Intrinsic and innate defenses

Session 13

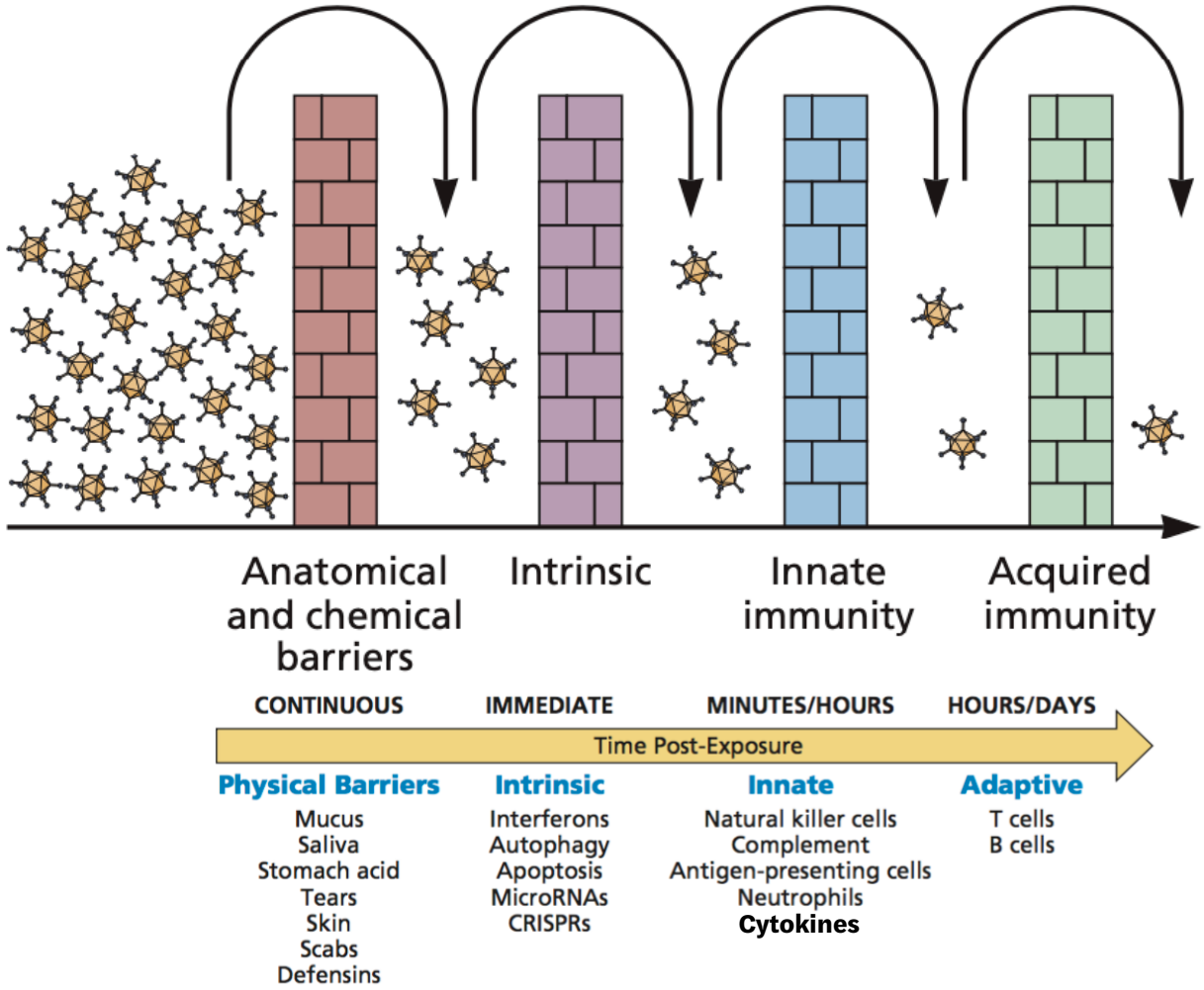
Virology Live

Fall 2021

The trouble with facts is that there are so many of them

–Anonymous

Host defenses



Principles of Virology, ASM Press

Host defenses

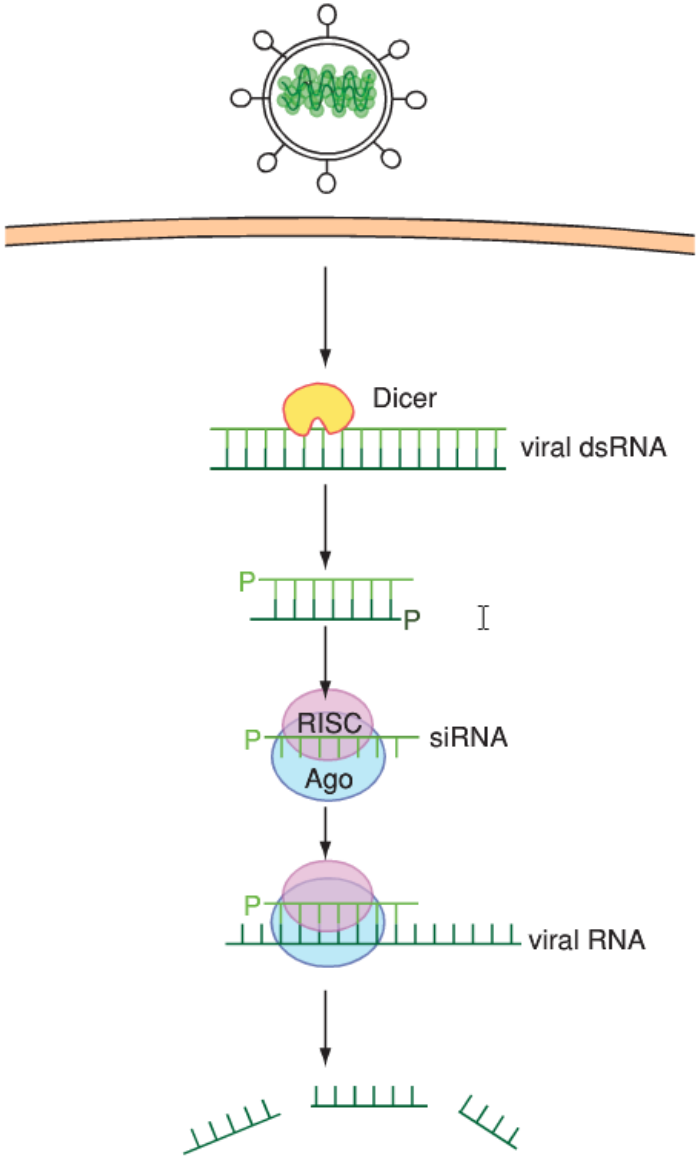
- Intrinsic
  - *Always present* in the uninfected cell
  - Apoptosis, autophagy, RNA silencing, antiviral proteins
- Innate immune system: *Induced* by infection
- Adaptive immune system: *Tailored* to pathogen

RNA interference

Plant & invertebrate cells

Mammals - present or not needed?

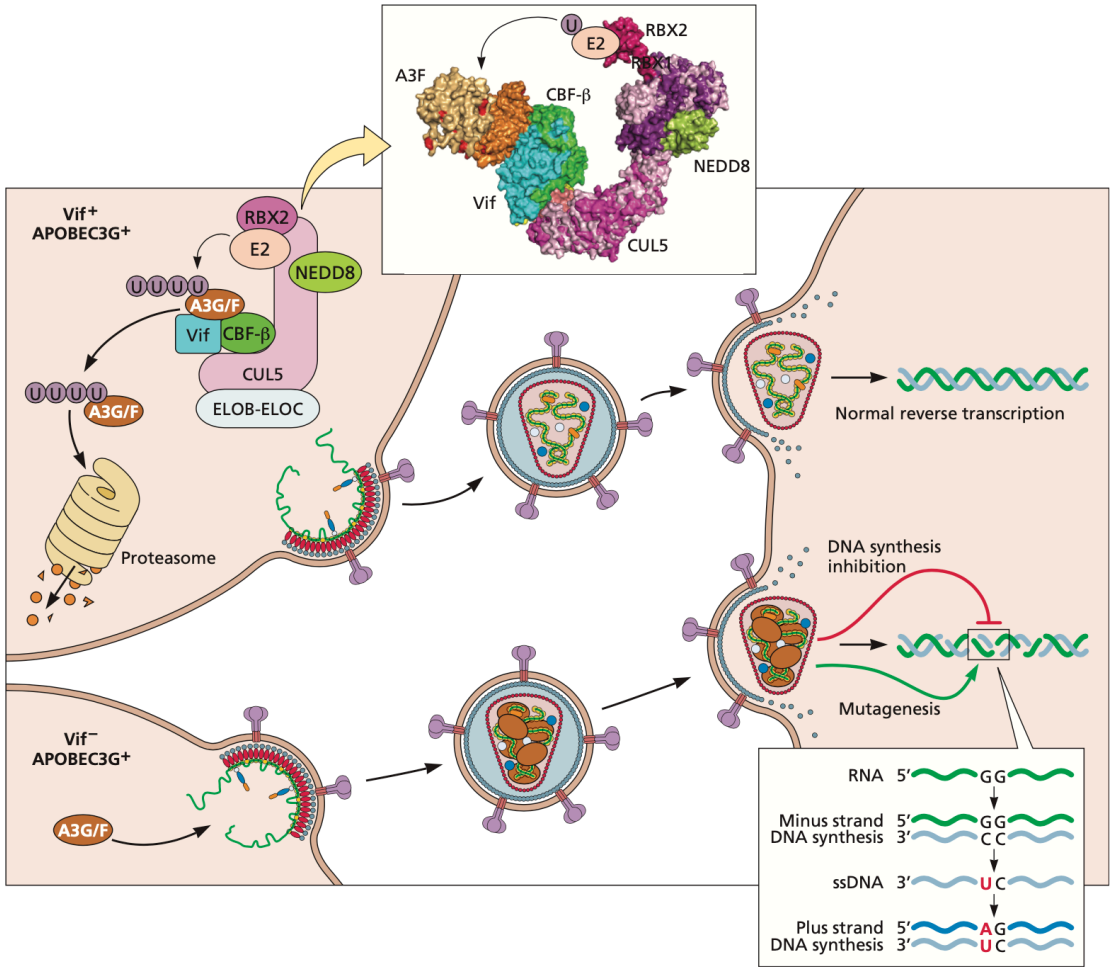
Countermeasures!

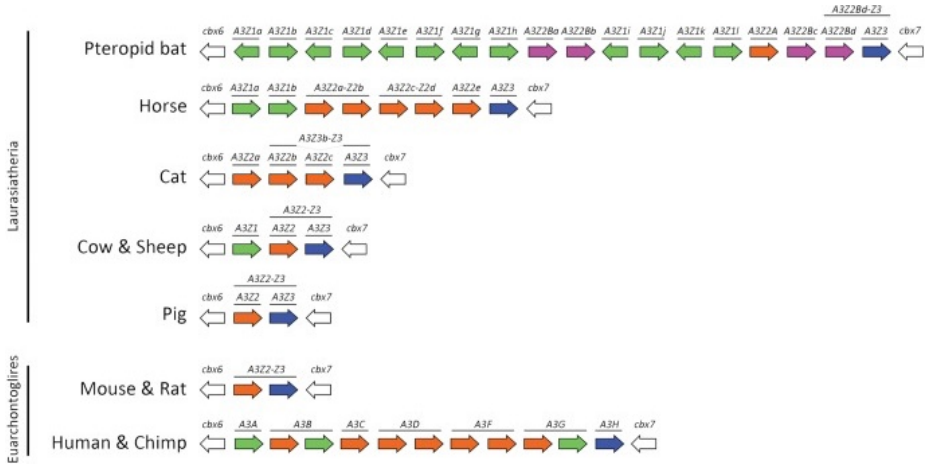


Fields Virology, Wolters Kluwer

APOBEC3 and HIV-1

(Apolipoprotein B mRNA editing catalytic polypeptide)

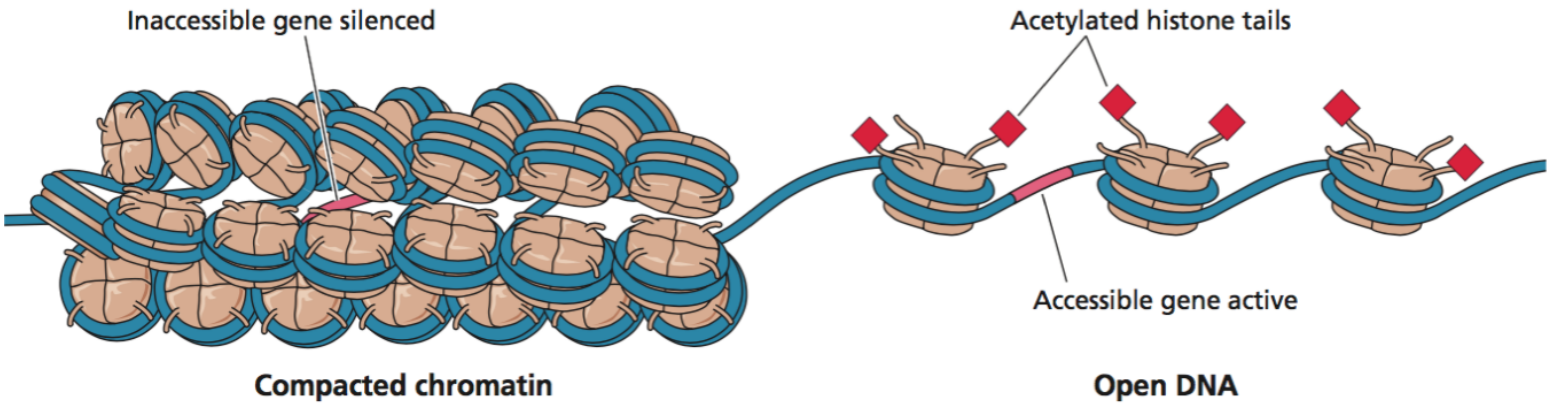


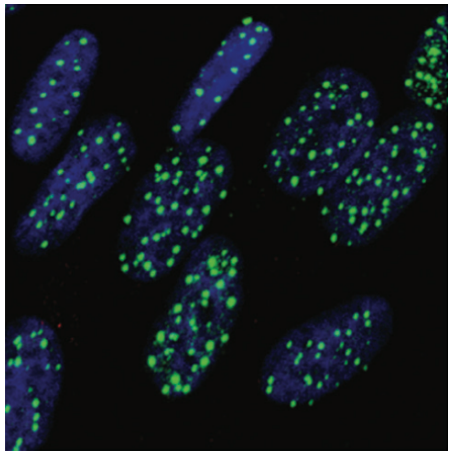


Principles of Virology, ASM Press

Virology 479-480 (2015) 131–145

Epigenetic silencing





Pml bodies

Countermeasures encoded in many viral genomes

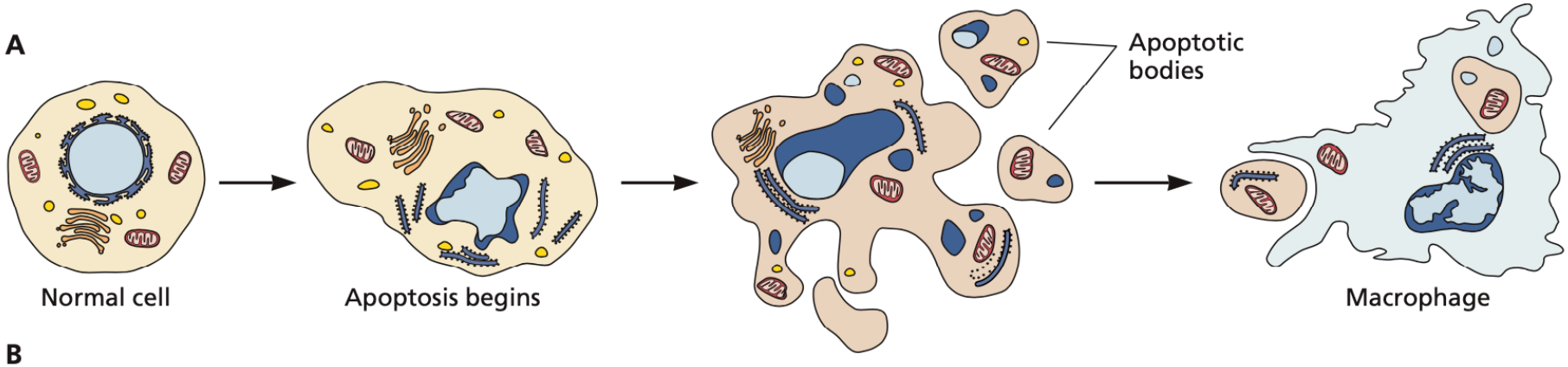
HCMV pp71 causes degradation of cell Daxx, needed for histone deacetylation

EBV Ebna5, Ad E4 Orf3 affect Pml protein localization or synthesis

Unintegrated but not integrated **retroviral** DNA is silenced

Principles of Virology, ASM Press

Apoptosis



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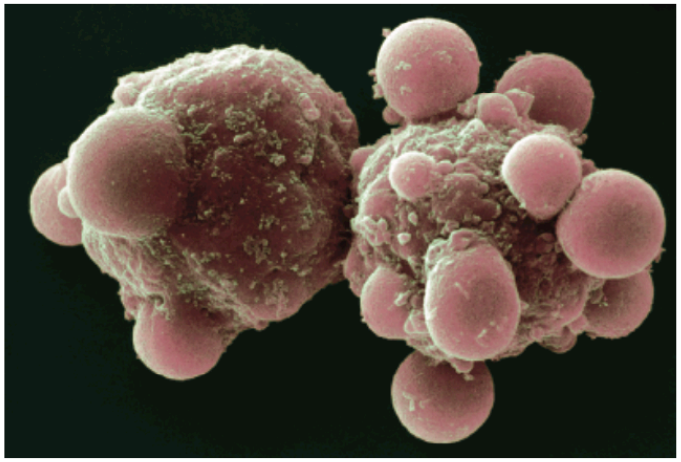
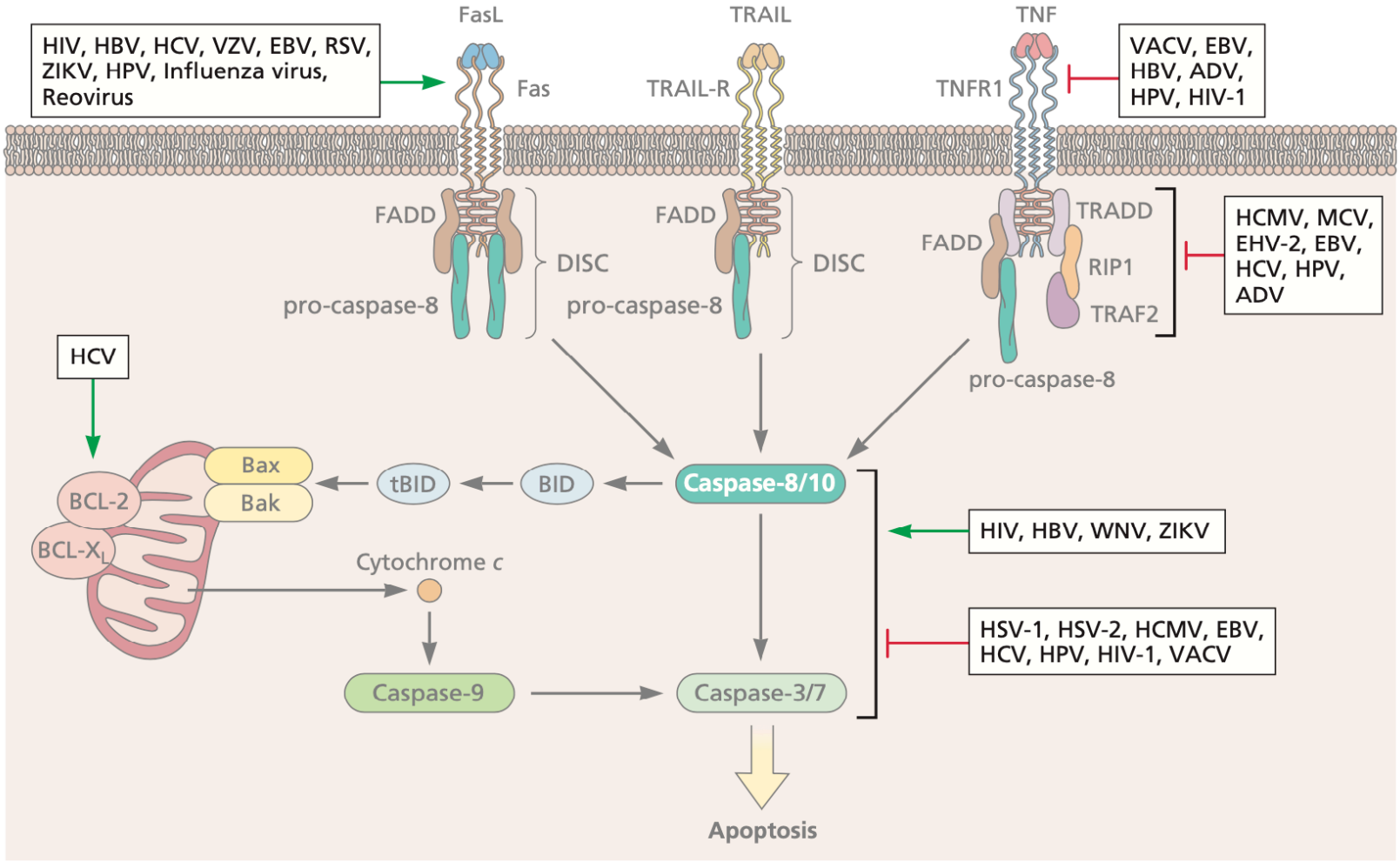


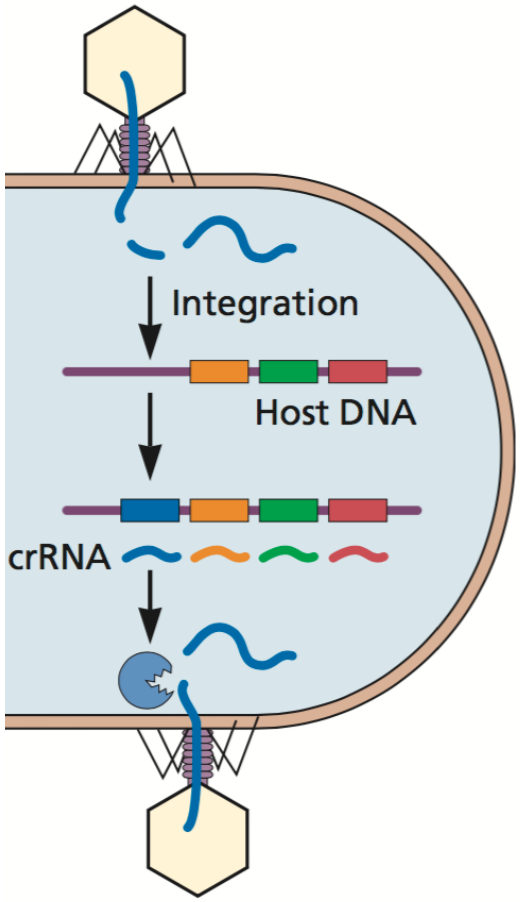
Apoptosis is monitored by sentinel cells

Viral regulators of apoptosis



Ancient intrinsic defense: CRISPR

Clustered regularly interspaced short palindromic repeats



90% of Archaea
50% of Bacteria

Principles of Virology, ASM Press

Go to:

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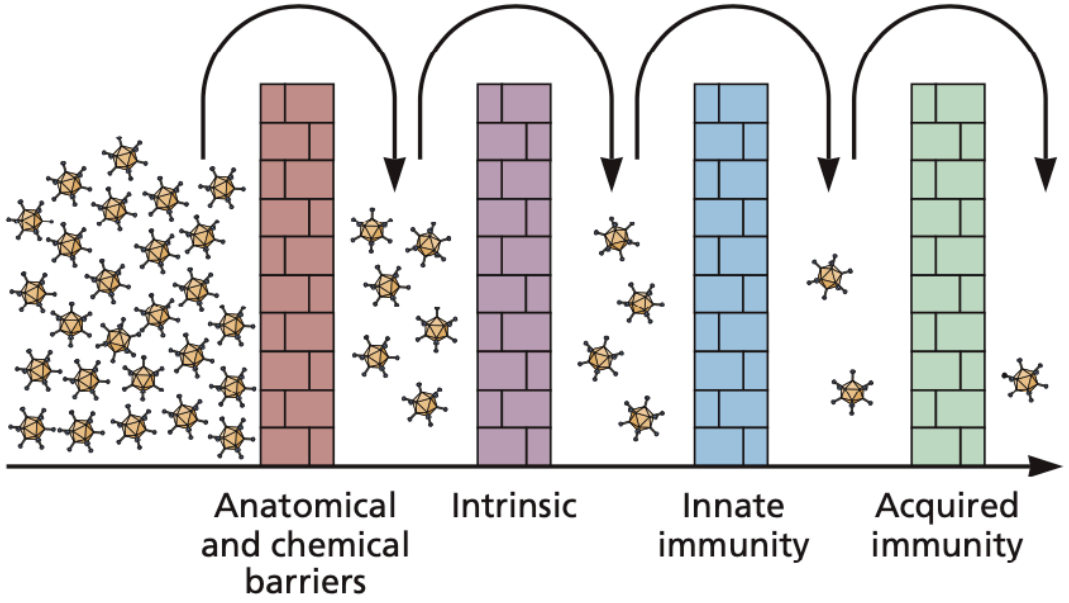
room number: virus

Intrinsic defenses are always present. Which of the following are included?

A. Antibodies
B. T cells
C. Epigenetic silencing
D. Skin
E. Mucus

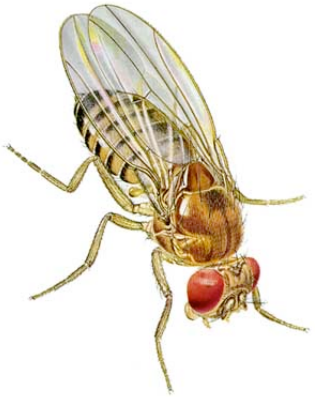
Innate immune system



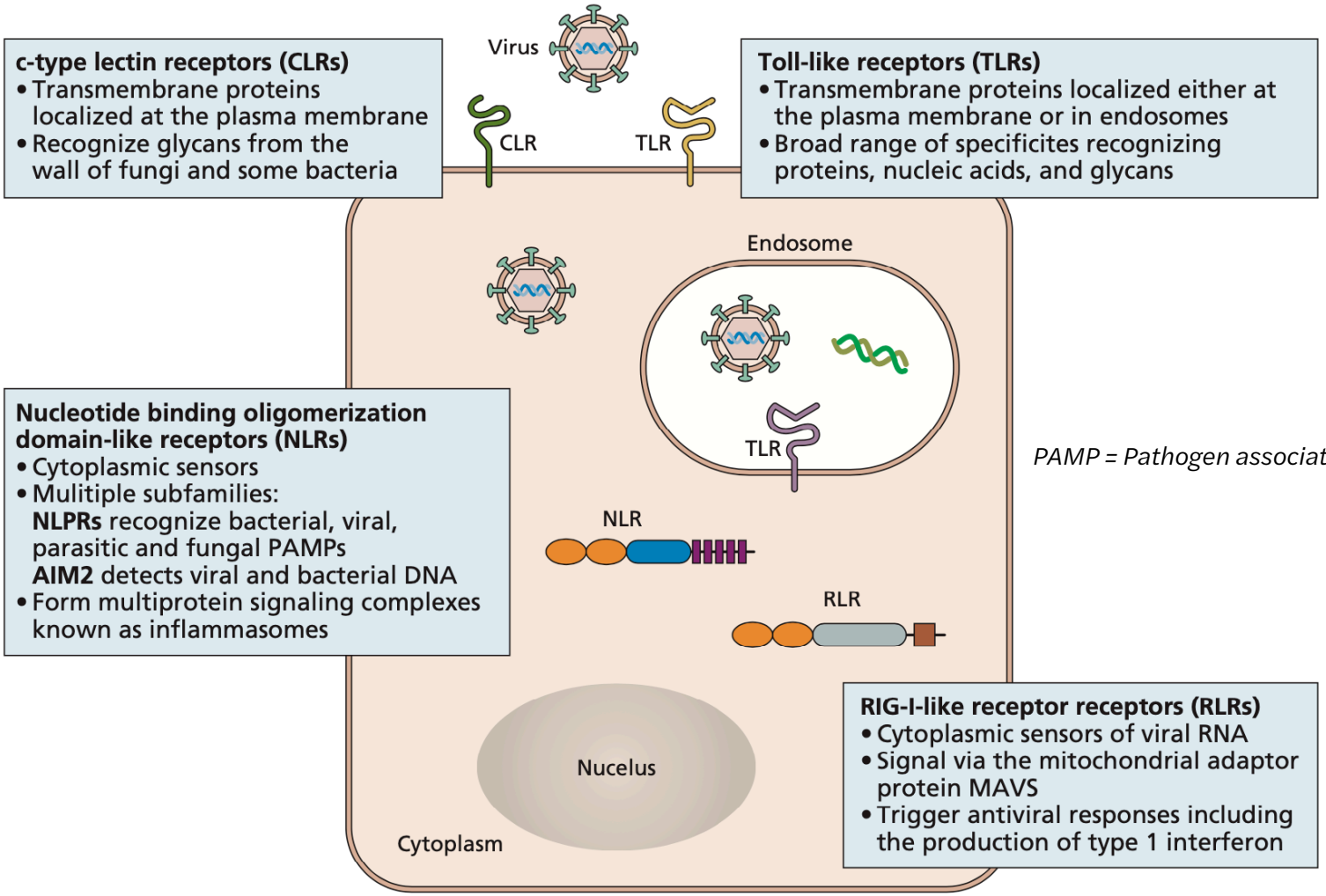
- Activated within minutes to hours after infection
- Cytokines, sentinel cells (dendritic cells, macrophages, NK cells), complement
- Can inform adaptive response when infection reaches dangerous threshold

How does the innate system recognize microbes and not self?

- 1980: Nusslein-Volhard and Wieschaus identify gene involved in establishing dorsal-ventral axis in *Drosophila* embryos. Called *Toll* gene. Nobel Prize, 1995 ("Das war ja toll!")
- 1996: Toll found to have a role in immunity of fly to microbes
- 1997: Toll-like receptors identified in mammals

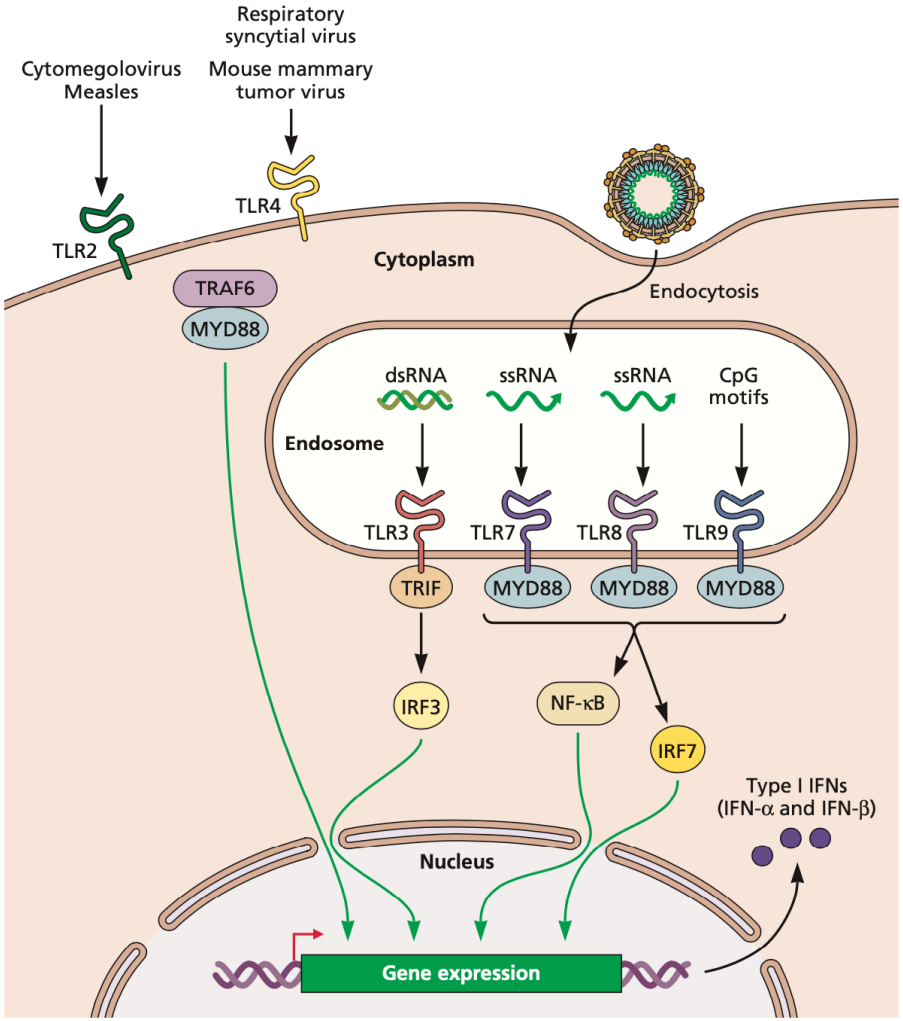


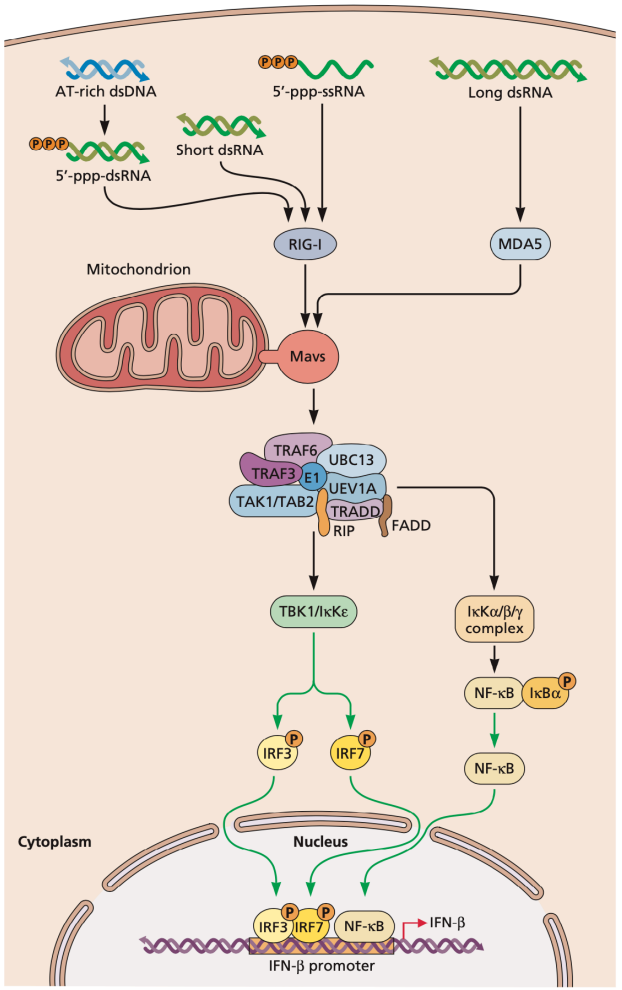
C/N/R/TLRs - Pattern recognition receptors (PRR)



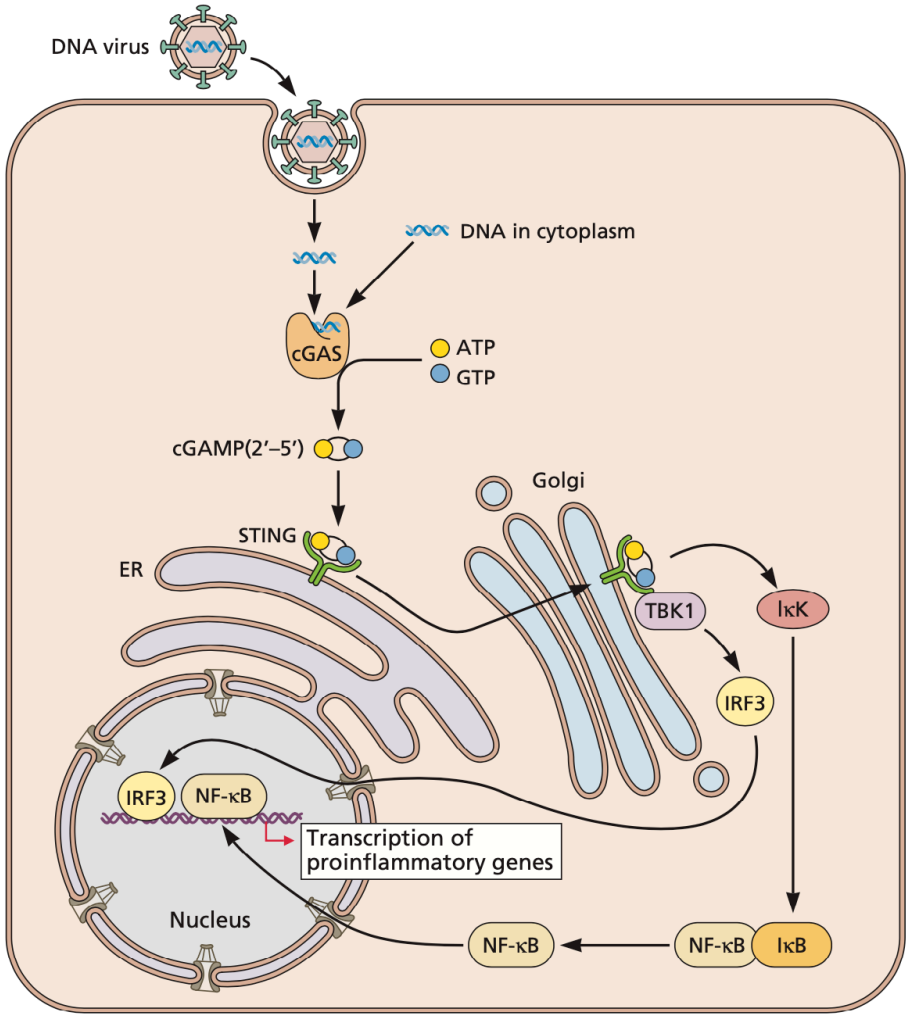
PAMP = Pathogen associated molecular pattern

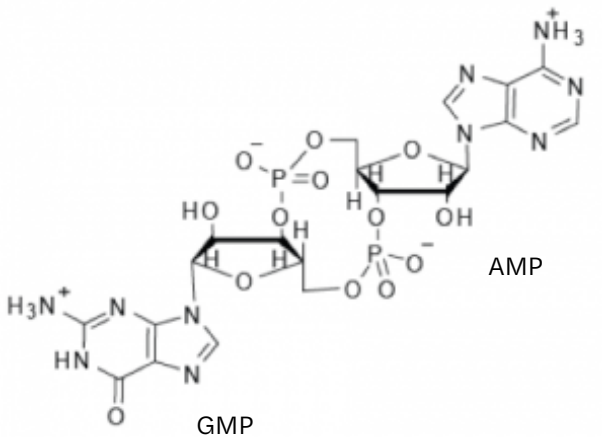
Recognition of PAMPS (pathogen-associated molecular patterns



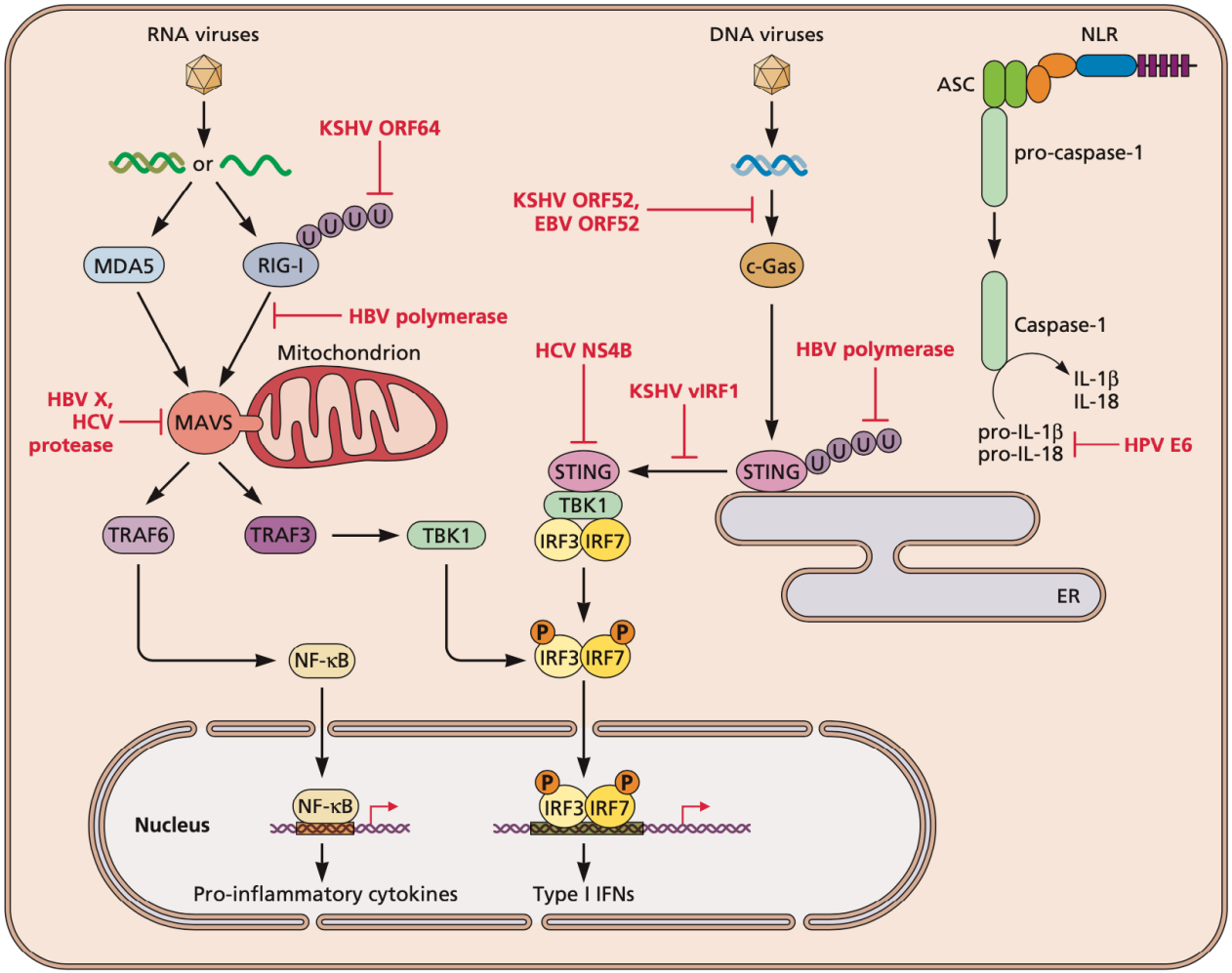


Sensing DNA


DNA virus
DNA in cytoplasm
cGAS
ATP
GTP
cGAMP(2′–5′)
Golgi
STING
ER
TBK1
IκK
IRF3
IRF3
NF-κB
Transcription of
proinflammatory genes
Nucleus
NF-κB
NF-κB
IκB


AMP
GMP

Viral modulators of sensing



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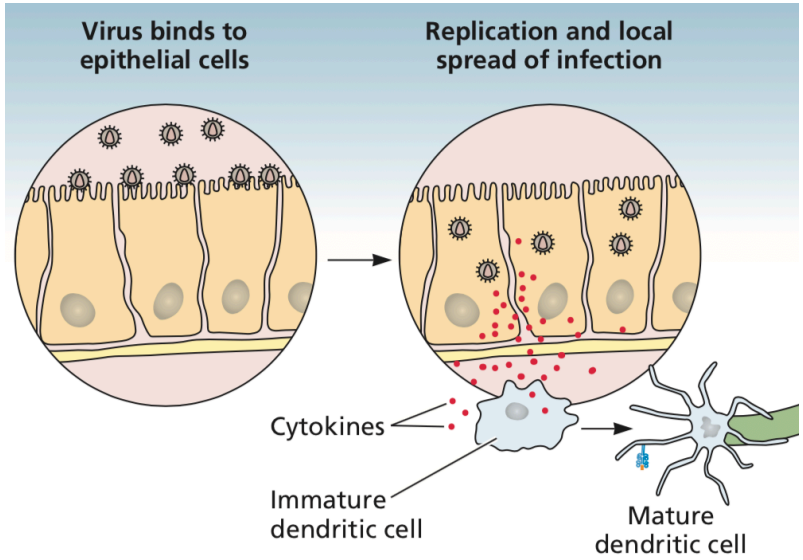
Which of the following allow the innate immune system to distinguish microbes from self?

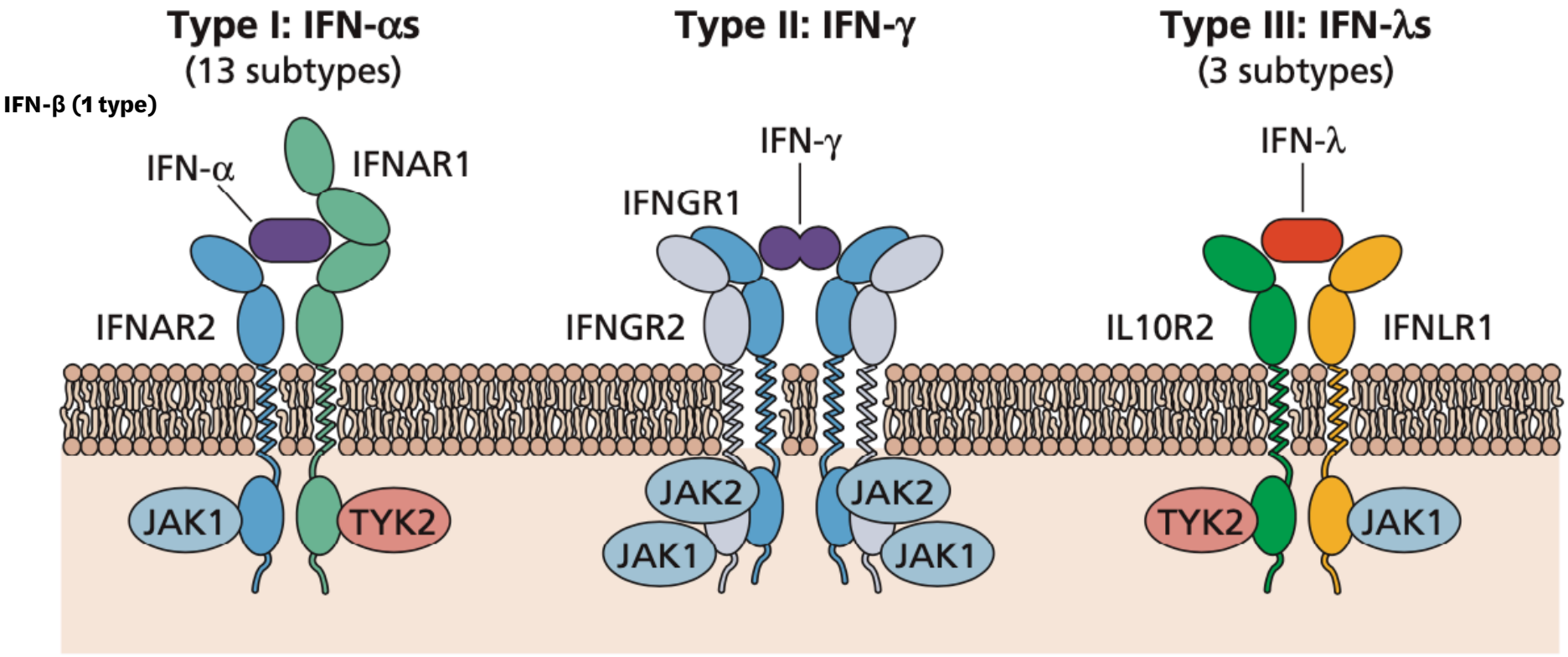
A. Cytoplasmic helicases and TLRs
B. Antibodies
C. Apoptosis
D. Apobec
E. All of the above

Interferons

- 1957: Issacs & Lindenmann; chicken cells exposed to non-infectious influenza virus produce substance that “interfered” with infection of other cells
- Produced by virus-infected cells and uninfected sentinel cells in response to products released from cells (e.g. viral nucleic acid)

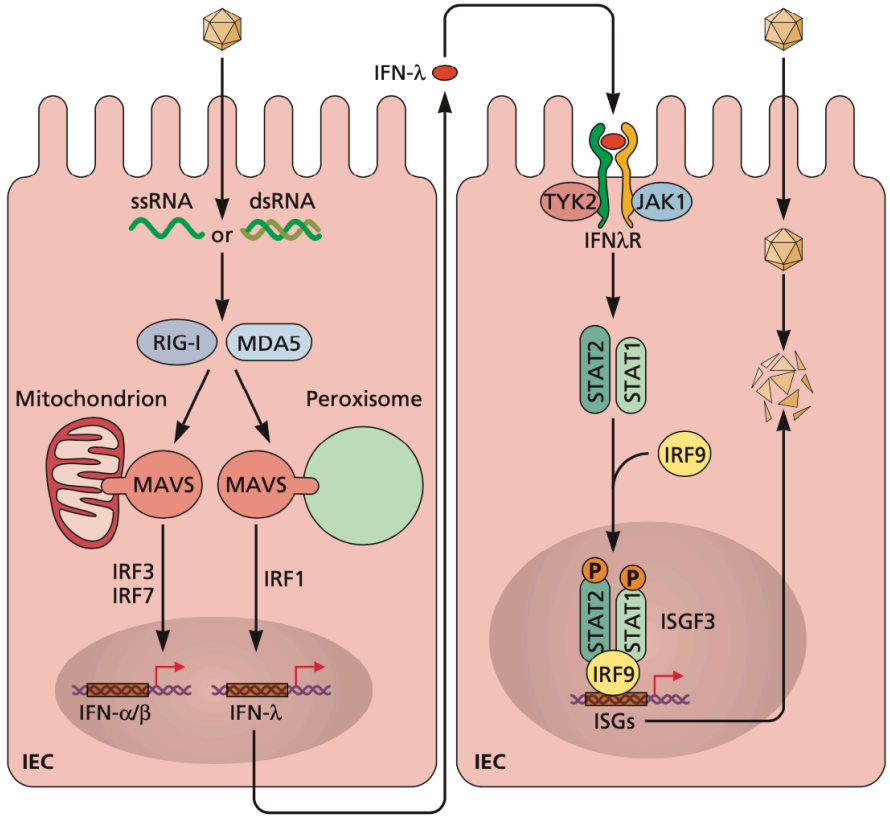


Interferons

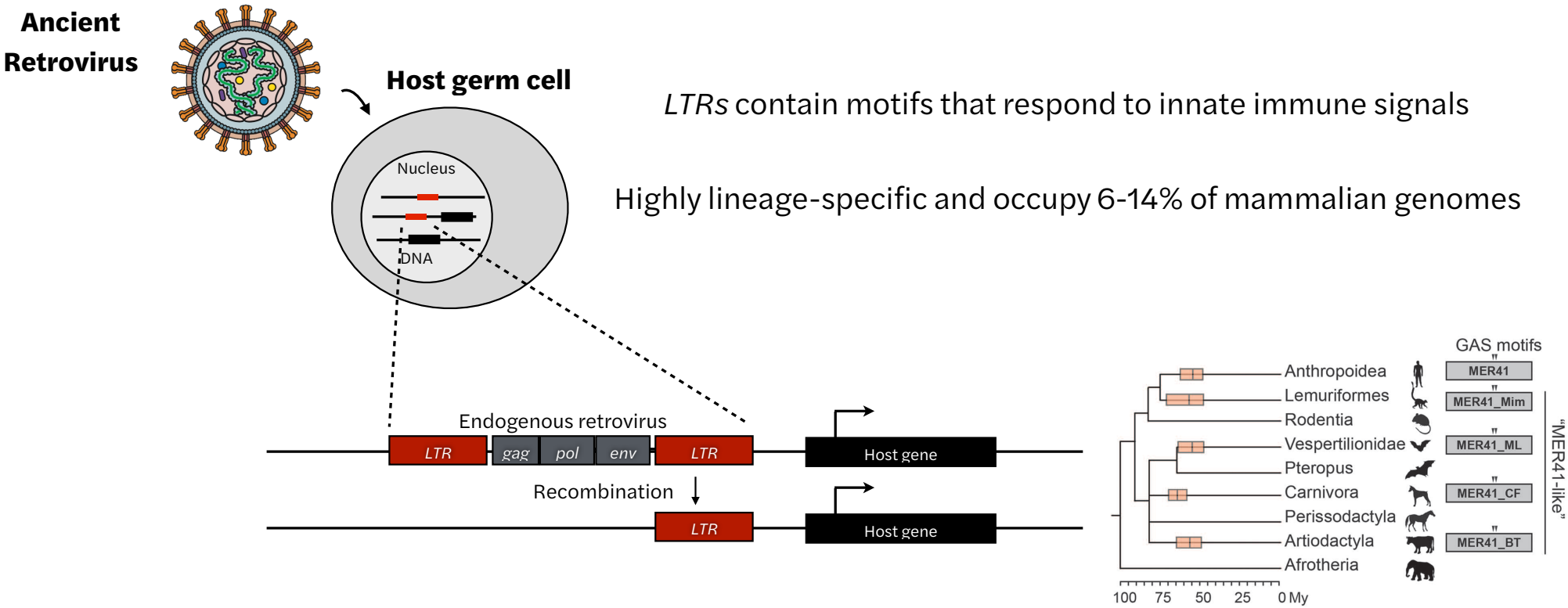


IFN signal transduction

- Production of IFNα/β is rapid: within hours of infection, declines by 10 h
- IFN binding to IFN receptors leads to synthesis of >1000 cell proteins (ISGs, IFN stimulated genes)
- Mechanisms of most ISGs not known



Endogenous retrovirus LTRs regulate the interferon response



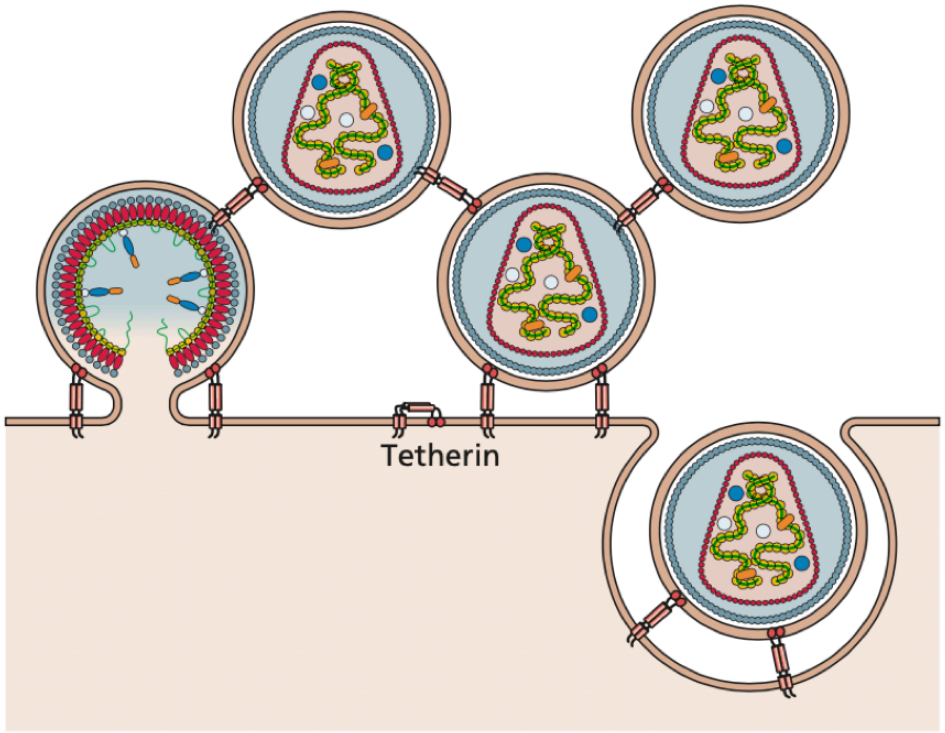
LTRs contain motifs that respond to innate immune signals

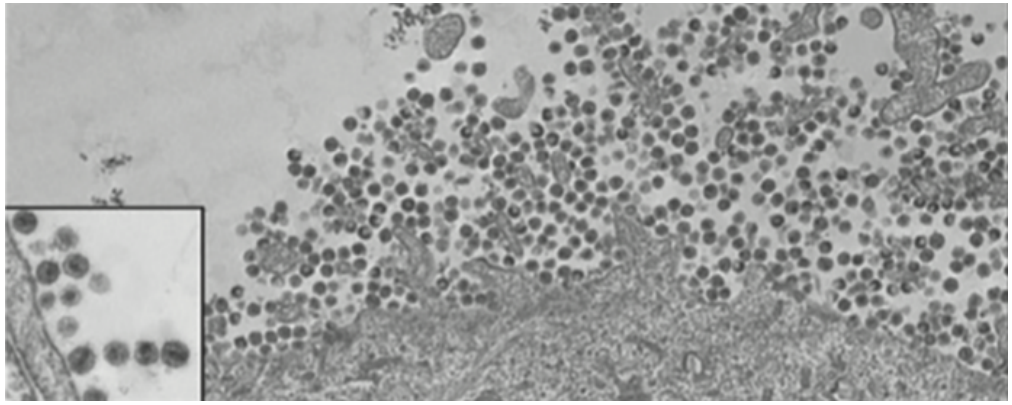
Highly lineage-specific and occupy 6-14% of mammalian genomes

TWiV 382: Everyone's a little bit viral

microbe.tv/twiv/twiv-382

Tetherin, CD317



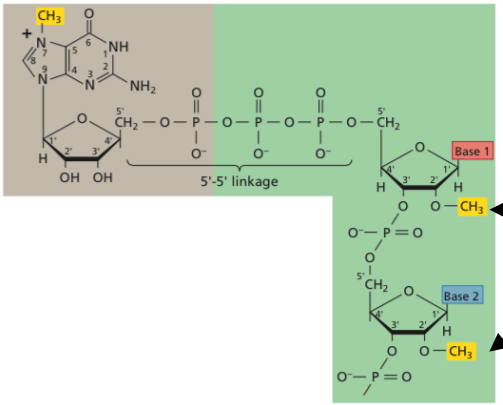


HIV-1 Vpu protein is a tetherin antagonist

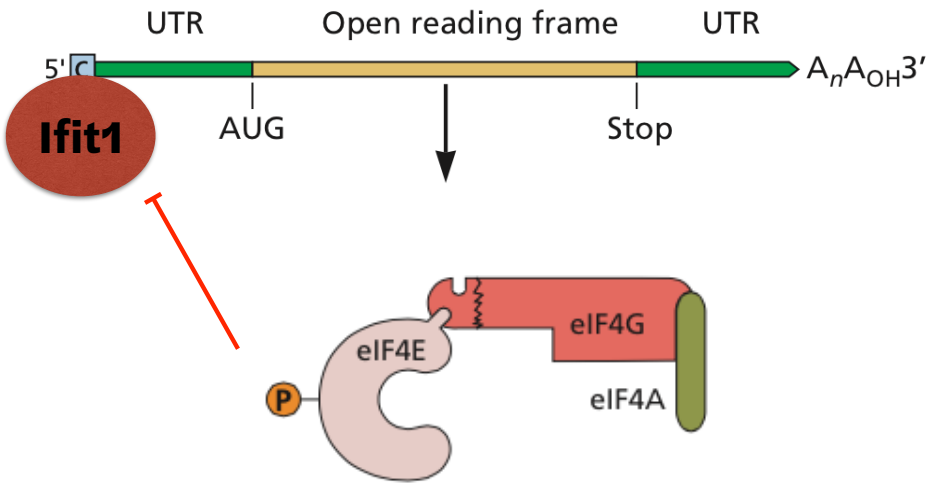
Principles of Virology, ASM Press

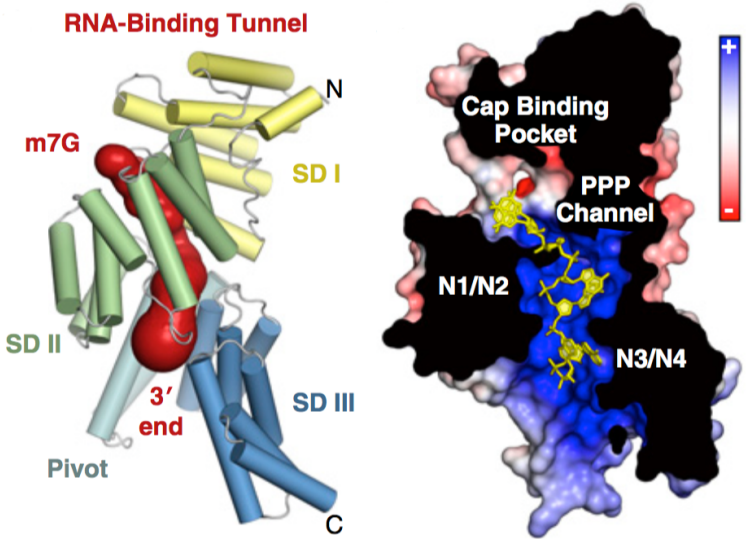
Interferon-induced proteins: IFIT1

IFN-induced protein with tetratricopeptide repeats 1



Ifit1 binds RNAs lacking 2'-O methylation





http://www.pnas.org/content/early/2017/02/28/1612444114.short?rss=1

Escape from IFIT1

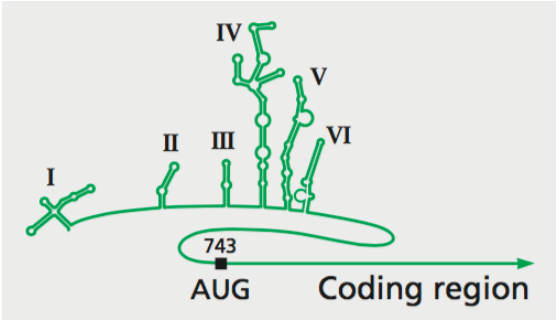
Cap snatching

Influenza virus

m7GpppNm

5'end—independent translation

Picornavirus



Ifit1

Viral N-7 and 2'-O methylase

Paramyxovirus
Rhabdovirus
Flavivirus
Reovirus
Poxvirus

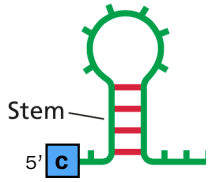
m7GpppNm

Host N-7 and 2'-O methylase

Polyomavirus
Herpesvirus
Parvovirus
Retrovirus

RNA structure

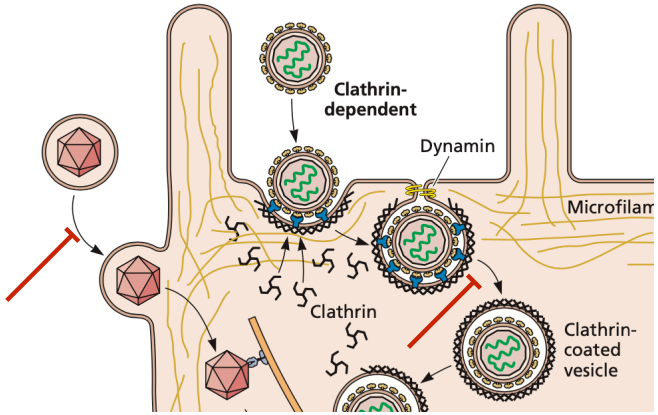
Alphavirus

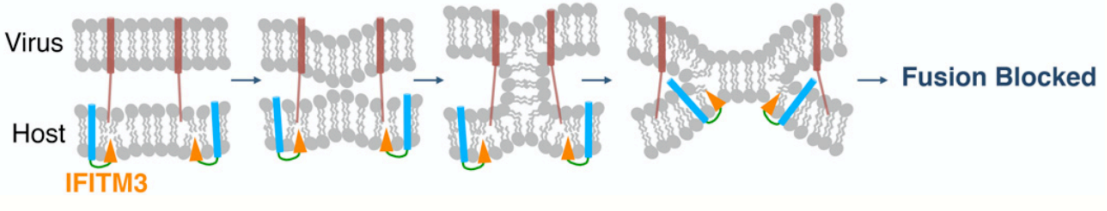


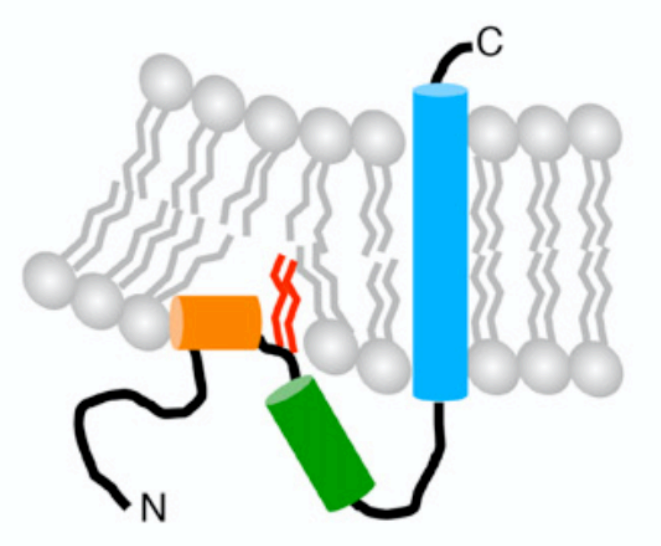
m7GpppN

Interferon-induced proteins: IFITM3

Inhibition of fusion during virus entry







EMBO Reports (2017) 18: 1740–1751

The IFN system is dangerous

- IFN induces the expression of many deleterious gene products - most of our cells have IFN receptors
- IFNs have dramatic physiological consequences: fever, chills, nausea, malaise
- *Every viral infection results in IFN production*, one reason why ‘flu-like’ symptoms are so common

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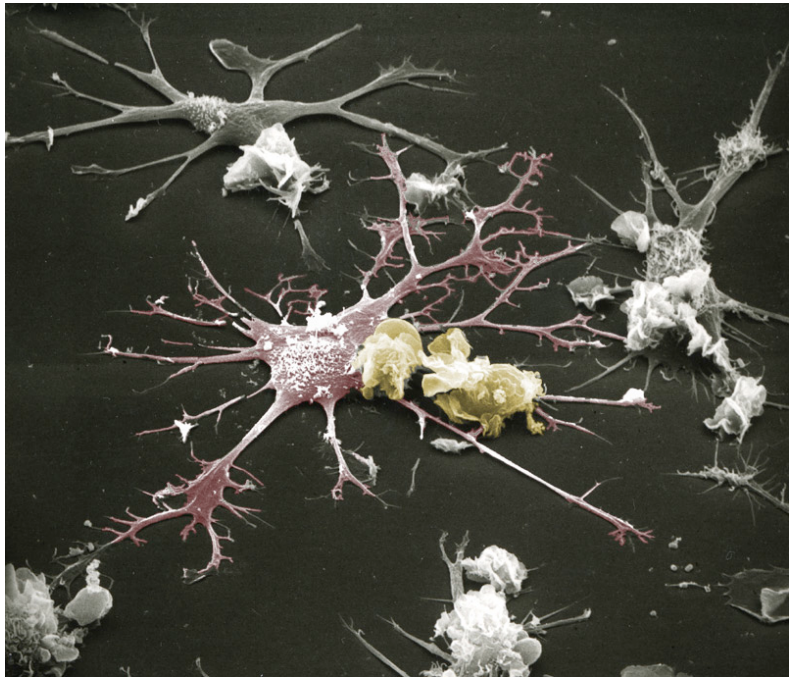
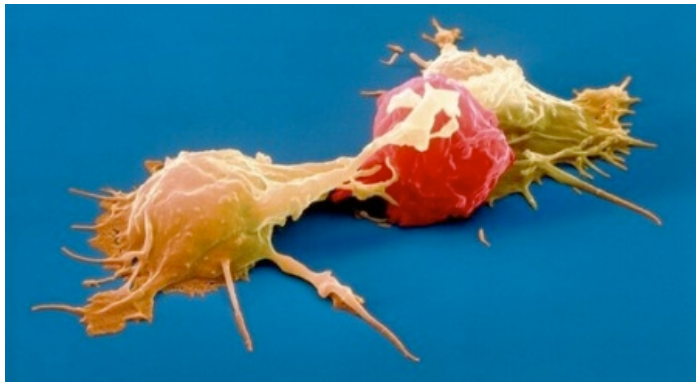
How do interferons (IFNs) limit viral replication?

A. IFNs directly inhibit viral translation
B. IFNs lyse viral particles
C. IFNs induce ISGs
D. IFNs damage cells
E. None of the above

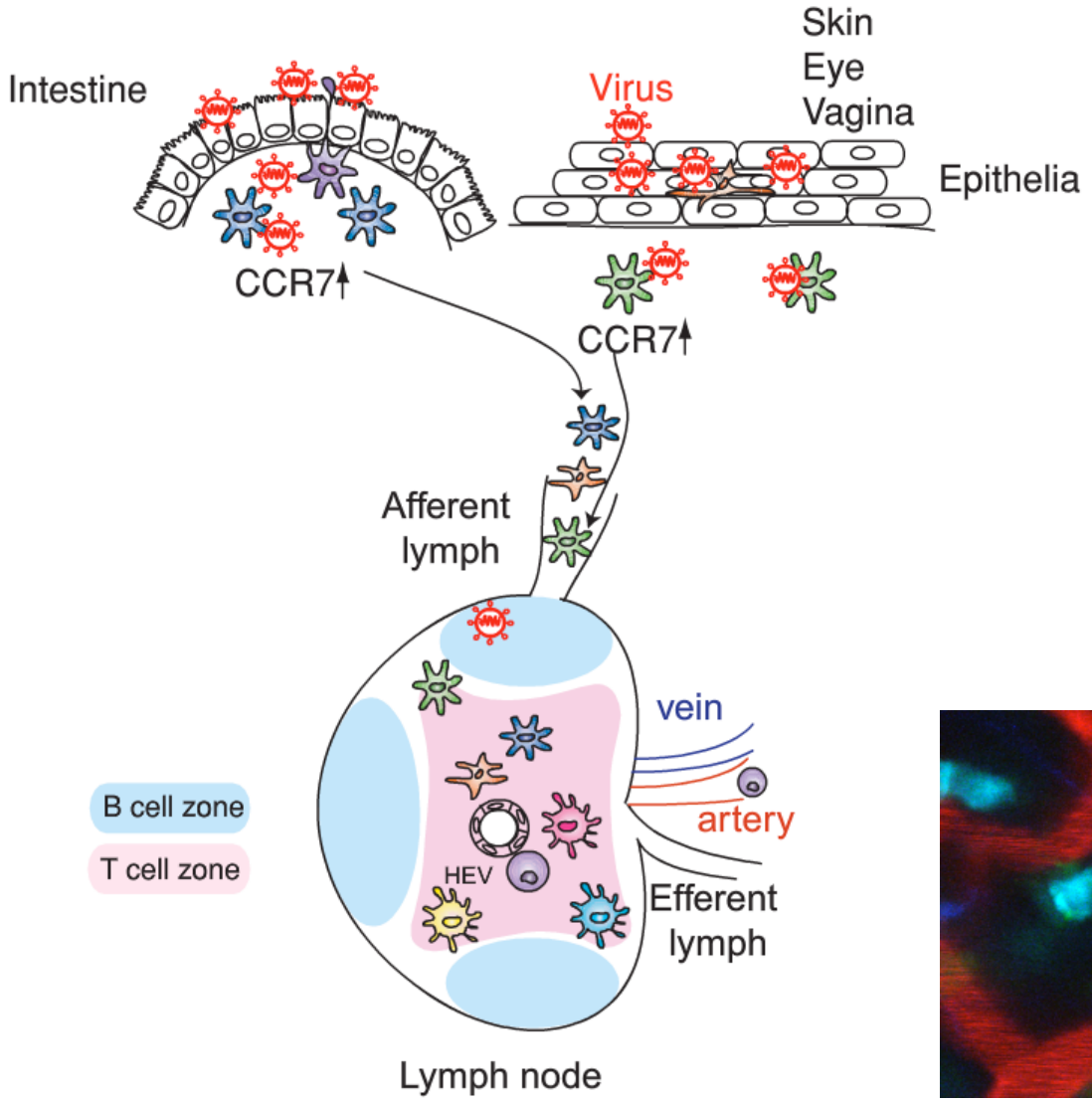
Sentinel cells

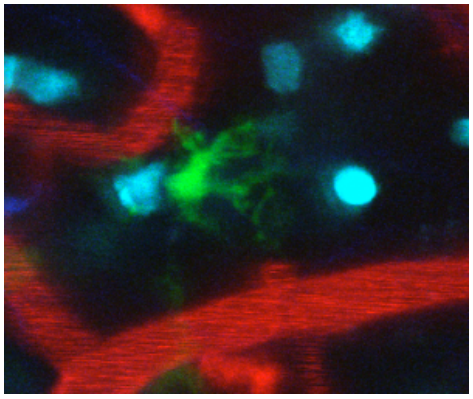
- Dendritic cells, macrophages, natural killer (NK) cells
- They patrol all our tissues looking for signs of change





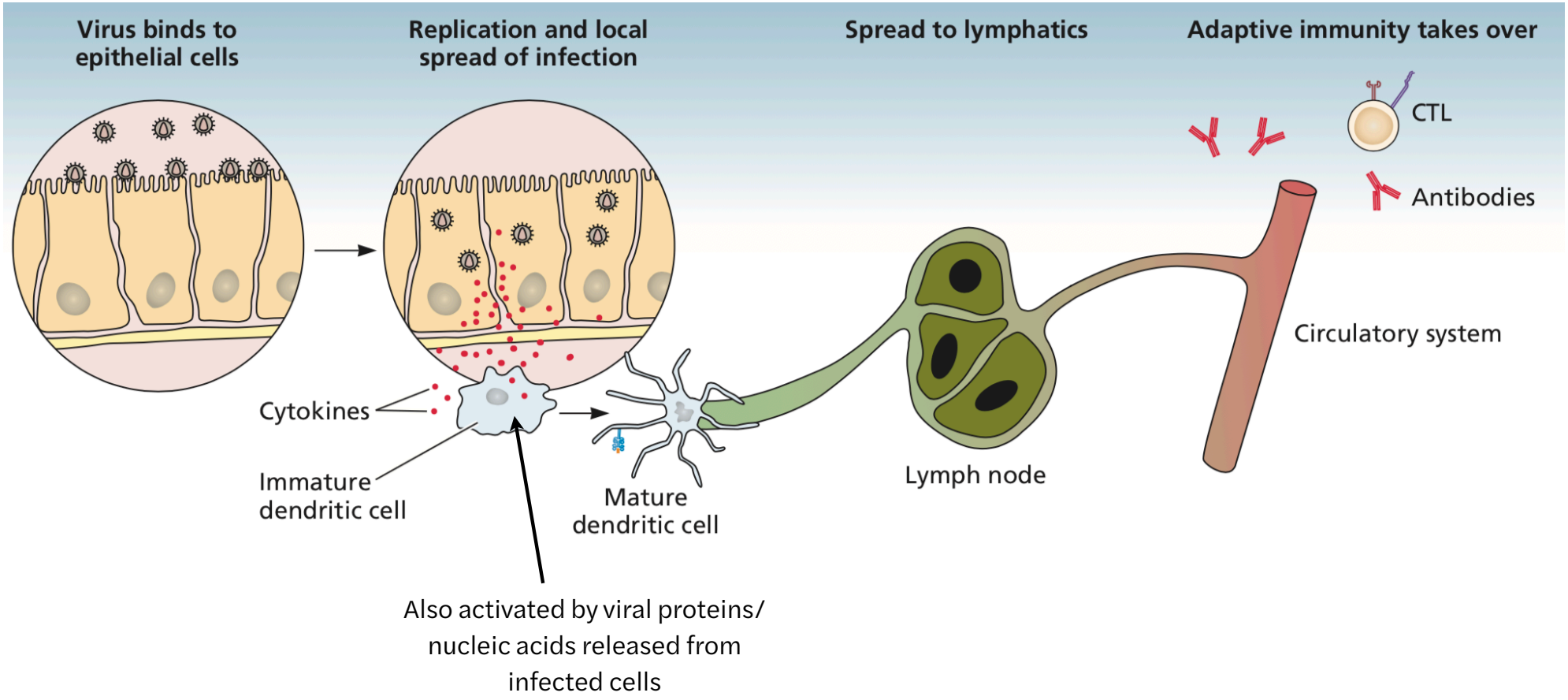
Dendritic Cells



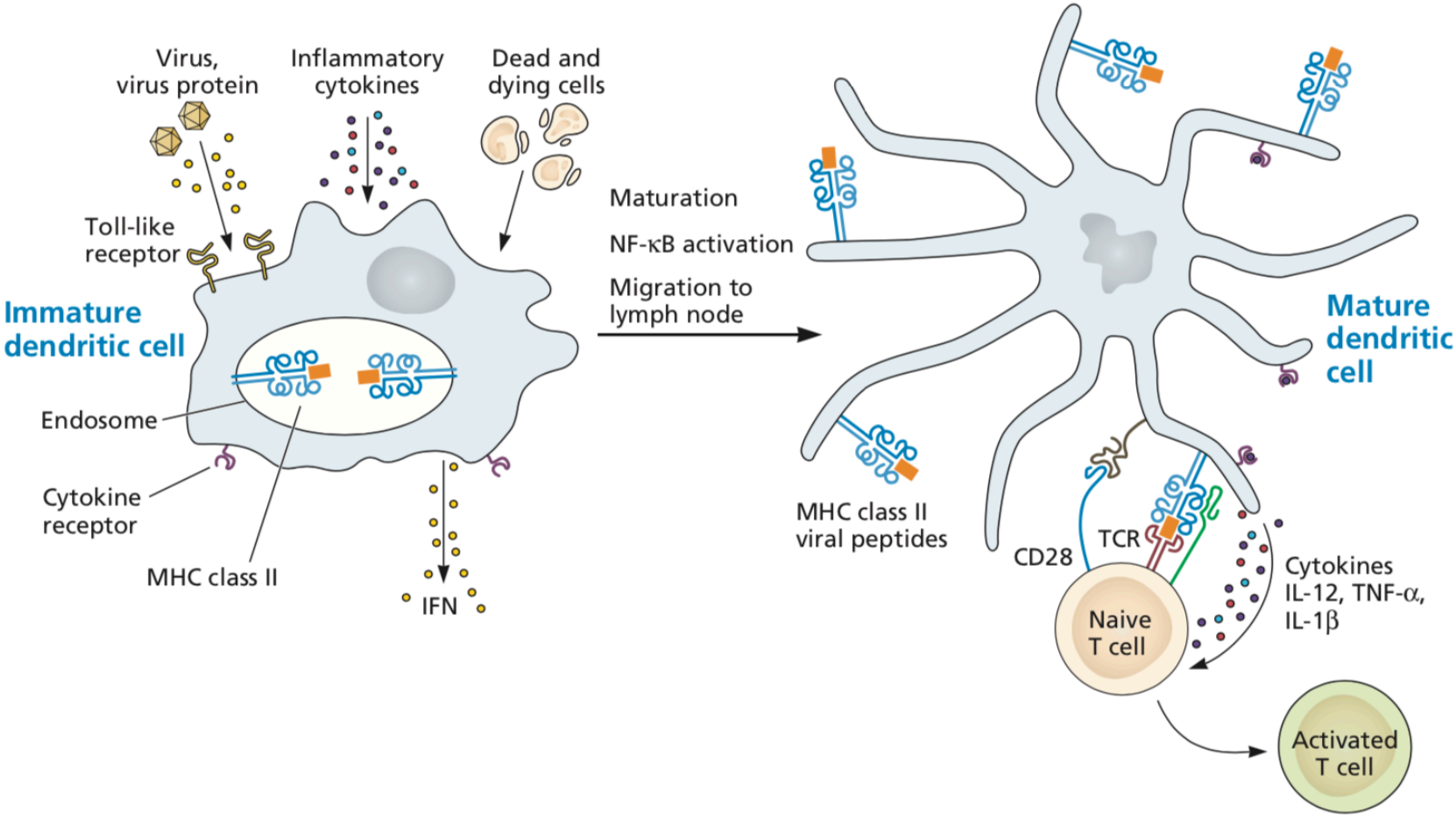


Fields Virology, Wolters Kluwer

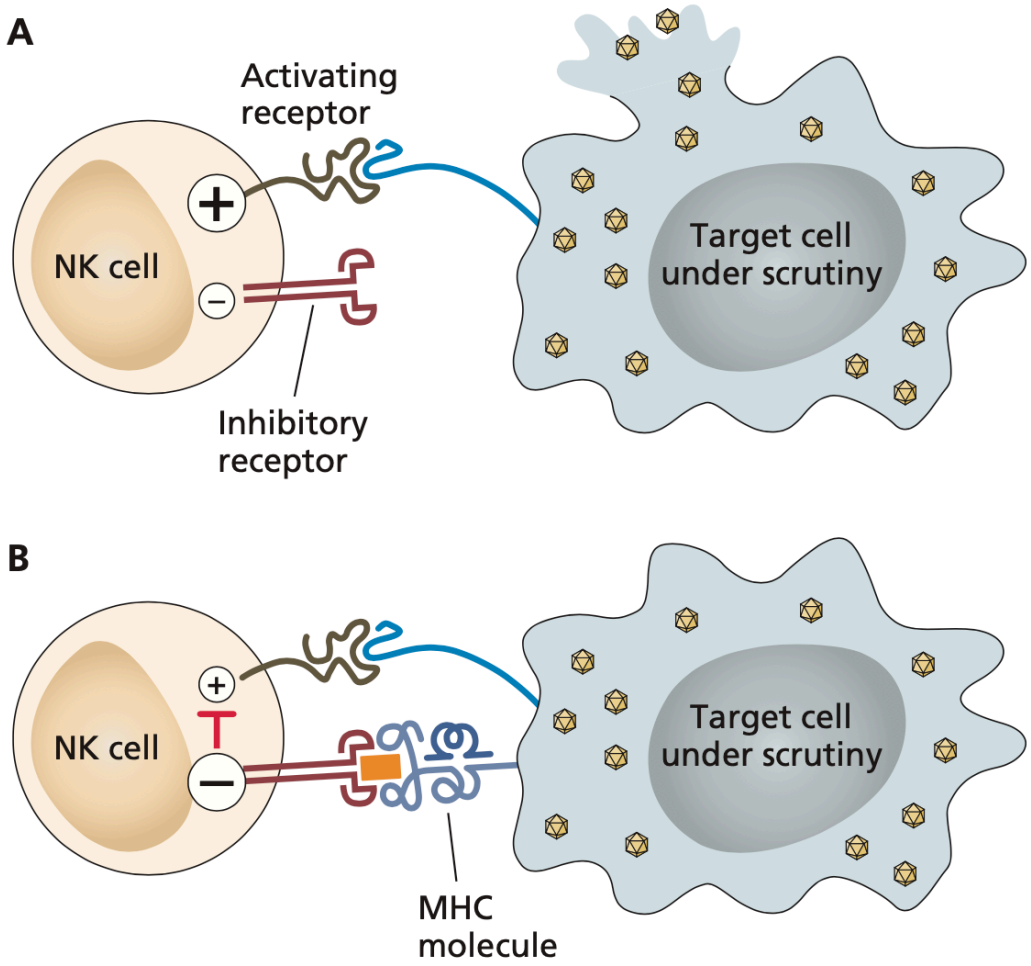
DCs


Virus binds to epithelial cells
Replication and local spread of infection
Spread to lymphatics
Adaptive immunity takes over
CTL
Antibodies
Circulatory system
Cytokines
Immature dendritic cell
Mature dendritic cell
Lymph node
Also activated by viral proteins/ nucleic acids released from infected cells

DCs

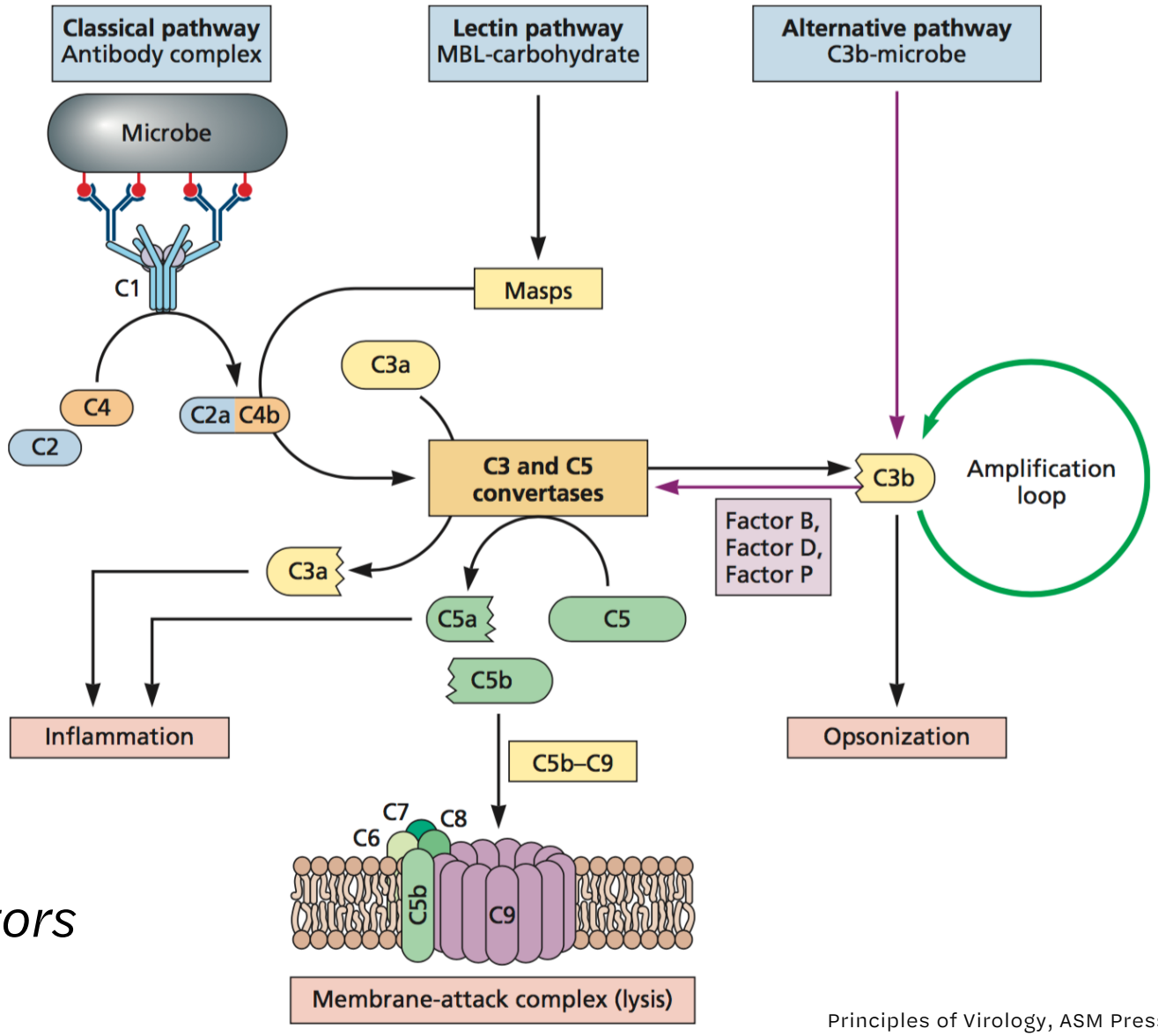

Virus,
virus protein
Inflammatory
cytokines
Dead and
dying cells
Toll-like
receptor
Immature
dendritic cell
Endosome
Cytokine
receptor
MHC class II
IFN
Maturation
NF-κB activation
Migration to
lymph node
Mature
dendritic
cell
MHC class II
viral peptides
CD28
TCR
Cytokines
IL-12, TNF-α,
IL-1β
Naive
T cell
Activated
T cell

NK cells



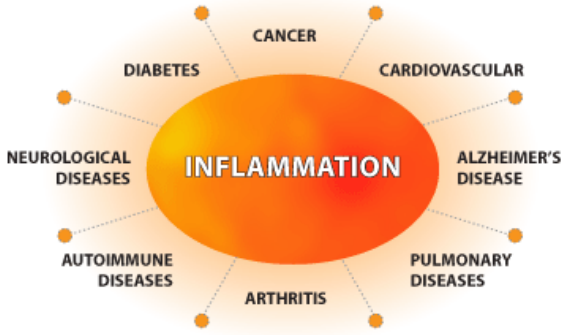
Yes, there are viral modulators of NK cells

Complement



Yes, there are viral modulators

Infection leads to the inflammatory response

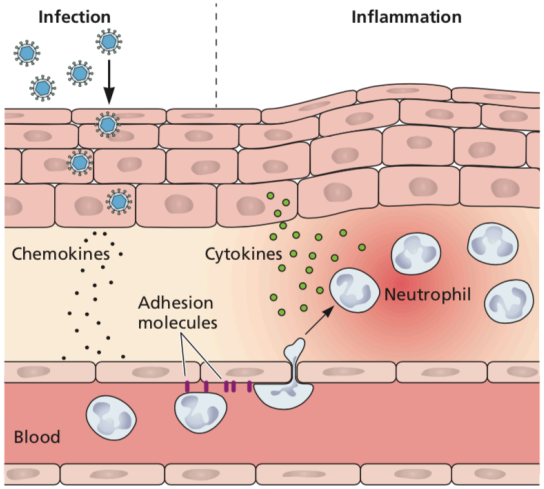


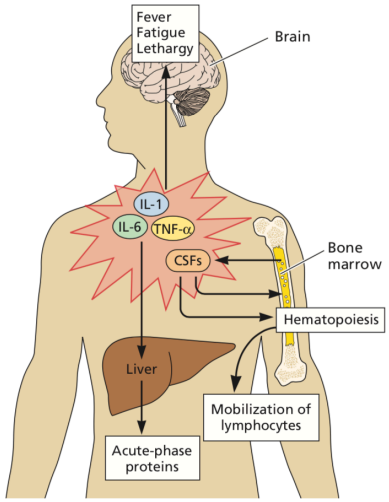
What is missing?

- Infected cells produce cytokines & chemokines
- Redness; pain; heat; swelling, the four classic signs of *inflammation* (rubor, dolor, calor, tumor, originally recorded by the Roman medical encyclopedist Celsus in the first century AD)
- Increased blood flow, increased capillary permeability, influx of phagocytic cells, tissue damage

Three classes of cytokines

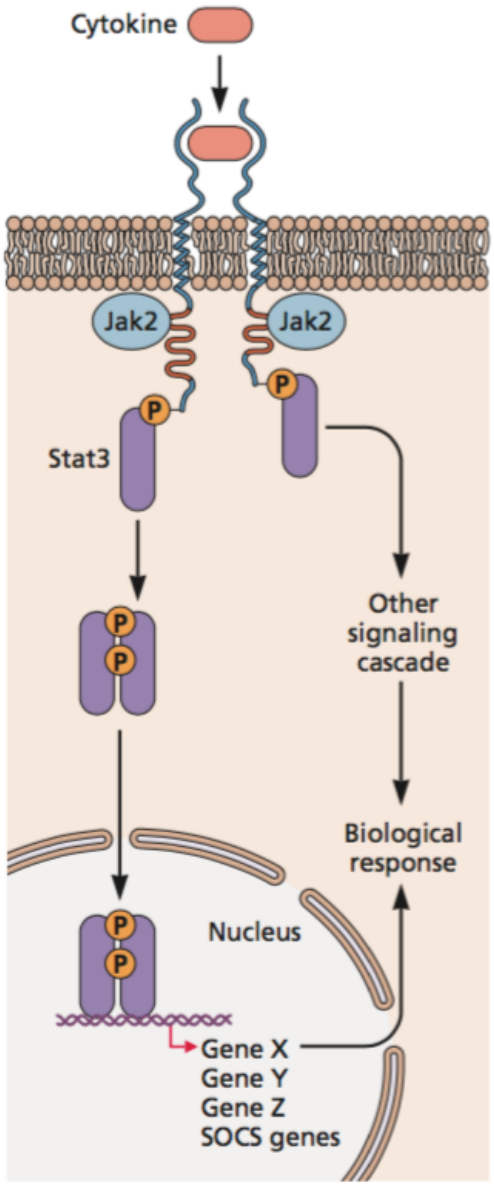
Group	Some members	Activity
Proinflammatory	IL-1, Tnf, IL-6, IL-12	Promote leukocyte activation
Antiinflammatory	IL-10, IL-4, Tgf-β	Suppress PICs
Chemokines	IL-8	Recruit immune cells

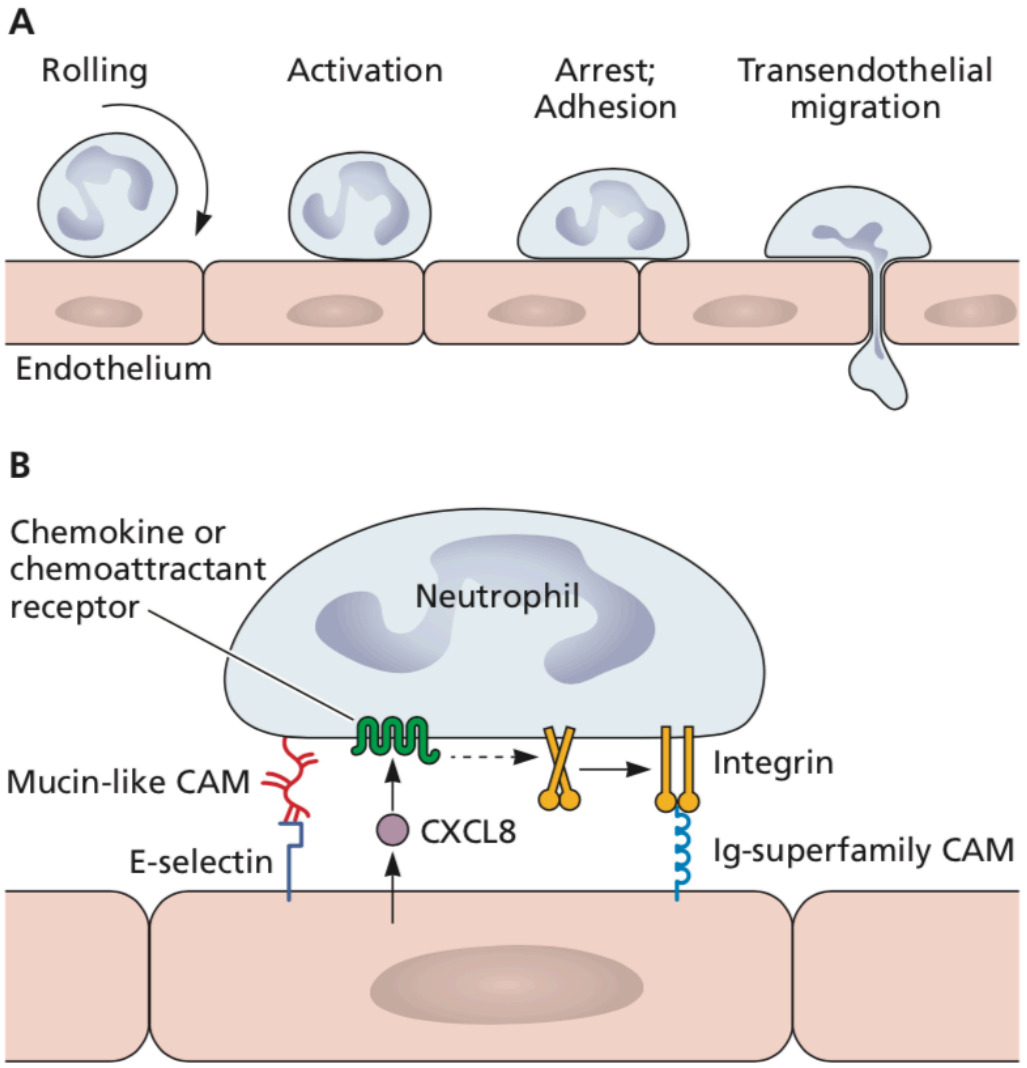




Initially function locally in antiviral defense
In larger quantities, enter circulation, have global effects (sleepiness, lethargy, muscle pain, no appetite, nausea)

A localized viral infection produces global effects





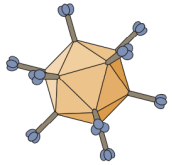
Principles of Virology, ASM Press

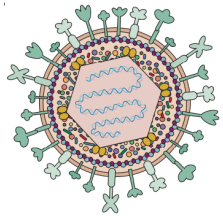
Viral Cytokine Countermeasures

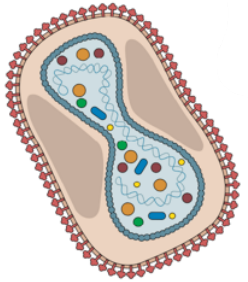
Interrupt cytokine production	Interfere with cytokine action	Interfere with cytokine effector function
Interfere with cytokine and chemokine synthesis	Encode homologs of cytokines to block receptors	Alter cytokine signaling pathway
Inhibit generation of functional cytokines	Encode soluble cytokine receptors to neutralize cytokines	

Inflammation usually stimulates potent immune responses

- Cytopathic viruses cause inflammation because they promote cell and tissue damage
  - *Activate the innate response*
- Consequently cytopathic viral genomes encode proteins that modulate this immune response
  - *Adenoviruses, herpesviruses, poxviruses*

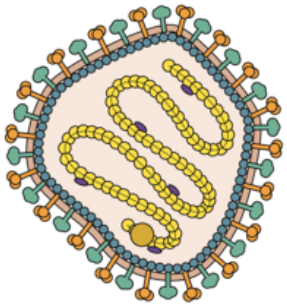






Some viruses do not stimulate inflammation

- Typically non-cytopathic viruses
  - Cells are not damaged, no apoptosis/necrosis
  - Low or ineffective innate immune response
  - Do not effectively activate adaptive immune response

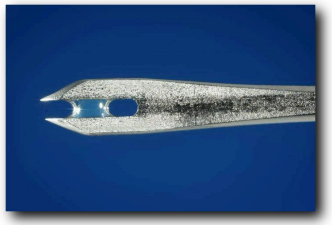


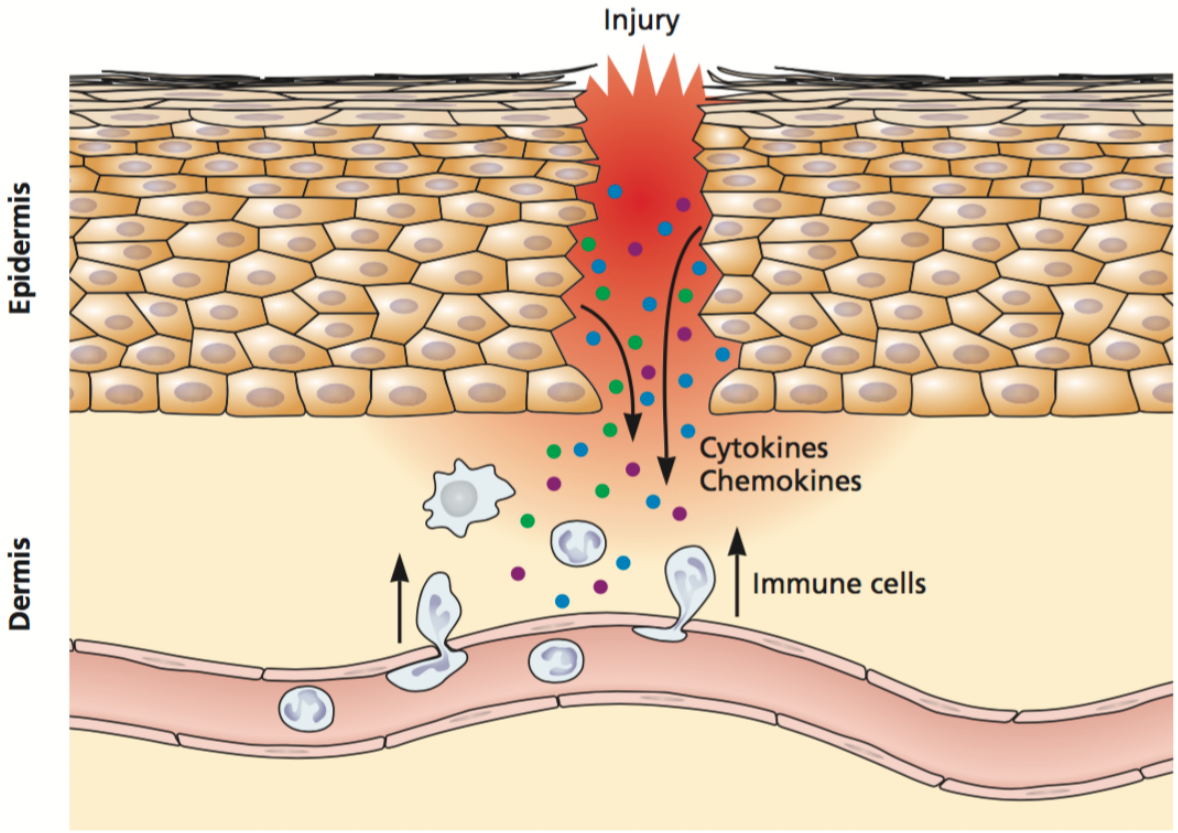
- Non-cytopathic viruses have dramatically different interactions with the host immune system
  - Persistent infections: rarely or inefficiently cleared

The lesson

- The classic inflammatory response (heat, swelling, redness, pain) reflects the communication of innate and adaptive immune defense
  - *No inflammatory response, ineffective adaptive response*
- One reason for using inflammation-stimulating adjuvants for noninfectious vaccines

Not all inflammation is caused by infection!





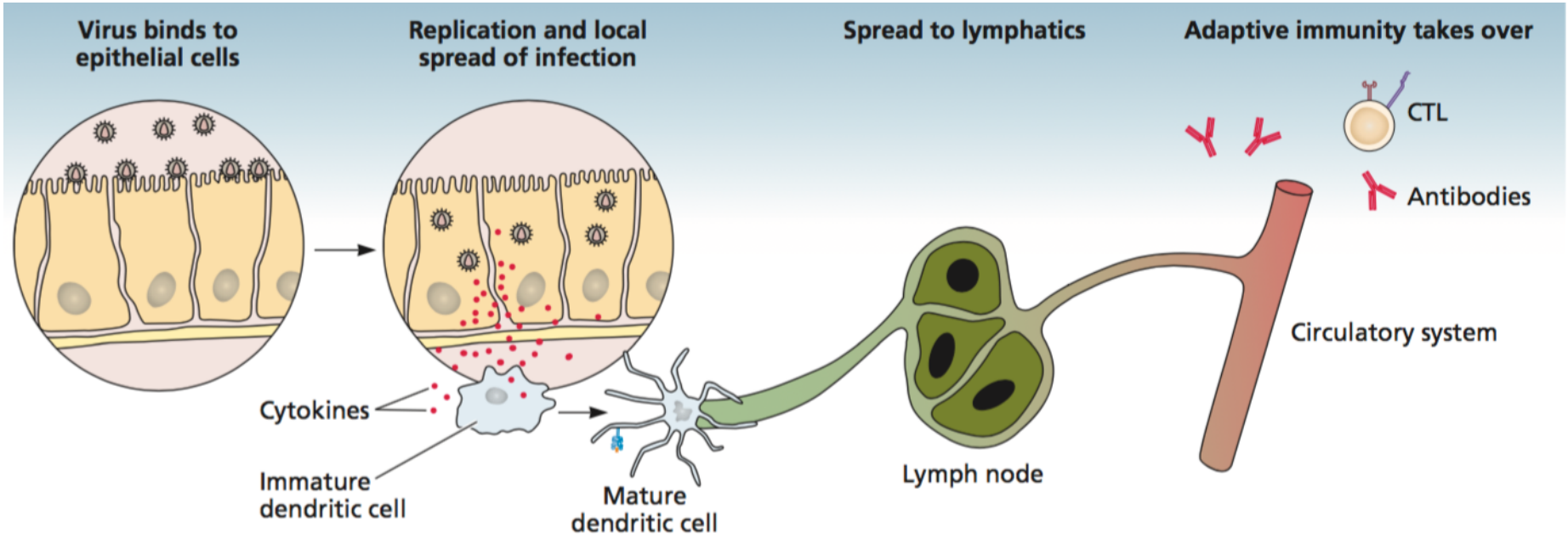
An important component of smallpox vaccine efficacy!

Principles of Virology, ASM Press

Viral countermeasures

All viruses must encode at least one regulator of intrinsic/innate defenses

Sensing, IFN production, IFN signal transduction, cytokines, chemokines, NK cells, DCs, complement


Virus binds to epithelial cells
Replication and local spread of infection
Spread to lymphatics
Adaptive immunity takes over
CTL
Antibodies
Circulatory system
Cytokines
Immature dendritic cell
Mature dendritic cell
Lymph node

Next time: Adaptive immunity