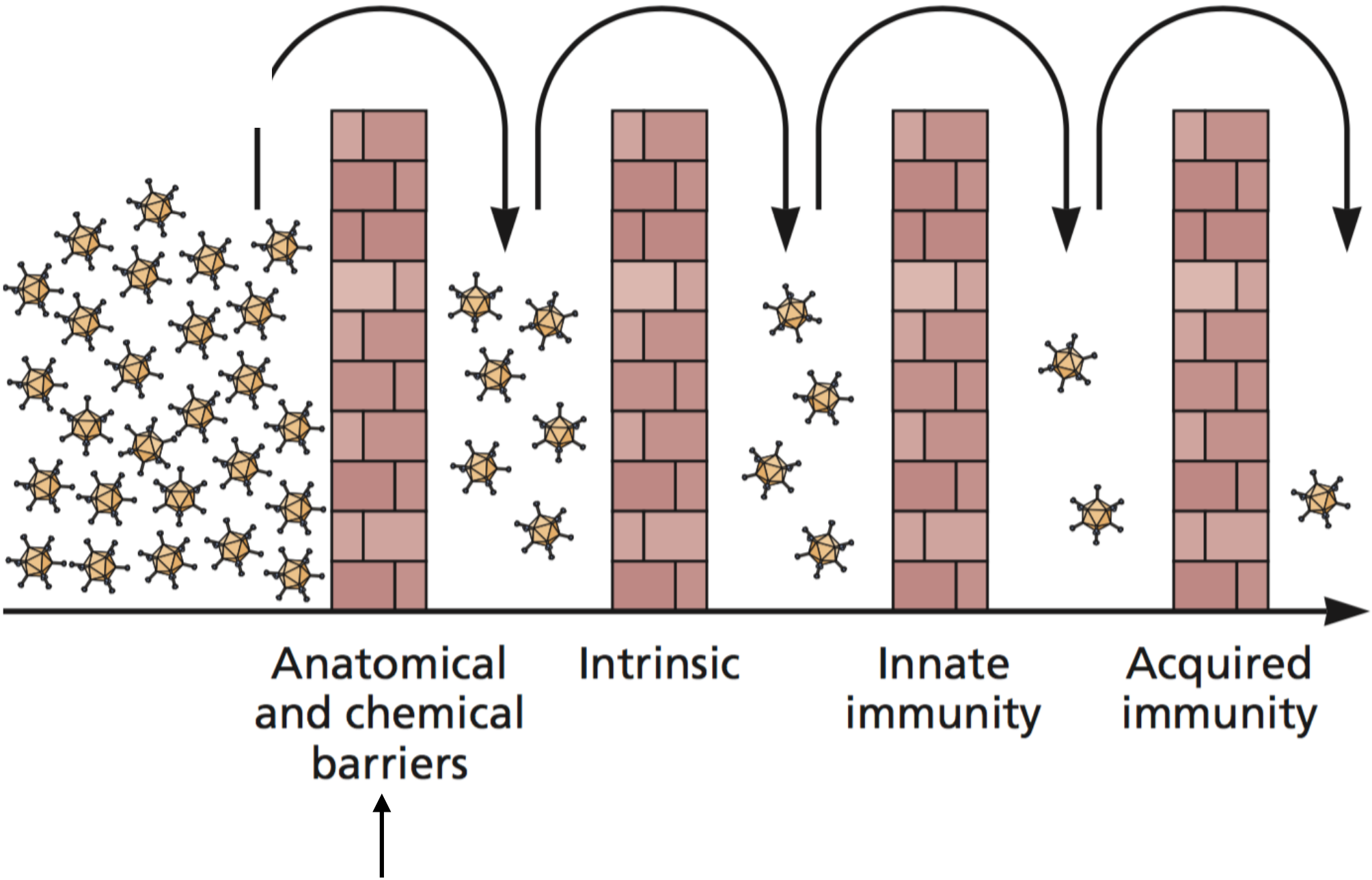
Intrinsic and innate defenses

Lecture 13
Biology W3310/4310
Virology
Spring 2016

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

Host defenses



Skin, mucus, tears, low pH, surface cleansing

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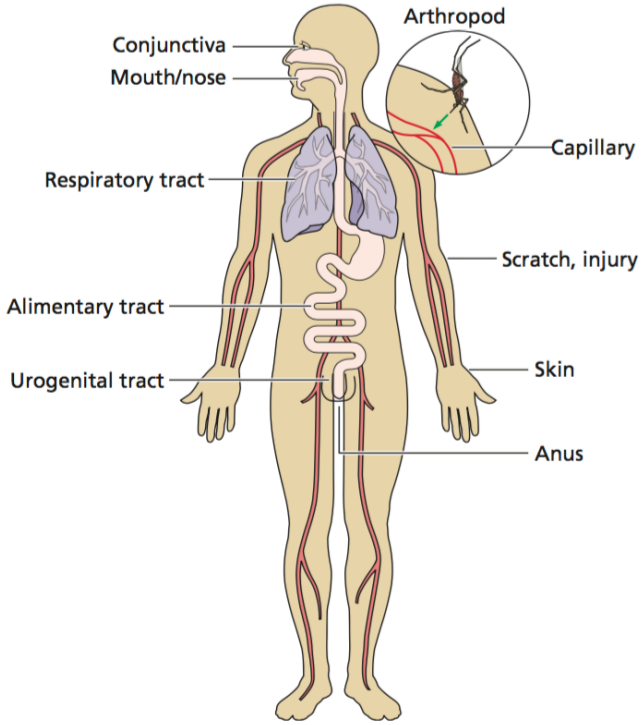
Host defenses



- 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

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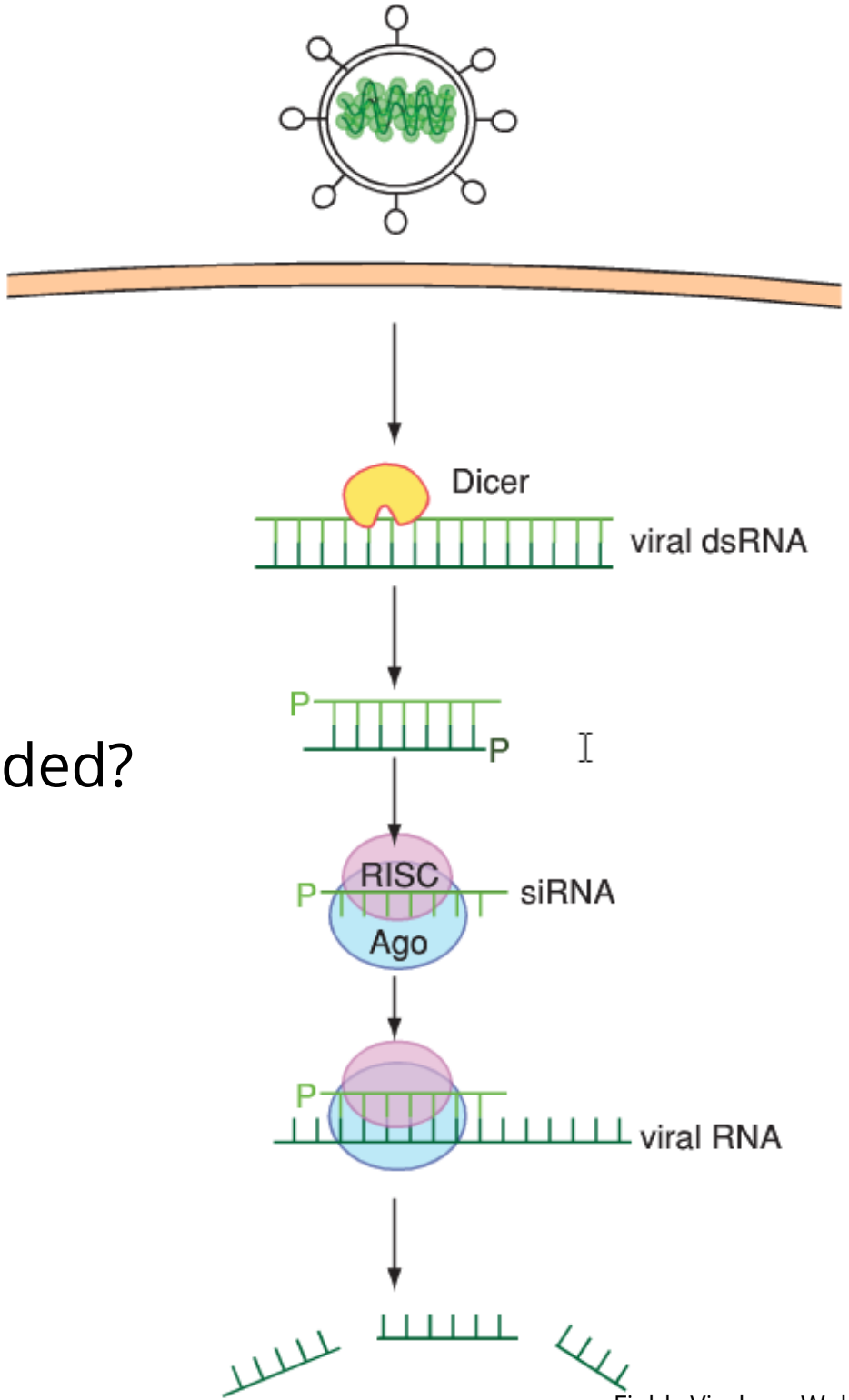
RNA interference

Plant & invertebrate cells

Mammals - present or not needed?



Countermeasures!

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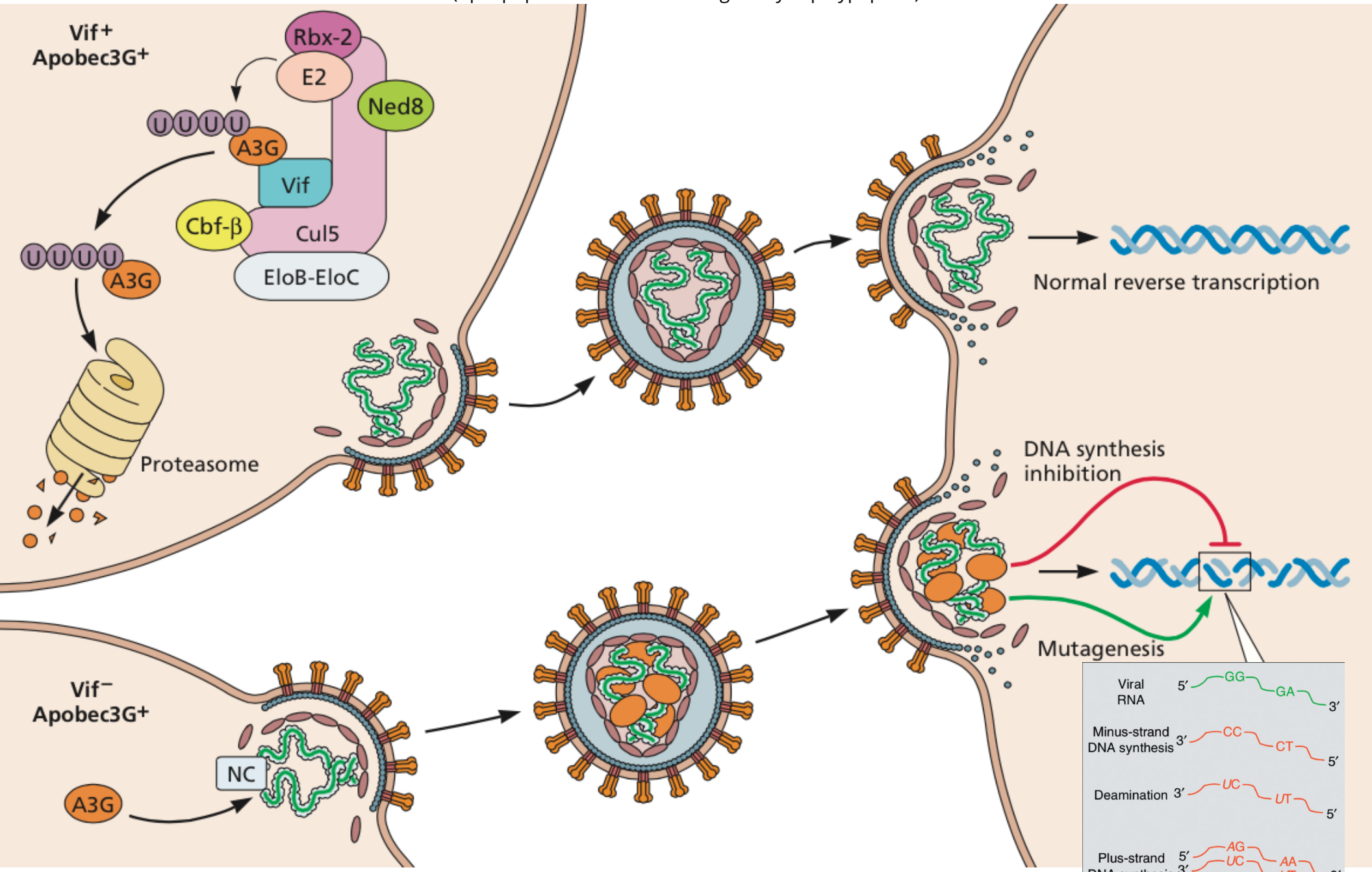
APOBEC3 and HIV-1

(Apolipoprotein B mRNA editing catalytic polypeptide)



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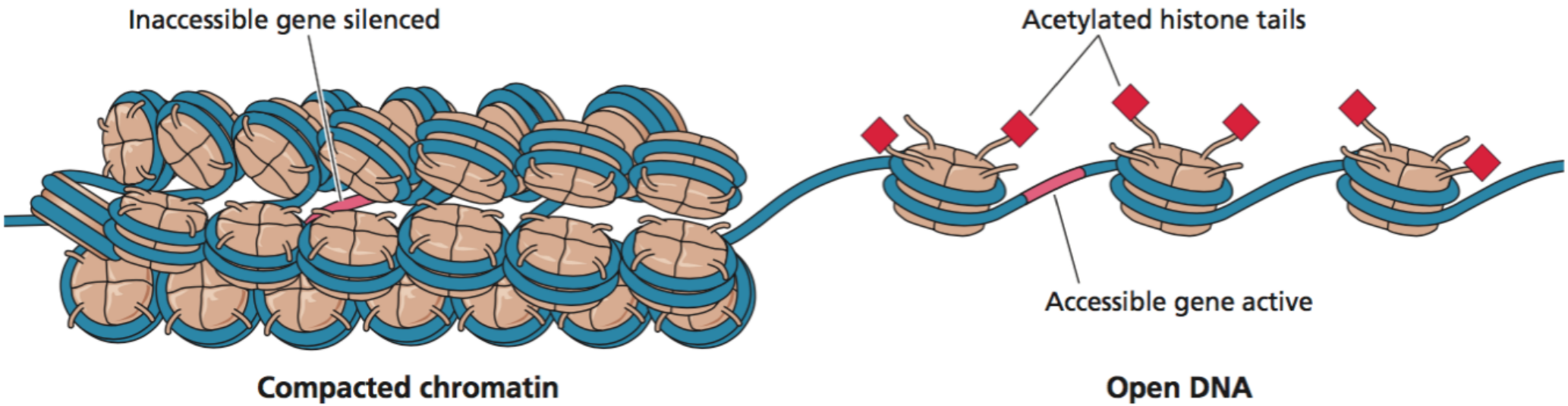
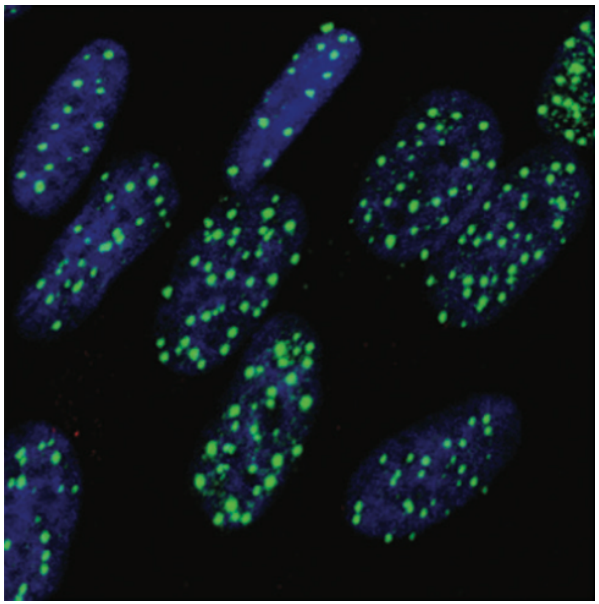
Epigenetic silencing





Pml bodies

Countermeasures

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

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

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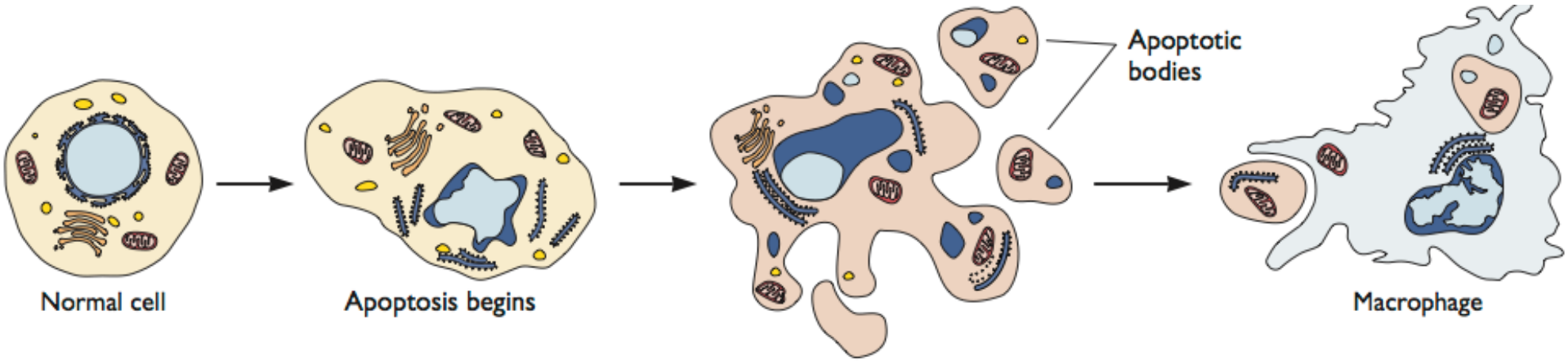
Apoptosis



Apoptosis is monitored by sentinel cells

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Viral regulators of apoptosis

Cellular Target	Virus	Gene	Function
Bcl-2	Adenovirus	E1B 19K	Bcl-2 homolog
	Epstein-Barr virus	LMP-1	Increases synthesis of Bcl-2; mimics CD40/Tnf receptor signaling
Caspases	Adenovirus	14.7K	Inactivates caspase-8
Cell cycle	Hepatitis B virus	pX	Blocks p53-mediated apoptosis
	Human papillomavirus	E6	Targets p53 degradation
	Simian virus 40	Large T	Binds and inactivates p53
Fas/Tnf receptors	Adenovirus	E3 10.4/14.5K	Internalizes Fas
	Cowpox	CrmB	Neutralizes Tnf and LT-α
	Myxoma virus	MT-2	Secreted Tnf receptor homolog
vFLIPs; DED box-containing proteins	Human herpesvirus 8	K13	Blocks activation of caspases by death receptors
Oxidative stress	Molluscum contagiosum virus	MC066L	Inhibits UV- and peroxide-induced apoptosis; homologous to human glutathione peroxidase
Transcription	Human cytomegalovirus	IE1, IE2	Inhibits Tnf-α but not UV-induced apoptosis

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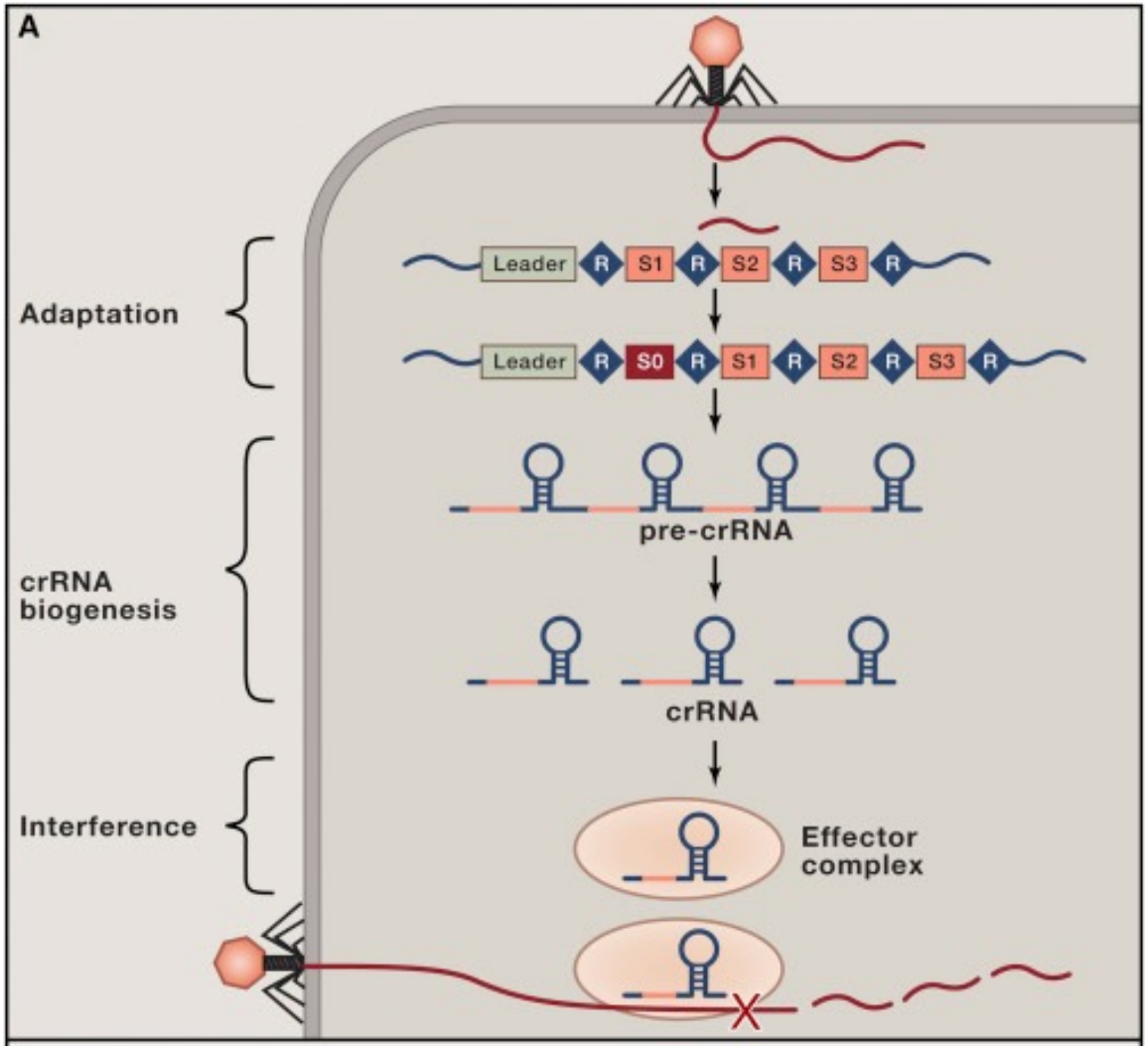
Ancient intrinsic defense: CRISPR

Clustered regularly interspaced short palindromic repeats



90% of Archaea
50% of Bacteria

http://dx.doi.org/10.1016/j.cell.2015.12.035

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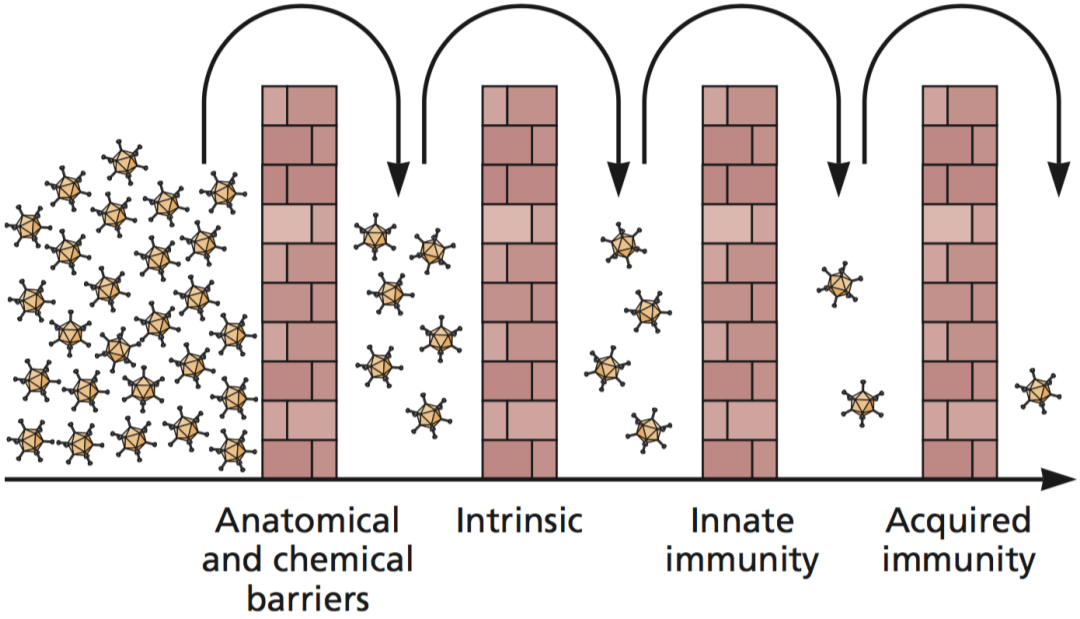
Intrinsic defenses are always present. Which of the following are included?

1. Antibodies
2. T cells
3. Epigenetic silencing
4. Skin
5. 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

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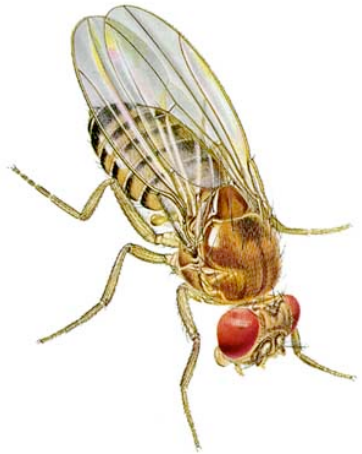
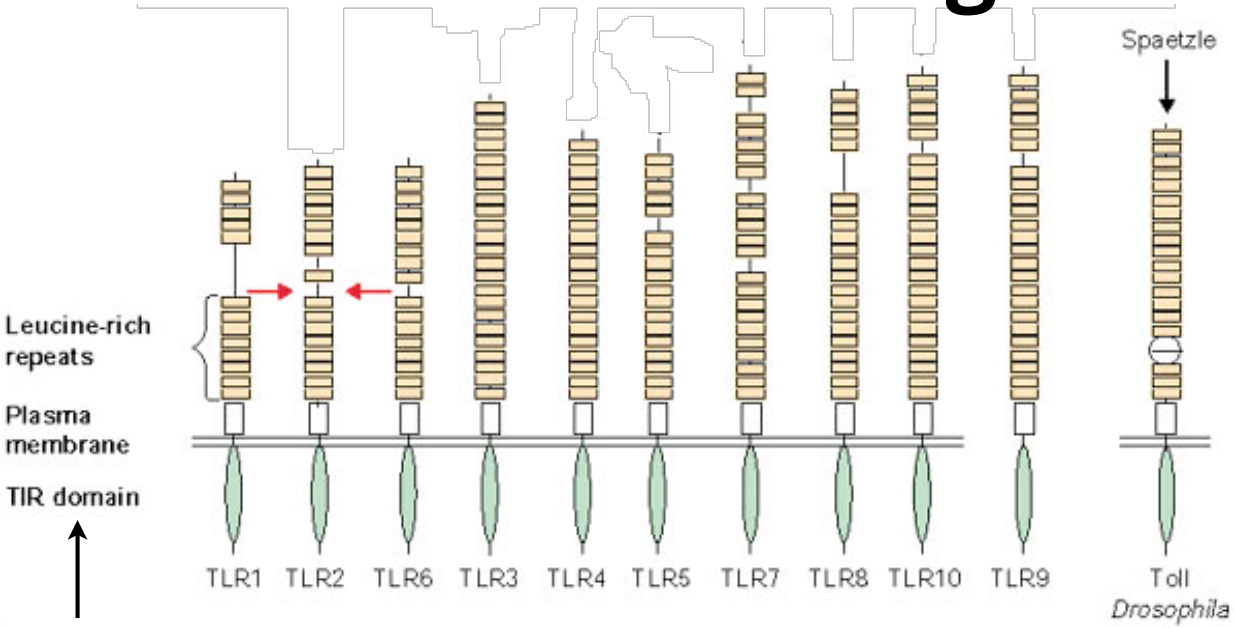
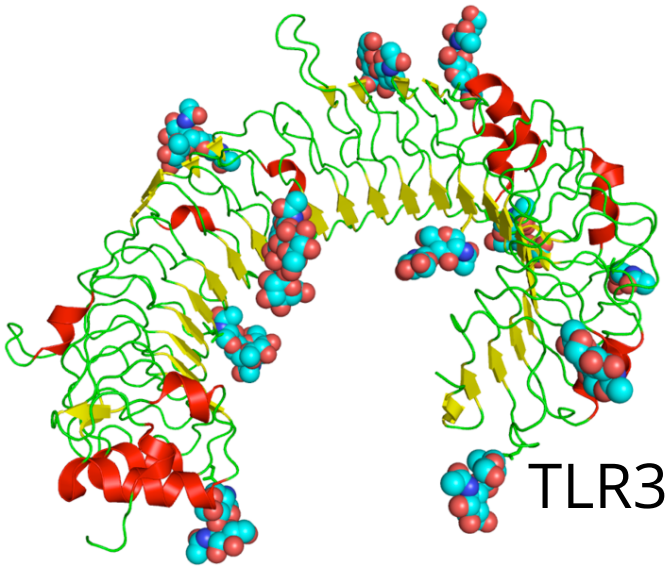
How does the innate system recognize microbes and not self?



- 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

TLRs - Pattern recognition receptors (PRR)





Toll/IL-1 receptor (TIR) domain

Intracellular detectors of viral infection

Receptor	Cellular compartment	Ligand(s) detected	Virus infection(s) detected
Rig-I	Cytoplasm	dsRNA; ssRNA with 5′ phosphate	Influenza virus
Mda5	Cytoplasm	dsRNA	Encephalomyocarditis virus, measles virus
Tlr2	Plasma and endosomal membranes	Measles virus HA protein	Human cytomegalovirus
Tlr4	Plasma and endosomal membranes	Mouse mammary tumor virus envelope protein	Respiratory syncytial virus
Tlr3	Plasma and endosomal membranes	dsRNA	Murine cytomegalovirus, reovirus, West Nile virus
Tlr7 and Tlr8	Plasma and endosomal membranes	ssRNA	Human immunodeficiency virus, influenza virus
Tlr9	Plasma and endosomal membranes	dsDNA; synthetic, unmethylated CpG DNA	Herpes simplex virus 1 and 2

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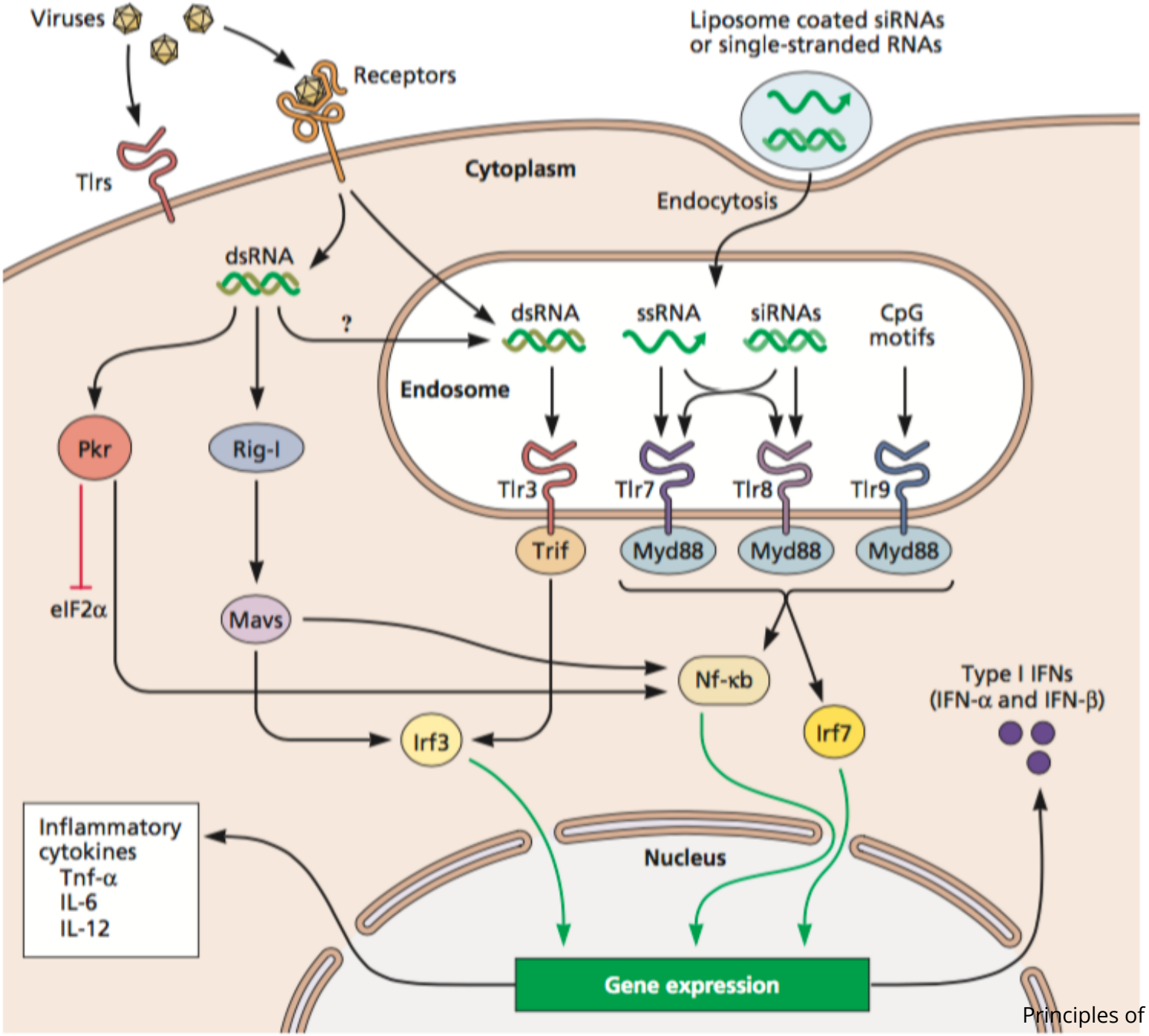
Recognition of foreign nucleic acids



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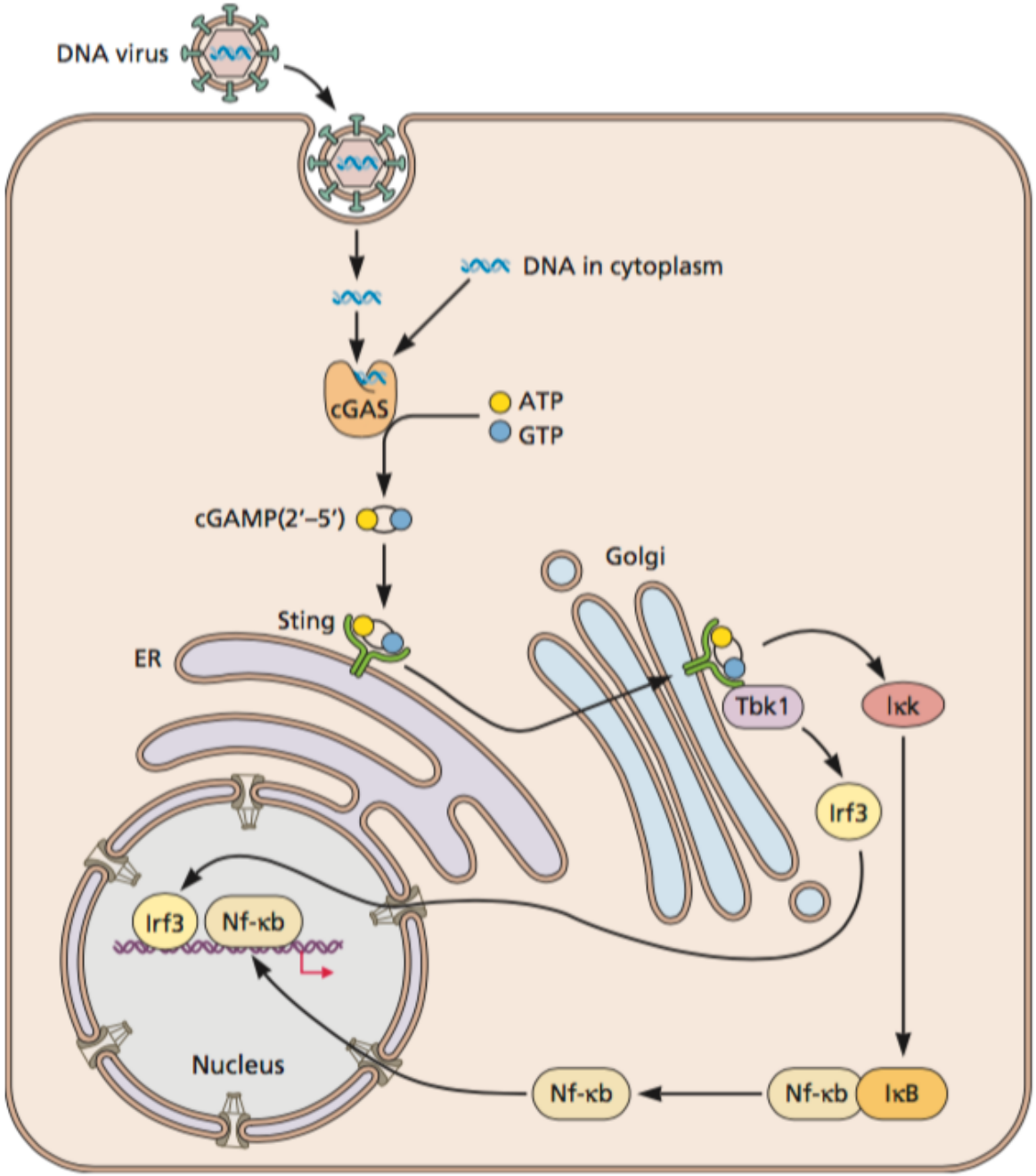
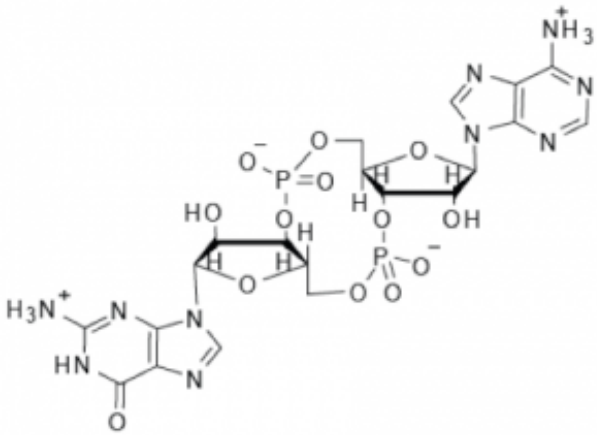
Sensing DNA





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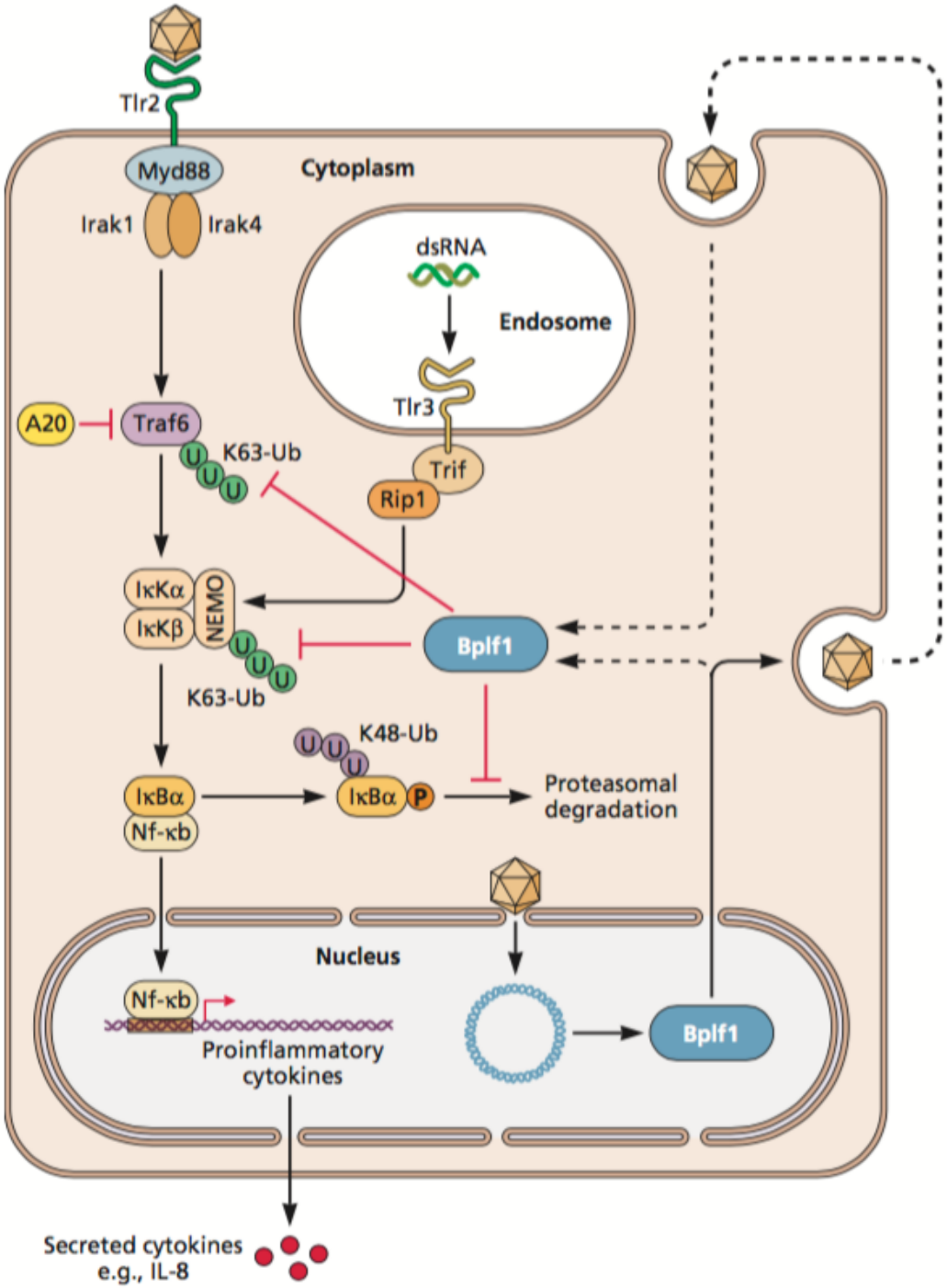
Viral modulators of sensing



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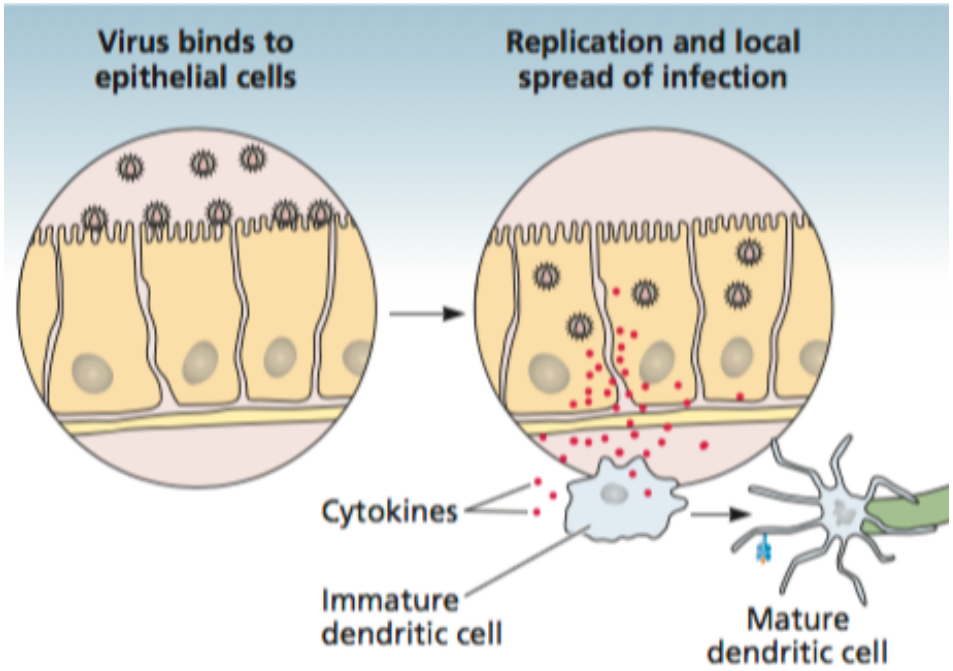
Which of the following allow the innate immune system to distinguish microbes from self?

1. Cytoplasmic helicases and TLRs
2. Antibodies
3. Apoptosis
4. Apobec
5. 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)



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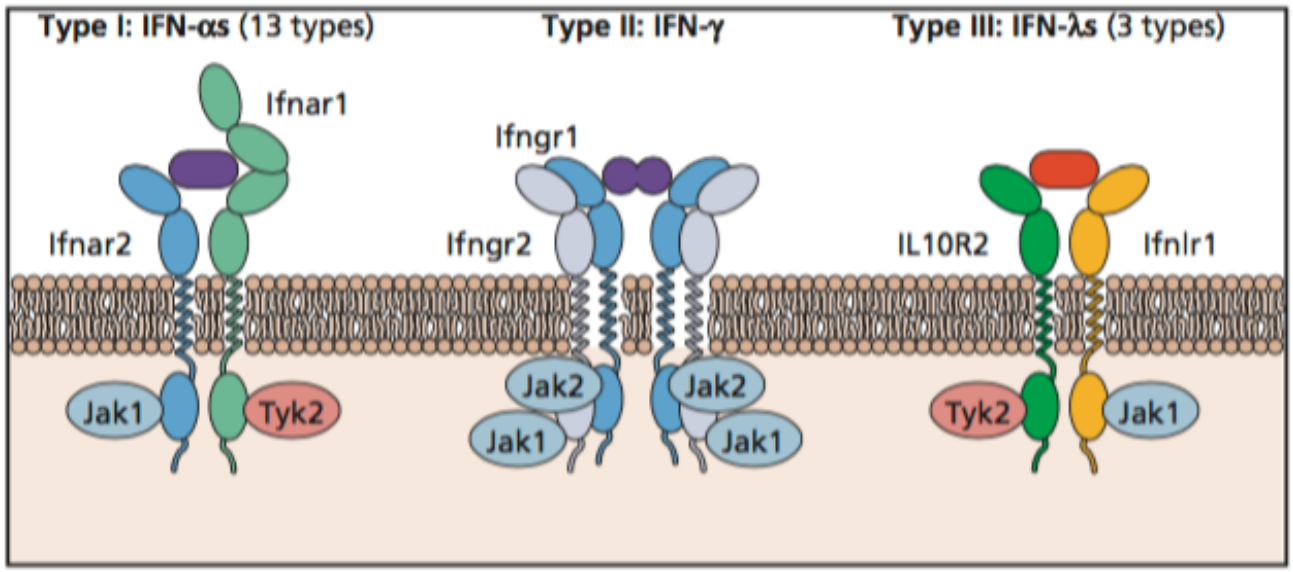
Interferons



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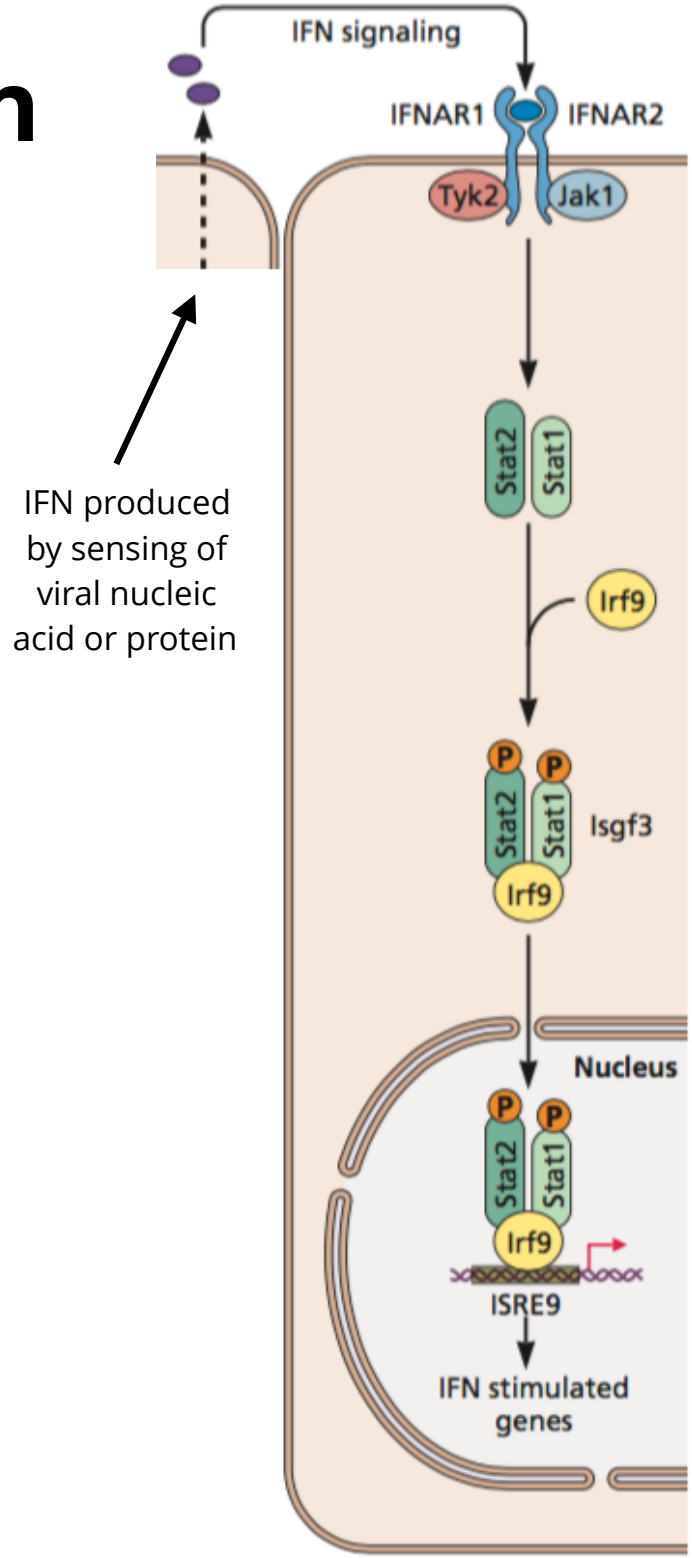
IFN signal transduction

- 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



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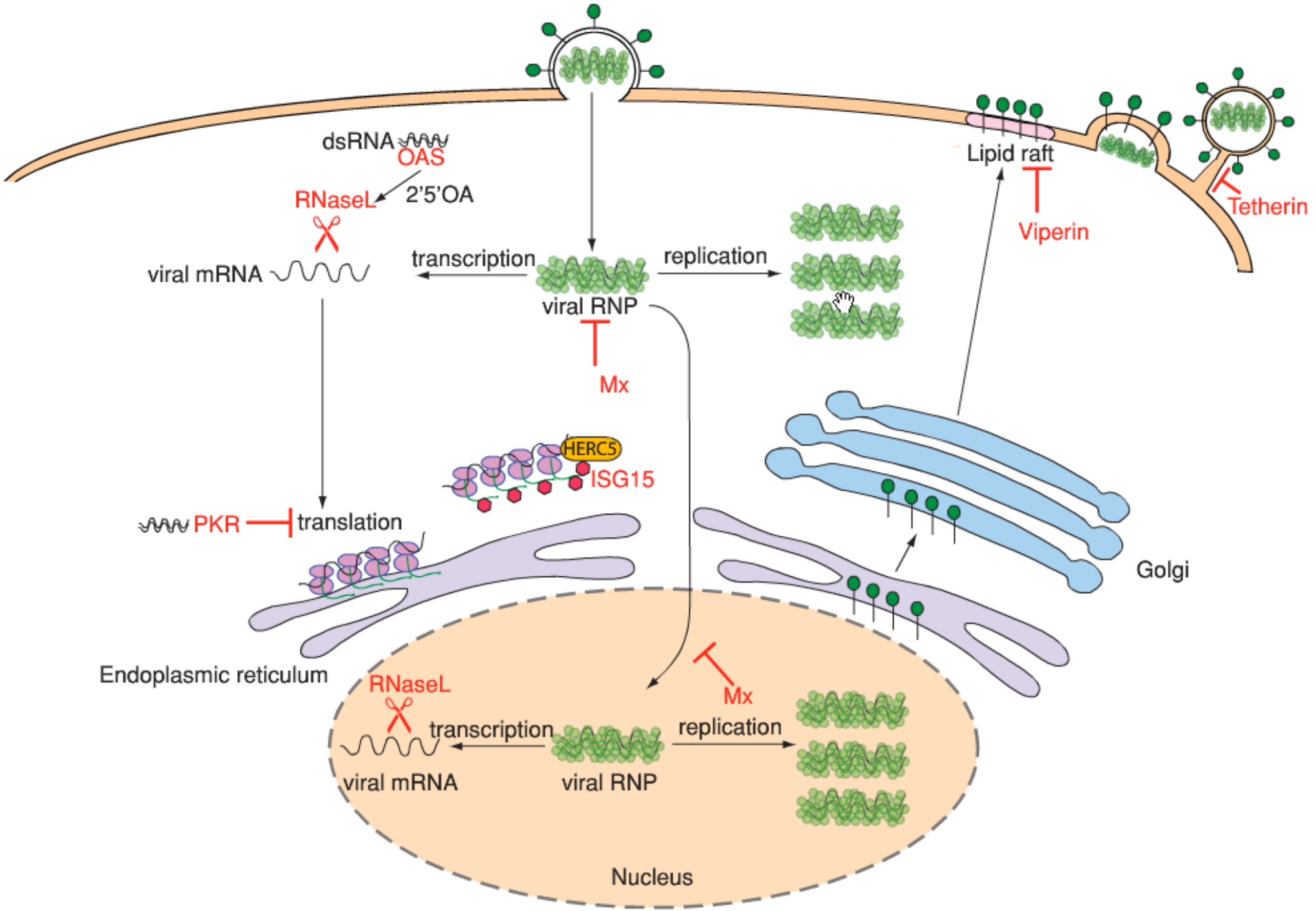

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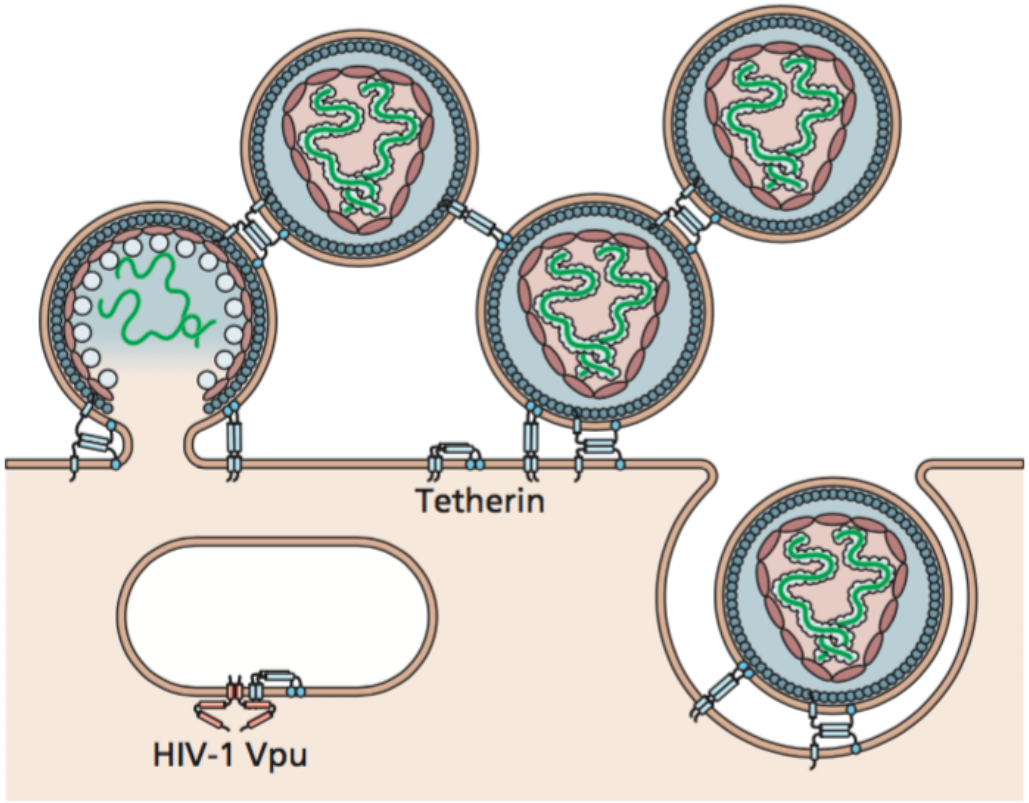
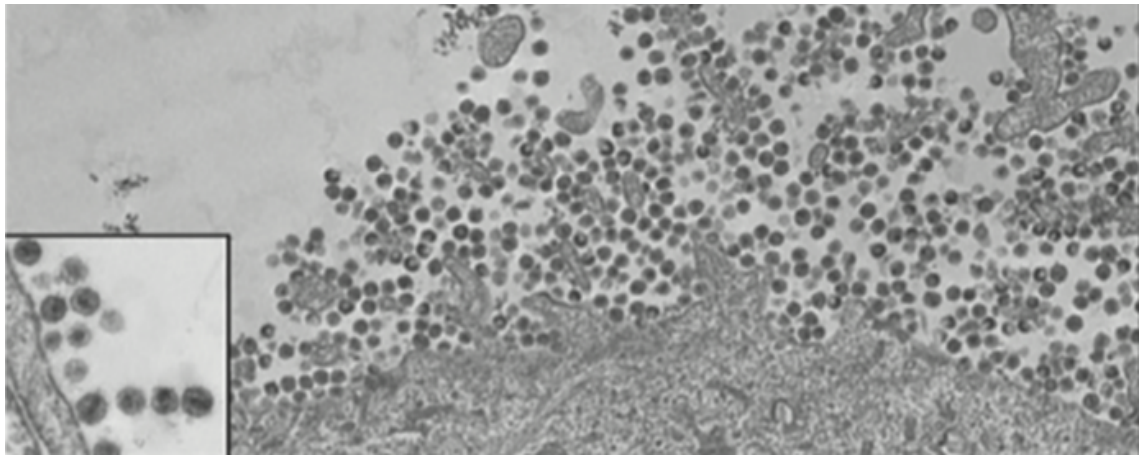
Tetherin, CD137





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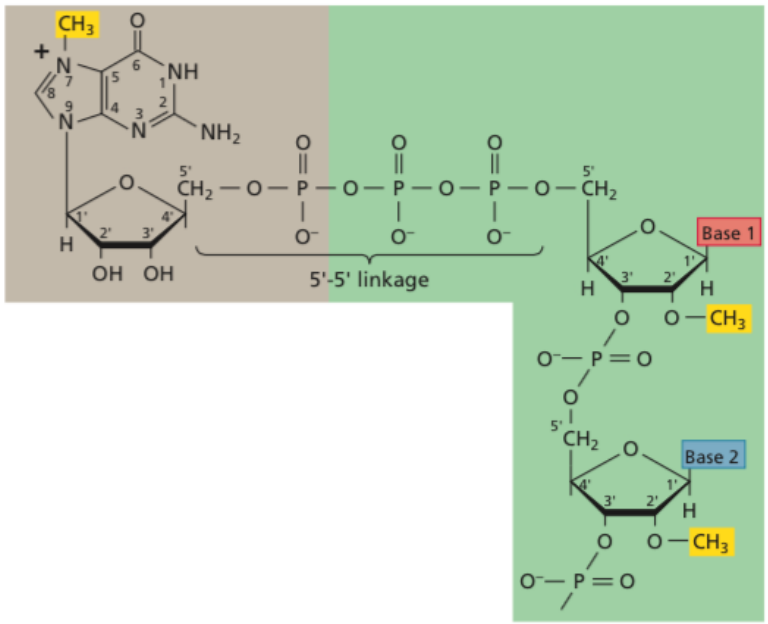
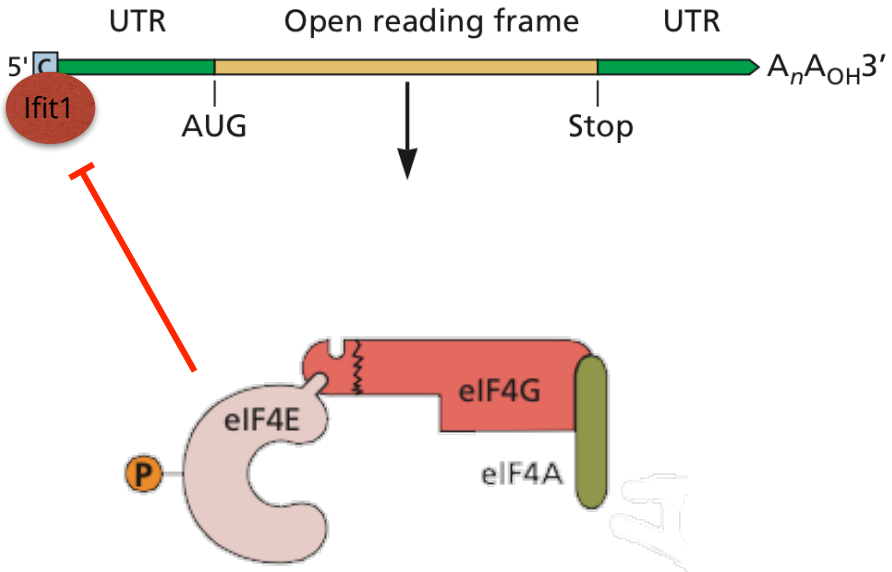
Interferon-induced proteins: Ifit1

IFN-induced protein with tetratricopeptide repeats 1

Ifit1 binds RNAs lacking 2’-O methylation





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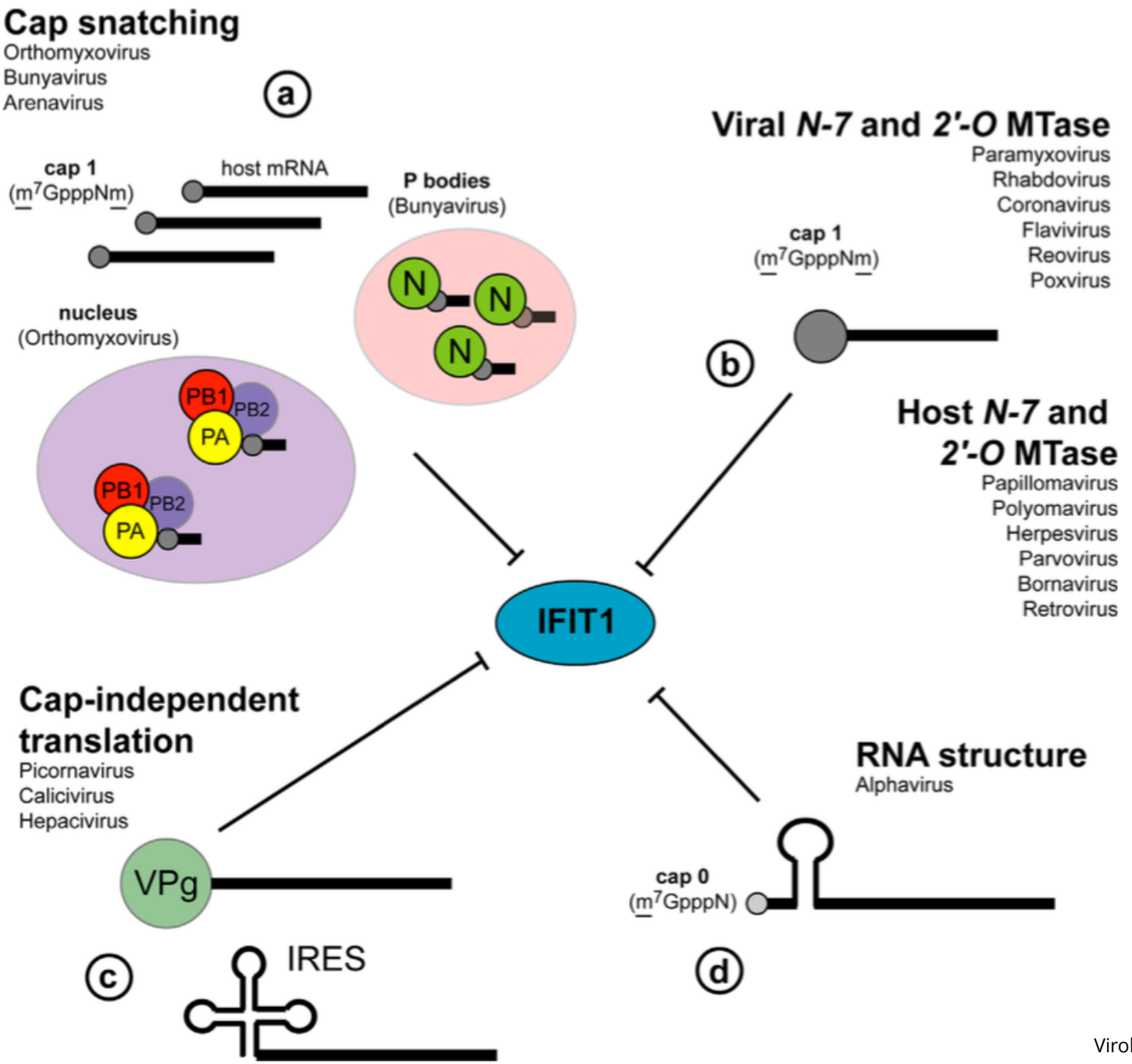
Escape from Ifit1



Virology 479-480 (2015) 66–74

The IFN system is dangerous

- IFN induces the expression of many deleterious gene products - most of our cells have IFN receptors
- Large quantities of IFN 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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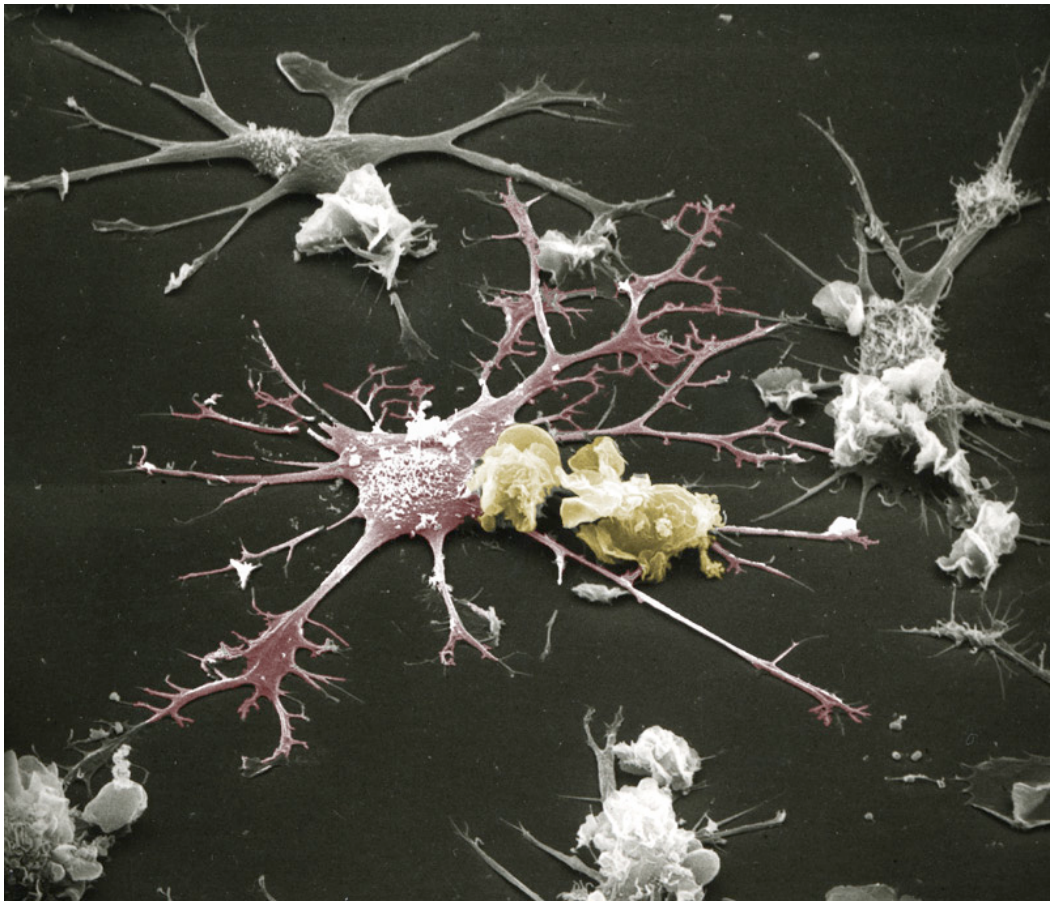
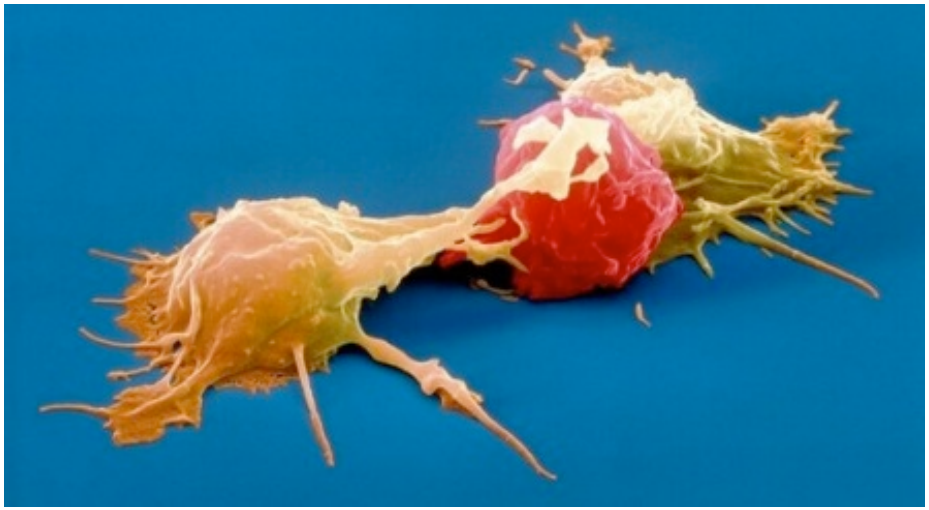
How do interferons (IFNs) limit viral replication?

1. IFNs directly inhibit viral translation
2. IFNs induce TLRs
3. IFNs induce ISGs
4. IFNs damage cells
5. None of the above

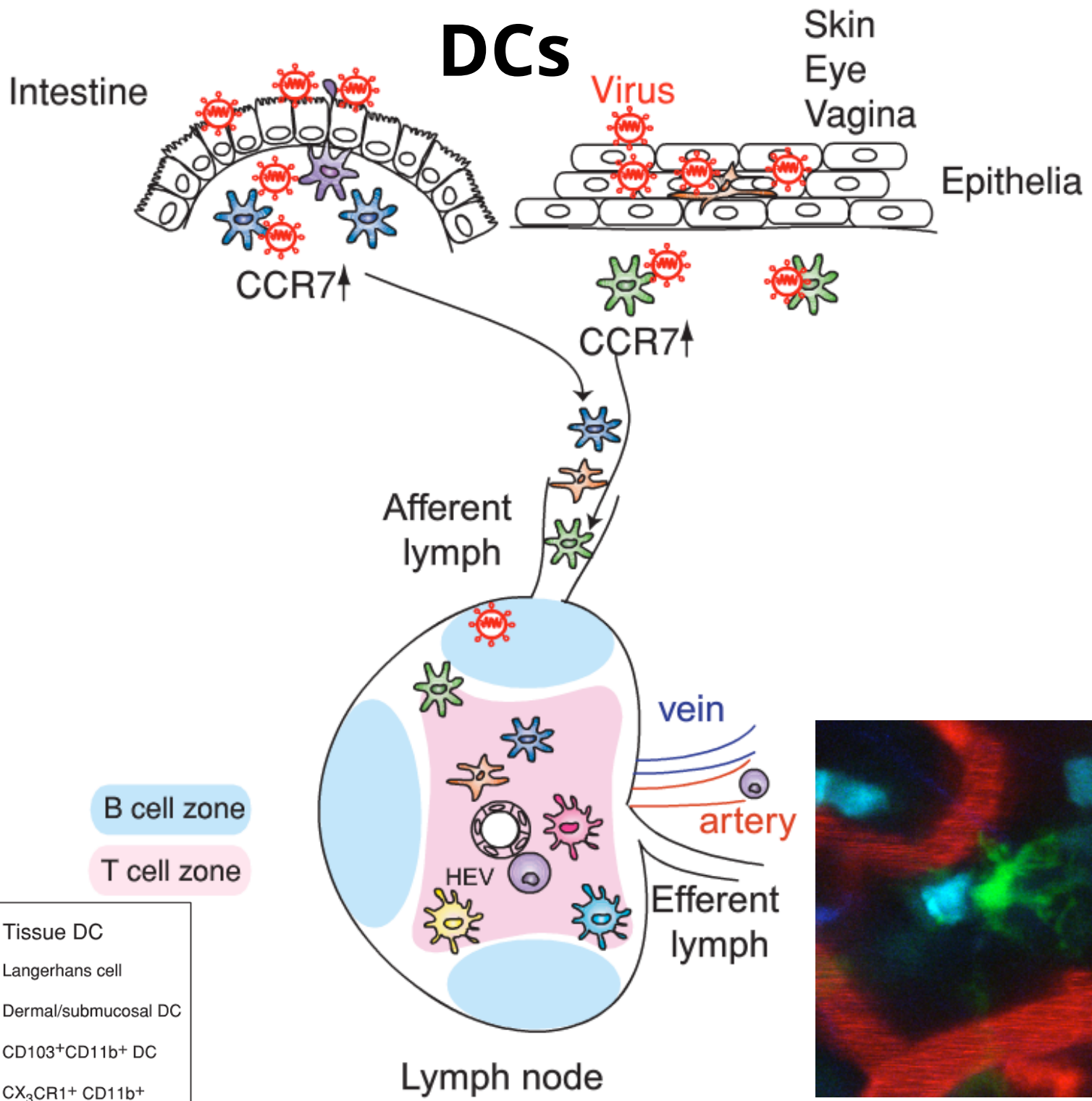
Sentinel cells

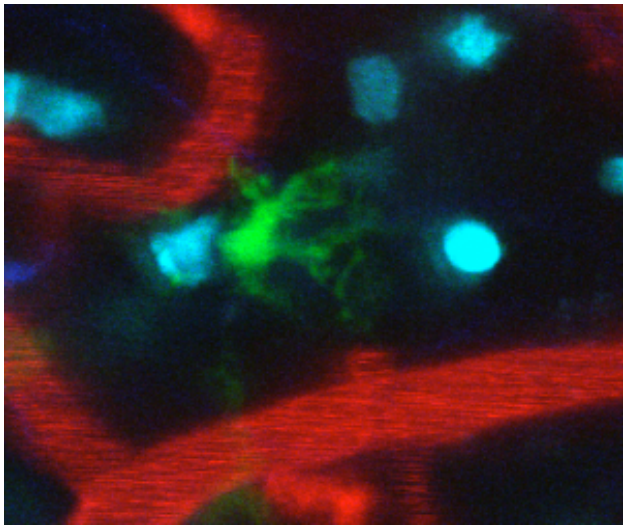
- Dendritic cells, macrophages, natural killer (NK) cells
- They patrol all our tissues looking for signs of change





DCs





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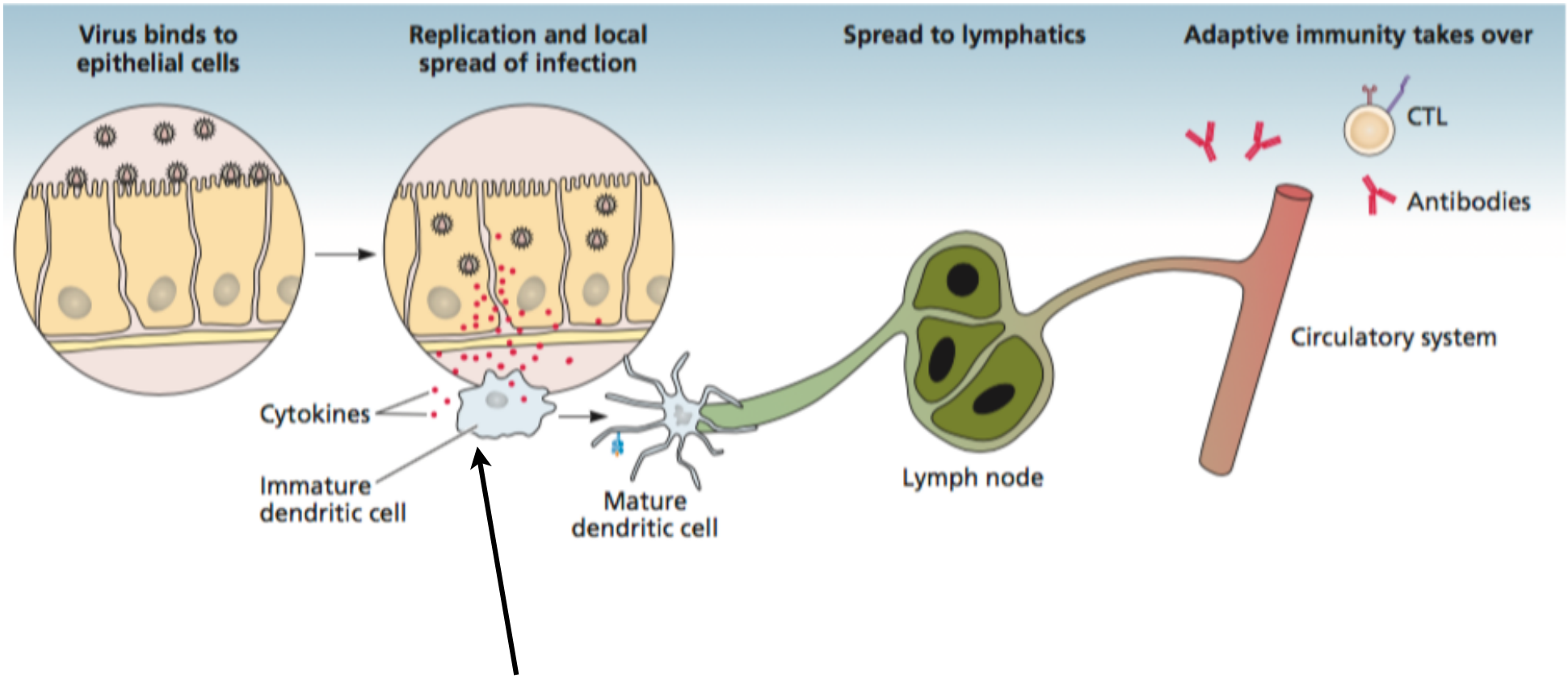
DCs



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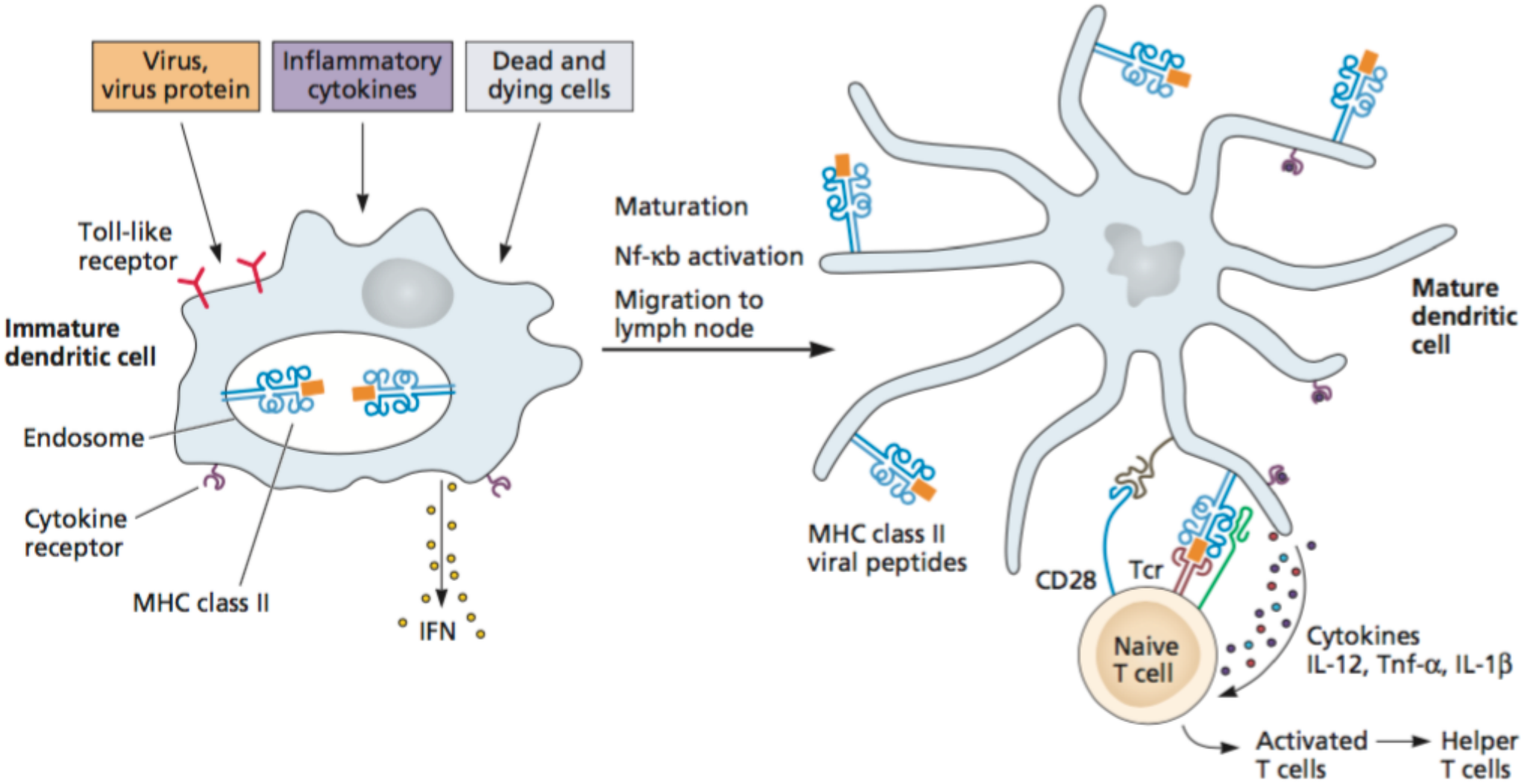
DCs



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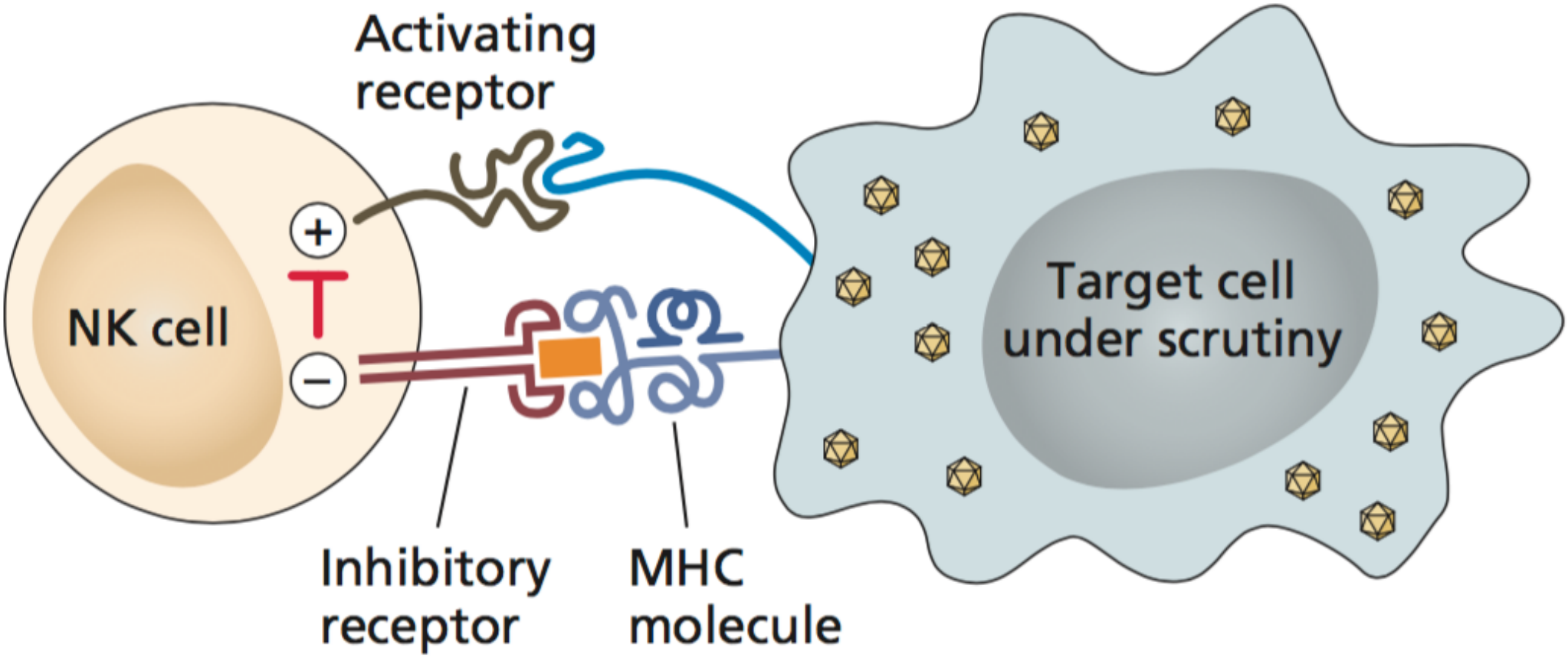
NK cells



Yes, there are viral modulators of NK cells

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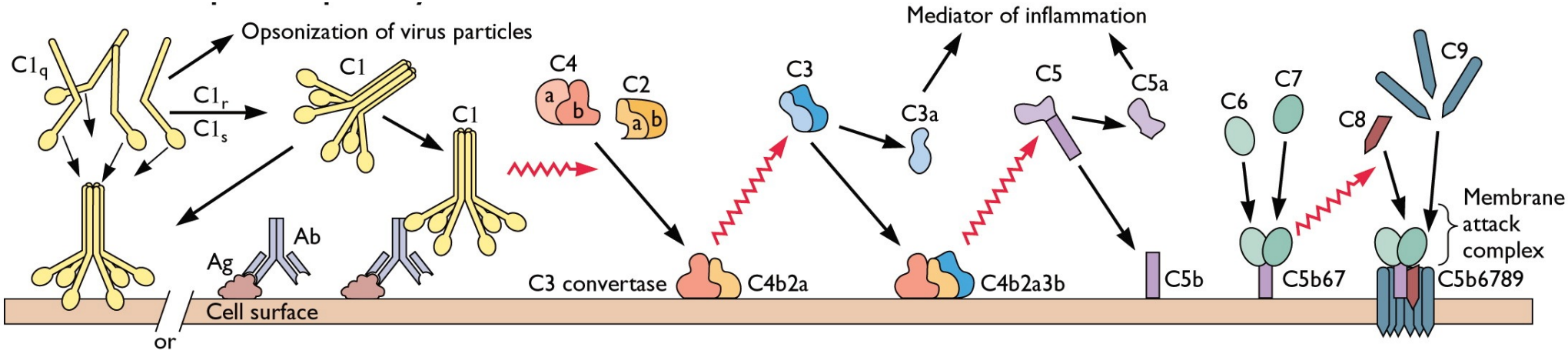
Complement



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Classical cascade begins when a pathogen is detected by C1q (there are two other detector systems)

Yes, there are viral modulators

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What is the main role of dendritic cells (DCs) in viral defense?

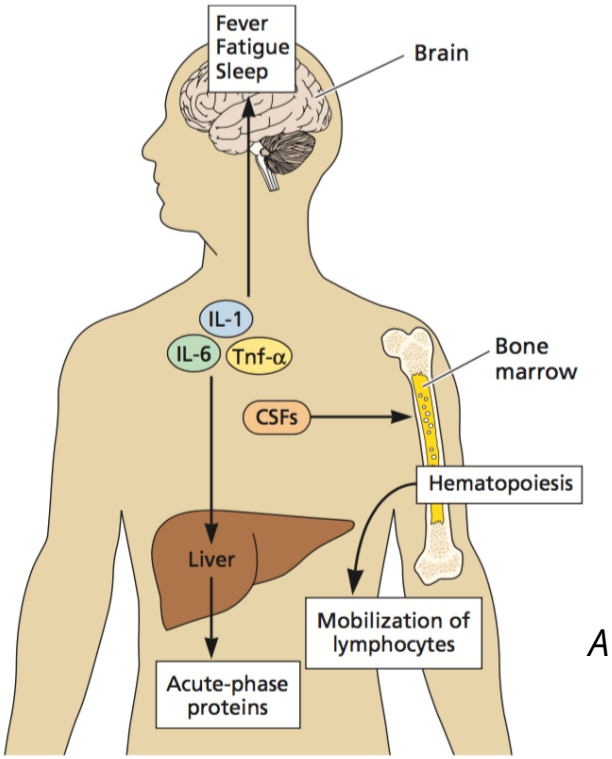
1. DCs destroy virus particles
2. DCs sense infected cells and produce IFNs
3. DCs only instruct the adaptive response
4. DCs lyse virus-infected cells
5. All of the above

Infection leads to the inflammatory response

- 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)
- Result from 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

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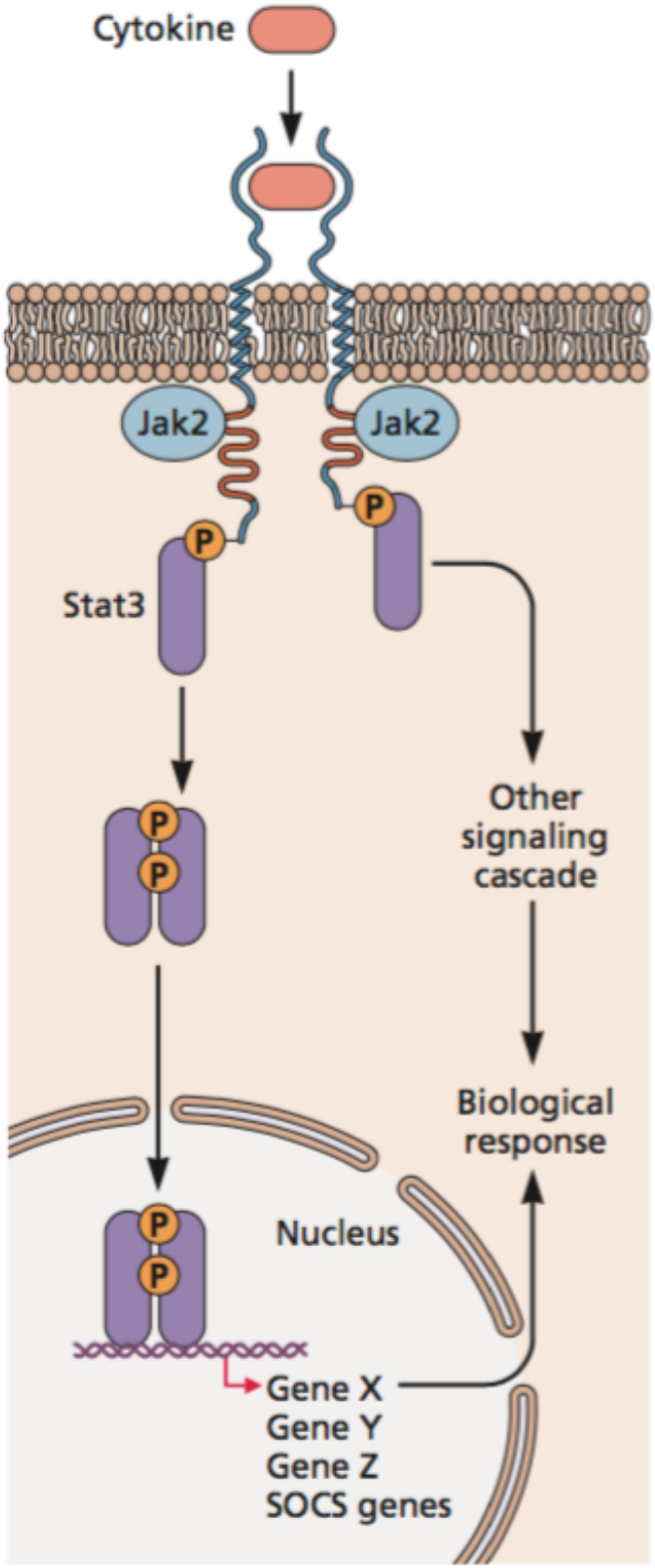

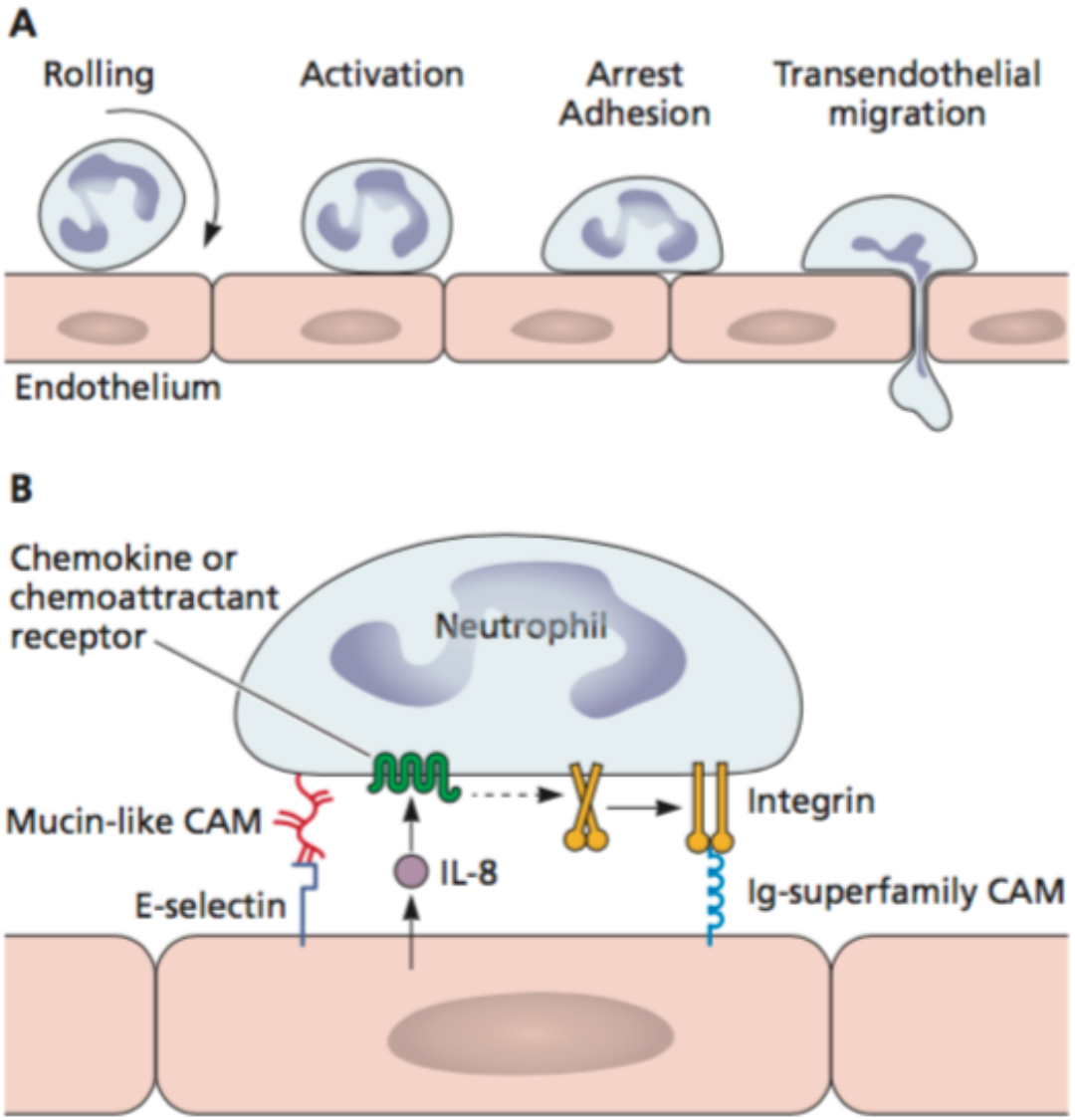

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Cytokine countermeasures

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

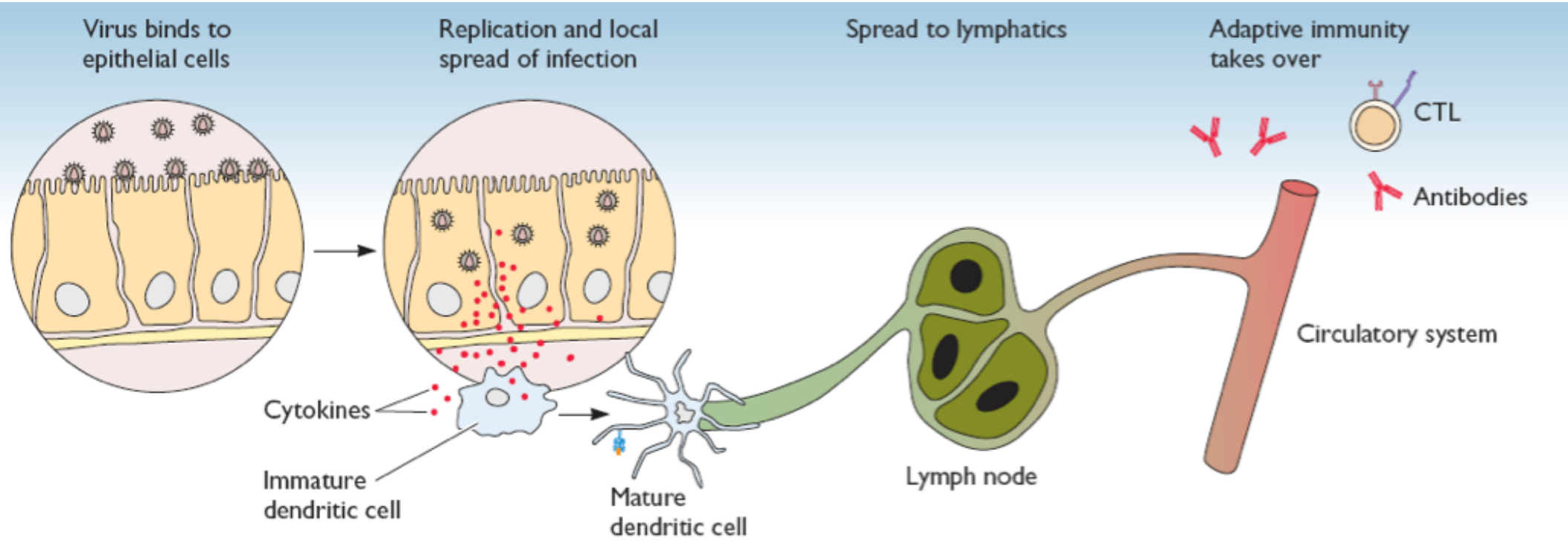
- Cytopathic viruses cause inflammation because they promote cell and tissue damage
  - *Activate the innate response*
- Consequently cytopathic viral genomes encode proteins that modulate this immune response
  - *Adenoviruses, herpesviruses, poxviruses*

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



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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