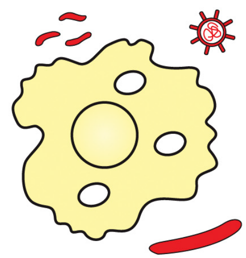
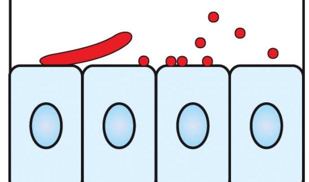
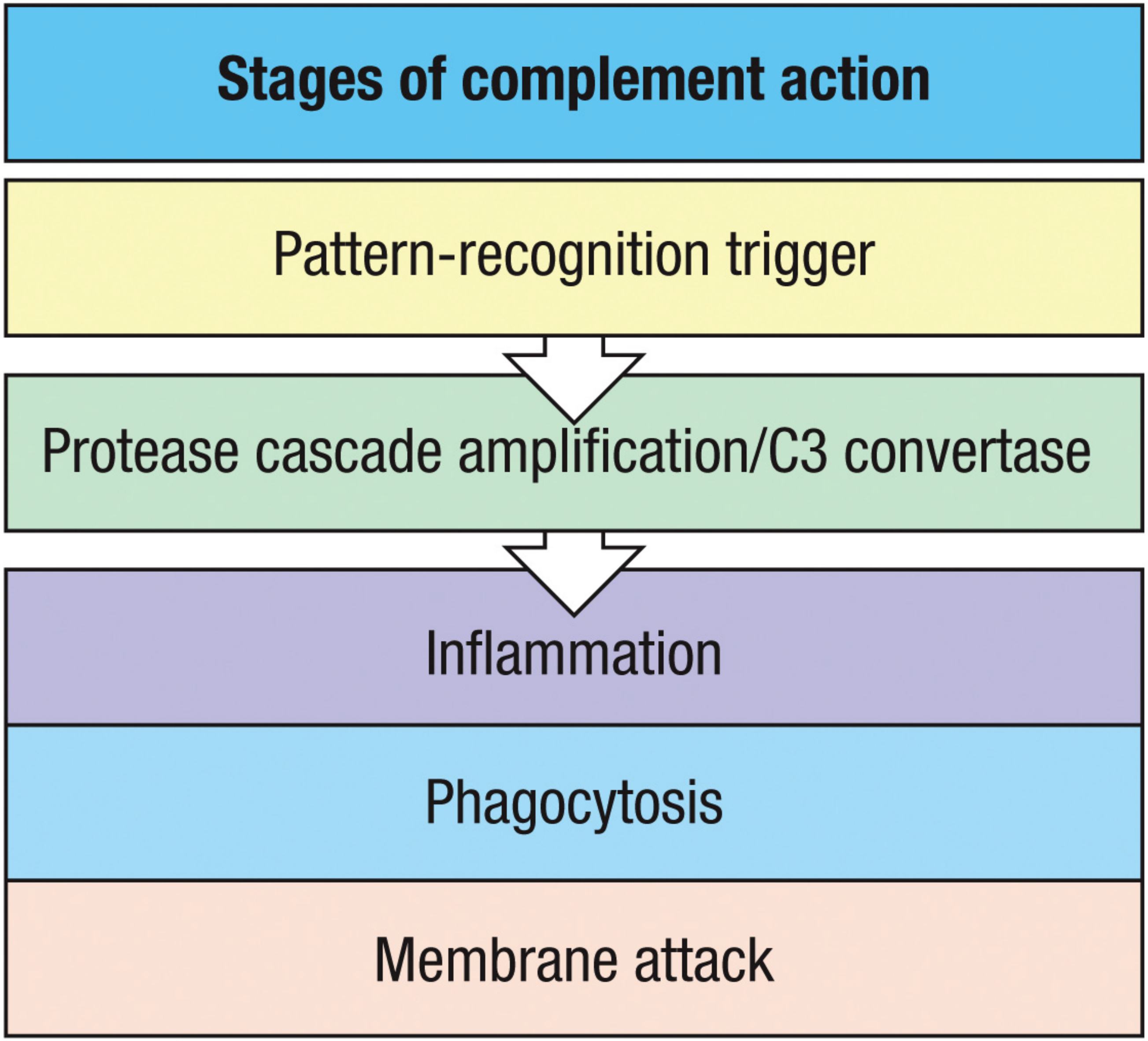
Extracellular Pathogens Activate Complement

	Extracellular	
	Interstitial spaces, blood, lymph	**Epithelial surfaces**
Site of infection		
Organisms	Viruses Bacteria Protozoa Fungi Worms	*Neisseria gonorrhoeae* *Streptococcus pneumoniae* *Vibrio cholerae* *Helicobacter pylori* *Candida albicans* Worms
Protective immunity	Complement Phagocytosis Antibodies	Antimicrobial peptides Antibodies, especially IgA

Stages of Complement Activation



Complement as a target in COVID-19

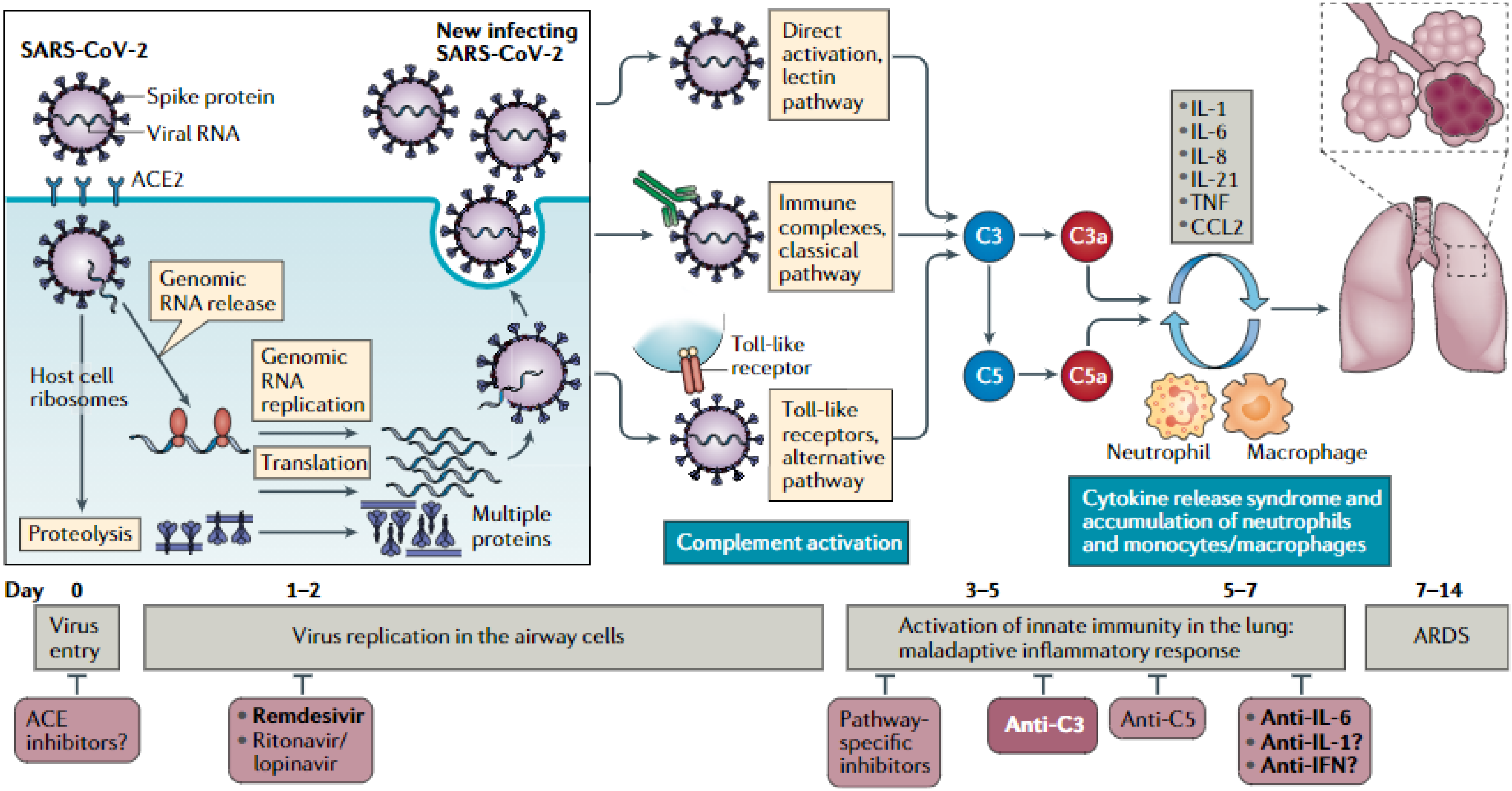


Fig. 1 | **Targeting complement in SARS-CoV-2-associated lung injury.** Complement activation may contribute to the maladaptive inflammatory response seen in some patients with severe COVID-19. Inhibition of C3 or C5 may have therapeutic potential. ARDS, acute respiratory distress syndrome.

Macrophages Express Receptors for Pathogen Constituents

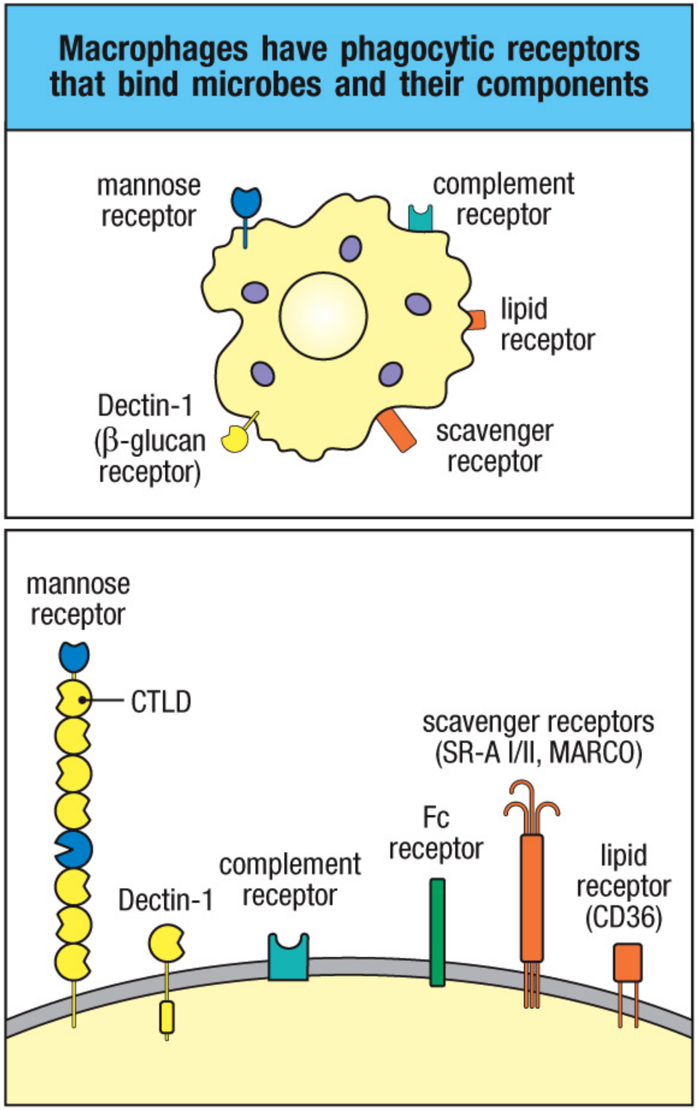


Figure 3.2 (part 1 of 2) Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Mannose receptor: sugars

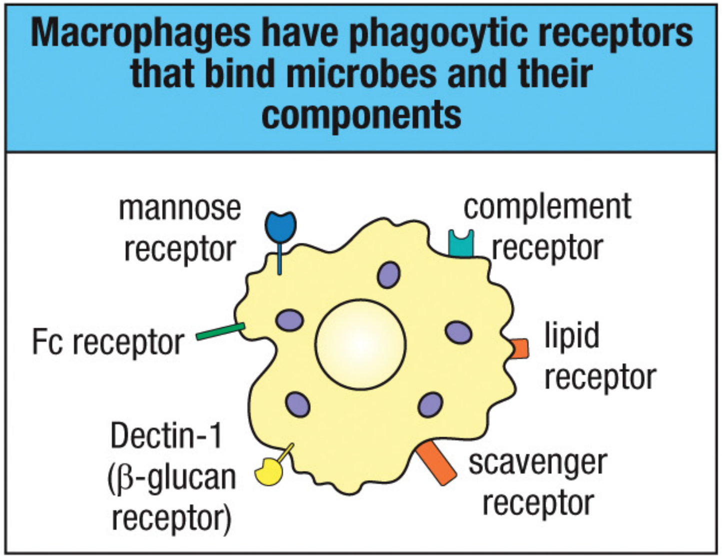
Dectin-1 receptor: yeast glycans

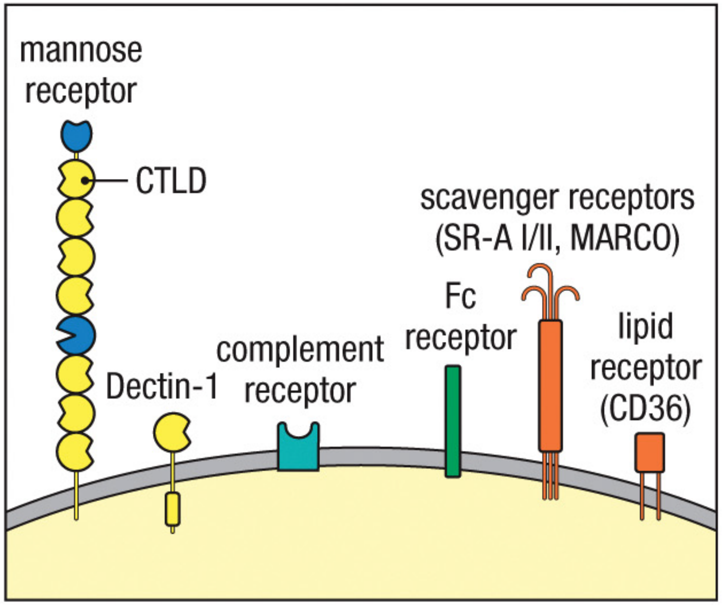
Scavenger receptor: uncharged lipoprotein.

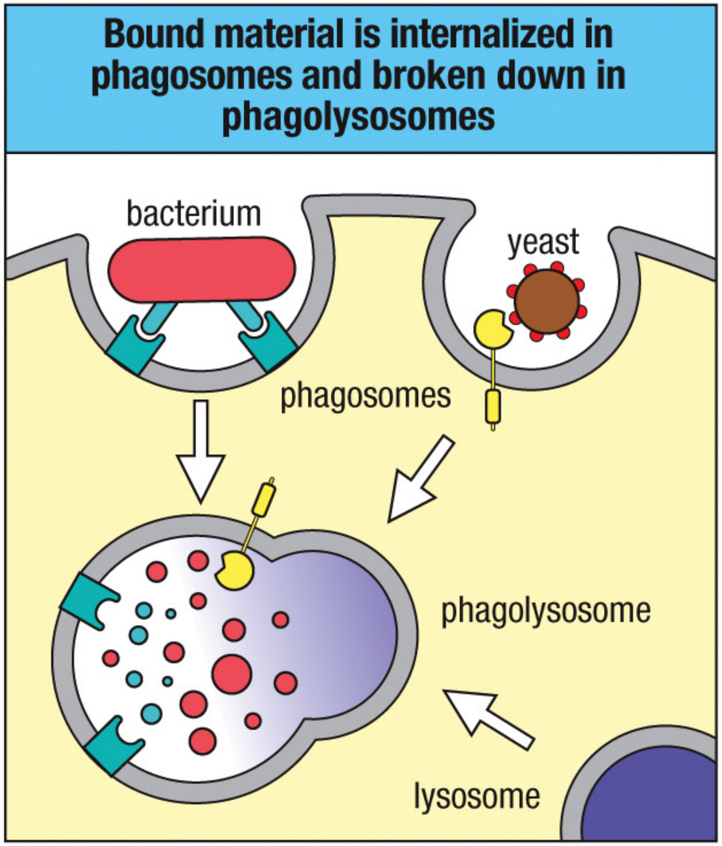
CD36 receptor: long lipids

Pathogen Surface molecules

Phagocytosis



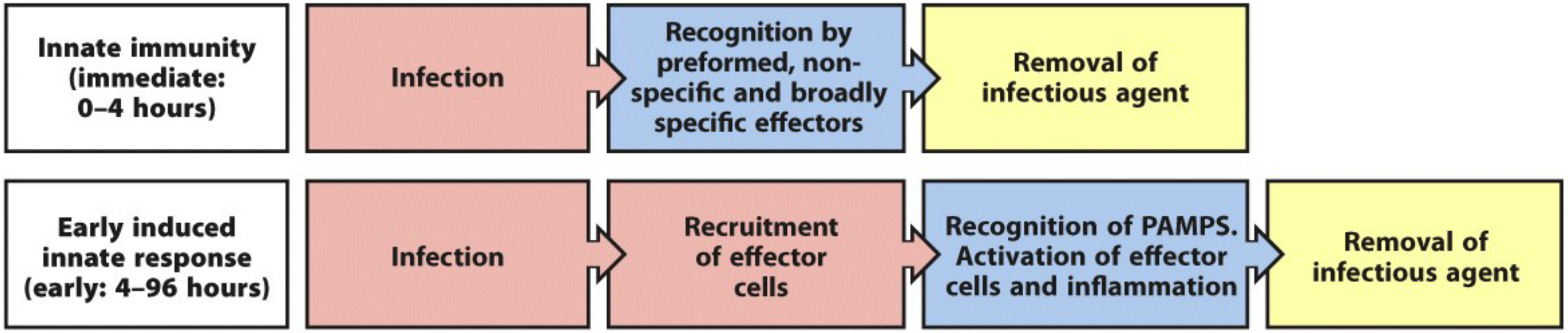




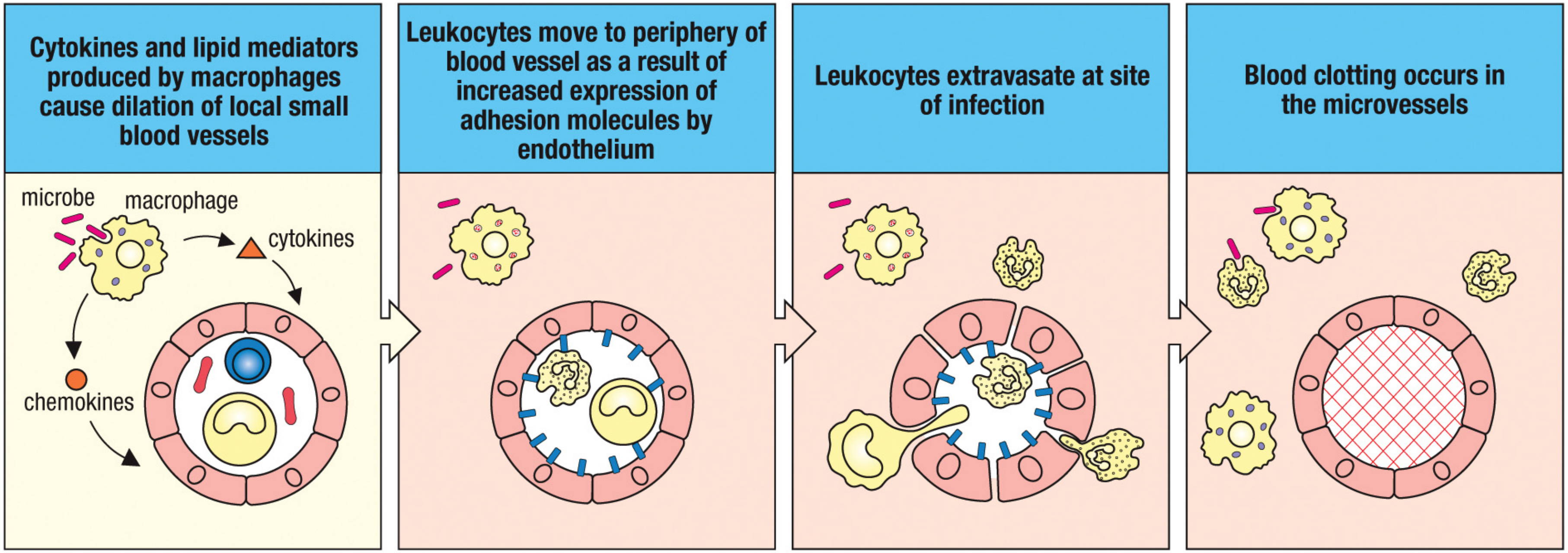
Phagocytosis

- Pathogens not immediately cleared by phagocytosis will trigger pattern recognition receptors
- Activation of PRRs causes inflammation
- Pathogen and microbes

Course of Immune Activation



Course of Immune Activation



Outline

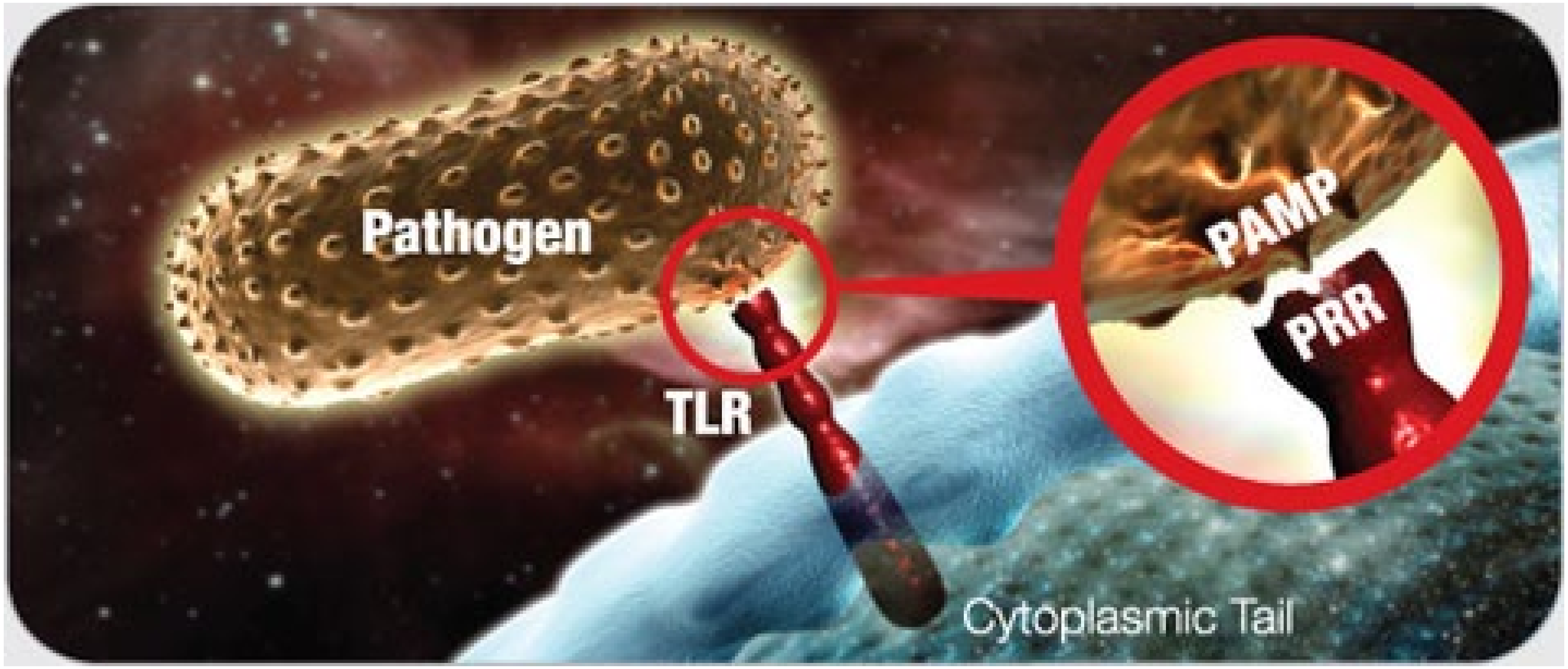
- Pattern recognition receptors
    - PAMS
    - TLRs
    - Cytosolic DNA/RNA sensors
    - NODs
    - Inflammasome
- Case study: Hereditary Periodic Fever Syndromes

Pattern Recognition Receptors

Receptor characteristic	Innate immunity	Adaptive immunity
Specificity inherited in the genome	Yes	No
Triggers immediate response	Yes	No
Recognizes broad classes of pathogens	Yes	No
Encoded in multiple gene segments	No	Yes
Requires gene rearrangement	No	Yes
Clonal expression	No	Yes
Able to discriminate between even closely related molecular structures	Yes	Yes

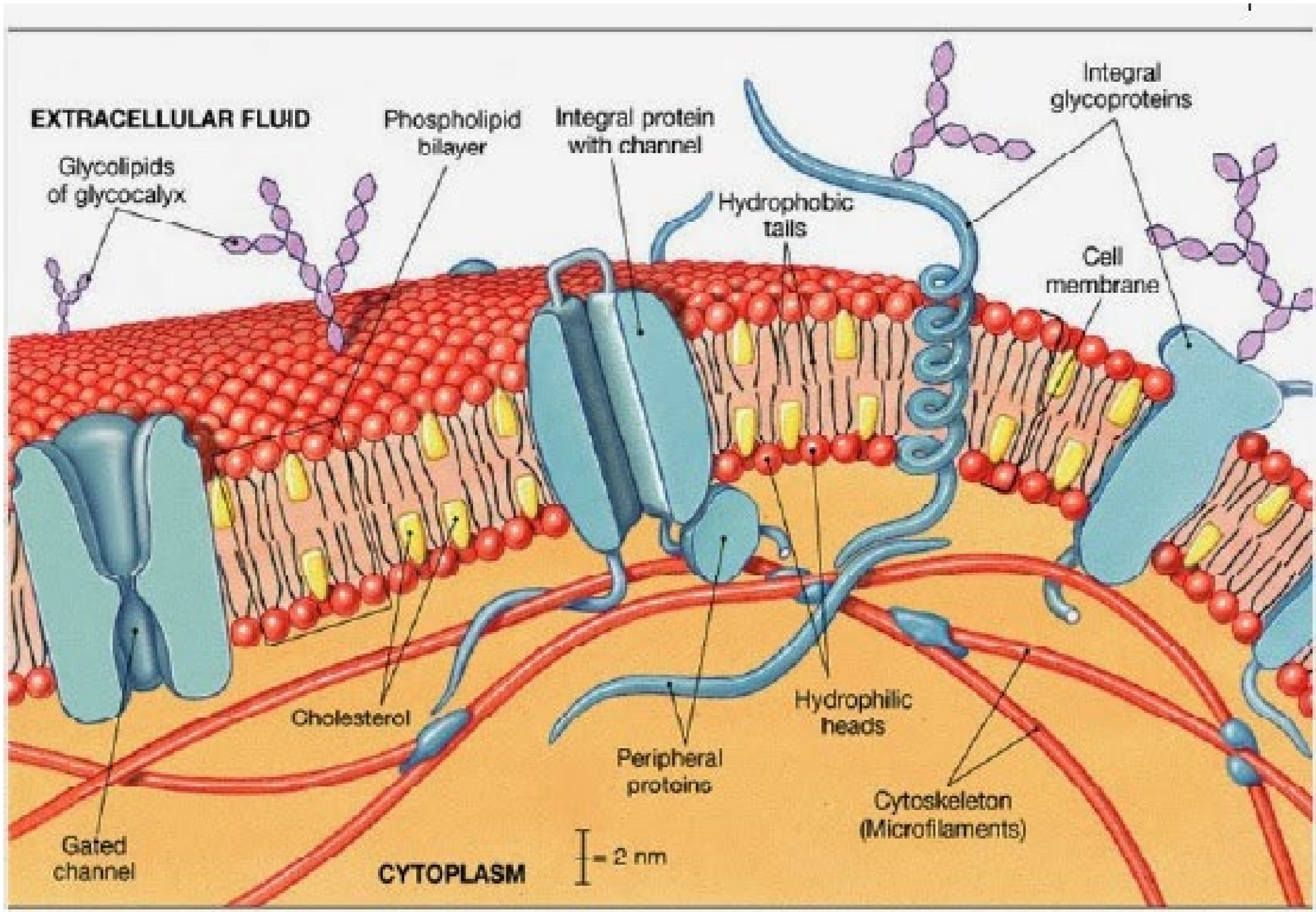
PAMP and PRR

Pathogen Associated Molecular Patterns

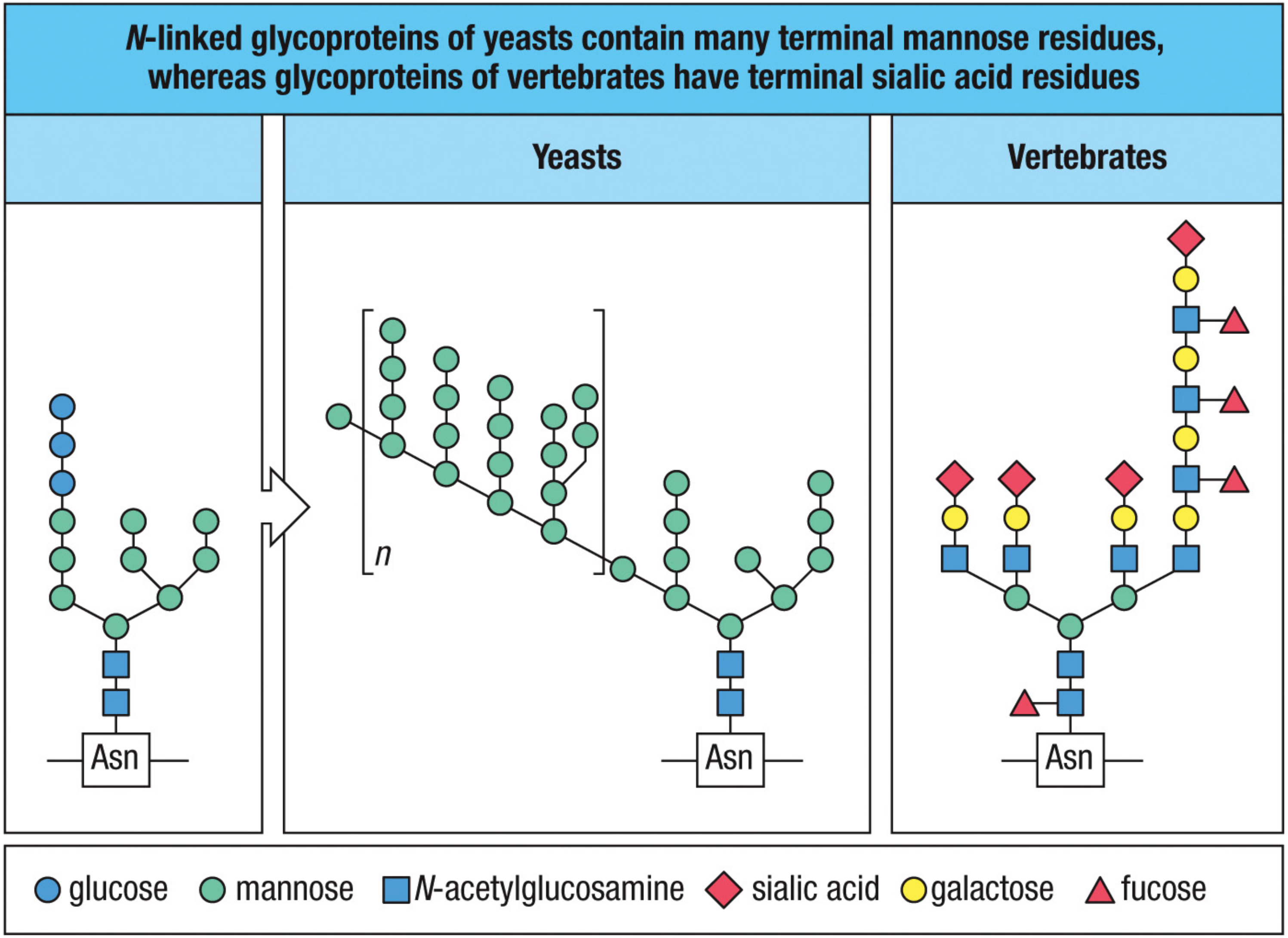


http://www.sabiosciences.com/pathwaymagazine/pathways7/toll-like-receptors-and-innate-immunity.php

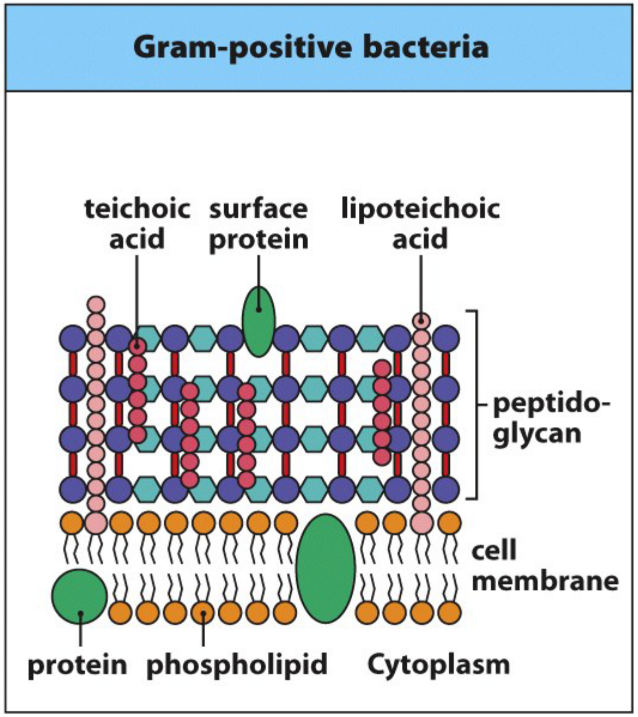
Mammalian Cell Surface

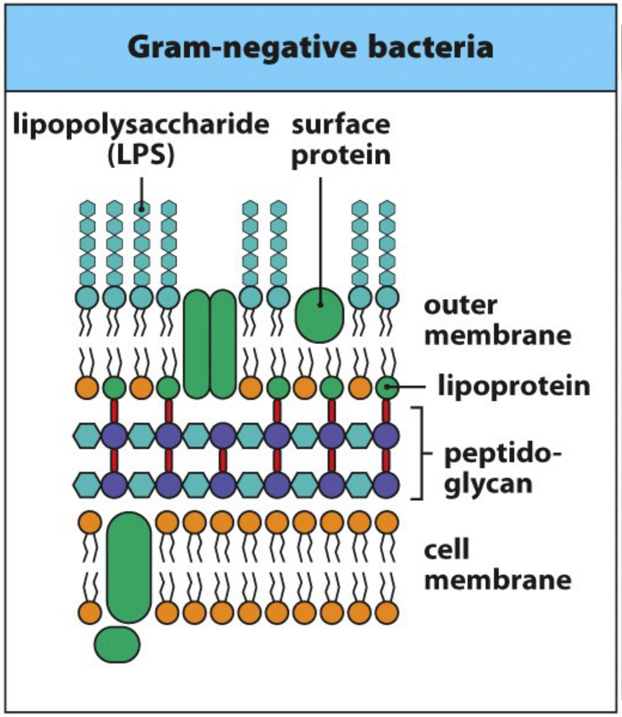


Surface Sugars

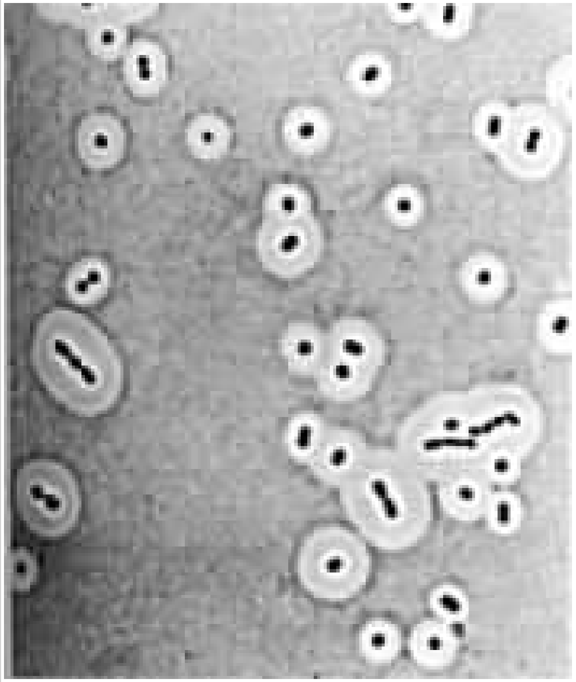


Bacterial Cell Wall





Streptococcus Capsule



Outline

- Pattern recognition receptors
  - PAMS
  - TLRs
  - NLRs
  - Inflammasome
- Case study: Hereditary Periodic Fever Syndromes

Discovery of Toll-like Receptors

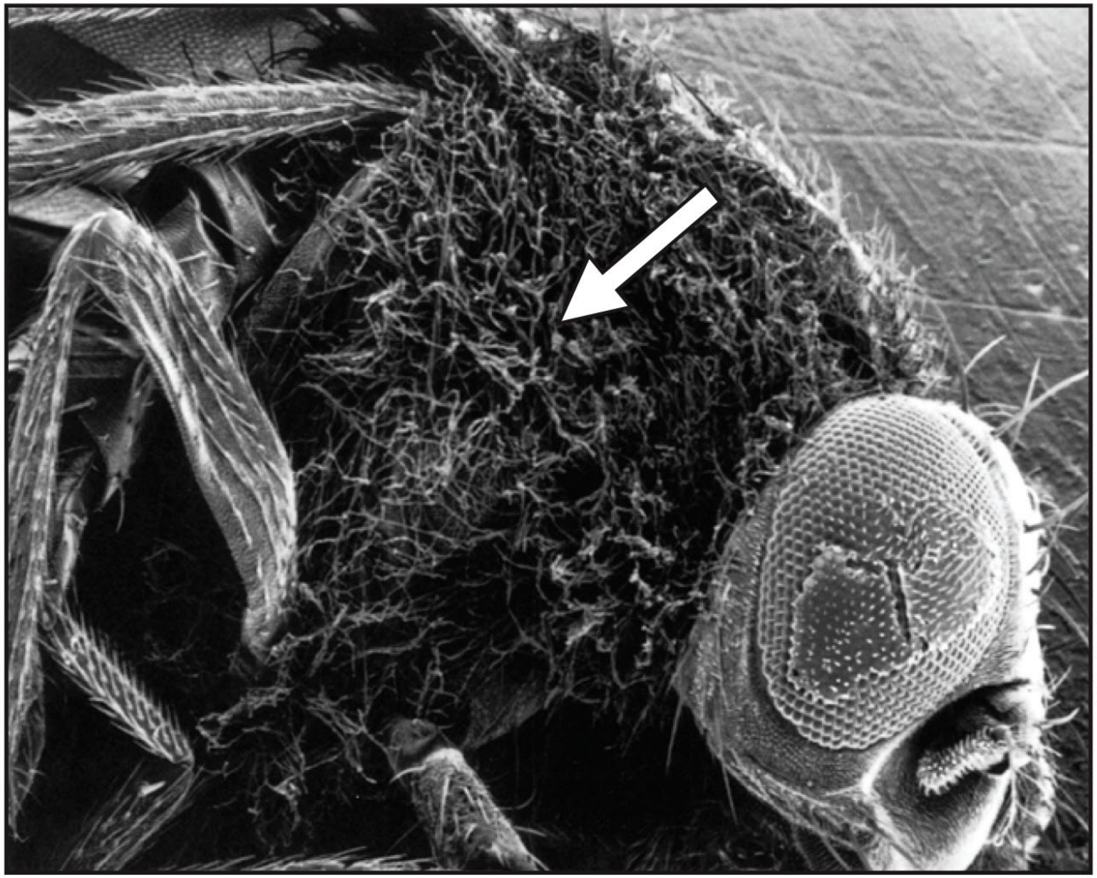
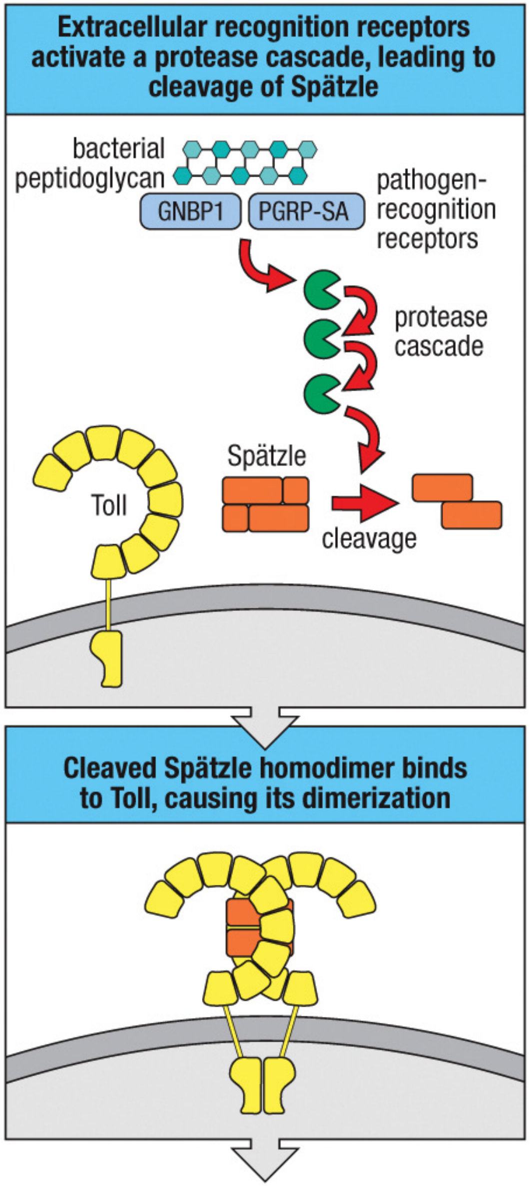


Photo courtesy of J.A. Hoffmann

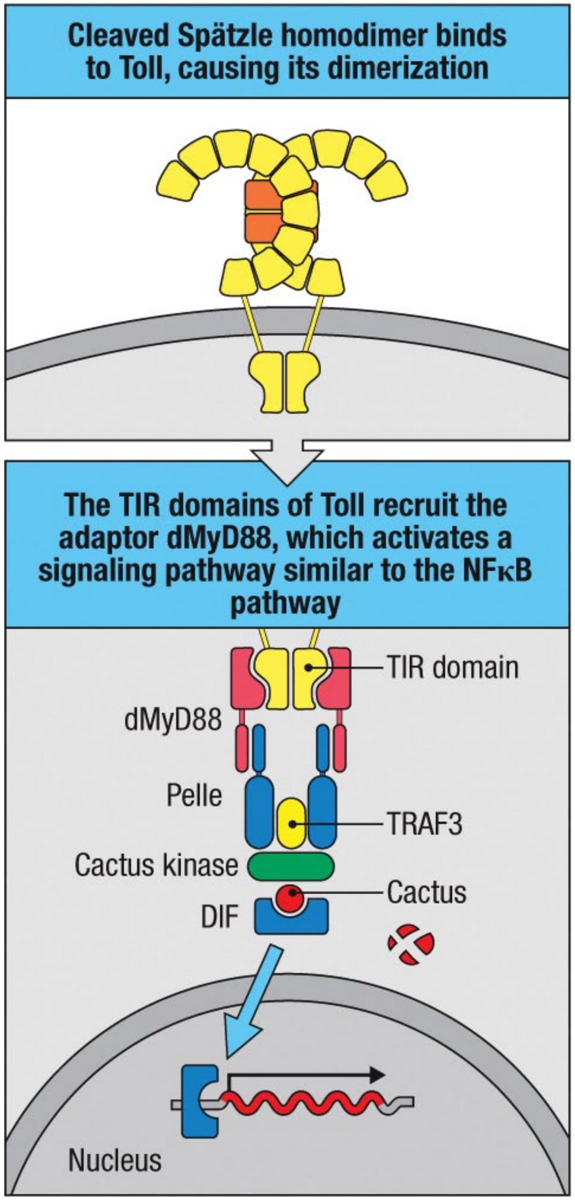
Jules A. Hoffmann: 2011 Nobel Prize in Physiology or Medicine

He found that this receptor has an immune function in 1996

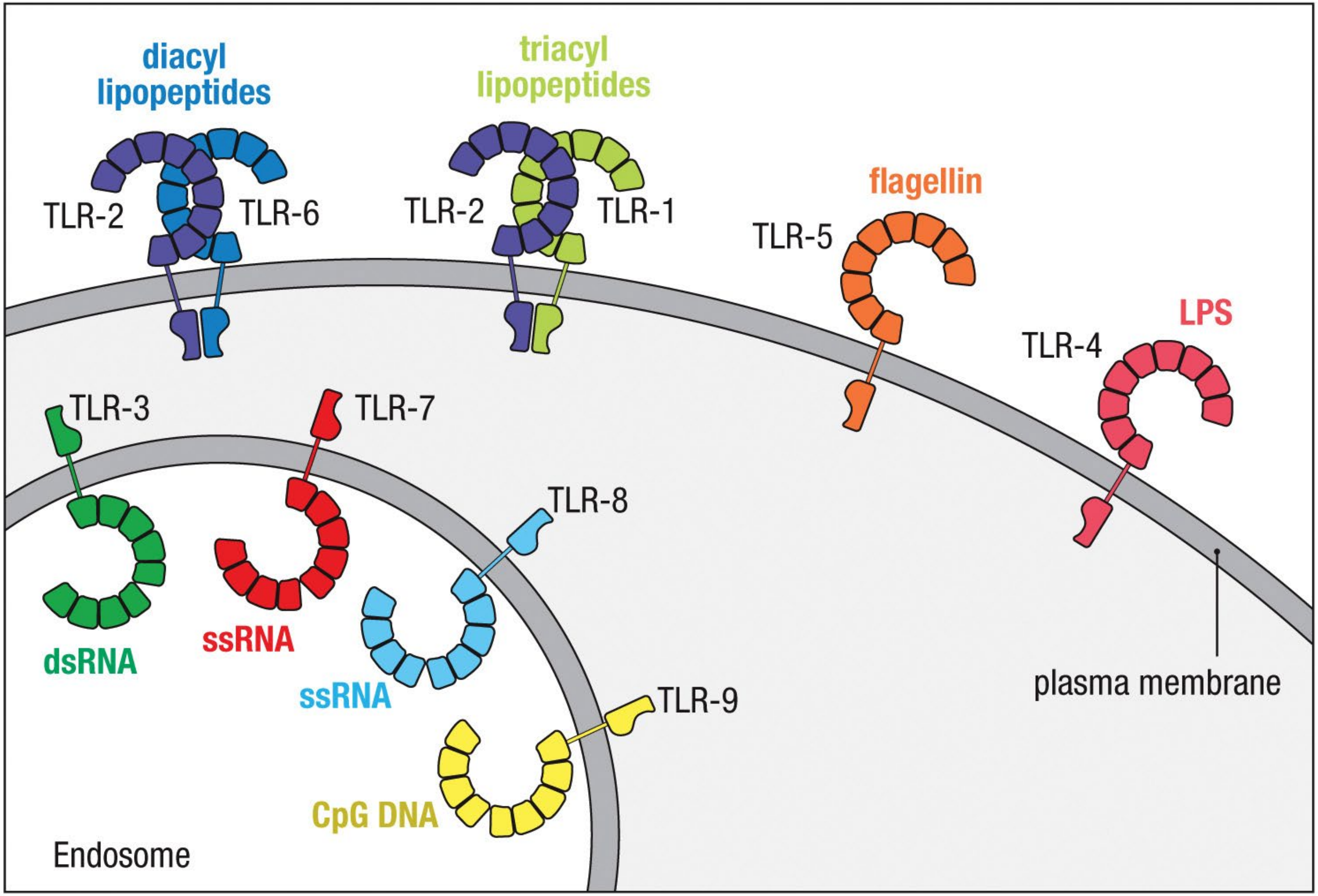
Drosophila TLR



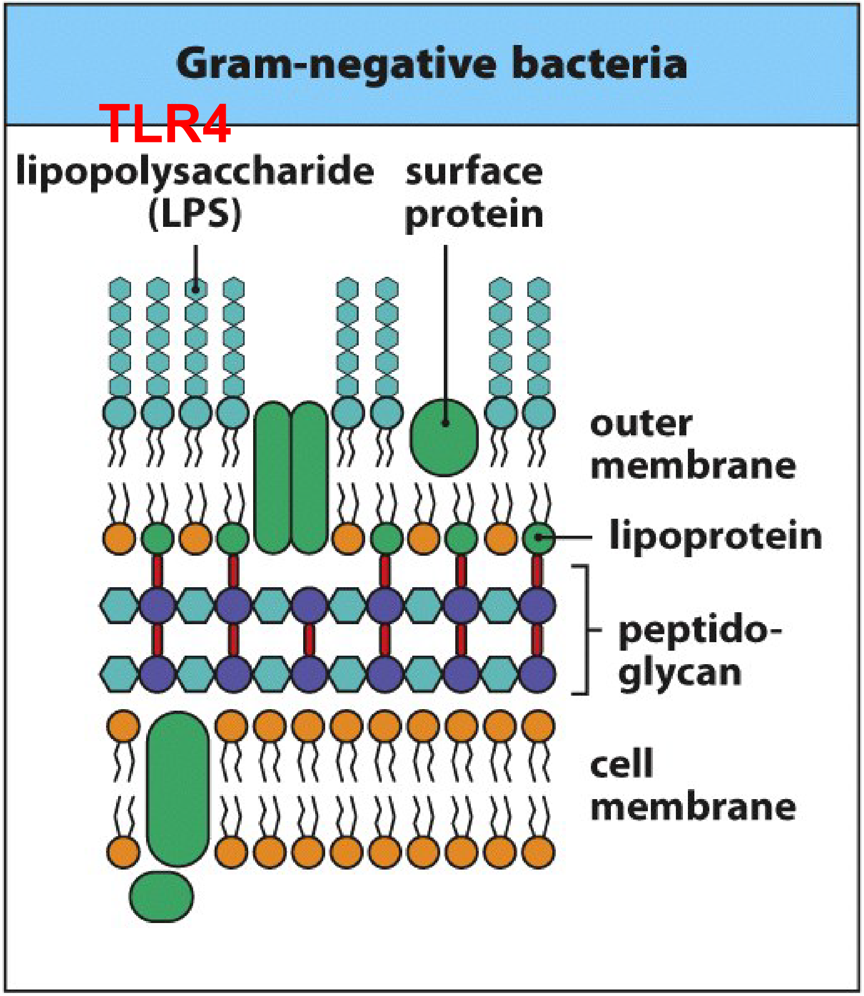
Drosophila TLR



Diversity of Toll-like Receptors

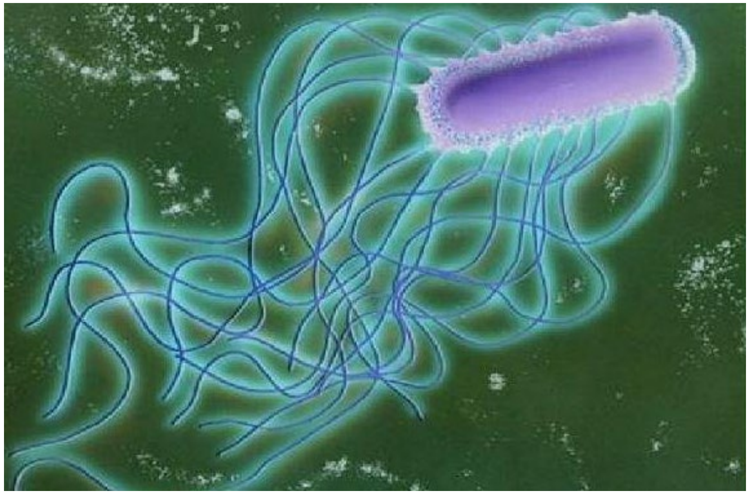


Bacterial Cell Surface

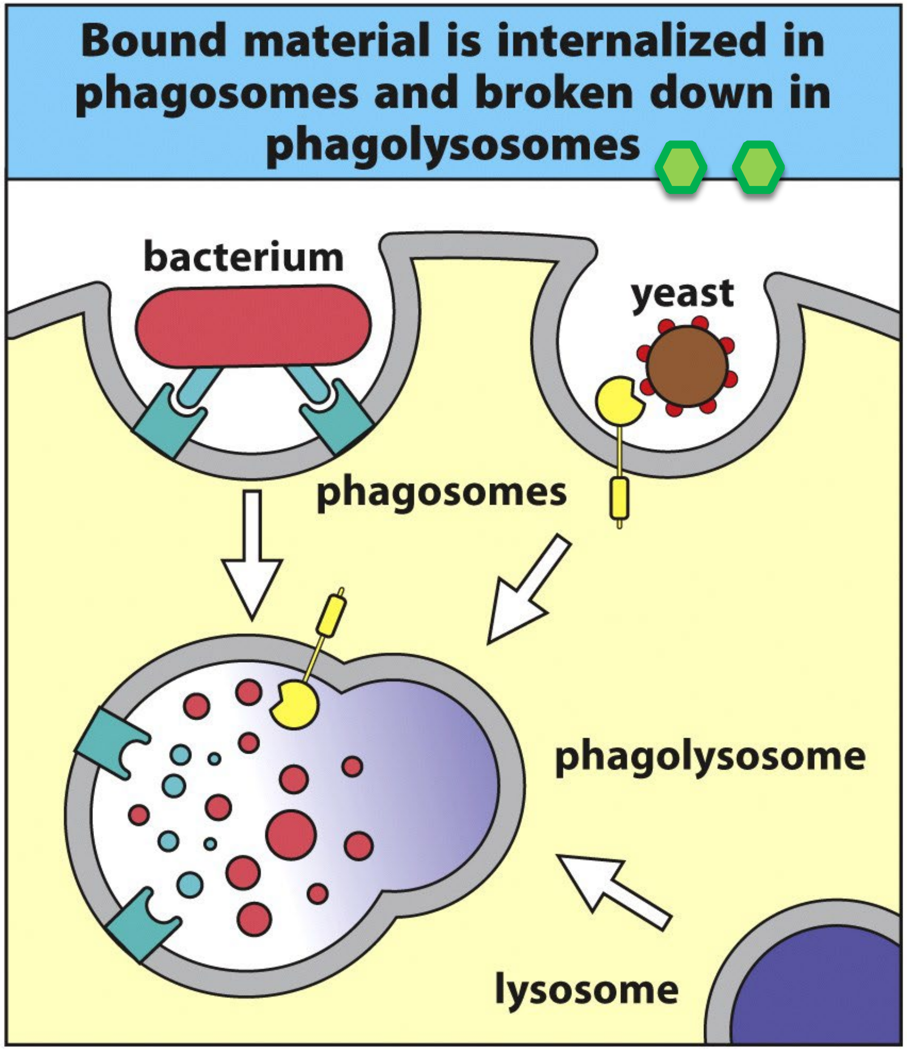


TLR5

flagella



PAMPs are on Cell Surfaces and Endosomes



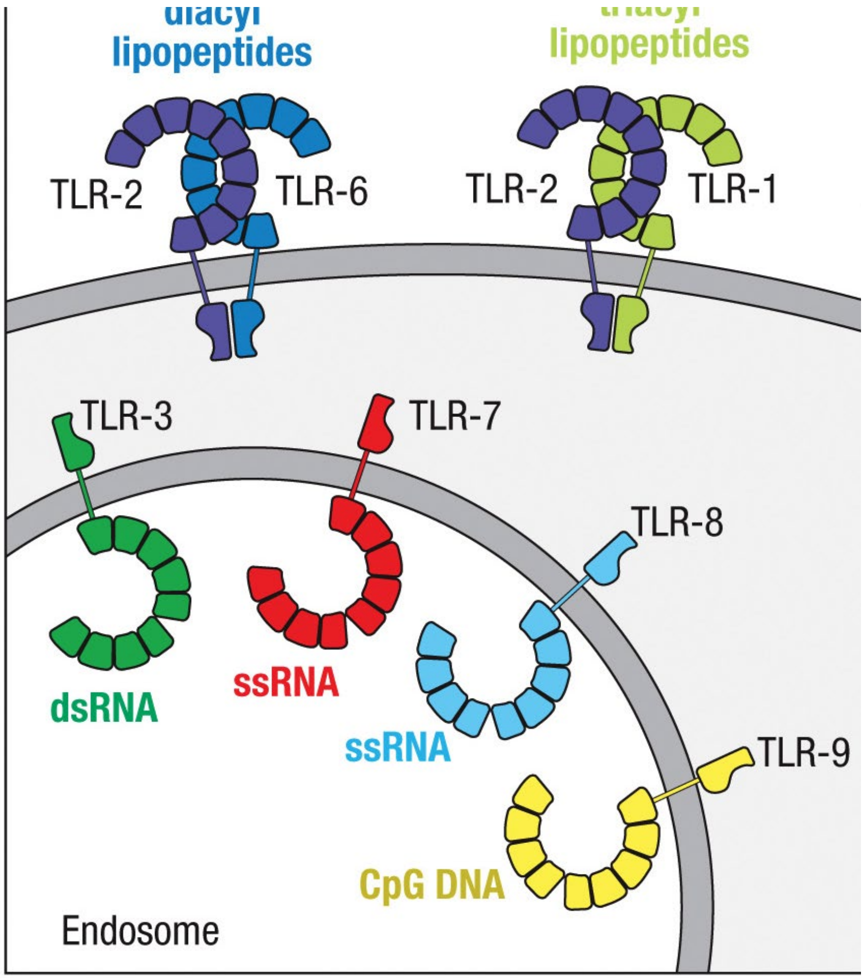
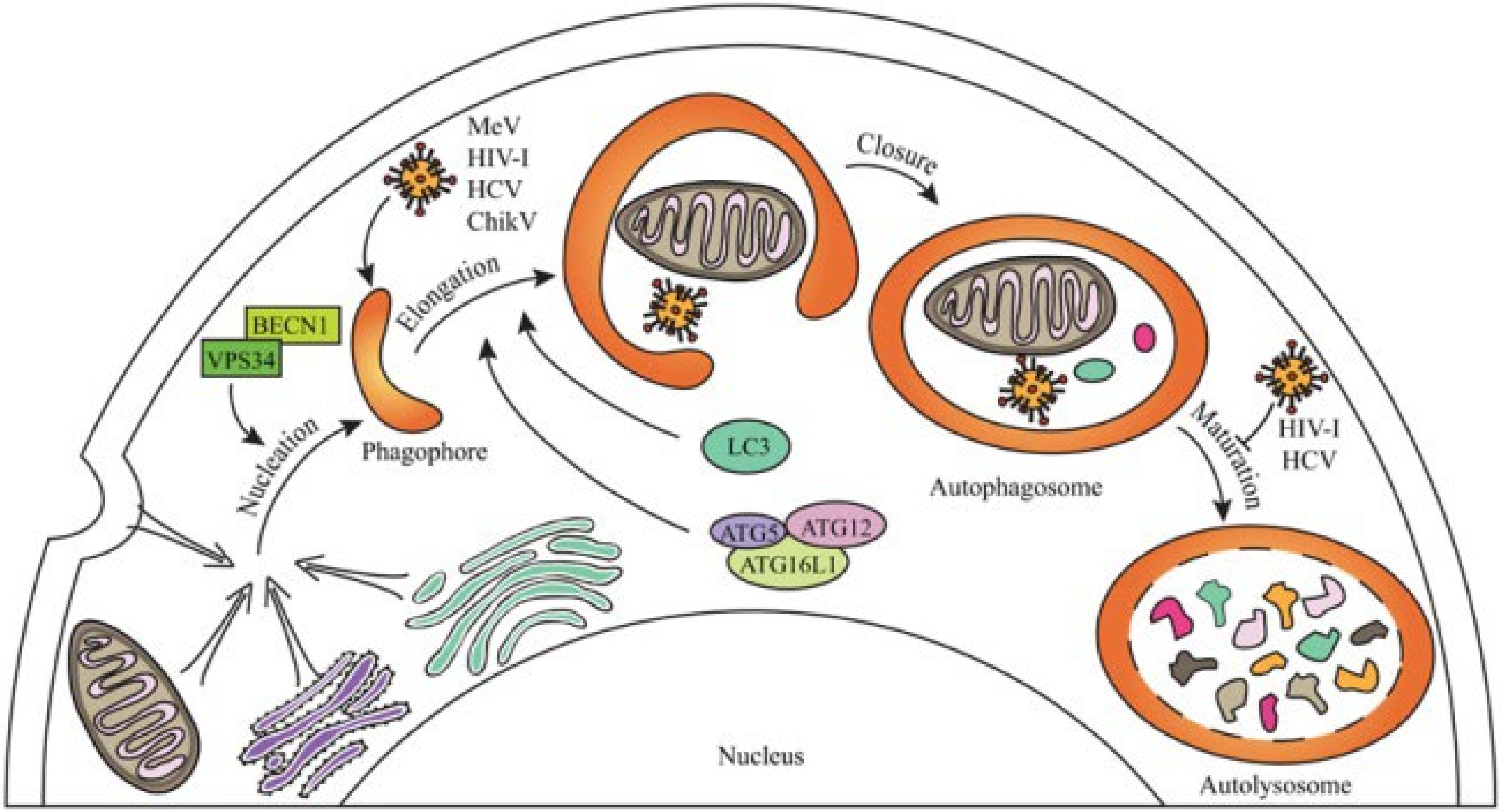


Figure 3.2 part 2 of 2 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

Autophagy



http://journal.frontiersin.org/Journal/10.3389/fimmu.2012.00426/full

Diversity of Toll-like Receptors

Innate immune recognition by mammalian Toll-like receptors	
Toll-like receptor	**Ligand**
TLR-1:TLR-2 heterodimer TLR-2:TLR-6 heterodimer	Lipomannans (mycobacteria) Diacyl and triacyl lipopeptides (bacteria) Lipoteichoic acids (Gram-positive bacteria) Cell-wall β-glucans (fungi)
TLR-3	Double-stranded RNA (viruses), poly I:C
TLR-4	LPS (Gram-negative bacteria)
TLR-5	Flagellin (bacteria)
TLR-7	Single-stranded RNA (viruses)
TLR-8	Single-stranded RNA (viruses)
TLR-9	DNA with unmethylated CpG (bacteria and DNA viruses)
TLR-10 (human only)	Unknown
TLR-11 (mouse only)	Profilin and profilin-like proteins (*Toxoplasma gondii*, uropathogenic bacteria)
TLR-12 (mouse only)	Profilin (*Toxoplasma gondii*)
TLR-13 (mouse only)	Single-stranded RNA (bacterial ribosomal RNA)

Structure of Toll-like Receptors

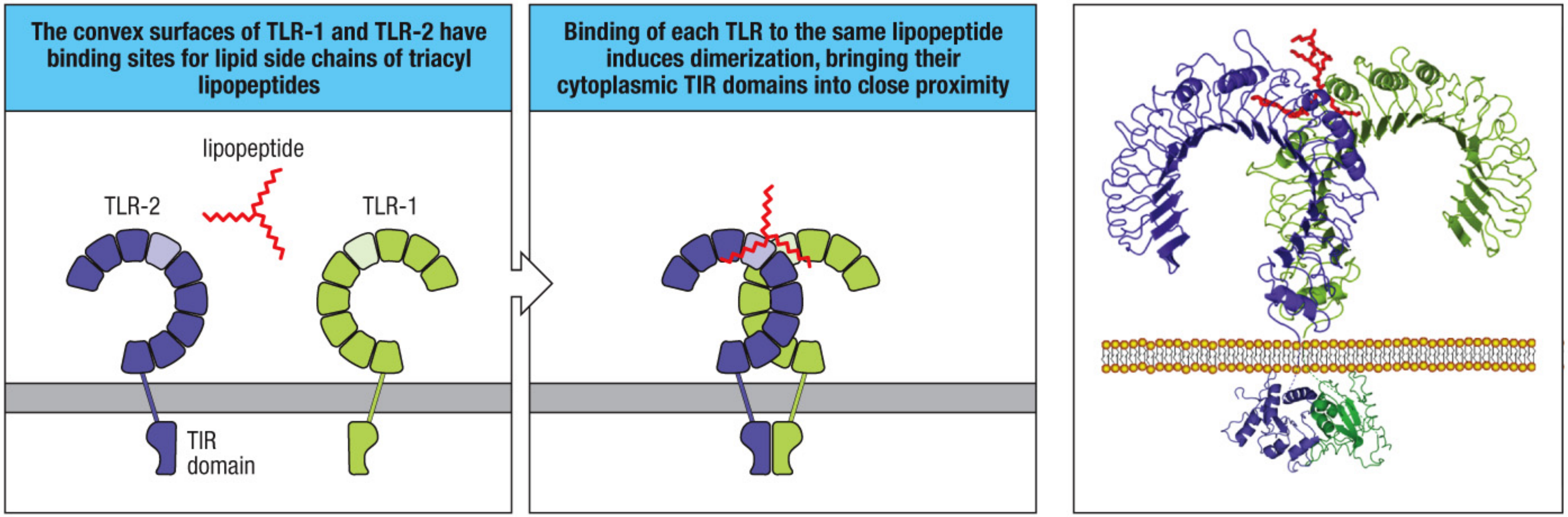
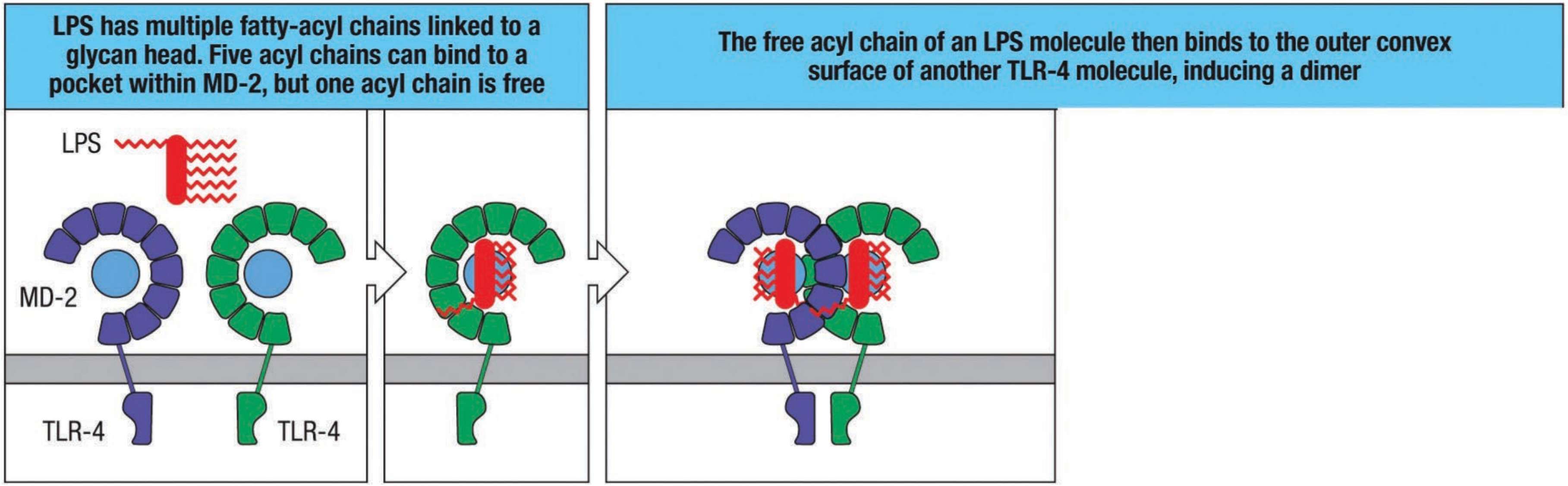
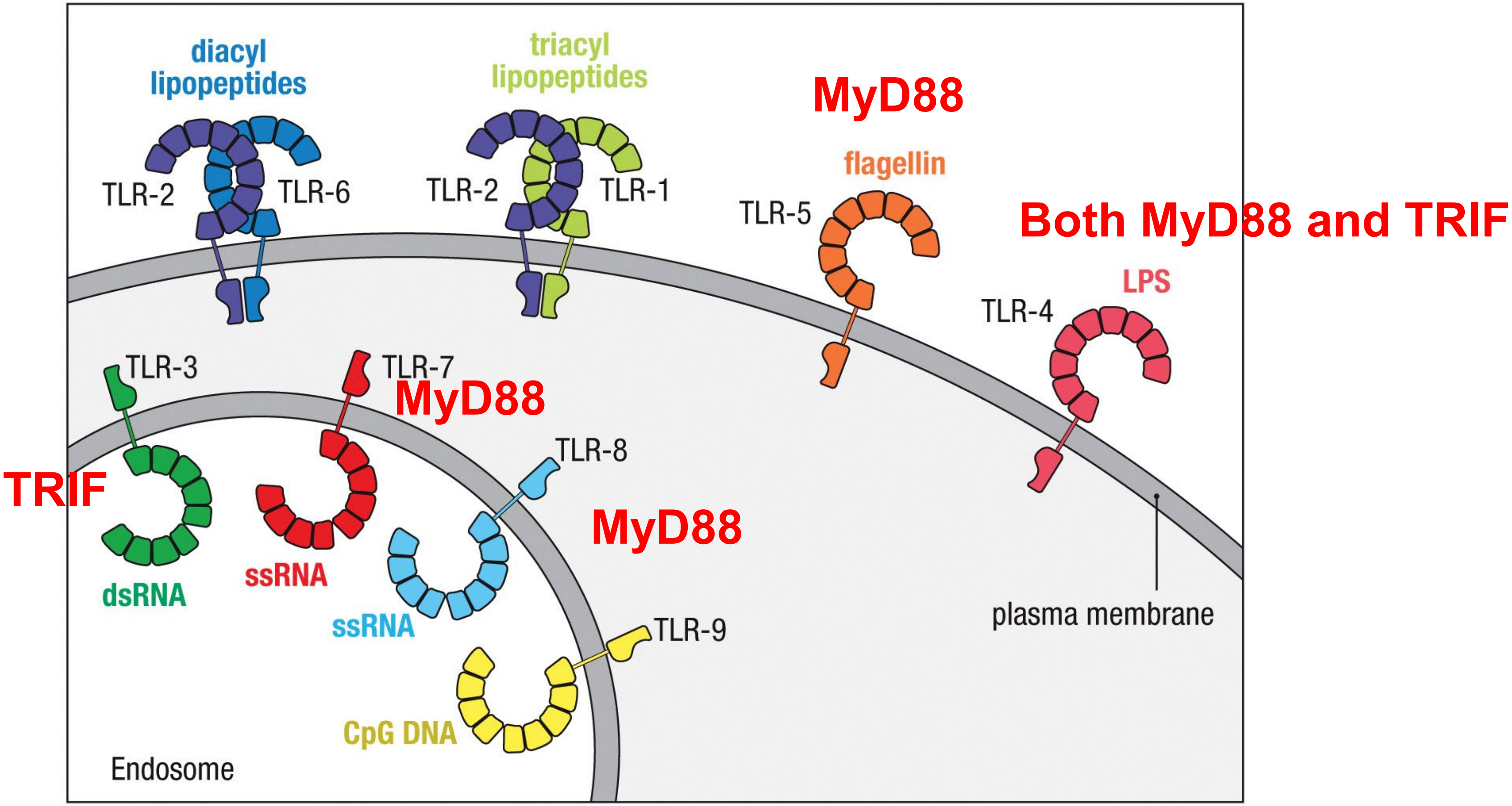


Figure 3.12 Janeway's Immunobiology, 9th ed. (© Garland Science 2017)

Structure of TLR4/LPS Complex

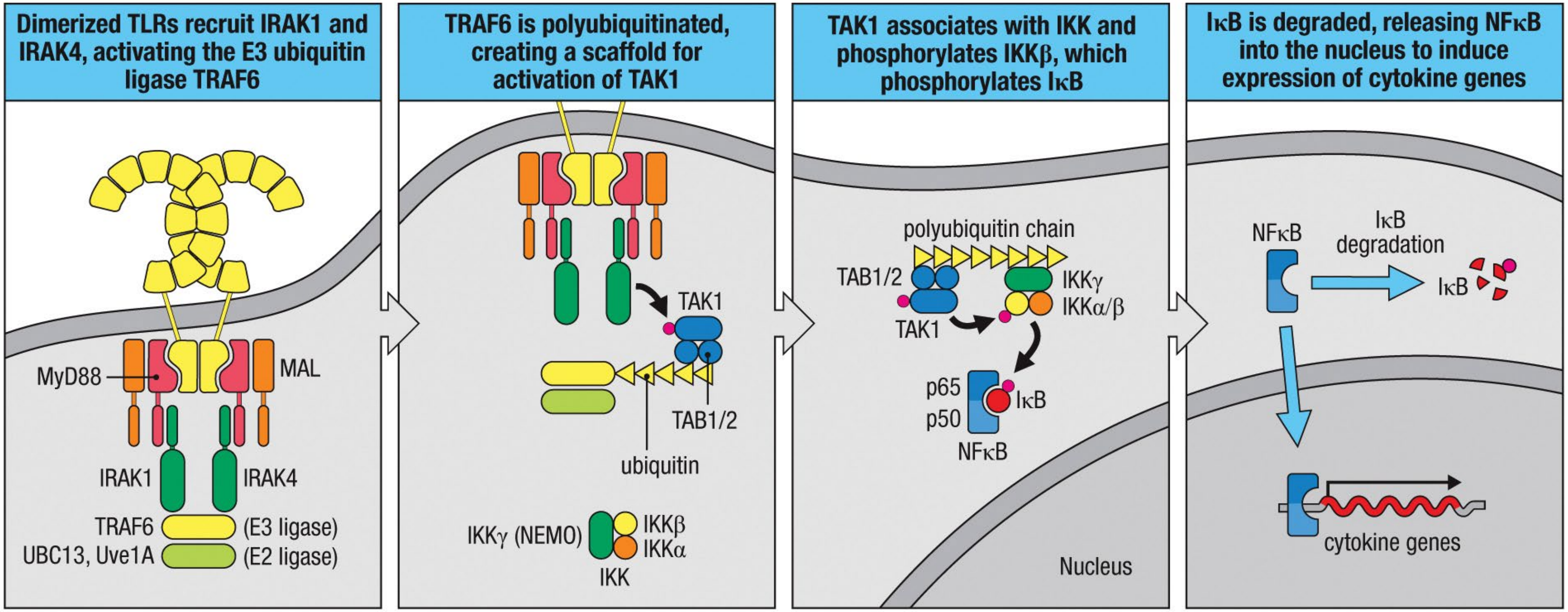


TLR adaptors

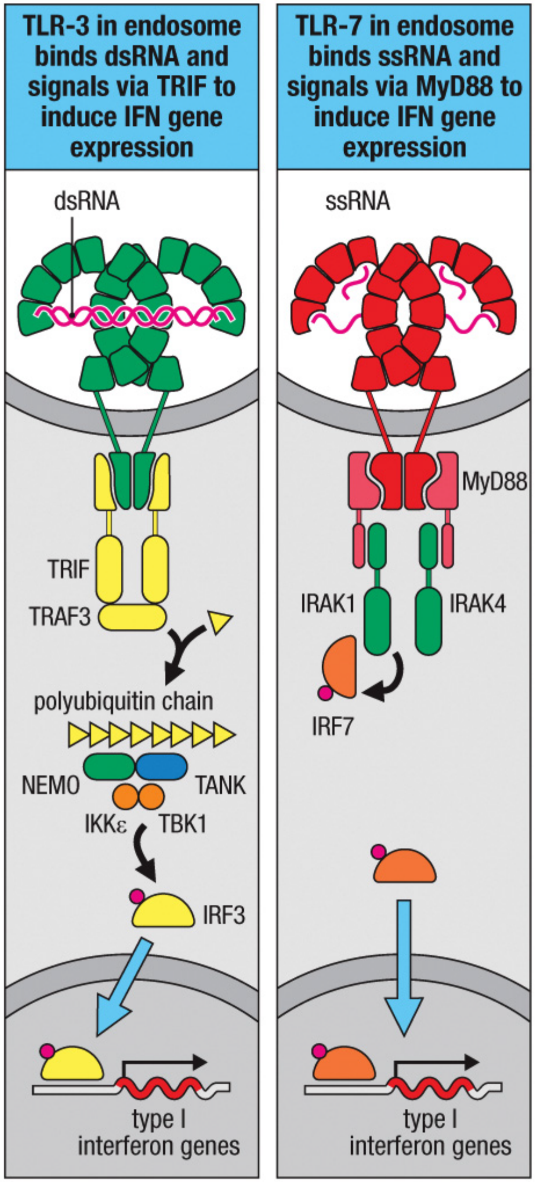


MyD88 activates both NF-kB and IFN response
TRIF activates IFN response

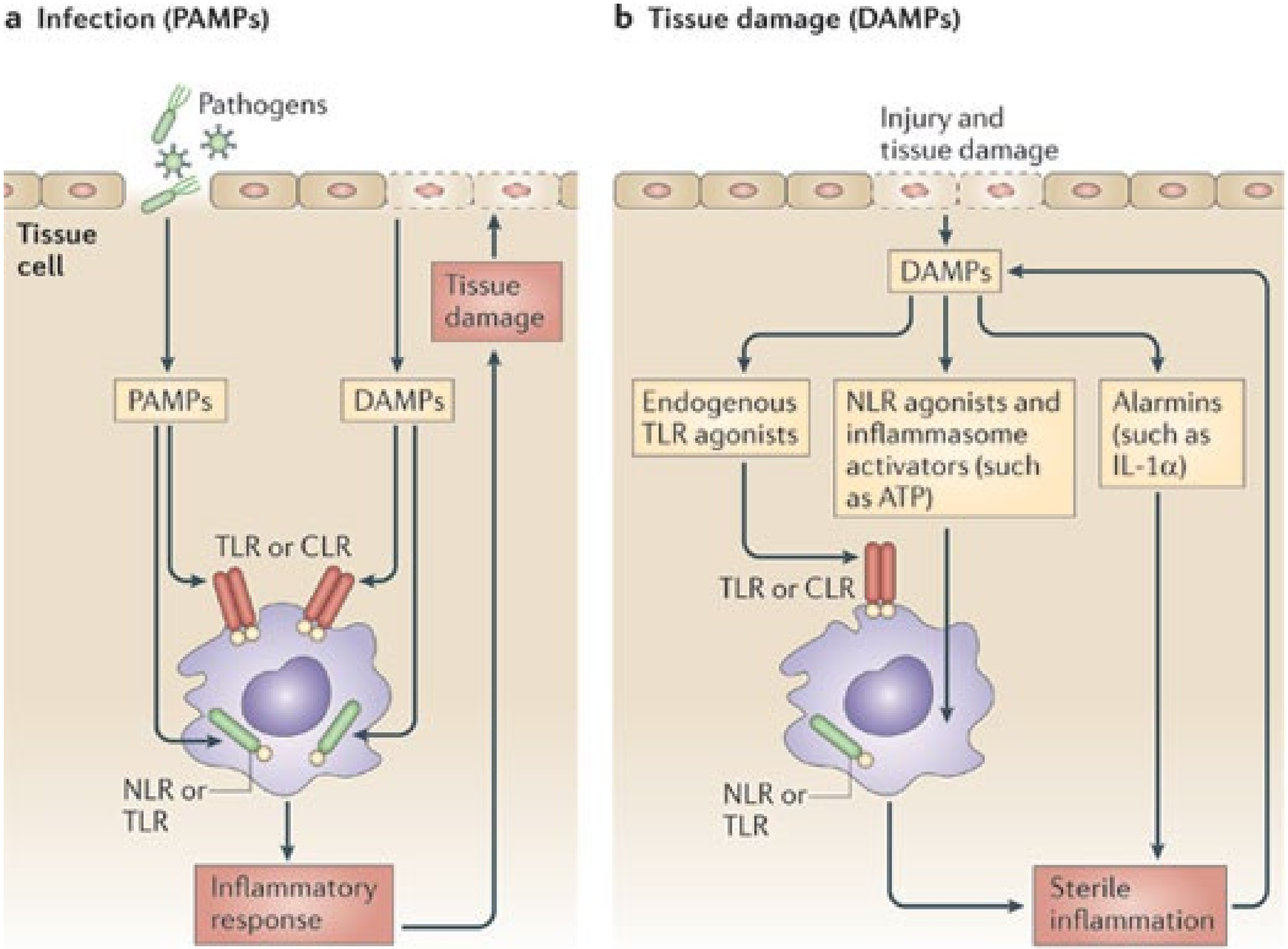
TLRs Activate NF-κB Pathway



Intracellular TLRs Activate IFN Pathway



TLRs Also Recognize DAMPs



http://www.nature.com/nrrheum/journal/v6/n3/full/nrrheum.2009.278.html

Question

- TLR

- What are they?
- What do they bind to? List two specific examples.
- What is the consequence of their activation?

Question

- What is true about Toll like receptors?
- A) They recognize microbial molecules but not host molecules
- B) They are only present on host cell surface
- C) They are expressed by all cell types
- D) They initiate both anti-bacterial and anti-viral responses

Outline

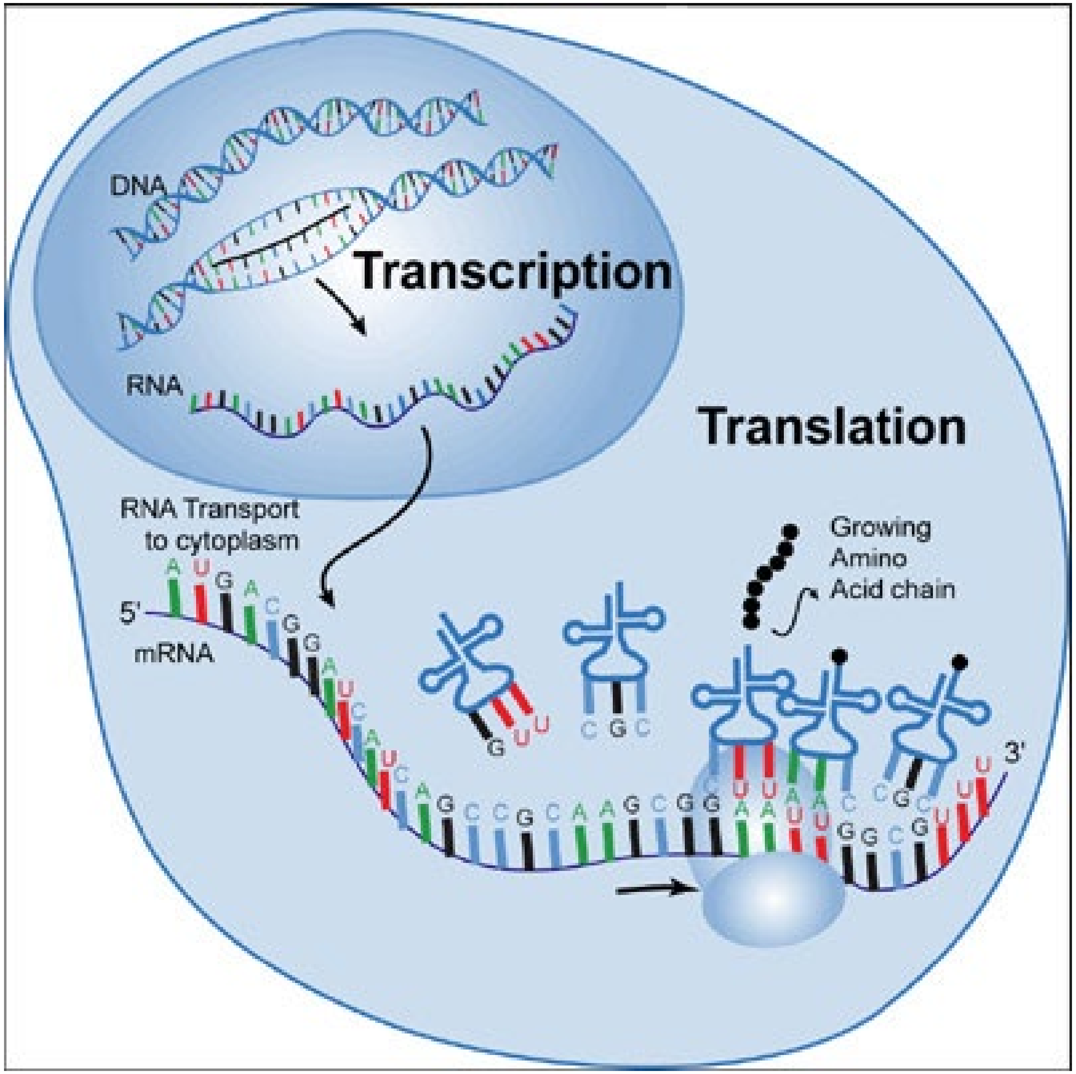
- Pattern recognition receptors
  - PAMS
  - TLRs
  - Cytosolic DNA/RNA sensors
  - NLRs
  - Inflammasome

- Case study: Hereditary Periodic Fever Syndromes

Cytosolic Innate Immune Receptors

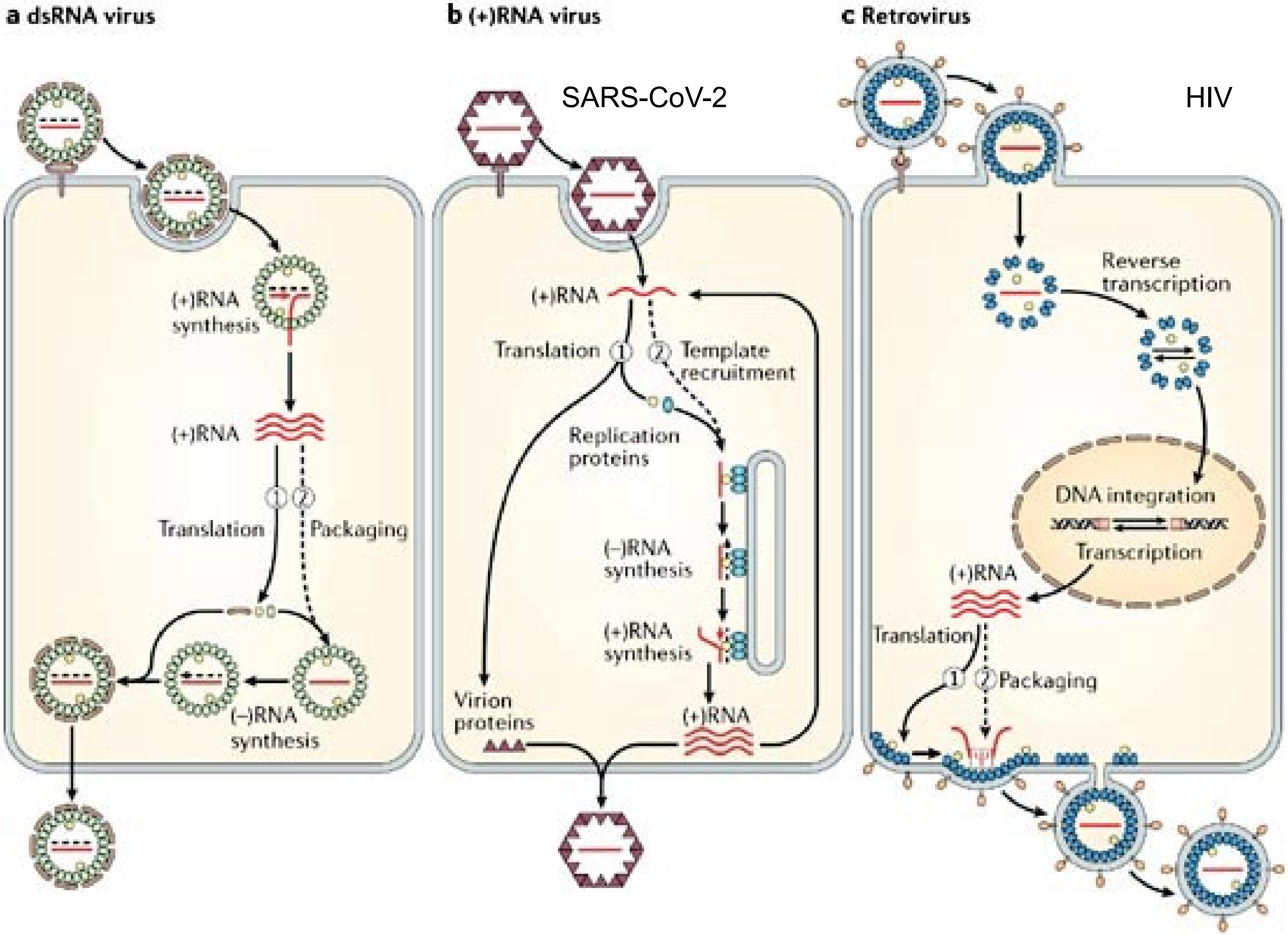
Ligand	Recognition strategies
RIG-I	Triphosphate dsRNA
MDA-5	dsRNA
cGAS	DNA
NOD1	γ-Glutamyl diaminopimelic acid (iE-DAP)
NOD2	Muramyl dipeptide (MDP)
NLRP1	Pathogen protease activity
NLRP3	Reduced intracellular potassium, ROS, disruption of lysosomes
NAIP1 with NLRC4 (mouse)	Needle subunit of bacterial T3SS
NAIP2 with NLRC4 (mouse)	Rod subunit of bacterial T3SS
NAIP5 with NLRC4 (mouse)	Flagellin
NAIP with NLRC4 (human)	Flagellin
Pyrin	Inactivation of Rho GTPases
AIM2	DNA

Mammalian Cellular DNA



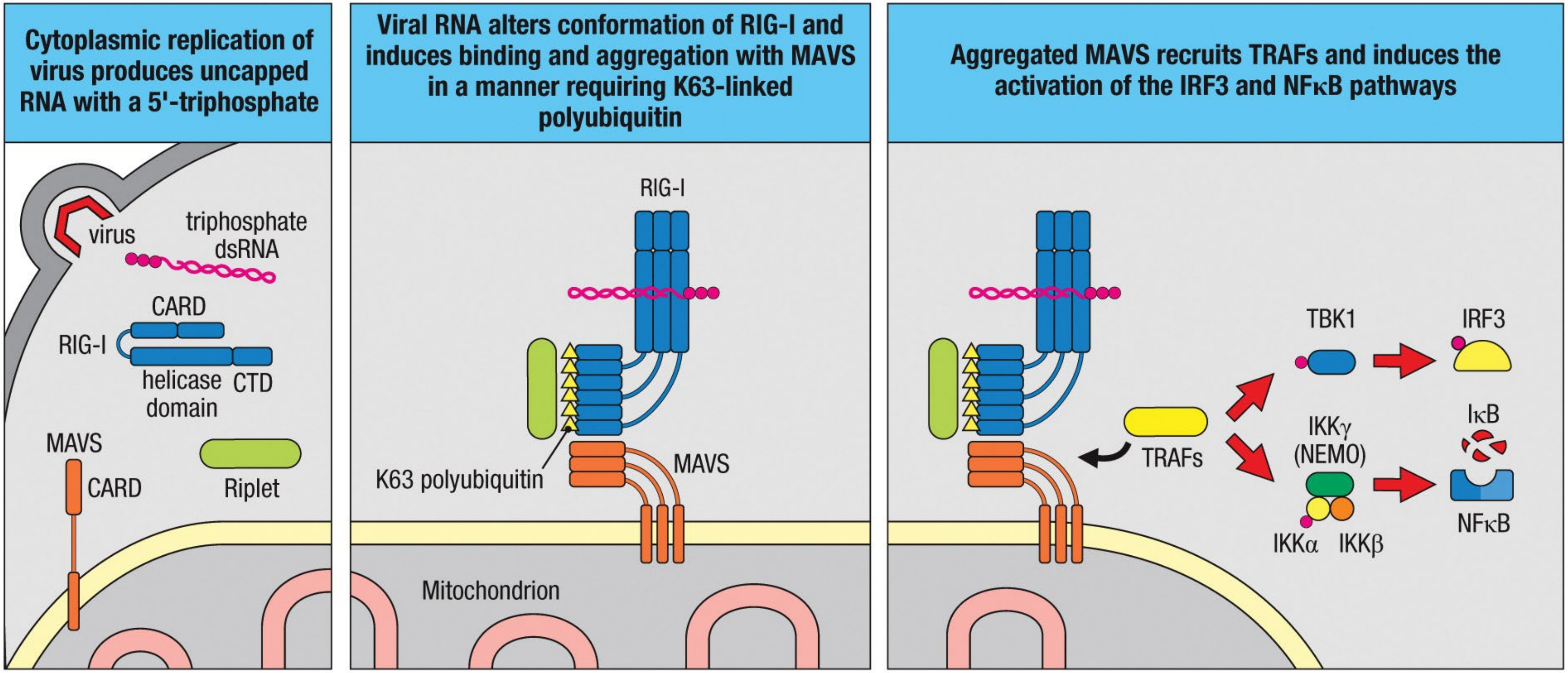
http://www.tokresource.org/tok_classes/biobiobio/biomenu/transcription_translation/

Cytoplasmic Viral RNA

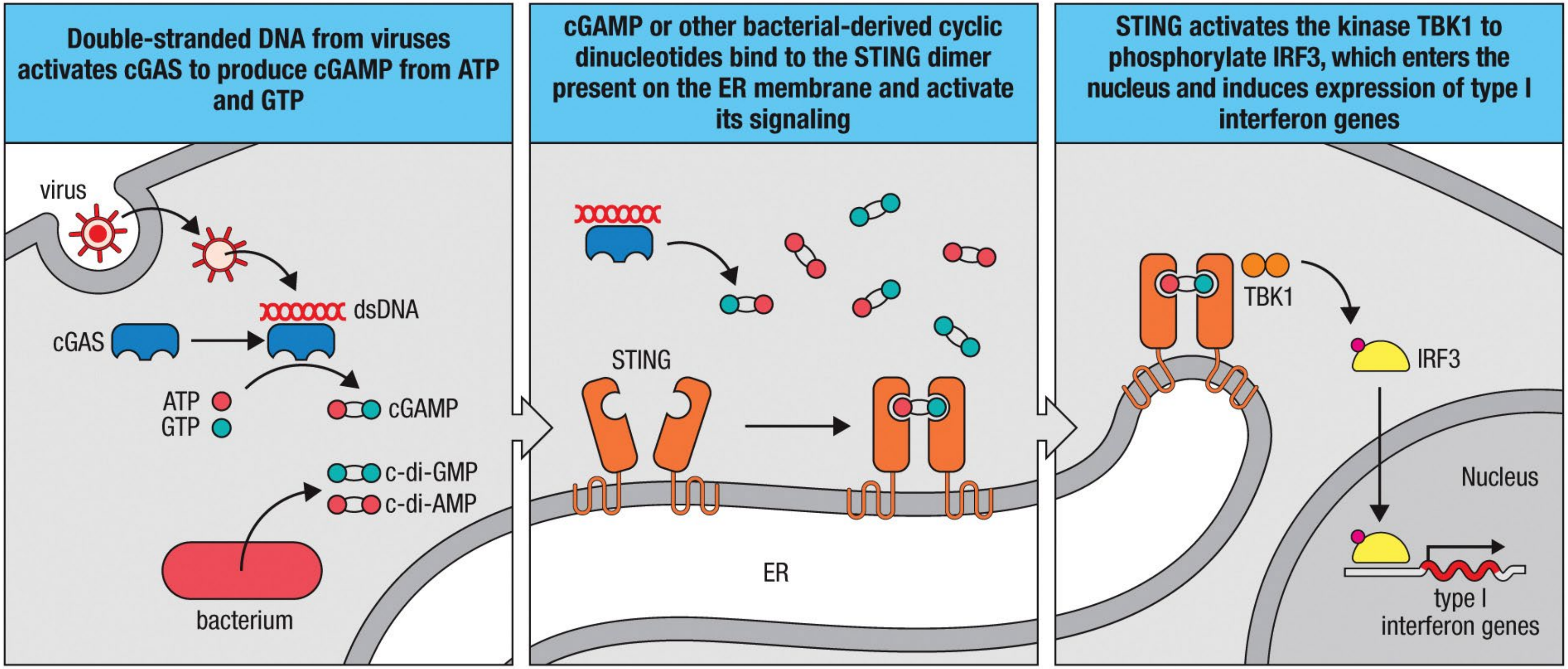


http://www.nature.com/nrmicro/journal/v4/n5/full/nrmicro1389.html

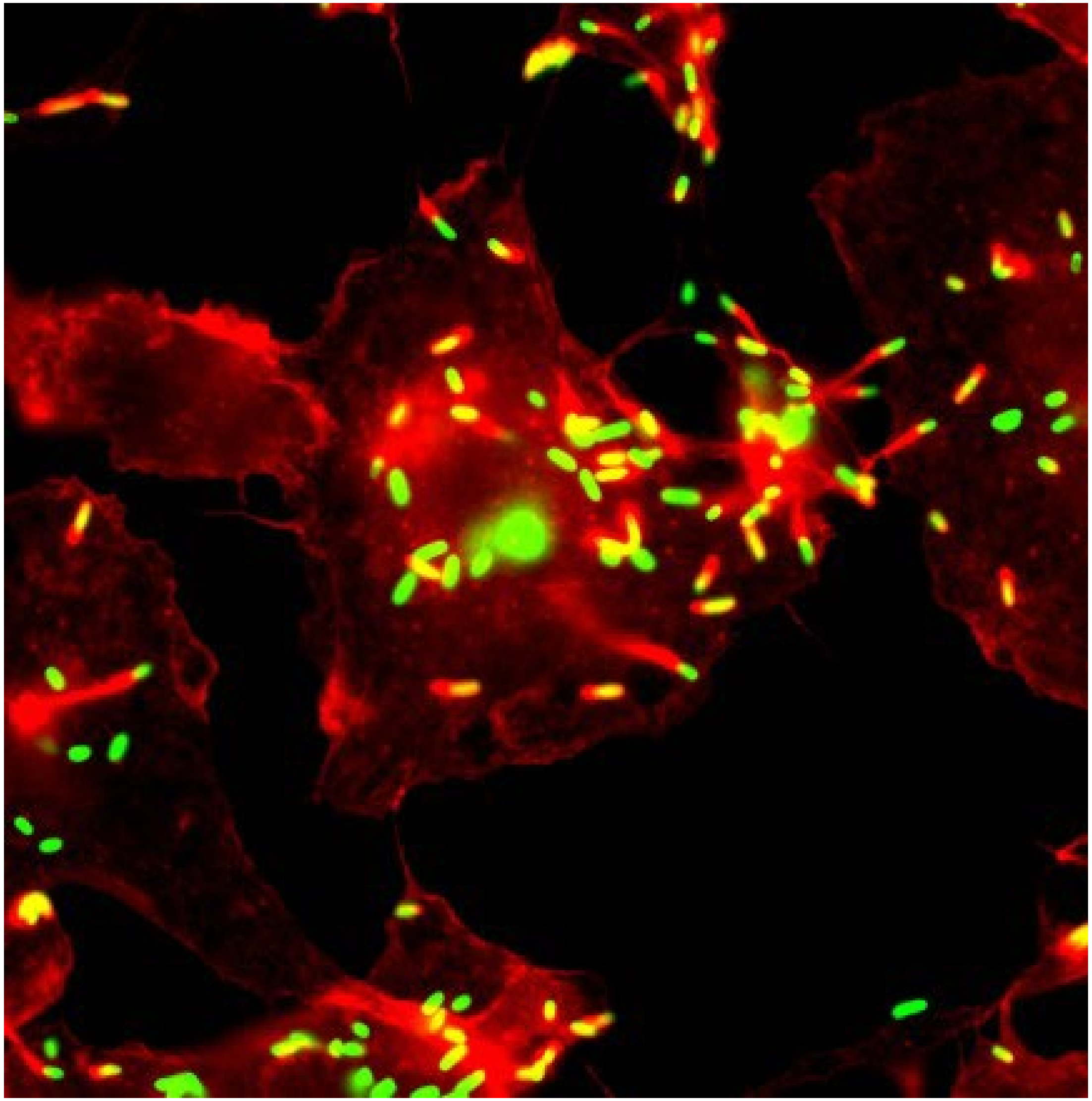
RIG-1 Senses Intracellular Virus



cGAS - Cytosolic Sensor of DNA



Intracellular Bacteria

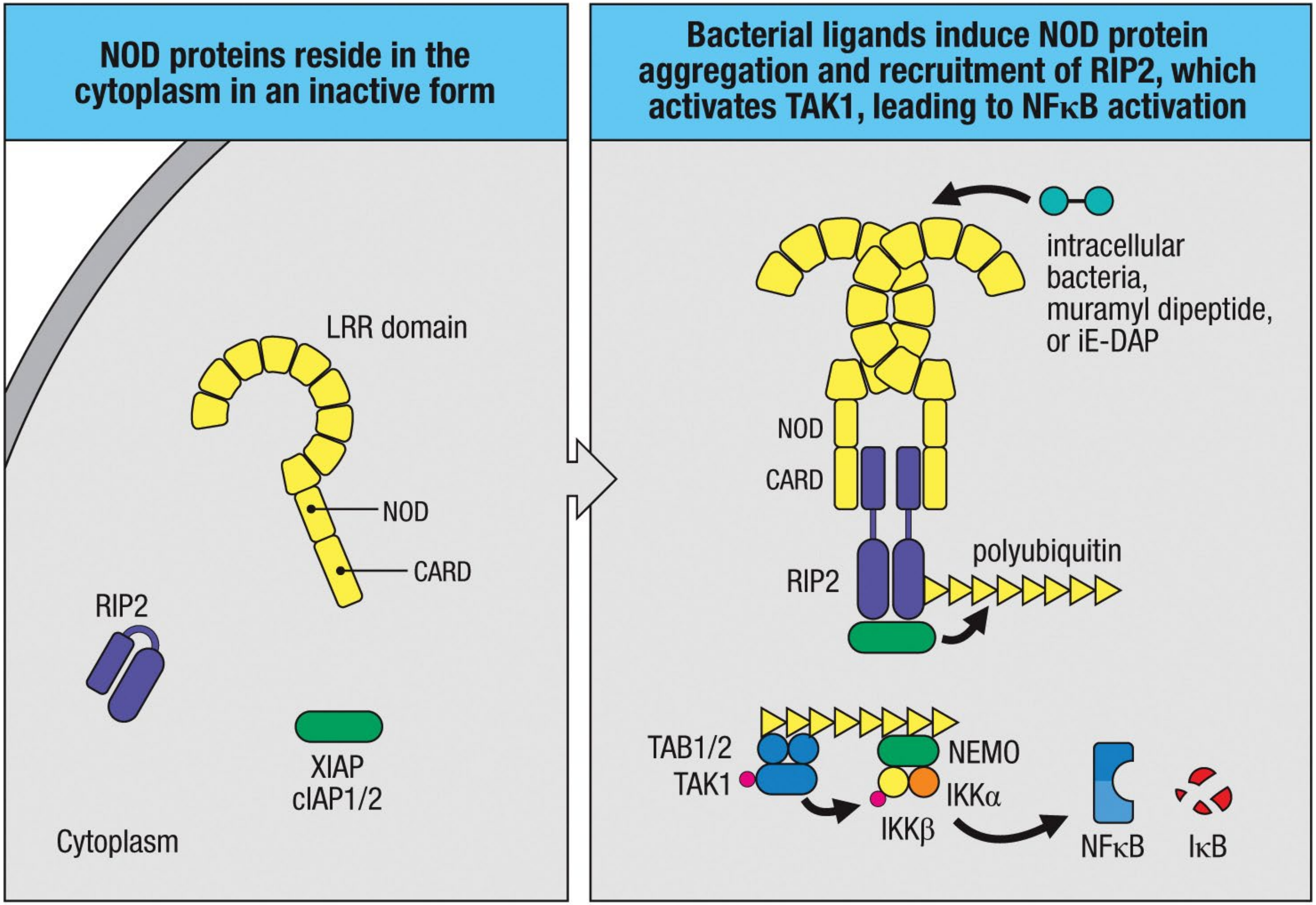


Outline

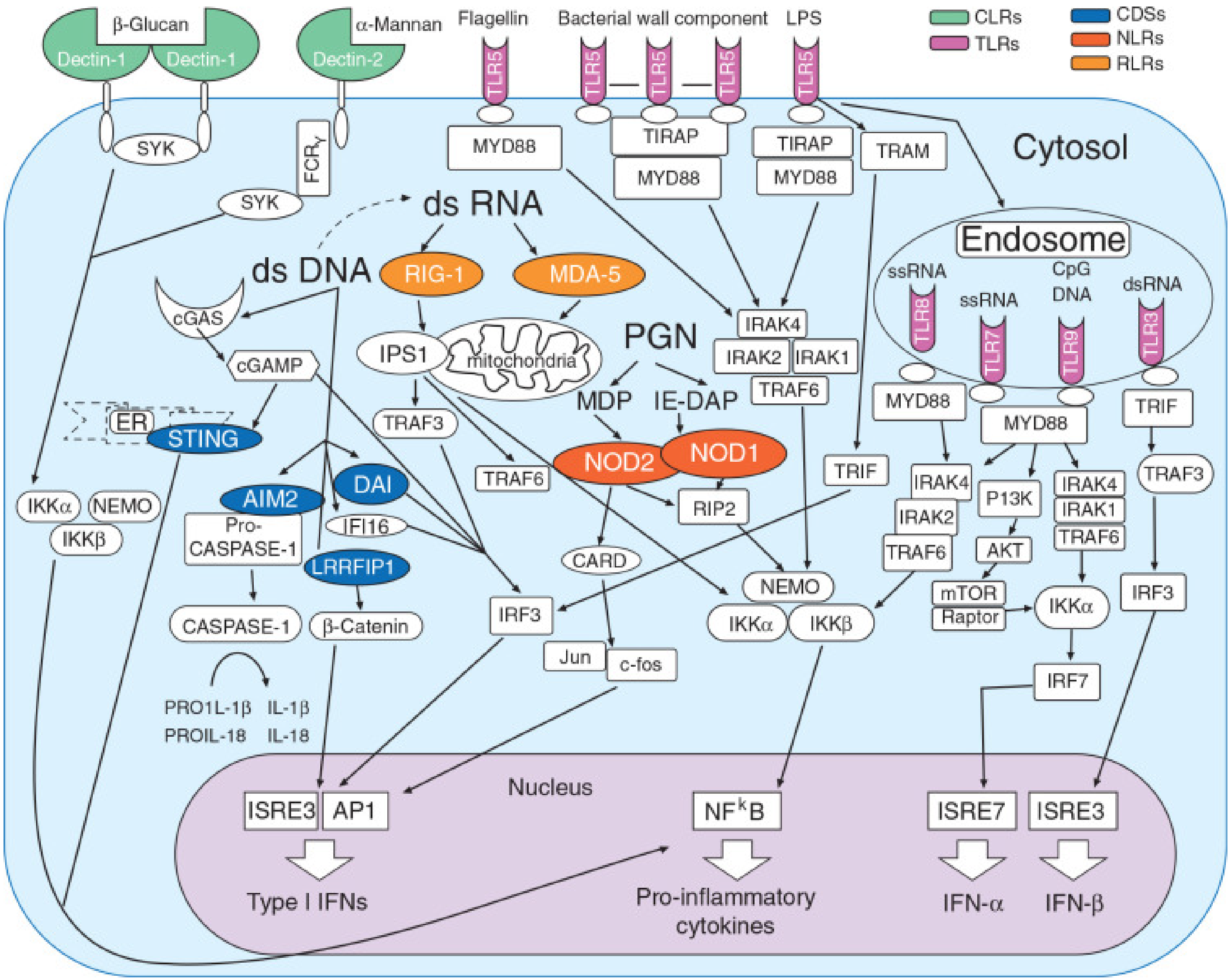
- Pattern recognition receptors
  - PAMS
  - TLRs
  - Cytosolic DNA/RNA sensors
  - NLRs
  - Inflammasome

- Case study: Hereditary Periodic Fever Syndromes

NOD-like Receptors



Pattern Recognition Receptors

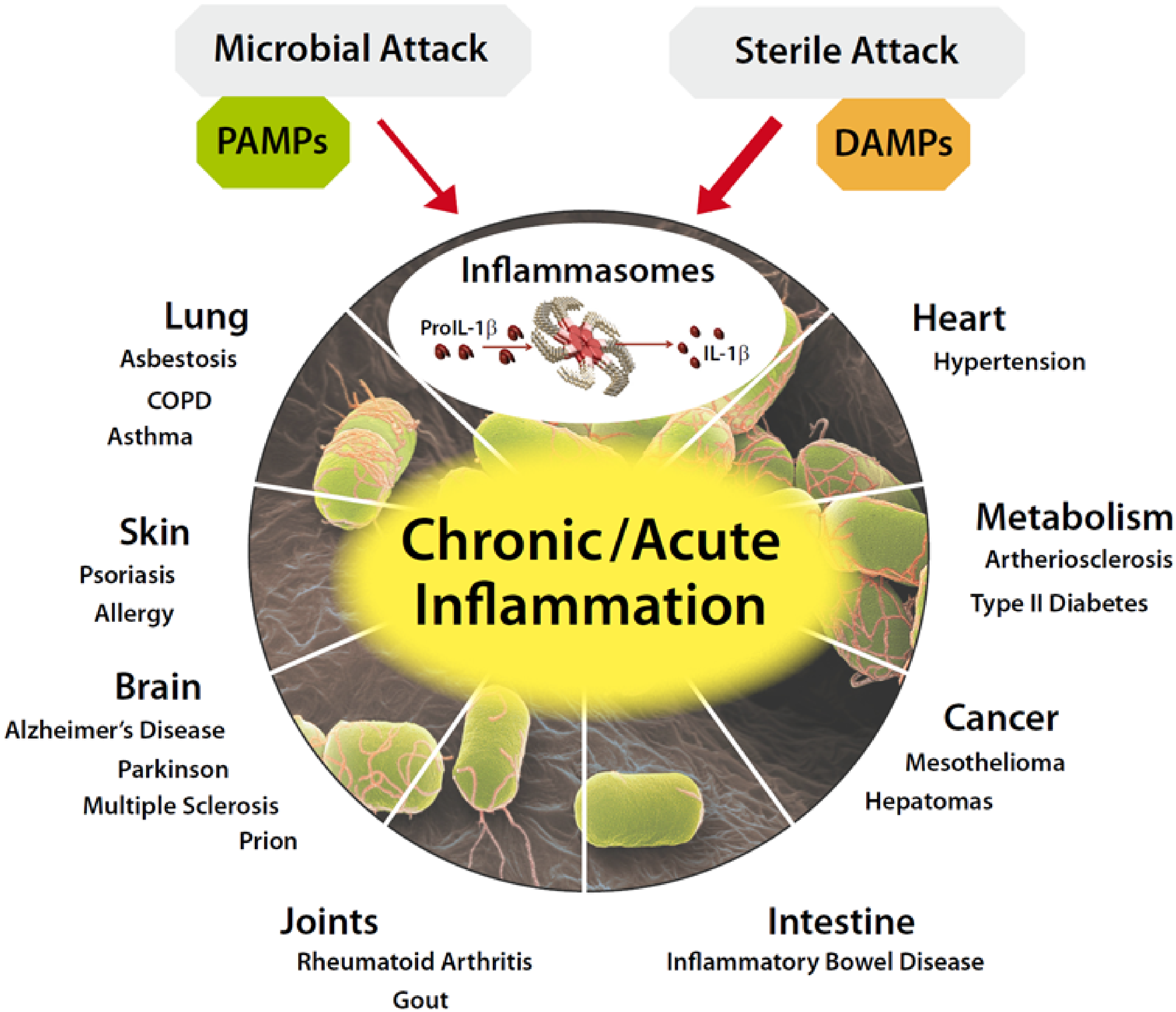


C-type lectins receptors
Toll-like receptors
RIG 1 like receptors
NOD-like receptors
cytosolic DNA sensors

peptidoglycans

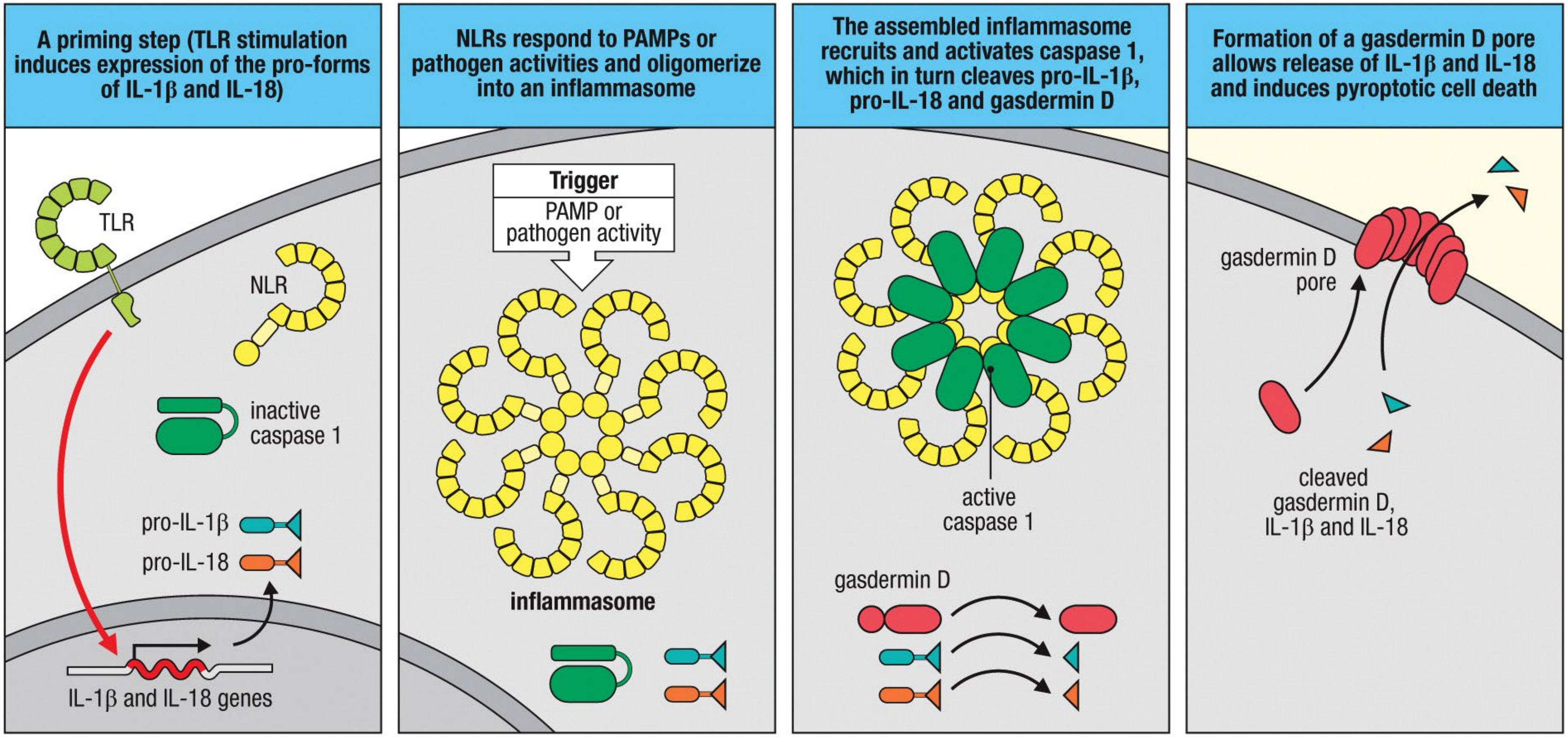
https://doi.org/10.1093/annonc/mdx179

Inflammation is Tightly Controlled

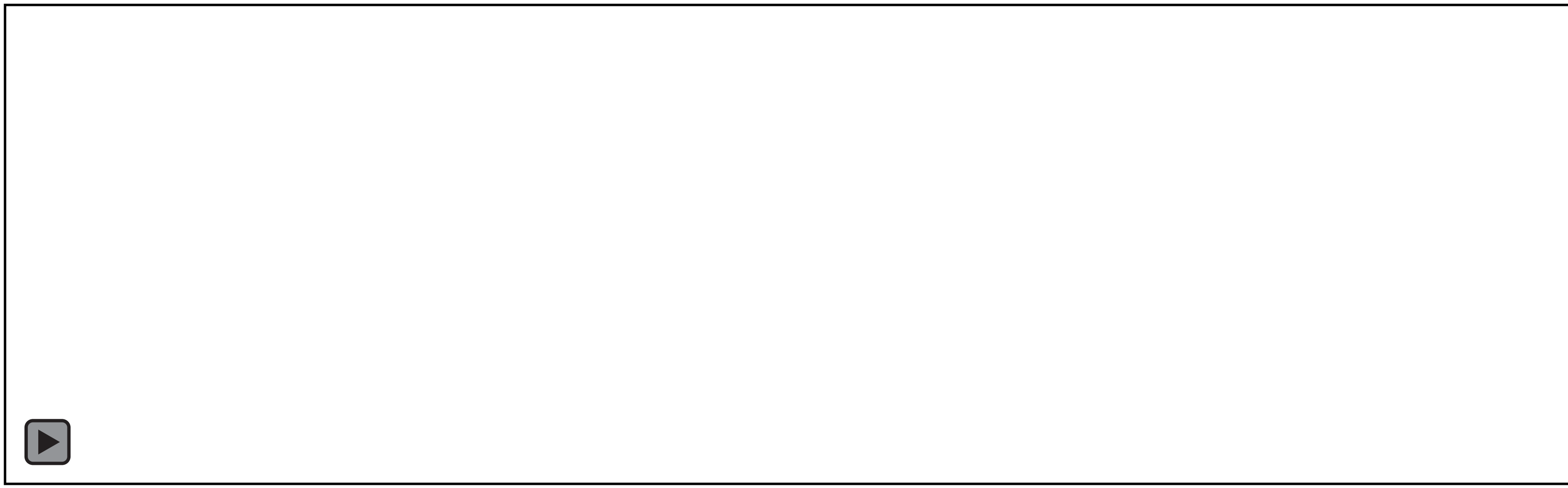


http://www.adipogen.com/inflammasomes/

Inflammasomes

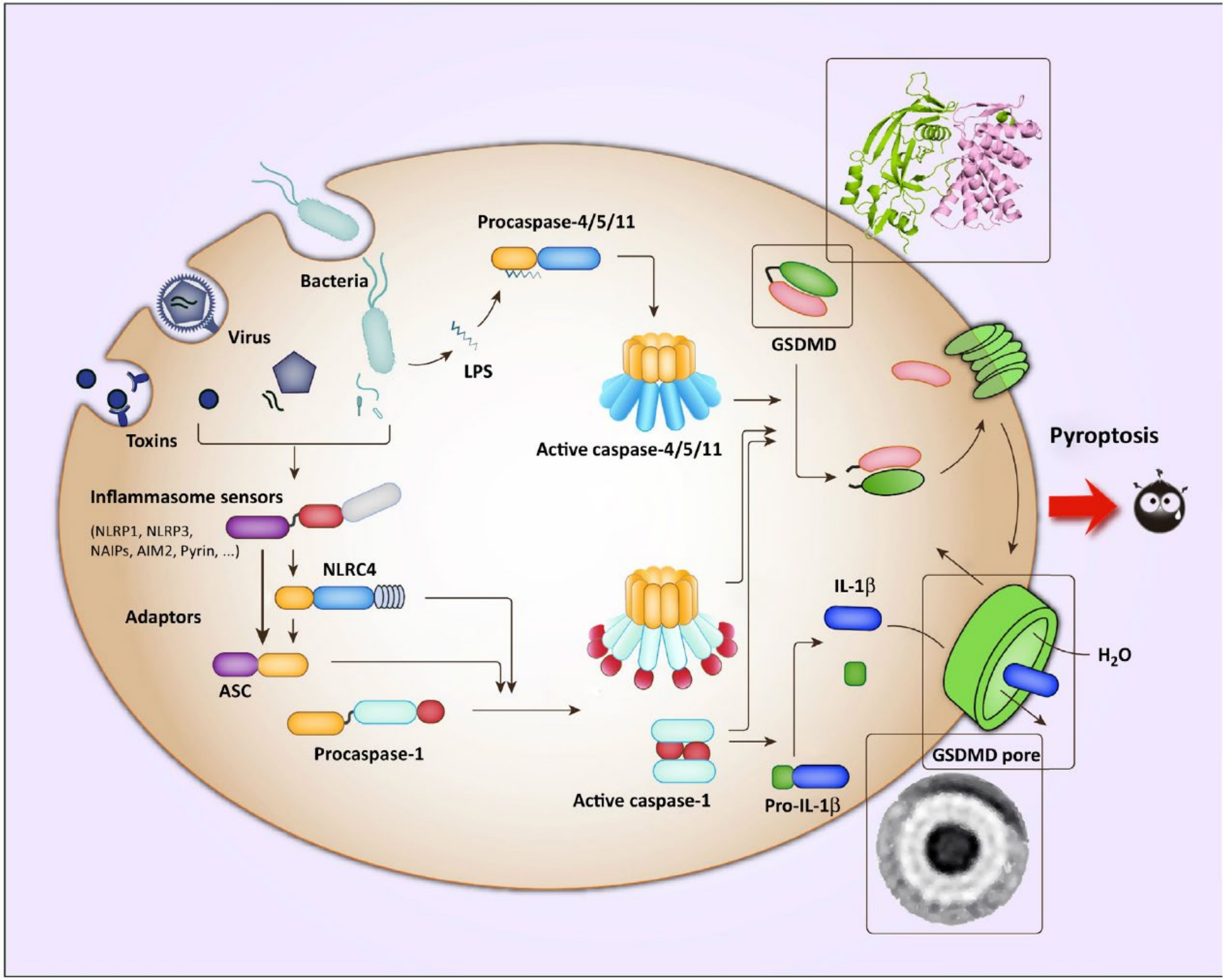


Pyroptosis



https://www.nature.com/articles/nature18590#supplementary-information
Movie 1. **Membrane targeting of the Gasdermin-N domain of GSDMD during pyroptosis**

Pyroptosis



http://www.cell.com/trends/biochemical-sciences/fulltext/S0968-0004(16)30182-7

Summary

- Pattern recognition receptors recognize both PAMPs and DAMPs
- PRRs are on cell surface, endosomal compartments and cytoplasm
- Their activation leads to signal transduction and secretion of inflammatory cytokines
- Defend against microbial pathogens but also cause host damage

Question

- What are the Pattern recognition receptors in the cytosol? What do they sense?

Outline

- Pattern recognition receptors
  - PAMS
  - TLRs
  - NODs
  - Inflammasome
- Case study: Hereditary Periodic Fever Syndromes

Hereditary Periodic Fever Syndromes

Patient:

- 1 week old
- Hearing loss detected at birth
- Fever, irritability
- WBC count 21,000 cells/microliter (normal range 5,000-10,000)
- No bacterial could be cultured

Treatment

- Antimicrobial drugs (suspicion of viral or bacterial meningitis)
- No alleviation of fever, no diagnosis

Follow-up

- Continued fevers
- Enlarged liver and spleen
- Evidence of arthritis in the knee joint
- Diffuse rash on most of the body
- Increased erythrocyte sedimentation rate
  - signals an increase in concentration of acute phase proteins
- Increased C-reactive protein levels (acute-phase response)

Treatment

- IL-1 receptor antagonist (Kineret)
- Symptoms disappeared
- Requires maintenance treatment with Kineret

Hereditary Periodic Fever Syndromes

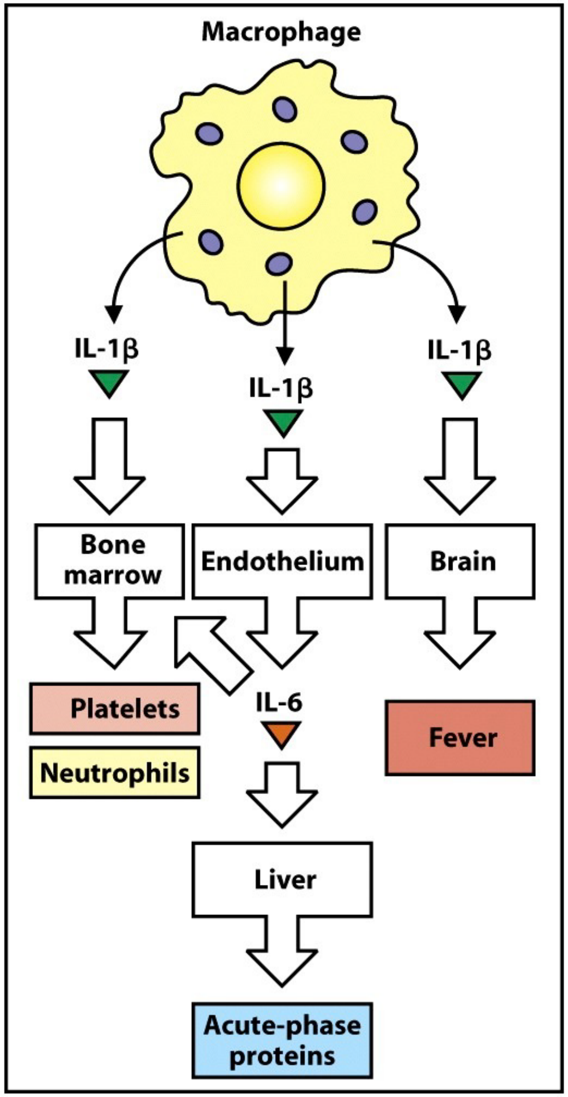


Figure 7-2 Case Studies in Immunology, 5ed. (© Garland Science 2008)

Hereditary Periodic Fever Syndromes

What is wrong with the patient?

- Genetic defect impairing regulation of of caspase-1, which is required to process IL-1β to the mature form.

- Thus, resulting in unchecked processing and secretion of IL-1β, which can be blocked with IL-1 receptor agonist.

IL-1 processing

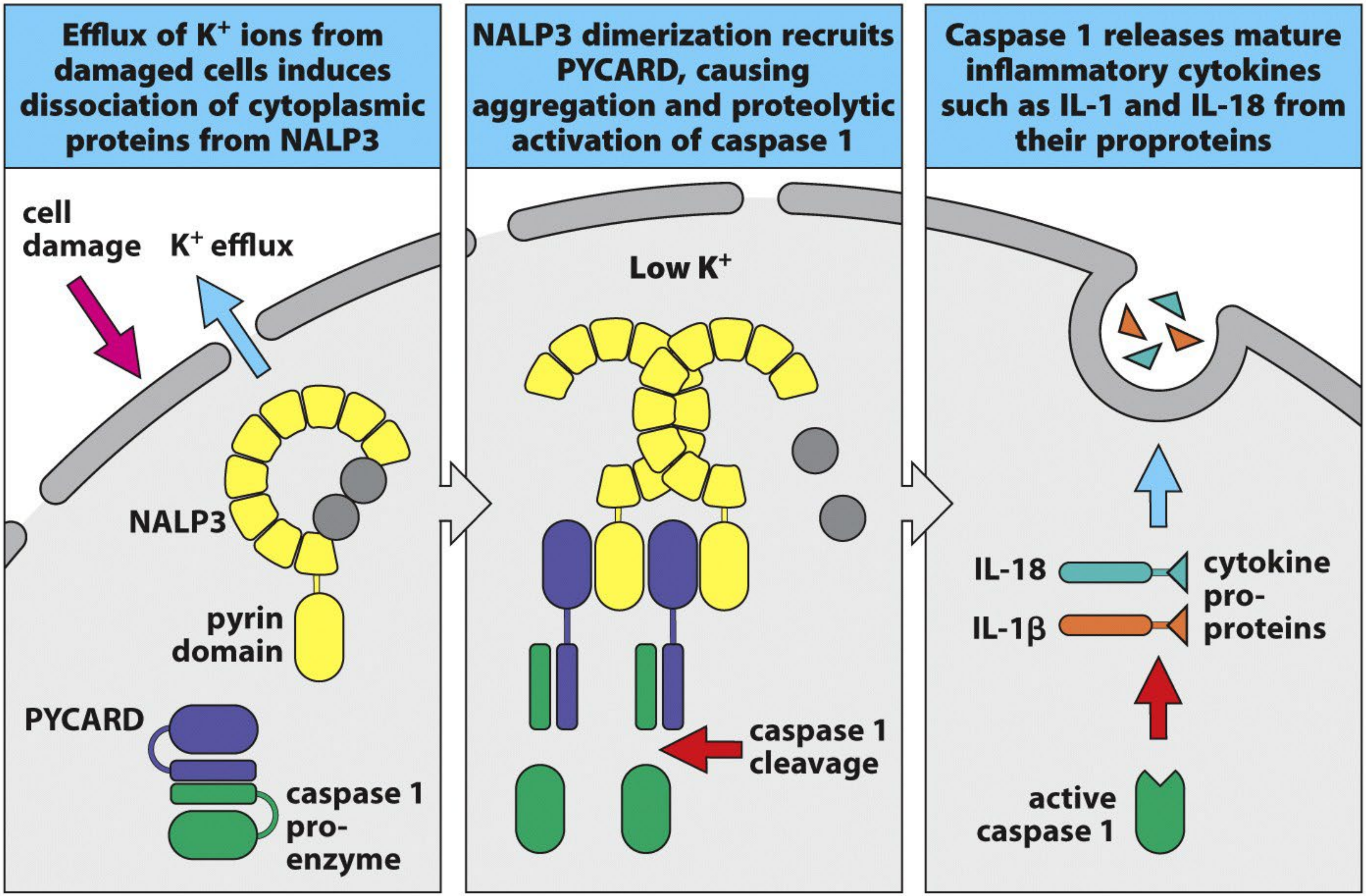


Figure 3.16 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

The Autoinflammatory Diseases

Disease (common abbreviation)	Clinical features	Inheritance	Mutated gene	Protein (alternative name)
Familial Mediterranean fever (FMF)	Periodic fever, serositis (inflammation of the pleural and/or peritoneal cavity), arthritis, acute-phase response	Autosomal recessive	*MEFV*	Pyrin
TNF receptor–associated periodic syndrome (TRAPS) (also known as familial Hibernian fever)	Periodic fever, myalgia, rash, acute-phase response	Autosomal dominant	*TNFRSF1A*	TNF-α 55 kDa receptor (TNFR-I)
Pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA)		Autosomal dominant	*PSTPIP1*	CD2-binding protein 1
Muckle–Wells syndrome	Periodic fever, urticarial rash, joint pains, conjunctivitis, progressive deafness	Autosomal dominant	*NLRP3*	Cryopyrin
Familial cold autoinflammatory syndrome 1 (FCAS1) (familial cold urticaria)	Cold-induced periodic fever, urticarial rash, joint pains, conjunctivitis			
Chronic infantile neurologic cutaneous and articular syndrome (CINCA)	Neonatal-onset recurrent fever, urticarial rash, chronic arthropathy, facial dysmorphia, neurologic involvement			
Hyper IgD syndrome (HIDS)	Periodic fever, elevated IgD levels, lymphadenopathy	Autosomal recessive	*MVK*	Mevalonate synthase
Blau syndrome	Granulomatous inflammation of skin, eye, and joints	Autosomal dominant	*NOD2*	NOD2