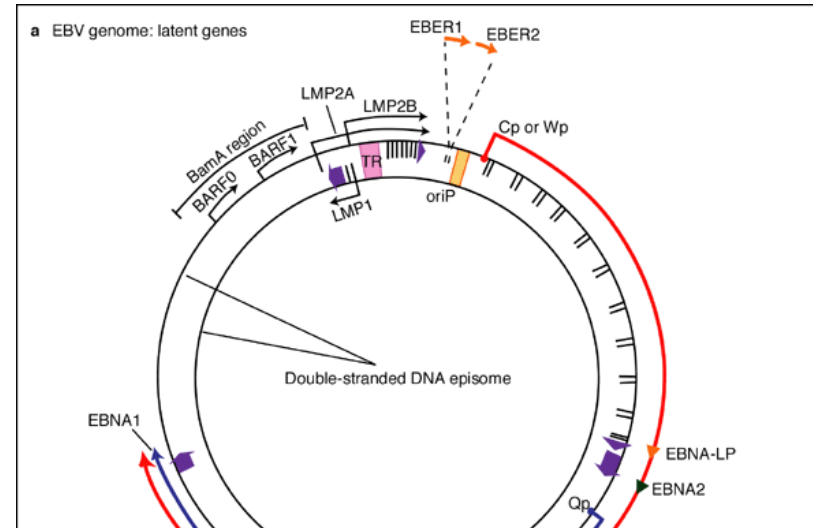
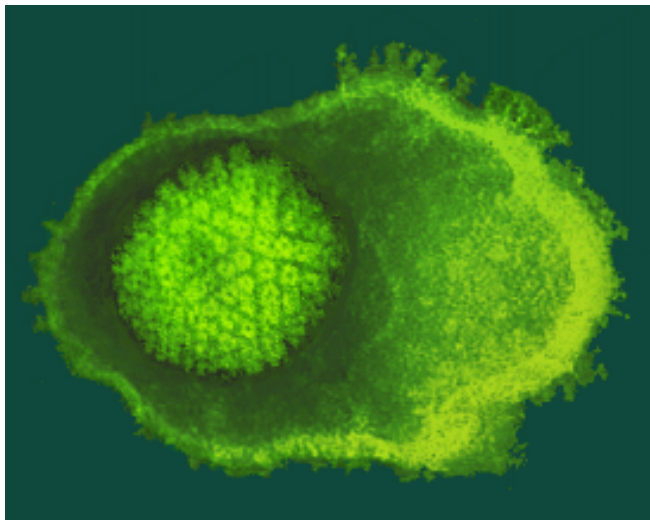
Vírus Epstein-Barr (EBV)



Vírus Epstein-Barr (EBV)

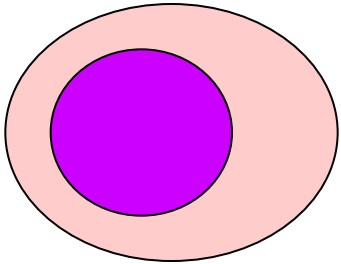
Receptor: CD21 (linfócitos B e células epiteliais da naso- e orofaringe)

- Mais de 90% da população mundial esta infectada por este vírus.
- É transmitido pela saliva infectando as células epiteliais de orofaringe e linfócitos B.

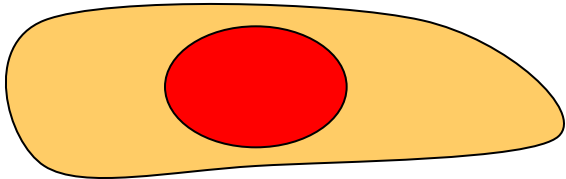


- Etiologicamente associado com:
- Mononucleose
- Linfoma de Burkitt,
- Doença de Hodgkin
- Carcinoma naso-faríngeo

Vírus Epstein-Barr (EBV)



Os linfócitos B são semipermissivos para a replicação viral. A infecção pode ser latente ou as células podem ser estimuladas e, eventualmente, transformadas pelo vírus.



As células epiteliais permitem o ciclo lítico completo.

HERPESVÍRUS

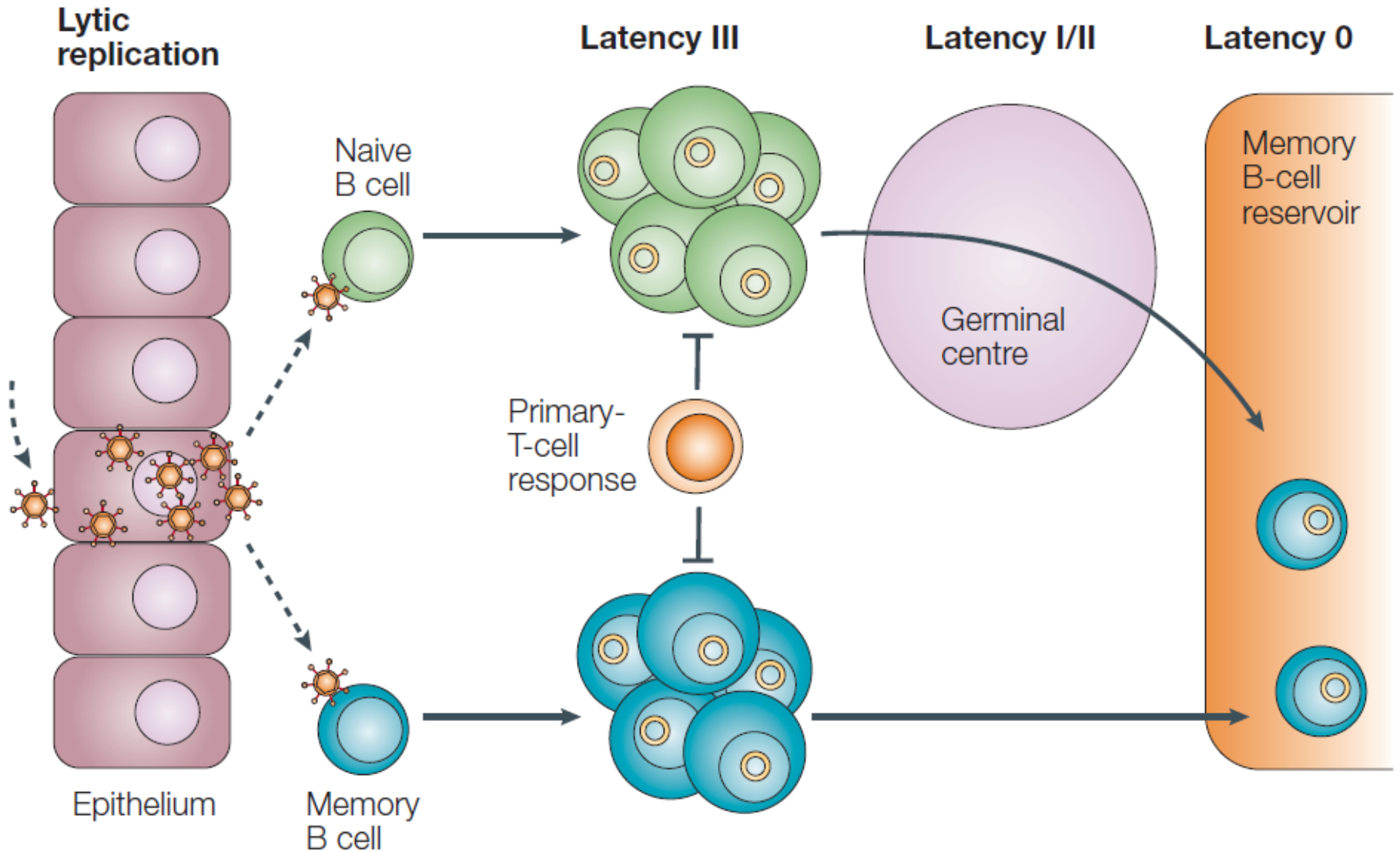
Table 1 | **Human herpesviruses**

Name	Subfamily	Sequence characteristics		Cell types infected		Pathophysiology
		GC content	% coding	Lytic infection	Latent infection	
HSV-1 (HHV1)	α	68%	79	Epithelial cells	Neurons	Orofacial infections, encephalitis
HSV-2 (HHV2)	α	70%	79	Epithelial cells	Neurons	Genital and neonatal infections
VZV (HHV3)	α	46%	89	Epithelial cells	Neurons	Chickenpox, shingles
EBV (HHV4)	γ	59%	68	B cells, epithelial cells	B cells	Infectious mononucleosis, lymphoma, carcinoma
CMV (HHV5)	β	57%	79	Macrophages, lymphocytes, epithelial cells	Macrophages, lymphocytes, epithelial cells	Congenital infection, retinitis, hepatitis
HHV6	β	42%	79 (subtype A); 82 (subtype B)	CD4 ⁺ T cells	Monocytes, macrophages	Exanthem subitum
HHV7	β	36%	79	T cells	T cells	Exanthem subitum
HHV8	γ	53%	83	Lymphocytes	Lymphocytes	Kaposi's sarcoma

CMV, cytomegalovirus; EBV, Epstein–Barr virus; HHV, human herpesvirus; HSV, herpes simplex virus; VZV, varicella-zoster virus.

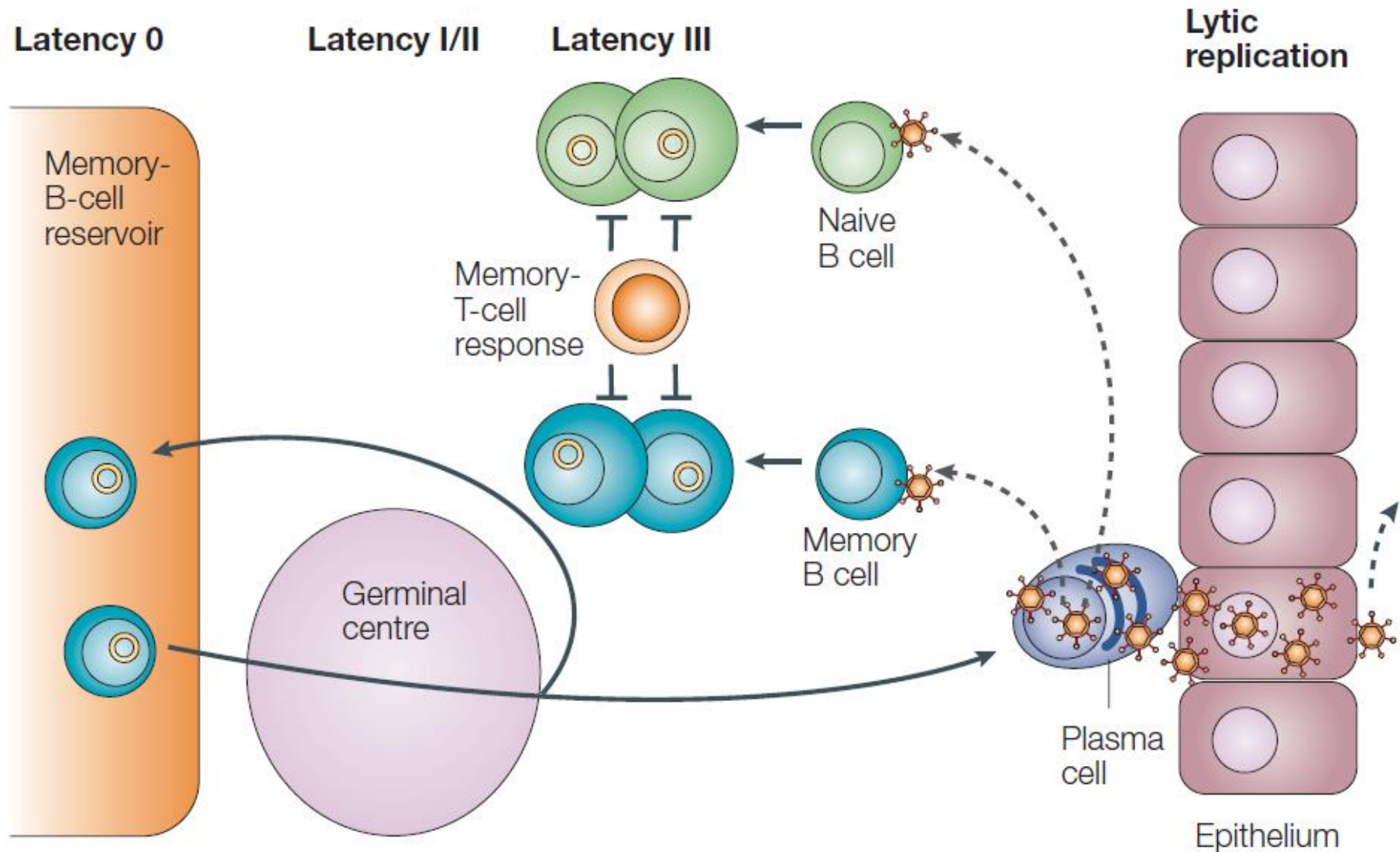
Virus Epstein-Barr (EBV)

a Primary infection

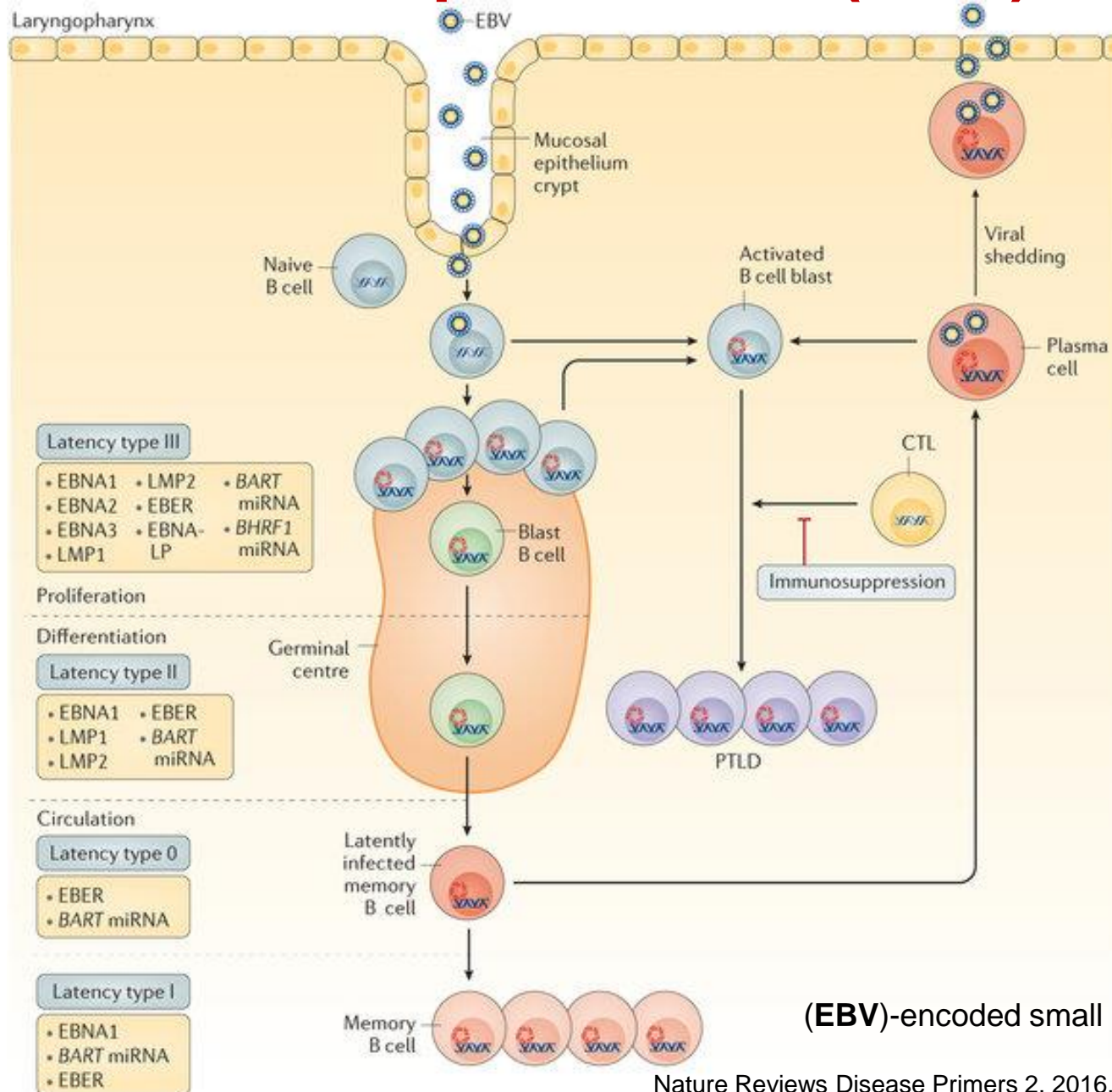


Virus Epstein-Barr (EBV)

b Persistent infection

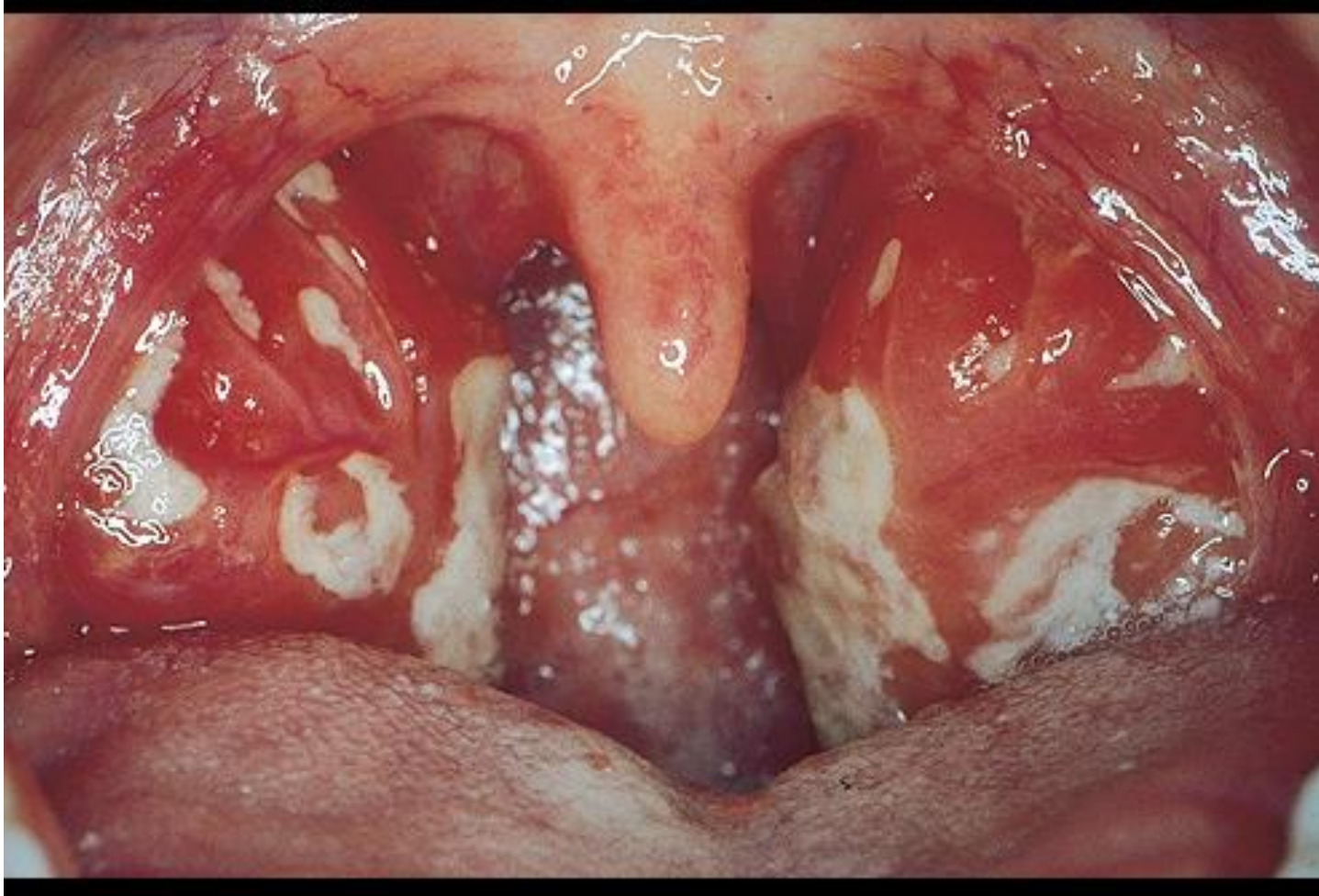


Virus Epstein-Barr (EBV)



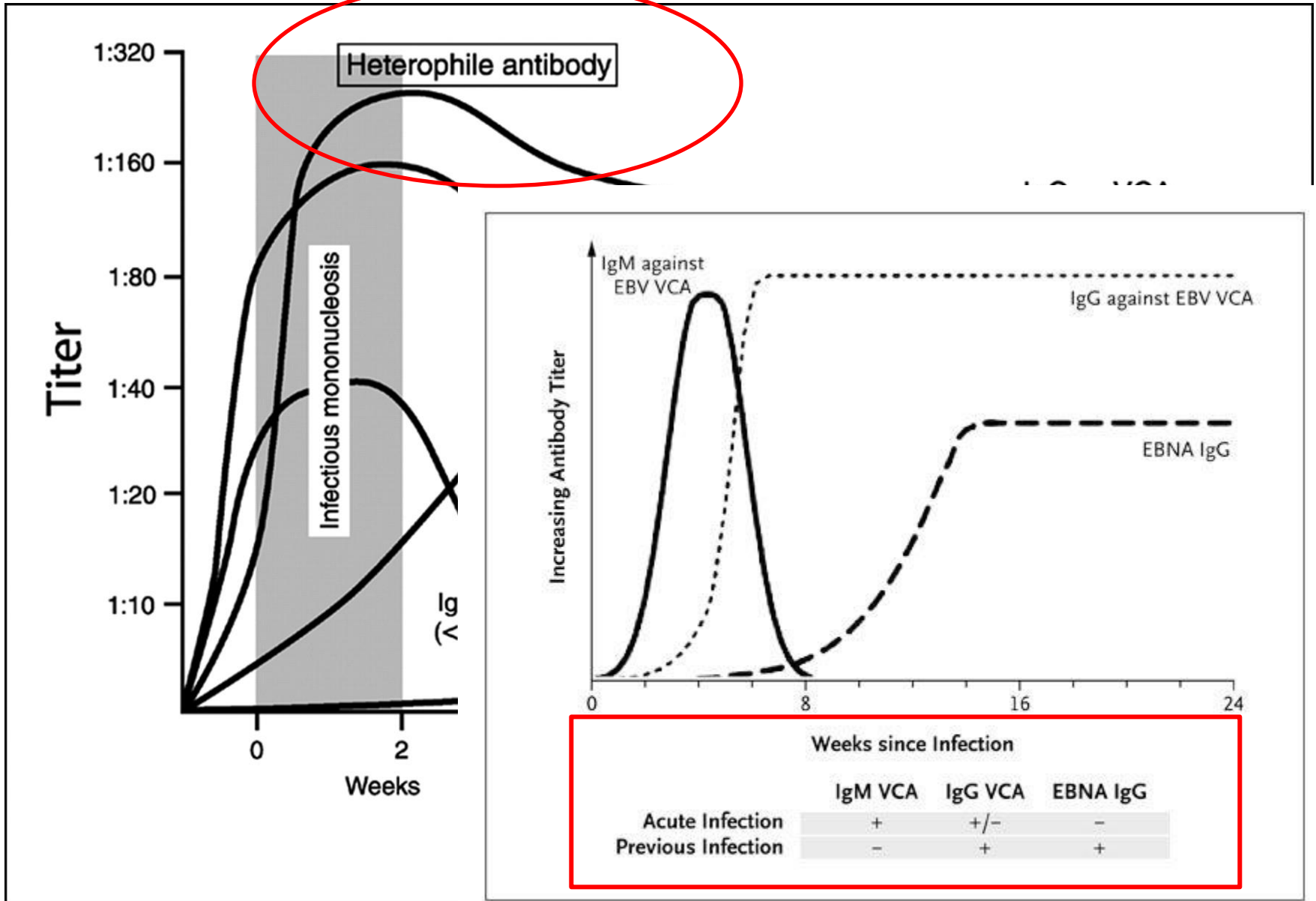
Vírus Epstein-Barr (EBV)

- **Mononucleose**



- Faringite e adenopatias...

DIAGNÓSTICO



Laboratory Testing

Epstein-Barr virus (EBV), also known as human herpesvirus 4, is a gamma herpes virus that occurs only in humans. Laboratory testing can help distinguish whether someone is susceptible to EBV infection or has a recent or past infection.

Healthcare providers can test for antibodies to the following EBV-associated antigens:

- **Viral capsid antigen (VCA)**

- Anti-VCA IgM appears early in EBV infection and usually disappears within four to six weeks.
- Anti-VCA IgG appears in the acute phase of EBV infection, peaks at two to four weeks after onset, declines slightly then persists for the rest of a person's life.

- **Early antigen (EA)**

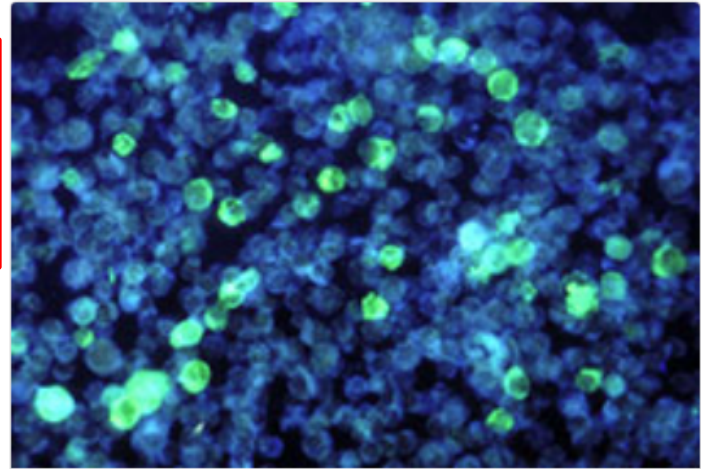
Anti-EA IgG appears in the acute phase of illness and generally falls to undetectable levels after three to six months. In many people, detection of antibody to EA is a sign of active infection. However, 20% of healthy people may have antibodies against EA for years.

- **EBV nuclear antigen (EBNA)**

Antibody to EBNA, determined by the standard immunofluorescent test, is not seen in the acute phase of EBV infection but slowly appears two to four months after onset of symptoms and persists for the rest of a person's life. Other EBNA enzyme immunoassays may report false positive results.

- **Monospot test**

The Monospot test is not recommended for general use. The antibodies detected by Monospot can be caused by conditions other than infectious mononucleosis. Moreover, studies have shown that the Monospot produces both false positive and false negative results. For example, the heterophile antibodies detected by Monospot are often not present in children with infectious mononucleosis. At best, the Monospot test may indicate that a person has a typical case of infectious mononucleosis, but does not confirm the presence of EBV infection.



This photomicrograph depicts leukemia cells that contain Epstein-Barr virus using an FA staining technique.

“Síndrome da mononucleose”

- Citomegalovírus (segunda causa viral mais importante)
- VZV
- HHV6
- Hepatite A ou B
- Rubéola
- HIV

Diagnóstico Laboratorial:

- Sorologia (anticorpos contra proteínas de superfície, anticorpos **Heterófilos**)
- PCR
- Biopsia

Vírus Epstein-Barr (EBV)

Linfoma de Burkitt



Vírus Epstein-Barr (EBV)

Leucoplasia pilosa



Vírus Epstein-Barr (EBV)

Leucoplasia pilosa



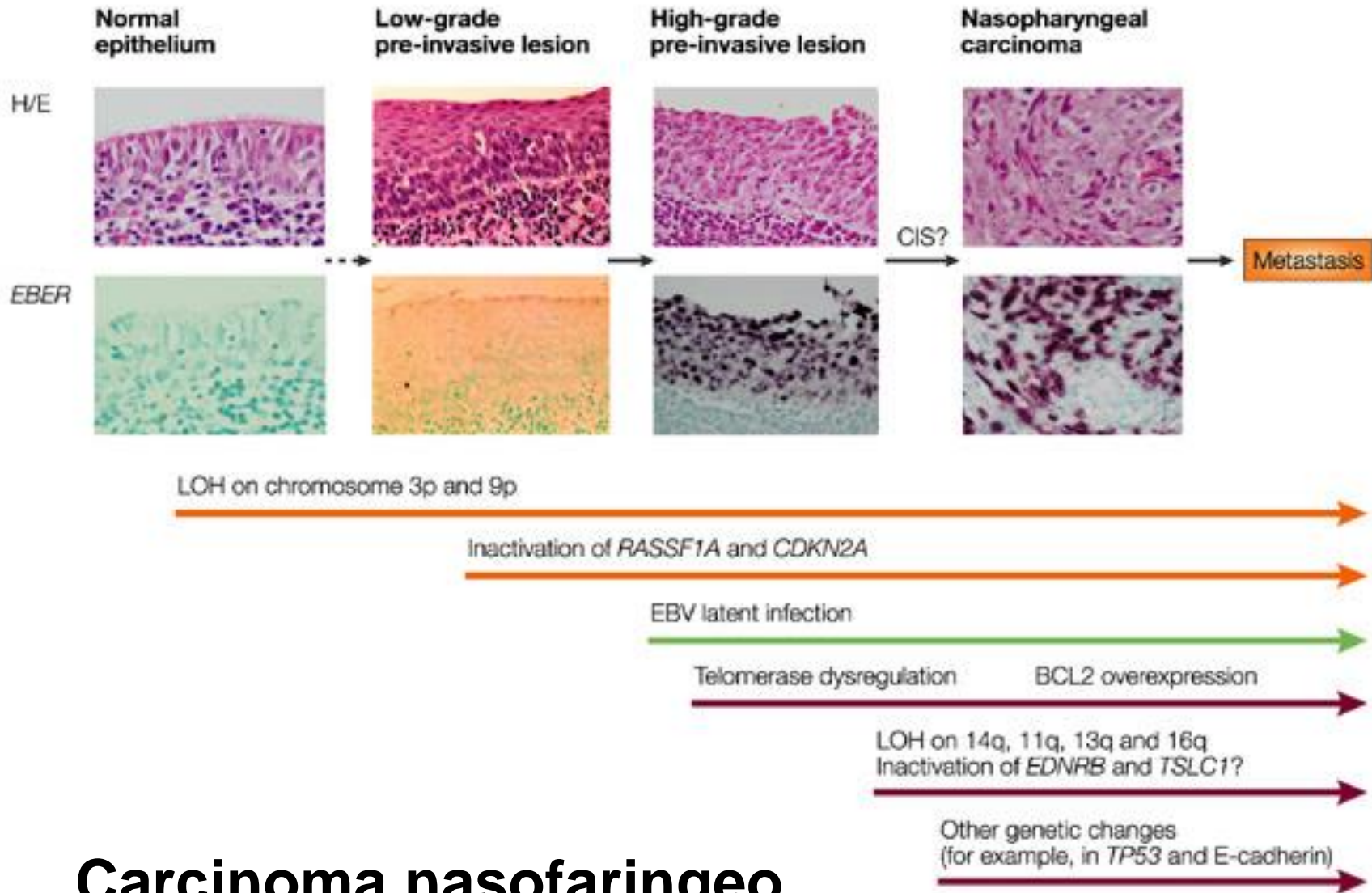
Vírus Epstein-Barr (EBV)

Carcinoma nasofaríngeo

Carcinoma da nasofaringe (NPC):

- Tumor maligno do epitélio escamoso da nasofaringe.
- A forma mais indiferenciada está sempre associada à infecção por EBV.
- Cópias de EBV podem ser detectadas nas células malignas de todos os NPC indiferenciados.
- As células malignas expressam EBNA-1 (algumas LMP).
- Linhagens celulares derivadas de NPC produzem partículas virais infecciosas

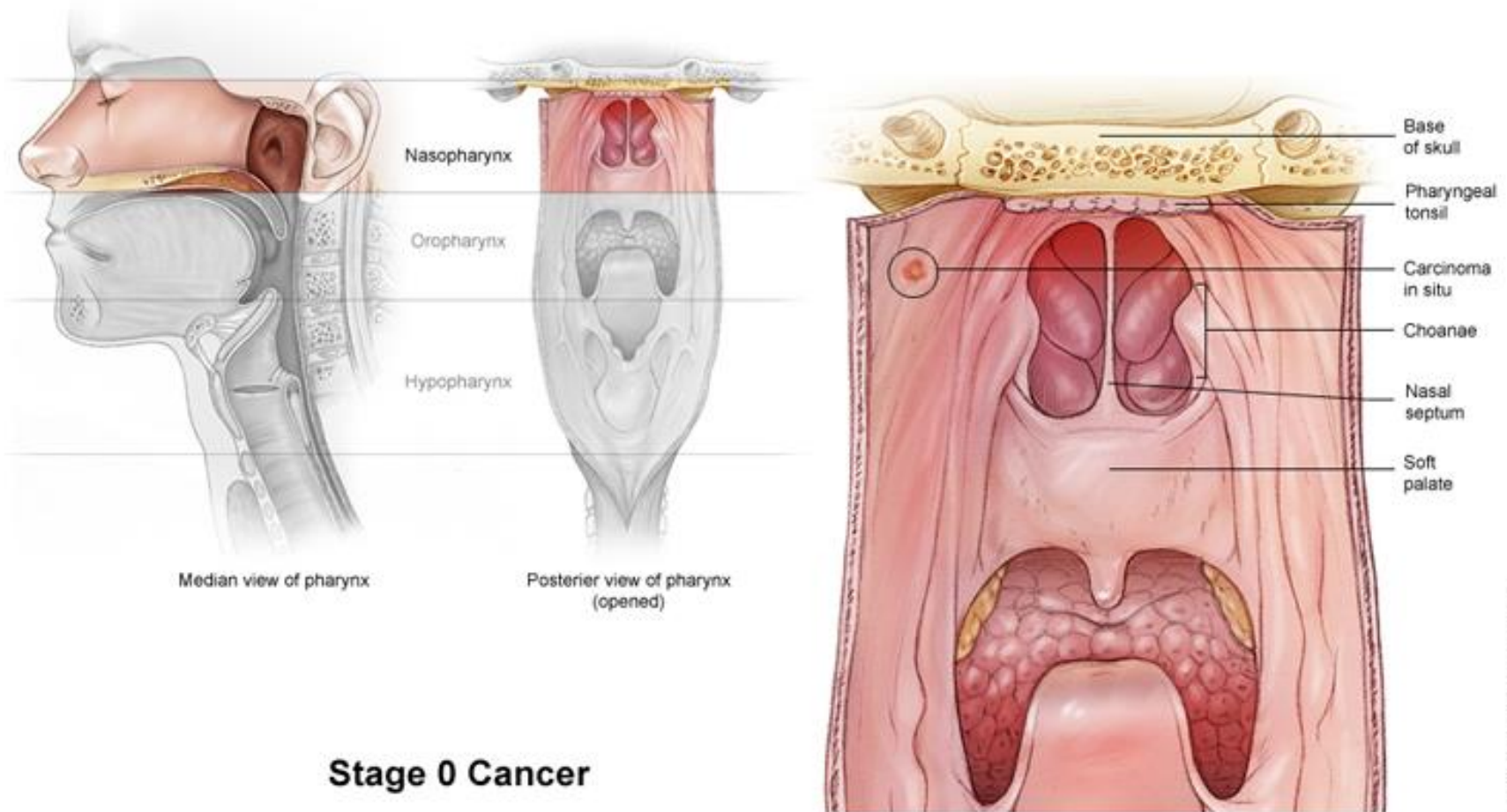
Virus Epstein-Barr (EBV)



Carcinoma nasofaringeo

Virus Epstein-Barr (EBV)

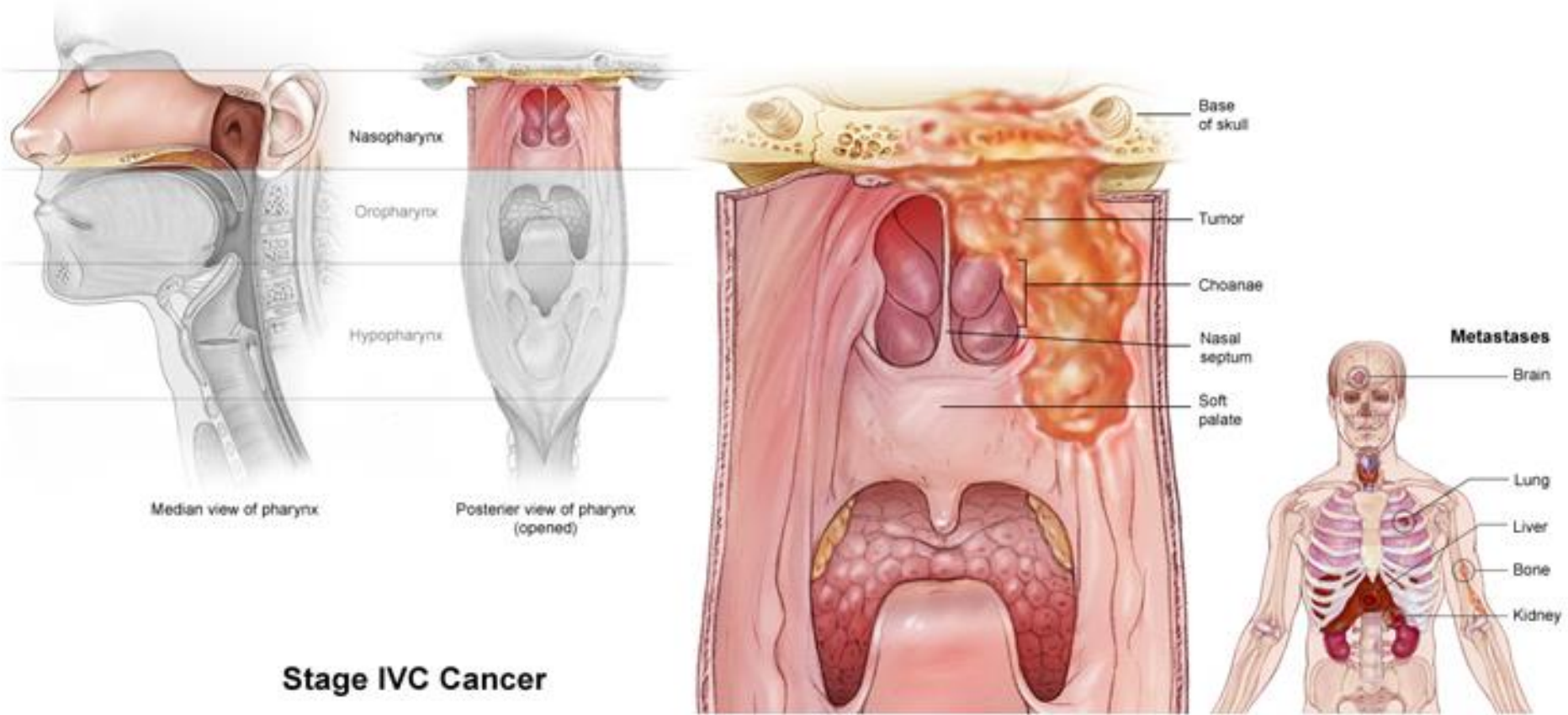
Carcinoma nasofaringeo



Stage 0 Cancer

Vírus Epstein-Barr (EBV)

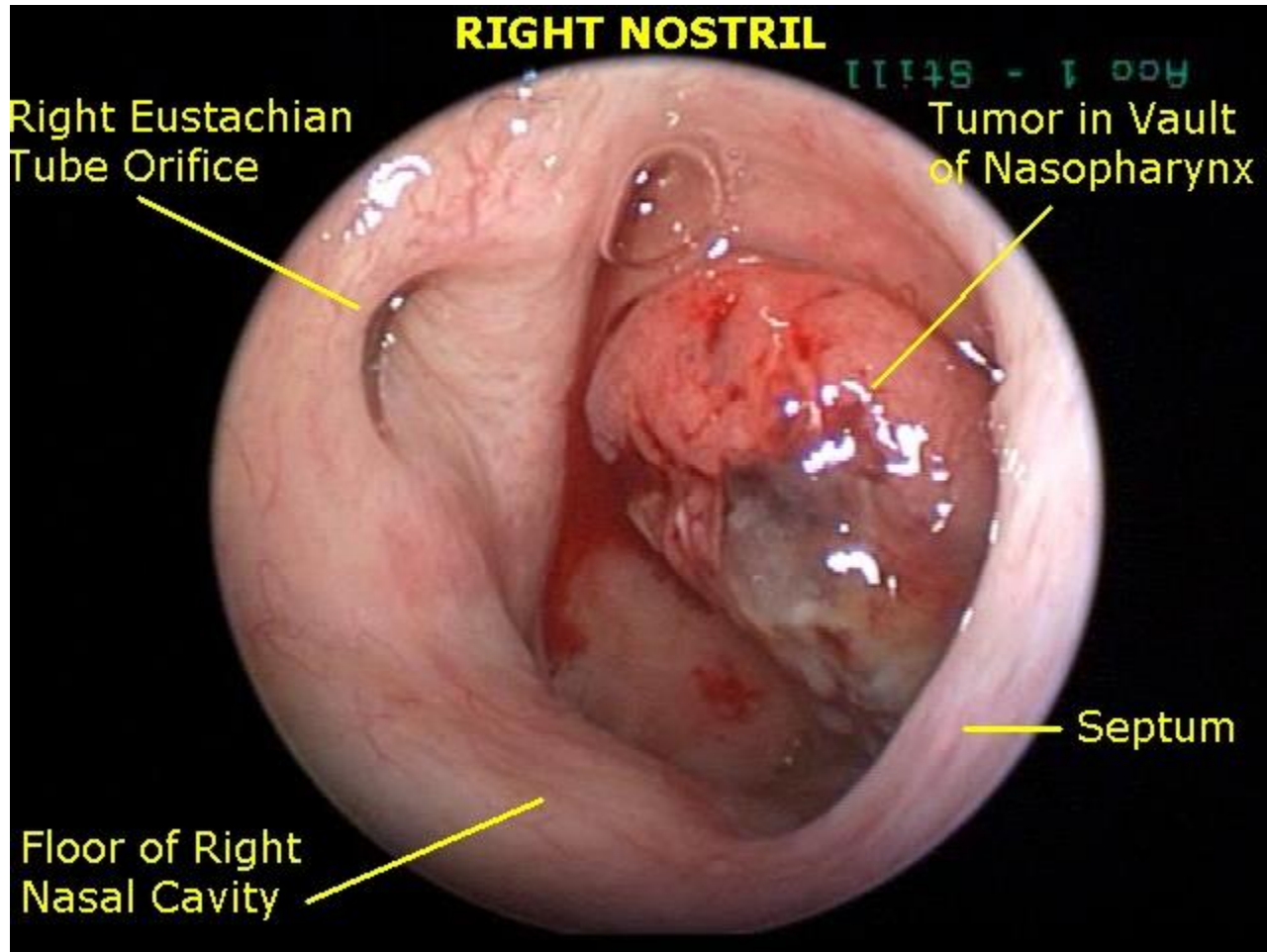
Carcinoma nasofaringeo



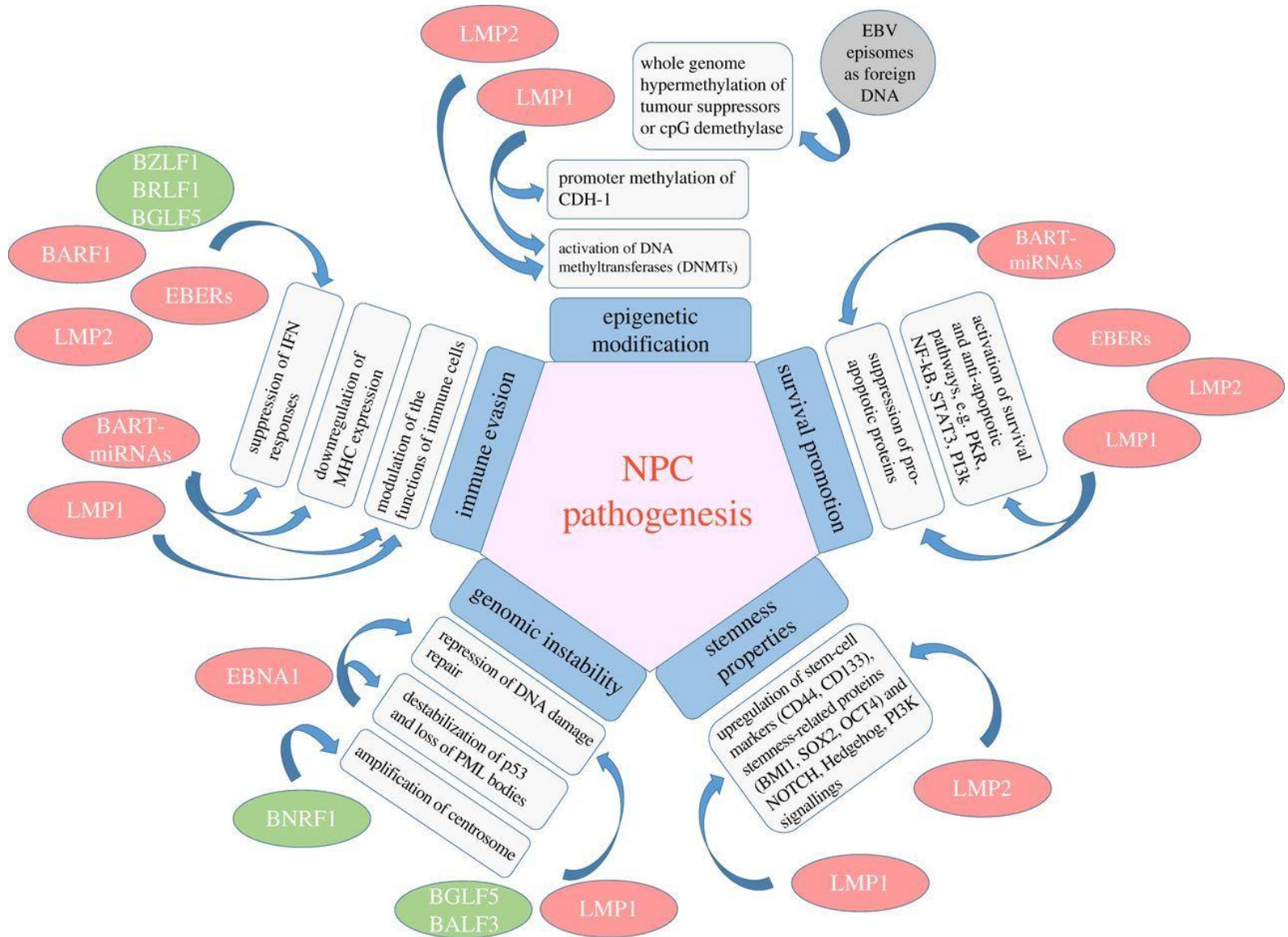
Stage IVC Cancer

Vírus Epstein-Barr (EBV)

Carcinoma nasofaringeo



EBV: Carcinoma nasofaringeo



Herpesvírus 8

(KSHV)

HERPESVÍRUS

Human tumor associated gammaherpesviruses



Angio-immunoblastic
T-cell lymphoma

Burkitt's lymphoma

Hodgkin's lymphoma

Non-Hodgkin's lymphoma

Leiomyosarcoma

Breast cancer

EBV

Gastric carcinoma

Nasal T/NK cell lymphoma

T/NK cell lymphoma

Nasopharyngeal carcinoma

KSHV

Kaposi sarcoma

Primary effusion
lymphoma

AIDS-related
lymphoproliferative disorder

Lympho-proliferative disorders

X-linked lymphoproliferative disorders

AIDS associated lymphoproliferative disorders

Post-transplant lymphoproliferative disorders

HERPESVÍRUS: KSHV

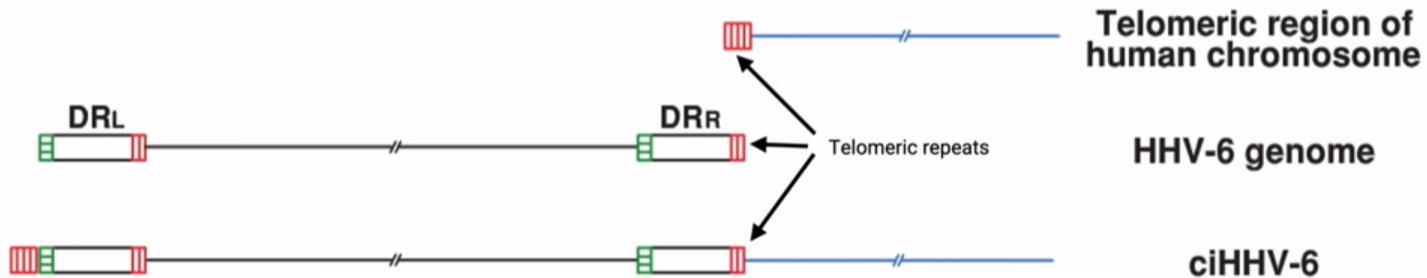


Herpesvírus 6 e 7

HERPESVÍRUS

- Outros mecanismos de persistência.

HHV-6 integration



- Integra nos telômeros de determinados tipos celulares.
- ~1% de transmissão pela via germinativa.
- Possível estratégia de latência e transmissão.
- Mecanismo geral para retrovírus.

HERPESVÍRUS

TABLE 1 Clinical syndromes associated with HHV-6 infections

Stage of HHV-6 infection	Putative pathogenic effect	Associated disease ^a
Congenital infection	Direct/indirect ^b	CNS developmental defects ^c
Postnatal primary infection	Direct	Exanthema subitum (roseola infantum, sixth disease) Fever, seizures Mild gastrointestinal and respiratory-tract symptoms Thrombocytopenia, infectious mononucleosis-like syndrome Hepatitis, gastroenteritis, colitis Meningoencephalitis and encephalitis Hemophagocytic syndrome ^c Temporal lobe epilepsy ^c
Acute reactivation	Direct	Fever Rash Thrombocytopenia, leukopenia, anemia, bone-marrow suppression Hepatitis Encephalitis, neurocognitive dysfunction Retinitis Pneumonitis Gastroenteritis, colitis Temporal-lobe epilepsy ^c
	Indirect	Drug-induced hypersensitivity syndrome Allograft rejection ^c Graft-versus-host disease ^c Thrombotic microangiopathy ^c Higher incidence and severity of infections with CMV, fungi, and other opportunistic pathogens ^c
Chronic infection	Indirect	Multiple sclerosis ^c Hashimoto's thyroiditis ^c Myocarditis, cardiomyopathy ^c Chronic fatigue syndrome ^c Acceleration of evolution to AIDS in HIV-positive individuals ^c

^aCNS, central nervous system; CMV, human cytomegalovirus; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

^bIndirect effect is mainly related to putative immune dysfunction.

^cTo be confirmed.

Obrigado!!!