Persistent Infections

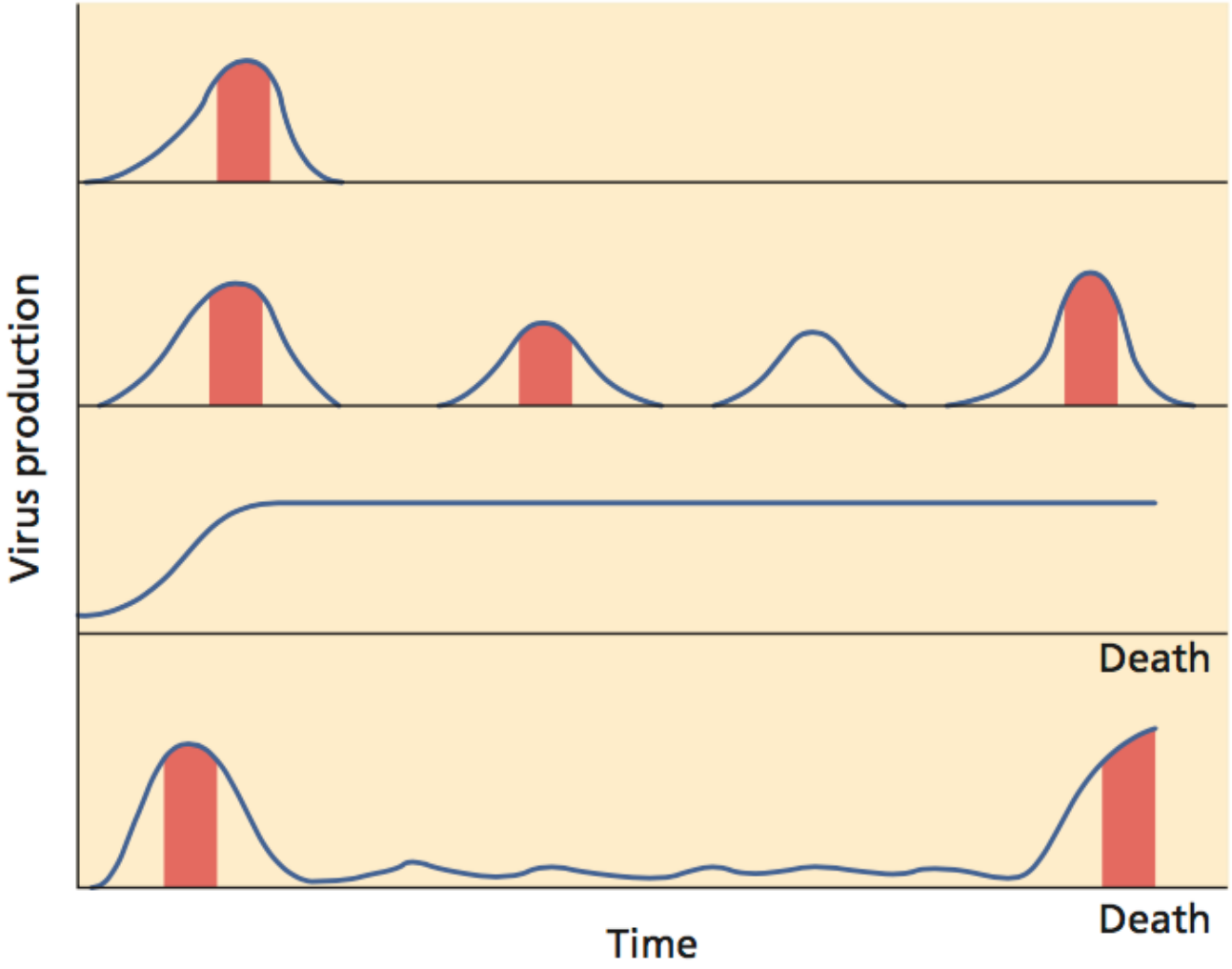
Lecture 17
Biology W3310/4310
Virology
Spring 2015

Paralyze resistance with persistence
–WOODY HAYES

Acute vs persistent infections

- Acute infection - rapid and self-limiting
- Persistent infection - long term, life of host
- Stable, characteristic for each virus family
- Most persistent infections probably begin as an acute infection

General patterns of infection



Acute
- Rhinovirus
- Rotavirus
- Influenza virus

Latent
- Herpes simplex virus

Persistent: asymptomatic
- Lymphocytic choriomeningitis virus
- JC virus

Persistent: pathogenic
- Human immunodeficiency virus
- Human T-lymphotropic virus
- Measles virus SSPE

Principles of Virology, ASM Press

Persistent infections

- Occur when primary infection is not cleared by immune response
- Virions, protein, genomes continue to be produced
- Viral genomes may remain after proteins are not detected

Persistent infections

- No single mechanism
- When cytopathic effects are absent and host defenses are reduced, persistent infection is likely
- Viral immune modulation

Persistent human infections

	Virus	Site(s) of persistence	Consequence(s)
	Adenovirus	Adenoids, tonsils, lymphocytes	None known
*	Epstein-Barr virus	B cells, nasopharyngeal epithelia	Burkitt's lymphoma, Hodgkin's disease
	Human cytomegalovirus	Kidneys, salivary gland, lymphocytes,[a] macrophages,[a] stem cells,[a] stromal cells[a]	Pneumonia, retinitis
*	Hepatitis B virus	Liver, lymphocytes	Cirrhosis, hepatocellular carcinoma
*	Hepatitis C virus	Liver	Cirrhosis, hepatocellular carcinoma
*	Human immunodeficiency virus	$CD4^+$ T cells, macrophages, microglia	AIDS
*	Herpes simplex virus types 1 and 2	Sensory and autonomic ganglia	Cold sore, genital herpes
	Human T lymphotropic virus types 1 and 2	T cells	Leukemia, brain infections
	Papillomavirus	Skin, epithelial cells	Papillomas, carcinomas
*	Polyomavirus BK	Kidneys	Hemorrhagic cystitis
*	Polyomavirus JC	Kidneys, central nervous system	Progressive multifocal leukoencephalopathy
*	Measles virus	Central nervous system	Subacute sclerosing panencephalitis, measles inclusion body encephalitis
	Rubella virus	Central nervous system	Progressive rubella panencephalitis
*	Varicella-zoster virus	Sensory ganglia	Zoster (shingles), postherpetic neuralgia

[a]Proposed but not certain.

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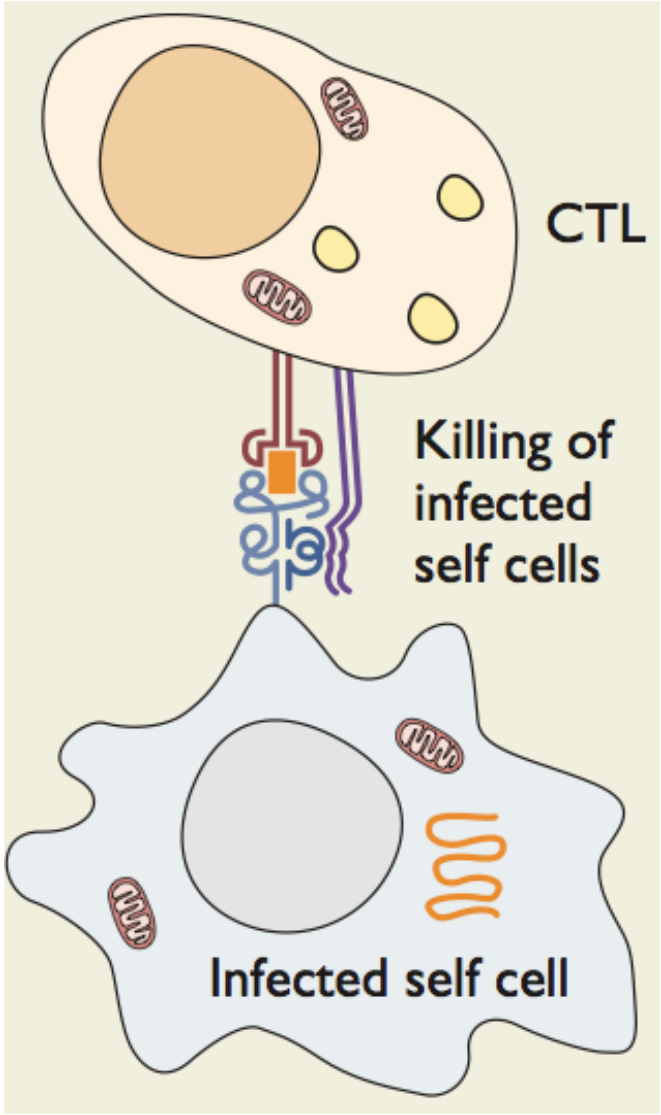
The cytotoxic T lymphocyte response



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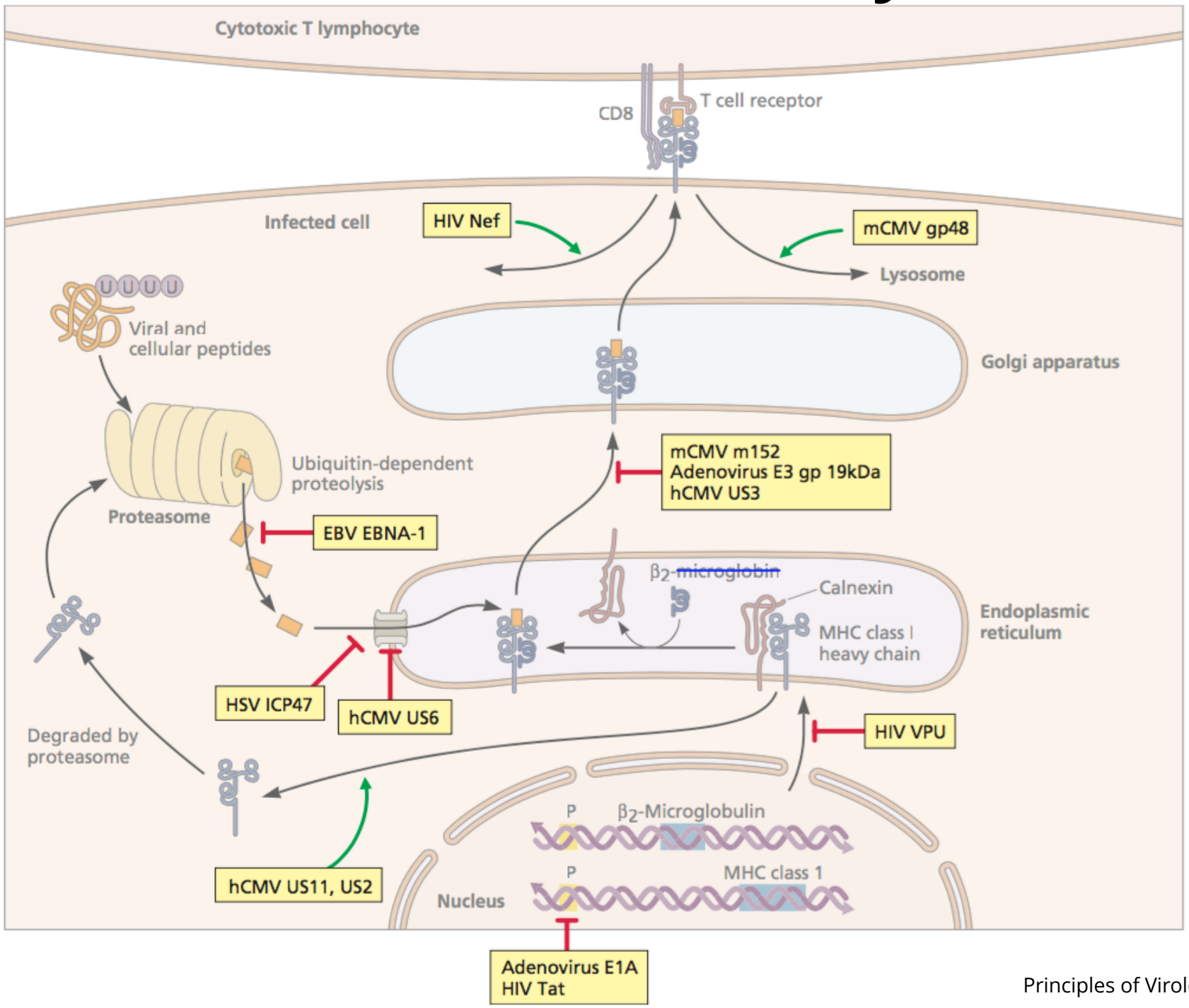
Modulation of MHC I system



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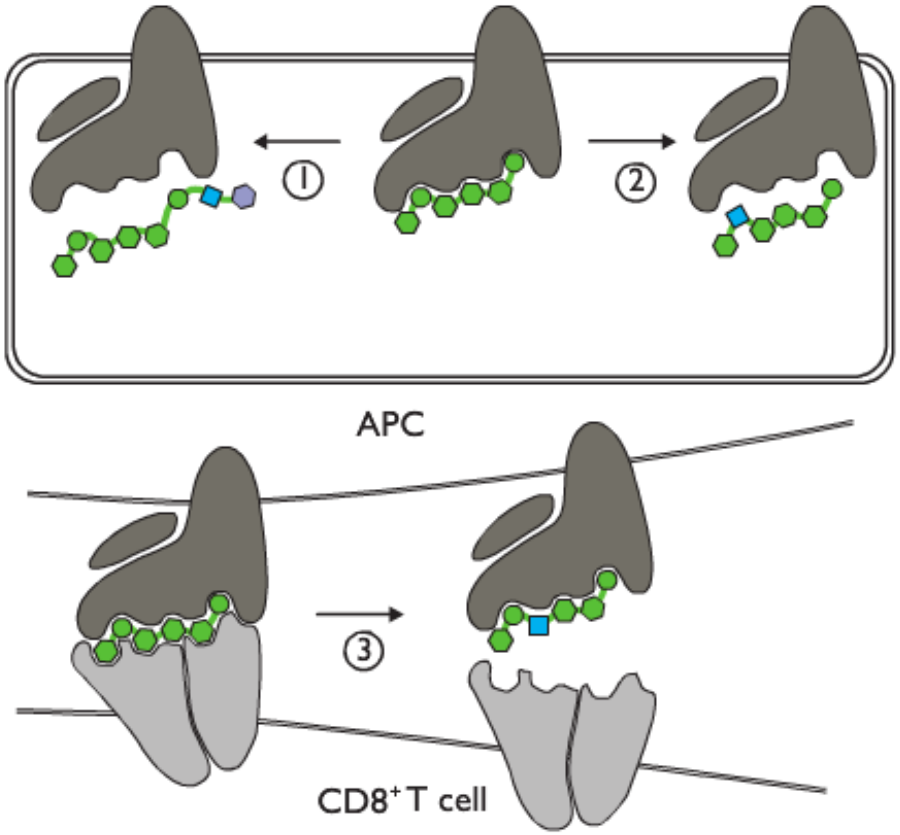
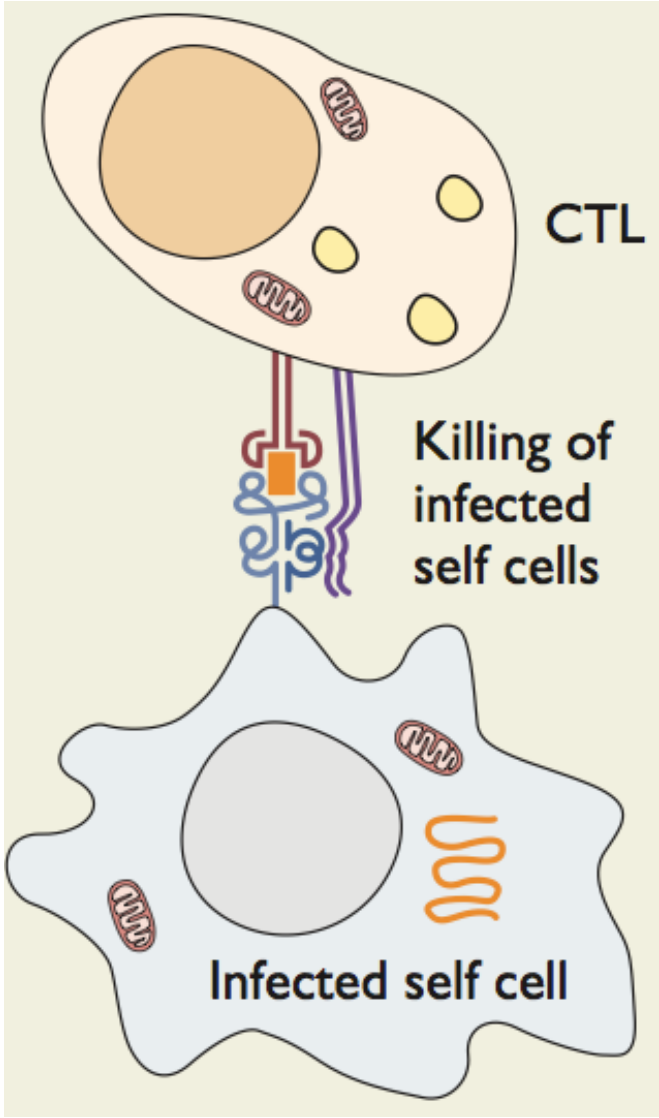
CTL escape mutants

- Herpes simplex virus
- Hepatitis C virus



Changes may also affect proteasomal processing



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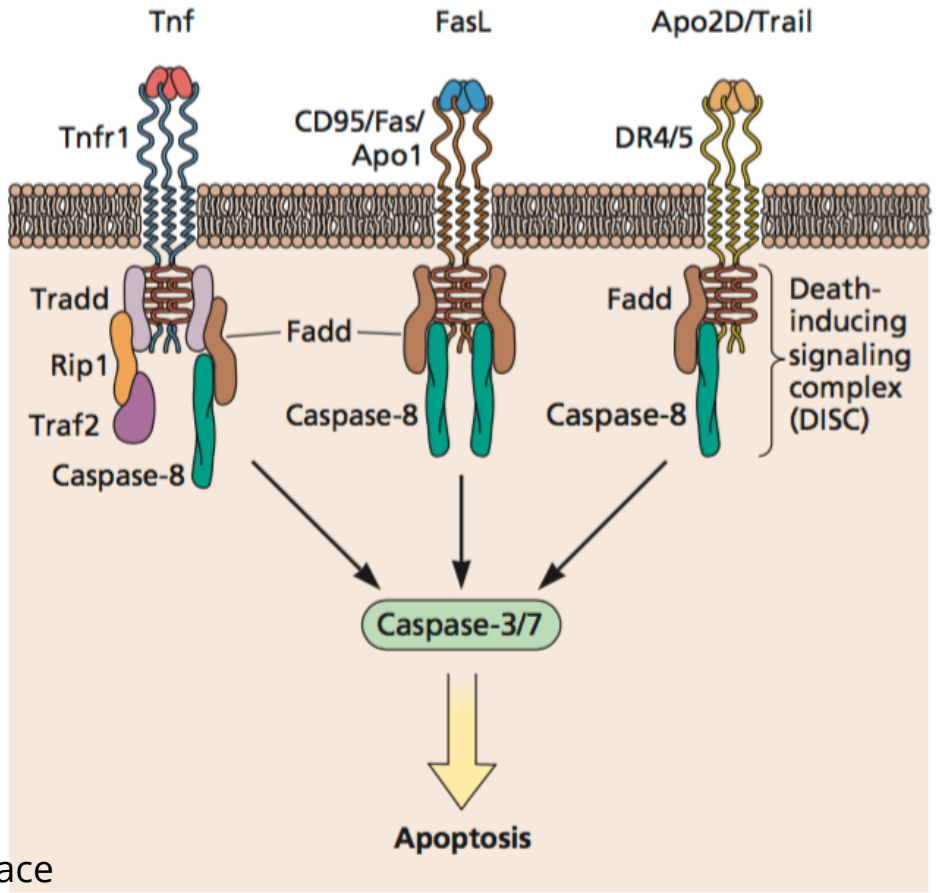
Killing activated T cells

- When CTL engages an infected cell, the CTL may die instead of the target
- An example of viral defense



HIV, CMV induce FasL on cell surface

Principles of Virology, ASM Press

Reduced immune surveillance

- Cells and organs differ in degrees of immune defense
- CNS, vitreous humor of eye, areas of lymphoid drainage devoid of initiators and effectors of immune response (eye, high FasL)
- Could be damaged by fluid accumulation, swelling, and ionic imbalances of inflammation
- Persistent infections of these tissues are common

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Persistence of Ebola Virus in Ocular Fluid during Convalescence

Jay B. Varkey, M.D., Jessica G. Shantha, M.D., Ian Crozier, M.D., Colleen S. Kraft, M.D., G. Marshall Lyon, M.D., Aneesh K. Mehta, M.D., Gokul Kumar, M.D., Justine R. Smith, M.B., B.S., Ph.D., Markus H. Kainulainen, Ph.D., Shannon Whitmer, Ph.D., Ute Ströher, Ph.D., Timothy M. Uyeki, M.D., M.P.H., M.P.P., Bruce S. Ribner, M.D., M.P.H., and Steven Yeh, M.D.

SUMMARY

Among the survivors of Ebola virus disease (EVD), complications that include uveitis can develop during convalescence, although the incidence and pathogenesis of EVD-associated uveitis are unknown. We describe a patient who recovered from EVD and was subsequently found to have severe unilateral uveitis during convalescence. Viable *Zaire ebolavirus* (EBOV) was detected in aqueous humor 14 weeks after the onset of EVD and 9 weeks after the clearance of viremia.

DOI: 10.1056/NEJMoa1500306

Infection of immune cells

- Many viruses infect cells of the immune system
- Measles virus infection of APCs
- HIV infection of CD4 T cells, monocytes, macrophages, dendritic cells

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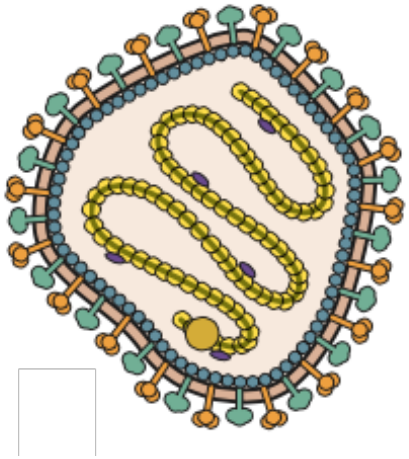
Which of the following are features of persistent infections?

1. They last the lifetime of the host
2. Viral immune modulation is involved
3. Immune cells may be infected
4. They may occur in areas of reduced immune surveillance
5. All of the above

Measles virus



- *Paramyxoviridae*
- One of most contagious human viruses
- 114,900 deaths globally in 2014 - preventable
- Lifelong immunity after infection
- A classic acute virus infection

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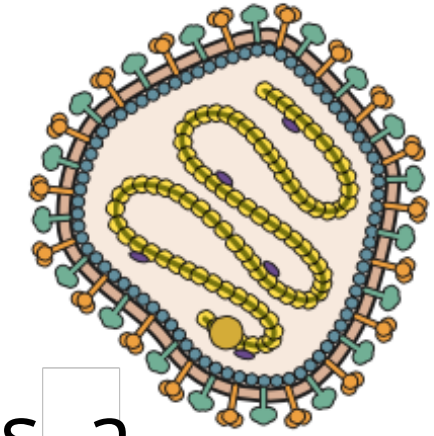
SSPE



- Subacute sclerosing panencephalitis, a progressive, degenerative encephalitis
- After measles, 1/million contract SSPE
- 6-8 yr incubation
- Viral nucleoprotein particles detected in brain, but no infections virus produced
- Genomes spread between synaptically connected neurons

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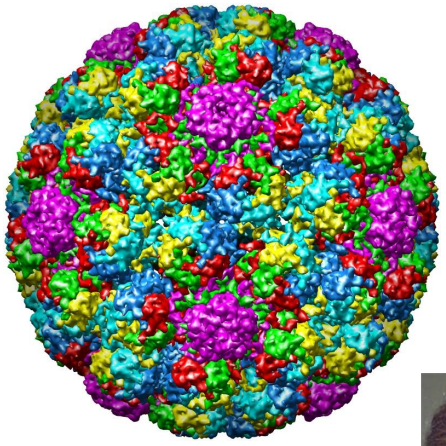

Polyomavirus

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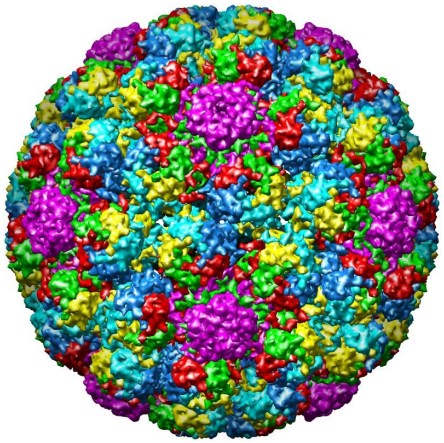
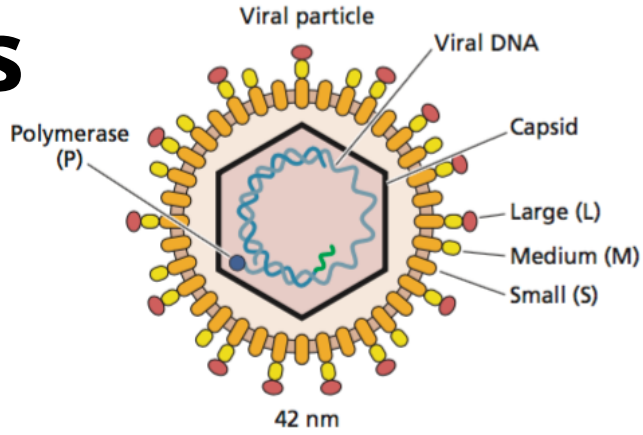


Polyomavirus persistence

- Infected for life
- Variety of organs - kidney, intestine, respiratory tract
- 100,000 particles/ml in urine
- Unknown mechanisms of persistence
- Progressive Multifocal Leukoencephalopathy (PML)
- TWiV #250 - Wookie viruses twiv.tv/2013/09/15/twiv-250-wookie-viruses/

Hepatitis B virus



- Transmitted by exposure to blood (childbirth, transfusion, sex, drug use, tattooing, nosocomial)
- Main target is hepatocyte
- 95% of adults, 5-10% newborns resolve acute infection

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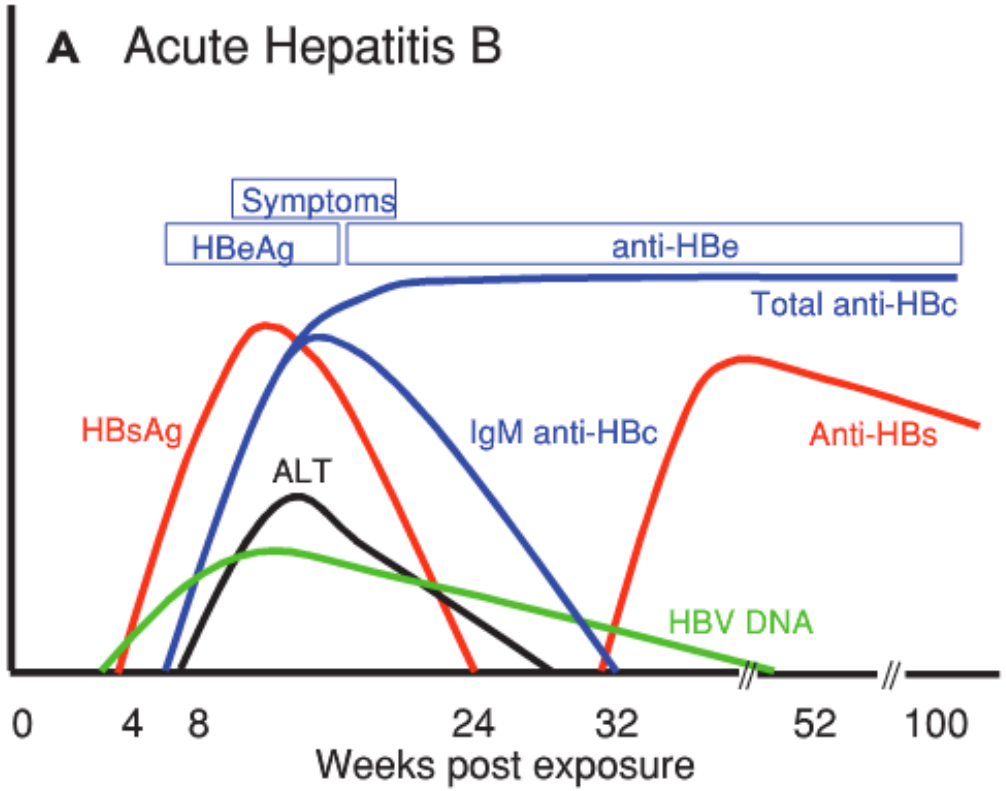
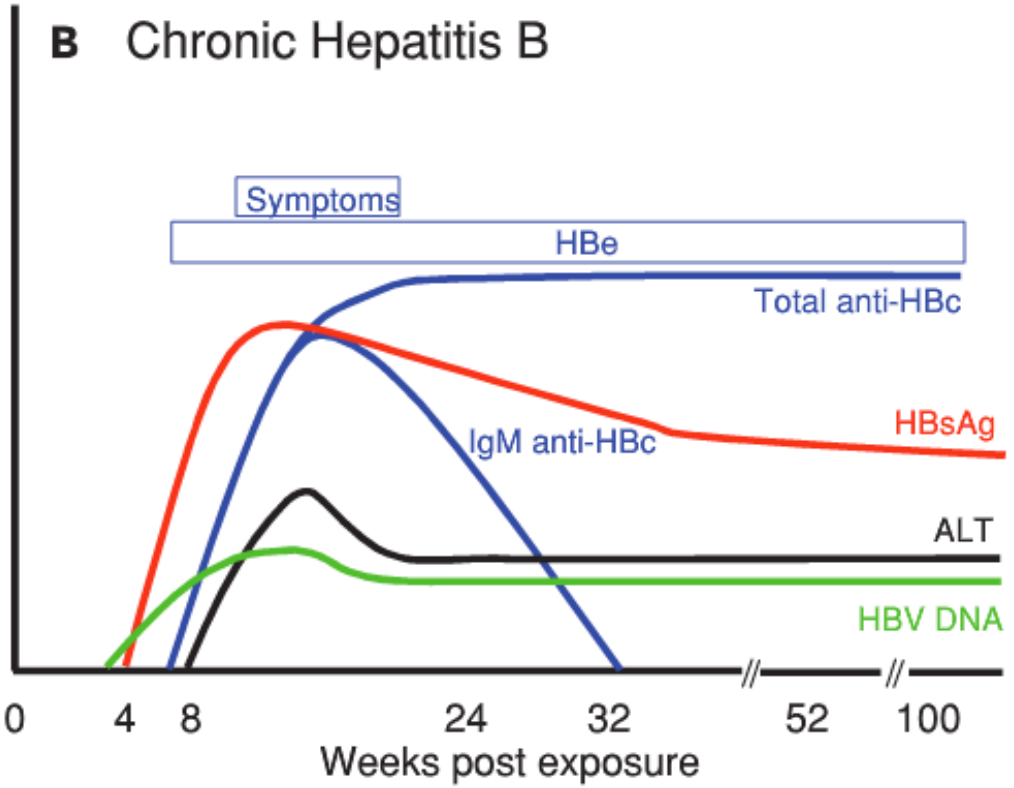
Hepatitis B virus

- ~350 million worldwide have chronic HBV
- Hepatocellular carcinoma



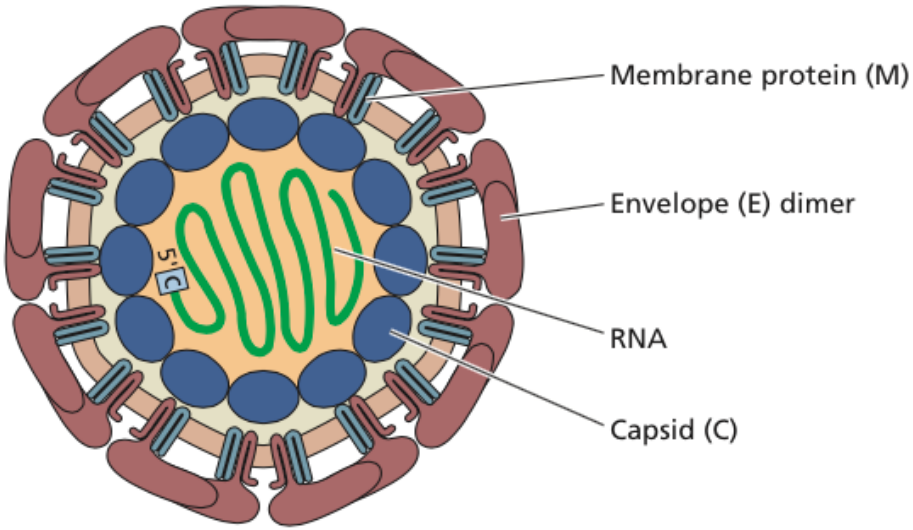


Fields Virology, Wolters Kluwer

Chronic HBV

- Virus is not cytopathic (!) for hepatocytes
- CTL kill infected hepatocytes
- During chronic infection, fibrosis leads to cirrhosis, liver failure
- HCC develops after 20-30 yr of chronic (often asymptomatic) infection

Hepatitis C virus



- + strand RNA virus, *Flaviviridae*
- Transmitted by exposure to contaminated blood (sex, drug use, tattooing, during birth)
- 2.2% of human population (185 million) infected

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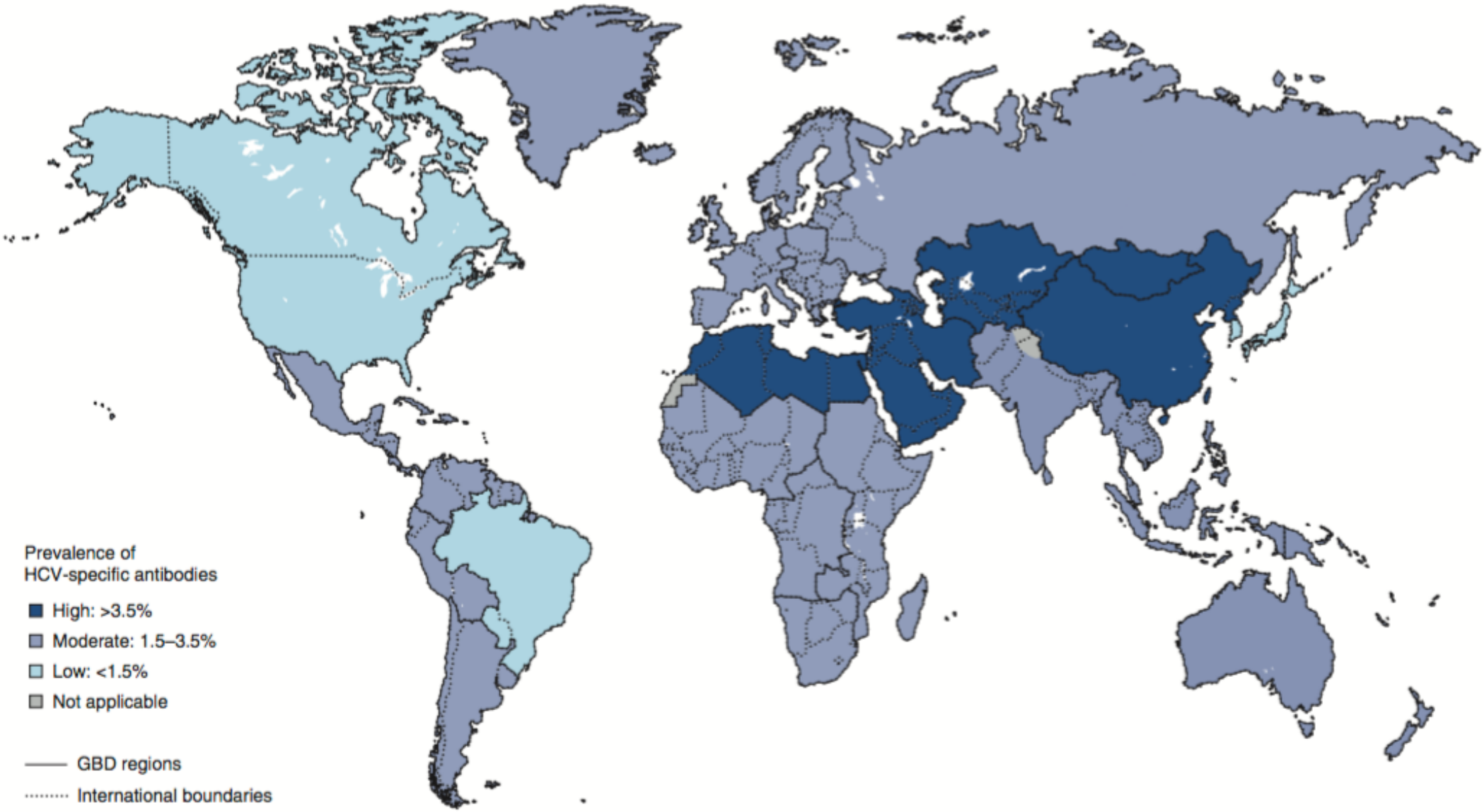
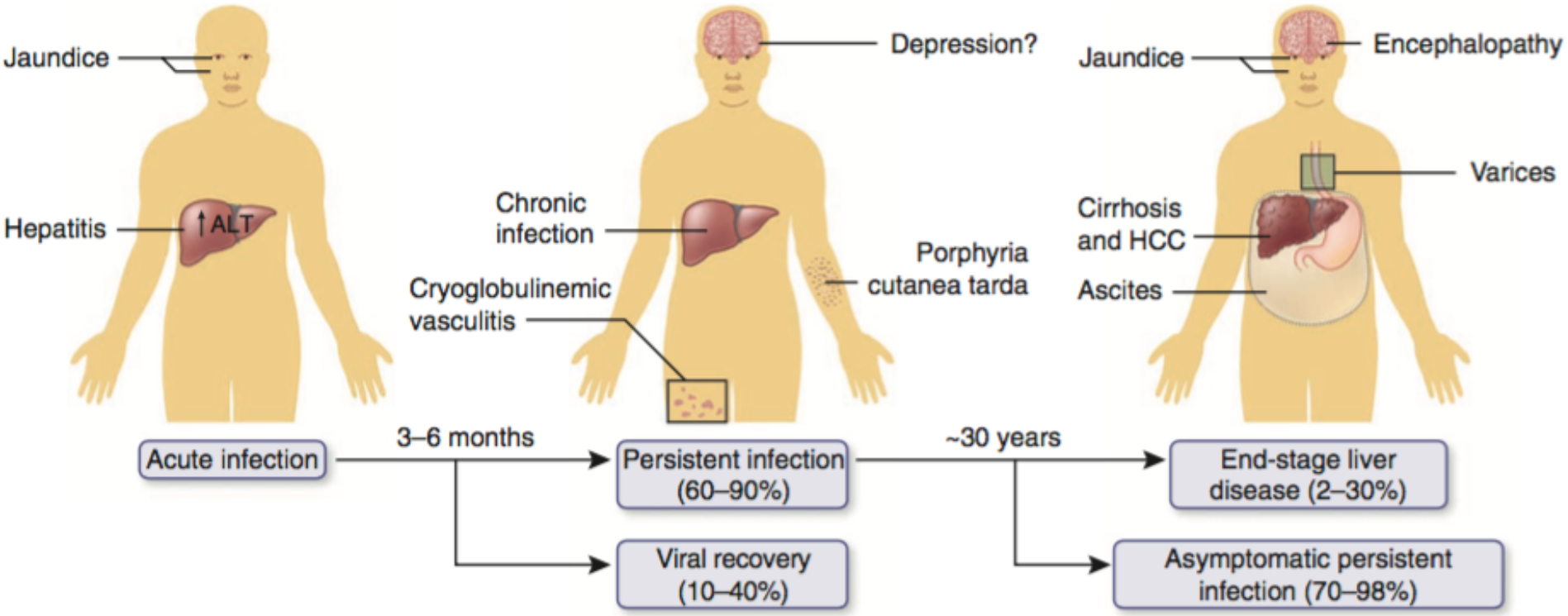
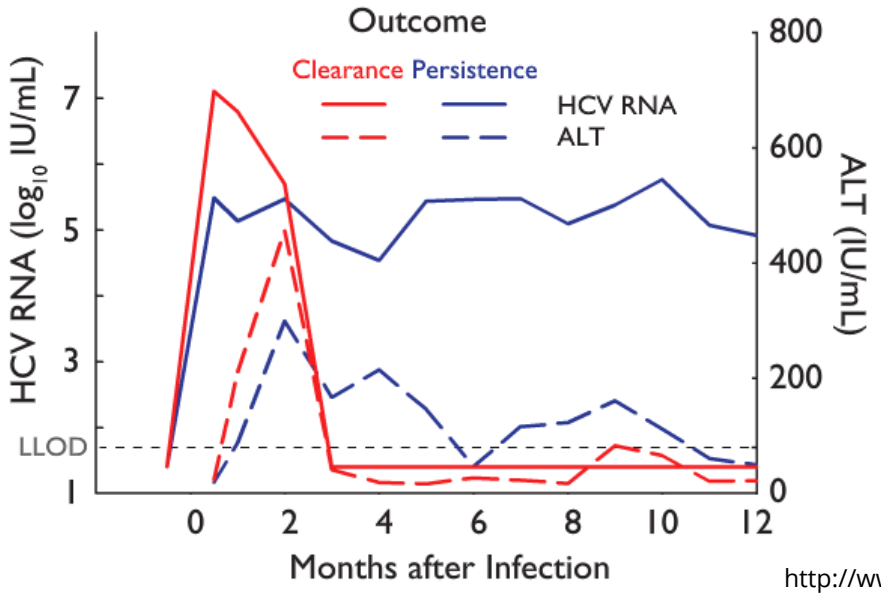
HCV specific antibodies



http://www.nature.com/nm/journal/v19/n7/full/nm.3184.html

HCV



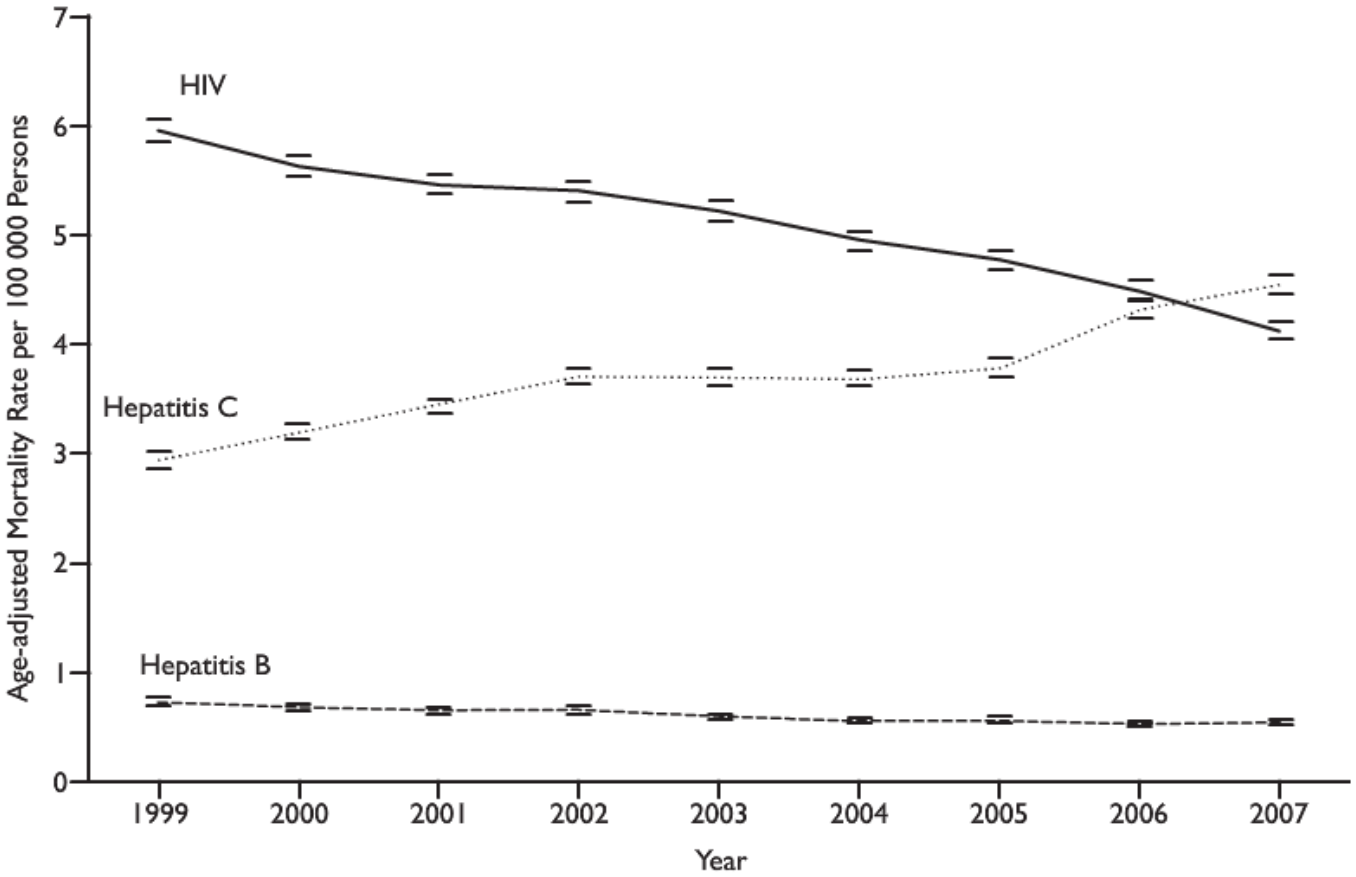


Fields Virology, Wolters Kluwer

http://www.nature.com/nm/journal/v19/n7/full/nm.3184.html

HCV

- HCV clearance associated with IFN-λ3 alleles (GWAS)
- Multiple immune modulation mechanisms



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Which are shared features of persistent infections with polyomavirus, HBV, and HCV?

1. Genomes are present but not expressed
2. Liver damage
3. Kidney damage
4. Virus particles are produced
5. All of the above

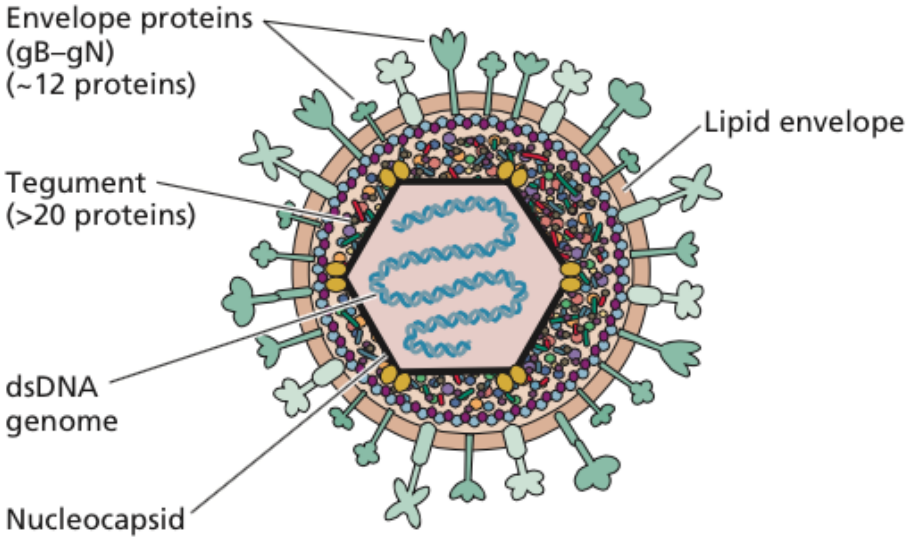
Latent infections - general properties

- Viral gene products that promote productive replication are not made or found in low concentrations
- Cells harboring the latent viral genome are poorly recognized by the immune system
- Viral genome persists intact so that productive infection can be initiated to *spread infection* to new hosts

State of the genome

- Non-replicating DNA in a non-dividing cell
  - HSV, VZV in neurons
- Autonomous self-replicating DNA in dividing cell
  - EBV, CMV, HPV, HBV, KSHV
- Integrated into host chromosome, replicates with host
  - HHV6

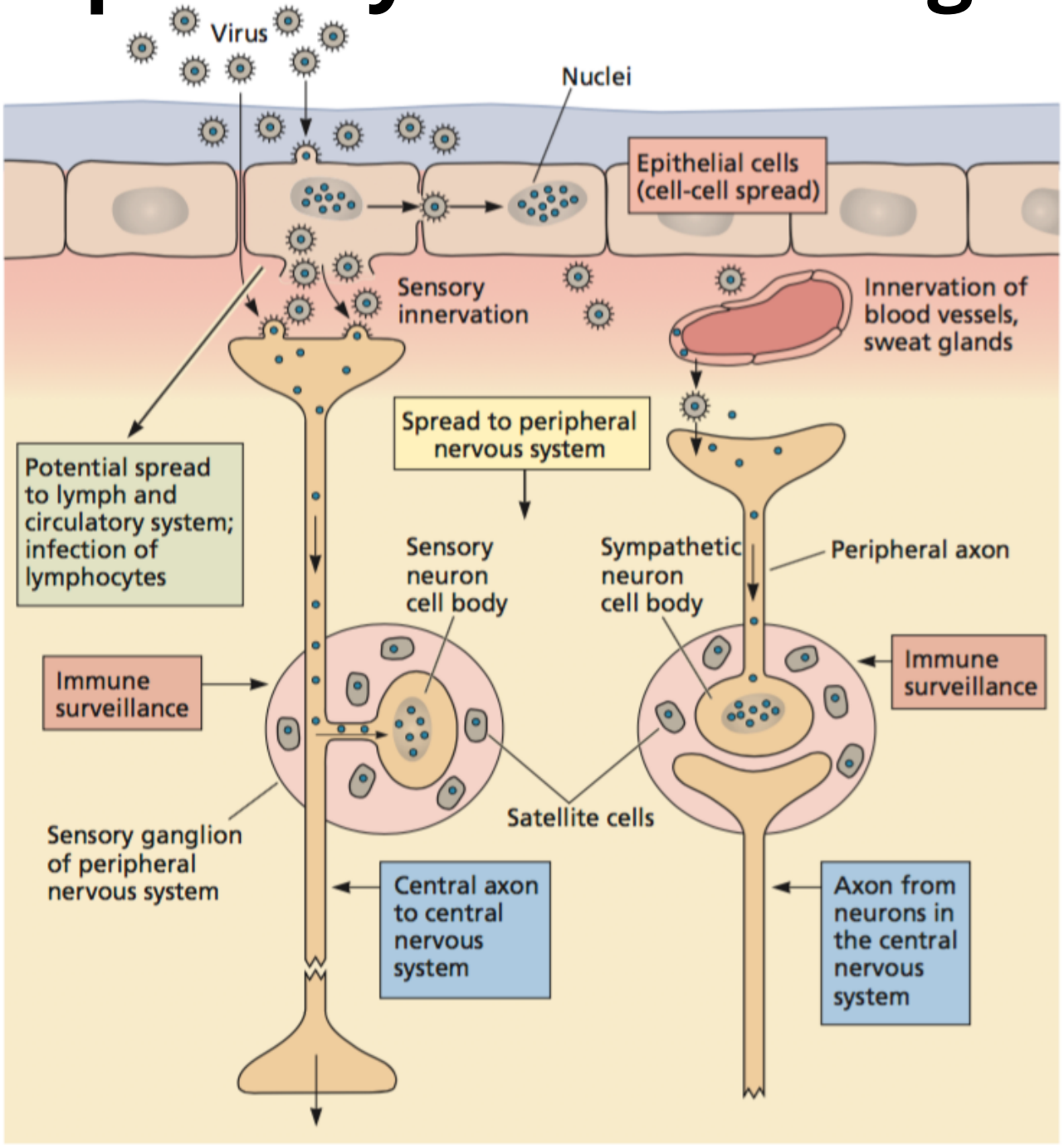
Herpes simplex virus infections



- US >80% seropositive with genomes in PNS
- Millions carry latent viral genomes in nervous system without symptoms
- 40 million experience recurrent herpes disease
- HSV-1, HSV-2
- A well-adapted pathogen

Principles of Virology, ASM Press

HSV primary infection of ganglia



80% of babies infected at birth

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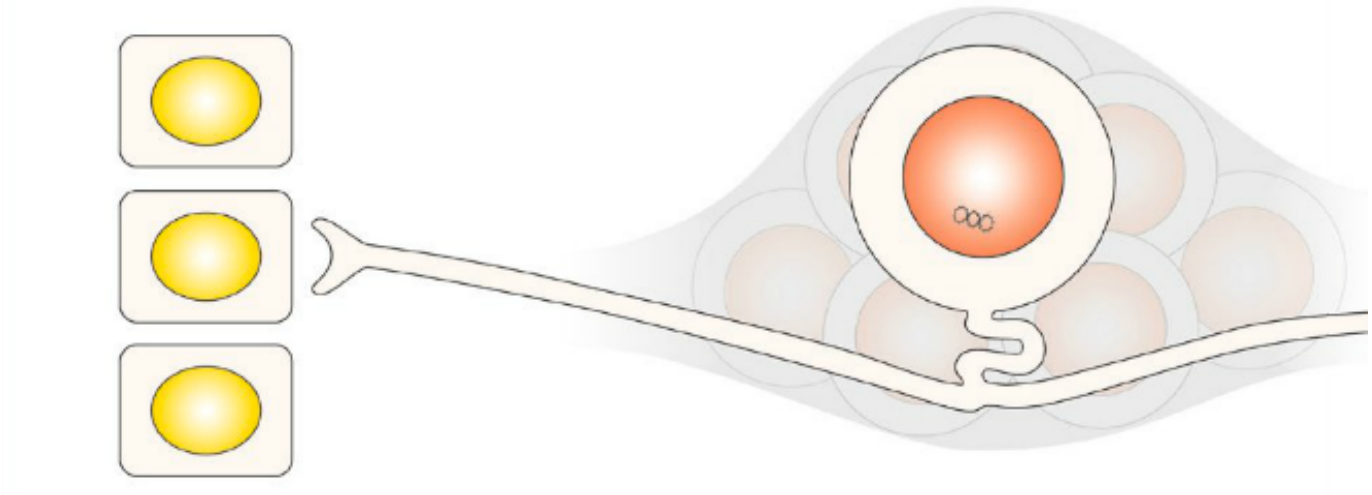
Post-infection events in neurons



- Viral genome silenced, coated with nucleosomes
- Multiple copies of episomal viral DNA remain in nucleus
- No further replication needed to persist - neurons do not divide
- Herpes is forever - drugs and vaccines cannot cure a latent infection

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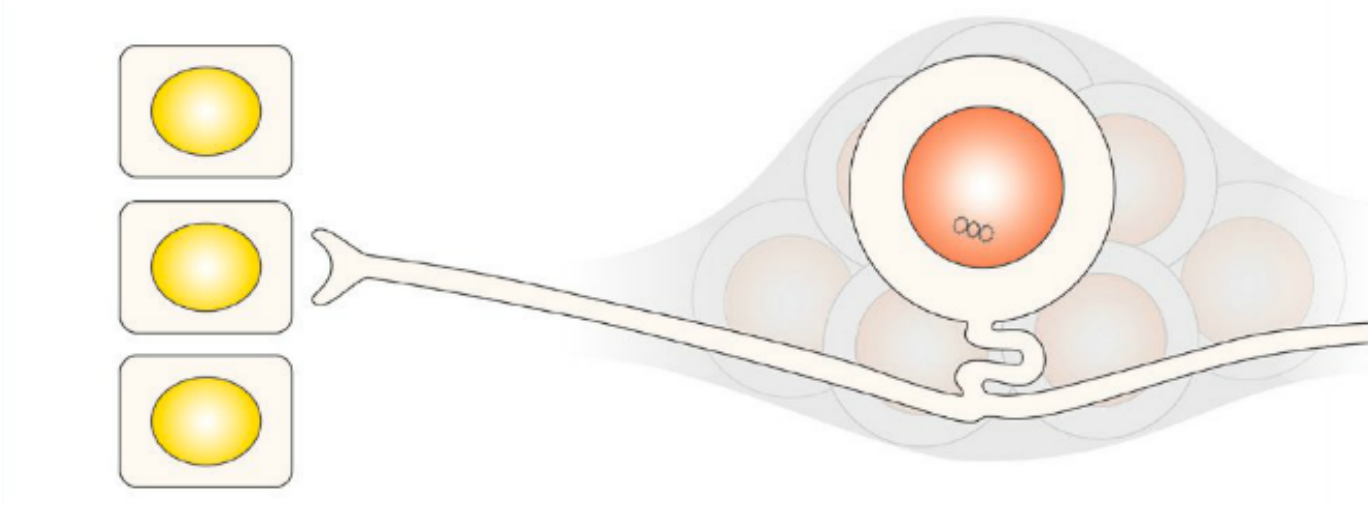
Latency associated transcript



- Only LATs, miRNAs made in latently infected neurons
- No proteins translated from LATs
- RNA silencing to maintain viral genome in latent state
- Host contribution

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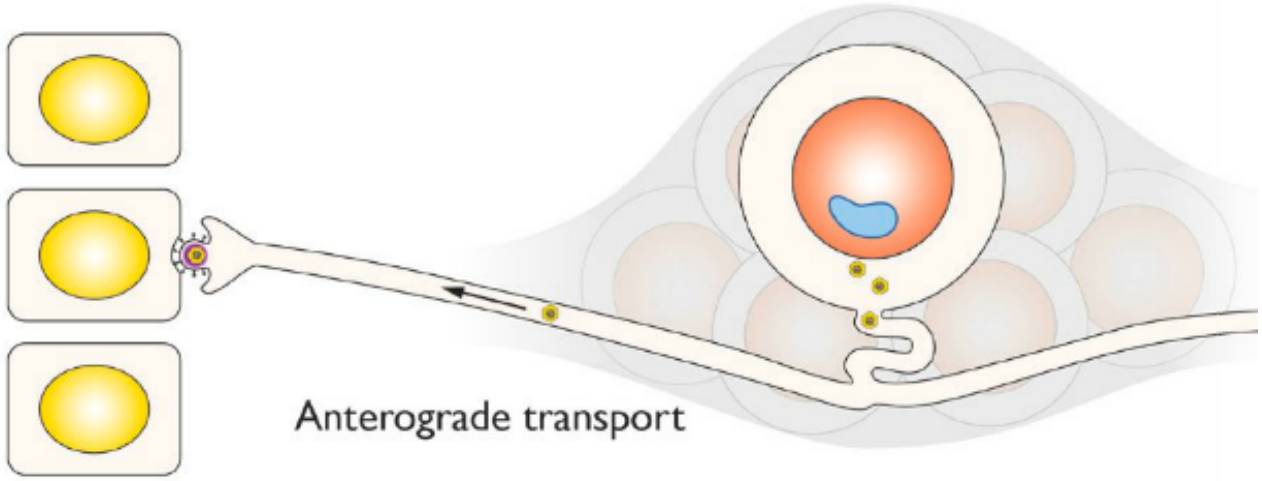
Reactivation



- Small number of neurons in ganglion reactivate
- Virions appear in mucosal tissue innervated by latently infected ganglia, blisters ensue (not always)
- This is how infection is transmitted (intimate contact)
- Immune response is too slow (viral antagonism) to prevent shedding
- Some reactivate every 2-3 weeks; others never

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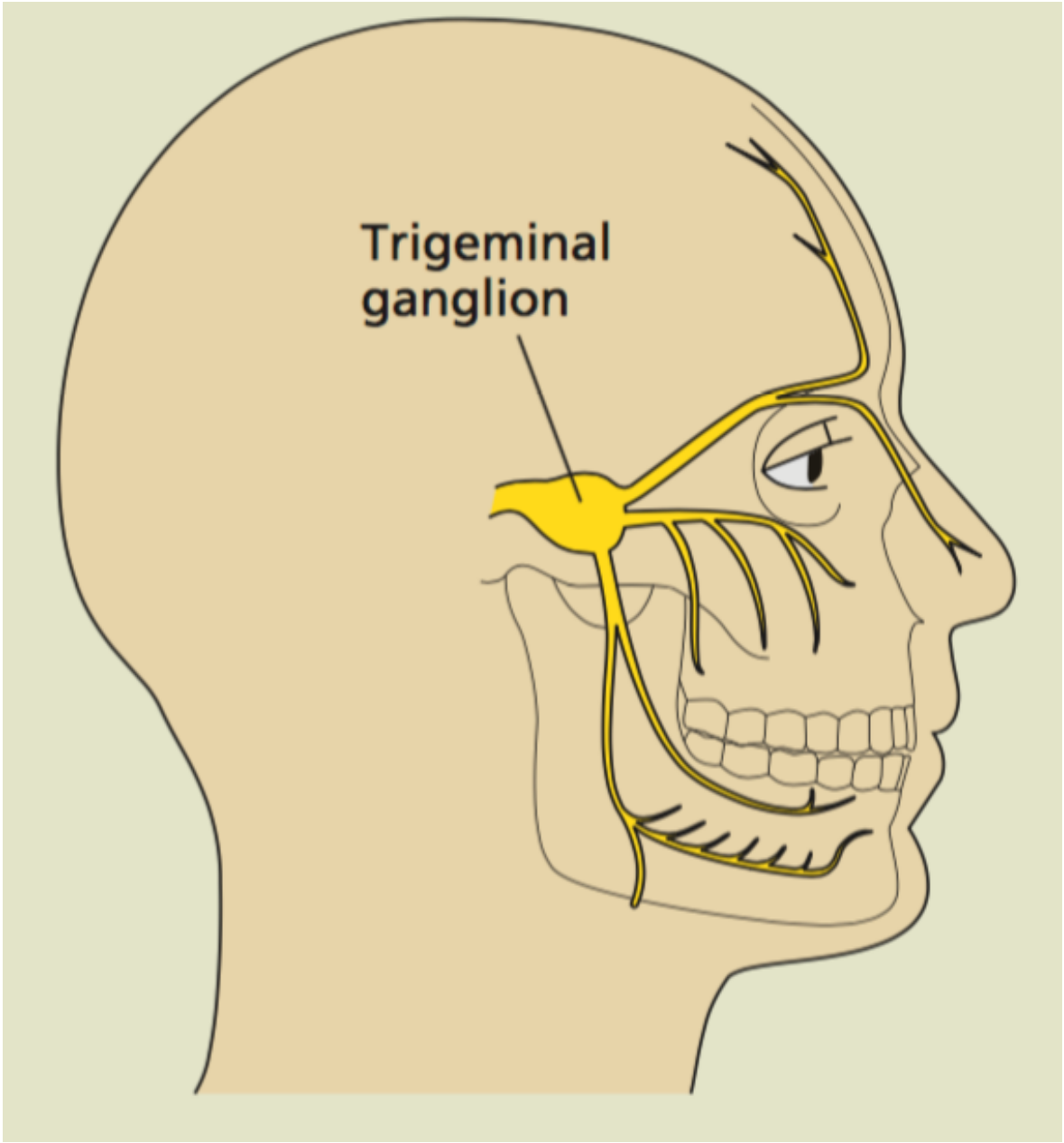

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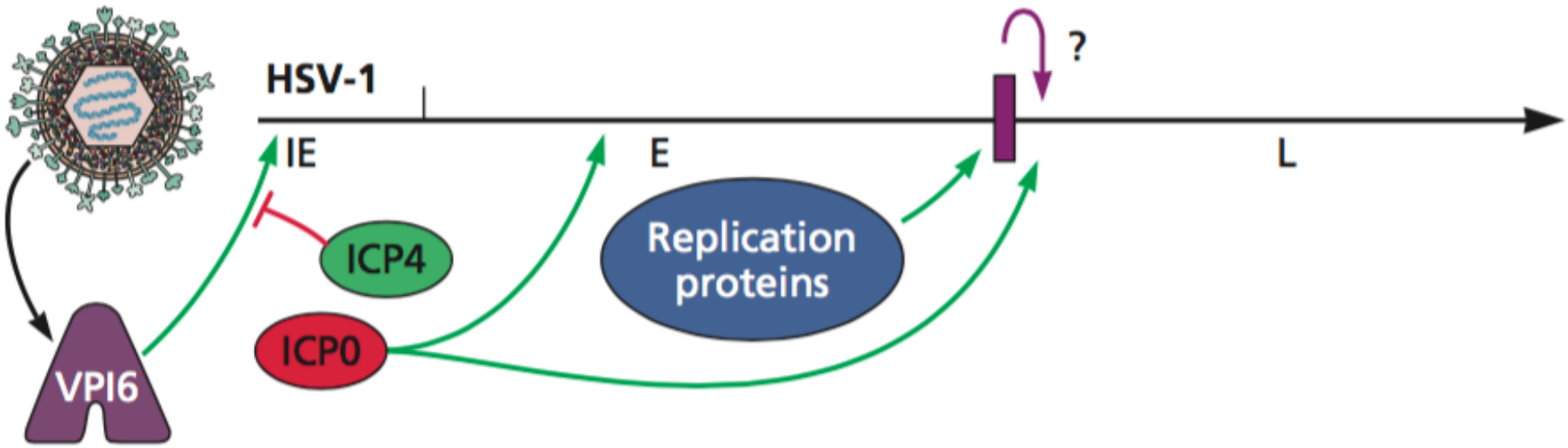
Triggers of reactivation

- Sunburn (UV), physical or emotional stress, nerve damage, hormonal imbalance, steroids
- Stimulate production of viral proteins needed to activate viral transcription program
- Immediate early proteins: ICP0 can reactivate



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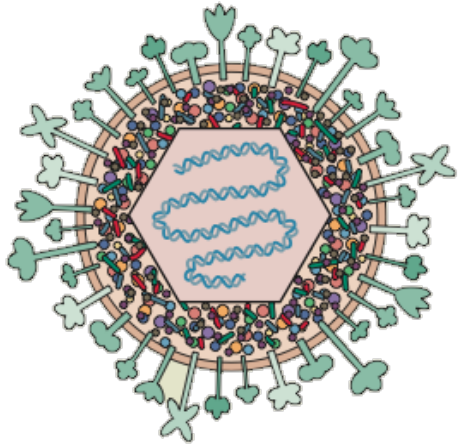
Persistence of herpes simplex virus in nerve ganglia requires which of the following?

1. Continuous episomal DNA replication
2. Low level production of virions
3. Silencing of all gene expression except LAT and miRNA
4. UV light, stress, or steroids
5. All of the above

Epstein-Barr virus



- 95% of US adults are seropositive and carry genome
- Genome resides in B lymphocytes
- Most are infected at an early age, are asymptomatic
- Causal agent of:
  - Infectious mononucleosis
  - Human cancers (Hodgkins lymphoma, nasopharyngeal carcinoma, Burkitt's lymphoma)

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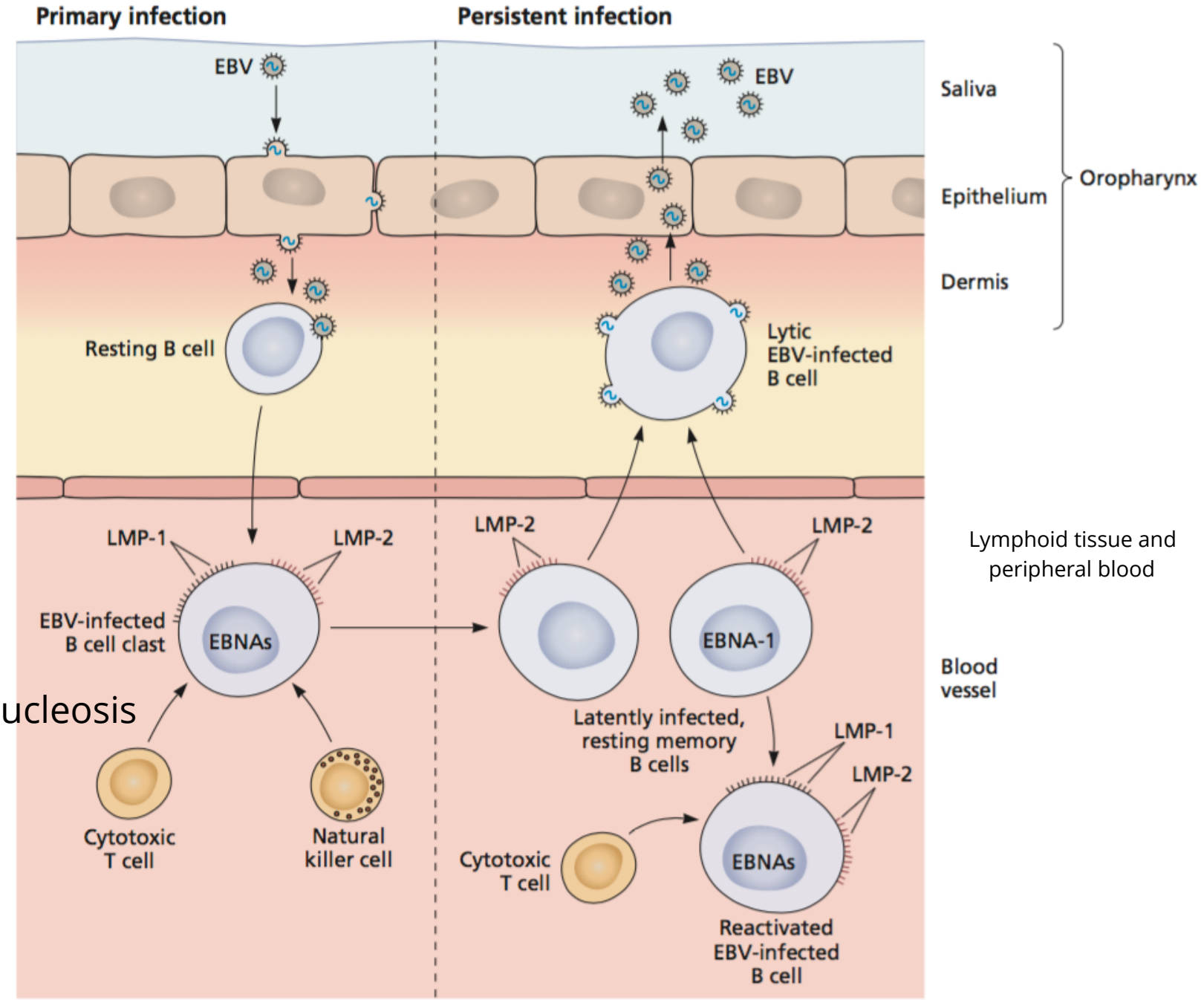
EBV primary and latent infection



nfectious mononucleosis

B cells are essential for EBV latency

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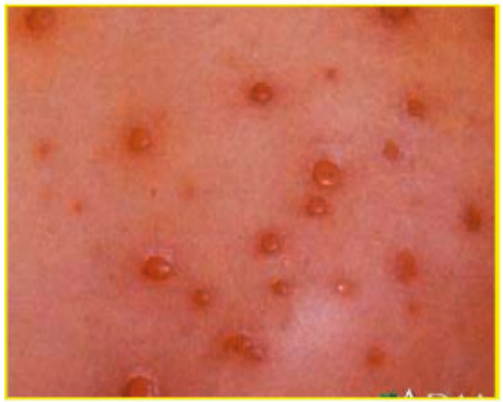
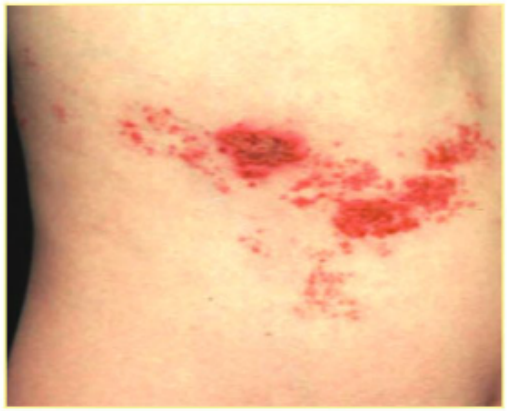
EBV latency

- Viral DNA is self-replicating episome, associates with nucleosomes in B cells
- Produces limited repertoire of viral genes
- B cells home to bone marrow and lymphoid organs
- Not killed by CTLs or antibody unless reactivation occurs (modulation of MHC)

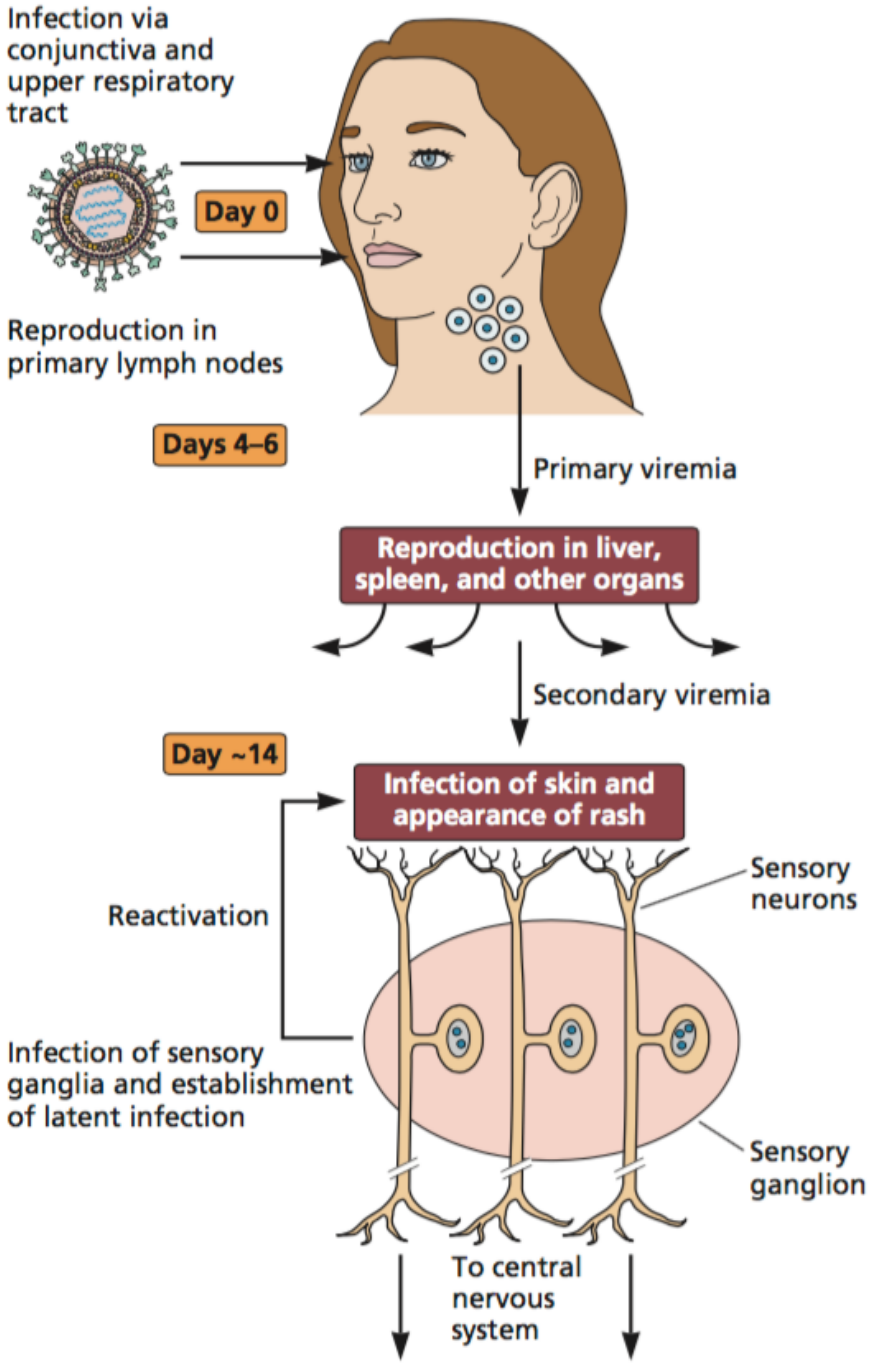
Varicella-zoster virus (VZV)

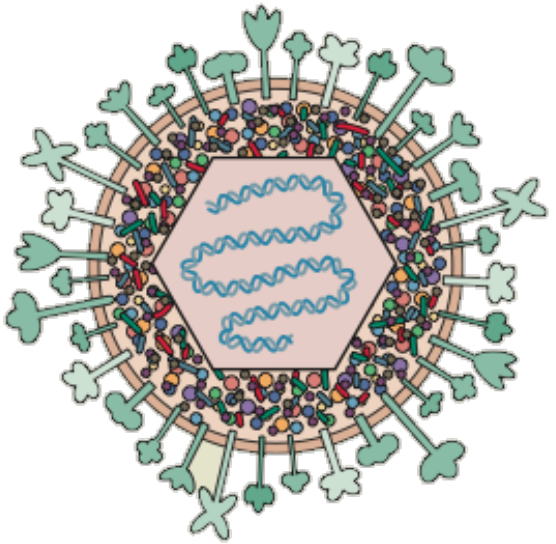


Varicella (chickenpox)



Herpes zoster (shingles)





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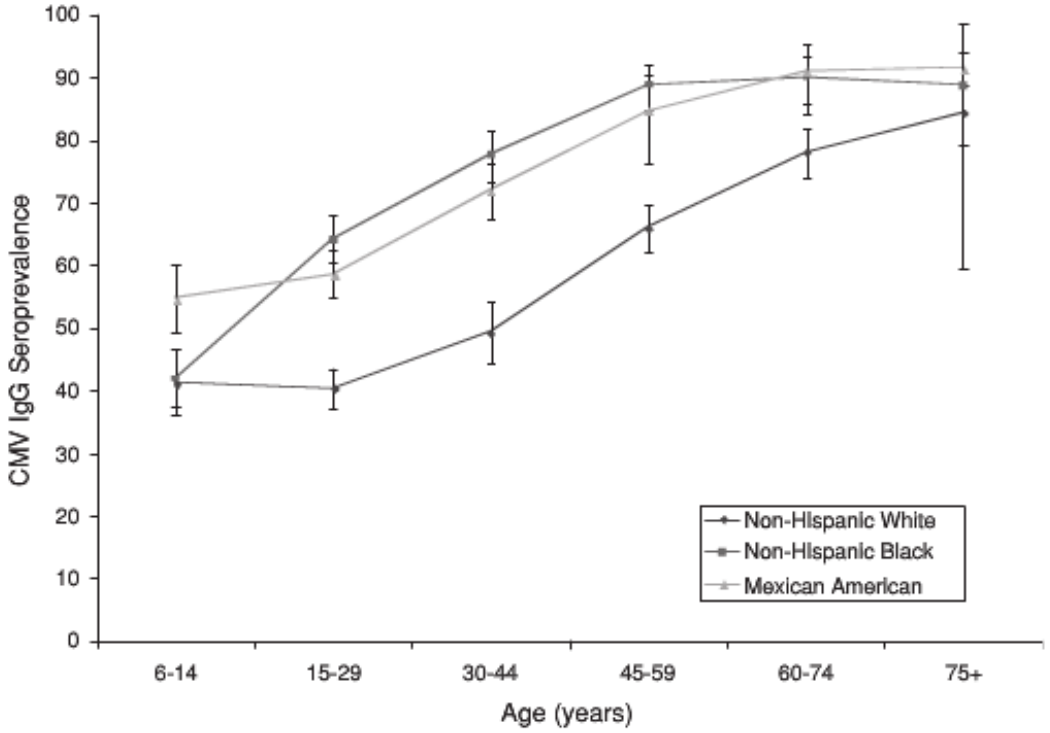
Principles of Virology, ASM Press

VZV

- 99% adults infected pre-vaccine, 30% develop zoster, 2/3 >50 years of age
- Latency: Episomal viral DNA, 2-9 genomes in 1-7% of neurons (non-replicating)
- Viral gene expression is restricted, IE, E, L genes
- Factors that trigger reactivation from neurons are unknown

Cytomegalovirus (HCMV)

- High seroprevalence (50-99%) globally
- Transmitted by respiratory routes (virus in saliva), urine, sex
- Replicates in peripheral blood leukocytes, endothelial cells



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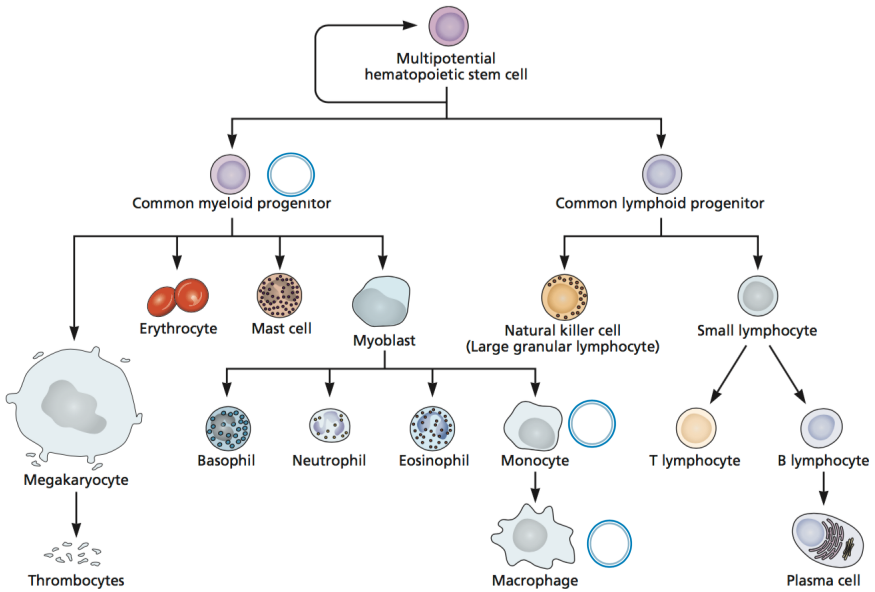
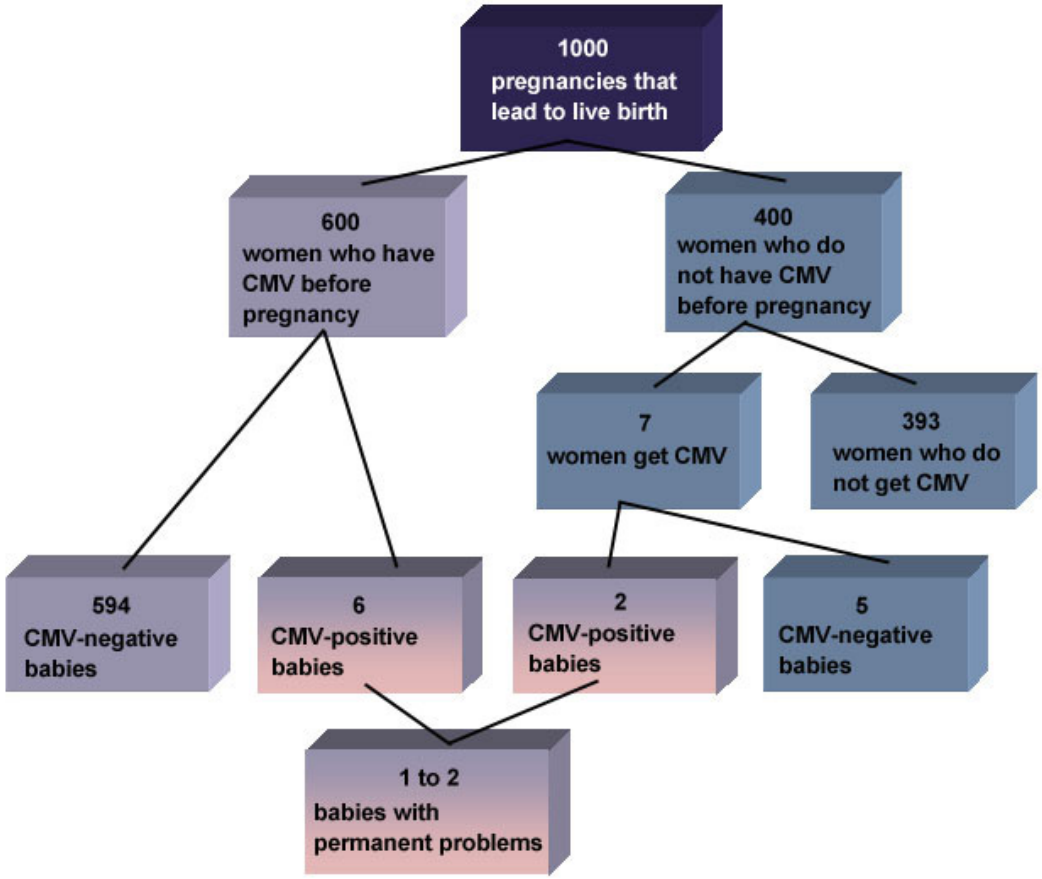
HCMV

- Primary infection in immunocompetent host usually asymptomatic or febrile, mono-like illness
- Persistent shedding of virus in saliva and urine for months to years
- Resolved by cellular immune response, but latently infected myeloid cells remain in bone marrow (precursors of monocytes, macrophages, dendritic cells)



HCMV

- Major problem in organ transplantation
- Virus crosses placenta, can cause severe multiorgan congenital defects, death



http://www.cdc.gov/cmv/trends-stats.html

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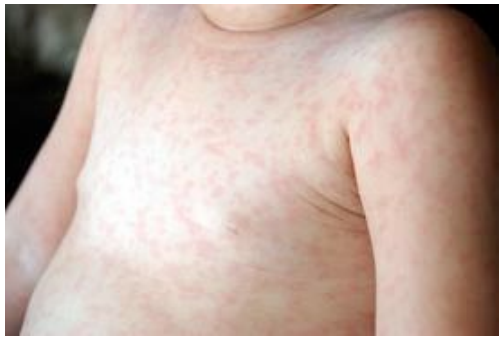
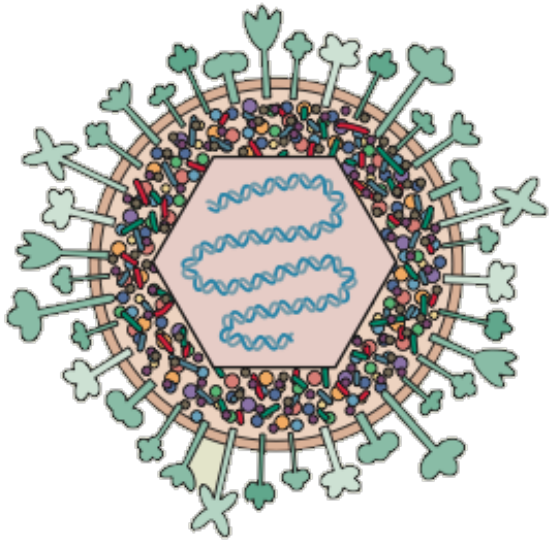
What do persistent infections with EBV, VZV, and CMV have in common?

1. B cells are essential for latent infection
2. May cause congenital birth defects
3. Viral DNA persists as an episome
4. The factors governing reactivation are well known
5. All of the above

HHV-6, HHV-7

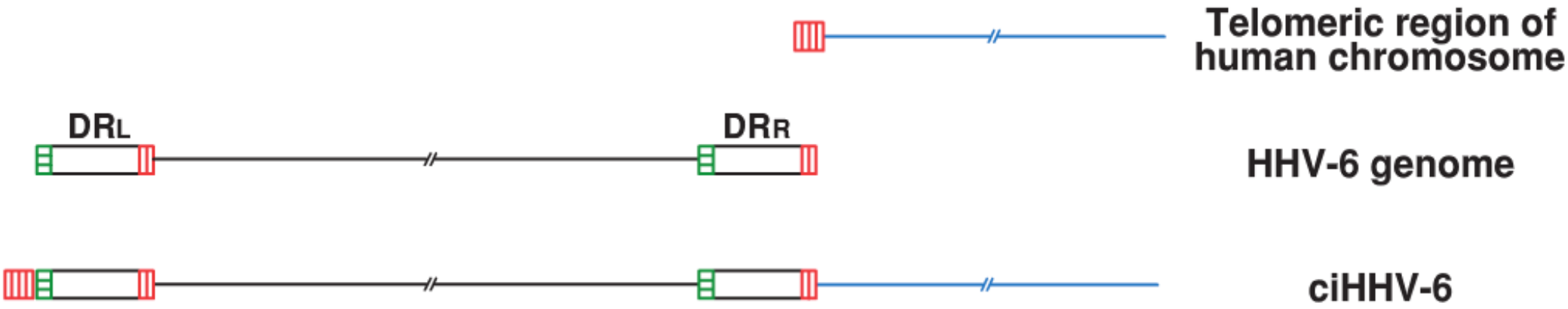




- Agents of exanthem subitum, mild childhood rash (sixth disease)
- >85% of adults have antibody to both viruses
- Horizontal infection through respiratory secretions, parent to child
- Infect lymphoid, endothelial, liver, CNS, salivary cells
- Latency: HHV-6 monocytes, macrophages, CD34+ progenitors; HHV-7 CD4+ lymphocytes

Principles of Virology, ASM Press

HHV-6 integration



- In some cell types viral DNA integrates into telomeres
- About 1% of transmission acquires HHV-6 via germline
- Plausible strategy for latency and transmission

Fields Virology, Wolters Kluwer